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CORONAVIRUS DISEASES AND PREGNANCY: COVID-19, SARS, AND MERS

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ABSTRACT

Around the end of December 2019, a new beta-coronavirus from Wuhan City, Hubei Province, China began to spread rapidly. The new virus, called SARS-CoV-2, which could be transmitted through respiratory droplets, had a range of mild to severe symptoms, from simple cold in some cases to death in others. The disease caused by SARS-CoV-2 was named COVID-19 by WHO and has so far killed more people than SARS and MERS. Following the widespread global outbreak of COVID-19, with more than 132758 confirmed cases and 4955 deaths worldwide, the World Health Organization declared COVID-19 a pandemic disease in January 2020. Earlier studies on viral pneumonia epidemics has shown that pregnant women are at greater risk than others. During pregnancy, the pregnant woman is more prone to infectious diseases. Research on both SARS-CoV and MERS-CoV, which are pathologically similar to SARS-CoV-2, has shown that being infected with these viruses during pregnancy increases the risk of maternal death, stillbirth, intrauterine growth retardation and, preterm delivery. With the exponential increase in cases of COVID-19 throughout the world, there is a need to understand the effects of SARS-CoV-2 on the health of pregnant women, through extrapolation of earlier studies that have been conducted on pregnant women infected with SARS-CoV, and MERS-CoV. There is an urgent need to understand the chance of vertical transmission of SARS-CoV-2 from mother to fetus and the possibility of the virus crossing the placental barrier. Additionally, since some viral diseases and antiviral drugs may have a negative impact on the mother and fetus, in which case, pregnant women need special attention for the prevention, diagnosis, and treatment of COVID-19.

Keywords: *pregnancy, neonates, COVID-19, SARS-CoV-2, 2019 novel coronavirus*

INTRODUCTION

The Coronaviridae family consists of enveloped, positive-sense, single-stranded RNA viruses. The genome length of these viruses is between 26 and 32 kb (1). This family is composed of two subfamilies: Coronavirinae, and Torovirinae. The Coronavirinae subfamily is further composed of four genrea : alpha-, beta-, delta-, and gamma-coronaviruses (2-4). Coronaviruses have been found in numerous hosts, including birds, dogs, camels, bats, mice, pigs, as well as humans (1, 5-7). Betacoronaviruses and Alphacoronaviruses may commonly lead to gastroenteritis in animals and respiratory diseases in the humans (8). Coronaviruses that infect humans often produce mild to severe symptoms. HCoV-HKU1, HCoV-NL63, HCoV-229E and HCoV-OC43, can cause modest symptoms similar to common cold (1, 3, 9), however, in infants and elderly, HCoV-OC43 and HCoV-229E may also lead to severe lower respiratory tract infections (3). Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) (Betacoronavirus) and the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) (Betacoronavirus) can also cause severe symptoms. Studies have shown 79% identity between SARS-CoV-2 genome and SARS-CoV and 50% identity between the SARS-CoV genome and MERS-CoV (10, 11).

The SARS-CoV, first observed in Guangdong province in southeast China in November 2002, infected more than 8,000 people in 37 countries and killed 774 people between 2002 and 2003 (12, 13).

MERS-CoV was first spotted in Saudi Arabia in 2012, infecting at least 2494 people and causing 858 deaths since then, including 38 deaths in South Korea (14, 15). SARS-CoV is easily transmitted by respiratory droplets or nosocomial contact (16-18). MERS-CoV was first transmitted to humans through camel-to-human contact and then spread through human-to-human contact (19). Common symptoms of SARS include malaise, chills, fever, myalgia, dry cough, dyspnea, and headache (20). Symptoms of MERS such as shortness of breath, chest pain, fever, cough, sore throat are mainly caused by lower respiratory tract infection(21).

In late December 2019, cases of viral pneumonia were observed in Wuhan, the capital of Hubei Province, China. On February 11, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses chose the name Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) for this new beta-coronavirus virus (22, 23). WHO also named the disease caused by the virus, COVID-19 (24). People infected with the virus can have symptoms such as high fever, dry cough, dyspnea, and shortness of breath. Chest radiography often shows invasion to both lungs (25, 26).

COVID-19 has been spreading rapidly around the world and WHO declared it as pandemic disease and a public health emergency of international concern in January 2020. According to WHO's July 22 report, there were 14 731 563 confirmed cases of COVID- 19 and 611 284 deaths all around the world. (24)

The transmission of the COVID-19 virus is mainly via contact, aerosols, and droplets. Nucleic acid of SARS-CoV-2 has also been detected in the fecal samples of patients with the COVID-19, which indicates that stool could be a factor in the transmission of the disease (27, 28).

Studies conducted during earlier viral infections and pandemics have led to some understanding of the effects of the infection on various demographics of the population. Chances of stillbirth, preterm delivery, maternal death and spontaneous abortion increase in viral pneumonia such as SARS (29-33). SARS-CoV-2 is very similar in terms of pathogenicity to SARS-CoV and MERS-CoV and studies have shown that SARS- and MERS-CoV pose many risks to the mother and fetus (19, 30, 33, 34).

This study is aimed at understanding the possible effects of SARS-CoV-2 on pregnant mothers and fetuses, based on studies of both SARS-CoV and MERS-CoV as well as studies on the SARS-CoV-2.

THE DIVERSITY AND ORIGIN OF THE CORONAVIRUSES

According to existing data, all of the coronaviruses that affect humans have animal origins. Accordingly MERS-CoV, and SARS-CoV, are reported to have bat origin (1, 35).

The SARS-CoV-2 genome analysis has indicated that the genome sequence of this virus, was 79.5% and 96.2% similar to the bat SARS-CoV and CoV RaTG13 genome sequence, respectively (36). According to these information, SARS-CoV-2 might have been originated from bats, like the MERS-CoV and SARS-CoV (37).

In March 2003, a novel CoV was identified as the main causative factor for SARS and hence was known as SARS-CoV. A retrospective serologic study proposed cross transmission of SARS-CoV or its other variants from the animals to the humans in the wet market with a high outbreak of 16.7% among the owners of asymptomatic animals (38). According to earlier studies, SARS CoVs, such as bats isolates, share 88%-92% sequence homology with the civet or human isolates. Furthermore bats can be considered a natural source of a close ancestor of SARS-CoV (20, 39).

Other animal strains may interfere with the appearance and evolution of SARS-CoV. At least seven strains of animals including red fox, wild boar, raccoon dog, mink, pig, rice field rat, and Chinese ferret may harbor SARS-CoV under certain conditions, (12)

In accordance to the genomic findings, MERS-CoV can be categorized as a lineage C *betacoronavirus. It is considered as* a comparatively new ancestor, which is defined as the bat coronaviruses HKU5 and HKU4. At the present time, 4 of 9 *Betacoronavirus* strains and 7 of 11 ICTV- assigned *Alphacoronavirus* strains have been found in bats. Therefore, bats are probably the main natural origins of *Betacoronaviruses* and *Alphacoronaviruses* (4, 8).

