

Original Research Article

Pregnancy and COVID – 19: From Early Diagnosis to Immediate and Effective Treatment

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Abstract

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"Coronavirus of Wuhan" or "new Coronavirus" or SARS – CoV – 2 (Severe Acute Respiratory Syndrome – Coronavirus – 2) causes an infection known as COVID – 19. Infection is transmitted mainly by inhalation or contact with infected droplets, after coughing and sneezing by symptomatic or asymptomatic patients. The main characteristic clinical feature of COVID – 19 is fever accompanied by cough and/or shortness of breath. To confirm the diagnosis, molecular testing is required for sputum smears or secretions, preferably from the lower respiratory tract, as well as computed tomography (CT) scan of the lungs. There is no specific treatment. Adherence to the basic principles of management during pregnancy, labor and postpartum is mandatory. This article reviews the COVID – 19 infections during pregnancy, with regard mainly to the diagnosis and basic principles of women's management, as well as during childbirth and puerperium, the proper application of which is estimated to ensure the lowest rates of viral transmission to the mother and the newborn.

Keywords: SARS – CoV – 2, COVID – 19, pregnancy, transmission, symptoms, management, prevention.

INTRODUCTION

The incidence of infections during pregnancy is generally limited. However, any infectious diseases that affect the non-pregnant women, can occur during pregnancy and puerperium and adversely affect the normal progression of the pregnancy, as well as the perinatal outcome. It is generally known that pregnant women demonstrate increased morbidity and mortality for certain diseases, due to the hematological and immune changes that characterize the normally developing pregnancy (Eppes, 2016). Certain infections, such as urinary tract infections, sexually transmitted diseases and vaginitis, often affect pregnant women and cause complications that require special treatment (Leeper and Lutzkanin, 2018). Similarly, pregnancy due to physiological changes in the cardiorespiratory system predisposes to respiratory viral infections which can lead to serious complications (Siston et al., 2010).

Coronaviruses cause infections of the respiratory system, as well as intestinal infections in animals and humans (Masters and Perlman, 2013). Most coronaviruses infect exclusively animals, but strains that are capable of transmission to humans have been identified. Coronaviruses were not initially considered highly pathogenic to humans, as they used to cause mild infections mainly in immunocompromised individuals, until they have been identified as the cause of severe acute respiratory syndrome in 2002 and 2003 in Guangdong Province, China (Zhong et al, 2003; Drosten et al, 2003; Ksiazek et al, 2003) and ten years later in countries of the Middle East (Zaki et al, 2012). Thus, the recent appearance of the new coronavirus in December 2019 in Hubei Province, China, marked the third introduction of a highly pathogenic and large-scale coronavirus epidemic to the human population, in the



Figure 1. The new coronavirus (SARS – Cov – 2) responsible for the onset of COVID – 19 pneumonia (WHO, 2019).

twentieth-first century. On January 30, 2020, the World Health Organization (WHO) officially declared the COVID – 19 pandemic a public health emergency of international concern (Guo et al, 2020).

Historical Background - Epidemiological Information

Human coronaviruses (HCoVs) were first described in the 1960s, in patients suffered by common cold symptoms. Since then, more strains have been identified, including those causing the Severe Acute Respiratory Syndrome (SARS – Cov) and the Middle East Respiratory Syndrome (MERS – Cov). SARS – Cov and MERS – Cov are two highly contagious and pathogenic viruses most likely derived from bats (Cui et al, 2019). Coronaviruses are coiled, unsegmented, ribonucleic viruses belonging to the family of Coronaviridae, series of Nidovirales (Su et al, 2016). Coronaviruses are RNA viruses with a diameter ranging from 60nm to 140nm. On the surface they have protrusions similar to a spike (figure 1) (WHO, 2019), which give them the appearance of a crown (corona), hence the name coronavirus (Richman et al, 2016).

