CASE REPORTS / OPISY PRZYPADKÓW

Acute respiratory distress syndrome in pregnant women infected with SARS-CoV-2 – a case report

MICHAŁ BRZEZIŃSKI[1,A,B,C,D,E,F], NATALIA BRZEZIŃSKA[2,C,D,E,F], URSZULA RUSEK[3,C,E,F], KAROL BRONIECKI[4,C,E,F]

[1]Infectious Disease Unit, PCK Marine Hospital in Gdynia, Gdynia, Poland; [2]Department of Gynaecology, Oncologic Gynaecology and Gynaecological Endocrinology, Medical University of Gdańsk, Poland; [3]St. Adalbert's Hospital, Gdańsk, Poland; [4]Intensive Care Unit, PCK Marine Hospital in Gdynia, Gdynia, Poland

A – research concept and design, B – data collection, C – data analysis and interpretation, D – article writing, E – critical review of the article, F – final approval of the article

Acute respiratory distress syndrome in pregnant women infected with SARS-CoV-2 – a case report

Brzeziński M[1], Brzezińska N[2], Rusek U[3], Broniecki K[4].

[1]Infectious Disease Unit, PCK Marine Hospital in Gdynia, Gdynia, Poland; [2]Department of Gynaecology, Oncologic Gynaecology and Gynaecological Endocrinology, Medical University of Gdańsk, Gdańsk, Poland; [3]St. Adalbert's Hospital, Gdańsk, Poland; [4]Intensive Care Unit, PCK Marine Hospital in Gdynia, Gdynia, Poland

The outbreak of the COVID-19 pandemic caused new diagnostic difficulties in the practice of many doctors. The disease is still not well understood. The group of people commonly considered to be the most sensitive to severe SARS-CoV-2 infection are the elderly and those with chronic diseases. However, we cannot forget about pregnant women, whose risk rates for various complications are also very high.
A case report. *We present the case of a 38-year-old woman in whom acute respiratory failure caused by infection with SARS-CoV-2 led to premature termination of pregnancy by caesarean section. It resulted in a multi-day stay in the intensive care unit with long-term respiratory therapy. Despite the treatment that was recommended at that time, the patient's condition did not improve for a long time, and the results of laboratory tests indicated a continuous, active inflammatory process. We prove that COVID-19 infection in pregnant women results in a more severe course of the disease, with relatively frequent complications. Our work is aimed at making doctors of various specializations aware of how dangerous SARS-CoV-2 infection can be in pregnant women and warning them against ignoring scanty symptoms in pregnant patients.*

Key words: *SARS-CoV-2, pregnancy, acute respiratory failure*

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Zespół ostrej niewydolności oddechowej u kobiety w ciąży zakażonej SARS-CoV-2 – opis przypadku

Brzeziński M[1], Brzezińska N[2], Rusek U[3], Broniecki K[4].

[1]Oddział Chorób Zakaźnych Szpitala Morskiego PCK w Gdyni; [2]Klinika Ginekologii, Ginekologii Onkologicznej i Endokrynologii Ginekologicznej Gdańskiego Uniwersytetu Medycznego; [3]Szpital im. Św. Wojciecha, Gdańsk, Polska; [4]Oddział Intensywnej Terapii Szpitala Morskiego PCK w Gdyni

Wybuch pandemii COVID-19 spowodował nowe trudności diagnostyczne w praktyce wielu lekarzy. Choroba ta wciąż nie została dobrze poznana. Grupą powszechnie uważaną za najbardziej wrażliwą na ciężki przebieg zakażenia SARS-CoV-2 są osoby starsze i obciążone chorobami przewlekłymi. Jednak nie można zapomnieć również o ciężarnych, u których wskaźnik ryzyka różnych powikłań jest również bardzo wysoki.
Opis przypadku. *Przedstawiamy 38-letnią kobietę, u której ostra niewydolność oddechowa spowodowana zakażeniem SARS-CoV-2 doprowadziła do przedterminowego rozwiązania ciąży drogą cięcia cesarskiego. Skutkowało to wielodniowym pobytem na oddziale intensywnej terapii z długotrwałą respiratoroterapią. Mimo stosowania ówcześnie zalecanego leczenia, stan chorej przez długi czas nie poprawiał się, a wyniki badań laboratoryjnych wskazywały na ciągły, aktywny proces zapalny. W dokonanym przez nas przeglądzie piśmiennictwa udowadniamy, że zakażenie SARS-CoV-2 u ciężarnych skutkuje cięższym przebiegiem choroby i stosukowo częstymi powikłaniami. Przedstawiony opis przypadku ma na celu uświadomienie lekarzom różnych specjalizacji, jak niebezpieczne może być zakażenie SARS-CoV-2 u kobiet ciężarnych i ostrzeżenie ich przed bagatelizowaniem skąpych objawów u kobiet w ciąży.*

