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Severe Coronavirus Infections in Pregnancy:

A Systematic Review

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Abstract

OBJECTIVE: To inform the current coronavirus disease 2019 (COVID-19) outbreak, we conducted a systematic literature review of case reports of Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, during pregnancy and summarized clinical presentation, course of illness, and pregnancy and neonatal outcomes.

DATA SOURCES: We searched MEDLINE and ClinicalTrials.gov from inception to April 23, 2020.

METHODS OF STUDY SELECTION: We included articles reporting case-level data on MERS-CoV, SARS-CoV, and SARS-CoV-2 infection in pregnant women. Course of illness, indicators of severe illness, maternal health outcomes, and pregnancy outcomes were abstracted from included articles.

TABULATION, INTEGRATION, AND RESULTS: We identified 1,328 unique articles, and 1,253 articles were excluded by title and abstract review. We completed full-text review on 75, and 29 articles were excluded by full-text review. Among 46 publications reporting case-level data, eight described 12 cases of MERS-CoV infection, seven described 17 cases of SARS-CoV infection, and 31 described 98 cases of SARS-CoV-2 infection. Clinical presentation and course of illness ranged from asymptomatic to severe fatal disease, similar to the general population of patients. Severe morbidity and mortality among women with MERS-CoV, SARS-CoV, or SARS-CoV-2 infection in pregnancy and adverse pregnancy outcomes, including pregnancy loss, preterm delivery, and laboratory evidence of vertical transmission, were reported.

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CONCLUSION: Understanding whether pregnant women may be at risk for adverse maternal and neonatal outcomes from severe coronavirus infections is imperative. Data from case reports of SARS-CoV, MERS-CoV, and SAR-CoV-2 infections during pregnancy are limited, but they may guide early public health actions and clinical decision-making for COVID-19 until more rigorous and systematically collected data are available. The capture of critical data is needed to better define how this infection affects pregnant women and neonates. This review was not registered with PROSPERO.

The Centers for Disease Control and Prevention activated its Emergency Operations Center on January 20, 2020, to respond to an outbreak of novel coronavirus disease 2019 (COVID-19) first detected in Wuhan City, Hubei Province, China. As of May 15, 2020, more than 1.4 million confirmed and probable cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, have been reported in the United States, including 85,990 deaths. Globally, more than 4 million cases have been reported, with most countries reporting having had cases.[1–4] Pregnant women are a population who may be at increased risk of susceptibility to infection, severe illness, and mortality associated with respiratory infections.[5] During pregnancy, physiologic changes take place, including increased heart rate and oxygen consumption, decreased lung capacity, and a shift away from cell-mediated immunity, which may increase the risk of more severe disease compared with nonpregnant adults.[6–8]

Coronavirus infections are a common cause of seasonal mild respiratory illness. The strain of the virus that causes COVID-19 is phylogenetically classified as genus *Betacoronavirus*, which includes Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV).[9] The first outbreaks of MERS-CoV and SARS-CoV occurred in 2012 and 2002, respectively. Symptoms commonly reported with COVID-19 are similar to those in MERS-CoV and SARS-CoV, including fever, cough, and shortness of breath. Reported severity of clinical illness ranges from asymptomatic infection or mild illness to severe illness and fatal disease.[10]

Given that SARS-CoV and MERS-CoV are similar to SARS-CoV-2 (the virus that causes COVID-19), previous outbreaks of these other coronaviruses may provide additional information to supplement emerging data about SARS-CoV-2 and guide the understanding of the potential effect of COVID-19 during pregnancy.[9] We conducted a systematic literature review to identify reports of SARS-CoV, MERS-CoV, and SARS-CoV-2 infection during pregnancy and summarize the clinical presentation, course of illness, and pregnancy and neonatal outcomes.

SOURCES

The systematic review of the literature was conducted per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The primary objective of the search strategy was to identify cases of MERS-CoV, SARS-CoV, and SARS-CoV-2 infection in pregnancy. Articles published as of April 23, 2020 were searched in the MEDLINE database and ClinicalTrials.gov. MeSH terms used included “betacoronavir*,” “corona virus*,” “coronavi*,” “CoV 2,” “CoV2,” “covid 19,” “covid19,” “Middle East Respiratory

Syndrome," "MERS," "MERS-CoV," "nCoV," "OC43," "respiratory tract infection," "SARS," "SARS Virus," "SARS-CoV," "sarscov2," "Severe Acute Respiratory Syndrome," "wuhan virus*," "2019nCoV." To target our population of interest, we also searched for articles that contained: "conception*,", "expectant," "gestat*,", "gravid*,", "matern*,", "mother*,", "obstetric*,", "parturiency," "pregnan*,", "pregnancy complications," "pregnancy trimesters," "pregnant women," "prenatal care."

