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OUR EXPERIENCE IN TREATING GRAVID WOMEN DURING INFLUENZA A (H1N1) EPIDEMIC

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One of the main characteristics of influenza A (H1N1) epidemic is that the complicated forms of the infection mostly occur in patients with previous comorbidity, with gravidity being one of the leading risk factors for developing even more complicated forms of the infection resulting in a complex clinical treatment. Five gravid women were observed, who had previously been admitted to the Intensive Care Unit with the influenza A (H1N1) virus confirmed by PCR method. The most severe clinical case studies were in the third trimester of gravidity. None of the patients had been inoculated and the period of time from the occurrence of the first symptoms to Oseltamivir administration was approximately 6 to 11 days. Timely inoculation is the only reliable way of flu prevention. In addition, it is essential to administer Oseltamivir within the time frame of 48 hours from the occurrence of the first symptoms. *Acta Medica Medianae 2017;56(3):25-30.*

Key words: *flu, PCR, gravidity, pneumonia, mechanical ventilation*

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Introduction

Influenza or the flu is a disease with a cosmopolitan distribution and specific epidemic and pandemic spreading. Due to the high incidence and mortality rate among people in the course of history, it has been known as one of the deadliest diseases.

The most infamous and lethal outbreak was certainly the one which occurred in 1918, also known as 'Spanish flu pandemic' caused by the H1N1 subtype. Approximately 500 million people suffered from the disease and the death toll was 20 million (1). Around 60% of those who died were young adults 20 to 45 years old.

Asian flu appeared in 1957 and was caused by the H2N2 subtype of the influenza A virus. It is estimated that that virus killed between 100,000 to 1 million people (2). In 1968, the world suffered from another outbreak, Hong Kong flu, caused by the subtype H3N2 of the influenza A virus, killing between 700,000 and million people (2).

It is clear that all the three pandemics were caused by the influenza A virus, with different subtypes responsible for each of the outbreaks. The mutation of the virus and the creation of the new serovariants result in epidemic or pandemic spread of the disease.

Influenza A (H1N1) first appeared in Mexico, in a small town of La Gloria, the state of Vera Cruz, in a four-year-old boy. The virus was clinically identified on April 24, 2009 and on June 11. The World Health Organization (WHO) declared that the influenza A (H1N1) pandemic was underway. This particular influenza virus is considered to be a mixture of four virus genes: North American and Eurasian pig flu viruses, North American bird flu virus and human flu virus. An unusual and characteristic feature of this pandemic was the high incidence among people younger than 15 years old (61%) (3). As opposed to other influenza types which cause higher mortality rate among the elderly and small children, this particular strain causes death in younger people due to a so-called cytokine storm.

The WHO considers people with underlying medical conditions such as obesity or chronic diseases as well as gravid women to be at higher risk of becoming infected with the influenza A (H1N1) virus.

There is no data that the influenza A (H1N1) virus can go through the placenta and reach the fetus. However, after birth, the newborn baby can be exposed to the virus from the infectious respiratory secretion of the sick mother (4).

Although there is no viremia in the fetus and the newborn baby afterwards, there is a possibility

that the cytokines created by the antiviral immune response of the mother can go through the placenta and cause organ and tissue damage in newborns (4-6). It has also been proven, on the animal model, that mother's viremia during pregnancy can cause damage to the brain of the fetus while in the process of developing, probably because of the aforementioned mechanisms at work.

It has also been observed that this particular type of the influenza virus causes predominantly pulmonary complications (the lower part of the respiratory system, the alveoles) and that it quite commonly causes primary viral pneumonia leading to severe respiratory insufficiency requiring Intensive Care Unit treatment.

Aim

The aim of this work is to emphasize the importance of the inoculation of gravid women and of the timely administration of antiviral therapy to the infected patients, as they are the most important factors influencing the severity of the disease and its final outcome.

Material and methods

Our work is a prospective study of the gravid women undergoing treatment in the IC Unit of the Clinic for the Infectious Diseases of the Clinical Center of Niš during the influenza A (H1N1) epidemic which lasted from October 2009 to April 2010.