Słowa kluczowe: *SARS-CoV-2, ciąża, ostra niewydolność oddechowa*

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In December 2019, a new virus from the *Coronaviridae* family – SARS-CoV-2 (*severe acute respiratory syndrome Coronavirus 2*) was detected in Wuhan. Its ability to spread dynamically around the world caused a pandemic of COVID-19 (*Coronavirus disease-19*). The latest WHO data (29.04.2021) shows 150 million confirmed cases and over 3 million deaths in 192 countries/regions. This infection can take place with the involvement of various systems, however, the virus exhibits a special tropism towards the respiratory system, which may lead to severe respiratory failure [7].

Older adults with multiple co-morbidities and individuals with complex underlying health conditions suffer the severest of COVID-19 outcomes [10]. However, pregnant women also require close attention. According to some studies, up to 10% of pregnant women admitted to the hospital were infected or suspected of being infected with the coronavirus. Moreover, this group of women is much more likely to go to the intensive care unit, invasive ventilation and need for extra corporeal membrane oxygenation [1,17]. Thus, pregnant women infected with SARS-CoV-2 should become a group of highest attention.

We present a case of a *Coronavirus* infection in a pregnant woman, which led to advanced respiratory failure forcing her to undergo long-term treatment in the intensive care unit. We also conducted a literature review to investigate complications after COVID-19 during pregnancy.

A CASE REPORT

38-years old women, pregnant for the third time (week 35+5), with negative SARS-CoV-2 RNA test, was admitted to the obstetrics and gynaecology department due to severe pain in the right upper quadrant under the ribs, characteristic for renal calculi.

Urological consultation was conducted and right renal colic with nephrocalcinosis was diagnosed. The calcium and parathyroid hormone (PTH) levels were normal. Hereunder, a double-J ureteric stent was placed into the right ureter and the diagnosis of metabolic causes of urolithiasis was planned on an outpatient basis..

The laboratory examination revealed increased level of markers of inflammation, coagulation and red blood count disorders as follows: CRP 17.1 mg/l, leucocytes 12.92 G/l, D-dimers 2926ng/ml, fibrinogen 4.25 g/l, haemoglobin 8.7g/dl. Moreover, clinical urine tests indicated numerous bacteria, proteins and leucocytes (15-20 per microlitre). An urosepsis inflammation was suspected. The oxygen saturation measurement (SpO_2 =84.8%) and arterial blood gas test (pH=7,46; pCO_2=22,9 mmHg; pO_2=47,4 mmHg) were conducted.

Due to the risk of intrauterine neonatal asphyxia and exacerbation of respiratory failure, a caesarean section was conducted. The Apgar score was 10 and the birth weight of infant was 3200g. The mother's respiratory failure development contributed to patient transfer to the intensive care unit in the state of tracheal intubation. Directly after parturition laboratory markers of inflammation increased: CRP 301.9 mg/dl, procalcitonin 52,89 ng/ml. D-dimers (>35.000 ng/ml), BNP pro (8612 pg/ml) and troponin (0.628 ng/ml) were also elevated.

