COVID-19 impact on perinatal care: risk factors, clinical manifestation and prophylaxis. Polish experts’ opinion for December 2020

Jaroslaw Kalinka1, Miroslaw Wielgos2, Bozena Leszczynska-Gorzelak3, Anna Piekarska4, Hubert Huras5, Piotr Sieroszewski6, Krzysztof Czajkowski7, Jacek Wysocki8, Ryszard Lauterbach9, Ewa Helwich10, Jan Mazela11

1Department of Perinatology, 1st Chair of Gynecology and Obstetrics, Medical University of Lodz, Poland
21st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
3Department of Obstetrics and Perinatology, Medical University of Lublin, Poland
4Department of Infectious Diseases and Hepatology, Medical University of Lodz, Poland
5Department of Obstetrics and Perinatology Jagiellonian University Collegium Medicum, Cracow, Poland
6Department of Fetal Medicine and Gynecology, Medical University of Lodz, Poland
72nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
8Chair and Department of Health Prophylaxis, Poznan University of Medical Sciences in Poznan, Poland
9Department of Neonatology, Jagiellonian University, Cracow, Poland
10Department of Neonatology, Institute of Mother and Child, Warsaw, Poland
11Department of Newborns’ Infectious Diseases, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT
Rapid spread of severe acute respiratory syndrome coronavirus-2 virus (SARS-CoV-2) caused the pandemic of Coronavirus Disease 19 (COVID-19). Clinical course of the disease presents symptoms mainly from the respiratory system such as: cough, dyspnea and fever, and among some patients, can deteriorate even further to acute respiratory distress syndrome (ARDS), eventually leading to death. This outbreak, as well as previous ones (SARS, MERS) pose a significant challenge for health care managers, epidemiologists and physicians. Below we are presenting the clinical profile of the COVID-19 among special group of patients; pregnant women and newborns, who require special clinical management during hospitalization. In the summary of this manuscript, we present practical guidelines for managing pregnant women infected with SARS-CoV-2, labor and care of the newborn of a positive mother, as well as practical guidelines for COVID-19 vaccinations. It is important to stress, that this manuscript is based on information available as of December 2020.

Key words: COVID-19 infection; Sars-CoV-2 virus; maternal and neonatal outcome; coronavirus disease

INTRODUCTION
SARS-CoV-2 belongs to a group of spherical enveloped RNA viruses, the beta subtype of coronaviruses. As of 2019, six viruses of this group were known to cause infections in humans. Four of them (229E, OC43, NL63, HKU1) are known to cause a mild infection in people. The remaining two have shown to be the cause life-threatening acute respiratory distress syndrome (ARDS): SARS (severe acute respiratory syndrome) caused by SARS-CoV and MERS (Middle East respiratory syndrome) caused by MERS-CoV [1–3]. COVID-19 is a disease caused by the Wuhan coronavirus (SARS-CoV-2). The name COVID-19 developed by the World Health Organization (WHO) stands for “CO” — corona, “VI” — virus, “D” — disease, and the number 19 indicates the year the virus appeared — 2019 (Corona-Virus-Disease-2019) [3]. By December 31, 2020, there were 85 899 563 confirmed cases and 1 858 412 deaths due to COVID-19. The rapid spread of the virus along with a severe clinical course of disease in most hospitalized patients raises questions about the risks of COVID-19 on people with an increased risk of infection. Based on this information, it is necessary to establish special procedures that will be used for the prevention, diagnosis and treatment of COVID-19, especially for pregnant women during labor and newborns who present to the hospital with symptoms of infection.
CLINICAL MANIFESTATION OF COVID-19 INFECTION IN PREGNANCY

The results based on 28 studies and 11,432 patients selected for the systematic review found that from 7–14% of pregnant women presenting or admitted to the hospital tested positive for COVID-19; 85% of them had infection identified in third trimester. Of these positive women 75% were asymptomatic, severe COVID-19 was diagnosed in 13% of pregnant women, 4% was admitted to Intensive Care Unit (ICU) and 3% required invasive mechanical ventilation. Pregnant women with COVID-19 manifested fewer symptoms than general population while the predominant features of symptomatic COVID-19 in pregnant women were cough (33%) and fever (29%). Compared to non-pregnant women with COVID-19 pregnant women were less likely to report fever (OR = 0.48 CI: 0.22–0.85) and myalgia (OR = 0.48 CI: 0.45–0.51) [1, 2].

