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SEVERE CORONAVIRUS INFECTIONS IN PREGNANCY: A SYSTEMATIC REVIEW

Yunike Putri Nurfauzia*

*Faculty of Medicine, General Achmad Yani University, Indonesia

Corresponding Author:
yunikeputrinurfauzia21@gmail.com

Abstract

Introduction: *A systematic literature review was undertaken to examine case reports pertaining to 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 causative agent of COVID-19, in the context of pregnancy.*

Objective: *The objective was to provide a comprehensive overview of the clinical manifestations, disease progression, and outcomes for both pregnant individuals and their neonates.*

Methods: *A comprehensive search was conducted on the MEDLINE and ClinicalTrials.gov databases, covering the period from their establishment up until August 3, 2023. The author incorporated articles that present case-level data about the infection of pregnant women with MERS-CoV, SARS-CoV, and SARS-CoV-2. The course of sickness, markers of severe disease, maternal health outcomes, and pregnancy outcomes were extracted from the articles that were included.*

Results: *A total of 1,328 distinct publications were found, with 1,253 articles being removed based on the evaluation of their titles and abstracts. A comprehensive examination was conducted on a total of 75 publications, out of which 29 papers were deemed ineligible and hence eliminated from the analysis throughout the full-text review process. Out of the 46 papers that provided case-level data, eight publications presented information on 12 instances of MERS-CoV infection, seven publications discussed 17 cases of SARS-CoV infection, and 31 publications detailed 98 cases of SARS-CoV-2 infection. The clinical presentation and progression of the illness varied over a spectrum, ranging from individuals who showed no symptoms to those who experienced severe and ultimately deadly disease. This pattern was consistent with what is typically observed in the broader population of patients. The occurrence of significant morbidity and mortality in women who contract MERSCoV, SARS-CoV, or SARS-CoV-2 during pregnancy has been documented. Adverse pregnancy outcomes such as pregnancy loss, preterm delivery, and laboratory findings indicating vertical transmission have also been recorded.*

Conclusion: *The available data on SARS-CoV, MERS-CoV, and SARS-CoV-2 infections during pregnancy are currently inadequate. However, these data can still provide valuable insights for informing early public health interventions and clinical decision-making in the context of COVID-19. It is important to note that more comprehensive and systematically gathered data are needed to further enhance our understanding of this topic.*

Keywords: *Corona virus, MERS-CoV, SARS-Cov, COVID-19, Pregnancy*

INTRODUCTION

As of 2 August 2023, WHO had received reports of 768,983,095 confirmed cases of COVID-19 worldwide, with 6,953,743 deaths.[1] Infection, serious sickness, and death from respiratory infections may be more common in pregnant women than in the general population.[2] Compared to nonpregnant people, pregnant women may be at a higher risk of more severe disease due to physiological changes such as increased heart rate and oxygen consumption, lower lung capacity, and a shift away from cell-mediated immunity.[3,4]

Seasonal mild respiratory disease is often caused by coronavirus infections. Phylogenetically speaking, the COVID-19 viral strain belongs to the same genus as MERS-CoV and SARS-CoV, which causes the Middle East respiratory illness and severe acute respiratory syndrome, respectively.[5] Both SARS-CoV and MERS-CoV had their first epidemics in the early 2010s and in 2012, respectively. Similar to the MERS-CoV and SARS-CoV, the most prevalent reports of illness from COVID-19 are high body temperature, a hacking cough, and difficulty breathing. Patients have reported experiencing everything from asymptomatic infection to terminal sickness.[6]

Previous outbreaks of other coronaviruses, such as SARS-CoV and MERS-CoV, 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, given the similarities between the three viruses.[5] To summarise the clinical presentation, course of illness, and pregnancy and neonatal outcomes, we undertook a comprehensive literature review to uncover reports of SARSCoV, MERS-CoV, and SARS-CoV-2 infection during pregnant.

Method

Search Strategy

The Prefered Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to guide the methodology of this comprehensive literature evaluation. Finding pregnant women who were infected with MERS-CoV, SARS-CoV, or SARSCoV-2 was the major goal of the search method. The databases of ClinicalTrials.gov and MEDLINE were searched for articles published until August 2, 2023. The phrases "betacoronavir*," "corona virus*," and "coronavi*" were among those entered into MeSH. "covid 19," "covid19," "CoV 2," "CoV2," MERS, or "Middle East Respiratory Syndrome," Words including "MERS," "MERSCoV," "nCoV," "OC43," "respiratory tract infection," "SARS," "SARS Virus," "SARS-CoV," "sarscov2," "Severe Acute Respiratory Syndrome," "wuhan virus*," and "2019nCoV" are used to describe this virus. The following terms were used in our article search to narrow our focus on the population of interest: "conception*," "expectant," "gestat*," "gravid*," "matern*," "mother*," "obstetric*," "parturiency," "pregnan*," "pregnancy complications," "pregnancy trimesters," "pregnant women," and "prenatal care."

