

Human Coronavirus Infections and Pregnancy

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Abstract

Human coronavirus (HCoV) causes potentially fatal respiratory disease. Pregnancy is a physiological state that predisposes women to viral infection. In this review, we aim to present advances in the pathogenesis, clinical features, diagnosis, and treatment in HCoV in pregnancy. We retrieved information from the Pubmed database up to June 2020, using various search terms and relevant words, including coronaviruses, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, 2019 coronavirus disease, and pregnancy. Both basic and clinical studies were selected. We found no evidence that pregnant women are more susceptible to HCoV infection or that those with HCoV infection are more prone to developing severe pneumonia. There is also no confirmed evidence of vertical mother-to-child transmission of HCoV infection during maternal HCoV infection. Those diagnosed with infection should be promptly admitted to a negative-pressure isolation ward, preferably in a designated hospital with adequate facilities and multi-disciplinary expertise to manage critically ill obstetric patients. Antiviral treatment has been routinely used to treat pregnant women with HCoV infection. The timing and mode of delivery should be individualized, depending mainly on the clinical status of the patient, gestational age, and fetal condition. Early cord clamping and temporary separation of the newborn for at least 2 weeks is recommended. All medical staff caring for patients with HCoV infection should use personal protective equipment. This review highlights the advances in pathogenesis, maternal-fetal outcome, maternal-fetal transmission, diagnosis and treatment in HCoV including severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, and coronavirus disease 2019 in pregnancy.

Keywords: Coronavirus; COVID-19; MERS-CoV; Pregnancy; SARS-CoV; SARS-CoV-2

Introduction

Human coronaviruses (HCoV) are a diverse group of viruses capable of infecting humans. HCoV are the second most prevalent cause of the common cold (rhinoviruses are the first). HCoV infections are transmitted through droplets, aerosols, and close contact. Most patients have asymptomatic infection or mild symptoms and good prognosis after infection. Some patients develop severe disease and die from multi-organ failure, including respiratory, gastrointestinal (GI), hepatic, and neurological complications.¹⁻⁴ Asymptomatic carriers could acquire

and transmit coronavirus disease 2019 (COVID-19).⁵ Some types of HCoV have caused outbreaks of severe acute respiratory syndrome (SARS) caused by SARS-CoV, Middle East respiratory syndrome caused by MERS-CoV and COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁶⁻⁹

The fatality rates of SARS, MERS, and COVID-19 are 10%, 35%–38%, and 5.6%, respectively.¹⁰⁻¹³ Poor prognostic factors include advanced age; viral loads; overweight or obese; and comorbidities such as hypertension, diabetes, and coronary heart disease.^{14,15} HCoV infection in pregnancy may be potentially life-threatening, representing complicated management issues for the mother and fetus.¹⁶⁻¹⁸ In the current review, we mainly discuss the three highly lethal and contagious HCoV infections, SARS-CoV, MERS-CoV, and SARS-CoV-2 infection.

Virology

Coronaviruses (CoVs) were so named because, when viewed by electron microscopy, they have club-shaped surface projections that give them a crown-like appearance. The Coronaviridae family includes two subfamilies: Coronavirinae and Torovirinae. HCoV are single-stranded positive-sense RNA viruses with a genome of approximately 30 kb, the largest genome among RNA viruses. HCoV are divided into four genera: alpha, beta, gamma, and delta HCoV, two of which contain viruses infecting humans. The beta genus is further subdivided into four lineages, A-D. Seven HCoV were identified. Four commonly detected HCoV are NL63 and 229E, which belong to the alpha-coronavirus genus, and OC43 and

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HCoV, which belong to the beta-coronavirus genus. The other three HCoVs, SARS-CoV, MERS-CoV, and SARS-CoV-2, belong to the beta-coronavirus genus and are the major causes of severe pneumonia in humans.^{8,19,20} The virus contains five structural proteins: the spike or S protein, the haemagglutinin-esterase protein, the M (matrix) protein, the E (envelope) protein, and the N (nucleocapsid) protein. HCoV cause a wide range of human respiratory, GI, neurological, and systemic illnesses.²⁻⁴ Figure 1 shows the coronavirus taxonomy and related diseases.²¹

Pathogenesis

SARS-CoV-2 and SARS-CoV use the angiotensin converting enzyme 2 receptor to facilitate viral entry into target cells.²²⁻²⁴ Dipeptidyl peptidase 4, which is found on the surface of cells in the lungs, kidneys, small intestine, T lymphocytes, and macrophages, is a functional receptor for MERS-CoV.²⁵ All the three highly lethal CoVs (SARS-CoV, MERS-CoV, SARS-CoV-2) induce excessive and aberrant non-effective host immune responses that are associated with severe lung pathology, which can lead to death.²⁶

In the acute phase of HCoV infection, rapid reduction of lymphocytes in peripheral blood, mainly T lymphocytes, is observed, and both CD4+ and CD8+ T lymphocytes are decreased. The loss of lymphocytes even precedes abnormal changes on chest X-ray.

HCoV-specific immunoglobulin G (IgG) antibodies are produced in the late acute stage for approximately 2 weeks and gradually increase with the course of the disease. Recovering patients have high and sustained levels of specific neutralizing antibody responses, which may play an important role in determining disease outcome. In the course of disease progression, patients may have increased pro-inflammatory cytokine and chemokine secretion levels, which peak in the early stage of recovery and gradually decrease with the progression of the disease.²⁷⁻³⁰

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection. The main pathologic findings from the lungs of fatal cases of

COVID-19 pneumonia include hyaline membrane formation, fibrin exudates, epithelial damage, and diffuse type II pneumocyte hyperplasia, which are all features of diffuse alveolar damage and bacterial pneumonia in some patients.³¹⁻³³

Jiang *et al.* found SARS-specific immunoglobulin G antibody in the maternal blood, umbilical cord blood, and amniotic fluid of a pregnant SARS patient and suggested potential protection of the fetus from infection. No SARS-CoV genes were detected in the maternal blood, umbilical blood, or amniotic fluid of the patient when using a SARS virus fluorescence quantitative PCR diagnostic kit.³⁴

