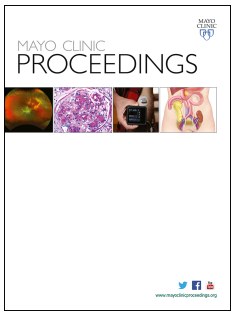

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SARS-CoV-2 Infection and COVID-19 During Pregnancy: A Multidisciplinary Review

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ABSTRACT: The global pandemic of SARS-CoV-2, the cause of Coronavirus disease 2019 (COVID-19), has been associated with worse outcomes in several patient populations, including the elderly and those with chronic comorbidities. Data from previous pandemics and seasonal influenza suggest that pregnant women may be at increased risk for infection-associated morbidity and mortality. Physiological changes in normal pregnancy and metabolic and vascular changes of high-risk pregnancies may affect pathogenesis or exacerbate the clinical presentation of COVID-19. Specifically, SARS-CoV-2 enters the cell via the angiotensin converting enzyme 2 (ACE2) receptor, which is upregulated in normal pregnancy. Upregulation of ACE2 mediates conversion of Angiotensin II (vasoconstrictor) to Angiotensin 1-7 (vasodilator) and contributes to relatively low blood pressures, despite upregulation of other components of the renin angiotensin aldosterone system. As a result of higher ACE2 expression, pregnant women may be at an elevated risk of complications from SARS-CoV-2 infection. Upon binding to ACE2, SARS-CoV-2 causes its downregulation, thus lowering Angiotensin 1-7 levels, which can mimic/worsen vasoconstriction, inflammation, and pro-coagulopathic effects that occur in preeclampsia. Indeed, early reports suggest that, among other adverse outcomes, preeclampsia may be more common in pregnant women with COVID-19. Medical therapy, during both pregnancy and breast feeding, relies on medications with proven safety, but safety data are often missing for medications in the early stages of clinical trials. We summarize guidelines for medical/obstetric care and outline future directions for optimization of treatment and preventive strategies for pregnant patients with COVID-19 with the understanding that relevant data are limited and rapidly changing.

Key words: SARS-CoV-2, COVID-19, ACE2, pregnancy, preeclampsia

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ARTICLE HIGHLIGHTS

- Physiologic, metabolic, and vascular changes in normal and high-risk pregnancies may affect risks for SARS-CoV-2 infection and modify/exacerbate the clinical presentation of COVID-19.
- Pregnant women may be at greater risk for SARS-CoV-2 infection, with more severe COVID-19 symptoms, and worse pregnancy outcomes.
- Studies to date have demonstrated higher risks of pregnancy complications, including preterm birth and preeclampsia, as well as higher rates of cesarean delivery.
- Pharmacological therapy is limited to medications with proven safety during pregnancy and lactation; safety data are often unavailable for medications in early stages of clinical trials.
- The current recommendations are based on a limited number of studies. Future, large, likely multi-center, studies will be critical in improving our understanding of the pathophysiology and clinical characteristics of COVID-19 and pregnancy, which may optimize COVID-19 preventive and treatment strategies during normal and high risk pregnancies.

LIST OF ABBREVIATIONS

COVID-19= Coronavirus Disease 2019; ACE 2=Angiotensin converting enzyme 2; TMPRSS2= transmembrane serine protease 2; RAAS=Renin angiotensin aldosterone system; Ang II=Angiotensin II; Th= T helper; IgG=Immunoglobulin G; IgM= Immunoglobulin M; RV= Residual volume; TV= Tidal volume; CD=Cesarean Delivery; NICU=Neonatal intensive care unit; ACOG=American College of Obstetrics and Gynecology; SMFM=Society for Maternal and Fetal Medicine; RCOG=Royal College of Obstetrics and Gynecology; ISUOG=International Society for Ultrasound in Obstetrics and Gynecology; CDC=Centers for Disease Control and Prevention; WHO=World Health Organization; qRT-PCR=Quantitative real time polymerase chain reaction; HCW=Healthcare workers; PPE=Personal protective equipment; CVS=Chorionic villus sampling

INTRODUCTION

Coronaviruses are a family of enveloped, single-stranded, positive-strand RNA viruses characterized by spherical morphology with surface spike projections. Human coronaviruses are divided into α- and β-coronaviruses. The rapid emergence and human-to-human transmission of a virulent novel lineage b β-coronavirus, SARS-CoV-2, has resulted in the global pandemic of coronavirus disease 2019 (COVID-19) associated with considerable morbidity and mortality. [1, 2] World-wide population studies to date have identified several patient characteristics, including age and comorbid conditions, as risk factors for poor outcomes, but data on pregnant patients are limited. Based on data from prior pandemics, pregnant women[3] are at higher risk of acquiring infection and dying compared to non-pregnant women. The current review will provide a multidisciplinary summary of the management of COVID-19 during pregnancy using an evidence base that has been published since identification of the first patients in Wuhan City, China, in December 2019.

TAXONOMY AND PHYLOGENY OF SELECT HUMAN CORONAVIRUSES

Virion and Viral Life Cycle

The capsid of SARS-CoV-2 contains a RNA genome complexed with a nucleocapsid protein. The membrane surrounding this nucleocapsid contains 3 proteins common to all coronaviruses, spike protein, membrane protein M, and small membrane protein E [**Figure 1a** and reference 4]. [4] Viral entry occurs via 2 routes. The first occurs when the spike protein attaches to the angiotensin converting enzyme 2 *(ACE2)* receptor, releasing the viral genome and nucleocapsid protein into the host cell cytoplasm. [5] The other pathway is the direct plasma membrane route via

transmembrane serine protease 2 *(TMPRSS2)*, which allows for the proteolytic cleavage of the spike protein and mediation of fusion with the cell membrane. [6] Intracellularly, the viral genome is translated into a replicase to produce more genome RNA, mRNA and viral protein. Viral membrane proteins, M, N & E assemble on intracellular membranes. The nucleocapsid protein and viral RNA complex form a helical capsid structure, which buds between the endoplasmic reticulum and Golgi apparatus. Mature viral particles are packaged in vesicles, transported to the cell membrane, and released from the cell [Reference 5 and **Figure 1b**]. [5]

