

# Coronavirus in pregnancy. What we know so far?

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## ABSTRACT

Coronaviruses are a group of viruses which, even if they are affecting mainly mammals and birds, could be transmitted to humans, generating common cold.

The new virus strain is named SARS-CoV-2 and has 85% sequence similarity to SARS-CoV. Until now, it has caused more than 100 000 confirmed cases of infection and almost 5000 deaths, having a mortality rate of 4%.

All information (symptoms, signs, management, complications) are taken from the other pandemic infections (SARS, MERS).

Information about viral infection concerning pregnant women are limited and are common to other SARS infections. There are very few cases of pregnant patients infected with SARS-CoV-2 and studies are ongoing.

**Keywords:** coronavirus infection, pregnancy.

## INTRODUCTION

Coronaviruses are a group of viruses that affect mainly mammals and birds, but being a zoonosis, infection could be transmitted to humans, causing the "common cold" in otherwise healthy people. The virus uses a densely glycosylated spike (S) protein to enter host cells, and the predominant human receptor is human angiotensin-converting enzyme 2 (ACE2), found primarily in the lower respiratory tract (1).

In humans, transmission occurs through close contact via respiratory droplets, generally causing mild flu-like symptoms such as fever, cough, nau-

sea, vomiting, diarrhea and in almost 10% of cases severe pneumonia requiring mechanical ventilation. Paraclinical tests include lymphopenia (70%), leukopenia (20%), thrombocytopenia (15%), prolonged prothrombin time (58%), elevated lactate dehydrogenase (40%). Chest radiographs are characterized by bilateral patchy infiltrates and chest CT scans demonstrate ground-glass infiltrates (2). The incubation time ranges from one day to 14 days, with a median of 4-5 days. The average age of hospitalized patients was 49-56 years, with 32-51% having an underlying illness. Children are less affected, accounting for less than 1% of the total population infected, and in most cases with mild symptoms (3, 4).

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In the past there were two major outbreaks of severe coronavirus infections with a high mortality rate: SARS-CoV (severe acute respiratory syndrome) in 2003 and MERS-CoV (Middle East Respiratory Syndrome) in 2013, each causing almost 800 and 400 deaths, respectively.

In December 2019, the first cases of pneumonia with a novel RNA beta-coronavirus were reported in Wuhan, China. The novel virus has almost 85% sequence similarity to SARS-CoV and is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (5). Since its discovery, the virus is rapidly spreading all over the world due to respiratory human-to-human transmission, long incubation time and mild symptoms. According to official data, it has caused more than 100 000 confirmed cases of infection and almost 5 000 deaths until now, having a mortality rate of 4% comparing to 1% mortality rate in normal seasonal flu (6, 7).

Given the rapid spread, WHO (World Health Organisation) has recently declared coronavirus disease a public health emergency of international concern and many radical safety measures have been adopted in order to limit the infection (7).

Limited data on coronavirus in pregnancy are published and many assumptions are made based on previous experience gained from SARS-Cov and MERS-CoV, also from influenza H1N1 outbreak and general information about pneumonia during pregnancy.

In this context, many questions arise and should be addressed: are pregnant women more prone to contact the infection due to their low immunity, is the maternal-fetal route a possible way of transmission, are symptoms more severe in pregnant women compared with the general population, which are the risks for the fetus and neonatal outcome, and should obstetricians follow a specific protocol to monitor and deliver these patients?

The aim of this paper is to review the current available data and summarize the main characteristics of the novel coronavirus infection (COVID-19) in pregnant women and present the latest protocol for monitoring and delivery of such patients.

### **Pneumonia in pregnancy**

Pneumonia, irrespective of etiology, is the most common non-obstetric infection during preg-

nancy and represents an important cause of morbidity and mortality among pregnant women (8). Mortality from pneumonia is uncommon in young women, but during pregnancy almost 25% of women with pneumonia will require hospitalisation in intensive care units and ventilatory support due to physiologic altered cell-mediated immunity and normal changes in their pulmonary function. Mortality rate is quoted as high as 17% (9). During pandemic influenza H1N1 infection in 2009, 10% of pregnant women were admitted to ICU with severe pneumonia and 11% of these patients died (10).

Hypoxemia and acidosis are poorly tolerated by the fetus and there is a higher risk of premature rupture of membranes, preterm delivery, growth-restricted infants or, in extreme cases, even intrauterine fetal demise or neonatal death (11, 12). Case review studies report an incidence of preeclampsia of 25% among pregnant women with pneumonia and a higher rate of placental abruption in patients with severe respiratory conditions requiring hospitalization (9, 12). The pathophysiological process relates to hypoxemia, which subsequently causes placental hypoxia. The hypoxic placenta releases antiangiogenic and proinflammatory factors that induce endothelial dysfunction, hypertension, and organ damage.