EPIDEMIOLOGY AND OUTBREAK

There is little information available about the effects of coronavirus infections in pregnant women, and now it seems likely that pregnant women have been infected during the recent SARS-CoV-2 outbreak (40). The World Health Organization (WHO) on March 11 classified COVID-19 as a pandemic. As of July 22, total of were 14 731 563 cases were infected ,which 611 284 of them were fatal cases (24).

Analysis on 41 hospitalized patients whose SARS-CoV-2 test was laboratory-confirmed showed that 30 of 41 patients were men (73%); 49.0 years old was the average age and fewer than one-half were suffering

from underlying co-morbid conditions including cardiovascular disease (6; 15%), hypertension (6, 15%) and diabetes (8 ,20%). Cough (31, 76%), sputum production (11, 28%), fever (40, 98%), headache (3, 8%) and myalgia or fatigue (18, 44%) were the most prevalent symptoms at the onset of their illness (25). For 13 of these 41 2019-CoV cases (32%) intensive care was required, 12 of them (32%) experienced acute respiratory distress syndrome (ARDS), and 6 of them (15%) died (40). 14 children who were younger than 10 years old were infected. The initial symptoms can be traced to 7 December 2019. Among the confirmed patients, the average time from infection to diagnosis was 5 days. The average delay between the beginning of symptom and diagnosis dropped significantly between before 14 January 2020 and after 22 January 2020 (41).

An odd outbreak of severe pneumonia occurred in Foshan, Guangdong Province in southern China in November 2002. On February 21, 2003, a 64 years old nephrologist traveling to HK from southern China was the indicator case causing subsequent epidemics in Toronto, Singapore and HK (20, 42-45).

Martha Anker reported that more than 100 cases of SARS-CoV infections happened in women who were pregnant and needs closer investigation (46). The clinical outcomes for women with SARS who were pregnant were worse than those that happened in non-pregnant infected women in Hong Kong (18). *Wong* et al. (30) appraised the obstetrical results from a cohort of women who were pregnant and affected by SARS. Four of the seven (57%) women during their first trimester experienced unplanned miscarriages, presumably due to the hypoxia which happened because of the acute respiratory distress (ARDS) related to SARS. Four of the five (80%) women who were more than 24 weeks pregnant, had early deliveries (40).

Between 2012 and 2016 Ministry of Health (MoH) of Saudi Arabia confirmed 1308 cases of MERS and from these cases, 5 of them were pregnant as reported by *Assiri* et al. (47) in a retrospective study, and all of them had unfavorable results. Patients were from 27 to 34 years old, with exposure that happened in second or third trimester. Intensive care was provided for all of 5 cases. Two of the pregnant women died and two perinatal deaths were reported. These results are associated with other reports of infection with MERS-CoV in pregnant women and outcomes of SARS-CoV infection (40, 47).

Many studies have reported pregnant women infected by SARS-CoV-2 (48-50), but it remains to be seen if the effect of SARS-CoV-2 on them and their pregnancy will be the same as that of the earlier MERS-CoV and SARS-CoV infections. There are several studies reporting on death cases of pregnant women due to SARS-CoV-2 infection (51-53). *Hantoushzadeh S* et al. (51) reported 7 cases of maternal death due to COVID-19 among 9 infected pregnant women. Also *Takemoto MLS* et al. (52) reported 20 maternal deaths related to COVID-19. To describe the possible adverse obstetrical consequence of infection in pregnant women and perinatal outcome of fetuses and neonates, this review explains the present state of understanding in accordance to the previous coronavirus infections (40).

CLINICAL FEATURES AND PATHOLOGICAL FINDINGS

As it was stated before, viruses of Coronaviridae family can cause a spectrum of illnesses ranging from a simple cold to severe respiratory distress condition (11). In general, Humans are susceptible to COVID-19, while pregnant women are in more danger (especially of respiratory complications), because of the physiologic alterations that pregnancy causes in their cardiopulmonary and immune systems (for example; alterations in pulmonary function (54, 55) and altered cell-mediated immunity (56)) (57, 58). Among non-obstetric infections in pregnant women, pneumonia is much more common than the others (59-61) and according to previous studies, among causes of indirect obstetric mortality, it is the third most common one (62). Viral pneumonia can cause higher mortality and morbidity than bacterial pneumonia (because of the effect of antibiotics) (63). The most common complications that happen to fetus as a result of maternal pneumonia include intra uterine growth retardation (up to 12%), prematurity as a result of preterm labor (up to 44%), neonatal demise (up to 12%), and intrauterine demise (up to 3%) (59-61). Furthermore, viral mid-trimester infections (such as varicella) can cause multiple congenital anomalies and embryopathies (64, 65).

In this section, the specific clinical features and pathogenesis of the COVID-19, SARS and MERS infections will be discussed, with focus on pregnant women.

Common symptoms of COVID-19 in hospitalized patients are fever (between 83-100%), cough (between 59-82%), myalgia (between 11-35%), headache (between 7-8%) and diarrhea (between 2-10%). Abnormalities on radiographic chest imaging have been observed in all cases. Thrombocytopenia, leukopenia and lymphopenia are other signs of abnormal testing. According to Initial reports, 17-29% of hospitalized patients had acute respiratory distress syndrome (ARDS) (11).

According to recent reports, in 18 pregnant women infected with COVID-19 (all were infected in their

third trimester) clinical findings were not different from non-pregnant adults. Although preterm delivery and fetal distress were observed in some patients, all tested babies were negative for COVID-19 (11).

In pathologic studies, COVID-19 infected patients demonstrated increased levels of plasma pro-inflammatory cytokines and higher leukocyte numbers. The major pathologic findings of COVID-19 in respiratory system were RNAemia, severe pneumonia, combined with the incidence of ground-glass opacities, and acute cardiac injury (25). A comparison between non-ICU and ICU cases demonstrated that the plasma concentrations of IL10, MCP1, IL2, IL7, GCSF, TNFα, MIP1A, and IP10 were lower in non-ICU patients than ICU patients. (25)

Common clinical features of SARS disease are persistent fever, dry cough, rigor/chills, myalgia, malaise, dyspnea, and headache. Less common features are sore throat, nausea (and vomiting), Sputum production, coryza, dizziness, and diarrhea (42, 45, 66-69). According to reports, case-fatality rate in the series of 12 pregnancies was 25%. Four of them showed ARDS, three of them presented with disseminated intravascular coagulopathy (DIC), three of them had renal failure, two of them were infected by secondary bacterial pneumonia, and sepsis occurred in two patients. Pregnant cases were more likely (three folds) ~~for~~ subjected to mechanical ventilation than non-pregnant women. Four of seven first-trimester infections resulted in spontaneous abortion. Preterm delivery after 24 weeks gestation occurred in four of five women infected with SARS (11).

