

Maternal and fetal outcomes of COVID-19, SARS, and MERS: a narrative review on the current knowledge

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Abstract. – OBJECTIVE: Coronavirus infections, including SARS, MERS and COVID-19 have significant impact on global health as well as on pregnancies. The aim of this review was to enlighten and summarize the cumulative knowledge regarding the relationship between Coronavirus outbreaks and pregnancy.

MATERIALS AND METHODS: Literature search was commenced in order to analyze the maternofetal effects of Coronavirus outbreaks.

RESULTS: Fever and cough are the most common presenting symptoms of COVID-19 which mostly affects pregnant women in their 3rd trimester with a maternal mortality rate of 0-77% and fetal and neonatal mortality rates of 1.2%. Fetal demise is common in critically ill pregnant. Pregnancy seems as a worsening factor for SARS and MERS epidemics and both infections affect prominently 3rd trimester pregnancies, although abortion (57%) is a significant risk for cases of early pregnancy. Clinical course of COVID-19, SARS and MERS may be rapid and worse in pregnant women than non-pregnant individuals. Cesarean section is the choice of delivery in most reported women due to mostly obstetrical reasons, although vaginal delivery seems not a worsening factor for the disease.

CONCLUSIONS: COVID-19, SARS and MERS have significant detrimental effect on pregnancy. Rapid intervention, treatment, and intensive care support are essential for infected pregnant. Timely delivery is important in order to avoid intrauterine fetal death.

Key Words:

Pregnancy, Infections, Mortality, Pandemics.

Introduction

Coronaviruses are enveloped, single-stranded positive-sense RNA viruses and are the largest family in the order Nidovirales¹. Pangolins, palm civets, raccoon dogs, and bats are the natural

hosts of different Coronavirus subfamilies, and ingestion of these animals is considered the main route for transmission to humans². The upper and lower respiratory systems and intestinal systems of humans and a variety of other animals are targeted by Coronaviruses¹.

In the last two decades, Coronaviruses have been the source of three global outbreaks, and coronavirus-related lung infections have been a significant threat to human beings. In 2002, the first coronavirus outbreak, named severe acute respiratory syndrome (SARS) caused by SARS coronavirus (SARS-COV), was reported in China and rapidly spread to other countries, with a case fatality rate (CFR) of 11%³. In 2012, a second outbreak of Coronavirus, named Middle East Respiratory Syndrome (MERS) which was caused by a novel coronavirus (MERS-COV) emerged in Saudi Arabia and affected patients from more than 20 countries, with an average mortality rate of 35%, and, at the end of 2019, the outbreak named 2019 Novel Coronavirus Disease (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) emerged from Wuhan, China, and became a global pandemic with an overall CFR of 2.3%³.

SARS-COV-2, SARS-COV, and MERS-COV appeared as zoonotic infections, and the viruses achieved person-to-person transmission through inhalation of infected droplets and respiratory secretions. Respiratory system involvement has been the common feature of all three Coronavirus outbreaks that caused the classic triad of symptoms in symptomatic cases: fever, cough, and dyspnea. However, the range of the clinical pictures of SARS-COV-2, SARS-COV, and MERS-COV infections varies from asymptomatic or mild, flu-like symptoms to severe broncho-

pneumonia with acute respiratory distress syndrome (ARDS) and multi-organ failure, which may result in mortality^{3,4}.

Normal pregnancy is characterized by immune tolerance and is associated with suppression of inflammatory and immune responses to protect the fetus from the mother's immune system⁵. It is well known that pregnancy-related immune suppression makes mothers more vulnerable than non-pregnant women to several viral infections, including SARS-COV, hepatitis E virus, influenza, and herpes simplex virus^{5,6}. Furthermore, changes in pulmonary function during pregnancy, including decreased total lung capacity and functional residual capacity, may cause susceptibility to viral pneumonia^{7,8}.

Protection of the lives of mothers and babies is one of the millennial developmental goals of the World Health Organization (WHO)⁹, and understanding of the feto-maternal effects of emergent Coronavirus outbreaks should be of great concern to all healthcare providers. In this context, this review focuses on investigating and comparing the three coronavirus outbreaks in terms of their possible detrimental effects on the fetus and mother.

All articles, reviews and case series considering the pregnancy and SARS-COV-2, SARS and MERS which were reported in English and indexed in PubMed database between the date of 01.01.2020 and 05.15.2020 were searched. Non-English reports and articles whose full text could not be available were excluded.

COVID-19 and Pregnancy

COVID-19, caused by SARS-COV-2, was first reported in the city of Wuhan, Hubei province, China, at the end of December 2019. The exact origin of human infection has not yet been clearly identified, but COVID-19 is considered a zoonotic infection that was likely transmitted through close contact with horseshoe bats and pangolins².

In only a short time, COVID-19 spread to a number of countries on different continents, and the WHO declared a global emergency¹⁰⁻¹². On 11 March 2020, COVID-19 was classified as the first pandemic of the 21st century by the WHO¹³. So far, more than 4 million people have been affected by the virus globally, and the death toll has exceeded 276,000.

Since the beginning of January 2020, 26 scientific reports in English, including case series and a case-control study, and 4 systematic review article, with a total of 127 pregnant patients

with confirmed COVID-19, have been reported^{14,23}, but the results are inconsistent. According to the early reports, pregnant women may have a milder clinical course and pregnancy may not adversely affect the severity of COVID-19, but, in most recent reports, severe disease and a considerably higher mortality in pregnancy have been suggested. Hantoushzadeh et al¹⁹ from Iran, in their most recent case series, reported seven deaths (77%) and one recovery (11%) out of nine pregnant women with severe COVID-19. Schnettler et al¹⁶ reported a 31-week-pregnant woman with COVID-19 who had a rapid course and required mechanical ventilation and intensive care unit (ICU) care within 10 hours of admission. Karami et al²⁰ from Iran also reported maternal death and in utero fetal death of a 30-week-pregnant woman who developed severe disease and multi-organ failure within 11 days of admission.