Among pregnant women with COVID-19 infection leukopenia (66.1%) and lymphopenia (48.3%) were the most common laboratory abnormality (66.1%) with other common abnormalities like elevated: CRP, D-dimer, lactate dehydrogenase (LDH) and IL-6. Combination of elevated D-dimer and IL-6 was associated with more severe disease and found in 60% of severely ill and in 80% of critically ill pregnant women, respectively.

Unilateral or bilateral ground-glass opacities were the most common imaging findings. Observed mortality rates for pregnant women with COVID-19 were 0.1-2.0% what is comparable to general population, but pregnant women were more likely to require mechanical ventilation and admission to an ICU; (OR = 1.62 CI: 1.33–1.96) [1]. As much as 40% of pregnant women who died from COVID-19 had obesity, diabetes or maternal age over 40 years.

CORONAVIRUSES AND THE OCCURRENCE OF FETAL MALFORMATIONS

There is currently insufficient evidence that coronavirus infection has a negative impact on the incidence of fetal defects. This applies to the "common cold" coronaviruses as well as SARS, MERS and SARS-CoV-2. The frequency of malformations in the offspring of infected women does not differ from the population average. This is possibly related to the low risk of vertical viral transmission due to short period of viremia and poor ACE-2 expression in the placenta. In the case of SARS-CoV-2, the estimated frequency of infection by this route may be 2.6% according to the CDC report. However, the negative impact of fever, one of the most common symptoms of COVID-19, on the occurrence of fetal malformations should not be underestimated. Among single congenital defects, the most common were heart defects, cleft lip palate, defects of the genitourinary system and chromosomal disorders. The use of anti-fever medica-

THE IMPACT OF COVID-19 INFECTION ON PREGNANCY OUTCOMES

Knowledge regarding impact of COVID-19 on perinatal outcomes is limited due to small study population, different testing methods ranging from universal SARS-CoV-2 testing for all pregnant women to symptom-based testing, high heterogeneity of study population and lack of long-term follow-up. Some studies showed higher incidence of preterm birth in COVID-19 positive patients, but the rate of preterm birth was increased in COVID-19 mothers regardless of the severity of the disease. It is important to stress that caesarean sections account for nearly all preterm deliveries, which suggests the iatrogenic origin of preterm delivery. The PRIORITY study found no increased risk of preterm birth in COVID positive mothers with exception to mothers who tested positive 0-14 day before delivery. Similarly, meta-analysis published by Allotey et al. [1], indicated that overall rate of spontaneous preterm birth was not elevated—and reached only six percent. Overall, it seems that spontaneous preterm labour is not increased compared to general population. There are some data, although limited, indicating that miscarriage and stillbirth rates are not increased in COVID-19 positive pregnant women [1]. A retrospective study showed that miscarriage rate in pandemic period did not differ to that observed in pre-pandemic period (14.2% vs 12.8%; p = 0.76). Further data of maternal exposure including the preconception period is needed to determine the effects of COVID-19 on early pregnancy outcomes. McDonnell et al. [6], found that in a tertiary referral center in Dublin, there was no correlation between monthly number of COVID-19 deaths in general population and the number of perinatal deaths, preterm births, GDM or pregnancy induced hypertension including pre-eclampsia. There are mixed data indicating COVID-19 impact on the SGA rate from 5.7% in meta-analysis from USA to even 17.4% reported in Chinese population. Women diagnosed with COVID-19 did not have a significantly higher quantitative blood loss during delivery and did not present increased risk of obstetric hemorrhage as compared to those without confirmation of COVID-19. Pregnant patients after kidney transplant and under immunosuppression complicated by COVID-19 infection had higher rates of ICU admission.
The course of COVID-19 can be divided into three clinical stages: viremic phase (day 1–7), pulmonary phase (day 5–10) and hyperimmune phase (after day 8) [13]. In patients with mild symptoms in the viremic phase (with normal oxygen saturation level, that is > 94%), only antipyretic drugs and home isolation are recommended. Hospitalization is required in all patients with oxygen saturation below 94%. In case of COVID-19 symptoms exacerbation, an intravenous of remdesivir should be administered for five days, but the treatment is effective if it is started within the first seven days from the onset of symptoms [13]. It is not contraindicated in pregnant women if the benefits of treatment outweigh the possible risk of side effects. The drug is generally well tolerated, although its effect on the fetus remains unknown [14].