Study Selection

Only articles reporting case-level data on MERS-CoV, SARS-CoV, or SARS-COV-2 infection in expectant women were included in the analysis. Excluded were review articles, dissertations, and management guidelines. 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 coronavirusrelated testing of amniotic fluid, placenta, cord blood, breast milk, and neonatal specimens. Not all variables' data were required for inclusion, and data that were unavailable were listed as "not reported."

According to the dichotomous or continuous nature of the data, absolute counts, ranges, medians with interquartile ranges, and percentages were used to describe the information. The case fatality proportion for MERS-CoV, SARS-CoV, and SARS-CoV-2 in pregnant patients was calculated. The analysis of the data was performed with SAS 9.4. Specific maternal fatalities were detailed.

Results

Out of the 1,338 articles that were initially discovered, a total of 10 duplicates were detected and subsequently excluded (see Figure 1). Two reviewers conducted a screening process on titles and abstracts to identify studies that reported cases of MERS-CoV, SARS-CoV, or SARS-CoV-2 infection in pregnant individuals. The discordant conclusions in the review were resolved through a process of conversation between the reviewers. The exclusion of articles was conducted through a review of their titles and abstracts, resulting in the identification of several distinct reasons for exclusion. These reasons were as follows: articles that did not present data pertaining to MERS-CoV, SARS-CoV, or SARS-CoV-2 infection in humans (n=51,083); articles that did not provide data specifically related to pregnant or postpartum women (n=92); articles that did not report on any aspects such as exposure, symptoms, course of illness, treatment, maternal outcome, or pregnancy outcome (n=30); articles categorised as review articles, dissertations, or management guidelines (n=44); and articles that were not available in full English text (n=4).