According to pathological findings, S protein (surface envelope spike protein) is an important protein that helps SARS-CoV to establish infection and determines cell and tissue tropism (20). The virus binds to the receptor, undergoes conformational change of the S protein and then cathepsin L–mediated proteolysis inside the endosome (70). ACE2 (angiotensin-converting enzyme 2), which is widely expressed on body tissues, is the host receptor of this virus. The ACE2 may also cause diffuse alveolar damage (DAD) (20).

Lung histopathology in severe SARS-CoV cases showed denudation of bronchial epithelia, DAD, loss of cilia, giant cell infiltrate, squamous metaplasia, and a remarkable increase in macrophages in the interstitium and alveoli. Even though the main pulmonary feature was DAD (42, 71, 72), subpleural lesions (resembling bronchiolitis obliterans organizing pneumonia) were also observed (73). Spleen's white pulp atrophy, hemophagocytosis, secondary bacterial pneumonia and hyaline membranes were also observed (42, 71, 72, 74).

Common clinical symptoms of MERS disease are fever, cough, shortness of breath, sore throat, chest pain, myalgia, malaise and gastro-intestinal symptoms (for example; abdominal pain, vomiting and diarrhea). More uncommon symptoms are wheezing, chills, confusion and palpitations (75-78). It also should be noted that respiratory symptoms are mostly observed in lower respiratory tract (fever, cough and dyspnea), while reports about upper respiratory tract disease were not frequent. Radiologic graphs of MERS patients demonstrated mild to severe pulmonary consolidation (21). For pregnant women, in 13 reported pregnant cases, two patients were asymptomatic, three patients died, two cases faced fetal demise and two of them were delivered preterm (11).

According to pathological findings, Dipeptidyl Peptidase 4 (DPP4, also known as CD26) is the primary receptor for MERS-CoV, which is a multifunctional cell surface protein (79). This protein is expressed in the epithelial cells in the alveoli, kidney, small intestine, prostate, liver, and on activated leukocytes (80). In the lungs of MERS animal models, alveolar edema and infiltration of macrophages and neutrophils were observed (81). MERS-CoV (unlike SARS-CoV) can infect human macrophages (82) and dendritic cells (83) in vitro; so this virus can affect the immune system. Other targets for MERS-CoV are T cells due to their high amounts of CD26 (84). MERS-CoV can cause immune dysregulation as well (85) (by stimulating innate immune responses), with delayed (in vivo and in vitro) pro-inflammatory cytokine induction (82, 86, 87).

DIAGNOSIS OF COVID-19 INFECTIONS IN PREGNANT WOMEN AND NEONATES

In pregnant women, diagnosis includes examining specific specimens; at present, upper and lower respiratory specimens and serum are suggested; further specimens [urine and stool] can be sent as well (88). In order to detect SARS-CoV-2, neonatal pharyngeal swabs are used; however, the probability of a false negative result cannot be eliminated. More specimens, if situations permit, such as gastric fluid, serum, anal swabs, or stools from infants and umbilical cord blood and amniotic fluid from the mother, should be obtained in order to optimize the nucleic acid test (NAT) detection rate. The placental tissue may further be tested for placental inflammation triggered by a viral infection (89) to detect placental transmission. Body temperature, respiratory rate, heart rate, gastrointestinal signs, as well as the neonate signs, must be checked carefully; for patients with abnormal signs, there must be prompt intervention (90).

RISK OF COVID-19 VERTICAL TRANSMISSION TO FETUS OF INFECTED PREGNANT WOMEN

A pathogen transmission during the prenatal or postnatal period from mother to fetus or neonate is called vertical transmission; e.g. during pregnancy period through placental blood or germ cells, during delivery or labor by the birth canal and during postpartum period via breastfeeding (57). Before the COVID-19 outbreak, HKU1, NL63, 229E, OC43, MERS-CoV and SARS-CoV were the coronavirus that caused infection in individuals. For HKU1, NL63, 229E and OC43, which generally cause common cold symptoms among humans, vertical transmission can occur via the placenta (9).

Zhu H et al. (91) studied 9 pregnant women (10 infants) infected by SARS-CoV-2 in their third trimester, and tested throat swab samples of 9 born infants for SARS-CoV-2. They reported that all were negative; although, some of the infants showed symptoms. From the negative test results, it may be said that the symptoms may not be associated with intrauterine transmission. A study by *Chen H* et al. (92) on 9 pregnant women infected by SARS-CoV-2 in their third trimester tested samples of cord blood, amniotic fluid, neonatal throat swab and also breast milk from six patients for SARS-CoV-2, and reported that all were negative for the virus. In addition, they reported no detection of the virus in the colostrum of mothers infected by COVID-19 and that there was no vertical transmission risk by breastfeeding. *Rasmussen SA* et al. (11) declared that it is unknown whether SARS-CoV-2 could be transmitted via breast milk or not.

According to *Yang* et al. (58), infection by SARS-CoV-2 within the pregnancy period cannot cause vertical transmission to the baby. Of course, we must consider that most studies in this field were done on cases that presented the disease in the third trimester and current data is limited. Isolation remains necessary after delivery, regardless of lack of evidence for SARS-CoV-2 vertical transmission (57). China recommended not to feed neonates with breast milk of the COVID-19 infected mother and also to separate the newborn and the infected mother. US-CDC has recommended it as well (93).

Many studies indicate that during the Asian SARS epidemic of 2002-2003, no vertical transmission was seen in the reported pregnant cases (94-96). *Wong SF* et al. (30) studied 12 pregnant women infected by SARS and subsequently their infants, and reported that no neonate was infected by SARS-CoV. *Robertson CA* et al. (97) tested the breast milk samples (collected around 130 days after onset of illness) of a mother recovered from infection by SARS and reported that there was no SARS-CoV RNA in them. Other researchers have reported no vertical transmission of the infection to the infants of MERS-CoV infected pregnant women (93) (19, 33). A few other researchers have alsoi demonstrated that there is no vertical transmission for MERS or SARS after vaginal delivery or cesarean section, which is supported by many other studies (11, 98, 99).