If the hyperimunization phase begins (pneumonia with saturation drop < 94%), which occurs mostly after seven days of treatment, the use of tocilizumab, an anti-IL-6 monoclonal antibody, should be considered. In patients requiring hospitalisation, glucocorticosteroids (dexamethasone given in a dose of at least 6 mg/day), low-molecular-weight heparin in a prophylactic dose (prophylaxis of pulmonary embolism) and antibiotics (prophylaxis of superinfection with bacterial pneumonia) should be used simultaneously [13].

THE MODE OF DELIVERY IN A PREGNANT WOMAN INFECTED WITH SARS COV-2

Rates of SARS-CoV-2 infection in neonates seem to be not affected by mode of delivery, feeding nor by direct contact with a mother suspected or being positive for SARS-CoV-2 infection [8]. The decision on caesarean delivery should be based on obstetric (fetal or maternal) indications or respiratory status instead of COVID-19 status alone. There is no evidence to favour one mode of birth over another in women with COVID-19. The final decision regarding the mode of delivery should be based on woman's preferences and any obstetric or fetal indications for the intervention [9]. In one systematic review, which included 666 neonates and 655 women, 28/666 (4%) neonates had confirmed COVID-19 infection postnatally. Infants born vaginally did not have higher risk for COVID infection; 8/292 (2.7%) compared with 20/374 (5.3%) born by Caesarean [10]. Gale et al. [11], in another publication included 82 infants of 116 positive mothers, from which 44% were delivered by Caesarean section and 56% vaginally, and none of the infants were positive for SARS-CoV-2 postnatally in follow-up at 14 of life days. The authors concluded that the decision on birth mode should be based on medical indications, the course of the COVID-19 infection as well as provision of safe working conditions for medical staff. In cases of pregnant women being positive for COVID-19, there are many issues to be considered, however, each medical case should be worked out individually.

ANTIVIRAL TREATMENT IN PREGNANT WOMEN WITH COVID-19

The vast majority of pregnant women with COVID-19 is only mildly symptomatic, however, cases of severe disease with pneumonia and respiratory failure have also been observed [12].

In general, the choice of treatment for COVID-19 in pregnancy should be based on the stage of the disease and recommendations for the general population. The course of COVID-19 can be divided into three clinical stages:
2. Patients stay in single or double rooms depending on their clinical condition. Medical visits take place twice a day and strict nursing supervision is of great importance, as patients with a severe course of COVID in the third trimester of pregnancy can worsen within a few hours.

3. There should be dedicated a separate operating room organized exclusively for caesarean sections of patients with COVID infection.

4. The most risky procedure for viral contamination is removing personal protective equipment after medical procedures on contagious patients, thus special training for this activity needs to be provided.

5. Appropriate protocols should be prepared regarding the order of entry, putting in and removing protective gear, moving patients, passing newborns after birth and providing postpartum care.

6. One-way traffic from entering the COVID zone to the exit should be implemented.

The only diagnostic test that guarantees highest quality of the presence of the SARS-CoV-2 is RT PCR test. However, due to the long waiting time for the result, new generation antigen test can be used instead.

Currently, every hospital with a maternity ward should be prepared to admit and temporarily hospitalize a patient with COVID infection. That is why it is so important to look for individual solutions suitable for a given place.