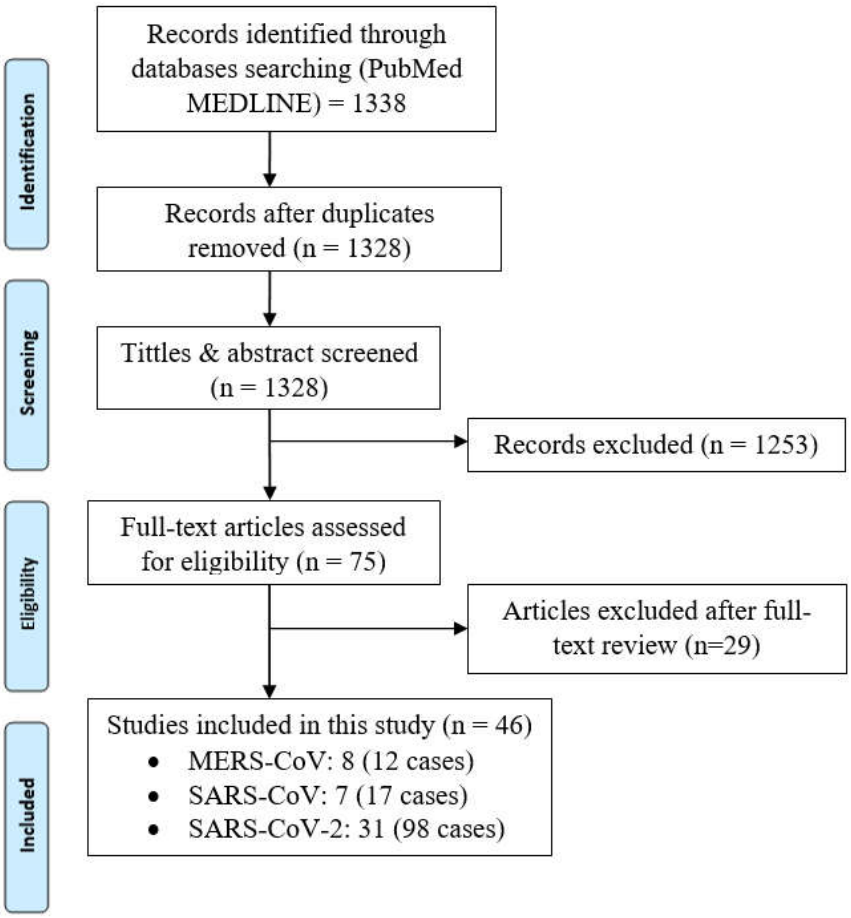

Figure 1. The search strategy based on PRISMA flow diagram

A comprehensive examination was conducted on a total of 75 articles in order to identify studies that had case-level data. A total of twenty-nine articles were excluded from the study. Among these, five were review articles or management guidelines, seventeen did not provide case-level data, five did not report data specifically among pregnant or postpartum women, one article provided data for the same patients as another included article without any additional details, and one article was withdrawn after publication. Out of the 46 articles that have documented primary case-level data on coronavirus infections during pregnancy, eight publications have provided details on 12 instances of MERS-CoV infection in pregnant individuals. Additionally, seven publications have described 17 cases of SARS-CoV infection, while 31 publications have reported on 98 cases of SARS-CoV-2 infection.[7–26]

Table 1. Comparison of Maternal Characteristics and Clinical Presentation among infection with MERS-CoV, SARS-CoV, and SARS-Cov-2

	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 findings and treatment among infection with MERS-CoV, SARS-CoV, and SARS-Cov-2

	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)
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 (%).

Within a cohort of 12 pregnant individuals diagnosed with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection, the age distribution spanned from 26 to 31 years, with a median age of 32 years and an interquartile range of 31 to 38 years. The gestational age at which symptoms first appeared or the diagnosis was made in pregnant individuals varied from 4 to 38 completed weeks, with a median of 24 weeks and an interquartile range of 21 to 33 weeks. Among the participants, two women experienced symptoms or were diagnosed in the first trimester, five in the second trimester, and five in the third trimester (Table 1). The study identified the source of exposure for nine individuals, which included interaction with family members who had proven MERS-CoV infection (n=54), acquiring the illness in a healthcare setting (n=51), and occupational exposure as a healthcare worker (n=54). Symptoms were documented in a cohort of 11 patients, with the following frequencies: fever (n=57), chills or rigours (n=51), myalgia (n=52), malaise (n=51), cough (n=58), shortness of breath (n=57), and chest pain (n=51). A single pregnant lady was identified as being asymptomatic, but underwent screening for MERS-CoV infection as a component of public health contact-tracing efforts.[7]

Table 3. Effects on Mothers and Infants of Coronavirus Infection During Pregnancy and Childbirth in Patients With MERS, SARS, and SARS-Cov-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).

The laboratory test findings pertaining to MERS-CoV were documented for a total of 12 individuals, as presented in Table 2. The detection of MERS-CoV infection was accomplished through the utilisation of MERS-CoV antibody testing, specifically employing enzyme immunoassay (EIA) with a positive result that was subsequently confirmed by either immunofluorescence assay or microneutralization titer assay. It is worth noting that the timing of specimen collection in relation to the onset of illness was not reported in this particular case.[20] The presence of Middle East respiratory syndrome coronavirus nucleic acid was identified in 11 female individuals by the utilisation of reverse transcription polymerase chain reaction (RT-PCR) technique. The specimens were taken between a period of 2 to 10 days following the manifestation of symptoms.[8,13,19–21] The study involved the analysis of chest imaging results, namely radiographs and computed tomography scans, obtained from a sample of seven female participants. The findings revealed the presence of lower lobe opacity in 52 cases, bilateral infiltration in 52 cases, bronchopneumonia in 52 cases, bilateral consolidation in 51 cases, and pneumonia in 51 cases.[8,11,19–21]

In Table 2, it is observed that two female individuals were administered a mixture of antibiotics, such as macrolides, cephalosporins, carbapenems, and glycopeptides, as well as antiviral drugs, such as ribavirin, oseltamivir, interferonalpha-2b, and peginterferon-alpha, as part of their therapy, as described in four separate reports. Additionally, a pregnant individual was administered dexamethasone to facilitate the development of foetal lungs in preparation for an expected premature delivery at 32 weeks of gestation due to the deteriorating clinical condition of the mother. Table 3 presents data on the health status of seven pregnant women, indicating the occurrence of severe sickness. Specifically, the reported cases include ICU hospitalisation for 57 individuals, mechanical ventilation for 55 individuals, renal failure for 52 individuals, and septic shock for 51 individuals. Out of the 11 women for whom outcome data was accessible, three experienced mortality while hospitalised after giving birth. Specifically, one death occurred during the second trimester of pregnancy, while the remaining two deaths occurred during the third trimester. This corresponds to a case fatality proportion of 27%, as indicated in Table 3. The available studies did not provide enough data to adequately illustrate the relationship between survival from MERS-CoV infection and the progression of the illness, as well as the time of initiating medical therapy.