Viral Tropism, normal and high-risk pregnancies

The ACE 2 enzyme plays a key role in in the conversion of Angiotensin I (Ang I) to Ang 1-9 and Ang II to Ang 1-7 (vasodilatory, anti-thrombotic, and anti-inflammatory activities) (**Figure 2**). The hormonal profile of normal gestation is characterized by an early increase of all of the components of the renin angiotensin aldosterone system (RAAS), including ACE 2.[7] This raises the possibility that pregnant women may be at a greater risk for SARS-CoV-2 infection. In addition, low blood pressure in pregnant women is maintained through a balance between being refractory to the pressor effects of Angiotensin II (Ang II) and increased levels of Ang-(1-7), which exhibit systemic vasodilatory responses.[8, 9] In preeclampsia, a pregnancy specific hypertensive disorder that affects 3.5% of all pregnancies[10] and clinically is characterized by multisystem involvement and, commonly, proteinuria, this balance is lost, with an over-exaggerated Ang II blood pressure response.[11] Preeclampsia has also been associated with decreased maternal plasma Ang-(1-7) levels.[9] As SARS-CoV-2 not only binds to ACE2, but also causes its downregulation, [12] infections during pregnancy may potentiate RAAS abnormalities i.e., increased Ang II relative to decreased Ang-(1-7), that are present in preeclampsia. COVID-

19 and preeclampsia share additional common mechanisms, including endothelial cell dysfunction, and coagulation abnormalities. Notably, ACE2 receptors are also expressed by endothelial cells [13] and endothelial cell infection and immune cell-mediated endothelial injury has been recently described in COVID-19. [14] As the hallmark of preeclampsia is endothelial dysfunction, [15] infection with SARS-CoV-2 during pregnancy could mimic and/or initiate microvascular dysfunction by causing endotheliitis. Systemic inflammation and microcirculatory dysfunction, characterized by vasoconstriction and resultant ischemia, ensue. This can further contribute to a pro-coagulopathic state, as demonstrated by high rates of deep vein thrombosis, stroke and pulmonary embolism, which are increasingly reported in COVID-19 patients. [16, 17 18] Infection with SARS-CoV-2 during pregnancy can be particularly pro-thrombotic, as coagulation abnormalities may potentiate a hypercoagulable state, which is already present in non-complicated pregnancy, and exacerbated by preeclampsia. [19] Similarly, complement activation, which is present both in preeclampsia[20] and COVID-19[21], may result in particularly severe thrombotic vascular injury when these two disease states are present concurrently. In summary, RAAS abnormalities, endothelial dysfunction, complement activation, and the pro-coagulopathic effects of COVID-19 are similar to those occurring in preeclamptic pregnancies, potentially resulting in progressive vascular damage. Therefore, pregnancy and its complications represent a vulnerable state for invasive infection with SARS-CoV-2 reflecting several overlapping cellular mechanisms.

In addition to the direct cytotoxic effect of the virus, tissue injury in COVID-19 is mediated through an excessive inflammatory response, commonly referred to as cytokine storm. Cytokine

storm is mediated via immune responses, which are significantly modified in pregnancy, and may contribute to COVID-19 laboratory and clinical characteristics during pregnancy.

IMMUNE RESPONSES TO COVID -19

During pregnancy, the maternal immune system must adjust to tolerate the semi-allogeneic fetus while maintaining its ability to respond to pathogenic insult.[22, 23] This is also known as T helper (Th) 2 polarization. However, near the end of pregnancy a switch to Th1 immunity occurs and the maternal immune system becomes pro-inflammatory, leading to the sequence of events that occur prior to parturition (i.e. cervical dilation, contractions). Data on immune responses to SARS-CoV-2 in pregnant women are lacking at this time, while data from prior pandemics suggest that pregnancy may increase the risk of acquiring infection and dying compared to non-pregnant women.[3] The timing of infection during gestation may induce differences in maternal immune responses, viral clearance and ultimately perinatal outcomes. As the first and third trimesters are pro-inflammatory to promote implantation and labor, [24] pregnant women infected with SARS-CoV-2 during these trimesters may be at higher risk of exaggerated responses to virus (cytokine storm). Furthermore, high levels of stress and inflammation occur during labor, and the physiologic changes that occur in a mother's body after the baby is born could lead to poor maternal SARS-CoV-2 outcomes postpartum. This has been observed clinically, where pregnant women with mild symptoms upon admission to the hospital for delivery required postpartum hospital admission for respiratory symptoms. [25, 26]

Conflicting data exist regarding vertical transmission of the virus; however, research on other coronavirus infections during pregnancy suggests that *in utero* transmission does not occur. However, mouse models and epidemiologic data have shown that inflammatory immune

responses generated by viral infection during pregnancy can result in negative effects on fetal brain development. [27-29] During the H1N1 pandemic, infected women had higher rates of preterm birth. [30] Therefore, while placental transmission of the virus may not occur with SARS-CoV-2 infection, other short and long term effects from inflammation may adversely impact the developing fetus. These require further characterization. Maternal immunity may be passed on to protect the fetus, conferring passive immunity. IgG specific to the 2003 SARS-CoV outbreak strain was found not only in maternal blood, but also in amniotic fluid and cord blood. [31] Another possible source of antibodies could be breast milk, but this has yet to be determined.

MATERNAL PHYSIOLOGY AND CLINICAL CHARACTERISTICS OF COVID-19 DURING PREGNANCY

Significant physiological changes to respiration occur during pregnancy[32] including increased secretions and congestion in the upper airways, increased chest wall circumference and upward displacement of the diaphragm. These changes result in decreased residual volume (RV) and increased tidal volume (TV) and air trapping, slightly decreased airway resistance, stable diffusion capacity, increased minute ventilation, and increased chemosensitivity to carbon dioxide. Hemodynamic changes include increased plasma volume of 20-50%, increased cardiac output and decreased vascular resistance.[32] These changes result in a state of physiological dyspnea and respiratory alkalosis as well as an increased susceptibility to respiratory pathogens. As has been seen with other viral respiratory infections, the early symptoms of COVID-19 infection may mimic physiological dyspnea in pregnancy, which could result in delayed diagnosis and more severe disease.[33]

Pregnant women with SARS-CoV-2 infection may experience more severe symptoms compared to non-pregnant women. Existing limited data have reported on rapid deterioration in women who had no symptoms upon arrival and were subsequently diagnosed with severe COVID-19.[25] In some, but not all cases, maternal comorbidities were present (hypertension, diabetes, cholestasis of pregnancy).[25, 34] Case reports have also described cases of quickly worsening maternal status with the ultimate diagnosis of cardiomyopathy. [35] Unfortunately, these rapidly progressive maternal complications have led to a high rate of cesarean deliveries (CD) for either worsening maternal status or non-reassuring fetal status secondary to the worsening maternal clinical state.