STUDY SELECTION

We included only articles reporting case-level data on MERS-CoV, SARS-CoV, or SARS-COV-2 infection in pregnant women. Review articles, dissertations, and management guidelines were excluded. Data abstracted included journal reference, year of publication, patient characteristics (age, pertinent medical history), pregnancy and delivery characteristics (timing and mode of delivery, indications for cesarean delivery if performed, and pregnancy or delivery complications), exposure type (occupational exposure, household exposure, health care–associated, or unidentified), clinical presentation (gestational age at symptom onset or diagnosis, days from symptom onset to presentation for clinical evaluation, reported symptoms), duration of hospitalization, indicators of severe illness (including intensive care unit [ICU] admission, intubation and mechanical ventilation, renal failure, disseminated intravascular coagulopathy, and sepsis), maternal diagnostic evaluation (laboratory testing and imaging), therapeutic approach (antibiotics, antivirals, corticosteroids), pregnancy complications (including maternal death), pregnancy outcomes (live birth, pregnancy loss, preterm delivery), neonatal outcomes, and coronavirus-related testing of amniotic fluid, placenta, cord blood, breast milk, and neonatal specimens. Data on all variables were not required for inclusion, and unavailable data were listed as not reported.

Data were described using absolute counts, ranges, medians with interquartile range, and percentages as was appropriate to the data characteristics (dichotomous or continuous). The case fatality proportion was calculated among included cases for MERS-CoV, SARS-CoV, and SARS-CoV-2 in pregnancy. Data were analyzed with SAS 9.4. Individual maternal deaths were described.

RESULTS

Of the 1,338 articles initially identified, 10 were duplicates and excluded (Fig. 1). Titles and abstracts were screened by two reviewers for reporting of MERS-CoV, SARS-CoV, or SARS-CoV-2 infection during pregnancy. Discordant review determinations were reconciled by discussion between reviewers. Articles were excluded based on title and abstract review for the following mutually exclusive reasons: did not report data related to MERS-CoV, SARS-CoV, or SARS-CoV-2 infection in humans (n=1,083); did not report data among pregnant or postpartum women (n=92); did not report on any exposure, symptoms, course of illness, treatment, maternal outcome, or pregnancy outcome (n=30); was a review article, dissertation, or management guideline (n=44); or full English text was unavailable (n=4).

We completed full-text reviews on 75 articles to identify studies with case-level data. Twenty-nine articles were further excluded (five were review articles or management

guidelines, 17 did not report case-level data, five did not report data among pregnant or postpartum women, one provided data for the same patients as another included article with no additional details, and one article was withdrawn after publication). Among the 46 publications reporting original case-level data on coronavirus infections during pregnancy, eight publications described 12 cases of MERS-CoV infection in pregnancy, seven described 17 cases of SARS-CoV infection, and 31 described 98 cases of SARS-CoV-2 infection.[11–30,31–56]

Among 12 pregnant women with MERS-CoV infection, ages ranged from 26 to 31 years (median 32, interquartile range 31–38). Gestational age at time of symptom onset or diagnosis among pregnant women ranged from 4 to 38 completed weeks (median 24, interquartile range 21–33); two women presented in the first trimester of pregnancy, five presented in the second trimester, and five presented in the third trimester (Table 1). The source of exposure was reported for nine patients: contact with family members with confirmed MERS-CoV infection (n=4), health care–associated infection (n=1), and occupational exposure as a health care worker (n=4). Symptoms were reported for 11 patients (fever [n=7], chills or rigors [n=1], myalgia [n=2], malaise [n=1], cough [n=8], shortness of breath [n=7], chest pain [n=1]). One pregnant woman was reported as asymptomatic but screened for MERS-CoV infection as part of public health contact-tracing activities.[11]

Laboratory test results for MERS-CoV were reported in 12 patients (Table 2). Infection with MERS-CoV was detected by MERS-CoV antibody testing (enzyme immunoassay [EIA] with a correlated positive result of either immunofluorescence assay or microneutralization titer assay) in one woman; however, timing of specimen collection relative to onset of illness was not reported in this case.[14] Middle East respiratory syndrome coronavirus nucleic acid was detected by reverse transcription polymerase chain reaction (RT-PCR) in 11 women whose specimens were collected 2–10 days after symptom onset.[12–15,25] Results of chest imaging by radiograph or computed tomography results were reported for seven women, with findings of lower lobe opacity (n=2), bilateral infiltrate (n=2), bronchopneumonia (n=2), bilateral consolidation (n=1), and pneumonia (n=1).[12–15,23]

Among four reports describing treatment, two women received antibiotics (including combinations of macrolides, cephalosporins, carbapenems, and glycopeptides) and antiviral medications (including combinations of ribavirin, oseltamivir, interferon-alpha-2b, and peginterferon-alpha) (Table 2). One pregnant woman also received dexamethasone to support fetal lung maturation in anticipation of preterm delivery at 32 weeks of gestation for worsening maternal clinical status. Severe illness was reported in seven pregnant women, including ICU admission (n=7), mechanical ventilation (n=5), renal failure (n=2), and septic shock (n=1) (Table 3). Among 11 women with available outcome data, three died during their hospital stay after delivery (one during the second trimester of pregnancy and two during the third trimester; case fatality proportion 27%) (Table 3). Data from available reports were insufficient to describe survival from MERS-CoV infection relative to course of illness and timing of medical treatment initiation.

