

Brief Original Article

Influenza A H1N1 virus infection among pregnant women in a tertiary hospital in Belgrade, Serbia

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Abstract

Introduction: Pregnant women are at higher risk of developing severe influenza. Our aim was to analyze clinical course and risk factors for fatal outcome in pregnant women with influenza (H1N1) infection.

Methodology: This retrospective study enrolled eleven pregnant women with confirmed Influenza A (H1N1) infection treated in the Clinic for Infectious and Tropical Diseases, Belgrade, Serbia in a 6-years period.

Results: The mean age of pregnant women was 28.9 ± 5.2 years, and mean gestational age was 23.1 ± 7.0 weeks. Nine (81.8%) pregnant women had pneumonia (six had interstitial and three had bacterial pneumonia). Pregnant women developed pneumonia more often than other women in the reproductive period, but without statistical significance (81.8% vs. 65.7%, $p = 0.330$, OR (95% CI) 2.35 (0.47-11.80)). Nine (81.8%) pregnant women recovered. None of them experienced preterm delivery or abortion. Two women (18.2%) died due to acute respiratory distress syndrome. In one of them fetal death occurred one day before she died. The other one was performed caesarean section three days before death. Her newborn and children of all recovered women were healthy at birth. Prolonged time to initiation of oseltamivir and higher body mass index were statistically significantly associated with fatal outcome ($p = 0.002$, and $p = 0.007$, respectively). Gestational week of pregnancy, the etiology of pneumonia and comorbidity were not found to be risk factors for death ($p = 0.128$, $p = 0.499$ and $p = 1.000$, respectively).

Conclusion: Pregnant women with H1N1 infection are at higher risk of pneumonia and death than other women in the reproductive period. Early antiviral therapy reduces the risk of unfavorable outcome.

Key words: influenza H1N1; pregnancy; oseltamivir; outcome.

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Introduction

During the 2009/2010 influenza season a pandemic caused by influenza A (H1N1) virus has occurred worldwide causing notable mortality reaching 19.6% among hospitalized patients reported by Romanian authors [1]. In the 2009/10 influenza A (H1N1) pandemic also reached Serbia, and individual cases of this diseases occurred in the following years. Milosevic *et al.* reported 63 hospitalized patients with confirmed pandemic influenza A (H1N1) infection in 2009/10, among which 3 (4.6%) patients died [2].

It has been recognized that pregnant women are at higher risk of developing severe disease and death. Pregnant women with flu also have a greater chance for spontaneous miscarriage and preterm labour. They might be reluctant to comply with public health recommendations during a pandemic because of concerns regarding effects of vaccines or medications

on the fetus. Pregnant women represented only about 1% of the United States population during influenza A (H1N1) pandemic, yet 5% of all deaths were among them [3]. In addition, 12 percent of pregnancy-related deaths were attributed to confirmed or possible H1N1 infection during the 2009 to 2010 pandemic season [4].

The aim of this study was to analyze clinical outcome of pandemic influenza A (H1N1) infection in pregnant women during the 2009-2015 in Serbia, as well to assess risk factors for fatal outcome in these patients.

Methodology

This retrospective study was performed in the Clinic for Infectious and Tropical diseases, Clinical Center Serbia in Belgrade. It enrolled women in the reproductive period with confirmed influenza A

(H1N1) infection treated in this clinic from 1 May 2009 until 30 April 2015.

The diagnosis of influenza A (H1N1) infection was established in the presence of typical signs and symptoms of influenza and detection of influenza A (H1N1) nucleic acid in samples from nasopharyngeal swabs using the real time PCR, with the equipment Gene Expert (Cepheid, Sunnyvale, CA, USA).

Chest X-ray was performed in patients with suspected pneumonia. Segmental or lobar pneumonia was considered to be of bacterial etiology, while interstitial pneumonia implied viral etiology (primary influenza pneumonia).

Pregnancy was confirmed by human chorionic gonadotropin hormone elevation, repeated manual and ultrasound examinations performed by gynecologist.

Body mass index (BMI) was calculated as patient's body weight in kilograms divided by the square of height in meters.

The study was approved by the Ethical committee of Clinical Center of Serbia and performed according to the declaration of Helsinki and subsequent revisions [5]. Patients signed an informed consent.

Patients' demographic and clinical characteristics, radiography and laboratory findings on admission and at discharge were recorded. Statistical analyzes were performed using Statistical Package for Social Sciences (SPSS) software for Windows (version 17.0). Student's t-test was applied for parametric and Fisher's exact test for non-parametric variables. The odds ratio (OR) and 95% confidence interval (95% CI) were obtained. Statistical significance was set at 0.05.

Results

During the study period 78 women in the reproductive period with confirmed influenza A (H1N1) infection were treated in the clinic. The

majority of patients were treated in the 2009/10, 2010/11 and 2014/15 season (45 (57.7%), 15 (19.2%), and 10 (12.8%), respectively). Five (6.4%) women were treated during 2012/13 and 3 (3.8%) during 2013/14. In the 2011/12 season no cases were reported.

