

Impact of COVID-19 on pregnancy and delivery — current knowledge

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ABSTRACT

The World Health Organization announced on 12 March 2020 a global pandemic of the new SARS-CoV-2 coronavirus causing COVID-19 disease associated with pneumonia and acute respiratory failure. SARS-CoV-2 has caused so far over 6.66 million recorded cases, of which 393,000 ended in death (as of June 1, 2020). Despite the demographic statistics of incidence, there is no current recording of cases in the group of pregnant or perinatal women. Changes occurring in the female body system during pregnancy also affect and alter the immune system, and as studies based on other viral respiratory infections have shown, the population of pregnant women is at risk of having a severe course of the disease. The aim of the study is to summarize current reports on the course of COVID-19 disease in a group of pregnant women and the possible impact of SARS-CoV-2 on the foetus and vertical transmission, taking into account changes occurring in the woman's immune system during pregnancy. Available advice and recommendations for antenatal and perinatal care of pregnant women during the pandemic period are also included.

Key words: COVID-19; SARS-CoV-2; coronavirus; pregnancy; delivery; breastfeeding

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INTRODUCTION

The global pandemic of the contagious COVID-19 disease, caused by the SARS-CoV-2 coronavirus, was announced by the World Health Organization (WHO) on March 12, 2020 as a result of the dynamic development of the epidemic in many countries and continents [1]. SARS-CoV-2 has caused so far over 6.66 million recorded cases, of which 393,000 have ended in death (as of 1.06.2020) [2]. The SARS-CoV-2 virus is structurally and functionally like the SARS virus and other pathogens from the Coronaviridae family [3–4].

Susceptibility to SARS-CoV-2 infection is observed in patients of all ages. However, according to the available studies, the full-blown COVID-19 disease develops much more frequently in elderly adults with associated comorbidities [5]. Despite the demographic statistics of incidence, there is no current recording of cases in the group of pregnant or perinatal women. Pregnancy is a special type of physiology during which several changes occur not only in the hormonal management, but also in the immune system. Ac-

ording to the available studies, the population of pregnant women is exposed to a severe course of infectious diseases affecting the upper respiratory tract [6–7]. The current state of knowledge is insufficient to clearly indicate and describe the above-mentioned clinical issue.

The aim of the study is to summarize current reports on the course of COVID-19 disease in a group of pregnant women and the possible impact of SARS-CoV-2 on the foetus and vertical transmission, taking into account changes occurring in the immune system of women during pregnancy. The available recommendations and suggestions for antenatal and perinatal care of pregnant women during the pandemic period are also included.

THE ROLE OF THE IMMUNE SYSTEM IN THE PREGNANCY

The immune system undergoes a change during pregnancy, outside the implantation site where suppression occurs. The response to microorganisms varies depending on the type of pathogen and stage of pregnancy. The

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trophoblast and mother's immune system reach a state of agreement where the immune response during pregnancy is a combination of the mother's systemic response and the local foetal-placental response. Therefore, the signals from the placenta are the ones that alter mother's immune system, and the immune system during pregnancy is focused on integrating the actions of placenta, foetus and pregnant woman [8].

Caring for the immune system is one of the elements of pre-conception, prenatal and perinatal education. Therefore, important are protective vaccinations before getting pregnant as well as proper diet and supplementation during pregnancy. Vitamin D3 facilitates the immune adaptation necessary to maintain pregnancy. It regulates the concentration of calcium and phosphate in the plasma, affects the state of mineralization of mother and foetal bones and alters the work of the system, among others immune system [9]. Vitamin D3 deficiency may affect up to 50% of pregnant women in the first trimester. The new guidelines assume that women planning pregnancy and during pregnancy should take vitamin D3 supplements, preferably in doses calculated based on blood tests. If it is not possible to determine D3 in the blood — the use 2000 IU/d is recommended [10]. During lactation, D3 supplementation does not differ from that taken during pregnancy - the dose is selected based on the vitamin D3 levels in the blood or 2000 IU/d [11–12].

Iron, as an essential microelement in the process of cellular respiration, is also responsible for the synthesis of red blood cells, DNA synthesis and regulation of the immune system function. Anaemia during pregnancy also affects the increased risk of preterm delivery and lower foetal birth weight. The demand of a woman's body during pregnancy is 26–27 mg/day, and during the lactation period 20 mg/day [13–14].