SARS DIAGNOSIS AND TREATMENT IN PREGNANCY

Prevalent laboratory features of SARS include Creatinine phosphokinase (CPK), low-grade disseminated intravascular coagulation (prolonged activated partial thromboplastin time, thrombocytopenia, increased D-dimer), lymphopenia and increased lactate dehydrogenase (LDH) (42, 44, 45, 100, 101). Lung periphery and lower area predominant involvement along with pleural effusion, hilar lymphadenopathy, or the absence of cavitation are typical radiographic traits of SARS (42, 102). Commonly, through the 2nd phase, radiographic development from focal unilateral air space opacity to bilateral or multifocal involvement, with radiographic betterment with treatment, is noticed (42, 69, 102). Furthermore, through optimization of RNA extraction methods, in addition to performing quantitative real time RT-PCR technologies, test sensitivity for early diagnosis of SARS could be greatly enhanced (103).

Various enzymatic targets such as protease have been shown by genomic analysis of the SARS-CoV (104-106). In human immunodeficiency virus (HIV) infection cases, ritonavir and lopinavir in combination is widely used as a boosted protease inhibitor regimen. Moreover, in viral infections, Type1 IFNs, like IFN-a, are produced early based on the innate immune response. Total inhibition of the SARS-CoV cytopathic effects has been reported in culture for human leukocyte IFN-a, a-n1, b-1b, IFN subpes and a-n3 (107). In addition, convalescent serum obtained from SARS recovered patients, includes neutralizing antibody and can be clinically beneficial for treating other patients with SARS (69, 108, 109).

MERS DIAGNOSIS AND TREATMENT IN PREGNANCY

Some diagnostic techniques such as current gold standard RT-rtPCR in-house assays and virus in LLCMK2 and Vero cells were discovered by ProMED, which announced first MERS case (110-112). A colorectal adenocarcinoma (Caco-2), has been suggested for MERS-CoV infection isolation epithelial

cell line (113). MERS-CoV RNA molecular detection can be performed in real time. In addition, MERS-CoV antigen detection has not been popular until now but in a combination of viral protein recognition, the high power and short rotation time of the test results makes this an attractive choice (114).

None of the agents that have been used for treating MERS have been tested in vast clinical studies. Present information is limited to the interferon and other drugs combination therapies in case series and case reports (115). Since MERS-CoV outbreaks have a sporadic nature, a randomized or prospective study may be challenging. No therapeutic choices are presently suggested for pregnant women because of a gap in MERS treatment in pregnancy research (33). Because of the risks for teratogenic effects, treatments under investigation and testing could be considered unsafe for pregnant women. For example, ribavirin was given to pregnant women who had serious illnesses at the time of the SARS epidemic in 2003, but it has been reported to increase the potential risk for teratogenic effects in infants. (33, 40).

CARING FOR THE PREGNANT WOMEN AND THE INFANTS

COVID-19 infection is considered an extremely contagious disease and this should be taken into account even when planning for intrapartum care. According to the H. YANG et al study, if an infected woman starts a natural delivery, provided that appropriate prevention techniques are taken, vaginal delivery is allowed, but with a brief second stage, as active pressure and pushing with a surgical mask are not common (58).

Neonates born to COVID-19 infected mothers should be monitored carefully. (93) and because of limited knowledge available so far, it appears sensible to suppose that an infant born to a 2010-nCoV infected mother is at the risk of infection at delivery, either perinatally or in-utero; therefore, it is better to isolate the newborn to avoid exposure of other infants to the infection (11).

E Mullins et al. have suggested that mothers who suffer from COVID-19 infection with symptoms indicating viral infection, must not breastfeed their newborns. If these mothers want to breastfeed their babies in future, they can express their milk and then continue breastfeeding whenever affirmed as non-infective (93).

One of the best suggestions for a healthy newborn with an infected mother is that the unhealthy mother and her newborn be temporarily separated in a healthy mother's room, in accordance with the recommendations made during pandemic H1N1 (11, 116).

With regard to the care of pregnant mothers and newborns who had SARS infection, we reproduce below, the recommendation based on the evaluation of evidence criteria in the Report of the Canadian Task Force on Preventive Health Care (18):

"Neonates of mothers with SARS should be isolated in a designated unit until the infant has been well for 10 days, or until the mother's period of isolation is complete. The mother should not breastfeed during this period."

To reduce the risk of exposure to MERS-CoV among pregnant women, further prevention, such as avoiding contact with sick people and animals such as fox, wild boar, raccoon dog, mink, pig, rice field rat, camels and bats has been suggested, especially in health care settings. Pregnant women who have the symptoms such as influenza-like illness (ILI), sepsis, or pneumonia on the Arabian Peninsula can gain from MERS-CoV screening to enhance the illness management and accelerate early diagnosis (117).

COVID-19 VACCINATION CHALLENGES IN PREGNANT WOMEN

Obstetrician–gynecologists are often vaccinators of women in general and pregnant women in particular. Pregnant women are prone to vaccine-preventable disorder–related mortality and morbidity and harmful pregnancy results, comprising spontaneous abortion, low birth weight, congenital anomalies, and preterm birth. Additionally, to achieve the direct maternal advantage, vaccination during pregnancy probably provides direct infant and fetal gain through passive immunity (trans-placental transfer of the maternal antibodies which induce vaccine) (118-120). Among the vaccines suggested for the adults by the Centers for Disease Control & Prevention (CDC), 2 are suggested during the postpartum period, 4 are suggested in pregnancy based on the additional venture factors, and 2 are directly suggested for management during pregnancy (121). [126]. In accordance to laboratory methods, vaccines are generally classified as inactivated or killed, live attenuated, toxoid, conjugate or subunit vaccines (121). Subunit vaccines contain particles of the pathogens against the disease they seek to protect. These vaccines stimulate protective immune responses (122). In HPV vaccine, for example, a single HPV protein expression results in production of virus-like particles. Virus-like particles generally contain no actual viral genetic material and are therefore, are not capable of causing infection. Subsequent to vaccination, the host immune system would recognize

the expressed proteins from recombinant vaccines and would develop protective antibodies against target pathogens as well (123). Such vaccines could also be developed for COVID-19 to lower the risk of infection as much as possible.

In diseases with high mortality and morbidity vaccines are only provided during pregnancy if a woman risk of infection and exposure is high enough (based on season, location, and activities planned during travel) and thus outweighs any possible theoretical risks of vaccination(121).

Discussion on different technical challenges involved in the development of an efficient and safe vaccine for human coronavirus infections are outside the scope of this work. This work has a few challenges; some of the challenges are

– protective antibodies to coronaviruses are not stable for a long term,
– tissue impairment occurs when subject to SARS-CoV,
– animal model development that resembles human infection is inadequate,
– the time and cost essential to carry out clinical trials in humans are very high (124-126).

In the design, clinical trial, and vaccine candidate implementation for SARS-CoV-2, it is important to consider the state of the pregnant women. When we analyze the process of vaccine development in general, the needs of pregnant women have hardly been in preclinical design and the clinical production trial stages (127). Ethical values, such as justice, equity, fairness, and benefit growth, are challenged by the exclusion of pregnant women and their babies from involvement in vaccine design and implementation, and it possibly puts their health at risk during outbreaks, besides other health emergencies (128, 129).

