Ginekol Pol. 2010, 81, 227-231

PRACE KAZUISTYCZNE
położnictwo

Severe A/H1N1 Influenza in Four Pregnant Women in Podkarpacie Province of Poland

Zakażenia wirusem grypy A/H1N1 o ciężkim przebiegu u ciężarnych w województwie podkarpackim

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Summary

Pregnant women, just like the rest of the population, are at risk of the novel A/H1N1 infection. However, since they belong to a more susceptible group of patients, the risk of a severe course of the disease is significantly higher when compared to their non-pregnant counterparts. This risk is especially great when the infection is accompanied by chronic conditions such as asthma or diabetes mellitus, resulting in an increased morbidity and mortality of both the mother and the fetus.

Objectives: *The aim of the study was to present the first four cases of A/H1N1 infection in advanced pregnancy in Podkarpacie Province of Poland that were noted in the course of six weeks in November and December 2009.*

Patients and Methods: *Maternal age ranged between 27 to 34 years, gestational age was between 29 to 38 weeks. One patient had been at first admitted to Infectious Disease Clinic, and later on transferred to the Intensive Care Unit due to respiratory distress syndrome. The remaining three patients were hospitalized in the obstetrical unit, two of them due to respiratory tract infection and one due to amniotic fluid leakage without any respiratory failure symptoms. Three patients required artificial ventilation. One patient delivered vaginally, and the remaining three had caesarean section, one of them had an emergency c-section in agonia. The fatal outcome in this patient was the result of improper diagnosis due to a false negative stripe-test result. In case of the other three patients, properly diagnosed with Real Time RT-PCR test, an immediate antiviral therapy was introduced. Two neonates died: one delivered by the woman in agonia, and one due to intrauterine hypoxia and prematurity.*

Conclusions: *Diagnostic and therapeutic difficulties in A/H1N1 infections in pregnant women may have their source in that fact that an unreliable stripe test alone is used (without confirmation of the infection with Real Time RT-PCR), risk factors are not taken into the account and antiviral therapy is delayed or postponed.*

Early antiviral therapy and delivery in case of respiratory distress syndrome improve the prognosis for both the mother and the child.

Key words: **influenza A virus – H1N1 subtype** / **pregnancy** / **infections** /

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Otrzymano: **05.01.2010**
Zaakceptowano do druku: **28.02.2010**

Ginekol Pol. 2010, 81, 227-231

Streszczenie

U kobiet w ciąży również występuje ryzyko infekcji grypą A/H1N1. Są one bardziej podatne na zakażenie i mają zwiększone ryzyko cięższego przebiegu choroby w porównaniu z kobietami niebędącymi w ciąży. Ryzyko to wzrasta jeżeli infekcji towarzyszą choroby przewlekłe takie jak astma czy cukrzyca, w takich przypadkach występuje zwiększona zachorowalność i śmiertelność zarówno matek jak i płodów.

Cel pracy: *Celem pracy była analiza 4 przypadków kobiet ciężarnych zakażonych wirusem grypy A/H1N1 w zaawansowanej ciąży na Podkarpaciu w Polsce, które wystąpiły w ciągu 6 tygodni od listopada do grudnia 2009 roku.*

Przypadki i metoda: *Pacjentki były w wieku od 27 do 34 lat. Wiek ciążowy wynosił od 29 do 38 tygodni ciąży. Jedna z pacjentek była przyjęta pierwotnie do Oddziału Chorób Zakaźnych a następnie przeniesiona z powodu niewydolności oddechowej do Oddziału Intensywnej Opieki Medycznej. Pozostałe trzy były przyjęte do Oddziału Położnictwa, dwie z powodu infekcji dróg oddechowych, jedna z powodu odpływania wód płodowych bez objawów ze strony układu oddechowego. Trzy pacjentki wymagały sztucznej wentylacji. Jedna pacjentka urodziła siłami i drogami natury, cięcie cesarskie wykonano u pozostałych 3 pacjentek, u jednej z nich w stanie agonalnym. U tej pacjentki niekorzystne zejście było spowodowane brakiem właściwego rozpoznania wynikającego z fałszywie ujemnego wyniku testu paskowego. U pozostałych 3 prawidłowo zdiagnozowanych testem Real Time RT-PCR niezwłocznie rozpoczęto leczenie lekami przeciwwirusowymi. Dwa noworodki zmarły: jeden urodzony przez kobietę w agonii a jeden z powodu wewnątrzmacicznego niedotlenienia i wcześniactwa.*