VIRAL RESPIRATORY DISEASES AND PREGNANCY

Pneumonia resulting from any infectious aetiology is an important cause of morbidity and mortality in pregnant women. This is the most common non-pregnancy condition that occurs during pregnancy. Twenty-five percent of pregnant women who develop pneumonia require hospitalization in intensive care units and require ventilation support. Viral pneumonia has an even higher level of morbidity and mortality during pregnancy than bacterial. Maternal physiological changes associated with pregnancy — including altered cellular immunity — may increase the susceptibility of pregnant women to illnesses [15].

Analysis based on data from SARS and MERS infections shows that both these coronaviruses can cause maternal death in a small number of cases (risk factors for death during pregnancy have not been clarified). Coronaviruses may also result in adverse effects on the foetus and infant, includ-

ing IUGR, preterm delivery, miscarriage and perinatal death. Unlike some viral infections, especially Ebola and Zika virus, the probability of coronavirus intrauterine transmission from mother to foetus is low — no cases of SARS or MERS have been documented. The novel coronavirus may influence obstetric diseases and outcomes depending on gestational age, drug effects or other treatment regimens, differences in host resistance reactions, occurrence of comorbidities and obstetric diseases and other accompanying variables [15].

CLINICAL MANIFESTATIONS AND THE COURSE OF COVID-19 DISEASE

According to one recent meta-analysis of the most common symptoms of COVID-19 disease which can be identified in the general population are: fever (87%), cough (58%), shortness of breath (38%), myalgia and fatigue (36%). Headache, excessive sputum production, or smell and taste disorders are less common symptoms. Some patients require admission to the Intensive Care Unit, of which, according to the authors, the risk of death was estimated at 7% [16]. Zaigham et al. performed systematic review based on 18 articles, covering 108 cases of pregnant women infected with SARS-CoV-2. Among the symptoms analysed, high fever (68%) and cough (34%) were the most common ones, while fatigue (13%) and shortness of breath (12%) were less common. Three percent of patients required admission to the Intensive Care Unit. There were no deaths in pregnant women, however one case of neonatal and one case of intrauterine death were recorded [17].

The study, which included the largest group of pregnant women infected with SARS-CoV-2 at one time, was published by Breslin et al. and included 43 women from the United States. Only 7% of women were hospitalized for COVID-19 symptoms while the others were admitted for obstetric reasons. In this group of patients, dry cough (66%) was described as the most common symptom followed by fever (48%) and muscle pain (39%) [18].

Based on the analysis of the available studies and literature, it can be concluded that no significant differences in clinical symptoms have been described in the pregnant women group infected with SARS-CoV-2 in relation to the general population [7]. Although, in most of the cases mentioned above the course of the disease was mild or even asymptomatic, some of them required intensive care and mechanical ventilation.

EFFECT OF SARS-COV-2 ON PREGNANCY AND DELIVERY

A meta-analysis conducted by Di Mascio et al. [19] on six studies which involved 41 pregnant women illustrates registered pathologies during pregnancy and delivery in patients infected with SARS-CoV-2. Premature delivery occurred in

Table 1. Occurrence of selectes pathologies during pregnancy and delivery in patients infected with SARS-CoV-2 [19]

Pathologies	n = 41
Premature birth	41%
PROM (premature rupture of the membranes)	19%
Pre-eclampsia	14%
Foetal intrauterine asphyxia	43%

41% of patients, and premature rupture of the membranes (PROM) was found in 19% of the patients. A significant proportion of patients (*i.e.* 43%) were at risk of foetal intrauterine asphyxia (Tab. 1). However, due to the small group of respondents and the fact that retrospective case studies have been included in the description, certain bias of the results obtained should be taken into account.

The available studies show large differences in the prevalence of preterm deliveries

Metaanalia Zagiham et al. [17] reports that 92% of COVID-19 gave birth via C-section. Studies carried out by Breslin et al. indicate that 44% of deliveries carried out by surgery [18]. Despite different percentages, it can be stated that the infection of the patient with SARS-CoV-2 is associated with an increased rate of giving birth via C-section in comparison to the pregnancies of healthy women population.