Taking into consideration the potential complications of pneumonia, current recommendations state that any pregnant woman suspected of having pneumonia should undergo chest radiography in order to facilitate early diagnosis and appropriate treatment.

### **Influenza H1N1 outbreak**

In front of a new pandemic coronavirus infection, specialists and health organisations recall the H1N1 influenza virus that produced the first pandemic infection in more than 40 years and caused more than 18 000 deaths globally in 2009 (13). At that time, pregnant women and newborns were among those at greater risk and special attention has been drawn to develop specific recommendations. In response, Centre for Disease Control (CDC) has made the several recommendations, as follows (14, 15).

- Pregnant women with confirmed or suspected H1N1 influenza, regardless of influenza vaccination status, should receive

prompt empiric treatment with oseltamivir starting within 48 hours of illness onset and continued for five days; present studies do not demonstrate increased fetal risk after maternal oseltamivir exposure, irrespective of gestational age.

- Fever during pregnancy might be associated with increased adverse outcome and antipyretic medication are required, acetaminophen being the safest option, although some studies show a correlation with asthma in offspring (16).
- All women who are pregnant during the influenza season, regardless the gestational age, should receive the inactivated influenza vaccine with potential benefits for the fetus due to transplacental antibodies passage (17). Despite recommendations and evidence-based safety and benefits, vaccination coverage of pregnant women remained less than 20%.
- Current data do not demonstrate a possible vertical transmission, but infants born to symptomatic mothers at the time of delivery should be closely monitored.
- Breastfeeding is not contraindicated if the mother is symptomatic or even under antiviral treatment. Oseltamivir administration during lactation poses no harm to breastfeeding infants.
- Pregnant women are not considered more susceptible to influenza infection, but they are at greater risks for severe complications than non-pregnant women once the infection is contracted, with a 4-fold increased risk of hospitalization, mechanical ventilation and death.

### SARS and pregnancy

In 2003, severe acute respiratory syndrome outbreak was caused by a novel coronavirus and has affected more than 8000 persons, of which almost 800 died. It was estimated that there were 100 pregnant women among those 8000 cases reported worldwide (18).

Although data about documented cases of SARS during pregnancy are limited, similarly to most viral pneumonia in pregnancy, SARS imposes a greater risk of morbidity and mortality in pregnant than non-pregnant patients.

The diagnosis was established based on clinical symptoms, radiological findings of pneumonia and a positive result on reverse transcriptase polymerase chain reaction (RT-PCR) or serological testing for SARS-CoV.

In a small series of 12 pregnant women with SARS, the common symptoms were fever over 38°C, cough, chill, malaise, myalgia and laboratory results showed lymphopenia, mildly elevated transaminase or lactate dehydrogenase. Maternal implications were severe: 50% admission to intensive care unit, 33% required mechanical ventilation and 25% mortality rate. Out of 12 cases, seven occurred in the first trimester and almost 60% ended in spontaneous miscarriage. The other five cases ranged from 26 to 32 weeks and 80% of those resulted in preterm delivery (19).

Viral cultures from cord blood, placenta or amniotic fluid were all negative. Although there was no evidence of vertical or perinatal transmission, fetal outcome was complicated by intrauterine growth restriction, oligohydramnios, fetal distress or prematurity. Histopathological analysis of the placenta showed normal findings in three cases and avascular fibrosis with thrombotic vasculopathy in cases complicated by intrauterine growth restriction (20).

In most cases, treatment consisted of antibiotics, intravenous hydrocortisone and ribavirin, despite its embryocidal and teratogenic effects. Patients using ribavirin in the first trimester should be offered the option for termination of pregnancy (19).

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.

### COVID-19 in pregnancy

Facing a novel, rapidly spreading infection, uncertainty and urgent questions regarding the most susceptible and at greater risk groups arise and need to be addressed. Based upon previous experience with coronavirus outbreaks like SARS, there is no evidence that pregnant women are more susceptible to infection; in fact, current data show that more men have been affected than women, with a higher mortality rate comparing to women (2.7% vs 1.7%).

