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OPIS PRZYPADKU
CASE REPORT

A case of COVID-19 in pregnancy complicated by fetal pleural effusion

Ciąża powikłana wysiękiem opłucnowym płodu u matki z COVID-19 – opis przypadku

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can lead to severe respiratory failure, has become a real threat to pregnancy. Although vertical transmission of the virus through the placenta appears to be rare, there is increasing evidence that a SARS-CoV-2 infection may cause complications during pregnancy. We report a case of COVID-19 in a pregnancy complicated by fetal pleural effusion in the third trimester of pregnancy. To our knowledge, only 4 similar cases have been reported to date. A 29-year-old woman in the 37th week of pregnancy admitted to the department of pregnancy pathology due to right fetal pleural effusion. In the 34th week of pregnancy, the patient suffered from COVID-19 with symptoms of fever and general weakness. The infection was confirmed by reverse-transcription polymerase chain reaction (RT-PCR). At 38 weeks, vaginal delivery occurred. The male newborn with a 6/7/8 point Apgar score required continuous positive airway pressure (CPAP) breathing assistance and was transferred to the intensive care unit. The rapid antigen test was negative. The ultrasound showed collapse of the right lung compressed by fluid in the pleural cavity. Inflammation, congenital TORCH and group B Coxsackie virus infection, chromosomal disorders and anatomical defects were excluded. During hospitalization 850 ml of lymphatic fluid was drained. We suspect a possible causal relationship between non-immune fetal hydrops and coronavirus disease.

KEYWORDS

SARS-CoV-2, COVID-19, fetal pleural effusion, hydrops fetalis, pregnancy

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STRESZCZENIE

Choroba COVID-19 (*coronavirus disease 2019*), powodowana wirusem SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*), który może prowadzić do ciężkiej niewydolności oddechowej, stała się realnym zagrożeniem dla kobiet w ciąży. Mimo iż wertykalna transmisja wirusa przez łożysko wydaje się rzadka, istnieje coraz więcej dowodów na to, że zakażenie SARS-CoV-2 może być przyczyną powikłań w czasie ciąży. Opisany przypadek dotyczy ciąży powikłanej wysiękiem w prawej jamie opłucnej płodu po potwierdzeniu zakażenia SARS-CoV-2 u matki w III trymestrze ciąży. Według naszej wiedzy do tej pory opisano cztery podobne przypadki. Kobieta, 29-letnia, w 37 tygodniu ciąży, zgłosiła się do kliniki z powodu wysięku w prawej jamie opłucnowej u płodu. W 34 tygodniu ciąży pacjentka chorowała na COVID-19 z objawami ogólnego osłabienia i gorączką. Zakażenie SARS-CoV-2 potwierdzono testem PCR. W 38 tygodniu ciąży odbył się poród siłami natury. Noworodek płci męskiej, żywy, donoszony, z oceną w skali Apgar 6/7/8 pkt; zastosowano wspomaganie oddychania CPAP (*continuous positive airway pressure*). Ze względu na zaburzenia oddychania dziecko przekazano na oddział intensywnej terapii bezpośrednio po urodzeniu. Wynik testu antygenowego był ujemny. W badaniu ultrasonograficznym stwierdzono zapadnięcie się płuca prawego oraz obecność płynu w prawej jamie opłucnej. W dalszych etapach wykluczono stan zapalny, wrodzoną infekcję TORCH, zakażenie wirusem Coxsackie z grupy B, zaburzenia chromosomalne oraz wady anatomiczne. W trakcie hospitalizacji zastosowano drenaż jamy opłucnej, uzyskując łącznie 850 ml płynu limfatycznego. Podejrzewamy możliwy związek przyczynowy między nieimmunologicznym obrzękiem płodu a chorobą COVID-19.

SŁOWA KLUCZOWE

SARS-CoV-2, COVID-19, wysięk opłucnowy płodu, obrzęk płodu, ciąża

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that mainly affects the respiratory system, causing coronavirus disease 2019 (COVID-19) leading to severe respiratory failure and even death [1]. At present, the evidence for intrauterine transmission from the mother to the fetus or intrapartum transmission from the mother to the neonate is sparse, thus further analysis and investigation are needed [1,2,3,4,5]. Despite this, there is evidence of SARS-CoV-2 transmission from the mother to the fetus, such as positive neonatal polymerase chain reaction (PCR) tests [5,6,7] and an elevated IgM antibody level [4,5,8]. Also, viral RNA and proteins are detected in placental swabs or biopsies and in the amniotic fluid, indicating that SARS-CoV-2 can cross the placenta [2,3,4,5,9,10,11]. Although the risk of SARS-CoV-2 transmission from the mother to the fetus is low [4,5,12], pregnancy complications such as premature ruptures of membranes, intrauterine fetal distress, intrauterine growth restriction, low birth weight, in utero fetal death, or premature neonatal death could be potentially real [2,10,11].

