Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know

Sonja A. Rasmussen, MD, MS, John C. Smulian, MD, MPH, John A. Lednicky, PhD, Tony S. Wen, MD, Denise J. Jamieson, MD, MPH

PII: S0002-9378(20)30197-6

DOI: https://doi.org/10.1016/j.ajog.2020.02.017

Reference: YMOB 13118

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 12 February 2020

Revised Date: 17 February 2020

Accepted Date: 18 February 2020

Please cite this article as: Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ, Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know, *American Journal of Obstetrics and Gynecology* (2020), doi: https://doi.org/10.1016/j.ajog.2020.02.017.

Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know

Sonja A. RASMUSSEN, MD, MS[1,2]

John C. SMULIAN, MD, MPH[3]

John A. LEDNICKY, PhD[4]

Tony S.WEN, MD[3]

Denise J. JAMIESON, MD, MPH[5]

Affiliations:

[1]Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida, USA

[2]Department of Epidemiology, University of Florida College of Public Health and Health Professions and College of Medicine, Gainesville, Florida, USA

[3]Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida, USA

[4]Department of Environmental and Global Health, University of Florida College of Public Health and Health Professions, and University of Florida Emerging Pathogens Institute, Gainesville, Florida, USA

[5]Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA, USA

Correspondence to:

Sonja A. Rasmussen, MD, MS, Department of Pediatrics, University of Florida College of Medicine, 1600 SW Archer Road, Box 100296, Gainesville, Florida 32610, email: skr9@ufl.edu

Running Title: 2019 Novel Coronavirus and Pregnancy

Key Words: novel coronavirus, 2019 novel coronavirus, 2019 nCoV, SARS-CoV-2, -novel coronavirus, 2019-nCoV, severe acute respiratory syndrome, SARS, Middle East Respiratory Syndrome, MERS, pregnancy, fetus, newborn, pneumonia, preterm birth, maternal death, fetal death, vertical transmission, perinatal infection, sepsis

Manuscript Word Count: 4290

Abstract Word Count: 497

Glossary of terms

- 2019-nCoV: 2019-novel coronavirus (previous name for COVID-19 and SARS-CoV-2)
- Basic Reproduction Number: estimate of number of individuals who will become infected from a single person in a population where all individuals are susceptible
- CDC: US Centers for Disease Control and Prevention
- COVID-19: Coronavirus Disease 2019 (previously called 2019 novel coronavirus (2019-CoV) - illness caused by SARS-CoV-2
- MERS: Middle East respiratory syndrome
- MERS-CoV: Middle East respiratory syndrome coronavirus – virus that causes Middle East respiratory syndrome (MERS)
- N95 respirator: respiratory protective device that removes at least 95 percent of very small (0.3 micron) test particles, also called N95 filtering facepiece respirator
- SARS: severe acute respiratory syndrome
- SARS-CoV: severe acute respiratory syndrome coronavirus – virus that caused severe acute respiratory syndrome (SARS)
- SARS-CoV-2: severe acute respiratory syndrome coronavirus-2 virus (current name of the novel coronavirus, according to International Committee on Taxonomy of Viruses) – virus that causes COVID-19
- WHO – World Health Organization

Abstract

Coronavirus Disease 2019 (COVID-19) is an emerging disease with a rapid increase in cases and deaths since its first identification in Wuhan, China, in December 2019. Limited data are available about COVID-19 during pregnancy; however, information on illnesses associated with other highly pathogenic coronaviruses (i.e., severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS)) might provide insights into COVID-19's effects during pregnancy.

Coronaviruses cause illness ranging in severity from the common cold to severe respiratory illness and death. Currently the primary epidemiologic risk factors for COVID-19 include travel from mainland China (especially Hubei Province) or close contact with infected individuals within 14 days of symptom onset. Data suggest an incubation period of ~5 days (range-2-14 days). Average age of hospitalized patients has been 49-56 years, with a third to half with an underlying illness. Children have been rarely reported. Men were more frequent among hospitalized cases (54-73%). Frequent manifestations include fever, cough, myalgia, headache, and diarrhea. Abnormal testing includes abnormalities on chest radiographic imaging, lymphopenia, leukopenia and thrombocytopenia. Initial reports suggest that acute respiratory distress syndrome (ARDS) develops in 17-29% of hospitalized patients. Overall case fatality rate appears to be ~1%; however, early data may overestimate this rate. In two reports describing 18 pregnancies with COVID-19, all were infected in the third trimester, and clinical findings were similar to those in non-pregnant adults. Fetal distress and preterm delivery were seen in some cases. All but two pregnancies were cesarean deliveries, and testing for SARS-CoV-2 was negative on all babies tested.

Data on SARS and MERS in pregnancy are sparse. For SARS, the largest series of 12 pregnancies had a case-fatality rate of 25%. Complications included ARDS in four, disseminated intravascular coagulopathy in three, renal failure in three, secondary bacterial pneumonia in two, and sepsis in two patients. Mechanical ventilation was three times more likely among pregnant compared to nonpregnant women. Among seven first-trimester infections, four ended in spontaneous abortion. Four of five women with SARS after 24 weeks gestation delivered preterm. For MERS-CoV, there were 13 case reports in pregnant women, of which two were asymptomatic, identified as part of a contact investigation; three patients (23%) died. Two pregnancies ended in fetal demise and two were born preterm. No evidence of *in utero* transmission was seen in SARS or MERS.