Given the potentially harmful impacts of the new coronavirus during pregnancy, a central question that needs to be addressed at this point is whether maternal immunization must be prioritized in research and development? Twelve groups, in the PHEIC announcement, have declared that they are developing SARS-CoV-2 vaccines, and seven further have declared new therapeutic initiatives (130). Experimental vaccines are difficult to be tested on pregnant women; and therefore, vaccines with such a population are not usually developed. Only a few clinical vaccine trials, thus far, have proactively involved pregnant women (131); a classic example is the exclusion of pregnant and breastfeeding women in the rVSV-ZEBOV vaccine test during the three Ebola virus epidemics (127-129). Considering the potentially serious nature of pregnancy, as shown in SARS and MERS maternal infections, pregnant women should be taken into account in all attempts to prepare for and prevent infection of the new coronaviruses (130). Production of vaccines builds on SARS and MERS vaccines and profits from their work (132). This is not clear, however, how soon an efficient and safe vaccine can be developed (88).

MANAGEMENT AND TREATMENT OF COVID-19 INFECTED WOMEN

An early sign of maternal respiratory worsening can be the changes in the pattern of heart rate. Extreme respiratory failure may arise in pregnant women as seen in earlier SARS and MERS situations, and in most of such cases, sufficient oxygenation may not be provided by mechanical ventilation. If this happens, a latent part of extracorporeal membrane oxygenation (ECMO) in pregnancy is indicated in some literature; it should merely be used in centers having experience with the method (133). It is unclear if delivery benefits a critically ill mother; decisions on delivery should be made based on the fetus gestational age and in conjunction with the neonatologist's adivise (134).

Currently, even though a wide-spectrum of antivirals used in MERS animal models are being assessed for use against SARS-CoV-2 (132), no antiviral medications licensed by the US Food and Drug Administration exist as yet for the COVID-19 treatment (90). Corticosteroids should be avoided for coronavirus-related pneumonia treatment since they were not effective in MERS and resulted in delayed MERS-CoV clearance (135). For fetal lung maturity, thus, decisions on the corticosteroids application should be made by consulting maternal-fetal medicine consultants and infectious disease specialists (88). However, in a clinical trial by Oxford University it has been shown that the rate of death was reduced to one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and one fifth in other patients who have recieved oxygen only (0.80 [0.67 to 0.96]; p=0.0021) by administering dexamethasone. No beneficial effects had been observed among other patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14) (136). Timely immunoglobulin intravenous injection can decrease severe sickness and mortality as, at present, neither a vaccine nor specific antiviral medicines against the SARS-CoV-2 infection exists (90). The two infected infants that have been studied so far, had thrombocytopenia accompanied by abnormal liver function, according to *Zhu* et al. s' report (90). One died, which may be because the virus was not detected in time, and the baby may have had poor immune function, rapid virus growth, and massive virus replication in several tissues results in major viremia, causing multiple organ failure, refractory shock, and DIC that blood transfusions

and symptomatic supportive treatments could not improve. The other infant was treated with intravenous infusion of gamma globulin, plasma, and platelets and survived, which shows that gamma globulin can be efficient in severe cases, which is in line with the current recommendations (137). As further data on pregnant women with COVID-19 become available, all recommendations should be revised.

SITUATION OF SARS-COV-2, SARS-COV AND MERS-COV INFECTION OF PREGNANT WOMEN AND NEWBORNS BY THE TIME

On 13 January 2020, a COVID-19 infected baby was delivered. After its birth its nanny and after days its mother were diagnosed with COVID-19. The baby showed symptoms after 16 days (138).

On February 5th 2020, a neonate born in Wuhan was positive for COVID-19 test after 30 hours (40). Another baby diagnosed with COVID-19 seems to have acquired the virus from the environment of the hospital (139). Neonates can become infected by ways other than vertical transmission e.g. inhalation of the virus via aerosols which are produced by coughing of healthcare workers or mother or relatives (40). Until May 2003, there had been 10 reported cases of pregnant women infected by SARS, of which four experienced early pregnancy loss (18, 140). Rate of case fatality among 11 MERS infected pregnant women was not different from the overall rate of case fatality (34).

CONCLUSION

At present, there is no proof that pregnant women are more susceptible to the COVID-19 infection than normal people. There is also no evidence of vertical transmission of SARS-CoV-2 from mother to infant.

Observations during the earlier MERS and SARS infection periods have shown that when the mother's infection appears in the third trimester, the pregnant women might have severe clinical symptoms. The prevalence of COVID-19 infection is quickly growing in the number of deaths, cases, and the countries that are affected. There is not enough information about the virus and its effects, its risk factors, modes of transmission, the number of basic reproduction, and the rate of case fatality.

Management systems for COVID-19 requires details on the pregnancy situation, such as fetal and maternal results. The standard actions to handle severe respiratory infection are considered as the care foundation for the pregnant woman suffering from COVID-19 and must be performed aggressively in a team-based protocol. Neonates born to COVID-19 infected mothers should be monitored carefully and therefore, it is better to isolate the baby to prevent exposure for the other infants. If these mothers want to breastfeed their babies in future, they can express their milk and then continue breastfeeding whenever affirmed as non-infective. Further research on the therapy of MERS, SARS, and COVID-19 is required to understand the benefits and the risks of novel vaccines and new treatments in pregnancy.

Conflicts of interest:
The authors confirm that they have no conflicts of interest.

REFERENCES

1. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends in microbiology. 2016;24(6):490-502.
2. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World Journal of Pediatrics. 2020:1-9.
3. King AM, Adams MJ, Carstens EB, Lefkowitz EJ. Virus taxonomy. Ninth report of the International Committee on Taxonomy of Viruses. 2012:486-7.
4. Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, Lau JH, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. Journal of virology. 2012;86(7):3995-4008.
5. Cavanagh D. Coronavirus avian infectious bronchitis virus. Veterinary research. 2007;38(2):281-97.
6. Ismail M, Tang Y, Saif Y. Pathogenicity of turkey coronavirus in turkeys and chickens. Avian diseases. 2003;47(3):515-22.
7. Zhou P, Fan H, Lan T, Yang X-L, Shi W-F, Zhang W, et al. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. Nature. 2018;556(7700):255-8.
8. Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. Nature reviews Microbiology. 2019;17(3):181-92.
9. Gagneur A, Dirson E, Audebert S, Vallet S, Legrand-Quillien M, Laurent Y, et al. Materno-fetal transmission of human coronaviruses: a prospective pilot study. European Journal of Clinical Microbiology & Infectious Diseases. 2008;27(9):863-6.
10. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for