In regard to SARS reports, there is an increased risk of miscarriage concerning infected pregnant women, especially at the beginning of pregnancy. Unfortunately, the available publications provide residual information about complications in maintaining pregnancy in the first trimester. Therefore, it cannot be explicitly stated whether SARS-CoV-19 infection increases the risk of miscarriage or not. However, it should be emphasized that one of the most common symptoms of COVID-19 is fever. According to Yin

et al. hyperthermia may be a teratogenic factor, especially at the stage of embryogenesis *i.e.* early pregnancy [20].

In the publication of Zhejiang University School of Medicine, the drugs recommended for pregnant women are lopinavir and ritonavir. Chloroquine and favipiravir were forbidden. The Table 2 shows the most important drug interactions [21].

Regarding the vertical transmission of SARS-CoV-2 from mother to foetus, current studies do not provide reliable reports on the eventual possibility of infection. One of the first studies conducted on nine neonates shows that there is no evidence of intrauterine coronavirus infection (Tab. 3). Nine women with laboratory-confirmed COVID-19 (*i.e.*, positive throat swab samples) participated in the study. Evidence of vertical transmission was evaluated by the presence of SARS-CoV-2 in samples of amniotic fluid, umbilical cord blood and neonatal throat swabs. Samples of breast milk were also taken from patients after the first lactation and tested. Nine live births were recorded — in the 1st minute Apgar score 8–9 and 5th minute Apgar score 9–10. Amniotic fluid, umbilical cord blood, neonatal throat swab and milk samples were negative [22]. To date, no SARS-CoV-2 virus has been found in umbilical cord blood, amniotic fluid or placental tissue [23].

PERINATAL CARE AND BREASTFEEDING

Most authors of the publication agree that the mere fact of contracting COVID-19 is not an indication of the urgent delivery of pregnancy. It is recommended, if the obstetric situation permits, to delay the planned intervention, induction of delivery and adopt a waiting attitude until the woman poses an epidemic threat [24–26]. However, increased CTG monitoring is recommended due to reported cases of foetal well-being disorders [26]. According to the recommendations of the Polish Society of Gynecology and Obstetrics, each hospital with a Maternity Ward should have

Table 2. The most important drug interactions [21]

Drug name	Potential interactions	Contraindication in combined medication
Lopinavir/ritonavir	When combined with drugs associated with CYP3A metabolism (<i>e.g.</i> , statins, immunosuppressors such as tacrolimus, voriconazole), the plasma concentration of the combined drug may increase; leading to 153%, 5.9 folds, 13 folds increase of the AUC of rivaroxaban, atrovastatin, midazolam, respectively. Pay attention to clinical symptoms and apply the TDM	Combined use with amiodarone (fatal arrhythmia), quetiapine (severe coma), simvastati (rhabdomyolysis) is prohibited
Darunavir/cobicistat	When combined with drugs associated with CYP3A and/or CYP2D6 metabolism, the plasma concentration of the combined drugs may increase. See lopinavir/ ritonavir	See lopinavir/ritonavir
Arbidol	It interacts with CYP3A4, UGT1A9 substrates, inhibitors, and inducers	–
Fapilavir	① Theophyllinum increases the bioavailability of fapilavir ② It increases the bioavailability of acetaminophen by 1.79 folds ③ Its combination with pyrazinamide increases the plasma uric acid level ④ Its combination with repaglinide increases the plasma repaglinide level	–
Chloroquine phosphate	–	Prohibit to combine with the drugs that may lead to the prolonged Q-T interval (such as moxifloxacin, azithromycin, amiodarone, etc.)