The virus was detected in the nasal and throat swabs of all the hospitalized women on admission or in the course of treatment by the real-time reverse transcription polymerase chain reaction (rRT-PCR) method.

More than 3,000 patients were examined in the specialized ambulance, out of which 1.434 were suspected with the influenza A (H1N1) and 245 were hospitalized. Fifty-six patients were treated in the IC Unit out of which 32 were on artificial ventilation. Seven gravid women were treated in the ward, whereas five were treated in the IC Unit.

The anti-viral therapy included Oseltamivir per os in two daily doses of 75 mg (as recommended by CDC) (7).

Clinical pictures of the sick women

The patient S.D. graviditas ml VII½ was admitted to hospital on December 2, 2009 with a severe respiratory insufficiency Sat O_2 44%. She had got sick approximately 10 days prior to the admission. There was a data in her anamnesis related to the surgery of neurinoma of the pontocerebellar angle in 2002 and 2007 resulting in the residual paralysis of the VII cranial nerve and the difficulty in moving. The patient had not been inoculated against the flu. On admission, the patient was intubated and artificial ventilation started. Chest x-ray was done on the same day and it showed a severe consolidation of the pulmonary parenchyma (bronchopneumonia), in line with ARDS. The therapy administered included a virostatic, antibiotic, bronchodilatator and a substitutional therapy (plasma, washed red blood cells, albumines), as well as other symptomatic therapy. In the days to follow, despite the therapy, the patient was still in the critical condition with insufficient pulmonary function and with no signs of improvement in the control chest x-ray.

After the ultrasound examination of the fetus done on December 4, 2009, it was decided that urgent C-section should be performed due to the deterioration of the mother's condition and the centralization of the fetal blood system (as the consequence of the fetal hypoxia because of the mother's hypoxia resulting from the acute pulmonary distress) as shown by the Doppler screening.

A baby girl, 1,650 gr heavy and 42 cm long, was taken to Children's Hospital of the Clinical Center of Niš immediately after the surgery. Ten minutes after the surgery there was a drop in the mother's TA and saturation and cardiac arrest ensued. The attempt at cardiopulmonary reanimation was unsuccessful and the patient died. The patient was proven to have been infected with the influenza A (H1N1) strain by the PCR method.

The patient A.N. graviditas ml IX-X, was admitted on November 12, 2009 with severe bronchopneumonia on both lungs. She had got sick seven days prior to the admission. She had not been inoculated against the virus. On admission, at 9.45 PM after the stimulation, she gave birth to a baby who died the following day. The patient received the therapy which included virostatic, antibiotic and bronchodilatator, as well as the substitution therapy. The extremely difficult clinical condition which required mechanical ventilation was accompanied by the development of spontaneous pneumothorax, which is in literature described as a relatively common complication in the condition of the patients who are on prolonged artificial ventilation. The patient recovered and was released from the clinic on December 29, 2009. The patient was proven to have been infected with the influenza A (H1N1) strain by the PCR method.

The patient V.S. graviditas ml.V had got sick eight days before she was admitted to hospital. She had not been inoculated. She was admitted on December 5, 2009 with the signs of peripheral cyanosis. She was adynamic, tachypneic with obviously indented jugular pits. Her respiration was 46 per minute, SF 141 per minute with a progredient fall in saturation from 85% to 67% . Since the patient developed further respiratory insufficiency two day after the admission, she was intubated and mechanical ventilation began. As she kept on refusing to take Oseltamivir, the family approval was asked for and the medicine was administered. After the constant cooperation with gynecologists and monitoring of the fetus, on December 18, 2009 a C-section was performed.

Regardless of all the measures taken, the disease progressed and the patient died on January 3, 2010. The patient was proven to have been infected with the influenza A (H1N1) strain by the PCR method.