Among the three instances of maternal mortality, the individuals affected were between the ages of 31 and 32. Notably, one of the women had a pre-existing pulmonary condition, specifically asthma, pulmonary fibrosis, and recurrent spontaneous pneumothoraces. The gestational age at presentation varied between 24 and 38 completed weeks. The duration between the beginning of symptoms and hospitalisation ranged from four to seven days. Intubation was necessary for all three female individuals due to the presence of acute respiratory distress. The fatalities transpired 17 days subsequent to the manifestation of symptoms, characterised by a culture-negative determination of septic shock. Additionally, deaths happened 27 days after symptom onset due to the failure of several organs, and 43 days after symptom onset as a result of refractory hypoxia and cardiac arrest.[19,21]

Out of a total of eight pregnancies that led to the successful delivery of liveborn neonates, three neonates were delivered via emergency caesarean section during the gestational period of 25 to 32 weeks. This intervention was necessary due to the critical respiratory condition of the mothers, who required mechanical ventilation.[8,19,21] A single neonate expired immediately following birth.[19] The remaining five neonates who were born alive were delivered at gestational ages

ranging from 37 to 40 weeks. One of these deliveries was an emergency caesarean section performed due to placental abruption, while the other four deliveries did not have any documented obstetric difficulties (see Table 3).

A total of five infants were observed to exhibit a healthy appearance, with no discernible clinical indications of MERS-CoV infection.[7,19,21] The neonate underwent consecutive RT-PCR testing of serum and nasopharyngeal samples, as well as antibody testing using enzyme-linked immunosorbent assay, indirect immunofluorescence testing, and plaque reduction neutralisation testing. All MERS-CoV tests yielded negative results for the baby (Table 3).[20]

One of the reported stillbirths took place when the lady was 21 weeks pregnant, which was 7 days after she started experiencing symptoms. The mother, who was previously in good health and had given birth to six healthy babies at full term in the past, was 39 years old at the time. The female individual exhibited symptoms of acute respiratory disease, although hospitalisation was not deemed necessary.[22] The occurrence of the second stillbirth took place during the 34th week of gestation in a 34-year-old woman who had previously experienced six successful deliveries and had no known health issues. The patient in question was admitted to the hospital three days subsequent to the onset of dyspnea. Following a thorough examination, the patient was diagnosed with preeclampsia, pneumonia, and the unfortunate occurrence of stillbirth.[19] No assessment of alternative factors contributing to stillbirth was reported in either of these cases (Table 3).

In the study sample, there were a total of 17 pregnant women who tested positive for SARS-CoV infection. The age distribution of these women ranged from 24 to 44 years, with a median age of 32 years and an interquartile range of 26 to 34 years, as shown in Table 1. The gestational age at which symptoms first appeared or were diagnosed varied between 3 and 32 completed weeks, with a median of 19 weeks and an interquartile range of 5 to 29 weeks. Among the pregnant women included in the study, eight experienced symptoms in the first trimester, three in the second trimester, and six in the third trimester. The study identified the source of exposure in a total of 11 patients. Among these patients, the reported sources of exposure included interaction with family members who had proven SARSCoV infection (n=4), community exposure (n=2), and occupational exposure as a healthcare worker (n=5). Seventeen patients presented with various symptoms, including fever (n=17), chills or rigours (n=13), myalgia (n=14), malaise (n=12), cough (n=13), shortness of breath (n=6), chest pain (n=1), and diarrhoea (n=2). The duration between the onset of symptoms and the time at which patients sought clinical examination was examined in a sample of 16 individuals. This interval varied between 0 and 11 days.