Preeclampsia is an example of a common pregnancy-related complication that may be exacerbated by, or may exacerbate, COVID-19, as discussed above. The picture becomes further complicated because the two processes share common laboratory abnormalities. Thus, it may be difficult to discern whether certain abnormal laboratory findings are due to SARS-CoV-2 infection or preeclampsia, and this interplay may have treatment implications. For example, thrombocytopenia [36] and liver function abnormalities, [37] both of which are diagnostic criteria for preeclampsia with severe features, are also associated with worsening COVID-19 disease.

MATERNAL DISEASE AND OUTCOMES

Physiological changes in normal pregnancy and metabolic and vascular changes in high-risk pregnancies may affect the pathogenesis or exacerbate the clinical presentation of COVID-19 disease during pregnancy. A systematic review by Di Mascio et al[38] evaluating and comparing obstetric outcomes in combined coronavirus infections (SARS, MERS and SARS-CoV-2) found SARS-CoV-2 alone resulted in higher rates of preterm birth (24.3%, 95% CI 12.5-38.6 for <37

weeks gestation; and 21.8%, 95% CI 12.5 -32.9 for <34 weeks gestation), preeclampsia (16.2%, 95% CI 4.2- 34.1) and CD (83.9%, 95% CI 73.8-91.9).

As of April 22, 2020, a total of 23 studies [26, 35, 39-59] (excluding overlapping of case reports) addressing obstetrical and neonatal outcomes of SARS-CoV-2 infection in pregnancy have been published. These studies span the time period from January 1, 2020 to April 22, 2020, and include 185 patients. The abstracted information is presented in **Table 1**, which summarizes maternal and neonatal outcomes. Briefly, most of the diagnoses occurred in the third trimester. Fever was the most common presenting symptom, followed by cough, dyspnea, and gastrointestinal alterations. Slightly > 25% of patients were asymptomatic at diagnosis. The most common laboratory findings were lymphopenia and neutrophilia. Pneumonia was a common diagnosis (40%) and a small percentage (3.24%) required ICU admission.

Management of patients varied according to institution. The majority were treated with medications that are considered to be relatively safe during pregnancy: antibiotics (cefoperazone, sulbactam, ceftriaxone, cefazolin, and azithromycin), antiviral therapy (lopinavir, ritonavir, oseltamivir, and ganciclovir), and a few were treated with corticosteroids (dexamethasone, methylprednisolone).

Due to the high false negative rates of the nasopharyngeal swab for the quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for the SARS-CoV-2 test, [60] a CT scan may be required to confirm the diagnosis in cases of high suspicion, as seen in 4 cases reported by Wu et al.[54] There were no patients who delivered before 28 weeks gestation and the majority of patients delivered at 36 0/7 weeks or later. The impact of infection on timing of delivery is still unclear. Yangli et al[42] reported a 46% preterm labor rate between 32-26 weeks of gestation in 10

patients admitted with positive COVID-19 infection, while Zhang et al[45] reported no difference in gestational age at delivery for 16 women with COVID-19 (38.7±1.4) and 45 women without COVID-19 (37.9±1.6).

A systematic review by Zaigham et al[61] including 108 pregnant women reported CD was the most common mode of delivery, with a rate of 92%. It can be speculated that SARS-CoV-2 infections are more likely to result in maternal hypoxia or increased oxygen requirements, resulting in a non-reassuring fetal heart tracing, warranting expedited delivery. There may also be lack of SARS-CoV-2 screening in some healthcare settings resulting in selection bias for CD in severe cases. The indication for CD needs to be further evaluated as current guidelines indicate that SARS-CoV-2 infection alone is not an indication for CD. [62, 63]

A recent multicenter cohort study of severe COVID-19 disease in pregnant patients from 12 US institutions reported that patients were usually admitted with severe disease seven days after onset of symptoms, and typically were intubated 2 days after admission. [64] Fifty percent of women required delivery resulting in a high rate of preterm birth.

NEONATAL OUTCOMES

Neonatal outcomes are shown in **Table 1**. There was one reported stillbirth[42] due to severe maternal disease with multi-organ failure, and one neonatal death[39] due to refractory shock with multi-organ failure following delivery at 34 5/7 weeks gestation. Among 145 livebirths, 2 neonates tested positive for SARS-CoV-2 infection. Both did well with supportive therapy and observation and were discharged from hospital in a stable condition. [49, 59]

Di Mascio et al [38] reported increased perinatal mortality and higher rates of Neonatal Intensive Care Unit (NICU) admissions, but all neonates tested negative for SARS-CoV-2 infection. Chen et al[44] confirmed no morphological changes related to infection in three placentas of COVID-19 positive mothers. All 3 neonates also tested negative for SARS-CoV-2. Although these findings are consistent with reports suggesting minimal to no risk of vertical transmission, [43, 44, 65] Penfield et al[66] reported positive SARS-CoV-2 results in 3 of 11 placental swabs from COVID-19 positive mothers. All of the 3 neonates also tested negative. Whether vertical transmission truly occurred, or whether neonates were swabbed too early- during the incubation period- is unclear.

Shah et al [67] published a well-structured classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates which gives the opportunity to consider the risk of maternal to fetal or neonatal transmission beyond just vertical transmission. The classification includes congenital infection from intrauterine death/ stillbirth, congenital infection in live born infants, neonatal infection acquired intrapartum, or neonatal infection acquired postnatally. In addition, several professional societies have provided guidelines for management of COVID-19 during pregnancy. The overall summaries from these professional bodies are consistent, with some variation in the strength of recommendations.

CURRENT GUIDELINES FOR COVID-19 MANAGEMENT IN PREGNANCY

Professional perinatal societies, including the Society for Maternal and Fetal Medicine (SMFM)[63, 68] and American College of Obstetrics and Gynecology (ACOG) [69, 70]from the United States, the Royal College of Obstetrics and Gynecology (RCOG)[62] from the United Kingdom, the International Society for Ultrasound in Obstetrics and Gynecology (ISUOG),[71] the Centers

for Disease Control and Prevention (CDC)[72, 73] and the World Health Organization (WHO)[74] have developed guidelines for the care of pregnant patients.

Here, we have summarized the most current guidelines, updated as of April 22, 2020. A total of 9 papers were identified from 6 societies - SMFM, ACOG, RCOG, ISUOG, CDC, and WHO.

A summary of these guidelines are outlined in **Table 2,** and divided into three sections - antepartum, intrapartum, and postpartum care. The guidelines provide practical management recommendations that institutions can adapt to their infrastructures and resource availability. The recommendations from the SMFM are focused on high risk pregnancies, while those from ACOG and RCOG focus on all pregnancies. The WHO and CDC both focus on recommendations that can be generalized across all patient populations, while ISUOG focuses on sonography and care of ultrasound equipment.