Wnioski: *Trudności diagnostyczne i terapeutyczne w zakażeniu ciężarnych wirusem A/H1N1 mogą wynikać z zastosowania samego testu paskowego bez potwierdzenia obecności wirusa metodą Real Time RT PCR, nieuwzględnienia czynników ryzyka i nie wdrożenia lub późnego wdrożenia leków przeciwwirusowych.*

Wczesne wdrożenie leczenia przeciwwirusowego i rozwiązanie pacjentki w wypadku niewydolności oddechowej poprawiają rokowanie dla matki i dziecka.

Słowa kluczowe: **wirus grypy A – podtyp H1N1** / **ciąża** / **zakażenie** /

Introduction

First cases of A/H1N1 virus infection were reported in early 2009, in Mexico. Shortly afterwards, the virus spread all over the world [1]. By January 2010, the A/H1N1 infection was confirmed in 208 countries. Recently, increased extension of the virus has been observed in Central and Eastern Europe, as well as in Northern Africa and Southern Asia [2]. Interestingly enough, the infection which originally started in spring 2009 in the USA is now in decrease in that country [3].

First cases of A/H1N1 infection in Poland were confirmed in May 2009. A significant increase in the infection rate was noted in Poland in December 2009 alone, with over 1000 registered cases, twice the number when compared to data from before December 2009. The mortality rate raised from 24 to 145 cases in the course of just one month.

The analysis of epidemiological data indicated that children and young people constitute the most susceptible groups. The highest risk of severe course of the infection, accompanied by an increased complications rate, was observed in the groups of newborns and younger children, especially under the age of two, patients over 65, patients with cardiovascular and respiratory diseases, particularly those suffering from asthma and chronic obstructive pulmonary disease, patients with metabolic diseases, kidneys and immune system disorders. The risk of severe course of A/H1N1 is also significant in pregnancy [1]. Pregnant women with A/H1N1 require hospitalization more often, especially when the pregnancy is complicated by diabetes mellitus and asthma. Moreover, the influenza infection in pregnancy is likely to cause higher rate of miscarriages, premature deliveries and elevated morbidity and mortality in newborns [1, 5-7]. In general, the symptoms in pregnant and in non-pregnant subjects are similar [1]. The most common signs in pregnant women are fever, cough, sore throat, rhinitis and headaches. Dyspnea, muscular pain, nausea and diarrhea are rarely observed.

Infected pregnant women more often require hospitalization in Intensive Care Units, presenting higher mortality rate when compared to non-pregnant patients. Often, the overall condition of the infected pregnant women incline obstetricians to advise preterm delivery [8].

Given the high risk of severe complications of the infection, women trying to conceive and/or those who already are pregnant during seasonal and pandemic influenza are advised to take the vaccination [9, 10]. According to WHO and CDC, pregnant women with suspected A/H1N1 infection should be strictly monitored and receive neuraminidase-inhibitors (Oseltamivir or Zanamivir) immediately, preferably within two days of symptoms starting [1, 11]. According to the FDA classification, both therapeutics belong to the 'C Group' and should only be administered if possible benefits exceed possible risks [12]. Data on the safety and side effects of these drugs in pregnancy is scarce, with little or no information regarding safety of administrating higher doses [13, 14].