Table 3. Maternal clinical characteristics [22]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
Age [years]	33	27	40	26	26	26	28	29	34	-
Gestational age on admission	37 weeks, 2 days	38 weeks, 2 day	36 weeks	36 weeks, 2 days	38 weeks, 1 day	36 weeks, 3 days	36 weeks, 2 days	38 weeks	39 weeks, 4 days	-
Epidemiological history	Yes (exposure to relevant environment)	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)	Yes (exposure to relevant environment)	Yes (contact with infected person)	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)	9 (100%)
Other family members affected	No	Yes	Yes	No	No	Yes	No	Yes	No	4 (44%)
Complications	Influenza	None	Gestational hypertension	Pre-eclampsia	Fetal distress	None	PROM	Fetal distress	PROM	-
Typical signs of viral infection	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8 (89%)
Method of delivery	C-section	C-section	C-section	C-section	C-section	C-section	C-section	C-section	C-section	-
Indication for C-section	Severely elevated ALT or AST; COVID-19 pneumonia	Mature; COVID-19 pneumonia	History of C-section (x 2); COVID-19 pneumonia	Pre-eclampsia; COVID-19 pneumonia	Fetal distress; COVID-19 pneumonia	History of stillbirth (x 2); COVID-19 pneumonia	PROM; COVID-19 pneumonia	Fetal distress; COVID-19 pneumonia	PROM; COVID-19 pneumonia	-

a separated so-called „Epidemiological emergency room”. It is proposed that it should be created on the model of existing “Departments of rapid prenatal diagnosis”. Such rooms have the conditions to perform ultrasound, CTG and examination of the patient maintaining an epidemiological regime whether patient’s condition requires hospitalization. If pregnancy is endangered, or there are symptoms that may threaten pregnancy, it’s necessary to inform the main doctor, or if there is no such possibility, go to the closest open hospital with obstetrics facilities. In the hospital, after TRIAG, if there is no suspicion of infection, every pregnant woman will be examined and further treatment will be established. If there are infectious symptoms, patient will be transferred to the „epidemiological” admission room, where, if the pregnancy threat symptoms requiring hospitalization are confirmed, the medical team will first have to rule out COVID19 infection [27]. Furthermore, according to recommendations to suspend visits to hospitals, an analogous procedure should apply to the family births. It is dictated by the overarching goal, i.e. ensuring epidemiological safety of patients, pregnant and giving birth hospitalized in maternity hospitals. All actions should be aimed at minimizing the possibility of spreading the above mentioned infection and minimizing virus transmission in the environment [28].

Limited studies in women suffering from COVID-19 or infected with other Coronaviridae (SARS-CoV) did not confirm the presence of the virus in human milk. However, it is not known for certain whether infection is transmitted through breast milk, but given the low rate of respiratory viral transmission through breast milk, the World Health Organization (WHO) states that mothers with COVID-19 can breastfeed [29]. It is not recommended to routinely isolate healthy new-borns from their suspected or COVID-19 mothers. Isolation can only be recommended if the mother’s and/or new-born’s health deteriorates and prevents them from being in the rooming-in system. Childcare is best entrusted to a healthy family member. These rules should be used to suppress symptoms in the mother (generally 5–7 days). So far, there are no reported cases regarding new-borns contracting Coronavirus through the milk of infected biological mothers. Furthermore, there is no evidence in favour of early clamping and cutting of the umbilical cord or early washing of the new-born [26, 31–33].

Recommendations regarding the participation of the neonatal team and clinical factors indicating the need for resuscitation remain unchanged, regardless of the status of the pregnant woman regarding COVID-19. These guidelines were issued on April 24, 2020, they will change as knowledge and experience in the field of COVID-19 treatment develops. Due to the varied level of pandemic severity, there may be differences in clinical practice in individual countries. The decision to separate the COVID-19 mother

from her child should be based on local guidelines. As a rule, the child should stay with the mother if her condition allows. If observation is required, it may be conducted by midwives. Skin-to-skin contact and breastfeeding is possible if proper precautions are taken, including strict hand hygiene and the use of masks [30].

SUMMARY

The current clinical knowledge does not present significant differences in clinical symptoms or the course of the disease in the pregnant women's group in relation to the general women's population and to the similar age. It can be assumed that the routine examination of pregnant women before planned hospitalization seems to be justified, due to the high percentage of asymptomaticity of pregnant women with SARS-CoV-2 infection. Based on the current research, patients with confirmed COVID-19 may be included in the risk group of preterm delivery, PROM or intrauterine infection during pregnancy. The dynamic development of the global pandemic emphasizes the need to constantly update knowledge and follow the latest recommendations to ensure the highest quality of health services and care for patients infected with SRARS-CoV-2.

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