Prenatal/Antepartum Care The consensus amongst all societies recommends the use of telehealth for prenatal visits. Ultrasound and antenatal surveillance should be combined with visits for labs or prenatal care. Patients should be screened for symptoms, travel history, and contact history before any face to face visits; and those who are symptomatic or meet criteria should undergo testing for SARS-CoV-2 using qRT-PCR. Appropriate personal protective equipment (PPE) should be worn by patients and health care workers (HCW). Administration of antenatal steroids for fetal lung maturation should still be considered if a pregnancy is between 24 0/7 to 33 6/7 weeks gestation, but the risk/benefit balance needs to be discussed by the multidisciplinary team. Data on use of steroids during late preterm (34 0/7 to 36 6/7 weeks) are still controversial, but routine administration is not advised. [68]

Intrapartum care Institutions should have a designated area for triaging, screening and admitting SARS-CoV-2 positive patients. The mode and timing of delivery should follow routine obstetric indications, keeping in mind that COVID-19 alone is not an indication for CD, unless there is fetal distress or deteriorating maternal clinical status. Societies recommend that only one consistent healthy asymptomatic individual providing support should be present during labor and delivery. Aerosol generating procedures, including forceful pushing during the second stage of labor and oxygen supplementation for intrauterine resuscitation, should be limited, and appropriate PPE (N95) worn. Water births are contraindicated due to limited ability to monitor mother and baby, and the risk of fecal transmission.

Postpartum care Mother and baby separation or discouraging breastfeeding is not advised unless the mother is acutely ill. However, mothers are advised to follow appropriate respiratory hygiene by wearing masks during skin to skin contact and breastfeeding. Mothers should wash hands before handling their babies, touching pumps or bottles and avoid coughing while their babies are feeding. All surfaces and breast pumps should be sanitized after each use. In an effort to limit infection exposure, hospital length of stay should be decreased to 1 day for vaginal deliveries and 2 days for CD. Postpartum visits should be performed through telehealth and patients advised to continue compliance with social distancing after discharge. The method of telehealth should be individualized based on institution resources and availability.

IMPLICATIONS OF COVID-19 IN SPECIAL PREGNANT PATIENT POPULATIONS

Evidence on the potential outcomes of SARS-CoV2 in pregnancies already complicated by congenital anomalies is lacking. Given the severity of some potentially life-threatening congenital conditions as well as the disease altering effects of fetal interventions, these

procedures are considered urgent essential medical services. Therefore, necessary adjustments to the prenatal work-up and selection of fetal intervention candidates have been proposed to better adapt this essential service to the ongoing pandemic. Perhaps the most important factor to consider is the potential risk of vertical transmission induced by the invasive nature of these procedures.

There is no definitive evidence of *in utero* transmission from SARS-CoV-2 to date. Some case reports [52, 59, 75] have reported possible vertical transmission due to positive amniotic fluid SARS-CoV-2 PCR, but the majority of the limited patient series reported in the literature indicate a low-to-negligible risk. [76, 77] Evidence is rapidly accumulating, however, and this consensus may change as more cases of COVID-19 in pregnancy are reported.

Prenatal diagnosis

In the event of a suspected or confirmed fetal anomaly, additional work-up (fetal echocardiography, amniocentesis, chorionic villus sampling (CVS) or cordocentesis) may be indicated to identify patients who could benefit from fetal interventions.

Prenatal diagnostic work-ups may be classified as invasive or non-invasive depending on the risk of vertical transmission and exposure of patients and HCW to SARS-CoV-2. Imaging studies, including ultrasound and fetal echocardiography, are considered non-invasive (with no risk of vertical transmission), but specific precautions including hygiene and use of appropriate PPE should be applied to the patient and examiner, as well as proper care of the sonogram and ultrasound suite. [78] For patients with suspected or confirmed SARS-CoV-2 infection,

consideration should be given to postponing prenatal imaging until asymptomatic, if safely feasible.

Invasive diagnostic tests (CVS, amniocentesis, and cordocentesis) are associated with a theoretical risk of vertical transmission, as these procedures may directly correlate with the risk of feto-maternal hemorrhage. [76] CVS, which is usually performed between 10 0/7 to 13 6/7 weeks gestation, may be offered to patients with low risk of SARS-CoV-2 infection (asymptomatic or negative screen). For symptomatic patients with suspected or confirmed SARS-CoV-2, invasive diagnostic tests can be delayed if safely feasible. If genetic testing cannot be delayed, amniocentesis (usually performed after 14 0/7 weeks gestation) should be performed instead of CVS, due to the theoretical lower risk of vertical transmission if trans-placental access is avoided. Amniocentesis can also be offered to all asymptomatic or confirmed SARS-CoV-2 negative patients. [76] Fetal blood sampling/transfusion is another invasive procedure with a theoretical risk of vertical transmission. This intervention may be offered to patients with confirmed negative SARS-CoV-2 PCR, but should be delayed (if feasible and safe) in symptomatic or positive SARS-CoV-2 cases. [76]

Fetal therapy

The Mayo Clinic Fetal Center follows the recommendations of the North American Fetal Therapy Network (NAFTNET) which currently recommends that fetal interventions should be provided as much as resources allow due to the time sensitive nature of conditions amenable to fetal therapy. [79] Specific institutional policies may vary, but in general, all fetal interventions which have been established as the standard of care (for select patients) should continue to be provided, taking the necessary perioperative precautions. Conversely, innovative or experimental

procedures which are yet to show proven benefit should be individualized. In general, for asymptomatic COVID-19 patients, fetal intervention can be offered. For symptomatic patients, it is recommended that fetal therapy be postponed until maternal conditions stabilize and patients have recovered from the disease. Some examples of fetal surgeries that are still currently offered at Mayo Clinic include: Fetoscopic laser ablation of placental anastomoses for twin-to-twin transfusion syndrome, [80] *in utero* repair of spina bifida,[81] intrauterine fetal blood transfusion, [82] *in utero* intervention for lower urinary tract obstruction, [83] fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia, [84], *in utero* procedure for fetal tumors associated with hydrops, [85] and *in utero* intervention for severe congenital heart defects.[86]

TREATMENT OF COVID-19 IN PREGNANT PATIENTS

No drugs have been proven to be effective and safe to use for the treatment of COVID-19 to date. **Table 3** outlines the medications or therapies used in various research protocols under investigation, as well as their safety for use in pregnancy. In addition, as the pro-coagulatory state of pregnancy may contribute to thrombotic risks associated with COVID-19, thrombo-prophylaxis, which is currently advised for COVID 19 patients, [87] should be considered for pregnant patients as well.