Literature offers only very few papers on A/H1N1 infection, with no multicenter/international studies. These reports are based on small series of patients, ranging from 3 to 83 cases. The described courses of infection in pregnant women varied in different centers and countries due to the following factors: vaccination, availability of tests confirming A/H1N1 and access to medical help, including the septic and intensive care units. The existence of the established algorithms and recommendations may influence the course of the infection in pregnancy. Geographical localization may also determine the incidence. For example, South Eastern Poland borders with Ukraine where particularly large epidemic was noted.

The aim of the study was to present the first four cases of the A/H1N1 infection in advanced pregnancy, that occurred within six weeks of November and December 2009 in Podkarpacie, Poland.

Case Report

Four cases of A/H1N1 infection in pregnant women are reported below in chronological order.

Patient A, a 27-year-old 3-gravida, 1-para (vaginally), in 29th week of pregnancy, smoker, diagnosed with asthma, hypothyroidism and pregnancy diabetes mellitus, presented in the Pathology of Pregnancy Department with symptoms of respiratory tract infection, persistent dry cough and fever up to 38,3°C for some days. The smear from nosopharynx for a quick stripe-test (Gecko Pharma A/B2 Panel test # 4A47 A/H1N1 virus infection) was taken with negative result. During hospitalization the patient was consulted by a pulmonologist due to chest crepitations. Chest X-ray revealed left lung pneumonia. The patient received antibiotics: at first Ceftriaxon 2x1g iv, Erythromycin 2x500mg per os, and after pulmonologist and specialist of infectious diseases consultation: Amoxicillin with Clavulanic Acid 2x1.2g iv. and Azithromycin 1x 500mg iv. In symptomatic treatment the patient received: Ambrosol 2x10ml Paracetamol 3x1g iv, Prometazyna 3x10mg and Flutykazon with Salmeterol – two inhalations daily. Despite the treatment auscultatory changes and fever continued.

On the sixth day the condition of the patient deteriorated, with symptoms of respiratory insufficiency. A council of doctors (obstetrician, specialist of infectious diseases, pulmonologist and anesthesiologist) decided to take smears from nosopharynx and throat for Real Time Reverse Transcriptase Polymerase Chain Reaction (Real Time RT – PCR) diagnostics, start treatment with Tamiflu (2x 75mg) and to perform a caesarean section. During the preparation of the patient for caesarean section, her condition has further declined, with symptoms of pulmonary edema. In spite of resuscitation the patient died. The simultaneously conducted caesarean section resulted in an immature fetus (1900g) without heart rate frequency. The reanimation of newborn was unsuccessful. Results from the RT-PCR test were available six days after the death of the patient.

Patient B, a 30-year-old 4-gravida, 3-para (3x vaginally) in 32nd week of pregnancy, without history of chronic diseases, was admitted to the Intensive Care Unit because of fever (39°C) and upper respiratory tract infection symptoms for a week, with exacerbation on the day of the admittance. The patient was administered Oseltamivir (Tamiflu, 75mg, twice a day). The patient developed a sudden respiratory insufficiency on the following day and was transferred to the Intensive Care Unit. Interstitial pneumonia was diagnosed on the basis of the symptoms and physical examination. Antibiotic therapy was introduced: Ampicillinum 2x1g iv, Meronem 3x1g iv, Targocid in the first twenty-four hours 2x400mg/24h iv and then 400mg/24h iv. PEEP-ventilation, pharmacologically induced sleep, tocolysis (MgSO4 2x4g iv.) was administered. Oseltamivir treatment was continued. The smear from nosopharynx for Real Time RT - PCR for the presence of A/H1N1 virus was taken. Material for quick stripe-test was not taken.

Fetal lung maturation was induced with Betamethasone (12mg). On the third day of the treatment the general condition of the patient further deteriorated. Despite artificial ventilation, O_2-saturation decreased. Immediate caesarean section was performed. An immature fetus weighting 2100g was born, receiving 2 points in Apgar score. A newborn who presented a left limb malformation, remained under artificial ventilation for three days before the child died. The result of A/H1N1 virus test from the fetus was negative, the autopsy indicated necrotizing enteritis.