Li et al¹⁵ reported a 35-week-pregnant woman who rapidly deteriorated within 4 days and required bedside emergency cesarean section, which resulted in the death of the neonate within 2 hours of delivery. Juussela et al¹⁷ suggested that two of seven pregnant women with confirmed COVID-19 who had no known cardiac pathology in their medical histories subsequently developed dilated cardiomyopathy and required prolonged ICU care.

Besides the above-mentioned reports, most pregnant women with SARS-COV-2 infection have a milder disease, according to the early reports. In their systematic review, Yang et al¹⁴ analyzed the results of 18 studies comprising 114 pregnant women. Most of the cases were in the third trimester, although 22 (19%) of the cases were in the first trimester. In general, the clinical course of the pregnant women with COVID-19 was no different from non-pregnant women, and the severity of the disease was mild in 85 (96.5%) of the 114 cases. Two patients were asymptomatic at admission and developed symptoms within days, and six patients (5.3%) showed severe disease or were critically ill. The most common presenting symptoms among pregnant women were fever (87%), cough, (53%) and fatigue (22%)¹⁴. No maternal deaths were reported among the 114 pregnant women; 98 pregnancies were delivered, and two were ended at the patient's request. Among the women who gave birth, 89 (90.8%) required cesarean section, mostly due to fetal distress, previous cesarean delivery, or preeclampsia. In the available data for 17 case series, 84 live births and one stillbirth were reported. The rate

of preterm delivery was 21.3% (n=17), and one neonate died after delivery (1.2%).

To date, vertical transmission of SARS-COV-2 from mother to fetus has not been confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) in amniotic fluid, cord blood, or placenta, although Dong et al²⁴ and Zeng et al²⁵ both reported the presence of SARS-COV-2 IgM antibodies in the cord blood of newborns delivered from COVID-19-positive mothers, which may suggest the possibility of vertical transmission of the virus.

SARS and Pregnancy

SARS-COV infection first emerged in November 2002 in Guangdong province, China, and rapidly spread to neighboring provinces and countries, including Hong Kong and Vietnam²⁶. A global emergency was declared by the WHO on 12 March 2003, and the epidemic affected more than 8,000 people and caused more than 900 deaths, with a CFR of 11%^{3,27,28}.

There are far fewer reports regarding SARS-COV infection during pregnancy in the relevant literature than COVID-19. Zhang et al²⁹ reports on five pregnant women with SARS showed that: fever was the most prominent symptom (100%), the clinical course was mild in four of the patients, and only one woman needed ICU care. All five women recovered well, and the newborns were delivered without sign of infection. On the other hand, Wong et al³⁰ from Hong Kong reported the maternal and perinatal results of 12 pregnant women with SARS and described worse outcomes. Three of the women died (CFR=25%); of the 12 cases, seven were in their first trimester, among whom there were four spontaneous abortions (57%). The remaining five patients were in the third trimester, and four had preterm delivery (80%). None of the delivered infants showed positivity for SARS based on PCR investigations of the cord blood and placenta.

Lam et al³¹ reported a case-control study from Hong Kong that included ten pregnant women and 40 non-pregnant women with SARS-COV and concluded that pregnant women had a significantly worse clinical course than non-pregnant women. The rates of ICU admission, renal failure, and disseminated intravascular coagulation (DIC) were significantly higher in the pregnant women than among non-pregnant women ($p<0.05$). There were three maternal deaths in the pregnant group, while no mortality was seen in the non-pregnant women ($p<0.005$).

MERS and Pregnancy

MERS-COV infection caused a more limited epidemic than SARS and was first seen in Saudi Arabia in September 2012³. Thereafter, approximately 2,500 cases and 858 deaths were reported in 27 different countries, although more than 80% of the cases of MERS-COV were reported in Saudi Arabia and adjacent Arabic countries³²⁻³⁴.

To date, 11 case reports of pregnant women with MERS-COV infection have been reported, with worse clinical courses than non-pregnant women, similar to the previous SARS-COV epidemic³⁵. The mean gestational age was 26 weeks and only one pregnancy was in the first trimester. All the reported cases were symptomatic and three of the women died (CFR=27%). Three fetal deaths (27%) also occurred. The PCR analyses for MERS-CoV and antibody tests in umbilical cord blood and placenta did not show intrauterine transmission of the virus^{35,36}.

Conclusions

The papers published so far on pregnancy and coronavirus infections, including COVID-19, SARS, and MERS, offer some important lessons for obstetricians, although the currently available data is insufficient. Most of the affected pregnant women have been in their third trimester, but for women in early gestation, abortion risk may be significantly higher with SARS infection. Pregnant women may have a significantly worse clinical course, and mortality rates may be significantly higher than in non-pregnant individuals.

Another important point is that pregnant women with Coronavirus infection who seem mild or asymptomatic at admission may rapidly progress to severely or critically ill, at which point fetal death might occur. Close surveillance of an infected mother and timely delivery of the fetus are therefore crucial to avoid further complications and mortality. The mode of delivery appears to be cesarean section in most cases, mainly due to fetal distress and other obstetric indications, but reported cases of spontaneous vaginal delivery that were not associated with poorer outcomes supports the avoidance of unnecessary cesarean sections in these cases.

Finally, IgM antibodies against Coronaviruses have been shown in the umbilical cords of newborns in a few reports, but there is currently no convincing evidence of intrauterine transmission of the virus based on the negative PCR results of samples from amniotic cavities and placentas.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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