There are 6 total candidate vaccines under phase 1 or 2 clinical trials and 77 more candidate vaccines in pre-clinical evaluation, as of April 23, 2020.[88] Many vaccines use the spike protein (S protein) as their platform and present as forms of recombinant protein based vaccines, live attenuated vaccines, inactive viral vaccines and viral-vector based vaccines. [89] Live, attenuated vaccines are generally contraindicated in pregnancy, but exceptions may be made during pandemic situations (exception for Smallpox vaccine). As with any drug under development,

assessment for safety in pregnancy is conducted after initial safety data become available from clinical studies.[90] Although it is essential to guarantee safety, an unfortunate impact of delaying research in pregnancy is that vaccinations for pregnant women may also be delayed. This is especially problematic during a pandemic or epidemic, as evident from lessons learned from the Ebola outbreak. [91]

FUTURE PERSPECTIVES

The presented data are preliminary, collected over a period of 4 months and likely to change once large datasets become available. However, the projected course of COVID-19 on the morbidity and mortality of pregnant patients during these challenging times is unprecedented. Racial disparities are known to exist in the obstetric literature.[92] Global health crises subject racial and ethnic minorities, as well as patients with immunocompromised comorbidities, to poorer outcomes. We envision that national and international perinatal societies will focus on the unique challenges faced by vulnerable patient populations that are burdened with physical, emotional and social crises, with a focus on improving outcomes for all pregnant patients.

CONCLUSION

In conclusion, given differing physiology during gestation, pregnancy represents a vulnerable state that may be associated with a greater risk for SARS-CoV-2 infection and subsequent worse COVID-19 outcomes. Global efforts to fast track publication of data on COVID-19 in pregnancy, albeit limited, have allowed us to form a framework to care for these patients. Early reports suggest higher rates of preeclampsia and other pregnancy-related complications with

SARS-CoV-2 infection during pregnancy, thus adding urgency to the pursuit of research into optimal COVID-19 treatment and preventive strategies during pregnancy.

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LEGENDS

Table 1: Summary of maternal and neonatal outcomes during COVID-19 pandemic

Table 2: Consensus on recommendations classified by phase of care of pregnancy

Table 3: Treatment options for COVID-19

Figure 1: Features and lifecycle of SARS-CoV-2

Figure 1a: Structure of the SARS-CoV-2 viron

Figure 1b: Viral entry methods and replication of SARS-CoV-2

Figure 2: **Pregnancy, COVID-19, and mechanisms of vascular damage**

Upregulation of ACE2 receptor in pregnancy may increase the risk for SARS-CoV-2 infection. Binding of virus to to ACE2 causes its downregulation and may increase Ang II relative to Ang-

(1-7), thus favoring vasoconstriction, which can mimic/worsen vascular dysfunction in preeclampsia

Maternal Characteristics	**Cases N (%); Total N = 185 (100%)**
Mean Age (years)	29.6 (range 20 to 41)
Trimester	
- First Trimester	3/185 (1.62)
- Second Trimester	5/185 (2.70)
- Third Trimester	177/185 (95.68)
Signs and symptoms	
- Fever	90/169 (53.20)
- Pneumonia	75/184 (40.76)
- Cough	56/169 (33.13)
- Asymptomatic	44/169 (26.04)
- Dyspnea/ Shortness of breath	22/169 (13.01)
- GI alterations	9/169 (5.32)
- ICU admission	6/185 (3.24)
Diagnostic method	
- RT-PCR SARS-CoV 2 only	179/185 (96.76)
- CT scan changes only	6/185 (3.24)
- RT-PCR SARS- CoV 2 and CT changes	100/185 (54.05)
Laboratory alterations	
- Lymphopenia (N=32 out of 93 reported)	32/93 (34.40)
- Neutrophilia (N= 8 out of 93 reported)	8/93 (8.6)
Interventions	
- Antibiotics	64/145 (44.13)
- Supportive measures	41/145 (28.20)
- Antiviral therapy	39/145 (26.90)
- Corticosteroids	12/145 (8.28)
Obstetric comorbidities **	
- Gestational Hypertension	6/182 (3.29)
- Preeclampsia	4/182 (2.20)
- Gestational Diabetes	11/182 (6.04)
- Prelabor rupture of membranes	13/184 (7.07)
- Fetal distress	23/184 (12.50)
Number of patients	
- N of patients delivered	152/185 (82.16)
- N of patients still pregnant	33/185 (17.83)
Mode of delivery **(N= 152)**	
- Cesarean delivery	129/152 (84.87)
- Vaginal Delivery	19/152 (12.5)
- Pregnancy termination	4/152 (2.63)
Gestational age at delivery of viable pregnancies **(N=148)**	
- <28 weeks	0/148 (0.00)
- 28 to 31 6/7 weeks	2/148 (1.35)
- 32 to 35 6/7 weeks	26/148 (17.56)
- ≥36 weeks	96/148 (64.86)
- Missing data	24/148 (16.2)
Neonatal Characteristics	**Cases N (%)**
Total N of neonates reported	146 (100)
- Livebirths	145/146 (99.3)
- Stillbirths	1/146 (0.68)
Comorbidities after livebirth **(Out of Total N= 145)**	
- NICU admission	27/145 (18.60)
- Low birth weight	15/145 (10.34)
- Pneumonia	9/145 (6.20)
- RT- PCR SARS-CoV 2 positive	2/145 (1.37)
- Neonatal death	1/145 (0.69)

Table 1- Summary of maternal and neonatal outcomes during COVID-19 pandemic*

* Please note that certain parameters were not evaluated or reported in all patients, so the denominators used for calculations represent only the numbers for which data are available

** 17.8% (33 of 185) patients were still pregnant at the end of this study; therefore, rates of complications occurring in late pregnancy or close to delivery, such as preeclampsia, might have been underestimated

():xx-xx.