The condition of the mother improved after the delivery, but she continued to require respiratory support. The chest X-ray revealed bilateral pneumonia. Due to radiological changes and positive result of Real Time RT-PCR test for A/H1N1 influenza virus, Zanamivir was introduced (two 5-mg-inhalations/twice a day for five days). In the days to follow, ventilation parameters improved and radiogram changes regressed. The patient was able to breathe independently on the ninth day of the therapy and was moved to Internal Medicine Unit for further rehabilitation.

Patient C, a 27-year-old 1-gravida, in 37th week of pregnancy, was admitted to the Pathology of Pregnancy Unit because of fever (38,4°C), sore throat, and dry cough. The patient complained of chest pains, particularly while taking deep breaths. Symptoms appeared a day prior to admittance. The patient had already been consulted by an infectious diseases specialist. She denied having had any contact with influenza-infected subjects. Upon admission smears from nosopharynx and throat for Real Time RT- PCR for A/H1N1 were taken. Treatment with Oseltamivir (75mg, twice a day) was started without delay, together with antibiotics (Cefotaxim 2x2g iv) and symptomatic treatment (Metamizol 1g iv.). She was afebrile on the second day after admission. The smears for RT-PCR for A/H1N1 were positive on the third day what confirmed the diagnosis. On the fifth day chest X-ray was performed. It did not revealed any pathology and on that day the patient delivered vaginally a mature child (3100g), without complications. The patient and the newborn were discharged in good condition on the sixth day after the delivery.

Patient D, a 34-year-old 1-gravida, in 38th week of pregnancy, was admitted to the Pathology of Pregnancy Unit with suspicion of premature amniotic fluid leakage. She was in good condition, with competent circulatory and respiratory systems, body temperature of 37,2°C, and no upper respiratory tract infection symptoms. Gynecological examination showed amniotic fluid leakage with a preserved consistency of the lower pole of the amniotic sac. The patient was monitored and her condition deteriorated on the next day, the body temperature raised to 39°C and was accompanied by cough with expectoration of mucous. Dyspnea, cyanosis, and blood pressure elevated to 150/110mmHg were observed. Vaginal discharge was found to be suppurative and bacteriological smears were taken. Simultaneously, the smears for Real Time RT-PCR test for A/H1N1 virus were taken from the throat and nose, and treatment with Oseltamivir (75mg, twice a day), together with antibiotics (Cefuroxime 2x1.5 g iv, Metronidazole 3x500mg iv) was started. No quick stripe-test for influenza virus was performed. Due to deterioration of her general condition and suspicion of influenza infection, the patient was qualified for immediate cesarean section. After a mature newborn (3520g) was delivered, the condition of the patient improved, body temperature dropped to 36.5°C, and blood pressure to 120/70mmHg. Due to the positive A/H1N1 Real Time RT-PCR test results on the first day after delivery, the patient was isolated in the Septic Obstetrics Subunit. In the absence of subjective symptoms and negative chest X-ray, the patient was discharged from the hospital in good condition on the fourth day after delivery.

Table I. Patients infected with A/H1N1 virus – summarized data and the course of treatment.

Patient	Age	Pregnancy / Weeks of pregnancy	Accompanying conditions (history)	Antiviral therapy	Days between first symptoms and the introduction of antiviral therapy	Days of antiviral treatment	Mode of delivery and newborn condition
A	27	G3/29	Asthma Hypothyroidism Nicotinism	none	none	none	C.S.* Newborn A.I. (1900g) Mother and fetus died.
B	30	G4/32	none	Tamiflu, Zanamivir	7	10 5	C.S.* Newborn A.I. (2100g) Newborn died on the 3rd day.
C	27	G1/37	none	Tamiflu	2	8	V.D.* Newborn A.M. (3100g)
D	34	G1/38	none	Tamiflu	1	4	C.S.* Newborn A.M. (3520g)

*Abbreviations: C.S. – caesarean section; V.D. – vaginal delivery; A.M. – alive mature; A.I. – alive immature.

