CASE REPORT
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A pregnant patient infected with influenza A virus – case report and literature review

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Abstract

Influenza A, B and C viruses are among the most important members of the Orthomyxoviridae family. Annual flu infections are caused by influenza A and B viruses. The virus is transmitted by droplets. Typical symptoms of influenza are respiratory symptoms and muscle aches. Sometimes there is also a fever, but it is not a rule. It usually takes about a week to feel better. However, in rare cases, serious and even fatal complications can occur. They usually occur in people whose immune system has been previously weakened, for example in pregnant women. Pregnant women have altered immunity and physiological adaptations. Due to this, they are at increased risk of developing pulmonary complications, especially in the second and third trimesters of pregnancy. *Anestezjologia i Ratownictwo 2023; 17: 225-232. doi:10.53139/AIR.20231729*

Keywords: influenza A virus, pregnancy, pneumonia

Introduction

The number of cases of seasonal influenza decreased significantly in 2020-2021 after the emergence of the SARS-CoV-2 virus [1]. An increase in infections was noticed between 2021-2022 [1]. Annual influenza outbreaks in temperate climates tend to occur during the cooler and lower humidity months [1].

Spherical or cylindrical influenza virions are pleomorphic. Their size ranges from 80 to 120 nm [2]. The lipid envelope consists of two glycoproteins: hemagglutinin (HA) and neuraminidase (NA), and a membrane protein (M2), which is internally connected to the matrix protein M1 (matrix-M1) [2]. The influenza A and B virus genome consists of 8 different helical nucleocapsid segments. Each of them contains RNA of negative polarity along with nucleoprotein (NP) and transcriptase (RNA polymerase with polymerase complex proteins: PB1, PB2 and PA) [2]. Unlike the others, the influenza C virus has only 7 segments [3]. The segments of virus A contain from 890 to 2340 bases [2,3]. All proteins, except the non-structural proteins NS1 and NS2 and the M1 and M2 proteins, are encoded in separate segments. HA is rod-shaped and forms spiny protrusions with a triangular cross-section (trimers) [3]. HA has several functions. It binds to sialic acid on the surface of epithelial cell receptors. This allows the envelope to fuse with the cell membrane at acidic pH [2]. It connects and glues human, chicken and guinea pig erythrocytes [3]. It also triggers the production of protective, neutralizing antibodies [2,3]. Mutations that cause changes in HA are responsible for smaller (antigenic shifts) and larger (antigenic jump) changes in antigenicity [2]. The antigenic jump occurs only within the A virus and the different varieties of hemagglutinin are designated as H1, H2....H16. NA glycoprotein exists in the form of a tetramer and has enzymatic activity. NA causes the cleavage of sialic acid into glycoproteins [2,3]. This cleavage prevents the virus from sticking together and facilitates its release from infected cells [2]. NA is the target site for zanamivir and oseltamivir [3]. NA of the influenza A virus also undergoes an antigenic jump [2]. M1, M2 and NP proteins have high specificity, thanks to which

they can distinguish influenza A virus from influenza B or C virus [2]. M1 proteins form the interior of the virion and facilitate its assembly [2]. The M2 protein creates channels in cell membranes and enables the uncoating and release of virus particles [3]. The M2 protein is, in turn, the target point for the antiviral drugs amantadine and rimantadine [3].

The virus particle is of considerable size and has a shell that is easily inactivated by drying, acids and detergents [3]. Influenza A virus infects numerous vertebrate species, including mammals and birds [2]. Virus transmission often precedes the appearance of symptoms [2,3]. The virus is spread by inhalation in the form of an aerosol, speaking, breathing and coughing [3]. The best conditions for the virus are warm and humid winters [2]. The virus feels very good in a cool, slightly humid atmosphere [2,3]. The influenza virus spreads particularly quickly among school-age children [2]. The first symptoms that may indicate infection are respiratory symptoms, such as dry cough, sore throat, nasal discharge and muscle pain [1]. Fever may also occur. In addition to the previously mentioned, children may experience additional gastrointestinal symptoms such as nausea, diarrhea, vomiting and abdominal pain [1].