The patient Đ.B. graviditas ml.VII was admitted to the Clinic on January 11, 2010 having been treated for the flu for five days. She had not been inoculated. On admission she was adynamic, tachycardic (133 per minute), tachypneic with the signs of peripheral cyanosis and with the saturation of O_2 of 76%. Mechanical ventilation began and gynecologist was called in. What was interesting was that PCR was negative but RVK was positive in 1:128 solution for the influenza A (H1N1) virus. The therapy included virostatic, antibiotic, substitutional and symptomatic therapy but the disease progressed into a severe bronchopneumonia and sepsis. On February 7, 2010 uterus contractions were registered and after a C-section a vital baby was born. Not long after the surgery the mother died.

The patient S.K. graviditas ml V had got sick on the same day she was admitted to hospital, December 24, 2009. On admission she was tachycardic (133 per minute), tachypneic (34 per minute) with the saturation of O_2 of 96%. Bronchopneumonia of both lungs was confirmed. After a seven-day treatment with antibiotic and antiviral medications and two days spent in IC Unit, the patient left hospital as healthy.

Discussion

RNK viruses, particularly the ones with the segmented genome (both influenza A and B viruses have got 8 segments in their genomes), belong to the group of extremely variable viruses. Casual mutations can change subunits on the surface antigens of the influenza A and B viruses (that is, on the H and N glycoproteins, which is also known as the antigenic 'drift'). In that way, new subtypes of the viruses A and B are created. The influenza A virus can go through even greater antigenic changes, which would produce new subtypes of the influenza A virus, for which there is no immunity in the population. These changes (the antigenic 'shift') result from the recombination of two viruses of the influenza A group (human and animal or bird), which simultaneously reproduce within an infected cell. The cell can be of a man or a pig (since a pig can be infected with human and animal and bird virus of the influenza A strain). Such a recombination of two viruses (human and animal or bird) produces a new subtype of the influenza A virus. Since there is no immunity in the population to this particular subtype, the pandemic ensues.

It is interesting to say that this virus does not cause viremia. The clinical picture at the beginning of the disease (fever and chill, high temperature) resembles a febrile-septic condition but it is not induced by viremia but by excreted inflammatory cytokines under the influence of the virus (a 'cytokine storm'). Those are inflammatory cytokines, the interleukine 1 (IL-1) before others. IL-1 is the co-factor of the clonal expansion of lymphocytes since it increases the number of the receptors for IL-2 on CD4 T- lymphocytes, and IL-2 is the main cytokine which induces clonal expansion of both CD4 and CD8 T antigen specific lymphocytes and B-antigen specific lymphocytes. It also incites unspecified cytotoxic influence of NK-cells on the virus-infected cells. Other excreted cytokines during the described 'cytokine storm' are the tumor-necrosis factor TNF and IL-6.

Recent research has shown that almost 80% of the H1N1 infected patients are virulent for 5 days, 40% remains virulent for 7 days whereas 10% can be virulent for 10 days and even longer (8). The longer virulence typically occurs in patients with compromised immune response and children (9, 10). In some cases, the patients were virulent up to 14 days from the outbreak (10).

Gravid women are at high risk of morbidity and mortality if infected with the influenza virus. It is known that the clinical picture of the gravid women infected with a new virus is a lot more complex and some of them were in a life-threatening situation and on mechanical ventilation. As gravidity generally represents a huge chemodynamic load, what could be expected in some cases is:

1. Spontaneous premature birth or induced premature birth due to the mother's condition with the aim of preserving mother's life, after the viability of fetuses has been estimated in those in the gestational week 23 and older.
2. The infection in the infant as the consequence of the mother's infection (if the birth of the chills occur 2 days before or 7 days after the disease outbreak in mother).
3. Postnatal infections in infant babies.

Although there is no influenza virus induced viremia in the fetus and later infant, there is a possibility that the cytokines created in the antiviral immune response of the mother go through the placenta and cause organ and tissue damage of the fetus (6). Patterson (5) and later Short et al. (6) have proven on the animal model that mother's viremia can cause damage to the brain of the fetus.