Maternal-fetal outcome

Pneumonia, an important non-obstetric infectious condition, is an important cause of morbidity and mortality among pregnant women.^{35,36}

Lam *et al.* compared 10 pregnant and 40 non-pregnant women with SARS. Four out of the 10 pregnant patients required endotracheal intubation, and six were admitted to the intensive care unit (ICU), compared with a 12.5% intubation rate and 17.5% ICU admission rate in the non-pregnant group. More pregnant patients with SARS than non-pregnant patients with SARS developed renal failure and disseminated intravascular coagulopathy. There were three deaths in the pregnant group, whereas there were no deaths in the non-pregnant control group. The authors concluded that pregnant women with SARS experience a worse clinical course and poorer outcomes than non-pregnant women.³⁷ SARS acquired during pregnancy carried a case fatality rate of 25% and was associated with a high incidence of spontaneous miscarriage, preterm delivery, and intrauterine growth retardation.⁴

The most common adverse obstetrical outcomes associated with maternal pneumonia from all causes include premature rupture of membranes and preterm labor, intrauterine fetal demise, intrauterine growth restriction (IUGR), and neonatal death.³⁴ Pregnancy with SARS is associated with a high incidence of adverse maternal and neonatal complications, such as spontaneous miscarriage, preterm delivery, IUGR, necessity for endo-

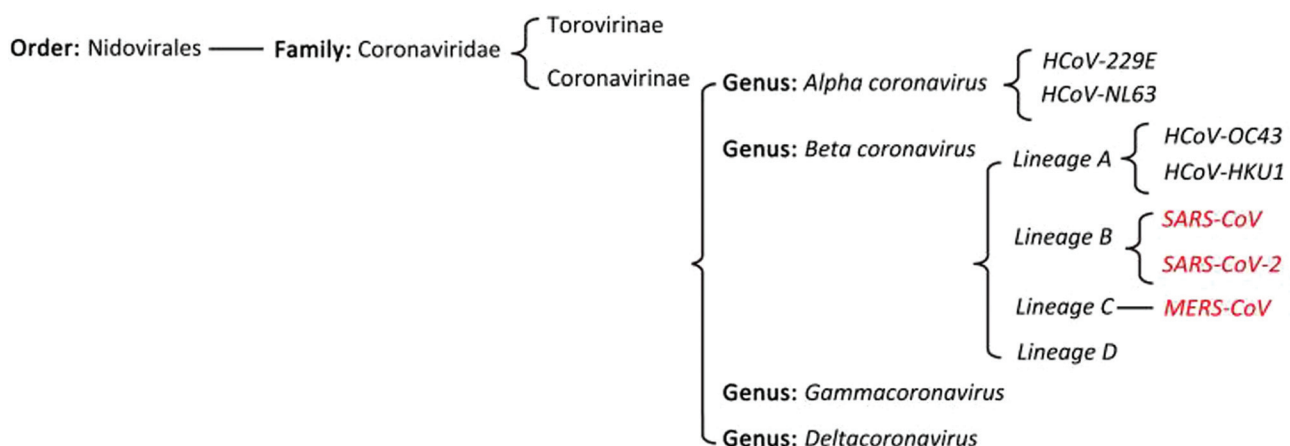


Figure 1. Coronavirinae taxonomy. CoV: Coronavirus; COVID-19: Coronavirus disease 2019; HCoV: Human coronaviruses; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome.

tracheal intubation, admission to the ICU, renal failure, and disseminated intravascular coagulopathy.^{37,38} Assiri *et al.* reported five pregnant patients with MERS based on a retrospective study, and all experienced adverse outcomes. Ages of patients ranged from 27 to 34 years, with the occurrence of exposure in either the 2nd or 3rd trimester. All five patients received intensive care. Two women died, and there were two cases of perinatal death: one stillbirth and one neonatal death shortly after emergency cesarean section.³⁹ Fassett *et al.* screened SARS-CoV-2 in 3923 women delivered during the study period and found 17 (0.43%) women positive. None of them were symptomatic on admission.⁴⁰

Chen reported 118 cases of women with COVID-19 and found 8% (nine cases) was severe disease. Severe disease developed in six of the nine women after delivery.⁴¹ COVID-19 seems to be less lethal than SARS or MERS based on the limited number of reported cases. COVID-19 increase low birth weight rate and premature birth rate.^{42–44} Pregnant women with COVID-19 had fewer adverse maternal and neonatal complications than those with SARS or MERS.⁴⁵ Knight *et al.* reported a prospective national population based cohort study using the UK Obstetric Surveillance System. Four hundred and twenty-seven pregnant women admitted to hospital with confirmed SARS-CoV-2 infection. Two hundred and eighty-one (69%) were overweight or obese, 175 (41%) were aged 35 or over, and 145 (34%) had pre-existing comorbidities. Forty-one (10%) women admitted to hospital needed respiratory support, and five (1%) women died. Twelve (5%) of 265 infants tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth.¹⁵ Ellington *et al.* reported 83,205 non-pregnant women of reproductive age (15–44 years) with laboratory-confirmed SARS-CoV-2 infections and 8207 pregnant women of reproductive age (15–44 years) with laboratory-confirmed SARS-CoV-2 infections in USA. The COVID-19-related deaths all were 0.2% (16 pregnant women and 208 non-pregnant women among aged 15–44 years). Hospitalization was reported by a substantially higher percentage of pregnant women (31.5%) than non-pregnant women (5.8%). Pregnant women were admitted more frequently to the ICU (1.5%) than were non-pregnant women (0.9%). Half a percent of pregnant women required mechanical ventilation compared with 0.3% of non-pregnant women.⁴⁶ We reviewed 235 cases of reported pregnancy with HCoV infection, including SARS (16 cases), MERS (11 cases) and COVID-19 (208 cases including 11 twin cases). Maternal deaths occurring during pregnancy with MERS, SARS, and COVID-19 were 19% (3/16 cases), 27% (3/11 cases), and 4% (8/208 cases), respectively. Table 1 shows the maternal–fetal outcome in pregnancies with SARS, MERS, and COVID-19.^{47–85} Table 2 shows cases of death in women affected by coronavirus during pregnancy.^{38,39,47,62,86}