Currently, no coronavirus-specific treatments have been approved by the US Food and Drug Administration. Because COVID-19 might increase the risk for pregnancy complications, management should optimally be in a health care facility with close maternal and fetal monitoring. Principles of management of COVID-19 in pregnancy include early isolation, aggressive infection control procedures, oxygen therapy, avoidance of fluid overload, empiric antibiotics (secondary to bacterial infection risk), SARS-CoV-2 and co-infection testing, fetal and uterine contraction monitoring, early mechanical ventilation for progressive respiratory failure, individualized delivery planning, and a team-based approach with multi-specialty consultations.

Information on the COVID-19 is increasing rapidly. Clinicians should continue to follow the CDC website to stay up-to-date with the latest information.

https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html

Emerging infections have been shown to have an important impact on pregnant women and their fetuses,[1] with the increased risk of complications in pregnant women with the 2009 pandemic H1N1 influenza virus[2] and the severe fetal effects of Zika virus as recent examples.[3,4] The emergence of a coronavirus not previously seen in humans, first reported in Wuhan, China, on December 31, 2019, has attracted much interest throughout the world. Since then, the number of reported cases has increased rapidly, with more than 51,800 laboratory-confirmed cases and 1,600 deaths as of February 16, 2020. In addition to China, cases have spread to 25 other countries (Figure 1) including 15 cases in the United States. Initial outbreak data from China show a near exponential growth of reported cases.[5] Reported numbers are likely underestimates of the true numbers since milder cases are less likely to be reported. On January 30, 2020, the World Health Organization declared the outbreak as a Public Health Emergency of International Concern; on January 31, 2020, the United States declared a public health emergency, and the Centers for Disease Control and Prevention (CDC) issued a federal quarantine for 195 Americans who traveled from Wuhan, China, its first federal quarantine in more than 50 years. On February 11, the new coronavirus disease (previously referred to as 2019 novel coronavirus (2019-nCoV)) received an official name from the World Health Organization (WHO), Coronavirus Disease 19 (COVID-19) (Figure 2).[6] The International Committee on Taxonomy of Viruses has proposed SARS-CoV-2 as the name of the virus that causes COVID-19.[7]

Coronaviruses are single-stranded RNA, nonsegmented, enveloped viruses, which cause illness ranging in severity from the common cold to severe and fatal illness. The term coronavirus derives from the Latin word “corona”, which means crown or “halo”; that designation arises from the appearance of coronavirus virions viewed by electron microscopy, where the virus particles display a crown-like fringe typically referred to as “spikes” (Figure 3).

In the past two decades, two other coronaviruses that cause severe respiratory illness in humans have emerged: severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). With the emergence of SARS-CoV-2, a third coronavirus that can cause severe respiratory illness has been identified. In a short period of time, this novel coronavirus has caused more cases of illness than were reported for MERS and SARS combined. Here we summarize what is currently known about COVID-19and what this means for practicing obstetricians and their pregnant patients. Since so little is currently known about COVID-19 in pregnancy, we also review available information on the effects of SARS and MERS during pregnancy to inform care of pregnant women with COVID-19 until additional data on pregnant women and their fetuses become available.

SARS and its effects on pregnant women

Severe acute respiratory syndrome (SARS) is caused by the SARS-coronavirus (SARS-CoV). Reports of the emergence of SARS-CoV appeared in February of 2003, with the first cases observed in Guangdong Province in China. The virus spread to nearly 30 countries throughout the world, resulting in more than 8000 cases and 770 deaths.[8] The outbreak was brought under control after public health control measures to reduce contact with infected persons were put into place, and no cases have been seen since 2004. Manifestations of SARS consist of fever, chills, headache, malaise, and myalgia. Diarrhea was seen in some patients. Pneumonia was nearly always seen in patients diagnosed with SARS, with mechanical ventilation being required in 10-20% of cases. Case fatality rate was estimated at 9-10% (Table).

The natural reservoir for SARS-CoV is believed to be bats; however, some evidence supported civet cats or raccoon dogs as possible intermediate sources of these illnesses.[8] SARS is transmitted by close person-to-person contact through contact of the mucus membranes of the respiratory tract with respiratory droplets formed when an infected person coughs or sneezes. Fecal-oral transmission and transmission via fomites have also been reported.[8] Airborne spread due to inhalation of small particle aerosols may also be possible. Transmission in health care settings was frequently seen during the 2003 outbreak, with superspreading (when a single patient transmits infection to a disproportionate number of contacts) reported.[9] The incubation period was estimated at a mean of 4.6 days, with a range of 2-14 days. Transmission appeared to occur most often during the second week of illness when viral excretion is highest; there is no evidence that a person with SARS is contagious before symptom onset.

The largest case series of pregnant women with SARS was from the 2003 outbreak in Hong Kong, in which 12 pregnant women were identified.[10] The case-fatality rate was 25% (3 deaths). Clinical and laboratory findings were similar to those seen in the non-pregnant population. Pneumonia on chest radiograph or CT was seen in all patients. Major medical complications included adult respiratory distress syndrome in four, disseminated intravascular coagulopathy (DIC) in three, renal failure in three, secondary bacterial pneumonia in two, and sepsis in two patients.