Eleven (14.1%) women were pregnant. Their demographic and pregnancy characteristics are shown in Table 1.

Nine pregnant women were admitted to hospital during the first three days and two were admitted five and six days after disease onset. Nine of them were previously healthy, one had chronic hepatitis B virus infection, and one had bronchial asthma. None of them had history of previous vaccination against influenza.

Dominant symptoms on admission which were present in all of pregnant women were fever, cough, arthralgia, and malaise. Myalgia and dyspnea were present in 7 (63.6%) and 3 (27.3%) pregnant women, respectively.

Pneumonia was diagnosed by chest X-ray in 9 (81.8%) pregnant women. Interstitial pneumonia was present in six (54.5%), and bacterial in three (27.3%) of them according to chest X-ray presentation. Pregnant women with viral pneumonia had higher BMI than those with bacterial pneumonia, but without statistical significance ($p = 0.503$) (Table 2). The etiology of pneumonia was not associated with fatal outcome ($p = 0.499$).

Pregnant women developed pneumonia more often than other women in the reproductive period, but this did not reach statistical significance (81.8% vs. 65.7%, $p = 0.330$, OR (95% CI) 2.35 (0.47-11.80)). In addition, although viral pneumonia was dominant in both pregnant and other women in the reproductive period, bacterial pneumonia was more often diagnosed in those who were pregnant, again without statistical

Table 1. Demographic and clinical characteristics of pregnant women with influenza A (H1N1) infection in Serbia 2009-2015.

Demographic and clinical characteristic	All pregnant women (n = 11)	Survived pregnant women (n = 9)	Pregnant women who died (n = 2)	p ^a
Age (years) mean ± SD	28.9 ± 5.2	29.2 ± 5.3	27.5 ± .4	0.770
Gestational week of pregnancy mean ± SD	23.1 ± 7.0	21.6 ± 6.4	30.0 ± 7.1	0.128
First trimester n (%)	1 (9.1)	1 (11.1)	0 (0)	1.000
Second trimester n (%)	6 (54.5)	5 (55.6)	1 (50)	1.000
Third trimester n (%)	4 (36.4)	3 (33.3)	1 (50)	1.000
First pregnancy n (%)	6 (54.5)	4 (44.4)	2 (100)	0.454
Second pregnancy n (%)	3 (27.3)	3 (33.3)	0 (0)	1.000
Third pregnancy n (%)	2 (18.2)	2 (22.2)	0 (0)	1.000
Body mass index (BMI) mean ± SD	26.2 ± 4.8	24.0 ± 2.4	32.8 ± 3.8	0.007
Comorbidity n (%)	2 (18.2)	2 (22.2)	0 (0)	1.000
Time to initiation of antiviral therapy (days) mean ± SD	3.4 ± 1.3	2.9 ± 0.8	5.5 ± 0.7	0.002

SD standard deviation; ^a Univariate analysis was performed to evaluate the difference between pregnant women who died and those who survived.

Table 2. Demographic, clinical and laboratory characteristics on admission of pregnant women with influenza A (H1N1) infection with interstitial vs. lobar pneumonia in Serbia 2009-2015.

	Interstitial pneumonia n = 6	Bacterial pneumonia n = 3	p ^a
Age (years) mean ± SD	30.2 ± 4.4	29.0 ± 7.2	0.766
Gestational week of pregnancy mean ± SD	27.5 ± 4.9	20.7 ± 5.0	0.089
Body mass index (BMI) mean ± SD	27.9 ± 4.9	25.3 ± 0.8	0.503
Erythrocyte sedimentation rate mean ± SD	47.2 ± 26.5	84.0 ± 22.6	0.148
Leukocytes x10 ⁹ /L mean ± SD	6.6 ± 1.7	8.6 ± 4.5	0.386
Fibrinogen (g/L) mean ± SD	5.4 ± 0.8	5.6 ± 0.9	0.810
C-reactive protein (mg/L) mean ± SD	101.4 ± 115.9	117.0 ± 11.3	0.865
Creatine kinase (IU/L) mean ± SD	115.8 ± 39.8	34.0 ± 4.2	0.041
Lactate dehydrogenase (IU/L) mean ± SD	1103.0 ± 352.7	341.0 ± 38.2	0.034
Aspartate aminotransferase (IU/L) mean ± SD	50.6 ± 36.1	15.0 ± 1.4	0.244
Alanine aminotransferase (IU/L) mean ± SD	49.0 ± 38.5	12.5 ± 3.5	0.262
Oxygen saturation (%) mean ± SD	92.8 ± 6.2	96.5 ± 2.1	0.471

SD standard deviation; ^a Univariate analysis was performed to evaluate the difference between different characteristics in pregnant women with interstitial and those with bacterial pneumonia.

significance (33.3% vs. 20.5%, $p = 0.665$, OR (95% CI) 1.94 (0.41-9.32).