Placental pathology

Ng *et al.* reported the placental pathology of seven mothers with SARS, of whom six were SARS-CoV RNA positive and one was seroconverted. The gestation ages at delivery were 15–38 weeks. Two placentas from women who were convalescing from SARS-CoV infection during the first

trimester of pregnancy were normal. Three placentas that were delivered from pregnancies with acute SARS-CoV infection were abnormal and demonstrated increased subchorionic and intervillous fibrin, a finding that can be associated with abnormal maternal blood flow to the placenta. Two placentas from women who were convalescing from SARS-CoV infection in the 3rd trimester of pregnancy were highly abnormal. The placentas showed extensive fetal thrombotic vasculopathy with areas of avascular chorionic villi-chronic findings of fetal vascular malperfusion. Two women also had oligohydramnios complications and had poor obstetrical outcomes. The infants had developed IUGR. No villitis was identified in any of the placentas.⁸⁷ Shanes *et al.* studied sixteen placentas from patients with SARS-CoV-2 (15 with live birth in the third trimester, one delivered in the second trimester after intrauterine fetal demise). They found the third trimester placentas have more feature of maternal vascular malperfusion, particularly abnormal or injured maternal vessels, and intervillous thrombi. The placenta from the patient with intrauterine fetal demise showed villous edema and a retroplacental hematoma. Rates of acute and chronic inflammation were not increased.⁸⁸ Baergen *et al.* studied 20 placentas whose mother tested positive for the SARS-CoV-2 cases. Ten of the 20 cases showed some evidence of fetal vascular malperfusion or fetal vascular thrombosis.⁸⁹ The placental pathology may explain the adverse fetal and neonatal outcomes in women with HCoV infection. The placental changes may reflect a systemic inflammatory or hypercoagulable state influencing placental physiology.

Materno-fetal transmission

In a prospective pilot study, Gagneur *et al.* studied 159 samples from mother–child couples: maternal vaginal and respiratory samples taken during labor and newborn gastric samples were tested for HCoV (229E, OC-43, NL-63, HKU1) by using real-time PCR (RT-PCR). HCoV were detected in 12 samples (229E: 11; HKU1: 1) from seven mother–child couples. All three samples (maternal vaginal, maternal respiratory, and newborn gastric) tested positive in two couples. The authors concluded that vertical transmission may be possible in HCoV infection.⁹⁰ Dong *et al.* reported one newborn with elevated immunoglobulin M (IgM) antibodies to SARS-CoV-2 who was born from a mother with COVID-19. Five RT-PCR tests of nasopharyngeal (NP) swab samples taken from 2 hours to 16 days of age were negative.⁹¹ Zeng *et al.* detected SARS-CoV-2 IgG and IgM antibodies at birth in the blood of six infants born to mothers with COVID-19 pneumonia and found two infants' blood was IgM positive. Five of six infants' blood was IgG positive. Neonatal throat swab and blood samples all demonstrated SARS-CoV-2-negative RT-PCR test results. IgM, which was detected in two infants, is not usually transferred from mother to fetus because of its larger macromolecular structure. IgM could have been produced by the fetus if the virus crossed the placenta.⁹² The two reports suggested the possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn in utero. High-quality research is needed to elucidate whether SARS-CoV-2 can be transmitted in utero from the mother to the fetus.⁹³

Table 1**Maternal-fetal characteristics and outcome in pregnancies with SARS, MERS and COVID-19.**

Items	SARS (<i>n</i> =16) no./total no. (%)	ERS (<i>n</i> =11) no./total no. (%)	COVID-19 (<i>n</i> =208) no./total no. (%)
Age (years) < 35	12/16 (75)	8/11 (73)	154/208 (74)
Age (years) ≥ 35	3/16 (19)	3/11 (27)	54/208 (26)
No pregnancy age reported	1/16 (6)	0/11 (0)	0/208 (0)
Nulliparous	6/16 (38)	3/11 (27)	79/208 (38)
Parous	8/16 (50)	7/11 (64)	83/208 (40)
No pregnancy history reported	2/16 (13)	1/11 (9)	46/208 (22)
Singleton pregnancy	16/16 (100)	11/11 (100)	197/208 (95)
Twin pregnancy	0/16 (0)	0/11 (0)	11/208 (5)
First trimester	8/16 (50)	1/11 (9)	46/208 (22)
Second trimester	5/16 (31)	4/11 (36)	34/208 (16)
Third trimester	3/16 (19)	6/11 (55)	151/208 (73)
Laboratory-diagnosed	16/16 (100)	11/11 (100)	174/208 (84)
Clinically-diagnosed	0/16 (0)	0/11 (0)	34/208 (16)
Asymptomatic	0/16 (0)	1/11 (9)	23/208 (11)
Symptomatic	16/16 (100)	9/11 (81)	185/208 (89)
No report	0/16 (0)	1/11 (9)	0/208 (0)
Mechanical ventilation	5/16 (31)	5/11 (45)	40/208 (19)
Extracorporeal membrane oxygenation	0/16 (0)	0/11 (0)	3/208 (1)
Pulmonary embolism	0/16 (0)	0/11 (0)	2/199 (1) [§]
Disseminated intravascular coagulopathy	3/16 (19)	0/11 (0)	4/199 (2) [§]
Kidney injury/renal failure	3/16 (19)	2/11 (18) [†]	6/199 (3) [§]
Secondary bacterial pneumonia	1/16 (6)	0/11 (0)	5/199 (3) [§]
Sepsis	2/16 (13)	0/11 (0)	7/199 (4) [§]
Respiratory failure/ARDS	5/16 (31)	5/11 (45)	34/199 (17) [§]
Cardiovascular collapse/shock	2/16 (13)	1/11 (9)	13/199 (7) [§]
Cardiac arrest	0/16 (0)	1/11 (9)	2/199 (1) [§]
Cardiomyopathy	0/16 (0)	0/11 (0)	2/199 (1) [§]
Acute hepatic failure	0/16 (0)	0/11 (0)	1/199 (1) [§]
Overlapping HELLP manifestation	0/16 (0)	0/11 (0)	2/199 (1) [§]
Cerebral infarction	0/16 (0)	0/11 (0)	2/199 (1) [§]
Acute severe ulcerative colitis	0/16 (0)	0/11 (0)	1/199 (1) [§]
Pancreatitis	0/16 (0)	0/11 (0)	1/199 (1) [§]
Multiple organ dysfunction syndrome	3/16 (19)	2/11 (18)	15/199 (8) [§]
Maternal mortality	3/16 (19)	3/11 (25)	8/208 (4)
Pregnancy ongoing	5/16 (31)	4/11 (27)	53/208 (25)
Delivery after recovery	5/16 (31)	4/11 (27)	0/208 (0)
Delivery when infection	3/16 (19)	6/11 (55)	144/208 (69)
Vaginal delivery when infection	0/16 (0)	2/11 (18)	19/144 (13)
Cesarean section when infection	3/16 (19)	4/11 (36)	125/144 (87)
Preterm birth	5/16 (31) [*]	6/11 (55) [‡]	43/155 (28) [¶]
Perinatal death	0/16 (0)	3/11 (27)	11/155 (7) [¶]
Neonatal infection	0/16 (0)	0/11 (0)	5/155 (3) [¶]
Intrauterine growth restriction	2/16 (13)	0/11 (0)	8/155 (5) [¶]
Abortion	8/16 (50)	0/11 (0)	11/208 (5)
Spontaneous abortion	4/8 (50)	0/11 (0)	5/11 (45)
Induced abortion	4/8 (50)	0/11 (0)	4/11 (36)
Ectopic pregnancy	0/16 (0)	0/11 (0)	2/11 (18)

SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; COVID-19: Coronavirus disease 2019; HELLP: Hemolysis, elevated liver enzymes, and low platelets; ARDS: Acute respiratory distress syndrome.

* Two cases preterm birth after recovery.

† One case with history of end stage renal disease (ESRD) and hypertension on hemodialysis.

‡ Two cases preterm birth after recovery.

§ Nine severe disease cases' details no report.

|| One case delivery way unknown.

¶ Eleven cases of twins.

Table 2**Characteristics of maternal death cases from women with coronavirus infection.**

Case No.	HCoV infection	Age (years)	G/P	GA (weeks)	CoV PCR	CXR or CT	Comorbidities	Delivery	Neonatal outcome	Comments
1	SARS	44	4/3	5	+	+	None	SM	–	Die from progressive respiratory failure
2	SARS	34	2/1	32	+	+	None	CS	Preterm labor; fetal distress	Die from progressive respiratory failure
3	SARS	34	2/1	27	+	+	None	CS	Preterm labor; RDS; NEC; PDA; Fetal distress	Die from methicillin-resistant <i>Staphylococcus aureus</i> pneumonia associated with shock
4	MERS	32	2/1	38	+	+	None	VD	Survived	Die from multiple organ failure
5	MERS	31	1/0	24	+	+	Asthma, Pulmonary fibrosis, Recurrent spontaneous pneumothoraces	CS	Death after CS 4 hours	Die from severe refractory hypoxia and cardiac arrest
6	MERS	32	3/2	32	+	+	None	CS	Health	Die from septic shock
7	COVID-19	25–29*	2/1	30 ^{3/7}	+	+	None	VD	Death	Die from multiple organ failure
8	COVID-19	25–29*	1/0	38 ^{3/7}	+	+	Obesity	CS	Health	Die from cardiopulmonary collapse
9	COVID-19	40–44*	2/1	30 ^{5/7}	+	+	Subclinical hypothyroid	CS	Preterm labor; negative [†]	Die from end organ failure
10	COVID-19	30–34*	3/0	24 ^{0/7}	+	+	None	Undelivered	Stillborn	Die from multiple organ failure
11	COVID-19	30–34*	2/1	36 ^{0/7}	+	+	Type A2 gestational diabetes	CS	Health	Die from cardiopulmonary collapse
12	COVID-19	35–39*	2/0	24 ^{0/7}	+	+	None	Undelivered	Dichorionic, diamniotic twin gestation in utero at the time of maternal death, undelivered	Die from multiple organ failure
13	COVID-19	45–49*	2/1	28 ^{0/7}	+	+	Underweight	CS	Experienced complications of premature birth and both died on day-of-life 3	Die from a failed cardiopulmonary resuscitation
14	COVID-19	29	2/1	29	+	+	Type 2 diabetes mellitus (T2DM) on metformin and insulin, renal tubular acidosis, asthma and vitamin D deficiency	CS	Preterm labor	Die from progressive respiratory failure and basilar artery thrombosis

COVID-19: Coronavirus disease 2019; CS: Cesarean section; CXR or CT: Chest X-ray or computed tomograph; G/P: Gravida and parity; GA: Gestational age; HCoV: Human coronaviruses; MERS: Middle East respiratory syndrome; NEC: Necrotizing enterocolitis; PCR: Polymerase chain reaction; PDA: Patent ductus arteriosus; RDS: Respiratory distress syndrome; SARS: Severe acute respiratory syndrome; SM: Spontaneous miscarriage; VD: Vaginal delivery; –: not applicable.

* For protection of patient identification, maternal age was gated in inclusive 5-year blocks in original report.

[†] As detailed in the case description, case 3 was negative on day of life 1, but converted to positive on day of life 7.