In the following study we report a case of a pregnancy complicated with an exudate in the fetal pleural cavity after the mother was confirmed to have SARS-CoV-2 infection in the third trimester.

CASE REPORT

A 29-year-old woman, 37 weeks of third gravida, two living children, was referred to the Department of Gynaecology, Obstetrics and Oncological Gynaecology in Bytom due to diagnosed fetal effusion in the right pleural cavity. The pregnancy was complicated by insulin-requiring gestational diabetes and cervical insufficiency requiring an assumption suture. Due to the Rh-negative blood type, anti-D immunoglobulin was administered at the 28th week of pregnancy. At the gestational age of 34 weeks the woman developed a fever (38.0°C) and general weakness. A reverse-transcription polymerase chain reaction (RT-PCR) test was positive.

As a standard upon admission, a COVID-19 rapid antigen test was performed and was positive. A negative RT-PCR test result excluded an active infection. The ultrasound revealed fluid in the right pleural cavity in the fetus with the dimensions of 7.6 × 4.9 cm (Figure 1). Common laboratory tests showed no significant deviations from the norm. Similarly, the C-reactive protein (CRP) and procalcitonin (PCT) levels were within the normal range. The patient was negative for TORCH (toxoplasmosis, cytomegalovirus, parvovirus B19, herpes, syphilis, rubella and HIV) antibodies. The fetal condition was systematically monitored by cardiotocography and ultrasound. The patient was asymptomatic throughout most of this period. At 38 + 2 weeks of pregnancy a spontaneous vaginal delivery occurred and a full-term male was born with a birthweight 3650 g and a 6/7/8 point Apgar score. The rapid antigen test for SARS-CoV-2 performed on the newborn was negative. Owing to single shallow breaths, nasal continuous positive airway pressure (nCPAP) breathing support was commenced. The ultrasound showed collapse of the right lung compressed by fluid in the pleural cavity with dominant B-line artifacts. The maximum fluid thickness was 1.7 cm at the base of the lung. The laboratory tests disclosed negative parameters of inflammation. The right pleural cavity was drained and 150 ml of the

yellow, cloudy liquid fluid was evacuated. Thereby, improvement in respiratory efficiency was achieved. The microbiological examination indicated fluid of a lymphatic nature. The computed tomography (CT) scan of the chest excluded pathological changes in the mediastinum. Serological tests ruled out congenital TORCH infection. Diagnostics was extended to a group B Coxsackie virus infection, which was negative. The karyotyping ruled out genetic disorders. On day 7, a continuous infusion of octreotide was ordered and reduction in lymphorrhagia was observed, until it resolved. RT-PCR tests for COVID-19 were performed twice, at the 16th and 19th days of life, with negative results. After 19 days of hospitalization and total evacuation of approximately 850 ml of lymph, the newborn was discharged in good general condition.