virus origins and receptor binding. The Lancet. 2020;395(10224):565-74.
11. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. American journal of obstetrics and gynecology. 2020.
12. Peiris J, Lai S, Poon L, Guan Y, Yam L, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. The Lancet. 2003;361(9366):1319-25.
13. Chan-Yeung M, Xu R. SARS: epidemiology. Respirology 8 Suppl S9–14. 2003.
14. Lee J, Chowell G, Jung E. A dynamic compartmental model for the Middle East respiratory syndrome outbreak in the Republic of Korea: a retrospective analysis on control interventions and superspreading events. Journal of theoretical biology. 2016;408:118-26.
15. Lee JY, Kim Y-J, Chung EH, Kim D-W, Jeong I, Kim Y, et al. The clinical and virological features of the first imported case causing MERS-CoV outbreak in South Korea, 2015. BMC infectious diseases. 2017;17(1):498.
16. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, et al. Identification of severe acute respiratory syndrome in Canada. New England Journal of Medicine. 2003;348(20):1995-2005.
17. Seto W, Tsang D, Yung R, Ching T, Ng T, Ho M, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). The Lancet. 2003;361(9368):1519-20.
18. Maxwell C, McGeer A, Tai KFY, Sermer M, Farine D, Basso M, et al. Management guidelines for obstetric patients and neonates born to mothers with suspected or probable severe acute respiratory syndrome (SARS): No. 225, April 2009. Elsevier; 2009.
19. Jeong SY, Sung SI, Sung J-H, Ahn SY, Kang E-S, Chang YS, et al. MERS-CoV infection in a pregnant woman in Korea. Journal of Korean medical science. 2017;32(10):1717-20.
20. Hui DS. Epidemic and Emerging coronaviruses (severe acute respiratory syndrome and middle east respiratory syndrome). Clinics in chest medicine. 2017;38(1):71-86.
21. van den Brand JM, Smits SL, Haagmans BL. Pathogenesis of Middle East respiratory syndrome coronavirus. The Journal of pathology. 2015;235(2):175-84.
22. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, et al. Coronavirus Disease 2019 (COVID-19): A Perspective from China. Radiology. 2020:200490.
23. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity. 2020:102433.
24. Organization WH. Coronavirus disease (COVID-19) outbreak. URL https://www who int/emergencies/diseases/novel-coronavirus-2019. 2020.
25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
26. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395(10223):514-23.
27. Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerging microbes & infections. 2020;9(1):386-9.
28. Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. Journal of Medical Virology. 2020.
29. Hardy JM, Azarowicz EN, Mannini A, Medearis Jr DN, Cooke RE. The effect of Asian influenza on the outcome of pregnancy, Baltimore, 1957-1958. American Journal of Public Health and the Nations Health. 1961;51(8):1182-8.
30. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. American journal of obstetrics and gynecology. 2004;191(1):292-7.
31. Takahashi N, Kitajima H, Kusuda S, Morioka I, Itabashi K. Pandemic (H1N1) 2009 in neonates, Japan. Emerging infectious diseases. 2011;17(9):1763.
32. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. American journal of obstetrics and gynecology. 2011;205(1):10-8.
33. Alserehi H, Wali G, Alshukairi A, Alraddadi B. Impact of Middle East Respiratory Syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC infectious diseases. 2016;16(1):105.
34. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. Journal of microbiology, immunology, and infection= Wei mian yu gan ran za zhi. 2019;52(3):501.

35. Forni D, Cagliani R, Clerici M, Sironi M. Molecular evolution of human coronavirus genomes. Trends in microbiology. 2017;25(1):35-48.
36. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Military Medical Research. 2020;7(1):1-10.
37. Liu P, Chen W, Chen J-P. Viral Metagenomics Revealed Sendai Virus and Coronavirus Infection of Malayan Pangolins (Manis javanica). Viruses. 2019;11(11):979.
38. Du L, Qiu J, Wang M, Zhou D, Liu X, Gao Y, et al. Analysis on the characteristics of blood serum Ab-IgG detective result of severe acute respiratory syndrome patients in Guangzhou, China. Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi. 2004;25(11):925.
39. Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. Virus research. 2008;133(1):74-87.
40. Schwartz DA, Graham AL. Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. Viruses. 2020;12(2):194.
41. Yang Y, Lu Q, Liu M, Wang Y, Zhang A, Jalali N, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. medRxiv. 2020.
42. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. New England Journal of Medicine. 2003;348(20):1986-94.
43. Tsang KW, Ho PL, Ooi GC, Yee WK, Wang T, Chan-Yeung M, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. New England Journal of Medicine. 2003;348(20):1977-85.
44. Hsu L-Y, Lee C-C, Green JA, Ang B, Paton NI, Lee L, et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. Emerging infectious diseases. 2003;9(6):713.
45. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. Jama. 2003;289(21):2801-9.
46. Organization WH. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). World Health Organization; 2003.
47. Assiri A, Abedi GR, Al Masri M, Bin Saeed A, Gerber SI, Watson JT. Middle East Respiratory Syndrome Coronavirus infection during pregnancy: a report of 5 cases from Saudi Arabia. Clinical Infectious Diseases. 2016;63(7):951-3.
48. Cabero-Pérez MJ, Gómez-Acebo I, Dierssen-Sotos T, Llorca J. [Infection by SARS-CoV-2 in pregnancy and possibility of transmission to neonates: A systematic revision]. Semergen. 2020.
49. Phoswa WN, Khaliq OP. Is pregnancy a risk factor of COVID-19? European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2020.
50. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2020;56(1):15-27.
51. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, Seferovic MD, Aski SK, Arian SE, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020;223(1):109.e1-.e16.
52. Takemoto MLS, Menezes MO, Andreucci CB, Knobel R, Sousa LAR, Katz L, et al. Maternal mortality and COVID-19. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2020:1-7.
53. Metz TD, Collier C, Hollier LM. Maternal Mortality From Coronavirus Disease 2019 (COVID-19) in the United States. Obstetrics and gynecology. 2020.
54. Leontic EA. Respiratory disease in pregnancy. Medical Clinics of North America. 1977;61(1):111-28.
55. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. American Review of Respiratory Disease. 1980;121(3):559-81.
56. Sargent I, Redman C. Immunobiologic adaptations of pregnancy. Medicine of the fetus and mother Philadelphia: JB Lippincott Company. 1992:317-27.
57. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. American journal of respiratory and critical care medicine. 2020(ja).
58. Yang H, Wang C, Poon L. Novel coronavirus infection and pregnancy. Ultrasound in Obstetrics & Gynecology. 2020.
59. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. American Journal of Obstetrics & Gynecology. 1982;144(4):413-7.
60. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome?