Pregnancy outcomes varied by trimester of presentation.[10] Among the seven women who became ill in the first trimester, four had a spontaneous abortion, two had pregnancy terminations for social reasons after recovery from SARS, and one delivered a full-term healthy infant. Among the five women who presented after 24 weeks gestation, four delivered preterm. Three women delivered by cesarean delivery due to deteriorating maternal condition from their SARS

illness at 26, 28 and 32 weeks gestation.[11] These babies had birth weights appropriate for gestational age. Two of the infants had respiratory distress syndrome requiring surfactant (born at 26 and 28 weeks gestation), with one later developing bronchopulmonary dysplasia. Gastrointestinal complications were observed in two infants, including a jejunal perforation in an infant delivered at 26 weeks and necrotizing enterocolitis with ileal perforation in an infant delivered at 28 weeks gestation. Whether these gastrointestinal complications were related to complications from SARS or its treatment or if they were secondary to preterm delivery is unknown.[11] The two infants who were delivered after their mothers' recovery from SARS had intrauterine growth restriction. No clinical, radiologic, or laboratory evidence for transmission from mother to fetus was observed, despite laboratory testing of different specimens.[12,13]

A matched case-control study[14] compared 10 of the 12 pregnant women noted above (two were excluded because they were unable to be matched) to 40 non-pregnant women with SARS. Women were matched on sex, age, timing of contracting SARS, health care worker status, underlying illness and whether the woman resided in a housing area where there was a large outbreak. Pregnancy appeared to have no effect on clinical symptoms or time to presentation after symptom onset. However, complications and adverse outcomes were more common among pregnant women: women who were pregnant had a longer hospital stay, were statistically significantly more likely to develop renal failure, sepsis, and DIC, and were more likely to require intensive care unit admission. Forty percent of pregnant women required mechanical ventilation, compared to 13% of non-pregnant patients (p=0.07). Pregnant women were also significantly more likely to die (p=0.01).

We identified five reports of additional cases of SARS during pregnancy treated in Hong Kong (n=2), United States (n=2), and Canada (n=1).[15-19] Two of the five women required

mechanical ventilation, one required hemodialysis for acute renal failure, and one had seizures and positive cerebrospinal fluid for SARS-CoV, suggestive of a central nervous system infection. All patients recovered from their illness. In one case, the pregnancy was terminated at the mother's request; the remaining pregnancies ended in liveborn infants (two at term and two preterm). Testing of neonatal specimens for SARS-CoV RNA was negative.

Several hospitals in Toronto and Hong Kong reported measures instituted on obstetrics services during the SARS outbreak to decrease transmission to pregnant women, their families, community members and health care workers.[20,21] For example, all hospital staff, patients, and visitors were screened for symptoms at the hospital entrance and wore N95 respirators. Visitors were limited to one per patient on labor and delivery, with no visitors allowed in the postpartum ward. Postpartum stays were reduced in length with a postpartum nurse home visit added. Postpartum patients were asked to observe a 10-day home quarantine. Health care workers were asked to observe a work quarantine in which they were asked to go directly from home to work and vice versa to minimize interaction in the community. Obstetric services considered to be non-essential such as routine ultrasound and prenatal diagnosis were suspended. Although the impact of these interventions was not evaluated, there may be some relevant lessons learned from these experiences during SARS that could help inform the approach to COVID-19.

MERS and its effects on pregnant women

Middle East Respiratory Syndrome (MERS) is a respiratory illness caused by MERS-CoV. The illness was first identified in Saudi Arabia in 2012, with spread to other countries in the Arabian peninsula and eventually to countries outside the Arabian peninsula, including the

United States.[22,23] The largest outbreak outside the Arabian Peninsula was in the Republic of Korea in 2015. Nearly 2,500 cases of MERS-CoV illness and over 860 deaths have been reported with continuing reports into the present. The manifestations of MERS include severe respiratory illness characterized by fever, cough, and shortness of breath. Some patients also have diarrhea. The case fatality rate is estimated to be 35-40 percent. Patients who developed MERS were more likely to be older (median age is 50 years) with about two-thirds of patients being male. Patients with MERS were also more likely to have an underlying illness. Some patients with MERS-CoV infection have been asymptomatic (identified through contact investigations). The mean incubation period is 5.2 days, with a range of 2-13 days. As with SARS, MERS is mainly spread person-to-person through close contact, with transmission in health care settings, and superspreading events have been observed. However, since 2016, the number of cases of MERS-CoV has been dramatically reduced after public health efforts to prevent MERS-CoV transmission were put into place.[24]

Information on MERS among pregnant women is limited. We identified reports of 13 cases of pregnant women with MERS from several countries, including Saudi Arabia (8), Korea (2), Jordan (1), United Arab Emirates (1), and Philippines (1).[13,25-31] Two women were asymptomatic, identified as part of a contact investigation. Among the 11 symptomatic women, manifestations were similar to those seen in non-pregnant patients with MERS. Seven of 13 patients were admitted to an intensive care unit for respiratory deterioration or ARDS, five required ventilator support, three died, and eight recovered. Among the three deaths, the mothers died 8-25 days post-delivery. Both babies born to asymptomatic women were born healthy at term; among those who were symptomatic, there was one intrauterine fetal demise, one stillbirth,

one baby delivered at 25 weeks who died 4 hours after birth, two healthy preterm infants and five healthy term infants (infant status was not mentioned for one).

Coronavirus Disease 2019 (COVID-19)

Clinical, epidemiologic, and viral characteristics

Respiratory illness caused by a novel coronavirus (now referred to as SARS-CoV-2) was first noted in December of 2019 in Wuhan, Hubei Province, China. The WHO China Country office was notified of an outbreak of pneumonia of unknown etiology on December 31, 2019 (Figure 2). Between December 31, 2019 and January 3, 2020, 44 cases were reported to the WHO. On January 7, 2020, Chinese authorities identified a novel coronavirus as the cause. The virus has quickly spread first through Wuhan and subsequently to other areas of China and other countries in the world (Figure 1). Early data suggested an association between the Huanan Seafood Wholesale Market and COVID-19 with 27 of 41 cases in one report[32] and 26 of 47 in another report[33] with epidemiologic links to the market, leading to closure of the market on January 1, 2020. Given that the earliest case reported (illness onset on December 1, 2019)[32] did not have exposure to the market raises the possibility that the initial emergence into humans occurred elsewhere. However, sampling of the market's environment supports the market's importance in early transmission of the virus. Later cases were much less likely to have visited the market, supporting the role of person-to-person transmission in later cases.