Every year around 300.000 people worldwide die from influenza, and more specifically from respiratory complications caused by the virus [1]. In the United States, of patients hospitalized for more than nine seasons, approximately 28% were pregnant and 62% were in the third trimester [1]. Every year, influenza affects every third child and every tenth adult, i.e. approximately 60 of the 500 million inhabitants of the European Union [4-7]. According to WHO (World Health Organization) data, every year from 330 million to 1.575 billion people suffer from influenza and influenza-like virus infections, 3-5 million people suffer from its acute symptoms, and from 500.000 to a million people die [4]. In Poland, until February 15, 2019, 2.665.494 cases and suspected cases of influenza were recorded, and as many as 9,628 patients required hospitalization (10.7% more than in the same season last year) [5]. Until February 15, 2019, as many as 48 cases were recorded fatalities [5,6]. This is a record number taking into account the same period in previous seasons [7]. In 2017/18, 0 influenza victims were recorded, in 2016/17 12 victims were recorded, in 2015/16 8 victims were recorded, and in the 2014/15 season there was only 1 fatality [4-7]. The number of victims of the A/H1N1 influenza virus pandemic is approximately 284.000 people [5]. Pregnant women constituted 1-2% of the population affected by the 2009 H1N1 virus infection pandemic, as many as 7 -10% of them required hospitalization, 6-9% of treatment in Intensive Care Units (ICU), and 6-10% of patients died [4-7]. In Poland, the number of victims according to GIS (Chief Sanitary Inspector) in 2010 from the beginning pandemic amounted to 182 people [5,6].

Influenza A virus infection has negative effects on both mother and fetus. All because of the adaptations of the mother's immune and cardiovascular systems to pregnancy [8]. It seems that these adaptations are one of the causes of delayed recovery, and thus promote a prolonged inflammatory phenotype, exacerbation of the disease, and causing health complications in both the mother and the fetus [8]. During pregnancy, the mechanisms of removing the virus from the body are very difficult and often cause an excessive immune response, which in turn leads to excessive inflammation of the body [8]. This may manifest itself, for example, in the form of acute cardiorespiratory failure in the mother, which may lead to perinatal complications. The most important are intrauterine growth restriction and numerous congenital defects: cleft lip and palate, neural tube defects and congenital heart defects [8-10]. In addition, the occurrence of long-term disorders of the nervous system, including schizophrenia, in children is possible [11].

Case report

A 29-year-old woman in the 33-rd week of pregnancy was admitted to the ICU due to respiratory failure in the course of pneumonia, without a specific etiological factor. Described situation took place in December. Before the admission the patient was hospitalized in the maternity ward (31-st week of pregnancy at that time) due to the risk of preterm delivery in her first pregnancy. During the stay in the maternity ward patient developed a cough, runny nose, fever reaching 39 degrees and chest pains. The patient was treated with antibiotics - cefuroxime, amoxicillin and clavulanic acid, and then clarithromycin due to disease progression. Due to the deterioration of the condition, she was transferred to the ICU. There, the patient was intubated and mechanical ventilation with the concentration of oxygen in the gas mixture (FiO2) 1.0 was performed. The patient underwent an urgent computed tomogra-

phy (CT) of the chest with contrast, which showed atelectasis of almost the entire left lung and the lower lobe of the right lung with a visible bronchogram there. In the right upper lobe and apical segments of the left lung, several locally confluent areas of ground glass with thickening of intralobular and interlobular septa were visible. In both cases of restriction and obstruction, the progression of the disease leads to a decrease in vital capacity (VC). Diseases causing a reduction in vital lung capacity are a non-obstetric indication for a cesarean section. Due to progressive respiratory failure, the patient was transported to the operating block where an emergency cesarean section was performed in the 33rd week of pregnancy. The newborn was in good condition. There were urgent indications for RCC (red cell concentrate) transfusion. Hb (hemoglobin) was 11.3, after transfusion of 6 units of RCC. Due to high inflammatory parameters and the presence of periodically distended abdomen, the patient was ordered to undergo a CT scan of the abdominal cavity. In the CT examination of the abdominal cavity, attention was drawn to an enlarged liver. Apart from that, everything in the abdominal cavity was normal.