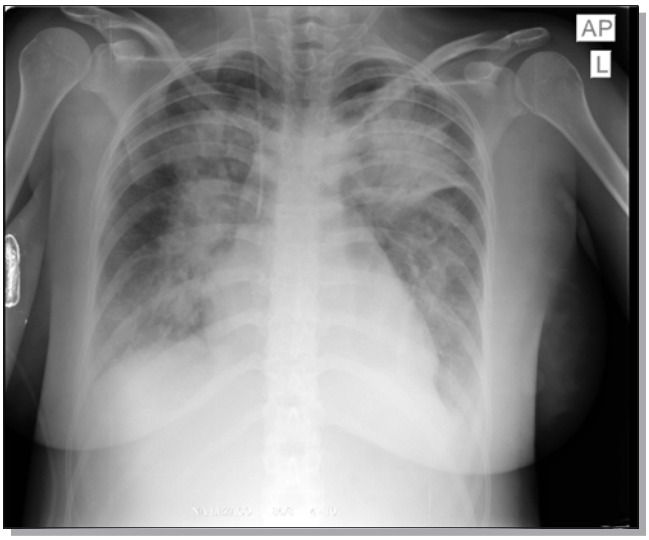

Figure 1. The X-ray shows extended, mottled, blending density affecting both lungs, probably as a result of inflammation
Rycina 1. Zdjęcie RTG ukazuje rozległe, plamiste, zlewające się ze sobą zagęszczenia obejmujące oba płuca, prawdopodobnie zmiany zapalne

In the first twenty-four hours after labour a cardiac echocardiography and ECG examination were performed, no abnormalities were detected. The x-ray exposed extended, mottled, blending density affecting both lungs, probably as a result of inflammation (fig.1). After the patient condition was stabilised, she was extubated and high flow nasal oxygen therapy was applied. Liquid therapy was started and 2 units of packed red blood cells were transferred. Two days later, in the follow-up x-ray, the progression of inflammatory lesions in lungs were detected. In order to confirm the suspicion of SARS-CoV-2 infection, the RNA test was redone with a positive result.

Patient in severe general state was transported to the Infectious Department in order to continue the treatment. She reported the acute pain in her chest, exacerbating during inhale, dyspnoea and cough. In the urine test a *Proteus mirabilis* was detected. According to the antibiogram piperacillin with tazobactam and ciprofloxacin were attached. The passive oxygen therapy with 30l/min flow, remdesivir and low-molecular-weight heparin (LMWH) in the therapeutic dose were applied.

According to the cardiac echocardiography and chest X-ray, the inflammatory lesions continued to intensify. The streaky-speckled inflammatory lesions in the right lung and bilateral accumulation of pleural effusion in both lungs were detected. Furosemid was used obtaining correct diuresis. Inflammatory markers and D-dimers decreased. Anaemia maintained on the level of haemoglobin 8,3 g/dl and thrombocytopenia was diagnosed (48 G/l). Haemolytic-uremic syndrome (HUS) was excluded by measuring the levels of LDH and bilirubin, the absence of schistocytes in the blood smear and correct kidney function. Despite the intensive treatment, patient's condition did not improve. In addition, pleural friction rub in right lung occurred. An anaesthesiologic consultation was commissioned and as a result the decision about a start of respiratory therapy in the intensive care unit was made.

After the transthoracic USG examination the pleural fluid was detected in both pleural cavities (1200ml in right lung, 1000ml in left lung). It was removed by insertion of intercostal drain. On the first day an angio-CT was performed (fig. 2), which revealed bilateral compaction of the lung parenchyma, with the image of a milk glass opacity in the upper lobes characteristic for COVID -19 infection. In the right lung, the pulmonary parenchyma affected by inflammation reached 80-90%, in the left – 70%. Additionally, fluid was found supra-diaphragm on the right side. A decision was made to continue treatment with antibiotics, remdesivir and low molecular weight heparin (LMWH). Steroid therapy was started. Moreover, a prone position was applied. Due to the low level of haemoglobin (Hb = 7.4 g / dl), 2 units of RBC were transfused. A follow-up CT scan was performed in the Intensive Care Unit after a week. There was a