The SARS-CoV-2 is a betacoronavirus similar to SARS-CoV and MERS-CoV (Table). Sequencing data show that the SARS-CoV-2 is most closely related to coronaviruses found in bats, with more than 85% nucleotide identity with a bat SARS-like CoV.[34,35] The virus has 79%

nucleotide identity to SARS-CoV and about 50% to MERS-CoV.[35] Bats appear to be the natural reservoirs of both SARS-CoV and MERS-CoV. The emergence of these viruses in humans has been attributed to host switching: the virus "jumped" from an intermediary host species (e.g., civet cats for SARS-CoV and dromedary camels for MERS-CoV) to humans. An intermediary host species is thought to be likely for SARS-CoV-2,[35] although it has been yet to be identified. Sequence data that show a high degree (>99.98%) of similarity of the virus among different patients, suggesting a recent emergence in humans.

Clinical manifestations of COVID-19 are similar to those with SARS and MERS (Table). Studies of hospitalized patients with COVID-19 show that patients commonly develop severe pneumonia with 23-32% admitted to the intensive care unit and 17-29% of cases progressing to acute respiratory distress syndrome (ARDS). [32,36,37] Among hospitalized patients, 4-15% have died.[32,36,37] Overall case fatality ratio estimates (including asymptomatic and symptomatic infections) appear to be in the range of 1% (95% confidence interval 0.5-4%),[38] although these estimates should be considered preliminary. Average age of hospitalized patients was 49-56 years, with 32-51% having an underlying illness. Most (54-73%) patients were men. Children with COVID-19 appear to be rarely identified, with only 28 children reported as of January 30, 2020 (<1% of total), and most of those identified had mild symptoms.[39] No pregnant women were reported in any of these initial cohorts. Common manifestations among hospitalized patients were fever (83-100%), cough (59-82%), myalgia (11-35%), headache (7-8%), and diarrhea (2-10%). All patients had abnormalities on radiographic imaging of the chest.

Person-to-person transmission of SARS-CoV-2 is thought to be similar to transmission of influenza and other respiratory pathogens; respiratory droplets are formed when an infected person coughs or sneezes and these droplets are inhaled by close contacts, generally within 6

feet. It is unclear if infection can be transmitted from fomites. Fecal-oral transmission might be possible, given that SARS-CoV-2 has been identified in stool specimens[40] and SARS-CoV might have been transmitted in this manner.[41] The basic reproduction number, R0 (the average number of people who will become infected from a single infected person in a population where all persons are susceptible) is affected by factors such as the duration of infectivity, the transmissibility of the pathogen, and the number of susceptible contacts. Measles, which is highly infective, has a R0 of 12-18, while 2009 H1N1 influenza and SARS have an R0 of 1.2-1.6 and 2-5, respectively.[42] Current estimates of R0 for SARS-CoV-2 places it at 2.2 (95% CI, 1.4 to 3.9)[33] As with SARS and MERS, nosocomial transmission is playing a key role in transmission, presumed to be responsible for infection of 29% of affected health professionals and 12% of hospitalized patients in a recent study.[37]

Implications of COVID-19 for pregnant women

In the midst of a rapidly evolving outbreak that could have significant effects on our public health and medical infrastructure, the unique needs of pregnant women should be included in preparedness and response plans. In previous outbreaks, clinicians have at times been reluctant to treat or vaccinate pregnant women because of concerns for fetal safety.[43] It is critical that pregnant women not be denied potentially life-saving interventions in the context of a serious infectious disease threat unless there is a compelling reason to exclude them. As with all decisions regarding treatment during pregnancy, carefully weighing of the benefits of interventions for the mother and fetus with potential risks is necessary. As surveillance systems for cases of COVID-19 are established, it is essential that information on pregnancy status, as well as maternal and fetal outcomes, be collected and reported.

Susceptibility to and severity of COVID-19 in pregnancy

Although data are limited, there is no evidence from other severe coronavirus infections (SARS or MERS) that pregnant women are more susceptible to infection with coronavirus. Thus far, in this outbreak of novel coronavirus infection, more men have been affected than women.[32,33,36,37] This observed gender difference could be due to differences in reporting, susceptibility, exposure, or recognition and diagnosis of infection. There are no data to inform whether pregnancy increases susceptibility to COVID-19.

Previous data on SARS and MERS suggest that clinical findings during pregnancy can range from no symptoms to severe disease and death. The most common symptoms of COVID-19 are fever and cough, with more than 80% of hospitalized patients presenting with these symptoms.[36] In a recent study by Chen et al.[44], nine women diagnosed with COVID-19 during the third trimester of pregnancy were reported. In this small series, clinical presentation was similar to that seen in nonpregnant adults, with fever in seven, cough in four, myalgia in three, and sore throat and malaise each in two women. Five had lymphopenia. All had pneumonia, but none required mechanical ventilation, and none died. All women had a cesarean delivery, and Apgars were 8-9 at 1 minute and 9-10 at 5 minutes. In a second series of nine pregnancies with ten infants (one set of twins) reported by Zhu et al.,[45] symptom onset was before delivery (1-6 days) in four, on the day of delivery in two, and after delivery (1-3 days) in three cases. Clinical presentation of COVID-19 was similar to that seen in nonpregnant patients. Among the nine pregnancies, intrauterine fetal distress was noted in six, seven were cesarean deliveries, and six infants were born preterm. Based on these limited reports, and the available data from other respiratory pathogens such as SARS and influenza, it is unknown whether pregnant women with COVID-19 will experience more severe disease.