The "Wuhan coronavirus" or "novel coronavirus" is a new member of the coronavirus family, whose codename is SARS – CoV – 2 and causes an infection called COVID – 19. The new coronavirus infection belongs to the same subgroup and has a genome similarity to SARS – CoV and MERS – CoV of approximately 80% and 50% respectively (Lu et al, 2020). All ages are estimated to be susceptible to COVID – 19, with the disease being more common among men than women (Liu et al, 2020). The incubation period of the infection varies from 2 to 14 days

(a median of 5 days). Studies have indicated that the viral loads are higher in the nasal cavity compared to the pharynx, but there is no difference in the viral load between symptomatic and asymptomatic patients (Zou et al, 2020). Cheng and Shan from their own research concluded that the angiotensin II receptor (ACE 2), is used by the virus in order to enter the respiratory mucosa (Cheng and Shan, 2020).

Transmission

SARS – CoV – 2 is estimated to be derived from bats and was transmitted to humans through unknown intermediates in Wuhan City of Hubei Province, China, in December of 2019. The infection is transmitted by inhalation or contact with contaminated droplets, generated during coughing and sneezing, from symptomatic or asymptomatic patients (Rothe et al, 2020; Lu CW et al, 2020). To and colleagues in their published study demonstrate saliva as a means of transmitting the virus, promising at the same time to provide a non-invasive rapid test for the diagnosis, monitoring and control of COVID – 19 patients (To et al, 2020). Furthermore, although there are references in the literature that the transmission of the infection can be through aerosols formed during medical procedures, or through feces, it is recommended that these data should be checked and confirmed by more well-designed clinical studies (Wax and Christian, 2020; Holshue et al, 2020). However, regardless of the mode of transmission, the new coronavirus is estimated to be spreading faster than its two ancestors (SARS - CoV and MERS - CoV), with a

Table 1. Clinical manifestations of the new coronavirus infection (COVID – 19) in pregnancy.

Fever
Cough
Shortness of breath
Myalgias
Fatigue
Sore throat
Headache
Haemoptysis
Diarrhea

global impact which can not yet be assessed (Singhal, 2020; Wang et al, 2020).

In the limited bibliography available to date, the particularly small number of positive obstetric cases worldwide does not allow safe conclusions to be drawn, regarding the vertical transmission of SARS – CoV – 2. In contrast to other viral infections, especially Ebola (Schwartz, 2020) and Zika viruses (Alvarado and Schwartz, 2017), that demonstrate a high incidence of intrauterine transmission, in no case to date has described a vertical transmission of SARS – CoV – 2 from the mother to the fetus during pregnancy. Chen and colleagues analyzing the results of their study, evaluated the clinical features of COVID – 19 in pregnancy and the potential for intrauterine vertical transmission. They concluded that there is currently no evidence to support the vertical transmission of the infection during pregnancy, or immediately after delivery from the mother to the fetus and newborn (Chen et al., 2020).

Similar to the results of other research studies, it has been indicated that there have been no confirmed cases of intrauterine transmission of SARS – CoV – 2 from affected mothers to their fetuses, but additional research is necessary in order to verify the accuracy of this finding (Schwartz, 2020; Fan et al, 2020; Stower, 2020; Karimi – Zarchi et al, 2020). In contrast, in a recent study published on March 26, 2020, Dong and his colleagues described a case of intrauterine transmission of the virus, as SARS – CoV – 2 IgM was detected to the newborn immediately after the delivery (Dong et al., 2020).

Diagnostic Approach

The data available to date regarding SARS – CoV – 2 infection during pregnancy are limited. Our knowledge of the virus' clinical behavior is constantly updated (Rasmussen et al, 2020). Although it is well known that pregnant women are more vulnerable to infectious diseases, due to the suppression of their immune system which normally occurs during pregnancy (Mor et al, 2011), there are no scientific data to date to classify them as a high risk group. The clinical features of COVID – 19 associated pneumonia among pregnant women are similar to those reported in non – pregnant adult patients

with pneumonia (Chen et al, 2020; Yu et al, 2020). The main clinical feature is fever which is observed in almost all cases (Table 1). Other symptoms such as cough, myalgias, sore throat and malaise are less common and in some cases the infection may present with headache, haemoptysis or diarrhea. Dyspnoea is estimated to affect more than half of the patients and occurs approximately on the eighth day after the onset of the disease (Chen et al, 2020; Huang et al, 2020).