Among the three maternal deaths, the women were 31–32 years of age and one had underlying pulmonary disease (asthma, pulmonary fibrosis, and recurrent spontaneous pneumothoraces). Gestational age ranged from 24 to 38 completed weeks at presentation. Hospitalization occurred from 4 to 7 days after symptom onset. All three women required intubation for acute respiratory distress. Deaths occurred 17 days after symptom onset, with a culture-negative diagnosis of septic shock; 27 days after symptom onset from multiorgan failure; and 43 days after symptom onset from refractory hypoxia and cardiac arrest.[13,15]

Among eight pregnancies known to result in the delivery of liveborn neonates, three neonates were delivered by emergency cesarean between 25 and 32 weeks of gestation for critical maternal respiratory status requiring mechanical ventilation.[12,13,15] One neonate died shortly after delivery.[13] The other five liveborn neonates were delivered between 37 and 40 weeks of gestation–one by emergency cesarean delivery for placental abruption[14] and four without mention of obstetric complications (Table 3).

Five neonates were reported as healthy-appearing without clinical evidence of MERS-CoV infection[11,13,15] One neonate received serial RT-PCR testing of serum and nasopharyngeal specimens and antibody testing (by enzyme-linked immunosorbent assay, indirect immunofluorescence testing, and plaque reduction neutralization testing), with negative results for all MERS-CoV testing (Table 3).[14]

Among two reported stillbirths, one occurred at 21 weeks of gestation (7 days after symptom onset) in a previously healthy 39-year-old woman with obstetric history of six prior full-term live births. The woman was symptomatic with acute respiratory illness but did not require hospitalization.[16] The second stillbirth occurred at 34 weeks of gestation in a previously healthy 34-year-old woman with history of six prior deliveries. This woman was admitted 3 days after onset of shortness of breath and was diagnosed with preeclampsia, pneumonia, and stillbirth.[13] No evaluation for other causes of stillbirth was described in either of these cases (Table 3).

Among the 17 pregnant women with SARS-CoV infection, ages ranged from 24 to 44 years (median 32, interquartile range 26–34) (Table 1). Gestational age at symptom onset or diagnosis ranged from 3 to 32 completed weeks (median 19, interquartile range 5–29); eight pregnant women presented in the first trimester of pregnancy, three presented in the second trimester, and six presented in the third trimester. The source of exposure was reported in 11 patients: contact with family members with confirmed SARS-CoV infection (n=4), community exposure (n=2), and occupational exposure as a health care worker (n=5). Symptoms were reported in 17 patients: fever (n=17), chills or rigors (n=13), myalgia (n=14), malaise (n=12), cough (n=13), shortness of breath (n=6), chest pain (n=1), and diarrhea (n=2). Days from symptom onset to presentation for clinical evaluation was reported for 16 patients and ranged from 0 to 11 days.

Laboratory test results for SARS-CoV were reported in all 17 patients (Table 2). Infection with SARS-CoV was detected by only SARS-CoV serology testing (EIA correlated positive result of either immunofluorescence assay or enzyme-linked immunosorbent assay) in eight women (specimens collected 12–28 days after symptom onset), by only RT-PCR in five

women (timing of specimen collection relative to onset of illness not reported), and by both serology testing and RT-PCR in four women, with both tests having positive results (specimen collected at 29 days after symptom onset in one woman).[17–22,24] Severe acute respiratory syndrome coronavirus nucleic acid was detected with RT-PCR of cerebrospinal fluid in a pregnant woman at 30 weeks of gestation who experienced generalized tonic-clonic convulsions on day 29 after symptom onset (hospital day 22).[24] In 16 women with chest imaging reported, findings showed pneumonia (n=12), diffuse or patchy infiltrates (n=3), and patchy consolidations (n=1).[17,19–21,24]

Among the 16 patients with treatment information available, all received antibiotics (eg, azithromycin, broad-spectrum antibiotics, beta-lactams, macrolides, fluoroquinolones), 12 received antiviral treatment with ribavirin and one with oseltamivir, and 12 received corticosteroid therapy (including hydrocortisone, dexamethasone, or methylprednisolone) (Table 2). Severe illness requiring ICU admission occurred in six women, and mechanical ventilation was required for seven women (Table 3). Renal failure (n=4), disseminated intravascular coagulation (n=3), and septic shock (n=2) were reported. Three women died during their hospital stay (one with SARS-CoV infection in the first trimester of pregnancy and two during the third trimester; case fatality proportion 18%). Severe illness and maternal death were observed among women who did and did not receive antibiotics, antiviral treatment, and corticosteroid therapy. Data from available reports were insufficient to describe clinical outcomes relative to symptom onset, severity, and initiation of medical treatment.