Travel guidance for pregnant women

Travel recommendations have been instituted to limit exposure to persons in the United States. All persons, including pregnant women, should not travel to China. On February 2, 2020, the U.S. State Department upgraded their travel advisory to level 4, the highest level of travel advisory. Obstetric providers should obtain a detailed travel history for all patients and should specifically ask about travel in the past 14 days to areas experiencing widespread transmission of SARS-CoV-2. Currently this is limited to China, but this situation is rapidly evolving and obstetricians should stay alert to the global situation by consulting the CDC website and following media coverage.

Vaccination in pregnancy

There is currently no vaccine to prevent COVID-19. Since posting of a SARS-CoV-2 virus genetic sequence online on January 10, 2020, multiple organizations, including the National Institutes of Health, have been working to rapidly develop a COVID-19 vaccine. Development of this vaccine builds on and benefits from work on SARS and MERS vaccines.[46] However, it is not known how quickly a safe and effective vaccine may be readily available.

Infection control measures and diagnostic testing

All patients, including pregnant women, should be evaluated for fever and signs and symptoms of a respiratory infection. Ideally, screening procedures begin before arrival on a labor and delivery unit or prenatal care clinic. For example, when scheduling appointments, patients should be instructed what to do if they have respiratory symptoms on the day of their appointment or if a patient calls triage prior to presentation, respiratory signs and symptoms should be assessed over the telephone. Those patients with respiratory symptoms should be

separated from other waiting patients and a facemask should be placed on them. Patients who meet criteria for a Person Under Investigation (Box 1) should be immediately placed in an Airborne Infection Isolation Rooms (single-patient rooms at negative pressure). Once in isolation, the patient's facemask may be removed. Health care personnel should adhere to standard, contact and airborne precautions. Infection control personnel and local/state health departments should be notified immediately; local/state health departments can help to arrange testing of relevant specimens (upper and lower respiratory specimens and serum are currently recommended; other specimens [stool and urine] may also be sent).

Management of COVID-19 in pregnancy

General principles regarding management of COVID-10 during pregnancy include early isolation, aggressive infection control procedures, testing for SARS-CoV-2 and co-infection, oxygen therapy as needed, avoidance of fluid overload, empiric antibiotics (due to secondary bacterial infection risk), fetal and uterine contraction monitoring, early mechanical ventilation for progressive respiratory failure, individualized delivery planning, and a team-based approach with multi-specialty consultations (Box 2). Team-based management is recommended for pregnancies managed in a health care facility and should include a determination of the optimal clinical unit on which to provide care. Ability to provide surveillance for early detection of a worsening maternal course of illness, as well as an ability to monitor for evidence of obstetric complications (e.g., preterm labor or fetal compromise), are needed.

Changes in fetal heart rate pattern may be an early indicator of maternal respiratory deterioration. Based on experience with SARS and MERS, severe respiratory failure might occur in pregnant women, and in the most severe cases, mechanical ventilation might not be sufficient to support adequate oxygenation. If that occurs, limited literature suggests a potential role of

extracorporeal membrane oxygenation (ECMO) in pregnancy; use should only be considered in centers that have experience with this technique.[47] Whether delivery provides benefit to a critically ill mother is unknown; decisions regarding delivery should consider the gestational age of the fetus and should be made in conjunction with the neonatologist.[48]

There are currently no antiviral medications approved by the US Food and Drug Administration for treatment of COVID-19, although broad-spectrum antivirals used in animal models of MERS are being evaluated for activity against SARS-CoV-2.[46] Corticosteroids for the treatment of coronavirus-associated pneumonia should be avoided unless other indications are present because they were not shown to be beneficial in MERS and could lead to delayed MERS-CoV clearance.[49] Therefore, decisions about the use of corticosteroids for fetal lung maturity should be made in consultation with infectious disease specialists and maternal-fetal medicine consultants. All guidance should be considered subject to revision as additional data on pregnant women with COVID-19 become available.

Care of infants born to mothers with COVID-19

Although the limited experience with newborn evaluations after delivery with SARS and MERS has not identified cases of maternal-to-fetal transmission, reports have appeared in the media of a 30-hour infant who was diagnosed with COVID-19, suggesting the possibility of *in utero* transmission.[50] However, insufficient information is included in media reports to rule out perinatal or postnatal modes of transmission. Data from the recent case series published by Chen et al.[44] and Zhu et al.[45]of 18 women (19 infants) infected in the third trimester of pregnancy with SARS-CoV-2 identified no laboratory evidence of vertical transmission. Testing of amniotic fluid, cord blood, and neonatal throat swab samples was negative for SARS-CoV-2 in the six patients reported by Chen et al.[44] In the report by Zhu et al.,[45] some infants were symptomatic