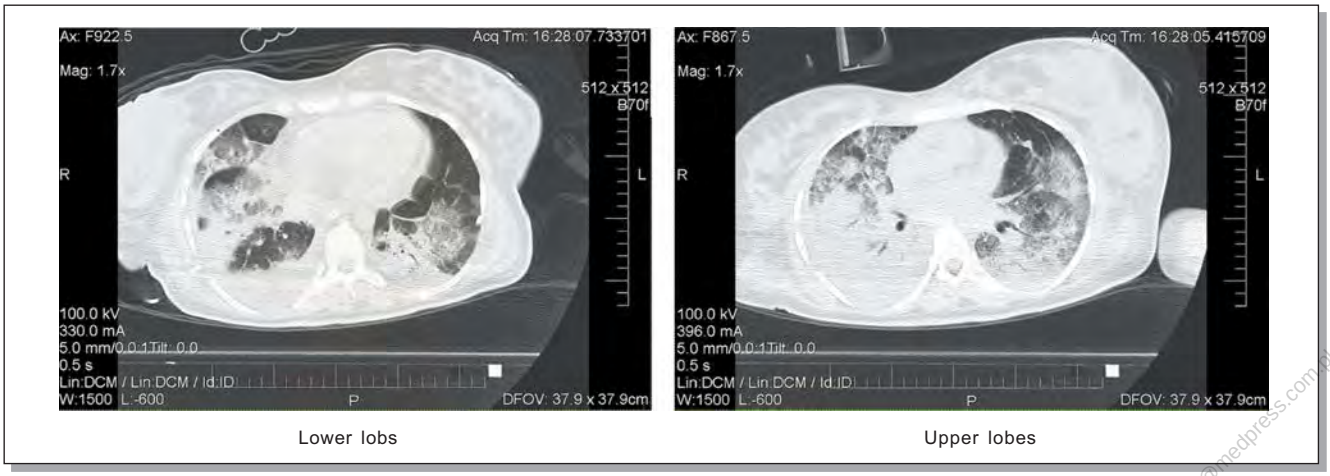

Figure 2. Angio-CT revealed massive lung involvement. In the right lung, the pulmonary parenchyma affected by inflammation reached 80-90%, in the left – 70%. Moreover, the image of a milk glass opacity in the upper lobes characteristic for COVID-19 was detected
Rycina 2. Angio-TK ujawniło masywne zajęcie płuc. W płucu prawym miąższ płucny zajęty stanem zapalnym w 80-90%, w lewym – w 70%. Ponadto wykryto obraz mlecznej szyby w płatach górnych charakterystyczny dla COVID-19

partial regression of changes in the lungs and a lack of fluid in the pleural cavities. Enterococcus faecium VRE was detected in the urine, teicoplanin was administered according to the antibiogram. In the next stage of hospitalization, analgesia was reduced, the respiratory therapy with a constant positive airway pressure was ended and then the patient was extubated with the subsequent application of high-flow nasal oxygen therapy, which allowed the patient to return to the Infectious Department.

Anticoagulant treatment and antibiotic therapy were continued. The parameters of inflammation and D-dimers began to reduce and the oxygen therapy was terminated. The patient reported significant weakness in the lower limbs and numbness of the feet. A neurological consultation was ordered, as a result of which a decision was made to start intensive rehabilitation. Vitamin B1, B6 and B12 treatment was started to counteract neuropathy. In the bacteriological tests performed, the presence of Enterobacter Cloacae was found apart from VRE. After taking fosfomycin, the patient began to report intense diarrhea, so the drug was changed into sulfamethoxazole with trimethoprim. A significant improvement in the patient's general condition and symptoms relief allowed the patient to be discharged from the hospital with a recommendation for further treatment in a neurological, nephrological and pulmonary clinic.

One month later, the CT scan performed in pulmonary department revealed that the confluent compaction of the lung parenchyma had subsided. Reticular changes in the peripheral parts were visible, representing a regression of inflammatory changes.