ANTEPARTUM CARE							
Title	**Prenatal Infection Screening**	**Prenatal appointment**	**Ultrasound frequency**	**Ultrasound equipment/ patient rooms**	**Antenatal surveillance**	**Antenatal corticosteroids**	**GBS screening**
Consensus on recommendations	-Triage symptomatic patients via telehealth -Test anyone with new flu like symptoms. Prioritize high risk patients- older, immune-compromised, advanced HIV, homeless, hemodialysis. -Utilize drive through or standalone testing area -All suspected cases should be screened with qRT-PCR -Symptomatic patients should be treated as positive till results are back -Repeat testing in 24 hours if negative, but still high suspicion	-Elective and non-urgent appointments should be postponed or completed by telehealth -Encourage use of telehealth for all visits -HCW meetings should all be virtual/ audio. -Reserve F2F visits for 11-13,20,28,36 weeks and weekly after 37 weeks -Complete labs and US on same visit day -Limit support person at outpatient F2F visits.	-Consensus: Continue US as medically indicated when possible. <u>SMFM Suggestions</u> -Combine dating and NT in 1st trimester -Anatomy scan at 20-22weeks - Consider stopping serial CL after anatomy US if TVUS CL ≥35mm, prior preterm birth at >34 weeks -BMI>40: schedule at 22 weeks to reduce risk of suboptimal views/need for follow up -Single growth F/U at 32 weeks -Low lying placenta F/U 34-36wks	-Must be cleaned with disinfectant per manufacturer guidelines after EVERY use -Deep clean of all instruments and room in case of positive patient	- Reserve for medically indicated screening -Limit NST <32 weeks -Twice weekly NST only for FGR with abnormal UA Doppler studies, complicated monochorionic twins, or Kell sensitized patients with significant titers -If patient needs US, perform BPP instead of NST -Kick counts instead of NST for low risk patients Daily NST if patient hospitalized	- Should continue if <34 weeks, even if tested positive for COVID-19 - Balance risks and benefits for 34 0/7–36 6/7 Weeks -Other modifications should be individualized	- As indicated between, 36 0/7–37 6/7 weeks gestation. -Consider grouping with other visits within the same time frame -Patients can self-collect with proper instructions if the resources and infrastructure allow

INTRAPARTUM CARE											
Title	**Pre-Delivery preparation/ screening**	**Delivery location**	**Delivery Time**	**Mode of delivery**	**Support person**	**Obstetric Analgesia and Anesthesia**	**Oxygen use**	**Second Stage of labor**	**Third stage of labor**	**Umbilical cord clamping**	**PPE**
Consensus on recommendations	-Social distancing and off work for 2 weeks prior to anticipated delivery (start at ~37wks) -Screen patient and partner on	-Designated isolation room, for suspected or confirmed cases of COVID-19	-Based on routine obstetric indications -Early delivery should be considered for critically	-Based on routine obstetric indications -COVID-19 infection is NOT an indication for CD	- Allowed one consistent asymptomatic support person	-No evidence against regional or general anesthesia. -Epidural analgesia is recommended to women with suspected or	-Do not use O2 for intrauterine resuscitation -Considered aerolizing, HCW must wear appropriate	-Do not delay pushing. -Consider shortening with operative delivery to minimize aerolization and maternal respiratory effort	-Consider active management to reduce blood loss (national blood shortage)	-Delayed cord clamping is still recommended in the absence of contraindications -Avoid delayed cord clamping in	-Asymptomatic or negative patients- Patient and provider wear surgical mask -Aerolizing procedures- N95 for patient

	phone day before admission -Limit HCW staffing to only essential staff		ill patients -No contraindications to IOL unless there are limited beds	-Expedite delivery by CD in setting of fetal distress or maternal deterioration -Water births should be avoided.		confirmed COVID-19 to minimize the need for GA if urgent delivery is needed. -Avoid use of nitrous oxide	PPE (N95)			confirmed and suspected cases	and N95,gown,gloves, face shield for provider
POSTPARTUM CARE											
Title	**Placental and fetal tissue**		**Length of stay**		**Breastfeeding**		**Skin to skin**		**Postpartum pain control**		**Postpartum visit**
Consensus on recommendations	ISUOG recommendations -Should be handled as infectious tissue in positive patients -Consider qRT-PCR on placenta		-Expedited discharge should be considered if stable. -VD → 1 day -CD → 2 days		-Limited evidence to advice against breastfeeding. -Advise patients to: 1) Practice respiratory hygiene during feeding, 2) wear a mask 3) Wash hands before and after touching the baby 4) Routinely clean and disinfect surfaces they have touched. -During separation, encourage dedicated breast pumping		-Routine precautionary separation of a healthy baby and mother is not advised -Encourage good hygiene and appropriate PPE for COVID-19 positive patients		-No contraindication to NSAID use		-Encourage telehealth for postpartum visit -Limit F2F visits only for medically necessary concerns

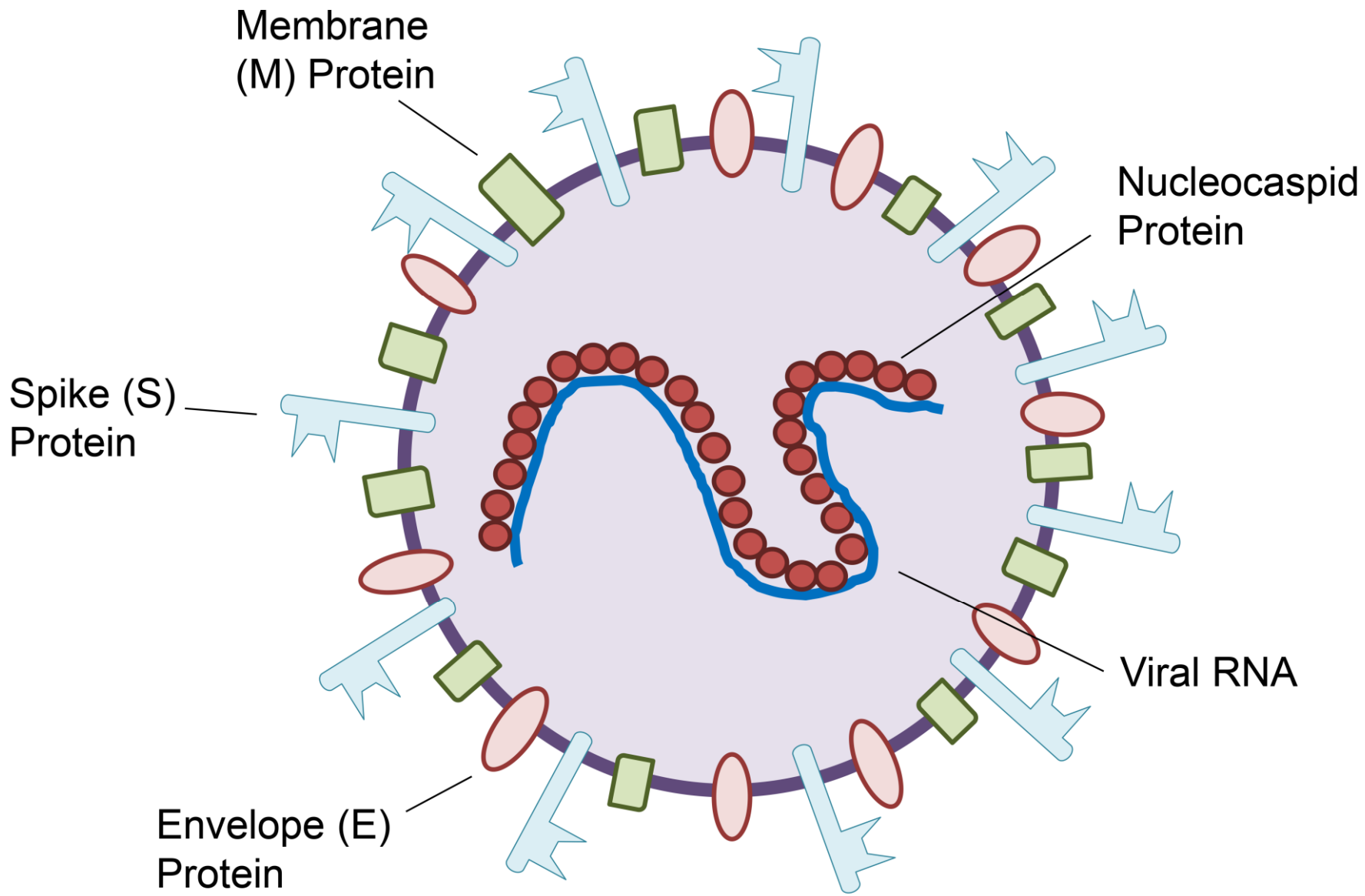
Footnote: qRT-PCR – Quantitative reverse transcriptase polymerase chain reaction, HCW- Health care workers, F2F- Face to face, F/U- follow up, CD- Cesarean Delivery, IOL- Induction of labor, VD-Vaginal delivery, GBS-Group B streptococcus, VD-Vaginal Delivery