After the operation, the patient was in the prone position for several hours. The patient had a very low PFR (Peak Flow Rate) <100 despite high O2. The patient's arterial blood gases were as follows: pH 7.3, pO2=65 mmHg, pCO2=50 mmHg, SpO2=90%. Respiratory ventilation parameters were constantly deteriorating, Cst (static lung compliance) on the day of admission was 35 ml/cm H2O, and the next day - 28 ml/cm H2O. For this reason the patient was qualified for extracorporeal membrane oxygenation therapy (ECMO). The patient underwent tests that confirmed her infection with influenza A virus. Due to its insufficiency, the circulatory system was supported by an infusion of norepinephrine. LDH (lactate dehydrogenase) on the first day of hospitalization was above the norm and amounted to 563 IU/l. The trend of this indicator was upward for three consecutive days of hospitalization. The greatest deviation from the norm was recorded on the third day, when the LDH value was 771 IU/l. AST (aspartate aminotransferase) on the first day of hospitalization was outside the norm and amounted to 104.2 IU/l. The greatest deviation from the norm was recorded on the second day of hospitalization, when this parameter was 115.5 IU/l. After the second day, the tendency of this indicator was downward and on the last day of hospitalization it returned to normal values. CK (creatine kinase) on the second day of hospitalization was 476 IU/l. Triglycerides were also not normal. On the first day of hospitalization, the patient's triglyceride level was 174 mg/dl. The trend of this parameter was constantly increasing. The greatest deviation from the norm was recorded on the last day of hospitalization, when the value of this parameter was 745 mg/dl. Total cholesterol also deviated significantly from the norm. The patient had this parameter tested three times, but unfortunately none of the results were within the norm. The result on the tenth day of hospitalization was 275.6 mg/dl, the result on the fifteenth day of hospitalization was 307.7 mg/dl, and the result on the last day of hospitalization was 319.5 mg/dl. The NT-proBNP value tested in the patient on the last day of hospitalization significantly exceeded the norm and amounted to 464 pg/ml.

The next day, that is on the first day after the cesarean section, the patient's general condition was stable. The patient's circulatory system remained ineffective and required support with norepinephrine infusion. Blood pressure was 117/70 mmHg, the heart rate was regular 100/min. The gynecological consultation revealed that the breasts were soft, not swollen and not red. The uterus is hard, the fundus is 2 fingers below the navel. The abdominal wound healed normally. A trace amount of bloody secretion seeped through the inserted drain. Bedside ultrasound performed with a transvaginal probe showed the uterine body in an anterior flexion and the presence of an intramural myoma measuring 27x33 mm on the posterior wall. Endometrial width 12 mm, in the area of the internal cervical os an area of heterogeneous echogenicity measuring 33x32 mm was found, which most likely corresponded to a blood clot. There was also a trace of fluid in the recto-uterine pouch. Due to the forced positioning of the patient, the examination was very difficult. During per vaginam examination, the cervical canal was mechanically unblocked, obtaining 2 tight fingers of dilation. Genital bleeding was within normal limits.

On the fourth and fifth days the circulatory system was continuously supported by an infusion of norepinephrine. In the first five days, the patient received antibiotics - ceftazidime and amikacin. On the fifth day, the parameters of gas exchange were the same. The patient's condition remained unchanged compared to the previous day.

On the seventh day the patient's condition deteriorated significantly. The patient experienced a decrease

in oxygen tension and an increase in carbon dioxide tension in arterial blood. There has been an increase in the demand for norepinephrine. Low cardiac output cardiac index (CI) 1.7 l/min/m^2, Inferior Vena Cava (IVC) 1.8 cm. The patient also developed a fever of up to 38.5 degrees Celsius. Due to the increase in inflammatory markers In response to this, the patient was replaced with an intravenous and arterial cannula, a gastric tube, and a urinary catheter. Material for microbiological tests was also taken, but all cultures turned out to be negative. The patient was placed in the prone position and antibiotic therapy was started, piperacillin and tazobactam were used alternately, and also linezolid. Fluconazole was added later.

On the ninth day, the patient was recannulated and, due to persistent hypoxia, massive consolidation and the inability to oxygenate with the use of a ventilator, VV ECMO therapy was started once more.