Among the three reported maternal deaths (from two articles that describe the same women), the women were 34–44 years of age and gestational age ranged from 5 to 32 completed weeks. Hospitalization occurred from 5 to 7 days after symptom onset. Medical complications included respiratory distress, secondary bacterial pneumonia, sepsis, disseminated intravascular coagulation, renal failure, cardiovascular collapse, abdominal wound dehiscence, and surgical emphysema. All three women were admitted to the ICU and required mechanical ventilation. Two deaths resulted from progressive respiratory failure. One woman died of cardiovascular collapse from methicillin-resistant *Staphylococcus aureus* pneumonia 19 days after symptom onset. The articles did not report medical comorbidities or information to determine timing of medical complications or maternal death relative to symptom onset or date of hospital admission.[18,20]

Four emergency cesarean deliveries between 26 and 36 weeks of gestation for critical maternal respiratory status resulted in three liveborn neonates and one stillbirth.[18–20,24] Two neonates were delivered at 37 and 38 weeks of gestation by cesarean for nonreassuring fetal heart tracing and for complete placenta previa, respectively (Table 3).[17,18,20]

Four pregnancies ended in pregnancy loss at 5–10 weeks of gestation.[20] In each of these pregnancies, the pregnant women experienced fever, chills, and rigor; pregnancy loss occurred 2–5 weeks after onset of symptoms. Three women underwent termination of pregnancy (Table 3).[20,22]

No neonatal deaths were reported; however, complications were reported for two preterm neonates, including respiratory distress syndrome (n=2), bowel perforation (n=1), patent ductus arteriosus (n=1), and necrotizing enterocolitis (n=1).[18,20] One preterm neonate was noted to be febrile 12 days after delivery and was treated with broad-spectrum antibiotics and ribavirin. Fever abated after 24 hours, and cultures of blood and cerebrospinal fluid were reported as negative for bacterial growth. Neonatal SARS-CoV testing for this neonate was not reported as performed (Table 3).

Nine neonates were reported as healthy-appearing without clinical evidence of SARS-CoV infection.[17,19–21] Infection with SARS-CoV was not detected in six neonates who received RT-PCR testing of nasal swab, blood, urine, and stool specimens and antibody testing by EIA.[20] Infection with SARS-CoV was not detected in one neonate who received RT-PCR testing of nasopharyngeal and throat swabs, gastric aspirate, urine, and meconium (Table 3).[21]

Among the 98 pregnant women with SARS-CoV-2 infection, ages ranged from 22 to 44 years (median 30, interquartile range 28–34). Gestational age at time of symptom onset or diagnosis was reported for 96 pregnant women (range 25–41 completed weeks, median 36 weeks, interquartile range 34–38 weeks); one woman presented in the second trimester, and 95 presented in the third trimester. The source of exposure was identified and reported in 22 patients: contact with family members with confirmed SARS-CoV-2 infection (n=15) and community exposure (n=7). Two pregnant women were health care workers and had family members with confirmed SARS-CoV-2 infection; however, reported data were insufficient to determine the primary exposure source for their infections. None of the women were identified as having exposure while receiving health care.

Symptoms were reported in all 98 patients (fever [n=76], chills or rigors [n=2], myalgia [n=5], malaise [n=14], cough [n=34], shortness of breath [n=12], chest pain [n=1], diarrhea [n=5]). One patient was described as having abdominal pain that was gastrointestinal in origin.[50] Number of days from symptom onset to presentation for clinical evaluation was reported for 25 patients (median 2 days, interquartile range 1–4 days, range 0–12 days).

Laboratory test results for SARS-CoV-2 from maternal respiratory specimens were reported in all 98 patients. Infection with SARS-CoV-2 was detected by only RT-PCR in 93 women (specimens collected 0–11 days from onset of illness) and by both serology testing and RT-PCR in five women, with both tests having positive results (specimens collected 2–7 days after symptom onset).[26,31,32,49,55] In 65 women with chest imaging reported, findings showed ground glass opacities (n=27), pneumonia (n=19), diffuse or patchy infiltrates (n=5), and patchy consolidations (n=11).[26–39,43,45–52,54,55]

Among the 46 patients with treatment information available, all 46 received antibiotics (including combinations of carbapenems, fluoroquinolones, cephalosporins, macrolides, glycopeptides, aminoglycosides, aminoquinolines, penicillins, antiprotozoals), 43 received antiviral treatment (including combinations of oseltamivir, lopinavir–ritonavir, umifenovir, interferon, ganciclovir, remdesivir, or ribavirin), and 17 received corticosteroid therapy (including hydrocortisone, dexamethasone, or methylprednisolone) (Table 2). Severe illness

was observed among women who did and did not receive antibiotics, antiviral treatment, and corticosteroid therapy. Data from available reports were insufficient to describe clinical outcomes relative to symptom onset, severity, and initiation of medical treatment.