By using electron microscopy, Algarroba *et al.* were able to identify virions invading syncytiotrophoblasts in placental villi of a pregnant woman SARS-CoV-2 infection.⁴⁹ Zhang *et al.* reported four newborn infected with COVID-19. The ages ranged from 30 hours to 17 days old. All four mothers were infected by SARS-CoV-2, three showing symptoms before and one after delivery. Cesarean

section was used for all four mothers.⁹⁴ Kamali Aghdam reported one cases of neonatal COVID-19 who was confirmed at 15 days after CS birth. Alzamora reported neonate SARS-CoV-2 infection confirmed at 16 hours after CS delivery. The six cases of neonate SARS-CoV-2 infection all were born from CS.⁹⁵ Chen *et al.* tested eight throat swabs from newborns whose mothers infected with

SARS-CoV-2 and three breast-milk samples of the mothers and did not find positive SARS-CoV-2.⁴¹

Ferrazzi *et al.* reported 42 women with COVID-19 and 24 women delivered vaginally. One newborn infected with COVID-19, who developed GI symptoms within a few hours after vaginal delivery. After 3 days of birth, the newborn developed respiratory symptoms and was transferred to the neonatal ICU, where he recovered after 1 day of mechanical ventilation. The mother did not breastfeed. In this case series, 11 newborns received breastfeed. No newborn infected COVID-19.⁹⁶

In current case review, none of the 20 neonates experienced HCoV infection when they were born through vaginal delivery. Only a newborn was asymptomatic but a nasopharyngeal swab was positive tested for SARS-CoV-2. A further RT-PCR was performed on the same neonatal nasopharyngeal swab 37 hours later and tested negative for SARS-CoV-2.

We summary that neonatal HCoV infection may have the possibility of occurring in utero, during delivery through the birth canal, or through postpartum contact. HCoV-specific immunoglobulin G passively transfers

across the placenta from mother to fetus at the end of the second trimester and reaches high levels at the time of birth, which may decrease the neonatal infection rate.^{34,97-} Figure 2 shown the systemic and respiratory disorders caused by HCoV infection and vertical transmission.

Diagnosis

Clinical features

Most infected patients have symptoms such as fever, fatigue, dry cough, and dyspnoea. Patients with mild symptoms may not present positive signs. Patients in a severe condition may have shortness of breath, moist rales in lungs, and weakened breath sounds. Patients with an asymptomatic carrier state may also be contagious and exist during pregnancy.⁵¹

Laboratory features

The diagnosis of SARS, MERS, and COVID-19 mainly requires the demonstration of virus. RT-PCR methods

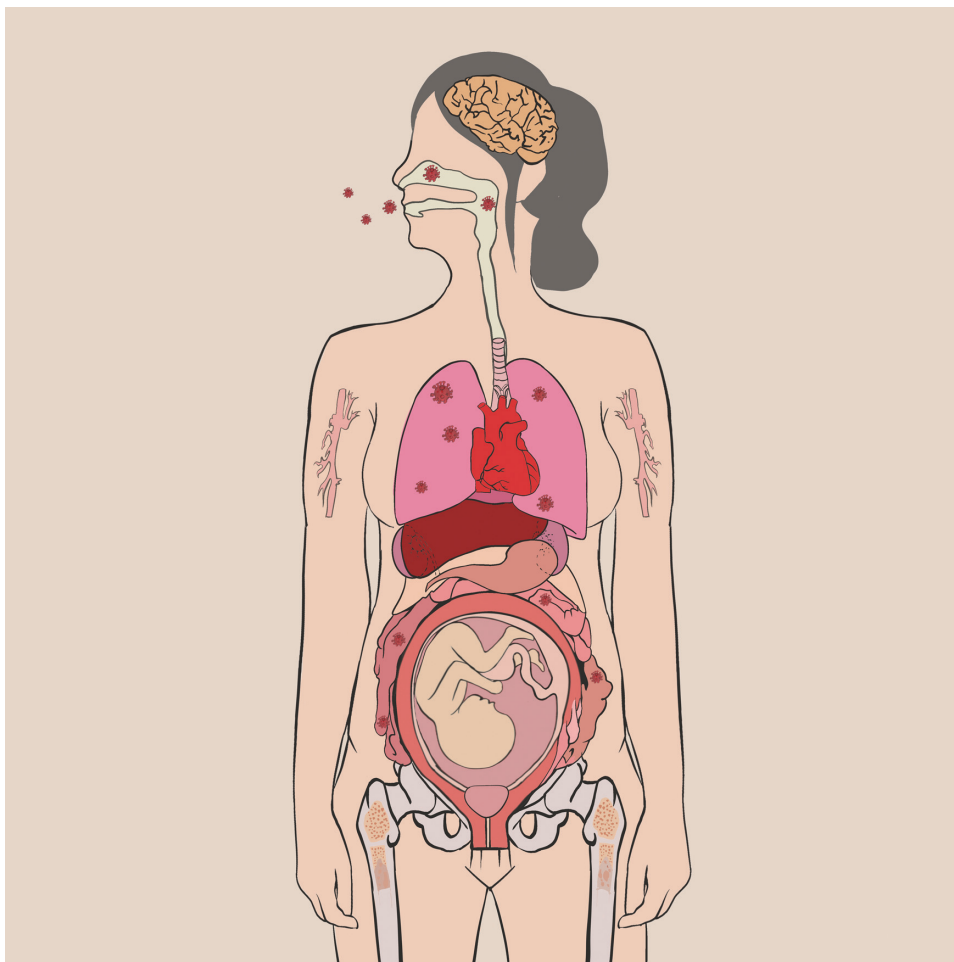


Figure 2. Systemic and respiratory disorders caused by HCoV infection and vertical transmission. One of 24 infant appeared SARS-CoV-2 infection when it was born through vaginal delivery suggests the possible vertical transmission of SARS-CoV-2 through birth canal.⁹⁶ That three newborns with elevated IgM antibodies to SARS-CoV-2 who born from mothers with COVID-19 suggests the possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn in uterine.^{91,92} That two neonates SARS-CoV-2 infection 16 hours⁹³ and 36 hours⁹⁴ after birth (through cesarean section) and one 15-day-old neonate⁹⁵ (birth through cesarean section) SARS-CoV-2 infection suggests their infection may be from postpartum contact. COVID-19: Coronavirus disease 2019; HCoV: Human coronavirus; IgM: Immunoglobulin M; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

may generate false-positive or false-negative results. The first generation of RT-PCR assays were more sensitive at the end of the first week of illness, with only 35%–65% of specimens testing positive in the first few days of SARS-CoV infection.⁹⁸ The positive test results from sputum ($n=104$), nasal swab ($n=8$), and pharyngeal swab specimens ($n=398$) were 75 (72%), 5 (63%), and 126 (32%), respectively.⁹⁹ False-negative result ranges from 17%–63% for NP swabs RT-PCR for SARS-CoV-2 have been reported in 12 studies in non-pregnant patients.¹⁰⁰