The symptoms of acute respiratory infection in each case (fever and at least one sign / symptom of respiratory disease, such as cough, shortness of breath), but also the history of travel to an area or country where the local spread of the infection is reported, or a contact with a confirmed or possible COVID – 19 case the 14 days before the onset of symptoms, raise a serious suspicion of infection with the new coronavirus (WHO, 2020). To confirm the diagnosis of any suspected case, it is necessary to perform a test with the available molecular techniques, such as the detection of the virus genome in a sputum smear or secretions from the lower respiratory tract with the use of the qRT – PCR, or the detection of the virus' antibodies in the peripheral blood. Samples from the lower respiratory tract are preferred, as they are estimated to have a higher diagnostic value in detecting COVID – 19 infection than samples from the upper respiratory tract. However, a false negative result, which is probably due to insufficient material sampling, can not be ruled out (Liu et al, 2020).

The role of chest imaging in the detection of COVID – 19 infections is of paramount importance. Compared to chest X – ray, the computed tomography scan (CT) demonstrates a higher sensitivity and specificity in the diagnosis and monitoring of pneumonia caused by the virus. Recently Guan and his colleagues indicated that in 76.4% of cases with findings of viral pneumonia, COVID – 19 infection was confirmed in CT scans and only 2.9% of patients with severe disease were without imaging findings consistent with viral pneumonia during the chest CT screening (Guan et al, 2020). Similarly, recent studies report cases of SARS – CoV – 2 infection with initially negative sputum smears, but with typical findings of the disease in chest CT scans, indicating the great benefit of imaging control, and in particular CT scans, in the diagnosis and monitoring of pneumonia caused by the

new Wuhan coronavirus (Xie et al, 2020; Huang P et al, 2020). Towards the same direction, Liu and his colleagues demonstrated that the CT scan consists the method of choice for the early detection, assessment of severity and the monitoring of therapeutic effects in patients with epidemiological and clinical characteristics of COVID – 19 infection, with or without laboratory confirmation (Liu et al, 2020). Based on the epidemiological characteristics of COVID – 19 pneumonia, patients with typical imaging findings from CT scans in Hubei Province were grouped as clinically diagnosed cases and included in the total number of confirmed cases according to the "Diagnosis and Treatment for COVID – 19 Pneumonia (Fifth Edition)" published by the National Health Commission (NHC) of China as of February 12, 2020 (NHC, 2020).

The diagnostic approach in pregnant women with COVID – 19 pneumonia must overcome the "traditional" phobias regarding the imaging radiological examination. The chest x-ray and especially the CT scan are both necessary for confirming the diagnosis and the clinical follow – up of a pregnant woman with a severe SARS – CoV – 2 infection. In those cases where the clinician considers that the use of a chest X – ray is essential, pregnancy should not be a deterrent (Li and Xia, 2020; Zhao et al, 2020; Ai et al, 2020). Based on valid bibliographic data, it is estimated that the radiation dose to the fetus from a posterior chest X – ray is 0.0005 – 0.01 mGy, while the radiation dose to the fetus after a computed tomography scan is 0.01 – 0.66 mGy. As the exposure of the fetus to radiation after a chest x – ray or a CT scan of the pregnant woman is much lower than the level which is associated with fetal defects, pregnancy should not lead to the unnecessary avoidance of these diagnostic tests, which in many cases may be proven very useful in the differential diagnosis between COVID – 19 pneumonia and other viral and bacterial infections of the respiratory system, with similar symptoms and clinical course (Committee on Obstetric Practice, 2017; American College of Radiology, 2018; Jin et al, 2020).

Treatment

Strict adherence to the basic principles of management of pregnant women with or without a confirmed infection of the new coronavirus during pregnancy, childbirth and in the immediate postpartum and lactation period, must be of paramount importance and necessity in order to ensure the most favorable outcome for both the mother and the newborn (Poon et al, 2020).