Severe illness requiring ICU admission occurred in six women, and mechanical ventilation was required in five women (Table 3). Other reported complications included renal failure (n=4) and septic shock (n=2). One woman presenting in the third trimester of pregnancy died during her hospital stay (case fatality proportion 1%) (Table 3). The woman was 22 years of age at 32 weeks of gestation; she had underlying hypothyroidism and was admitted 4 days after symptom onset. She was admitted to the ICU for respiratory support, was mechanically ventilated, and received peritoneal dialysis. The woman died 24 days after symptom onset from critical illness not otherwise specified in the report.[52]

Among 94 women with SARS-CoV-2 infection whose pregnancies were reported as completed at the time of publication, 52 neonates were delivered by emergency cesarean between 29 and 40 weeks of gestation. Four neonates were delivered for SARS-CoV-2 infection-control reasons.[50] Nineteen neonates were delivered for maternal indications, 17 for fetal distress, and 12 for other obstetric indications. Maternal indications included deteriorating maternal respiratory status (n=6), coagulopathy (n=2), preeclampsia (n=5), transaminitis (n=2), and acute illness that was not otherwise specified (n=4).[26,27,30,32–35,44,48,50,52] Other obstetric indications included prior cesarean delivery or scarred uterus (n=4), preterm prelabor rupture of membranes (n=2), placental abnormality (n=2), placental abruption (n=1), abnormal labor progression (n=2), and gestational diabetes (n=1).[27–29,37–39,41,43,46,48,51,54,56] Three neonates were born after spontaneous preterm labor between 32 and 34 weeks of gestation, and nine neonates were born by spontaneous vaginal delivery between 37 and 40 weeks of gestation (Table 3).[29,30,36,42,48,49,53,56]

Two pregnancies resulted in stillbirth at 34 and 35 weeks of gestation, respectively.[41,55] In both of these pregnancies, the women experienced critical illness characterized by multiorgan system dysfunction and acute respiratory distress syndrome requiring mechanical ventilation. Both of the women received respiratory support by extracorporeal membrane oxygenation (Table 3).[41,55]

One neonatal death was reported in a neonate delivered at 34 weeks of gestation by cesarean for fetal distress. The neonate appeared well at birth, but 30 minutes after birth had respiratory difficulty. The neonate received respiratory support and 8 days later developed refractory shock, gastric bleeding, multi-system organ failure, and disseminated intravascular coagulopathy and then died. Neonatal testing for SARS-CoV-2 infection on day 9 after birth did not detect viral RNA.[56]

Complications were reported in seven term neonates and included fever (n=3), vomiting or feeding intolerance (n=3), increased work of breathing without mention of etiology (n=2), radiographic evidence of pneumonia (n=2), small for gestational age (n=2), lethargy (n=2), diffuse rash (n=1), and a mild increase in myocardial enzymes without symptoms (n=1). Complications were reported in 10 preterm neonates and included respiratory difficulty without mention of etiology (n=3), radiographic evidence of pneumonia (n=2), respiratory

distress syndrome (n=2), fever (n=1), gastrointestinal bleeding and coagulopathy (n=2), fever (n=1), feeding intolerance (n=1), small for gestational age (n=1), and multiorgan failure (n=1). Seventy-two neonates were reported as healthy-appearing without clinical evidence of SARS-CoV-2 infection (Table 3).[26–33,35,36–46,49–54,56]

Severe acute respiratory syndrome coronavirus 2 RNA was detected in 7 of 68 neonates who received RT-PCR testing (Table 3).[28–31,33,35,36–42,45,46,49–53,56] Immunoglobulin M and G antibodies were detected in 1 of 13 neonates who received serology testing (including solid-phase immunochromatographic assay or chemiluminescence immunoassay).[31] Severe acute respiratory syndrome coronavirus 2 RNA was detected in 1 of 24 amniotic fluid specimens but not in cord blood, placental, or breast milk specimens (Table 2).

DISCUSSION

Detailed data on MERS-CoV, SARS-CoV, and SARS-CoV-2 infections in pregnancy are limited; however, similarities in clinical course and differences in outcomes between these infections are emerging. The clinical manifestations of these coronavirus infections during pregnancy range from asymptomatic or mild disease to severe or fatal disease, similar in range to those found in cases of infection among nonpregnant persons.[10,57,58] Severe morbidity and mortality were reported primarily among pregnant women in the second and third trimesters of pregnancy. These findings are similar to other respiratory infectious diseases.[59,60] No outcomes among patients with first-trimester SARS-CoV-2 infections were reported. Adverse pregnancy outcomes, including pregnancy loss, preterm deliveries, and small for gestational age, were observed among women whose pregnancies were complicated by MERS-CoV, SARS-CoV, or SARS-CoV-2 infection.