During hospitalization, the patient had chest X-rays performed five times. Initially, changes in the lungs appeared as confluent parenchymal densities. Later, the changes regressed and were less consolidated. Then, there was a slight progression, as the entire lung fields were reduced in volume on both sides, and in addition, confluent parenchymal and interstitial densities were present. Later, compared to the previous day, a slightly smaller intensity of changes in the apex of the lungs and a greater intensity of inflammatory changes

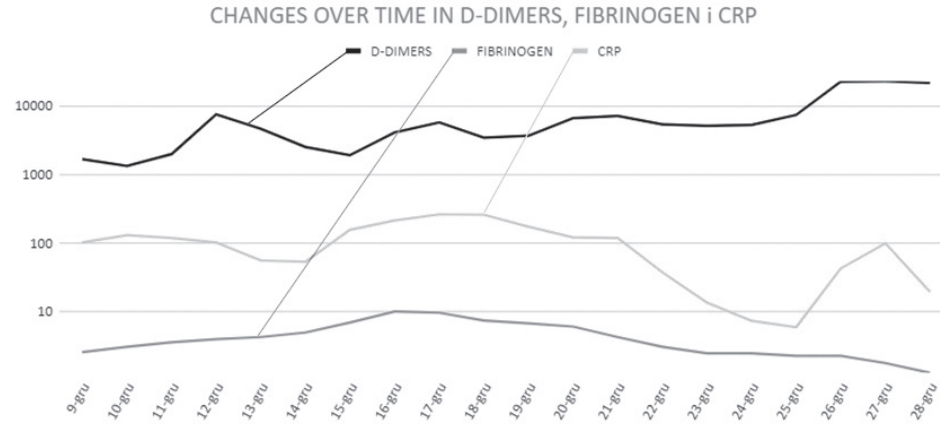

Figure 1. Changes over time in D-dimer, fibrinogen and CRP. D-dimer in the chart is given in ng/ml, fibrinogen in g/l, and CRP in mg/l

Table I. Results of morphological tests during hospitalization

DATE	WBC [k/Ul]	RBC [m/Ul]	PLT [K/uL]	HCT [%]	HGB [g/dl]
09.12	5.65	3.69	100	31.5	11.3
19.12	9.03	3.18	732	29.5	9.4
24.12	12.66	3.02	513	27.1	9.2

WBC- White Blood Cells, RBC- Red Blood Cells, PLT- Platelets, HCT- Hematocrit, HGB-Haemoglobin
WBC- leukocyty, RBC- erytrocyty, PLT- trombocyty, HCT-hematokryt, HGB- hemoglobina

Table II. The patient's test results on the day of admission

LACTATE DEHYDROGENASE (LDH)	TOTAL BILIRUBIN	AMYLASE	SODIUM	CHLORIDES
563 IU/l	1.73 mg/dl	53.0 IU/l	139.0 mmol/l	105.5 mmol/l

Table III. Results of basal hemostasis tests on the second day after cesarean section

PROTHROMBIN TIME	INR FACTOR	APTT (KAOLIN-CEPHALIN TIME)	D-DIMERS	FIBRINOGEN
10.4 sec	0.91	45.4 sec	1979 ng/ml	3.6 g/l

in the remaining parts of the lungs were noted (stronger consolidation of densities, suspicion of fluid in the pleural cavities). The last examination showed no signs of pneumothorax, uniform, almost complete shading of both lung fields corresponds to the presence of massive inflammatory consolidations of the lung parenchyma and the coexisting presence of free fluid in both pleural cavities; these changes were more extensive compared to the previous day.

During treatment, the patient also developed episodes of significant hypertension. Nitroglycerin and urapidil infusions and antihypertensive drugs were used for this purpose. Unfortunately, the patient did not respond to the treatment given to her. Satisfactory ventilation parameters could not be achieved, the presence of massive inflammatory consolidations of the lung parenchyma and the coexisting presence of free fluid in both pleural cavities and therefore, a decision was made to qualify the patient for lung transplantation. For this purpose, the patient was transported to the Lung Transplantation Department of the Silesian Center for Heart Diseases in Zabrze.