Management during the prenatal period

Isolation of pregnant women with mild symptoms at home, as well as recommendations that are largely

based on what we know well from seasonal flu, such as avoiding contact of pregnant women with sick people, avoiding touching their face, covering the mouth and nose in case of coughing or sneezing, proper washing of hands with soap and cleaning of contaminated surfaces with appropriate disinfectants, could lead to a reduction in the spread of the epidemic, as a large increase in the number of seriously infected women could endanger the lives of pregnant women in the third trimester of pregnancy (Rasmussen et al, 2020). Thus, all pregnant women, especially those over 28 weeks, as well as pregnant women with a history of heart disease should be particularly careful with their social lives, minimizing their contact with other individuals (COVID – 19, 2020; COVID – 19, 2020; COVID – 19, 2020). On the other hand, it is useful to notice that the social isolation combined with financial difficulties, insecurity and inability to access health systems, is estimated to significantly increase the risk of perinatal stress, depression and domestic violence (Fraser, 2020).

The obstetric monitoring is necessary in any case, unless pregnant women are qualified for self-isolation at home. A well-organized health system is therefore desirable, in order to allow pregnant women to access obstetric attendance with minimal risk of viral exposure during the epidemic (Chen Y et al, 2020). Pregnant women and accompanying visitors entering obstetric units should be screened for fever and respiratory symptoms, while the symptomatic ones should be isolated and wear a personal protective mask. The perinatal care has been proven, according to past and newer studies, highly important, as it is estimated that women who do not have the proper regular monitoring in pregnancy are at increased risk of perinatal complications. The possibility of videoconferencing in order to examine which appointments can be held remotely, could be an objective among obstetric hospitals, in order to avoid unnecessary overcrowding of pregnant women at the outpatient clinics (Dowswell et al, 2015; Knight et al, 2018).

Pregnant women with possible or confirmed COVID – 19 infection who are asymptomatic or recovering with mild symptoms, should be monitored by ultrasound (biophysical profile, amniotic fluid volume, Doppler umbilical artery) every two to four weeks depending on their gestational age (Favre et al, 2020), as it is well known that the viral pneumonia in pregnancy is associated with an increased risk of preterm birth, impaired intrauterine fetal development and perinatal mortality (Madinger et al, 1989; Wong et al, 2004; Chen YH et al, 2012). After the end of the ultrasound examination it is necessary to clean and disinfect the surfaces of the ultrasound probes, according to the specifications of the manufacturer. In the case of a highly infectious pregnant woman, it is necessary to clean all the equipment thoroughly, including the surfaces of the bedside tables and the entire equipment area

(Basseal et al, 2017).

If the pregnant woman with a confirmed COVID – 19 infection experiences more severe symptoms or a significantly delayed recovery, which are indicative of a serious respiratory infection, admission to a hospital able to manage pregnant women may be required, taking into consideration and priority the safety of the pregnant woman, newborn and health care professionals (Dashraath et al, 2020). To date, specific proven antiviral therapy for COVID – 19 patients does not exist, although antiretroviral drugs are being tested therapeutically in patients with severe illness (Boseley, 2020; NIH, 2020). The health care unit in which the pregnant woman will be admitted, should be a tertiary hospital (reference hospital), which will have effective isolation facilities, the necessary protective equipment for medical and nursing staff, a negative pressure operating theatre and a neonatal isolation ward. In the event that a negative pressure isolation room is not available, the pregnant woman should be isolated in a single room or grouped with other confirmed cases (Maxwell et al., 2017; Poon et al., 2020).

Management during childbirth

The labor of possible and confirmed COVID – 19 pregnant women should ideally take place into a negative pressure isolation room. The time and mode of delivery should be individualized, depending mainly on the clinical condition of the pregnant woman, the age of pregnancy and the condition of the fetus (Qi et al, 2020). Thus, immediately after the admission of the pregnant woman into the specially designed area of the maternity hospital, the assessment of the severity of the symptoms of the COVID – 19 infection by a multidisciplinary team is of paramount importance. In addition, the confirmation of the onset of the labor requires continuous external cardiotocographic monitoring of the fetus, in order to detect an early fetal distress that is very common during the course of childbirth among COVID – 19 infected mothers (Zhu et al, 2020). The spouse – partner should be encouraged to be present at the childbirth, as it is estimated to have an important role to the safety and good psychology of the pregnant woman (Bohren et al, 2017; Shakibazadeh et al, 2018; Bohren et al, 2019), except of course in those cases where the birth takes place by caesarean section (Zeng et al, 2020).