Among the few cases in this review, case fatality proportions for MERS-CoV and SARS-CoV infections in pregnant women were high (27% and 18%, respectively), as seen in the general population.[20,61] The case fatality proportion for SARS-CoV-2 infection in pregnant women was 1%, which was near the range of 1.8–3.4% observed in the general population.[62]

Mother-to-child transmission of MERS-CoV or SARS-CoV was not observed among the few pregnancies and neonates with testing in this review. By contrast, SARS-CoV-2 RNA was detected in seven newborns, and immunoglobulin M antibodies were detected in one newborn. Additionally, SARS-CoV-2 RNA was detected in amniotic fluid in one report. These limited case reports suggest vertical transmission of SARS-CoV-2 is possible, and many questions remain, including the absolute or relative risk, clinical significance, and the route of transmission (eg, transplacental, intrapartum, respiratory droplet postpartum).[63]

Treatment for MERS-CoV, SARS-CoV, and SARS-CoV-2 varied among reported patients and included combinations of antibiotics, antiviral mediations, and corticosteroids. Variation in treatment might be expected early in an outbreak, when data from clinical trials are not yet available. The National Institutes of Health has developed treatment guidelines to inform clinicians on how to care for patients with COVID-19; these guidelines are updated as new information becomes available.[64] At present, there are no U.S. Food and Drug

Administration–approved drugs to treat COVID-19, and clinical trials are underway to study medications and investigational agents for the treatment of COVID-19, though early clinical trials during public health emergencies often exclude pregnant women. These trials can be accessed at ClinicalTrials.gov.

There are limitations to the type of reports included in this review. First, early case reports of novel infectious disease may be biased toward those with adverse maternal or neonatal outcomes. Definitive conclusions cannot be made regarding absolute or relative risk of illness and death among pregnant women with MERS-CoV, SARS-CoV, or SARS-CoV-2 infection; however, pooled findings may aid hypothesis generation, informing surveillance for adverse outcomes, and developing early recommendations. Second, most descriptions in early case reports were clinical and demographic, with virtually no information regarding PCR testing among the neonates or fetuses, so transplacental transmission cannot be determined. Finally, conclusions cannot be extrapolated from these small numbers of cases because they may not be representative of all cases in the target pregnancy population. Proportions are based on small counts and should be used only for descriptive purposes, with the caveat that the results may be biased.

This review demonstrates that data from case reports of MERS-CoV, SARS-CoV, and SARS-CoV-2 infections during pregnancy reported to date are useful for describing a range of clinical findings but are limited in their utility to estimate risk of adverse outcomes. Timely reporting of pregnancy status as part of surveillance and laboratory testing is important to improve knowledge about emerging threats with potential for adverse pregnancy and neonate outcomes. Additionally, detailed information on timing of exposure, symptom onset, clinical presentation, course of illness, pregnancy and neonatal outcomes, and laboratory results among pregnant women with SARS-CoV-2 infection or COVID-19 needs to be collected in a more consistent manner, with findings rapidly disseminated. These data may directly inform clinical recommendations and guidance on preventive strategies, care, and management of infection and obstetric issues and may affect prioritization of health care resources. Until data from rigorous and systematic studies are available, compiled information from case reports can inform early public health actions and clinical guidance for treating COVID-19 during pregnancy. As we have learned from other recent infectious public health emergencies, it is imperative that we define and capture critical data to better understand how coronavirus infections affect pregnancy.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Each author has confirmed compliance with the journal’s requirements for authorship.