The laboratory findings pertaining to SARS-CoV were documented for all 17 individuals, as presented in Table 2. The detection of SARS-CoV infection was accomplished through the utilisation of SARS-CoV serology testing, specifically the EIA method, which yielded positive results in correlation with either the immunofluorescence assay or the enzyme-linked immunosorbent assay. This testing approach identified infection in a total of eight women, whose specimens were collected between 12 and 28 days after the onset of symptoms. Additionally, the detection of infection in five women was solely achieved through the use of RT-PCR, although the timing of specimen collection in relation to the onset of illness was not specified. Furthermore, four women were identified as infected through both serology testing and RT-PCR, with positive results obtained from both tests. Notably, in one of these cases, the specimen was collected 29 days after the onset of symptoms.[9,10,12,23–26] The presence of severe acute respiratory syndrome coronavirus nucleic acid was identified in the cerebrospinal fluid of a pregnant woman at 30 weeks of gestation. This woman had a history of generalised tonic-clonic convulsions on day 29 after the commencement of symptoms, which occurred on hospital day 22. The detection of the virus was achieved using reverse transcription polymerase chain reaction (RT-PCR) methodology.[12] Among the cohort of 16 female individuals who underwent chest imaging, the results indicated the presence of pneumonia in 5 cases, diffuse or patchy infiltrates in 3 cases, and patchy consolidations in 1 case.[9,10,12,23,25,26] Out of the 16 patients for whom treatment information was accessible, it was observed that all of them were administered antibiotics such as azithromycin, broad-spectrum antibiotics, beta-lactams, macrolides, and fluoroquinolones. Additionally, 12 patients were subjected to antiviral treatment using ribavirin, while one patient received oseltamivir. Furthermore, 12 patients underwent corticosteroid therapy, which involved the administration of hydrocortisone, dexamethasone, or methylprednisolone. This information is summarised in Table 2. Six women experienced severe sickness that necessitated hospitalisation to the intensive care unit (ICU), while mechanical breathing was necessary for seven women, as seen in Table 3. The occurrence of renal failure (n=4), disseminated intravascular coagulation (n=3), and septic shock (n=2) was documented. Three female individuals expired while under medical care at the hospital, with one of them being infected with SARS-CoV during the initial trimester of pregnancy, and the other two succumbing during the final trimester. The case fatality proportion for these cases was determined to be 18%. The study detected instances of severe sickness and maternal mortality in both the group of women who received antibiotics, antiviral medication, and corticosteroid therapy, as well as the group of women who did not get these interventions. The available reports did not provide enough data to adequately explain the clinical outcomes in relation to the timing of symptom onset, the intensity of symptoms, and the beginning of medical treatment.

Within the context of the two publications under consideration, a total of three maternal deaths have been documented. These unfortunate incidents involved women who were between the ages of 34 and 44. Additionally, the gestational age of the pregnancies in question varied between 5 and 32 completed weeks. The duration between the beginning of symptoms and hospitalisation ranged from 5 to 7 days. The medical consequences observed in this study encompassed a

range of conditions, such as respiratory distress, secondary bacterial pneumonia, sepsis, disseminated intravascular coagulation, renal failure, cardiovascular collapse, abdominal wound dehiscence, and surgical emphysema. All three female patients were admitted to the Intensive Care Unit (ICU) and necessitated the use of mechanical ventilation. Progressive respiratory failure led to the occurrence of two fatalities. A female individual succumbed to circulatory collapse resulting from pneumonia caused by methicillin-resistant Staphylococcus aureus, 19 days after the manifestation of symptoms. The publications did not provide any information regarding medical comorbidities, the timing of medical problems or maternal death in relation to the onset of symptoms or the date of hospital admission.[25,26] A total of four emergency caesarean deliveries were performed over the gestational period ranging from 26 to 36 weeks due to the critical respiratory condition of the mothers. These deliveries led to the birth of three neonates who survived, while one neonate was unfortunately stillborn.[24–2612] Two neonates were born at 37 and 38 weeks of gestation via caesarean section due to nonreassuring foetal heart tracing and full placenta previa, respectively (Table 3).[23,24,26]

There were a total of four instances in which pregnancies resulted in pregnancy loss occuring between the gestational period of 5 to 10 weeks.[26]20 In each instance of these pregnancies, the pregnant individuals exhibited symptoms such as fever, chills, and rigour. Subsequently, the loss of pregnancy took place within a timeframe of 2 to 5 weeks following the onset of these symptoms. Three female individuals received the procedure of pregnancy termination, as indicated in Table 3.[10,26]

There were no instances of infant mortality reported. Nevertheless, two preterm neonates experienced problems, which included respiratory distress syndrome (n=2), intestinal perforation (n=1), patent ductus arteriosus (n=1), and necrotizing enterocolitis (n=1).[24,26] A single infant born prematurely exhibited signs of fever 12 days following birth and received treatment involving the administration of broad-spectrum antibiotics and ribavirin. The fever subsided within a 24-hour period, and laboratory analyses of the blood and cerebrospinal fluid indicated no evidence of bacterial growth. The neonate's SARS-CoV testing was not documented as being conducted, as indicated in Table 3.