Discussion

In the literature, we can find many cases of pregnant women infected with influenza A virus. Lwin S et al presented a case of a 26-year-old woman who was in the 35th week of pregnancy was described [12]. She was pregnant for the third time [12]. The patient's condition deteriorated, she was restless and short of breath also arterial blood gas analysis showed metabolic acidosis. Due to the lack of progress in labor, a decision was made to perform a cesarian section [12]. A follow-up auscultation after giving birth and an X-ray confirmed the diagnosis of Acute Respiratory Distress Syndrome (ARDS), similarly to the case of our patient, in whom chest CT showed atelectasis of almost the entire left lung and the several locally confluent areas of ground glass were visible. Changes in the lungs indicated that our patient was developing pneumonia or acute respiratory distress syndrome (ARDS).

Prabhu TRB describes a cohort study of 32 hospitalized pregnant women infected with influenza A virus of the H1N1 subtype [13]. In most patients, influenza virus infection occurred in the third trimester [13]. Moreover, none of them required hospitalization in the ICU or mechanical ventilation [13]. No death of any pregnant woman was recorded [13]. At the time of discharge, 19 women had given birth and the remaining 13 had not given birth [13]. Patients who underwent cesarean section had special indications: in 6 cases it was a mobile head, in one case it was placenta praevia, no progress of labor in 3 cases and failed induction in 3 cases [13]. There have been cases of neonatal deaths [13]. Infection of humans with influenza A virus is associated with significant mortality and morbidity [14]. Frequently, a viral infection may be associated with a later bacterial infection, usually pneumonia [13,15]. Viral infection accompanied by pneumonia is quite common. It directly leads to approximately 10% mortality in 3-5 million patients infected with influenza A virus registered each year [14]. Influenza can be fatal for certain human populations [16]. This is due to the huge number of complications that a single infection with this virus brings [17]. The Centers for Disease Control and Prevention (CDC) high-risk groups include children under 5 years of age, the elderly, health care workers, and pregnant women [8]. In addition, this group of people can also include people with comorbidities, especially those with cardiovascular diseases and cancer [18]. Both seasonal and pandemic influenza can cause a significant loss of health not only in the mother, but also in the fetus [19,20]. It should be emphasized that seasonal infection with influenza A virus is associated with an increase in perinatal mortality with miscarriages, as well as may be the cause of early neonatal illness and death [21, 22]. Studies have been conducted on influenza A virus infection during pregnancy. The study group included, among others, women who had anemia, obesity and asthma. They were in the group with a higher rate of influenza virus infection [23]. Studies have found a higher rate of stillbirths in mothers suffering from influenza, moreover, if the delivery was successful, the children born had a low 5-minute APGAR [21]. In addition, the birth weight index <2500 g was increased [21]. These studies also showed that infection with influenza A virus itself did not affect the likelihood of caesarean section [23]. In addition, it is worth noting that influenza A infection during pregnancy increases the risk of having a low birth weight baby, which in turn is a risk factor for susceptibility to diseases later in life [23].

Adaptive changes associated with the preparation of the mother's body for pregnancy, including changes in the cardiopulmonary system, changes in heart rate, stroke volume and reduced lung retention capacity,

are believed to affect the severity of IAV-related morbidity and mortality in the mother [8]. However, the exact pathophysiology of this phenomenon is not fully understood. It is said that the severity of the course of influenza, as well as many complications, result from the fact that such women are exposed to seasonal epidemics very much, and moreover, women do not trust category C drugs that cause side effects in fetal animals [8]. Category C drugs include those that have not been tested on animals, because they are most likely to have a teratogenic effect on the fetus, or have not been tested on women to confirm their safety [8]. However, these drugs have some benefits, which in some situations may outweigh the risks also associated with the use of drugs in this category. Category C drugs include, among others, gentamicin, amlodipine, fluoroquinolones and saccharin [20].