American journal of obstetrics and gynecology. 1989;161(3):657-62.
61. Berkowitz K, LaSala A. Risk factors associated with the increasing prevalence of pneumonia during pregnancy. American journal of obstetrics and gynecology. 1990;163(3):981-5.
62. Visscher HC, Visscher RD. Indirect obstetric deaths in the state of Michigan 1960–1968. American Journal of Obstetrics & Gynecology. 1971;109(8):1187-93.
63. Rigby FB, PASTOREK JG. Pneumonia during pregnancy. Clinical obstetrics and gynecology. 1996;39(1):107-19.
64. Balducci J, Rodis JF, Rosengren S, Vintzileos AM, Spivey G, Vosseller C. Pregnancy outcome following first-trimester varicella infection. Obstetrics and gynecology. 1992;79(1):5-6.
65. Pastuszak AL, Levy M, Schick B, Zuber C, Feldkamp M, Gladstone J, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. New England Journal of Medicine. 1994;330(13):901-5.
66. Twu S-J, Chen T-J, Chen C-J, Olsen SJ, Lee L-T, Fisk T, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. Emerging infectious diseases. 2003;9(6):718.
67. Organization WH. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. http://www who int/csr/sars/country/table2004_04_21/en/index html. 2003.
68. Rainer TH. Severe acute respiratory syndrome: clinical features, diagnosis, and management. Current opinion in pulmonary medicine. 2004;10(3):159-65.
69. Hui DS, Chan PK. Severe acute respiratory syndrome and coronavirus. Infectious Disease Clinics. 2010;24(3):619-38.
70. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proceedings of the National Academy of Sciences. 2005;102(33):11876-81.
71. Kuiken T, Fouchier RAM, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. The Lancet. 2003;362(9380):263-70.
72. Nicholls JM, Poon LLM, Lee KC, Ng WF, Lai ST, Leung CY, et al. Lung pathology of fatal severe acute respiratory syndrome. The Lancet. 2003;361(9371):1773-8.
73. Tse GM-K, To K-F, Chan PK-S, Lo AWI, Ng K-C, Wu A, et al. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). Journal of Clinical Pathology. 2004;57(3):260-5.
74. Franks TJ, Chong PY, Chui P, Galvin JR, Lourens RM, Reid AH, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Human Pathology. 2003;34(8):743-8.
75. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. The Lancet infectious diseases. 2013;13(9):752-61.
76. Al-Abdallat MM, Payne DC, Alqasrawi S, Rha B, Tohme RA, Abedi GR, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clinical Infectious Diseases. 2014;59(9):1225-33.
77. Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, et al. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. Clinical Infectious Diseases. 2014;59(2):160-5.
78. Memish ZA, Al-Tawfiq JA, Assiri A, AlRabiah FA, Al Hajjar S, Albarrak A, et al. Middle East respiratory syndrome coronavirus disease in children. The Pediatric infectious disease journal. 2014;33(9):904-6.
79. Meyerholz DK, Lambertz AM, McCray Jr PB. Dipeptidyl peptidase 4 distribution in the human respiratory tract: implications for the Middle East respiratory syndrome. The American journal of pathology. 2016;186(1):78-86.
80. Widagdo W, Raj VS, Schipper D, Kolijn K, van Leenders GJ, Bosch BJ, et al. Differential expression of the Middle East respiratory syndrome coronavirus receptor in the upper respiratory tracts of humans and dromedary camels. Journal of virology. 2016;90(9):4838-42.
81. Alagaili AN, Briese T, Mishra N, Kapoor V, Sameroff SC, de Wit E, et al. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. MBio. 2014;5(2):e00884-14.
82. Zhou J, Chu H, Li C, Wong BH-Y, Cheng Z-S, Poon VK-M, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. The Journal of infectious diseases. 2014;209(9):1331-42.
83. Chu H, Zhou J, Wong BH-Y, Li C, Cheng Z-S, Lin X, et al. Productive replication of Middle East respiratory syndrome coronavirus in monocyte-derived dendritic cells modulates innate immune response. Virology. 2014;454:197-205.

84. Chu H, Zhou J, Wong BH-Y, Li C, Chan JF-W, Cheng Z-S, et al. Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. The Journal of infectious diseases. 2016;213(6):904-14.
85. Liu WJ, Lan J, Liu K, Deng Y, Yao Y, Wu S, et al. Protective T Cell Responses Featured by Concordant Recognition of Middle East Respiratory Syndrome Coronavirus–Derived CD8+ T Cell Epitopes and Host MHC. The Journal of Immunology. 2017;198(2):873-82.
86. Chan RW, Chan MC, Agnihothram S, Chan LL, Kuok DI, Fong JH, et al. Tropism of and innate immune responses to the novel human betacoronavirus lineage C virus in human ex vivo respiratory organ cultures. Journal of virology. 2013;87(12):6604-14.
87. Lau SK, Lau CC, Chan K-H, Li CP, Chen H, Jin D-Y, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. Journal of General Virology. 2013;94(12):2679-90.
88. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. American journal of obstetrics and gynecology. 2020.
89. Wang J, Xu H, Mu C, Chen C, Guo L, Chen L, et al. A study on mother-to-fetus/infant transmission of influenza A(H7N9) virus: Two case reports and a review of literature. The clinical respiratory journal. 2018;12(11):2539-45.
90. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Translational pediatrics. 2020;9(1):51-60.
91. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Translational Pediatrics. 2020;9(1):51.
92. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507-13.
93. Mullins E, Evans D, Viner R, O'Brien P, Morris E. CORONAVIRUS IN PREGNANCY AND DELIVERY: RAPID REVIEW AND EXPERT CONSENSUS. medRxiv. 2020.
94. Ng P, So K, Leung T, Cheng F, Lyon D, Wong W, et al. Infection control for SARS in a tertiary neonatal centre. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2003;88(5):F405-F9.
95. Li A, Ng P. Severe acute respiratory syndrome (SARS) in neonates and children. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2005;90(6):F461-F5.
96. Shek CC, Ng PC, Fung GP, Cheng FW, Chan PK, Peiris MJ, et al. Infants born to mothers with severe acute respiratory syndrome. Pediatrics. 2003;112(4):e254-e.
97. Robertson CA, Lowther SA, Birch T, Tan C, Sorhage F, Stockman L, et al. SARS and pregnancy: a case report. Emerging infectious diseases. 2004;10(2):345.
98. Jiang X, Gao X, Zheng H, Yan M, Liang W, Shao Z, et al. Specific immunoglobulin g antibody detected in umbilical blood and amniotic fluid from a pregnant woman infected by the coronavirus associated with severe acute respiratory syndrome. Clin Diagn Lab Immunol. 2004;11(6):1182-4.
99. Stockman LJ, Lowther SA, Coy K, Saw J, Parashar UD. SARS during pregnancy, United States. 2004.
100. Hui DS, Sung JJ. Severe acute respiratory syndrome. Chest. 2003;124(1):12-5.
101. Wong G, Hui D. Severe acute respiratory syndrome (SARS): epidemiology, diagnosis and management. BMJ Publishing Group Ltd; 2003.
102. Wong K, Antonio GE, Hui DS, Lee N, Yuen EH, Wu A, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. Radiology. 2003;228(2):401-6.
103. Poon LL, Chan KH, Wong OK, Yam WC, Yuen KY, Guan Y, et al. Early diagnosis of SARS coronavirus infection by real time RT-PCR. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2003;28(3):233-8.
104. Rota PA, Oberste MS, Monroe SS, Nix WA, Campagnoli R, Icenogle JP, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. science. 2003;300(5624):1394-9.
105. Marra MA, Jones SJ, Astell CR, Holt RA, Brooks-Wilson A, Butterfield YS, et al. The genome sequence of the SARS-associated coronavirus. Science. 2003;300(5624):1399-404.
106. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science. 2003;300(5626):1763-7.
107. Yuan FF, Boehm I, Chan PK, Marks K, Tang JW, Hui DS, et al. High prevalence of the CD14-159CC genotype in patients infected with severe acute respiratory syndrome-associated coronavirus. Clin Vaccine Immunol. 2007;14(12):1644-5.