A total of nine infants were observed to be in a healthy state, exhibiting no clinical signs of SARS-CoV infection.[9,23,25,26] No instances of SARS-CoV infection were identified in six newborns who underwent RT-PCR testing on nasal swab, blood, urine, and stool samples, as well as antibody testing using enzyme immunoassay (EIA).[26] The absence of SARS-CoV infection was seen in a neonate who underwent RTPCR testing of nasopharyngeal and throat swabs, gastric aspirate, urine, and meconium (Table 3).[9]

Within the cohort of 98 pregnant individuals who tested positive for SARS-CoV-2 infection, their ages spanned from 22 to 44 years, with a median age of 30 and an interquartile range of 28–34. The study included 96 pregnant women, with gestational ages ranging from 25 to 41 completed weeks. The median gestational age at the time of symptom start or diagnosis was 36 weeks, with an interquartile range of 34 to 38 weeks. Out of the total participants, one woman presented with symptoms in the second trimester, while the remaining 95 women presented in the third trimester. The study identified and reported the source of exposure in a total of 22 individuals. Among these patients, 15 had contact with family members who had proven SARS-CoV-2 infection, whereas 7 had exposure within the community. Two pregnant individuals who were employed in the healthcare sector and had relatives who tested positive for SARS-CoV-2 were included in the study. However, the available data did not provide enough information to establish the main source of exposure for their infections. No identification was made regarding the exposure of any of the women during the provision of healthcare services.

Symptoms were observed in the entirety of the 98 patients included in the study. These symptoms included fever (n=76), chills or rigours (n=2), myalgia (n=5), malaise (n=14), cough (n=34), shortness of breath (n=12), chest discomfort (n=1), and diarrhoea (n=5). The patient had gastrointestinal-related abdominal pain.[27] The study included a sample of 25 patients, and the duration between the onset of symptoms and the time of seeking professional examination was examined. The median number of days was found to be 2, with an interquartile range of 1 to 4 days. The range of days varied from 0 to 12.

The laboratory test findings for SARS-CoV-2 obtained from respiratory specimens of the mother population were documented for all 98 individuals. The presence of SARS-CoV-2 infection was identified only using RT-PCR in 93 female individuals, who had provided specimens within 0-11 days from the commencement of their illness. Additionally, in five women, both serology testing and RT-PCR yielded positive results, with specimens obtained 2–7 days following the onset of symptoms.[14,27–31] The study included a cohort of 65 female participants who underwent chest imaging. The results of the imaging revealed the presence of ground glass opacities in 52.7% of the cases, pneumonia in 51.9% of the cases, diffuse or patchy infiltrates in 5.5% of the cases, and patchy consolidations in 5.1% of the cases.[14–18,27–29,31–43]

Out of the 46 patients for whom treatment information was available, all of them were administered antibiotics. These antibiotics included various combinations of carbapenems, fluoroquinolones, cephalosporins, macrolides, glycopeptides, aminoglycosides, aminoquinolines, penicillins, and antiprotozoals. Additionally, 43 of these patients received antiviral treatment, which consisted of combinations of oseltamivir, lopinavir–ritonavir, umifenovir, interferon, ganciclovir, remdesivir, or ribavirin. Furthermore, corticosteroid therapy was administered to 17 patients, with the corticosteroids

used being hydrocortisone, dexamethasone, or methylprednisolone. This information is summarised in Table 2. The study detected a high prevalence of severe sickness in both groups of women, regardless of whether they received antibiotics, antiviral treatment, or corticosteroid therapy. The existing studies did not provide enough data to adequately explain the clinical outcomes in relation to the timing of symptom onset, the severity of symptoms, and the beginning of medical treatment.

Six women experienced a severe sickness that necessitated admission to the intensive care unit (ICU), while five women required mechanical breathing, as indicated in Table 3. Additional problems that were observed in the study were renal failure (n=4) and septic shock (n=2). A female patient who was in the advanced stage of pregnancy, specifically the third trimester, experienced a tragic outcome during her hospitalisation, resulting in a case fatality proportion of 1% (Table 3). The female individual was 22 years old and in her 32nd week of gestation. She had a pre-existing condition of hypothyroidism and was admitted to the hospital four days following the onset of symptoms. The patient was admitted to the Intensive Care Unit (ICU) in order to get respiratory assistance. Subsequently, mechanical ventilation was initiated, and peritoneal dialysis was administered. The female individual succumbed of serious sickness, which was not further defined in the report, 24 days following the commencement of symptoms.[41]