(shortness of breath in six, cyanosis in three, gastric bleeding in two, and one baby died of multiple organ failure and DIC); however, throat swab testing of all infants was negative for SARS-CoV-2 , suggesting that these neonatal complications might not be related intrauterine transmission. Thus, at this time, it is unknown if SARS-CoV-2 can be transmitted from mother-to-fetus. Given the current lack of information, it seems reasonable to assume that a newborn born to a mother with COVID-19 at delivery could possibly be infected, either *in utero* or perinatally, and thus should be placed in isolation to avoid exposure to other newborns. Although the ideal setting for a healthy infant is within a healthy mother's room, temporary separation of an ill mother and her infant, as was recommended during pandemic H1N1,[51] seems prudent. Whether COVID-19 can be transmitted through breastmilk is unknown. We are aware of a single report of SARS-CoV testing of breastmilk in a mother who had recovered from SARS and no viral RNA was detected; however, the specimen was collected ~130 days after illness onset.[15] SARS-CoV antibodies were seen in breastmilk of that patient,[15] but not in another patient who was infected at 7 weeks gestation with breastmilk tested at postpartum days 12 and 30.[16] Breastmilk was tested for SARS-CoV-2 in six of the mothers reported by Chen et al.[44]; all specimens were negative. Until additional data are available, mothers who intend to breastfeed and are well enough to express breastmilk should be encouraged to do so; breastfeeding can be instituted after she is no longer considered infectious. No data are available to guide length of separation and will need to be decided on a case-by-case basis after discussion between infection control experts and neonatologists.

Conclusions

The COVID-19 outbreak is rapidly increasing in number of cases, deaths, and countries affected. Much is unknown about the virus and its effects, including its modes of transmission, the basic reproduction number, risk factors for illness, and case fatality rate. Although cases are primarily in China, it is highly likely that there will be additional global spread of the virus. At the present time, limited data are available on pregnant women with COVID-19 on which to base recommendations for pregnancy-specific care; however, early reports and lessons from SARS, MERS, and other respiratory infections suggest that pregnant women could have a severe clinical course. Surveillance systems for cases of COVID-19 need to include information on pregnancy status, as well as maternal and fetal outcomes. It is important to be vigilant about the spread of the disease and be able to provide rapid implementation of outbreak control and management measures once the virus reaches a community. Standard interventions to manage any severe respiratory infection is the foundation of care for any pregnant woman with COVID-19 and should be implemented aggressively in a team-based care model.

Table – Comparison of Characteristics of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus Disease 2019 (COVID-19)

Characteristics	Severe Acute Respiratory Syndrome	Middle East Respiratory Syndrome	Coronavirus Disease-2019
First patients reported	Guangdong, China, November 2002	Zarga, Jordan, April 2012 and Jeddah, Saudi Arabia, June 2012	Wuhan, China, December 2019
Virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Type of coronavirus	betacoronavirus	betacoronavirus	betacoronavirus
Host cell receptor	Angiotensin converting enzyme 2	Dipeptidyl peptidase 4	structural analysis suggests Angiotensin converting enzyme 2 receptor[52]
Sequence similarity	reference		79% to SARS-CoV, 50% to MERS-CoV[35]
Animal hosts	Bats (natural reservoir), masked palm civet and raccoon dogs may be intermediate hosts	Bats (natural reservoir), dromedary camel (intermediate host)	Bats, animal sold at the seafood market in Wuhan might represent an intermediate host[35]
Incubation period			
Mean (95% CI: days)	4.6 (3.8-5.8)	5.2 (1.9-14.7)	5.2 days (95% confidence interval [CI], 4.1 to 7.0); 95th percentile of the distribution was 12.5 days[33]
Range (days)	2-14	2-13	2-14
Time from illness onset until hospitalization	2-8 days	0-16 days	12.5 days (mean) (95% CI, 10.3 to 14.8) - onset before January 1 9.1 days (mean); 95% CI, 8.6 to 9.7 (onset January 1-11)[33]
Basic reproduction number (R0) **	2-3	<1	2.2 (95% CI, 1.4 to 3.9)[33]
Patient characteristics			
Adults	93%	98%	Nearly all reported patients are adults
Children	5-7%	2%	Children have been infrequently reported (<1% of cases)[39]
Age range (years)	1-91	1-94	10-89 years
Average age (years)	Mean 39.9	Median 50	59 years (median)[33]
Sex ratio (M:F)	43%:57%	64.5%:35.5%	56%:44%[33]
Mortality			
Case fatality rate overall	9.6%	35-40%	Initial estimate is

			1%[38]
Clinical Manifestations			From hospitalized patients[32,36,37]
Fever	99-100%	98%	83-100%
Cough	62-100%	83%	59-82%
Myalgia	45-61%	32%	11-35%
Headache	20-56%	11%	7-8%
Diarrhea	20-25%	26%	2-10%
Laboratory findings			
Radiographic abnormalities on chest imaging	94-100%	90-100%	100%
Leukopenia	25-35%	14%	9-25%
Lymphopenia	65-85%	32%	35-70%
Thrombocytopenia	40-45%	36%	5-12%

*Modified from Rasmussen et al.[23]

**Basic reproduction number – defined as average number of people who will become infected from a single infected person

Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Box 1

Criteria to Guide Evaluation of Persons Under Investigation for Coronavirus Disease 2019 (COVID-19)

Clinical Features	AND	Epidemiologic Risk
Fever* **or** signs/symptoms of lower respiratory illness (e.g., cough or shortness of breath	AND	Any person, including health care workers, who has had close contact** with a laboratory-confirmed COVID-19 patient within 14 days of symptom onset
Fever* **and** signs/symptoms of a lower respiratory illness (e.g., cough or shortness of breath	AND	A history of travel from Hubei Province China within 14 days of symptom onset
Fever* **and** signs/symptoms of a lower respiratory illness (e.g., cough or shortness of breath) requiring hospitalization	AND	A history of travel from mainland China within 14 days of symptom onset

*Fever may be subjective or confirmed

**Close contact is defined as:

a) being within ~6 feet (2 meters) of a COVID-19 case for a prolonged period of time while not wearing recommended personal protective equipment (e.g., gowns, gloves, NIOSH-certified disposable N95 respirator, eye protection); close contact can occur while caring for, living with, visiting, or sharing a health care waiting area or room with a COVID-19case

OR

b) having direct contact with infectious secretions of a COVID-19 case (e.g., being coughed on) while not wearing recommended personal protective equipment.