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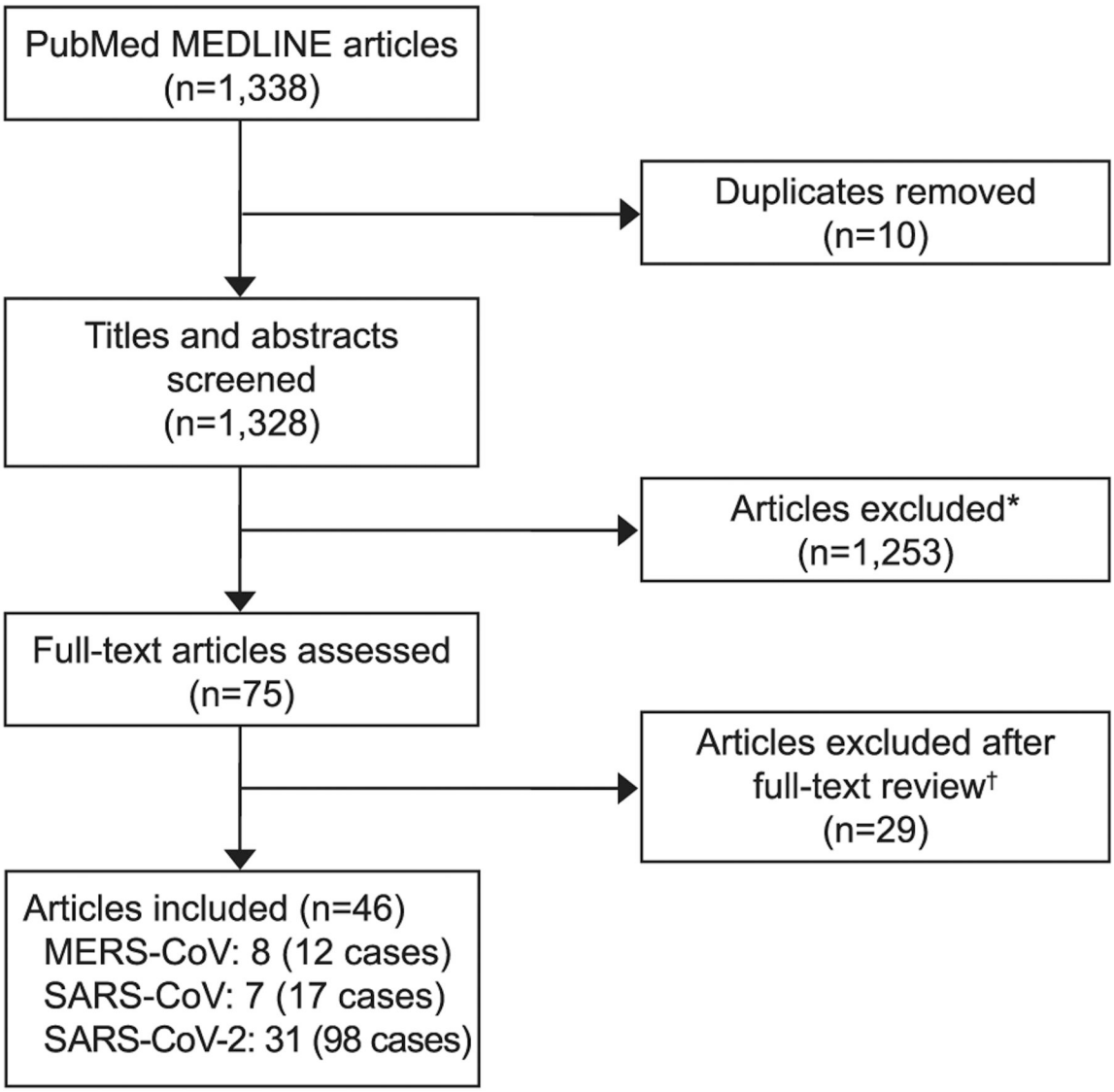

Fig. 1.

Flowchart summarizing literature search and selection process for review of Middle East respiratory syndrome–related coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy. *Reasons for exclusion from title and abstract screening: did not report data related to MERS-CoV, SARS-CoV, or SARS-CoV-2 infection in humans (n=1,083); did not report data among pregnant or postpartum women (n=92); did not report on any exposure, symptoms, course of illness, treatment, maternal outcome, or pregnancy outcome (n=30); review article, dissertation, or management guideline (n=44); and full English text not available (n=4). †Reasons for exclusion after full-text review: case-level data not reported (n=17), population not pregnant women (n=5), review article or management guideline (n=5), reporting of same case (n=1), withdrawn after publication (n=1).

Table 1.

Maternal Characteristics and Clinical Presentation Among Patients With Middle East Respiratory Syndrome Coronavirus, Severe Acute Respiratory Syndrome Coronavirus, and Severe Acute Respiratory Syndrome Coronavirus 2 Infection

	MERS-CoV (n=12)	SARS-CoV (n=17)	SARS-CoV-2 (n=98)
Age (y)	32 (31–38)	32 (26–34)	30 (28–34)
Comorbidities	4/11 (36)	3/4 (75)	19/69 (28)
Health care worker	4/4 (100)	5/12 (42)	2/2 (100)
Type of exposure			
Household	4/12 (33)	4/11 (36)	15/25 (60)
Community	NR	2/11 (18)	7/25 (28)
Health care-associated	1/12 (8)	NR	NR
Occupational	4/12 (33)	5/11 (45)	NR
Unidentified	3/12 (25)	NR	3/25 (12)
GA at symptom onset or diagnosis (completed wk)	24 (21–33)	19 (5–29)	36 (34–38)
Time from symptom onset to presentation for clinical evaluation (d)	5 (3–6)	3 (2–5)	2 (1–4)
Symptoms			
Fever	7/9 (78)	17/17 (100)	76/92 (83)
Myalgia	2/4 (50)	14/14 (100)	5/21 (24)
Malaise	1/3 (33)	12/13 (92)	14/31 (45)
Chills and rigors	1/3 (33)	13/14 (93)	2/21 (10)
Cough	8/9 (89)	13/16 (81)	34/66 (52)
Headache	1/3 (33)	8/14 (57)	4/15 (27)
Shortness of breath	7/8 (88)	6/15 (40)	12/47 (26)
Runny nose	1/3 (33)	4/13 (31)	5/17 (29)
Sore throat	0/2 (0)	2/13 (15)	7/29 (24)
Diarrhea	0/2 (0)	2/12 (17)	5/42 (12)
Chest pain	1/3 (33)	1/12 (8)	1/24 (4)

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NR, not reported; GA, gestation age.

Data are median (interquartile range) or n/N (%).

Table 2.