Out of a cohort of 94 women who were diagnosed with SARS-CoV-2 infection and had completed pregnancies at the time of publication, a total of 52 neonates were delivered via emergency caesarean section at gestational ages ranging from 29 to 40 weeks. A total of four neonates were delivered with the primary objective of implementing infection-control measures for SARSCoV-2.[27] Nineteen neonates were born due to maternal indications, 17 were delivered due to foetal distress, and 12 were delivered for other obstetric indications. The maternal indications encompassed several conditions, such as declining respiratory status (n=6), coagulopathy (n=2), preeclampsia (n=5), transaminitis (n=2), and unspecified acute sickness (n=4).[14,15,18,27,29,39,41,44–47] Additional obstetric indications comprised of previous caesarean delivery or uterine scarring (n=4), preterm prelabor rupture of membranes (n=2), placental abnormalities (n=2), placental abruption (n=1), irregular labour progression (n=52), and gestational diabetes (n=1).[15–17] A total of three neonates were delivered following spontaneous preterm labour occuring between 32 and 34 weeks of gestation. Additionally, nine neonates were delivered through spontaneous vaginal delivery between 37 and 40 weeks of gestation, as indicated in Table 3.[17,18,43,48]

Two instances of foetal demise occurred at 34 and 35 weeks of gestation, respectively, following two pregnancies.[31,49] In each of these instances of pregnancy, the women encountered a severe medical condition marked by failure in several organ systems and the onset of acute respiratory distress syndrome, necessitating the use of mechanical ventilation. Both female individuals were provided with respiratory assistance through the use of extracorporeal membrane oxygenation, as indicated in Table 3.[31,49]

A single instance of neonatal mortality was documented in a neonate who was born via caesarean section at 34 weeks of gestation due to foetal discomfort. The newborn had satisfactory condition upon delivery, however, experienced respiratory distress approximately 30 minutes postpartum. The baby was provided with breathing assistance and afterwards, over a span of 8 days, experienced refractory shock, gastrointestinal haemorrhage, multisystem organ failure, and disseminated intravascular coagulopathy, ultimately resulting in mortality. The neonatal screening conducted on the ninth day following birth did not yield any positive results for the presence of viral RNA associated with SARS-CoV-2 infection.[50]

A total of seven term neonates experienced various complications, which consisted of fever (n=3), vomiting or feeding intolerance (n=3), increased work of breathing without specified cause (n=2), radiographic confirmation of pneumonia (n=2), being small for gestational age (n=2), lethargy (n=2), diffuse rash (n=1), and a slight elevation in myocardial enzymes without accompanying symptoms (n=1). A total of 10 preterm neonates experienced various complications, which encompassed respiratory difficulty without specified aetiology (n=3), radiographic confirmation of pneumonia (n=2), respiratory distress syndrome (n=2), fever (n=1), gastrointestinal bleeding and coagulopathy (n=2), fever (n=1), feeding intolerance (n51), small for gestational age (n=1), and multiorgan failure (n=1). A total of seventy-two newborns were observed to exhibit a healthy appearance and showed no clinical indications of being infected with SARS-CoV-2, as indicated in Table 3.

The presence of RNA from the severe acute respiratory syndrome coronavirus 2 was identified in 7 out of 68 newborns who underwent RT-PCR testing, as indicated in Table 3. One out of thirteen newborns who underwent serology testing, which involved the use of solid-phase immunochromatographic assay or chemiluminescence immunoassay, exhibited the presence of immunoglobulin M and G antibodies.[28] The presence of severe acute respiratory syndrome coronavirus 2 RNA was observed in one out of twenty-four samples of amniotic fluid, but no traces of the virus were found in cord blood, placental, or breast milk samples (refer to Table 2).

Discussion

There is a scarcity of comprehensive data about the impact of MERS-CoV, SARS-CoV, and SARS-CoV-2 infections on pregnant individuals. Nonetheless, there is a growing body of evidence highlighting parallels in the clinical progression and disparities in outcomes among these illnesses. The clinical presentations of coronavirus infections during pregnancy

span from asymptomatic or moderate illness to severe or deadly disease, comparable to the spectrum observed in cases of infection among individuals who are not pregnant.[6] The occurrence of severe morbidity and mortality was predominantly observed among pregnant individuals throughout the second and third trimesters of gestation. These findings exhibit similarities to other respiratory infectious illnesses.[51,52] There were no documented results observed in patients with SARS-CoV-2 infections during the first trimester. Women who experienced MERS-CoV, SARS-CoV, or SARS-CoV-2 infection throughout their pregnancies exhibited unfavourable pregnancy outcomes, such as pregnancy loss, premature births, and infants with low birth weight.

Within the limited number of cases included in this analysis, it was observed that the case fatality rates for MERS-CoV and SARS-CoV infections in pregnant women were notably elevated, standing at 27% and 18% respectively, mirroring the rates observed in the broader community.[26,53] The case fatality proportion for pregnant women infected with SARS-CoV-2 was found to be 1%, a figure that falls within the range of 1.8-3.4% seen in the general population.