MASKS AND FAMILY ASSISTED BIRTHS

According to the orders of the Polish government and Ministry of Health, everybody should wear masks in public spaces and observe the rules of keeping an appropriate distance. The hospital should also be recognized as a form of public space. The principle of wearing masks applies to the staff, patients and those accompanying childbirth. Both sides can be a mutual source of infection. This applies to all departments, sick rooms, corridors and on-call duty rooms for both doctors and midwives. For obvious reasons, women in the active phase of labor should be exempt from wearing masks in public space. The principle of wearing masks applies for individual solutions suitable for a given place.

TRANSMISSION OF SARS-COV-2

SARS-CoV-2 is highly infective at 4°C which is decreasing in the temperature of 25°C, although is still present at 33°C, and even at 38°C. Infectiousness depends on the environmental temperature and humidity and can even last for 3-5 days. SARS-CoV-2 is very stable in the urine as well as stool and can be contagious for 96 and 72 hours respectively [15]. This indicates existing risks for fecal-oral infection route as well as potential risk for infection via fresh water [16].

SARS-CoV-2 is very sensitive for wide array of disinfection products and chemical inactivators [2]. Bilal et al. [15] tested hospital rooms and bathrooms in 15 different locations occupied by COVID-19 patients revealing 87% and 60% positive samples, respectively. After routine cleansing and disinfection procedures all samples were negative.

Walsh et al performed systematic review based on 113 publications from December 30, 2019 till May 12, 2020. Analysis showed that viral load in the upper airway peaks at first days of clinical signs and remains high through first few days of infection. Viral shedding is not present after 14 days from the beginning of infection. Viral load in the stool reaches highest values later and remains present for longer time than in the upper airways. Viral load in the upper airway depends on the severity of the diseases and can be even 60 times higher in patients with severe course of the disease. Viral transmission may occur two days before the first symptoms appear and lasts for seven days of clinical symptoms, which was shown in the early publications. The authors stressed that presence of viral RNA in the upper airways is not proof of infectiousness, which depends directly on viral load. There is no correlation between viral load and patient’s age, which has been reported this same for children and adults [17].
ULTRASOUND EXAMINATION DURING COVID-19 PANDEMIC

Ultrasound diagnostics during ongoing pregnancy following the recommendations of the Ultrasound Section of the Polish Society of Gynecologists and Obstetricians must meet special requirements to minimize the risk of SARS-CoV-2 transmission. Naturally, the recommendations include triage — pre-selection of patients allowing ultrasound examinations only for asymptomatic patients with a negative history and when possible having recently made a negative SARS-CoV-2 test as a best option.

During COVID-19 infection in pregnancy, ultrasound examination of fetal growth, amniotic fluid and umbilical artery blood flow should be performed when clinically necessary.

In outpatient clinic, according to the Polish guidelines only the first, second and third trimester scans should be performed. As a precaution the number of vaginal scans should be minimized, when possible it is recommended to perform cervical length measurement by transabdominal examination [18].

NEONATAL CARE DURING COVID-19 PANDEMIC

COVID-19 pandemic forced health care providers to establish guidelines focused on care of the newborns born to mothers infected with SARS-CoV-2. In the beginning of the pandemic during its first wave, in March and April 2019 there were a series of the initial guidelines on this topic issued by The World Health Organization, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and European Academy of Pediatrics which were based on very limited knowledge of SARS-CoV-2 effect on newborns' health. There were very diverse approaches to neonatal care, from strict isolation of the newborn from mother with formula feeding to almost normal, unaffected care with skin-to-skin and rooming-in.