CoV IgG and IgM could be used in the diagnosis of CoV infection. Serological tests using enzyme linked immune sorbent assay and indirect immunofluorescence assays have been used to monitor convalescent patients and perform serosurveys. The majority of infected patients will seroconvert: IgM values peak between weeks 2 and 3 after the onset of symptoms while remaining detectable up to 12 weeks post-infection; IgG values reach peak titres more slowly and may persist for a long time.^{101,102} Other laboratory tests include analyses of blood gases, liver and kidney function, myocardial enzymes, myoglobin, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, lactate, D-dimer, coagulation factors, routine urine parameters, and inflammatory factors (interleukin-6, interleukin-10, tumor necrosis factor- α). Lymphopenia, disseminated intravascular coagulation, elevated lactate dehydrogenase, and creatinine kinase were the common laboratory features of HCoV infection.^{4,103}

Imaging features

Computed tomography and X-ray imaging may be used in the diagnosis of CoV infection. In the pandemic area, Computed tomography and X-ray imaging may be the main diagnostic tool. Common radiographic features of HCoV infection include the predominant involvement of the lung periphery and the lower zone in addition to the absence of cavitation, hilar lymphadenopathy or pleural effusion. Radiographic progression from unilateral focal air-space opacity to either multifocal or bilateral involvement occurred during the second phase of the disease, followed by radiographic improvement with treatment.^{4,102}

Typical ultrasound features include diffuse hyperechoic vertical artifacts with thickened pleural line and “white lung” with patchy distribution.^{104,105}

Differential diagnosis

HCoV infection should mainly be distinguished from other known viral causes of pneumonia, such as influenza viruses, parainfluenza virus, adenovirus, respiratory syncytial virus, and rhinovirus, and from *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and bacterial pneumonia. In addition, HCoV infection should be distinguished from non-infectious diseases, such as vasculitis, dermatomyositis, and organizing pneumonia.^{12,106}

Management

Preparation

When managing patients with some kinds of HCoV infection during pregnancy, healthcare workers are

particularly at risk and must take appropriate infection control precautions. One or two designated hospitals should be prepared for the management of patients with confirmed HCoV infection, including pregnant women. A group of tertiary hospitals should be prepared for screening pregnant women with possible HCoV infection. These hospitals should also manage the pregnant women who are persons under investigation (PUIs) and patients with confirmed cases in emergency.^{107–124}

For hospital

A labor room/delivery room/operation room (OR) complex comprising several separate rooms, two with a negative-pressure environment, which is separate from the main labor room/delivery room/OR, should be designated for delivery and CS of patients with suspected or confirmed cases of HCoV infection. The labor room/delivery room/OR should have its own ventilation system with an integrated high-efficiency particulate air filter. The hospital that is designated to care for patients with HCoV infection, including infected pregnant women or PUIs, must ensure that their personnel are correctly trained and capable of implementing recommended infection control interventions. Hospital should have recommended infection control practices for hospitalized pregnant patients who are confirmed to have HCoV infection or are PUIs. Hospital should follow the infection control guidance on managing visitor access, including essential support persons for women in labor. Hospital should have a policy of limiting visitors, with the exception of a healthy parent or caregiver. Hospital should have a policy of instructing visitors to wear appropriate personal protective equipment (PPE), including gowns, gloves, face masks, and eye protection. In the United Kingdom (UK), there already exist significant protections in law for pregnant workers. In light of the limited evidence, pregnant women of any gestation should be offered the choice of whether to work in direct patient-facing roles during the COVID-19 pandemic.¹⁰⁷ The ideal OR/labor room/delivery room, which is a complex and two with negative pressure environment and the isolation wards with a negative pressure environment are shown on Figures 3–4 (The figures were draw based on Third People’s Hospital of Shenzhen).^{110–113}

For staff

A team of dedicated doctors and nurses should be designated to handle potential HCoV-infected patients. The team caring for pregnant women with confirmed or suspected HCoV infection should not care for other low-risk patients at the same time. All healthcare workers should be trained and fitted appropriately for N95 masks and powered air-purifying respirator. Individual healthcare personnel should ensure that they understand and can adhere to infection control requirements. The healthcare workers working in the triage areas should wear protective N95 masks and be strictly compliant with hand hygiene requirements. All healthcare workers should wear a powered air-purifying respirator when collecting NP swab specimens. The team caring for