No instances of mother-to-child transmission of MERS-CoV or SARS-CoV were detected in the limited number of pregnancies and newborns included in this study. In contrast, the presence of SARS-CoV-2 RNA was observed in seven neonates, but immunoglobulin M antibodies were found in only one neonate. Furthermore, a single report has indicated the presence of SARS-CoV-2 RNA in amniotic fluid. The available case reports provide preliminary evidence indicating the potential for vertical transmission of SARS-CoV-2. However, other uncertainties persist, such as the precise level of risk, clinical implications, and the specific mode of transmission (e.g., transplacental, intrapartum, or respiratory droplet postpartum).

The treatment regimens administered to patients with MERS-CoV, SARS-CoV, and SARS-CoV-2 exhibited variability and encompassed a combination of antibiotics, antiviral medications, and corticosteroids. Variability in therapy may be anticipated during the initial stages of an outbreak, particularly in cases when clinical trial data is not yet accessible. The treatment guidelines for patients with COVID-19 have been prepared by the National Institutes of Health (NIH) with the purpose of providing doctors with informed recommendations on patient care. These guidelines are regularly updated to incorporate the latest available evidence.[54] Currently, there is a lack of pharmaceuticals approved by the U.S. Food and Drug Administration (FDA) for the treatment of COVID-19. However, ongoing clinical trials are being conducted to investigate the efficacy of various medications and investigational agents in managing COVID-19. It is worth noting that pregnant women are generally excluded from early clinical trials conducted during public health emergency.

This review encompasses a restricted range of reports. Initially, it is important to acknowledge that early case reports of emerging infectious diseases may exhibit a certain degree of bias towards instances characterised by unfavourable maternal or newborn outcomes. It is not possible to draw definitive conclusions about the absolute or relative risk of illness and death among pregnant women with MERS-CoV, SARS-CoV, or SARSCoV-2 infection. However, combining the findings from multiple studies can help generate hypotheses, provide information for monitoring negative outcomes, and guide the development of early recommendations. Furthermore, it is worth noting that the majority of early case reports mostly consisted of clinical and demographic descriptions, without substantial details pertaining to polymerase chain reaction (PCR) testing conducted on neonates or foetuses. Consequently, the possibility of transplacental transmission cannot be definitively ascertained based on the available evidence. Ultimately, it is not possible to draw general conclusions from these limited case studies due to their potential lack of representativeness for the broader population of pregnancies under consideration. Proportions are derived from limited sample sizes and should be employed just for descriptive intents, acknowledging the potential presence of bias in the obtained outcomes.

This review illustrates that the available data from case reports on MERS-CoV, SARS-CoV, and SARS-CoV-2 infections in pregnant individuals have been valuable in characterising various clinical observations. However, their usefulness in accurately estimating the likelihood of negative consequences is constrained. The prompt emphasises the need of promptly reporting pregnancy status as a component of monitoring and laboratory testing. This practise is crucial for enhancing our understanding of developing risks that may have detrimental effects on both pregnancy and newborn health. Furthermore, it is imperative to gather comprehensive data regarding the timing of exposure, onset of symptoms, clinical manifestations, progression of the disease, pregnancy outcomes, neonatal outcomes, and laboratory findings in pregnant women affected by SARS-CoV-2 infection or COVID-19. This data should be collected in a standardised and consistent manner, and the findings should be promptly shared and disseminated. The information provided by this data has the potential to significantly impact clinical recommendations and guidance for preventative strategies, treatment, and management of infection and obstetric issues. Additionally, it may also influence the prioritisation of health care resources. In the absence of comprehensive and methodical investigations, the utilisation of aggregated data from case reports might provide valuable insights for informing initial public health interventions and clinical recommendations pertaining to the management of COVID-19 in pregnant individuals. As evidenced by previous instances of viral public health crises, it is of utmost importance to establish clear definitions and gather essential data in order to enhance our comprehension of the impact of coronavirus infections on pregnancy.

Conclusion

It is crucial to ascertain whether pregnant women are susceptible to experiencing unfavourable maternal and neonatal consequences as a result of severe coronavirus infections. The available data on SARS-CoV, MERS-CoV, and SARS-

CoV-2 infections during pregnancy are currently inadequate. However, these data can still provide valuable insights for informing early public health interventions and clinical decision-making in the context of COVID-19. It is important to note that more comprehensive and systematically gathered data are needed to further enhance our understanding of this topic. The acquisition of essential data is necessary in order to more accurately delineate the impact of this virus on pregnant women and newborns.

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