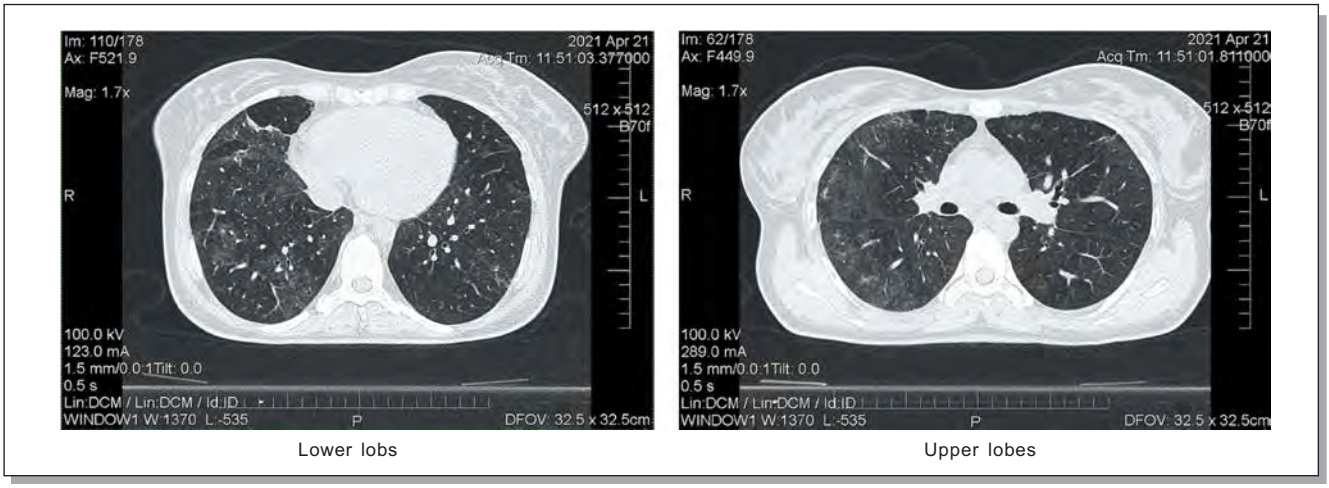

Figure 3. A follow-up CT scan 4 weeks after discharge from the hospital. The confluent compaction of the lung parenchyma had subsided. Reticular changes in the peripheral parts were visible, representing a regression of inflammatory changes
Rycina 3. Kontrolne badanie TK 4 tygodnie od opuszczenia szpitala. Zlewne zagęszczenia w obrębie miąższu płuc ustąpiły. W obwodowych częściach widoczne zmiany siateczkowate, będące obrazem zejściowym zmian zapalnych