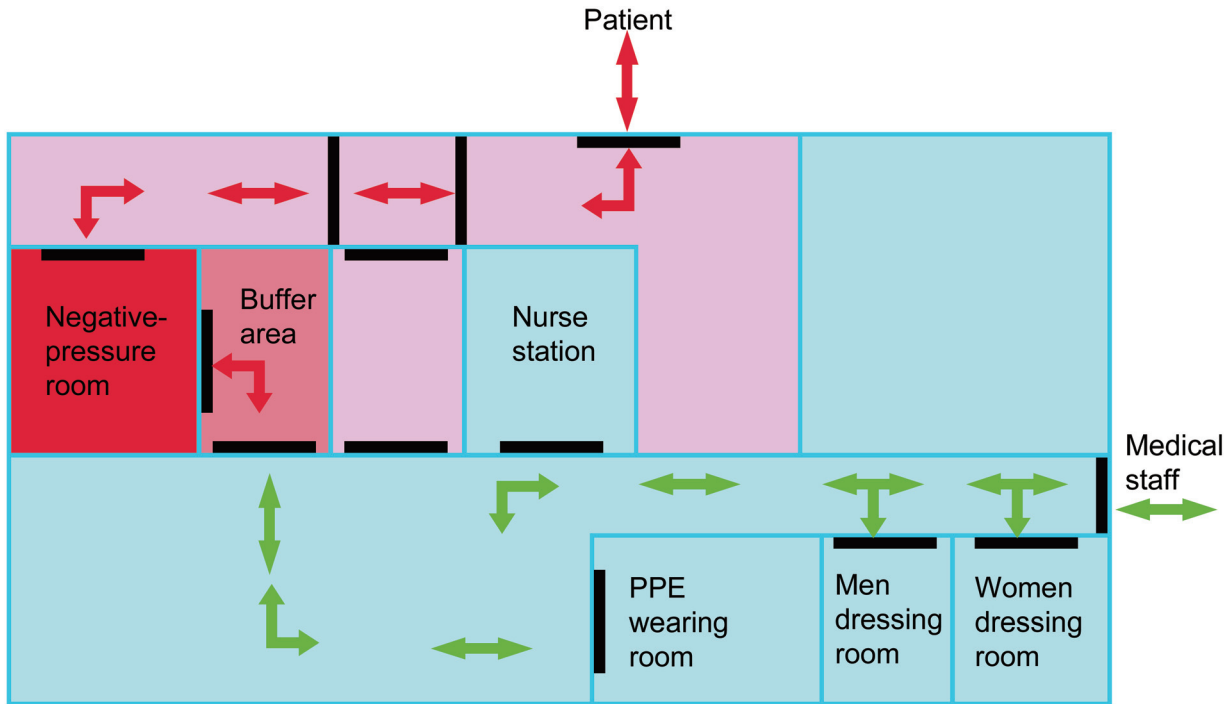
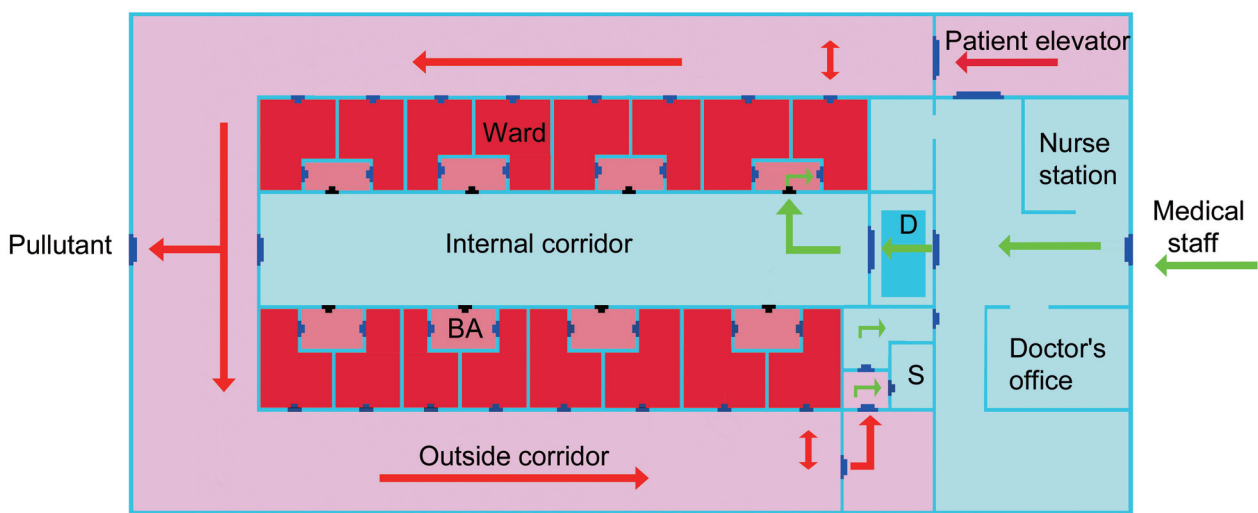


Figure 3. Operation room complex with a negative pressure environment. PPE: Personal protective equipment.

pregnant women with HCoV infection or PUI should use PPE, including a disposable gown, N95 mask, gloves, and eye protection, before they enter the isolation rooms. The team caring for patients with suspected or confirmed cases of HCoV infection should be closely monitored for fever or other signs of infection and should not be working in the presence of any individuals with HCoV infection symptoms.^{107–110}

General management

All pregnant women presenting to the hospital should be screened using a standard questionnaire. On presentation to the triage areas, pregnant patients who meet the screening criteria should be placed in a negative-pressure isolation room, if available, to complete the screening procedure. The screening criteria are as follows: (1) travel to or residence in an outbreak area within the last 14 days;



D:dressing room S:shower BA:buffer area

■ locked door

■ closed door

Figure 4. Isolation ward with a negative pressure environment.

(2) a history of contact with a healthcare facility in an outbreak area; (3) a history of close contact with an individual with a confirmed case of HCoV infection within 14 days before the onset of illness; (4) person accompanying patient has been to an outbreak area within the last 14 days; (5) frequent or close contact with recent travellers from outbreak areas (travel history in the last 14 days); and (6) full pneumonia criteria regardless of travel/contact history. All pregnant women should be screened and assessed for symptoms and risk factors for HCoV infection.^{107,108,114–121}

If a pregnant patient who has confirmed HCoV infection or is a PUI is arriving via transport by emergency medical services, the driver should contact the receiving emergency department or healthcare facility and follow previously agreed-upon local or regional transport protocols. Healthcare providers should promptly notify infection control personnel at their facility of the anticipated arrival of a pregnant patient who has confirmed HCoV infection or is a PUI. If negative-pressure isolation rooms are not available, patients should be isolated in single rooms or grouped together once HCoV infection has been confirmed. Patients should be categorized based on clinical evaluation, into mild or critical.^{18,107}

The general management include oxygen therapy, antiviral drugs, antibacterial drugs, glucocorticoids, and symptomatic treatment based on doctor recommendations. Antiviral treatment may reduce the incidence of or mortality from acute respiratory distress syndrome.^{102,122–125} Antiviral therapy may have some benefits for parents with HCoV infection. Well designed therapy clinical trials in pregnant women with HCoV infection is still lack. Only one national guideline has the recommendation of antiviral therapy for pregnant women with COVID-19.¹²⁶ There were some reported pregnant women with HCoV infection who had been cured and discharged from hospital.^{39,41} Antibacterial treatment is indicated only if there is evidence of secondary bacterial infection or if bacterial sepsis is suspected. Intravenous third-generation cephalosporins can be administered initially while awaiting culture and sensitivity results.