The criteria are intended to serve as guidance for evaluation. Patients should be evaluated and discussed with public health departments on a case-by-case basis if their clinical presentation or exposure history is equivocal (e.g., uncertain travel or exposure).

From: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html#foot1

Box 2

Principles for Management of Pregnant Women with Confirmed or Suspected Coronavirus Disease 2019 (COVID-19) [48,53,54]

- Patients with respiratory symptoms should adhere to respiratory hygiene, cough etiquette, and hand hygiene. Ensure rapid triage of pregnant patients with respiratory symptoms. Patients with respiratory symptoms should wear a facemask and wait in a separate, well ventilated waiting area at least 6 feet from other people.
- Confirmed and suspected cases of COVID-19 should be isolated as soon as possible in an Airborne Infection Isolation Room (AIIR). If an AIIR is not available, consider transfer to a hospital with an AIIR.
- Implement CDC infection prevention and control procedures for healthcare providers including standard, contact, and airborne precautions. Eye protection and properly-fitted N95 respirators should be used. Provide additional staff training in correct use of personal protective equipment (PPE) including correct donning, doffing and disposal of PPE.
- Contact hospital infection personnel.
- In coordination with local/state health department, collect and send relevant specimens for diagnostic SARS-CoV-2 testing.
- Limit visitor and health care personnel access to patient rooms with a confirmed or suspected case.
- Pregnancy should be considered a potentially increased risk condition and monitored closely including fetal heart rate and contraction monitoring.
- Consider early oxygen therapy (target O_2 saturations $\geq$95% and/or pO_2 $\geq$70mmHg). Consider early mechanical ventilation with evidence of advancing respiratory failure. Non-invasive ventilation techniques may have a small increased risk of aspiration in pregnancy.
- Use intravenous fluids conservatively unless cardiovascular instability is present.
- Screen for other viral respiratory infections and bacterial infections (due to risk of co-infections).
- Consider empiric antimicrobial therapy (because of risk for superimposed bacterial infections).
- Consider empiric treatment for influenza, pending diagnostic testing.
- Do not routinely use corticosteroids. Use of steroids to promote fetal maturity with anticipated preterm delivery can be considered on individual basis.
- If septic shock is suspected, institute prompt, targeted management.
- Delivery and pregnancy termination decisions should be based on gestational age, maternal condition, and fetal stability, and maternal wishes.
- Consult with specialists in obstetrics, maternal-fetal medicine, neonatology, intensive care, anesthesia, and nursing.
- Communicate with patients and families regarding diagnosis, clinical status and management wishes.

*All guidance should be considered subject to revision as additional data on pregnant women with COVID-19 become available.

Figure Legends:

Figure 1: Global map of confirmed Coronavirus Disease 2019 (COVID-19) cases (as of February 14, 2020) – from

https://www.cdc.gov/coronavirus/2019-ncov/locations-confirmed-cases.html

Figure 2: Timeline showing key events in the Coronavirus Disease 2019 (COVID-19) outbreak -- December 1, 2019 through February 15, 2020. Abbreviations: CDC – Centers for Disease Control and Prevention, COVID-19 - Coronavirus Disease 2019, US – United States, WHO – World Health Organization

Figure 3: Illustration of the causative virion for Coronavirus Disease (COVID-19). Credit to CDC/ Alissa Eckert, MS – Obtained from CDC's Public Health Image Library. https://phil.cdc.gov/Details.aspx?pid=23312

References

1. Rasmussen SA, Hayes EB. Public health approach to emerging infections among pregnant women. *Am J Public Health.* 2005;95:1942-1944.
2. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA.* 2010;303:1517-1525.
3. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. *JAMA Pediatr.* 2017;171:288-295.
4. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika vrus and birth defects--Reviewing the evidence for causality. *N Engl J Med.* 2016;374:1981-1987.
5. Zhao S, Lin Q, Ran J, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. *Int J Infect Dis.* 2020.
6. World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 Accessed February 17, 2020. 2020.
7. Gorbalenya AE, Baker SC, Baric RS, et al. Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1.full.pdf Accessed on February 16, 2020.
8. Hui DSC, Zumla A. Severe acute respiratory syndrome: Historical, epidemiologic, and clinical features. *Infect Dis Clin North Am.* 2019;33:869-889.
9. Wong G, Liu W, Liu Y, Zhou B, Bi Y, Gao GF. MERS, SARS, and Ebola: The role of super-spreaders in infectious disease. *Cell Host Microbe.* 2015;18:398-401.

10. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol.* 2004;191:292-297.

11. Shek CC, Ng PC, Fung GP, et al. Infants born to mothers with severe acute respiratory syndrome. *Pediatrics.* 2003;112:e254.

12. Ng PC, Leung CW, Chiu WK, Wong SF, Hon EK. SARS in newborns and children. *Biol Neonate.* 2004;85:293-298.

13. Park MH, Kim HR, Choi DH, Sung JH, Kim JH. Emergency cesarean section in an epidemic of the middle east respiratory syndrome: a case report. *Korean J Anesthesiol.* 2016;69:287-291.