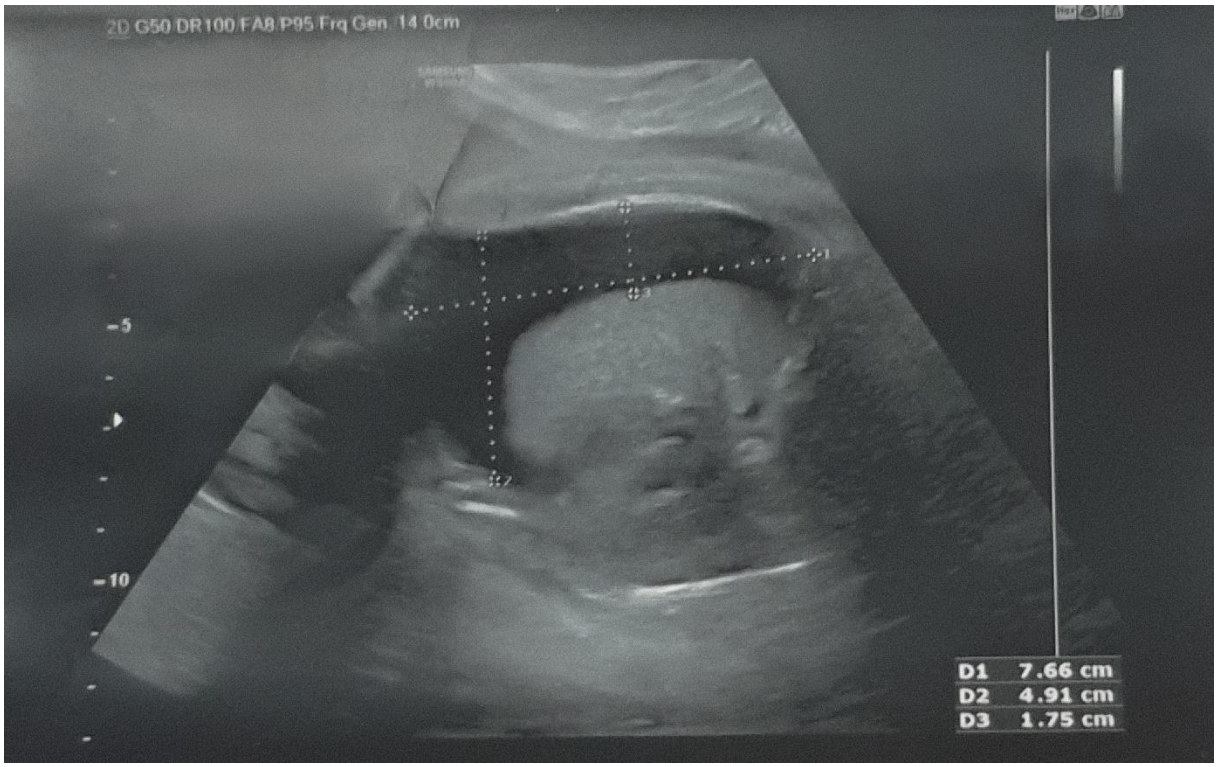

Fig. 1. Fetal pleural effusion – maximum dimensions.
Ryc. 1. Wysięk opłucnowy płodu – wymiary maksymalne.

DISCUSSION

Secondary pleural effusion, like ascites, pericardial effusions or subcutaneous tissue edema in the fetus, is usually caused by generalized fluid retention in non-immune hydrops [13]. Bellini et al. [14] in their systematic literature review made a classification based on the cause: cardiovascular causes (20.1%), lymphatic dysplasia (15.0%), hematologic (9.3%), chromosomal (9.0%), infections (7.0%), syndromic (5.5%), TTTF--placental (4.1%), miscellaneous (3.6%), thoracic (2.3%), inborn errors of metabolism (1.3%), gastrointestinal (1.3%), urinary tract malformations (0.9%), and extra thoracic tumors (0.7%). In our case, all of the potential threats were excluded. From the available reports, we know of several pregnancies complicated by non-immune hydrops with symptoms such as pericardial effusion [15], peritoneal effusion [8,9,13] and subcutaneous tissue edema [2,9,13]. Nevertheless, to the best of our knowledge, only four confirmed SARS-CoV-2 infections during pregnancy complicated by pleural effusion have been reported [2,3,8,9].

The RT-PCR of the nasopharyngeal swab was positive for SARS-CoV-2 in every pregnant woman. Of the four newborns we know of, only one was born alive. At 34 weeks of gestation, during the COVID-19 infection, fetal right ventricular dilation, fluid collection in the peritoneal and bilateral pleural cavities were observed in an ultrasound scan. The ultrasound scans in the first and second trimesters were normal. In this case, the woman was infected in the third trimester like in our report. Premature labor was induced and the baby required intubation at birth. Dobutamine infusion with frusemide and antibiotics treatment was started because of cardiac overload and elevated CRP. Radiological examination confirmed cardiomegaly, and ultrasound confirmed free fluid in the abdominal cavity. The newborn improved by day 5.

On 7 day the baby started accepting nourishment and was discharged on day 17. Her nasopharyngeal swab was PCR negative, but anti-COVID-19 antibodies were elevated (total – 37.4 IU/L, IgG – 0.77 IU/L) [8]. It is known IgG can cross the placenta barrier from the mother to the fetus beginning at the end of the second trimester and reaches high levels at the time of birth [16]. This would not confirm the infection in utero. Nonetheless, Pilarska et al. [4] conducted a meta--analysis of research on the impact of SARS-CoV-2 infection, where they found elevated levels of SARS--CoV-2 IgG or IgM antibodies in the umbilical cord blood in nine newborns, reported as evidence of vertical infection. As we know, IgM is not usually transferred from the mother to the fetus because of its larger macromolecular structure. Further evidence of vertical transmission was provided by Zeng et al. [16]. In their retrospective review there were 6 infants who had antibodies in their serum, but the RT-PCR test results were all negative in the throat swabs and blood. Two infants had IgG and IgM concentrations higher than the normal level (< 10 AU/mL). Three infants had elevated IgG levels but normal IgM levels.