Two recent small series of COVID-19 in nine and 10 pregnant women, respectively, have been published (21, 22). Symptoms were similar to those encountered in the general population and in 80% of cases, infection starts with fever and cough. The diagnosis was confirmed based on positive RT-PCR for SARS-CoV-2 on samples collected from the respiratory tract (4).

In the first series by Chen *et al* (21), all nine cases occurred in the third trimester and all underwent caesarean section. Patients were treated with empirical antibiotics and antiviral therapy. Unlike SARS, there were no deaths or cases with severe pneumonia requiring mechanical ventilation. No fetal or neonatal deaths were recorded, but there was a 50% rate of preterm labour with a favourable neonatal evolution in all cases, although it was unclear whether the preterm delivery was always iatrogenic or spontaneous. The presence of SARS-CoV-2 was tested in the amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples, and none of these was positive.

In a second series of nine patients and ten infants, reported by Zhu *et al* (22), the clinical presentation, evolution and pregnancy outcomes were in agreement to previous report results. Fetal distress and preterm delivery were the most common perinatal complications, being thought to be related to maternal hypoxemia. In this series, one case of neonatal death and one case of a patient who required mechanical ventilation at 30 weeks were reported.

Although there is no evidence of vertical transmission, data are insufficient to draw a pertinent scientific conclusion. Moreover, on the 5<sup>th</sup> of February 2020, a newborn infant to a mother with COVID-19 pneumonia was tested positive for SARS-CoV-2 30 hours after birth (23).

### Recommendations for pregnant women

There is currently no specific antiviral treatment or vaccine against the novel coronavirus. General principles and symptomatic treatment include intravenous fluids, antipyretics, empiric antibiotic therapy, considering the risk for superimposed bacterial infections, early oxygen therapy aiming for O<sub>2</sub> saturations  $\geq 95\%$  and/or pO<sub>2</sub>  $\geq 70$  mm Hg, broad-spectrum antivirals, such as remdesivir, or lopinavir/ritonavir and interferon beta are an option against 2019-nCoV

based on previous observations in MERS-Cov outbreak (4, 24). Recently, China approved the use of favilavir, an antiviral drug used for influenza, as investigational therapy for COVID-19 (1). Corticosteroids did not show benefits in the treatment of coronavirus-associated pneumonia; moreover, they could prolong viral clearance (24).

Based on current data, international medical organisation proposed a management algorithm for healthcare providers dealing with pregnant patients exposed to COVID-19 (25, 26):

- Any pregnant woman who has travelled in a country affected by SARS-CoV-2 within the previous 14 days or who has had close contact with a patient with confirmed SARS-CoV-2 infection should be tested with a SARS-CoV-2 nucleic acid amplification test.
- Pregnant women with laboratory-confirmed SARS-CoV-2 infection who are asymptomatic should be self-monitored at home for at least 14 days. Due to the potential risk of intrauterine growth restriction, these patients should be monitored with bimonthly fetal growth ultrasounds and Doppler evaluation.
- Pregnant women with COVID-19 pneumonia should be managed by a multidisciplinary team at a tertiary care centre, in an isolated room, with negative pressure if available.
- During hospitalization, maternal evaluation should be undertaken through regular measurements of temperature, heart and respiratory rate and blood pressure (3-4x/day) plus chest imaging (high resolution CT-scan or X-ray).
- Fetal evaluation undertaken through fetal heart rate monitoring (1x/day) and consider dexamethasone injection for lung maturation, depending on gestational age and maternal pulmonary inflammation.
- Admission to an intensive care unit should be decided based on the following criteria: systolic blood pressure  $< 100$  mm Hg, respiratory rate  $> 22$ , Glasgow conscious score  $< 15$ .
- Emergency caesarean section required in case of septic shock, acute organ failure or signs of fetal distress.

Regarding delivery and postpartum monitoring, the following recommendations are in place:

- before 24 weeks (fetal viability), in case of severe maternal illness, consider termination of pregnancy if legal
- after 24 weeks: vaginal delivery is recommended when possible, early clamping of the umbilical cord and early cleaning of the newborn
- newborns of mothers positive for SARS-CoV-2 should be isolated for at least 14 days or until viral shedding clears, and during this time interval direct breastfeeding is not recommended. All babies of women with suspected or confirmed COVID-19 need to be tested for COVID-19 too. □

## CONCLUSION

Although current evidence show that the novel coronavirus infection in pregnant women seems to be less aggressive than previous SARS and MERS infections, pregnant women should be considered a vulnerable group requiring special care. Further clinical research is critical to understand the potential risks, to improve the care and to develop specific treatment of the current or future outbreak. □

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