108. Cheng Y, Wong R, Soo Y, Wong W, Lee C, Ng M, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. European Journal of Clinical Microbiology and Infectious Diseases. 2005;24(1):44-6.
109. Soo Y, Cheng Y, Wong R, Hui D, Lee C, Tsang K, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clinical microbiology and infection. 2004;10(7):676-8.
110. Corman V, Eckerle I, Bleicker T, Zaki A, Landt O, Eschbach-Bludau M, et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Eurosurveillance. 2012;17(39).
111. Corman V, Müller M, Costabel U, Timm J, Binger T, Meyer B, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Eurosurveillance. 2012;17(49).
112. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. New England Journal of Medicine. 2012;367(19):1814-20.
113. Muth D, Corman VM, Meyer B, Assiri A, Al-Masri M, Farah M, et al. Infectious Middle East respiratory syndrome coronavirus excretion and serotype variability based on live virus isolates from patients in Saudi Arabia. Journal of clinical microbiology. 2015;53(9):2951-5.
114. Mackay IM, Arden KE. MERS coronavirus: diagnostics, epidemiology and transmission. Virology journal. 2015;12(1):222.
115. Al-Tawfiq JA, Memish ZA. Update on therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV). Expert review of anti-infective therapy. 2017;15(3):269-75.
116. Rasmussen SA, Kissin DM, Yeung LF, MacFarlane K, Chu SY, Turcios-Ruiz RM, et al. Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns. American journal of obstetrics and gynecology. 2011;204(6):S13-S20.
117. Malik A, El Masry KM, Ravi M, Sayed F. Middle east respiratory syndrome coronavirus during pregnancy, Abu Dhabi, United Arab Emirates, 2013. Emerging infectious diseases. 2016;22(3):515.
118. Leader S, Perales PJ. Provision of primary-preventive health care services by obstetrician-gynecologists. Obstetrics & Gynecology. 1995;85(3):391-5.
119. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. New England Journal of Medicine. 2008;359(15):1555-64.
120. Control CfD, Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)--United States, April 2009-August 2010. MMWR Morbidity and mortality weekly report. 2011;60(35):1193.
121. Swamy GK, Heine RP. Vaccinations for pregnant women. Obstet Gynecol. 2015;125(1):212-26.
122. Plotkin SA. Vaccines: past, present and future. Nature medicine. 2005;11(4):S5-S11.
123. Vorsters A, Van Damme P, Bosch FX. HPV vaccination: Are we overlooking additional opportunities to control HPV infection and transmission? International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2019;88:110-2.
124. Gillim-Ross L, Subbarao K. Emerging respiratory viruses: challenges and vaccine strategies. Clinical microbiology reviews. 2006;19(4):614-36.
125. Tseng CT, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PloS one. 2012;7(4):e35421.
126. Wu L-P, Wang N-C, Chang Y-H, Tian X-Y, Na D-Y, Zhang L-Y, et al. Duration of antibody responses after severe acute respiratory syndrome. Emerg Infect Dis. 2007;13(10):1562-4.
127. Schwartz DA. Clinical Trials and Administration of Zika Virus Vaccine in Pregnant Women: Lessons (that Should Have Been) Learned from Excluding Immunization with the Ebola Vaccine during Pregnancy and Lactation. Vaccines (Basel). 2018;6(4):81.
128. Schwartz D. Maternal and Infant Death and the rVSV-ZEBOV Vaccine Through Three Recent Ebola Virus Epidemics-West Africa, DRC Équateur and DRC Kivu: 4 Years of Excluding Pregnant and Lactating Women and Their Infants from Immunization. Current Tropical Medicine Reports. 2019.
129. Schwartz DA. Being Pregnant during the Kivu Ebola Virus Outbreak in DR Congo: The rVSV-ZEBOV Vaccine and Its Accessibility by Mothers and Infants during Humanitarian Crises and in Conflict Areas. Vaccines (Basel). 2020;8(1).
130. Schwartz DA, Graham AL. Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. Viruses. 2020;12(2).
131. Graham A. When Is It Acceptable to Vaccinate Pregnant Women? Risk, Ethics, and Politics of

Governance in Epidemic Crises. Current Tropical Medicine Reports. 2019;6.
132. Paules CI, Marston HD, Fauci AS. Coronavirus Infections-More Than Just the Common Cold. Jama. 2020.
133. Pacheco LD, Saade GR, Hankins GDV. Extracorporeal membrane oxygenation (ECMO) during pregnancy and postpartum. Seminars in perinatology. 2018;42(1):21-5.
134. Lapinsky SE. Management of Acute Respiratory Failure in Pregnancy. Seminars in respiratory and critical care medicine. 2017;38(2):201-7.
135. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. American journal of respiratory and critical care medicine. 2018;197(6):757-67.
136. Horby P, Landray M. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 [Internet]. RECOVERY trial, 2020.
137. [Perinatal and neonatal management plan for prevention and control of 2019 novel coronavirus infection (1st Edition)]. Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics. 2020;22(2):87-90.
138. Steinbuch Y. Chinese Baby Tests Positive for Coronavirus 30 Hours after Birth. 2020.
139. Woodward A. A Pregnant Mother Infected with the Coronavirus Gave Birth, and Her Baby Tested Positive 30 Hours Later. . 2020.
140. Wong S, Chow K, de Swiet M. Severe acute respiratory syndrome and pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology. 2003;110(7):641-2.

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