Rodrigues et al. [3] in their report mention asymptomatic, COVID-19 positive, pregnant woman in the third trimester. An ultrasound scan revealed fetal pleural effusion, cardiomegaly and ascites, oligohydramnios and an umbilical arterial pulsatility index > 95th percentile. During an autopsy on the fetus, lung samples were taken by fine needle puncture, a technique similar to fine needle aspiration. The PCR for SARS-CoV-2 was positive for this preparation. In contrast, Shende et al. [2] also reported on an asymptomatic COVID-19 patient in the gestational age of 8 weeks, who five weeks later was diagnosed with intrauterine fetal demise. Extensive bilateral pleural effusion and subcutaneous edema suggestive of hydrops were revealed in the ultrasound. To confirm congenital infection, they carried out RT-PCR for viral RNA in the amniotic fluid and the immunofluorescence of spike proteins in the fetal membrane. The *E* gene the *RdRp* gene which indicates transmission of the virus was detected in the amniotic fluid. Viral S proteins were also detected in cells of the fetal membrane by immunofluorescence. On the other hand, Popescu et al. [9] provide information about a COVID-19 positive patient with fever of 38.2°C, taste and smell loss, dry cough, and fatigue in the 18th week of pregnancy. 7 weeks later a routine ultrasound revealed hydrops fetalis with skin edema and severe thoracic and abdominal effusion. Thoracentesis and amniocentesis were performed. In the 28th week of pregnancy, intrauterine death occurred. Neither a PCR test or a test for the level of antibodies against SARS-CoV-2 was conducted; however, immunohistochemistry was performed with the SARS-CoV-2 nucleocapsid protein, which showed strong positivity of the trophoblast and fetal villous macrophages.

The PCR test on newborns were of low diagnostic value. Many publications report that all the tested newborns were negative [16,17,18] for SARS-CoV-2 or only single cases were positive [4,5,6,7,15,19]. In 3 out of the 4 described cases, the authors drew attention to the characteristic features that could be observed in the histopathological examination of fetal and/or placental tissues. Rodrigues et al. [3] and Popescu et al. [9] showed that systemic thrombosis, massive vascular congestion, and stasis were apparent throughout all the organs in the histological examination. Thrombi were identified in the fetal circulation including the umbilical vein, chorionic vessels, and stem villi vessels [3,5,9]. The placenta revealed confluent acute infarcts, with vascular congestion and thrombi in the vessels. Furthermore, intervillous thrombi and perivillous fibrin deposition were noted in the intervillous space [2,3,9]. Additionally, widespread inflammation in the intervillous spaces composed of neutrophils, a few monocytes, large numbers of leucocytes including polymorphonuclear leucocytes in the decidual bed and the intervillous spaces was mentioned [2,9]. Gram stain and periodic acid Schiff stain did not reveal either bacterial or fungal infection [9]. In the meta-analysis by Pilarska et al. [4] 12 different publications were collected, the results of which coincide with the above--mentioned results of histopathological tests and conclusions on the vertical transmission of the virus.

We suspect a possible causal relationship between non--immune fetal hydrops and coronavirus disease. The limitations of our case are no SARS-CoV-2 tests performed for the placenta, amniotic fluid or the fetal tissues. After birth a rapid antigen test was performed, which was negative. Therefore only the clinical symptoms and the exclusion of other possibilities, i.e. TORCH infections, genetic disorders, Rh immunization and the proliferative process, may indicate vertical transmission of the virus. We hypothesize a possible causal connection. This case may constitute the basis for further studies as pleural effusion is a serious emergency for a newborn.

CONCLUSIONS

Including the presently reported newborn, three cases of infection occurred in the last trimester, of which two children survived to discharge from hospital, and one died in utero. In the other two cases, fetal death occurred after infection during the first or second trimester. The probability of infection most likely

varies with the route of transmission of the virus, the stage of pregnancy and the mother's overall health. The presented case of a fetal pleural effusion shows differences in procedures and circumstances when dealing with SARS-CoV-2 in pregnancy. Furthermore, the study may suggest a possible transmission of the virus through the placenta and may indicate risks associated with it. More research is needed to shed more light on the vertical transmission of SARS--CoV-2 so that universal screening of all pregnant women can be performed to avoid the adverse effects of the infection.

Conflict of interest

All the authors declare no conflict of interest.

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Declarations

Patient consent for the use of their medical data and history for preparation and publishing of the article was obtained after finishing the treatment.

Author's contribution

Study design – N. Filochowska, Ł. Witek, H. Sławska
Manuscript preparation – N. Filochowska, Ł. Witek
Literature research – N. Filochowska, Ł. Witek
Final approval of the version to be published – N. Filochowska, Ł. Witek, A. Olejek

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