During the first wave of COVID-19 until the second wave of the pandemic more information on neonatal effect of maternal COVID-19 diseases has been gathered. Zhu and colleagues retrospectively analyzed the clinical course of 10 newborn babies of mothers with COVID-19 symptoms. This analysis showed that none of the women had been treated with antivirals prior to delivery despite the presence of clinical symptoms in two patients. The remaining pregnant women developed symptoms within a few days following delivery. Fetal life-threatening symptoms such as hypoxemia associated with respiratory failure occurred in six pregnant women. The studied cohort was eight male newborns and two female newborns of which six were born prematurely. The most observed clinical signs of respiratory failure in neonates were to be shallow breathing, fever and tachycardia. Disorders of the gastrointestinal tract such as reflux, regurgitation (spitting up), and bloody discharge from the stomach were observed in four newborns. Radiographic changes of the chest were observed in seven neonates: pneumonia (4), respiratory distress syndrome (2), pneumothorax (1) and none presented with SARS-CoV-2 in nasopharyngeal discharge. Two neonates, born at 34 weeks of gestation presented with very serious symptoms of respiratory failure, thrombocytopenia and liver failure. One of the newborns developed intravascular coagulation syndrome but despite the administration of plasma, platelets and red blood cells, the child died on the ninth day of life. Another severely ill newborn was treated with blood products, immunoglobulin, glucocorticosteroids and low molecular weight heparin and was cured on the 15th day of life [19].

One of the largest retrospectively analyzed cohort of newborns from SARS-CoV-2 infected mothers is study by Dumitriu et al. [20], from New York City. There were 101 newborns included in the study. Only one newborn was positive for the presence of SARS-CoV-2 but was asymptomatic. Out of all of them, 18 were admitted to neonatal intensive care unit (NICU) with non-COVID-19 related pathology. Newborns born to mothers with severe/critical COVID-19 (10%) were born one week earlier [37.9 (IQR) 37.1–38.4 vs 39.1 (IQR) 38.3–40.2, p = 0.02] and required more often phototherapy (30% vs 7%). None of the newborns presented any pathology in the follow-up. It is important to mention that direct breastfeeding after appropriate hygiene was encouraged in this study. Authors concluded that there was no clinical evidence of vertical transmission in 101 newborns of mothers positive for or with suspected SARS-CoV-2 infection, despite most newborns being cared for in rooming-in and directly breastfed.

Salvatore et al., analyzed cohort of pregnant women who were tested for COVID-19. Out of 1481 deliveries positive were eight percent, which accounted for 120 neonates. None of them were positive for SARS-CoV-2 on the first day of life, 83% were roomed in with mothers, and all were breastfed. Eight-two newborns had repeat PCR test at days 5–7 of life and all of them were also negative. Authors concluded that perinatal transmission of COVID-19 does not occur with optimal hygiene regime and rooming in with mothers is not increasing the risk for COVID-19 [21].

On the other hand, a less liberal approach for neonatal care is proposed by authors of the study by Farghaly et al. [22], in which their analysis showed significant association between symptoms and SARS-CoV-2 status regarding skin-to-skin contact (p < 0.001). Both studied groups showed significant differences regarding isolation patterns (p < 0.001). There was only one newborn with positive results for SARS-CoV-2 admitted to the neonatal ward.
intensive care unit (NICU). It has been shown that newborns of SARS-CoV-2 positive mothers were three times as likely to have desaturations, four times more likely to have poor feeding and ten times more likely to be symptomatic at the 2nd week follow-up in comparison to newborns from negative mothers. This group concluded that neonates born to mothers with confirmed or suspected SARS-CoV-2 are most of the time asymptomatic. Nevertheless there is still possibility for COVID-19 infection among newborns, thus in some cases isolation precautions should be considered and studied. In addition, testing these newborns by nasopharyngeal swab at least at 24 hours after birth and monitoring them for the development of symptoms for 14 days after birth is needed.

So, one of the most important question from the neonatologist point of view is: What is the risk for intrauterine vertical COVID-19 infection? Recently, Kotlyar AK et al. [23] published results of quantitative analysis and revealed that out of 936 neonates from COVID-19 mothers, 27 neonates had SARS-CoV-2 viral RNA positive nasopharyngeal swab, indicating a pooled proportion of 3.2% for vertical transmission. SARS-CoV-2 viral RNA testing in neonatal cord blood was positive in 2.9% of samples, 7.7% of placenta samples, 0% samples of amniotic fluid and urine samples and 9.7% of fecal swabs. Neonatal serology was positive in 3.7% (based upon the presence of IgM). Although these results suggest possibility for vertical SARS-CoV-2 transmission more studies are needed to clinically proof for this route of infection.