Nine (81.8%) pregnant women had favorable outcome and recovered. None of them experienced preterm delivery or abortion. Two women (18.2%) with viral pneumonia died due to development of acute respiratory distress syndrome, seven and eight days after hospital admission and 13 days after disease onset. Both of succumbed patients were admitted in intensive care unit and treated with prolonged oseltamivir therapy, in contrast to 5-days oseltamivir treatment in those who recovered. In one of these two women fetal death occurred one day before she died. The other one was performed caesarean section three days before fatal outcome. Her newborn and children of all recovered pregnant women were healthy at birth.

All patients were given oseltamivir immediately upon hospital admission. In nine women who recovered, antiviral therapy was introduced within 72h, and in patients who died, five and six days after first symptoms onset. Prolonged time to initiation of antiviral therapy and higher BMI were statistically significantly associated with fatal outcome ($p = 0.002$, 95% CI 1.24-3.98, and $p = 0.007$, 95% CI 3.48-14.08, respectively) (Table 1).

Case fatality ratio (CFR) was higher in pregnant women in comparison to CFR of other women in the reproductive period, but this difference was not statistically significant (18.2% vs. 4.5%, $p = 0.143$, OR (95% CI) 4.74 (0.69-32.35)).

Discussion

Pregnancy is a risk factor for severe influenza, both pandemic and seasonal [6]. During H1N1 influenza

pandemic pregnancy was one of the most prevalent underlying medical conditions among succumbed patients [7]. Romanian authors reported 44.4% mortality among pregnant women and 18% in nonpregnant population [1]. In our study CFR among pregnant women was 18.2% in comparison to 4.5% in other women in the reproductive period.

Physiological changes that occur during pregnancy affect cardiovascular, respiratory, and immune system, leading to severe forms of influenza infection. There is no exact explanation for the unfavorable outcome of influenza in pregnancy, but the assumed reasons could be altered concentrations of sex hormones, obesity, increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity [6]. There is an increased production of T-helper cells in pregnant women in order to reduce the risk of fetus rejection [8]. Pregnant women are more susceptible to viral pathogens due to shift away from cell-mediated towards humoral immunity [6,8]. Forbes et al. also showed that pregnant women have attenuated innate interferon responses to H1N1 2009 virus [9].

Fetal hyperthermia, which develops during maternal influenza infection, increases the risk of complications such as premature birth and birth defects [3]. The risk of complications and fatal outcome is higher in pregnant women in the second and third trimester [3]. Our succumbed patients were in the second and third trimester of pregnancy. In addition, in both of them oseltamivir was initiated later, five and six days after first symptoms onset. Previous studies showed that the delay in antiviral treatment was significantly associated with admission to intensive care unit (ICU), unfavorable course of the disease and

poor outcome [3,8]. As opposed, treatment with antiviral agents within two days of disease onset was associated with an 84% decrease in ICU admission as well as with better outcome in pregnant women [8,10]. In our study time to initiation of antiviral therapy was statistically significantly longer in patients who died. Therefore, it is necessary to advise pregnant women to contact a physician immediately after first symptoms of influenza appear.

Obesity was another significant factor associated with admission to ICU and poor outcome [8]. In our group of patients women who died had higher BMI than other pregnant women.

In 2009/10 there was not enough data about the safety and efficacy of oseltamivir use during pregnancy. It is now known that the benefit of treatment with oseltamivir overcomes the risk of its use in pregnancy. Oseltamivir is considered the drug of choice for treatment of pandemic influenza in pregnant women. None of the children of our pregnant women treated with oseltamivir had any birth defects.

Vaccination is the best protection for pregnant women. Only a small number of Serbian citizens were vaccinated against influenza due to medical ignorance and probably weak engagement of health personnel to motivate the population for vaccination.

Another reason for poor vaccine compliance might be the women's concern regarding safety of vaccination during pregnancy [6]. Since 2012 vaccination against seasonal influenza is recommended for pregnant women regardless of trimester of pregnancy [11]. Recent study showed that vaccination can significantly improve the attenuated innate and adaptive immunity in pregnant woman [9]. Others demonstrated that the levels of specific antibodies in children of vaccinated mothers were significantly higher compared to babies of unvaccinated mothers, suggesting a benefit for both mother and newborn [12].

Our study has potential limitations. This is a single center study, but having in mind the importance of morbidity and mortality of pregnant women as a parameter of health system quality, we presented our experience, despite the small number of treated pregnant women.

Pandemic is over, but influenza A (H1N1) continues to circulate seasonally worldwide. In Serbia more cases were reported in 2014/15 season in comparison to previous three seasons. Pregnant women with H1N1 infection are at higher risk of pneumonia and fatal outcome than other women in the reproductive period. Timely antiviral therapy is essential and reduces the risk of unfavorable outcome.

Conclusion

Pregnant women with H1N1 infection have increased disease severity and mortality rates in comparison with non-pregnant women. It has been demonstrated that early oseltamivir therapy reduces the risk of unfavorable outcome. Vaccination is the best method for the prevention and control of influenza, according to all relevant medical authorities.

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