14. Lam CM, Wong SF, Leung TN, et al. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. *BJOG.* 2004;111:771-774.

15. Robertson CA, Lowther SA, Birch T, et al. SARS and pregnancy: a case report. *Emerg Infect Dis.* 2004;10:345-348.

16. Stockman LJ, Lowther SA, Coy K, Saw J, Parashar UD. SARS during pregnancy, United States. *Emerg Infect Dis.* 2004;10:1689-1690.

17. Yudin MH, Steele DM, Sgro MD, Read SE, Kopplin P, Gough KA. Severe acute respiratory syndrome in pregnancy. *Obstet Gynecol.* 2005;105:124-127.

18. Jiang X, Gao X, Zheng H, et al. Specific immunoglobulin g antibody detected in umbilical blood and amniotic fluid from a pregnant woman infected by the coronavirus associated with severe acute respiratory syndrome. *Clin Diagn Lab Immunol.* 2004;11:1182-1184.

19. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis.* 2004;10:342-344.

20. Haines CJ, Chu YW, Chung TK. The effect of Severe Acute Respiratory Syndrome on a hospital obstetrics and gynaecology service. *BJOG.* 2003;110:643-645.

21. Owolabi T, Kwolek S. Managing obstetrical patients during severe acute respiratory syndrome outbreak. *J Obstet Gynaecol Can.* 2004;26:35-41.

22. Bialek SR, Allen D, Alvarado-Ramy F, et al. First confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the United States, updated information on the epidemiology of MERS-CoV infection, and guidance for the public, clinicians, and public health authorities - May 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63:431-436.

23. Rasmussen SA, Watson AK, Swerdlow DL. Middle East Respiratory Syndrome (MERS). *Microbiol Spectr.* 2016;4.

24. Donnelly CA, Malik MR, Elkholy A, Cauchemez S, Van Kerkhove MD. Worldwide reduction in MERS cases and deaths since 2016. *Emerg Infect Dis.* 2019;25:1758-1760.

25. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. *J Microbiol Immunol Infect.* 2019;52:501-503.

26. Alserehi H, Wali G, Alshukairi A, Alraddadi B. Impact of Middle East Respiratory Syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. *BMC Infect Dis.* 2016;16:105.

27. Assiri A, Abedi GR, Al Masri M, Bin Saeed A, Gerber SI, Watson JT. Middle East respiratory syndrome coronavirus infection during pregnancy: A report of 5 cases from Saudi Arabia. *Clin Infect Dis.* 2016;63:951-953.

28. Malik A, El Masry KM, Ravi M, Sayed F. Middle East respiratory syndrome coronavirus during pregnancy, Abu Dhabi, United Arab Emirates, 2013. *Emerg Infect Dis.* 2016;22:515-517.

29. Payne DC, Iblan I, Alqasrawi S, et al. Stillbirth during infection with Middle East respiratory syndrome coronavirus. *J Infect Dis.* 2014;209:1870-1872.

30. Racelis S, de los Reyes VC, Sucaldito MN, Deveraturda I, Roca JB, Tayag E. Contact tracing the first Middle East respiratory syndrome case in the Philippines, February 2015. *Western Pac Surveill Response J.* 2015;6:3-7.

31. Jeong SY, Sung SI, Sung JH, et al. MERS-CoV Infection in a pregnant woman in Korea. *J Korean Med Sci.* 2017;32:1717-1720.

32. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020.

33. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med.* 2020.

34. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020.

35. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020.

36. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020.

37. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients With 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020.

38. Dorigatti I, Okell L, Cori A, et al. Report 4: Severity of 2019-novel coronavirus (nCoV). WHO Collaborating Centre for Infectious Disease Modelling, MRC Centre for Global Infectious Disease Analysis, Imperial College London. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-2019-nCoV-severity-10-02-2020.pdf Accessed February 11, 2020.

39. Shen KL, Yang YH. Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. *World J Pediatr.* 2020.

40. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel noronavirus in the United States. *N Engl J Med.* 2020.

41. Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med.* 2004;350:1731-1739.

42. Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. *Microbes Infect.* 2020.

43. Haddad LB, Jamieson DJ, Rasmussen SA. Pregnant women and the Ebola crisis. *N Engl J Med.* 2018;379:2492-2493.

44. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020; Published online February 12, 2020.

45. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020.

46. Paules CI, Marston HD, Fauci AS. Coronavirus infections-More than just the common cold. *JAMA.* 2020.

47. Pacheco LD, Saade GR, Hankins GDV. Extracorporeal membrane oxygenation (ECMO) during pregnancy and postpartum. *Semin Perinatol.* 2018;42:21-25.

48. Lapinsky SE. Management of acute respiratory failure in pregnancy. *Semin Respir Crit Care Med.* 2017;38:201-207.

49. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med.* 2018;197:757-767.

50. D'Amore R. Can coronavirus pass from mother to baby? Maybe, but experts need more research. Global News. https://globalnews.ca/news/6515302/coronavirus-mother-baby-transmission/ Posted February 7, 2020. Accessed February 10, 2020.

51. Rasmussen SA, Kissin DM, Yeung LF, et al. Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns. *Am J Obstet Gynecol.* 2011;204:S13-20.

52. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J Virol.* 2020.

53. CDC. Interim infection prevention and control recommendations for patients with confirmed 2019 novel coronavirus (2019-nCoV) or patients under investigation for 2019-nCoV in healthcare settings. Centers for Disease Control and Prevention. Updated February 3, 2020. https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html Accessed February 11, 2020.

54. CDC. Interim guidance for implementing home care of people not requiring hospitalization for 2019 novel coronavirus (2019-nCoV). Updated January 31, 2020 https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fguidance-home-care.html. Accessed February 11, 2020.