Table 2: Consensus on recommendations classified by phase of care of pregnancy

Treatment Strategy	Mechanism of Action	Effectiveness	Safety in Pregnancy
Hydroxychloroquine (HCQ)/ Chloroquine [93]	Reduces inflammatory cytokines; [94] interferes with ACE 2 receptor synthesis [94, 95]	Reduction of body temperature recovery time and cough remission, pneumonia recovery, improved CT scan findings, nasopharyngeal viral clearance [96-98]	Generally considered safe in pregnancy and frequently used for patients with autoimmune disease. [99] Efficacy unproven. Concern for prolonged QTc.
HCQ and Azithromycin	Reduction of viral replication and Interleukins 6 and 8 production [94, 100]	Improved nasopharyngeal viral clearance [97]	HCQ : as above Azithromycin: considered safe [101]
Lopinavir/ rotinavir	Inhibition of 3-chymotrypsin-like protease [102-104]	Reduced mortality [105]	Good safety profile in pregnant patients with HIV [106]
Remdesivir	Inhibition of viral RNA-dependent RNA polymerase[107]	Clinical trial still underway Reduction in duration of hospital stay and mortality [108]	Not yet FDA approved
Anakinra	Interleukin – 1 inhibitor	Clinical trial still underway	Insufficient data to determine risk in pregnancy [109]
Siltuximab	Human-mouse chimeric monoclonal antibody against Interleukin-6	Improvement in clinical condition in 1/3 patients [110]	Insufficient data to determine risk in pregnancy [111]
Sarilumab	Recombinant interleukin-6 receptor monoclonal antibody	No data yet from randomized clinical trials or observational studies [93]	Insufficient data to determine risk in pregnancy [93]
Tocilizumab	Recombinant interleukin-6 receptor monoclonal antibody	No data yet from randomized clinical trials or observational studies [93]	Insufficient data to determine risk in pregnancy [93]
Interferon	Antiviral cytokines	No data yet from randomized clinical trials or observational studies [93]	Varying side effect profiles in various preparations
Corticosteroid	Anti-inflammatory actions [112]	Reduced mortality in ARDS patients [113] Faster improvement of severe COVID pneumonia patients [114]	Considered safe, approved for lung maturation in preterm birth [115]
Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB)	ACE receptor 2, is the cell receptor for viral entry for COVID 19 virus [116, 117]	No data yet from randomized clinical trials or observational studies [93]	Contraindicated in pregnancy [118, 119]
Convalescent Plasma	Convalescent plasma from recently recovered donors targeted COVID 19 virus	10 clinically severe COVID 19 patients were given 200ml of convalescent plasma. Increase in oxyhemoglobin saturation by 3rd day, and improved lymphocyte count as well as CRP levels were noted. Several studies are currently underway [120]	No data on safety in pregnancy. However, specific immunoglobulins as for varicella are used in pregnancy [111]