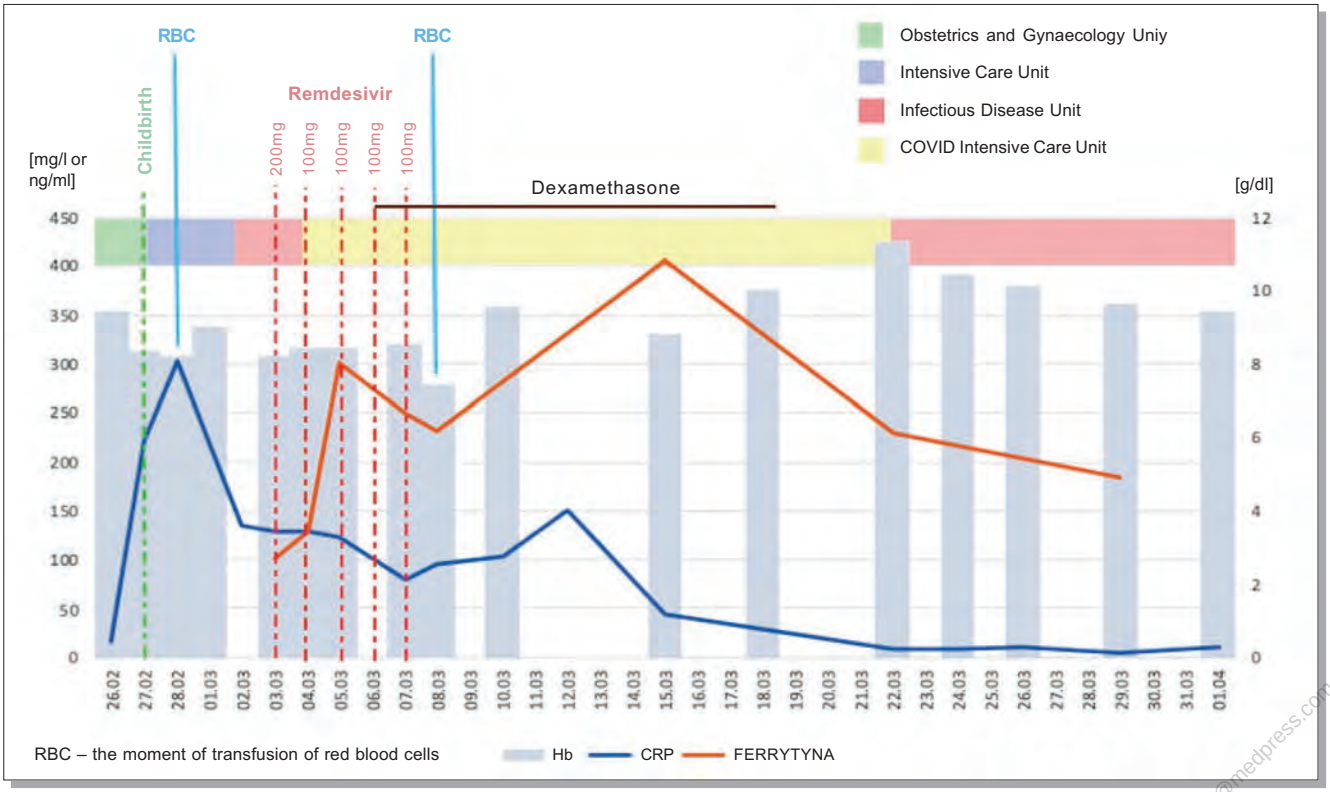

Figure 4. Graph showing change in CRP, ferritin, and haemoglobin levels over time. The duration of specific treatment and the stay ad individual wards is also marked
Rycina 4. Schemat przedstawia zmiany stężeń CRP, ferrytyny i hemoglobiny. Zaznaczono również czas stosowania specyficznego leczenia oraz pobytu na poszczególnych oddziałach

DISCUSSION

The presented case shows how dangerous the infection of SARS-CoV-2 can be in pregnant women. Despite the intensive and rapidly implemented therapy, our patient spent over a month in the hospital, most of which was in the intensive care unit using a ventilator. During this time, she could not see neonate. The treatment included high-flow oxygen therapy with steroid therapy and a specific drug against SARS-CoV-2 infection: remdesivir. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), could not be administered due to suspicion of urosepsis. At that moment, it was the best treatment we could offer the patient. Still, it was a long time before the parameters of inflammation returned to normal.

Sparse clinical symptoms during the first contact of the patient with the obstetrician, along with a negative (possibly false negative) result of the covid test, contributed to the delayed diagnosis of the infection. Until the result of saturation and arterial blood gas measurement, COVID-19 was suspected. In such cases, lung imaging, e.g. X-ray or even a CT scan, can be decisive. These are also a helpful tool for monitoring the course of the disease and for accurately determining the degree of lung involvement.

One of the more serious complications in COVID-19 patients is pulmonary embolism (PE). It occurs even in every third person treated in the intensive care unit [13]. Moreover, pregnancy and the puerperium are also conditions that increase the risk of pulmonary embolism. In our patient, we suspected PE due to high levels of D-dimers (>35.000 ng/ml), BNP pro (8612 pg/ml) and troponin (0.628 ng/ml). For this reason, we have applied therapeutic doses of LMW. However, the result of cardiac echocardiography examination and angio-CT finally excluded PE.

Although more than a year has passed since the outbreak of the COVID-19 pandemic, we still do not know enough about it. One such example is infection in pregnant women, which continues to be a challenge in the daily practice of many obstetricians.

In one of the first reviews that looked at the effects of the virus on pregnant women, the authors found that pregnant women had less COVID-19 symptoms than non-pregnant women [1]. It is now known that this is not true [16]. Pregnant women who have COVID-19 appear more likely to develop respiratory complications requiring intensive care than women who are not pregnant [1,17]. Pregnant women are also more likely to be placed on a ventilator [5]. This results in higher mortality in this group even by 70% [17]. The high mortality rate of 25 to 30% in pregnant women with related SARS and MERS is also disturbing [3]. The risk factors for hospitalization are the same as in the group of non-pregnant people: severe obesity, chronic kidney disease, diabetes, hypertension, asthma [8,9].