Maternal-fetal management

Antepartum

Pregnant women with confirmed HCoV infection who are asymptomatic may select self-monitoring for clinical features of HCoV at home or at designated hospitals for at least 14 days based on the local policy. Pregnant women with any of the three high fatal and contagious HCoV infections who are asymptomatic or are recovering from mild illness should be monitored with 2–4 weekly ultrasound assessments of fetal growth and amniotic fluid volume, with umbilical artery Doppler if necessary.

Pregnant women with confirmed HCoV infection should be managed by a multi-disciplinary team of midwives, obstetricians, and specialists in intensive care medicine, microbiologists, anesthetists, and neonatologists at a designated tertiary care center. Close monitoring and timely interventions should be performed to minimize maternal hypoxia. Supplemental oxygen should be administered to maintain oxygen saturation values above

95%; if requiring mechanical ventilation, pregnant patients should be maintained in the left lateral position to maximize uterine blood flow. Delivery of the fetus should be considered to improve maternal oxygenation. For preterm cases requiring delivery, the use of antenatal steroids for fetal lung maturation in a critically ill patient can potentially worsen the clinical condition, and the administration of antenatal steroids would delay the delivery that is necessary for the management of the patient. The use of antenatal steroids should be considered in discussion with infectious disease specialists, maternal-fetal medicine subspecialists, and neonatologists. In the case of an infected woman presenting with spontaneous preterm labor, tocolytics should not be used in an attempt to delay delivery to administer antenatal steroids.^{106,107}

Labor and delivery

The timing of delivery should be individualized based on disease severity; existing comorbidities such as preeclampsia, diabetes, and cardiac disease; obstetric history; and gestational age and fetal condition. In mild and stable patients responding to treatment and in the absence of fetal compromise, pregnancy may be continued to term under close surveillance. The termination of pregnancy should be considered as an option before fetal viability is reached to save the pregnant woman's life after careful consultation with the patient, her family and an ethics board. In critical patients, continuing pregnancy may endanger the safety of the mother and her fetus. Criteria that have been considered for early delivery include: (1) rapid maternal deterioration; (2) failure to maintain adequate blood oxygenation; (3) difficulty with mechanical ventilation due to the gravid uterus; (4) multi-organ failure; (5) fetal compromise; and (6) other obstetric indications.¹²³ The mode of delivery is mainly determined by obstetric indications. Solid evidence for vaginal shedding of virus and vertical transmission is lacking, and vaginal delivery may be considered in stable patients. In the event that an infected woman has spontaneous onset of labor with optimal progress, provided that appropriate preventative measures are in place, patients with HCoV infection can be allowed to deliver vaginally, but with a shortened second stage.^{106,107}

Operation management

If the pregnant woman is very sick and/or far from term, cesarean section is likely to be chose. Careful consideration should be given regarding the choice of anesthesia when delivery by cesarean section is required. Those who have severe respiratory involvement without being ventilated would be better managed with elective general anesthesia. Women who are already being ventilated will be delivered with general anesthesia. A designated anesthesiologist should be called in to care for HCoV-infected patients. An OR with a negative-pressure environment is ideal to reduce the dissemination of the virus from CS.^{106,107,112}

Postpartum

Workflow needs to be established to coordinate care among obstetricians, neonatologists, midwives, and nurses

to ensure the safety of the mother and baby. Routine postoperative visits from anesthesiologists should be suspended and replaced by phone calls when applicable to reduce the movement of staff around the hospital. If possible, a dedicated breast pump should be provided. Before expressing breast milk, mothers should practice hand hygiene.¹¹⁴

During temporary separation, mothers who intend to breastfeed should be encouraged to express their breast milk to establish and maintain milk supply. After each pumping session, all parts that come into contact with breast milk should be thoroughly washed, and the entire pump should be appropriately disinfected per the manufacturer's instructions. If the newborn is rooming with his/her ill mother in the same hospital room in accordance with the mother's wishes, or if this is unavoidable due to facility limitations, facilities should consider implementing measures to reduce exposure of the newborn to HCoV. If no other healthy adult is present in the room to care for the newborn, a mother who has confirmed HCoV infection or is a PUI should wear a face mask and practice hand hygiene before each feeding or other close contact with her newborn. If another healthy family or staff member is present to provide care and feeding for the newborn, they should use appropriate PPE. The face mask should remain in place during contact with the newborn.^{106,107}

Neonatal management

A sample from the neonatal NP suction before the first breath may be collected and sent for testing for HCoV infection. Early cord clamping is recommended. The decision to temporarily separate the mother from her baby should be made on a case-by-case basis in consultation with clinicians, infection prevention and control specialists, and public health officials.

The decision should take into account disease severity, illness signs and symptoms, and results of laboratory testing for HCoV. Mothers with confirmed or suspected HCoV infection should refrain from breastfeeding until they have fully recovered or have been confirmed not to have HCoV infection.

Neonates born to mothers with confirmed HCoV infection should be considered PUIs. As such, infants should be isolated at least 14 days or until the mother's viral shedding clears. The neonate should be cared for in an isolation ward and carefully monitored for any signs of infection.

Direct breastfeeding is not recommended. If a mother and newborn do room together and the mother wishes to breastfeed, she should put on a face mask and practice hand hygiene before each feeding.^{42,106,107,116}

Conclusions

HCoV may infect pregnant women as it infects non-pregnant women. There is no evidence that pregnant women are more susceptible to HCoV infection or that those with HCoV infection are more prone to developing severe pneumonia. Similar to non-pregnant women, pregnant women with MERS had the highest mortality, followed by those with SARS and COVID-19. Fetal

infection may occur in the uterus. There is also no solid evidence of the time when vertical transmission occurs in mothers with CoVs infection. Antiviral treatment is the main management for pregnant women with three highly fatal and contagious CoVs infections, similar to non-pregnant women. Timing and the mode of delivery should be individualized. The neonate should be cared for in isolation ward and carefully monitored for any signs of infection. All staff should use PPE when caring for a patient with HCoV infection.

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Conflicts of Interest

None.

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