Clear indications on the optimal timing of delivery, the safety of vaginal birth against caesarean section and whether performing a caesarean section can prevent vertical transmission of the virus from the mother to the newborn based on the bibliographical data to date, do not exist. The mode and time of delivery, as mentioned above, should be individualized on the basis of obstetric indications and the condition of the fetus (Chen D et al, 2020). The small number of pregnant women included in

the studies to date cannot ensure safe and definitive conclusions, as to whether a caesarean section should be preferred over vaginal delivery, in order to minimize the risk of transmission of SARS – CoV – 2 from the infected mother to the newborn (Li Y et al, 2020).

At the same time, a recent study published by Zhang and his colleagues focusing on the effect of COVID – 19 infection on pregnancy and neonatal prognosis in China's Hubei Province, indicated that when there is an indication for caesarean section in pregnant women with COVID – 19, early termination of pregnancy does not increase the risk of prematurity and respiratory distress of newborns, but it is highly beneficial for the early initiation of treatment and the full recovery of COVID – 19 pneumonia (Zhang et al, 2020).

In addition, the preoperative evaluation of pregnant women with COVID – 19 infection and the application of the appropriate anesthesia plan before performing the caesarean section, is of very significant in order to be ensured the uncomplicated course of both the operation and the postoperative period for the mother and the newborn. Since COVID – 19 disease affects the cardiopulmonary function of the pregnant women, the application of anesthesia during the caesarean section as well as the protection of the medical personnel, should differ significantly from the routine procedures. For patients with mild symptoms, regional anesthesia, that offers a minimal effect on the respiratory system and systematic circulation of the mother and newborn is preferred, while for patients with severe or critical disease general anesthesia with intratracheal intubation should be selected (Kang et al, 2020).

At the same time, the safety of the medical and nursing personnel must be ensured and standard protection should be taken by anesthesiologists (Kang et al, 2020). In the negative pressure delivery suits or operating theatres of the designated reference hospitals, all the personnel involving in the care of confirmed COVID – 19 cases should use a protective personal mask, wide field protective glasses, Tyvek-type uniform, disposable gloves with long cuffs, surgical mask and overshoes (Maxwell et al, 2017; Lee et al, 2020). In the case of vaginal delivery of a pregnant woman with an unconfirmed COVID – 19 infection, special attention is required during the second stage as the strong exhalation of the woman significantly reduces the effectiveness of her individual protective mask, which may contribute to the spread the virus to the medical personnel who do not use a personal protective equipment (Yang et al, 2020).

Management postpartum and during puerperium

Limited data to date are provided to guide the postnatal management of newborns, born from mothers positive for COVID– 19 infection in the late third trimester of pregnancy. The experience from China recommends the

separate isolation of the infected mother and newborn for 14 days. However, the preventive separation of the mother from the newborn should not be a routine practice and should not be attempted without a second thought in any case, as it can have harmful effects on the newborn, concerning both the feeding and its emotional – psychological status. In any case, the discussion between the couple and the team of neonatologists, regarding the room-in next to their mother during the immediate postpartum period, is considered paramount and necessary (Health RCoPaC, 2020).

Taking into account the available bibliographical data, it is indicated that the SARS – CoV – 2 has not been detected in the milk of positive women and there is no information on possible transmission of the virus through the breast milk. The risk of transmission of the virus from the mother to newborn during breast-feeding is associated with the close contact, especially through droplets of the respiratory system and excretions during coughing or sneezing. Given the limited data on the behavioral status of the new coronavirus and the infection it causes, at this stage and subject to changes, the decision on the breast-feeding procedure should be individualized and should take seriously into account the benefits of breastfeeding versus the potential risks. Pumping breast milk in compliance with sterilization rules and possibly administering it by another person to the newborn should be an alternative (CDC, 2019; EOΔY, 2020).