In a large meta-analysis on 1100 patients, *Di Toro et al*. found that the most common symptoms of COVID-19 in pregnant women are fever and cough followed by symptoms of anosmia, ageusia, myalgia, fatigue, sore throat, malaise, rigor, headache, and poor appetite [4]. The most common laboratory deviations are elevated concentration of C-reactive protein and reduced lymphocyte count, whereas leucocytosis was rarely found. Clinical symptoms and laboratory deviations do not differ between pregnant and non-pregnant women.

Wei et al. in their meta-analysis proved that pregnant women with SARS-CoV-2 infection have a higher risk of preeclampsia (OR 1.33), preterm birth (OR 1.82), stillbirth (OR 2.11), ICU admission (OR 4.78), lower weight (mean difference -68.96 grams), NICU admission (OR 3.69). However, they did not show any association of infection with increased risk of gestational diabetes, caesarean delivery, postpartum haemorrhage or neonatal death. The authors of this study also compared the asymptomatic course of the infection with the symptomatic one. The symptomatic course was associated with increased risk of preterm birth and caesarean section, which was statistically confirmed. The result of comparing the incidence of complications in pregnant women with severe and moderate infection is also interesting. The severe COVID-19 was more often associated with preeclampsia, gestational diabetes, preterm birth and low birth weight in compare to mild one [16].

The mechanism explaining the increased risk of preeclampsia in pregnant women with COVID-19 is not fully understood, but scientists suggest that the cause may be deregulation of the renin-angiotensin-aldosterone system. The virus binds to the angiotensin converting enzyme 2 receptor and as a result, vasoconstriction of the vessels in the placenta occurs. Therefore, it is not a classic form of preeclampsia but a disease with a similar clinical course. This is confirmed by the study by *Mendoza et al*., who suggest that they can be distinguished by assessing angiogenic factors (soluble forms-like tyrosine kinase-1/placental growth factor [sFlt-1/PlGF]), LDH and uterine artery pulsatility index (UtAPI) [11].

The most common symptoms in neonates are hyperthermia and poor feeding or vomiting. Coryza, respiratory signs, and lethargy are also commonly reported. In addition, it is believed that new-borns suffer more from infections than older children, which is confirmed by a relatively higher rate of receiving intensive care or mechanical respiratory support, as opposed to older children [6].

Despite recommendations and guidelines suggesting natural childbirth in women infected with the COVID-19 virus, most of them undergo caesarean section [2,4]. However, in various studies the authors suggest, that infection with the virus itself does not increase the risk of termination of delivery by caesarean section. The decision on invasive termination of pregnancy is made in order to facilitate the treatment of respiratory failure in the mother, prevention against vertical infection or the fear of unknown perinatal complications [4].

Wang et al. showed that the presence of SARS-CoV-2 that is virus RNA in the peripheral blood of infected patients is found only in 1% of people [15]. There are only a few described cases of perinatal transmission of SARS-CoV-2 [12]. However, it is still not known whether this occurred through the transplacental or other routes during delivery. In another study, the authors hypothesized that the lack of infection in neonates of mothers with SARS-CoV-2 infection was due to the presence of anti- SARS-CoV-2 antibodies in the cord blood and breast milk [14]. According to the current state of knowledge, vertical infections should be treated as a case study and should not be used as an excuse for preterm delivery or routine caesarean section in pregnant women.

CONCLUSIONS

The present case shows how unpredictable and what complications can be associated with SARS-CoV-2 in a pregnant woman. Despite the fact that our patient was in a generally good condition on admission and did not report any symptoms of respiratory failure, her condition began to deteriorate rapidly, threatening her life.

The aim of our study was to increase the awareness of doctors of various specializations, not only obstetrician, about the side effects and possible complications of SARS-CoV-2 infection in pregnant women and the impact it may have on the neonate. Pregnant women should be considered as a group of people particularly vulnerable to the severe course of SARS-CoV-2 infection. Therefore, we believe that each such case should be monitored with extreme caution, and treatment should be conducted by a multidisciplinary team that will have a holistic approach.

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Address for correspondence:
Michał Brzeziński
Infectious Disease Unit, PCK Marine Hospital in Gdynia
Powstania Styczniowego 1 str., 81-519, Gdynia, Poland
Phone: +48 50517427
e-mail: m.brzezinski@gumed.edu.pl