The most common maternal complications among pregnant women infected with influenza A, undoubtedly include respiratory failure as well as acute cardiovascular disease [8]. As a result of seasonal epidemic, there is a significant increase in hospitalization and mortality indicators among pregnant women. In hospitalized pregnant patients with influenza A infections there is a fivefold increase in influenza complications [24]. Research was carried out in the United States, where the research group was pregnant women infected with the H1N1 pandemic virus [25]. 34 cases were reported [25]. Among them, 11 women required hospitalization, while among those 11, six cases ended in death [25]. In patients whose hospitalization ended in death, pneumonia developed, which has evolved into an syndrome of acute respiratory failure, requiring mechanical ventilation [25]. Research results clearly indicate the need for immediate treatment of pregnant women infected with influenza virus with anti-infant drugs [25]. Complications are the worst for pregnant women. Often, during or after already completed viral infection, bacterial pneumonia develops secondary development [26]. Both bacterial and viral pneumonia are the two most common complications of flu infection in the respiratory system. As for the incidence of pneumonia, it is similar in pregnant and not pregnant women [8]. In contrast, incidence and mortality are much higher for pregnant patients [8]. Pregnancy has been classified as one of the risk factors for severe disease caused by influenza infection [27-29]. The motive of this activity was the pandem of influenza in the 1950s and 1960s, which caused 20% mortality of pregnant women [8]. The data collected during the 2009 pandemic only confirm the previously adopted findings [29]. In addition to pneumonia, we can find respiratory failure especially often as a complication of influenza. It is usually caused by an acute respiratory failure syndrome, which is characterized by lung edema, incorrect excretion of carbon dioxide from the body, as well as hypoxemia. ARDS mortality is rare. Nevertheless, in complicated pregnancies or during viral infections, for example, influenza infection, mortality can reach up to 50% [8].

Former theory of fetal tolerance says that temporary immunosuppression must occur in the mother's body to properly implant and develop pregnancy [28, 29]. The development of new techniques, especially microscopy, cytometry and sequencing of individual cells meant that this theory was slightly corrected. The new findings suggest a strictly regulated balance between inflammation and toleogenic conditions during immune chronology of normal pregnancy. Research indicates that the early invasion of trophoblasts and during delivery is dominated by the pro-inflammatory environment, while during the second and third trimester anti-inflammatory effects dominate to facilitate fetal growth. Studies conducted on mice showed that an important component in the pathogenesis of influenza A infection is disturbed by TLR signaling (TOLL-like receptors) [30]. Virions penetrate into the cell, are included in endosomes, where the decrease in pH causes conformational changes that result in the release of nucleocapside protein to cytosol [30]. This is necessary for the virus to replicate. This also has one more purpose, namely it stimulates the innate immune response [30]. Mice that had a TLR3 deficiency showed a muted response to influenza A infection [30]. This is manifested by a decrease in the expression of pro-inflammatory cytokines and recruitment of T CD 8+ cells to the broncho-alveolar space [30]. However, despite the greater load on viremia, this gives an advantage in survival of immunocompetent mice in relation to TLR3 [30].

Our patient's case is certainly not isolated. The discussion included various cases of pregnant women infected with influenza A virus. In 13 out of 68 pregnant women, including our patient, pneumonia or ARDS developed as a result of the infection. These patients required hospitalization in the ICU and were mechanically ventilated. There have been 6 deaths reported among pregnant women suffering from

pneumonia or ARDS. The remaining 55 women did not require hospitalization in the ICU or mechanical ventilation. However, neonatal deaths were recorded among them. None of the previously mentioned patients, including our patient, was vaccinated against influenza. The reasons why some patients tolerated influenza A virus infection worse could be the later presentation of symptoms, lack of public health preparedness and insufficiently quick access to antiviral treatment. Moreover, the course of all types of infections is also influenced by individual conditions.

Summary

The presented case of the patient is serious, it shows how dangerous infection with influenza A virus can be and what changes it can lead to in the body. In pregnant women with symptoms of influenza, it is recommended to immediately start antiviral treatment. The decision to start therapy should not be delayed while waiting for the test results, so treatment should be empirical. The drug of choice is oseltamivir. Treatment should be started no later than 48 hours after the appearance of flu symptoms. If complications occur, such as pneumonia, oseltamivir should be started regardless of the time that has passed since the onset of the disease. This medicine is category C, which means there is no data on its safety during pregnancy. However, there is general agreement that the benefits of the therapy far outweigh the risks. Patients are usually successfully treated with oseltamivir and mechanical ventilation, but our patient's condition was so advanced that she was qualified for lung transplantation. It is difficult to assess where and what failed in our case. That is why it is so important to see a doctor when the first symptoms appear so that appropriate medical treatment can be initiated as soon as possible.

Conflict of interest
None

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