The Hellenic Society of Perinatal Medicine, based on the "Protocol for the management of a neonatal born to a mother with a suspected or confirmed COVID – 19" infection, indicates that, although there is no evidence that the virus is transmitted through the breast milk, breast-feeding is contraindicated in order to avoid exposure of the newborn to the respiratory secretions of the mother. In the event that the mother wishes to breastfeed, it is recommended for the maintenance of lactation, the extraction of the milk with the use of a breast pump and its rejection, while starting the breastfeeding with the assurance that the mother is negative for the virus and her treatment has been discontinued or completed. It is estimated that Lopinavir-Ritonavir combined medication is not a contraindication to breast-feeding, but it should be avoided if the mother is under chloroquine treatment (EEΠI, 2020).

Prognosis

The published studies so far have not correlated the risk of infection among pregnant women with the new SARS – CoV – 2, compared to the general population. There is no indication so far that pregnant women are more vulnerable to COVID – 19, or that pregnant women with COVID – 19 infection are more susceptible to severe pneumonia. However, according to the available data

from cases of infections by other coronaviruses in the past, such as the SARS – CoV and MERS – CoV, as well as from other viral respiratory infections as influenza, the possibility of severe disease and an increased morbidity and mortality among pregnant women in comparison to the general population cannot be excluded (Schwartz and Graham, 2020; Rashidi Fakari and Simbar, 2020).

Despite the high mortality rate of pregnant women with SARS – CoV infection, which amounts to 25% of cases (Wong et al., 2004), recently Schwartz in a limited numerical study of 38 pregnant women with COVID – 19 indicated that no maternal death was caused (Schwartz, 2020). Towards the same outcome, Liu and co analyzing the data of their study, the purpose of which was to describe the clinical manifestations and imaging findings on CT scans of 15 pregnant women with COVID infection – 19, concluded that pregnancy and childbirth did not exacerbate the course of clinical symptoms, or the imaging findings of CT scans of pregnant women with COVID – 19 pneumonia. All pregnant women with COVID – 19 pneumonia demonstrated mild symptoms and fully recovered, some of which without the administration of specific anti-viral therapy. There were no reported cases of miscarriage, fetal distress or neonatal death (Liu D et al, 2020).

However, for the accurate and safer control of complications concerning the mother, the fetus and the newborn, data analysis of more cases with SARS – CoV – 2 and COVID – 19 pneumonia is required. Regarding the limited number of pregnant women with COVID – 19 infection published to date, there were reported cases of adverse events such as miscarriage, preterm birth and respiratory distress of the newborns of infected mothers, without any clear evidences that these complications are causally related to the new COVID – 19 infection (Peyronnet et al, 2020; Panahi et al, 2020). Furthermore, although previous studies have not reported any cases of congenital infection with SARS – CoV, the scientific data to date cannot correlate the risk of congenital fetal abnormalities with the onset of COVID – 19 infection during the first or second trimester of pregnancy (Shek et al, 2003).

CONCLUSION

The infection caused by the new coronavirus (COVID - 19) is a serious public health issue with a rapid increase in the cases and deaths since its first detection in Wuhan of China, in December 2019. Previous experiences with other coronaviral infections during pregnancy were associated with negative clinical outcomes for the maternal health, demonstrating high morbidity and mortality. In the contemporary context of the pandemic from the new SARS – Covid – 2, various proposals have been submitted by the competent scientific organizations, concerning the management of possible and confirmed

cases among pregnant women. Although relevant guidelines were proposed by the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention, based on the best available data, additional information and in-depth analysis of affected pregnancies are needed for an advanced level of knowledge about this issue. Furthermore, as the next decade is likely to highlight global challenges affecting the public health and the healthcare systems, it is mandatory to ensure the future resilience of the national health services by adequately supporting the state hospitals with all the healthcare staff needed, in order to combat the possible future health challenges (Giwa et al, 2020; Catton, 2020).

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