Table II. Dynamics of changes of laboratory determinations*.

Patient	CRP (mg/l)				PCT (ng/ml)	
A	11.36	87.48	246.6	269.0	0.47	-
B	139.0	105.0	52.0	-	2.11	1.3
C	26.7	14.8	8.0	20.0	0.11	0.11
D	14.0	91.0	25.4	-	0.1	-

* Laboratory determinations were performed on average in three-day intervals.

The patient data and the data on dynamics of changes in laboratory markers CRP and PCT are summarized in tables. (Table I, Table II).

Discussion

This case report presents only four cases of the A/H1N1 infection in pregnant patients thus, not allowing us to generalize. Nevertheless, these cases may be an example of treating pregnant patients with influenza. This is particularly important at present as further spreading of the present A/H1N1 virus infection cannot be excluded. In the course of just one month, diagnostic and therapeutic management evolved significantly, as the four described cases clearly demonstrate.

In the first case the possibility of A/H1N1 infection was not taken into consideration due to negative results of an unreliable stripe test. Low sensitivity of this test was reported in several studies [1, 15]. Antibiotic therapy without antiviral therapy was applied in case of the first patient, with fatal outcome. Acute respiratory distress was the cause of death and interstitial pneumonia was confirmed at autopsy. Other authors also report a similar cause of death in pregnant patients who died due to A/H1N1 infection. Our patient suffered from asthma, hypothyroidism and nicotinism, the first two being classic examples of risk factors of severe course of the infection [1, 5, 15]. Nicotinism was considered to be a risk factor in only one paper [15]. According to WHO, antiviral therapy is recommended in pregnant women from the high-risk group who are suspect of influenza infection [1].

Remarkably, high CRP-values in the first presented patient, higher than in the other patients, were accompanied by relatively low PCT-values. One may conclude that both laboratory tests may be useful in differential diagnostics and prognosis.

In the next presented case antiviral therapy was introduced before A/H1N1 virus infection was confirmed. That case had a severe course of the disease and the pregnant patient was admitted to the Intensive Care Unit and submitted to artificial respiration. Due to lack of improvement, the patient underwent a caesarean section. Consequently, the mother recovered from the disease and was discharged on the ninth day in good condition. The newborn with multiple malformations and signs of asphyxia died.

In cases of patients who developed the infection about the term of the delivery, antiviral drugs were introduced immediately, before the test results were known. One of those patients was suspected of premature amniotic fluid leakage, and the intrauterine infection as the reason of fever could not be excluded at the time.

It seems that in such cases proper diagnosis of influenza infection may be difficult. One of the two patients had a caesarean section, another one delivered vaginally. Prompt administration of antiviral medicines seems to have been essential for successful treatment of both the mothers and the fetuses.

It is worth noting that the patients had been primary admitted to different units, three of them to the Obstetric Unit and one to Infectious Diseases Unit who was transferred to Intensive Care Unit. Patient who died stayed in Obstetrics Unit without isolation because she was not suspected of the influenza infection.

According to WHO, such isolation, immediate antiviral therapy, collecting material to Real Time RT-PCR, saturation monitoring, oxygenation therapy and prophylactic antibiotic therapy are obligatory. The last recommendation was fulfilled in all four cases.

Conclusions

1. Diagnostic and therapeutic difficulties in A/H1N1 infections in pregnant women may result from application of unreliable stripe tests without Real Time RT PCR confirmation, not taking into account risk factors and delayed or postponed antiviral therapy.
2. Early antiviral therapy and delivery in cases of respiratory distress syndrome improve the prognosis both for the mother and the child.

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