Based on published retrospective analysis, observational studies and guidelines up to date of December 30th, 2020 the following procedures for neonatal care during the COVID-19 pandemic should be followed:

1. There is currently no clear evidence of intrauterine fetal infection with SARS-CoV-2. Although there is presence of viral genetic material in amniotic fluid, placenta and umbilical cord.
2. Every newborn baby of a COVID-19 positive mother should be tested for SARS-CoV-2 as soon as possible – to prevent contamination occurring after birth. Standard method is rt-PCR. Antigen test can be used to proof for end of viremia after infection,
3. After birth of a newborn from an infected COVID-19 mother, the newborn does not need to be isolated from mother and can be cared in “rooming-in”. Mother and child should be hospitalized in special units dedicated to COVID-19 patients in separate rooms in order to avoid cross-infections with other women. There should be dedicated personnel appointed to care.
4. A newborn baby of a COVID-19 mother should be breastfed if mother’s clinical status is stable or may receive mother’s milk if the milk is pumped in accordance with all basic hygiene regulations. Up to date there is no evidence that mothers milk contains replicable RNA of SARS-CoV-2, contrary to the evidence for IgM antibody presence [24].
5. Newborns of mothers infected with SARS-CoV-2 should undergo all mandatory vaccinations. Newborns who have tested positive for SARS-CoV-2 and who have no clinical symptoms should receive vaccination for viral hepatitis B and tuberculosis preferably with consultation of a vaccinologist.
7. Discharge home as soon as possible, newborn should be picked by family member who is negative and not under quarantine.
8. Neonatal resuscitation:
   a) should be performed in designated room by trained personnel secured with protective clothing, N95 masks, goggles, and gloves;
   b) Resuscitation Equipment (based on NRP or ERC guidelines):
      • infant radiant warmer, dry linen sheets, plastic bag,
      • suction (pressure 80–100 mm Hg); preferred closed systems,
      • T-piece resuscitator or nasal CPAP (settings: PEEP = 6 cm H2O, PIP = 20–25 cm H2O, FiO2 according to gestational age, flow 6–10 L/min), masks with optimal size ranges, endotracheal tubes and laryngoscope of appropriate size, laryngeal mask if applicable, self-inflating bag,
      • other equipment: Videolaryngoscope if available and used at site, drugs according to local list, stethoscope, pulse ox, ECG electrodes.
   c) transport incubator equipped with ventilator for neonatal transfer,
   d) delayed cord according to regular local guidelines.
9. Skin-to-skin contact possible based on the clinical and organizational conditions [25].

VACCINATION

At the end of December, the vaccinations against COVID-19 were initiated in Poland. There were various doubts and questions raised regarding the safety of the new mRNA vaccine. During perinatal care there are two major issues related to vaccination that may need further explanations:

1. Vaccinations of the pregnant women
Since manufacturers of the vaccines did not include pregnant women in the phase III clinical trials, there is insufficient evidence to recommend routine use of COVID-19 vaccines during pregnancy. Joint Committee on Vaccination and Immunization (JCVI) advises that, for women who are offered vaccination, vaccination in pregnancy should be considered only where the risk of
development of Acute Respiratory Distress Syndrome (ARDS) is very high, or where the woman has underlying conditions that put them at very high risk of serious complications of COVID-19. In these circumstances, clinicians should discuss the risks and benefits of vaccination with the woman, who should be told about the absence of safety data for the vaccine during pregnancy [26, 27].

2. Vaccinations of the breastfeeding women

Due to outweighed benefits of breastfeeding as well as lack of evidence of associated risks to non-live vaccines during breastfeeding, JCVI allow for vaccination against COVID-19 of breastfeeding women. Nevertheless, absence of safety data for the vaccination procedure among breastfeeding women should be explained by medical personnel.

JCVI does not advise routine pregnancy testing before receipt of a COVID-19 vaccine. Those who are trying to become pregnant do not need to avoid pregnancy after vaccination. These recommendations are in sync with recommendations by The Royal College of Obstetricians and Gynaecologists.

In summary: Women should discuss the benefits and risks of having the vaccine with their healthcare professional and commonly seek decision [26, 27].

REFERENCES:


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