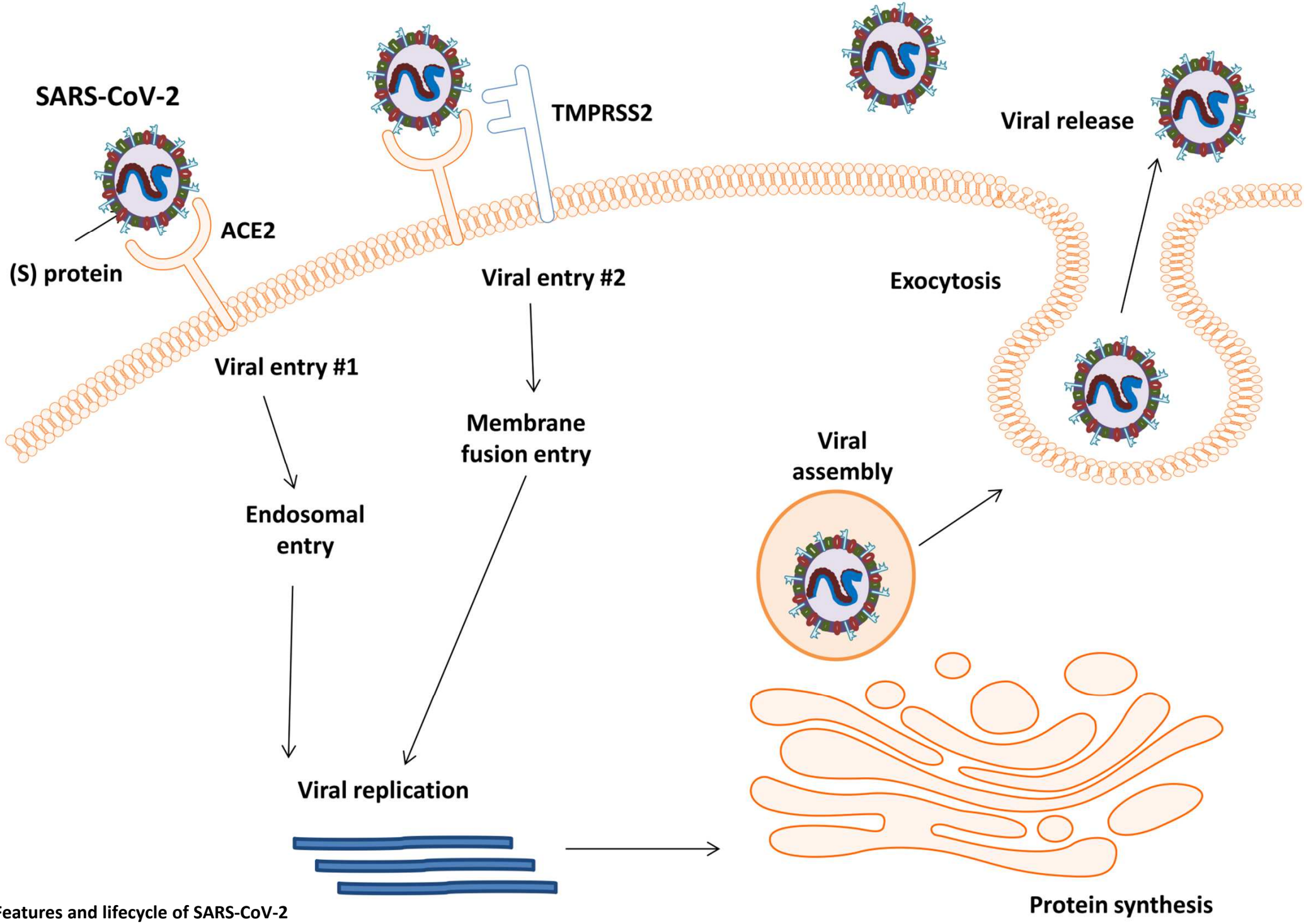
Table 3: Treatment options for COVID-19

Footnote: ARDS- Acute respiratory Distress Syndrome, CRP- C-reactive protein



Features and lifecycle of SARS-CoV-2

Figure 1a. Structure of the SARS-CoV-2 viron



Features and lifecycle of SARS-CoV-2

Figure 1b. Viral entry methods and replication of SARS-CoV-2

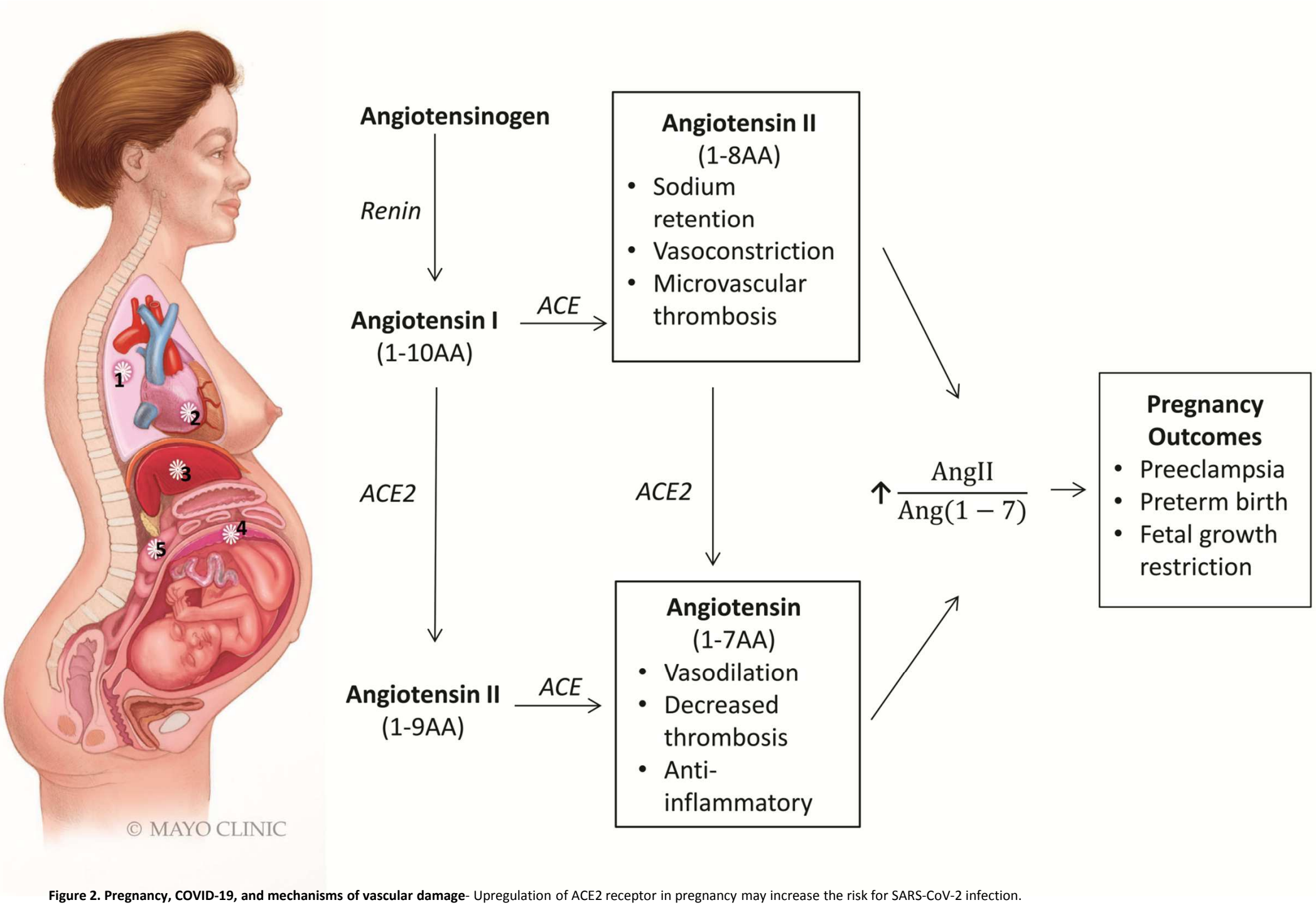


Figure 2. Pregnancy, COVID-19, and mechanisms of vascular damage- Upregulation of ACE2 receptor in pregnancy may increase the risk for SARS-CoV-2 infection.
Binding of virus to ACE2 causes its downregulation and may increase Ang II relative to Ang-(1-7), thus favoring vasoconstriction, which can mimic/worsen vascular dysfunction in preeclampsia
Figure Legend: 1- Lungs, 2- Heart, 3- Kidneys, 4- Placenta and endothelial cells , 5- Intestine