Laboratory Results and Treatment Received Among Patients With Middle East Respiratory Syndrome Coronavirus, Severe Acute Respiratory Syndrome Coronavirus, and Severe Acute Respiratory Syndrome Coronavirus 2 Infection

	MERS-CoV (n=12)	SARS-CoV (n=17)	SARS-CoV-2 (n=98)
Maternal laboratory results			
Anemia	NR	0/3 (0)	7/24 (29)
Leukocytosis	0/1 (0)	6/15 (40)	12/47 (26)
Lymphopenia	1/1 (100)	10/15(67)	27/50 (54)
Thrombocytopenia	1/1 (100)	6/14 (43)	8/18 (44)
Elevated blood urea nitrogen	1/1 (100)	NR	1/12 (8)
Elevated serum creatinine	1/1 (100)	5/5 (100)	1/17 (6)
Elevated AST	1/1 (100)	1/1 (100)	7/28 (25)
Elevated ALT	1/1 (100)	1/1 (100)	6/28 (21)
Maternal specimen coronavirus testing			
PCR	11/11 (100)	9/15 (60)	98/98 (100)
Antibody testing	1/1 (100)	12/13 (92)	5/5 (100)
Imaging			
Abnormality on chest imaging (X-ray or computerized tomography)	7/7 (100)	16/16 (100)	59/65 (91)
Perinatal specimen coronavirus testing			
Amniotic fluid PCR	NR	0/6 (0)	1/24 (4)
Amniotic fluid antibody testing	NR	0/1 (0)	NR
Cord blood PCR	NR	0/10 (0)	0/24 (0)
Cord blood antibody testing	NR	2/4 (50)	NR
Placental PCR	0/1 (0)	0/12 (0)	0/12 (0)
Breast milk PCR	NR	0/2 (0)	0/8 (0)
Breast milk antibody testing	NR	1/2 (50)	NR
Treatment(s)			
Antibiotics	2/3 (67)	16/16 (100)	46/49 (94)
Antivirals	2/4 (50)	13/15 (87)	43/57 (75)
Intravenous hydrocortisone	0/1 (0)	11/13(85)	1/30 (3)
Methylprednisolone	1/2 (50)	10/13 (77)	12/30 (40)

	MERS-CoV (n=12)	SARS-CoV (n=17)	SARS-CoV-2 (n=98)
Oral prednisolone	0/1 (0)	11/13 (85)	0/29 (0)
Dexamethasone or betamethasone	1/2 (50)	0/1 (0)	4/31 (13)

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NR, not reported; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PCR, polymerase chain reaction.

Data are n/N (%).

Table 3.

Maternal and Newborn Outcomes Among Patients With Middle East Respiratory Syndrome Coronavirus, Severe Acute Respiratory Syndrome Coronavirus, and Severe Acute Respiratory Syndrome Coronavirus 2 Infection

	MERS-CoV (n=12)	SARS-CoV (n=17)	SARS-CoV-2 (n=98)
Duration of hospitalization (d)	19 (13–28)	21 (15–27)	2 (0–17)
Hospitalization events			
Admitted to ICU	7/11 (64)	6/12 (50)	6/42 (14)
Mechanically ventilated	5/9 (56)	7/14 (50)	5/41 (12)
Renal failure	2/4 (50)	4/4 (100)	3/32 (9)
Disseminated intravascular coagulopathy	0/2 (0)	3/3 (100)	0/29 (0)
Sepsis	1/4 (25)	2/3 (67)	1/30 (3)
Maternal death	3/11 (27)	3/17 (18)	1/89 (1)
GA at pregnancy completion (completed wk)	35 (32–38)	31 (26–36)	37 (35–38)
Pregnancy outcome			
Live birth			
GA 37 weeks or more	5/10 (50)	3/17 (18)	57/94 (61)
GA less than 37 weeks	3/10 (30)	6/17 (35)	35/94 (37)
Spontaneous abortion or termination	NR	6/17 (35)	NR
Stillbirth	2/10 (20)	2/17 (12)	2/94 (2)
Route of delivery			
Vaginal	1/5 (20)	10/16 (63)	12/84 (14)
Cesarean	4/5 (80)	6/16 (38)	72/84 (86)
Postpartum hemorrhage	0/1 (0)	0/2 (0)	1/18 (6)
Neonatal death	1/4 (25)	0/6 (0)	1/49 (2)
Neonatal complications *	0/5 (0)	2/10 (20)	17/54 (31)
Neonatal specimen coronavirus testing			
PCR	0/1 (0)	0/7 (0)	7/68 (10)
Antibody testing	0/1 (0)	0/6 (0)	1/13 (8)
Birth weight (g)			
GA 37 weeks or more	3,140 (3,140–3,140)	3,086 (1,985–3,145)	3,250 (3,070–3,530)
GA less than 37 weeks	1,015 (240–1,790)	1,395 (1,035–1,650)	2,570 (2,050–2,890)

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; GA, gestational age; NR, not reported; PCR, polymerase chain reaction.

Data are median (interquartile range) or n/N (%).

* Neonatal complications include those requiring immediate medical intervention after delivery (eg, respiratory distress, necrotizing enterocolitis, patent ductus arteriosus).