During the 1918 Spanish flu pandemic, gravid women in the third trimester were particularly at risk of becoming infected. In the 1957 pandemic, in the state of Minnesota, gravid women comprised one half of all the cases among the productive age women that had lethal outcome. In the previous pandemics, the most common consequences of the influenza infection of gravid women were spontaneous miscarriage, premature miscarriage or missed abortion.

One of the most striking characteristics of this epidemic is that the severe forms of the infection appeared even in the patients with no previous comorbidity with gravidity being one of the leading risk factors for developing a more complex form of the infection and more demanding clinical course (11).

Center for Disease Control and Prevention (CDC) suggests that gravid women in the third

trimester in particular are more prone to develop complex forms of the disease, that is, to develop complications (12). The research conducted by the California Public Health Association showed that up to 10% of the patients infected with a more severe form of the influenza A (H1N1) pneumonia who required hospitalization were gravid women, with more than 70% of them being in the second and third trimester. The same source showed that the number of the infected patients who required hospitalization was four times higher among gravid women than general population (13). The data presented by Canadian Health Association showed that 4% of the infected women were gravid, out of which 85% needed to be hospitalized with 16% of them being in IC Units, 4% of which had lethal outcome (14).

Louie et al. described the influenza infection in 94 gravid women and 8 postpartum in California, comprising 22 % of the total number of the infected patients with the mortality rate of 8% (15).

All these cases have one thing in common: none of the gravid women had been inoculated prior to becoming infected. Three gravid women in which the disease lead to the lethal outcome came to the clinic too late when the clinical picture had already been developed as dominant respiratory insufficiency and Oseltamivir therapy was administered only after 6 to 11 days from the outbreak. In one gravid woman, who was treated in IC Unit, the disease had a rapid and favorable evolution but the therapy had been administered on the first day of the symptom onset.

Siston et al. described the flu in 788 gravid women in the USA and stated that the possibility of developing a more complex clinical picture which would require hospitalization and ICU treatment rose in those cases in whom the therapy had been administered four days after the outbreak. The mortality rate in the first trimester was 7.1%, in the second trimester 26.8%, and 64.3% in the third trimester. Only one case of lethal outcome was described in which the patient had received the therapy 2 days after the onset of the symptoms (16).

A.N. showed a severe clinical picture. She had got sick seven days prior to the hospital admission and since then she did not receive the adequate therapy. Her clinical picture became even more complex since she developed a spontaneous pneumothorax. After 47 days of hospital treatment, she left hospital as clinically healthy.

A severe form of the influenza infection is characterized by a strong inflammatory reaction which becomes destructive. It also refers to the inflammatory reaction caused by bacterial superinfection.

The most common bacterial superinfections in the influenza A (H1N1) infection are pneumococcal and staphylococcal. The pneumococcal superinfection very often progresses into sepsis. It has been proven that the influenza A infection induces a selective defect in the immunity against *Pneumococcus*, which causes bacterial superinfection.

Mortality in the influenza A (H1N1) infection is linked with a severe bacterial superinfection and uncontrollable immune response (17).

In the end, it can be debated as to the reasons why some people get the milder forms of the influenza A (H1N1) viral infection and others get more complex forms which often have a lethal outcome. A group of Canadian and Spanish authors published a clinical study in December 2009 in which they showed that all the patients with more severe forms of the influenza A (H1N1) virus had high values of the interleukin 17 as opposed to the patients with milder forms in which those values were low. In the future, blocking of interleukin 17 might lead to the reduction in number of the patients with more severe forms of the influenza A (H1N1) infection. Until then, what can be done to reduce the number of the infected people and the number of the lethal outcomes is to try to increase the collective or herd immunity through inoculation and resistance through exposure.

Conclusion

It takes a lot of work in health education of people, gravid women in particular, to debunk certain prejudices related to inoculation. Inoculation against the flu must be an obligatory measure of protection of gravid women and immunocompromised people against the disease. It is the only way to prevent the outbreak that can lead to more severe forms with lethal outcome. Timely administration of the adequate antiviral therapy is one of the most decisive factors influencing the course and the final outcome of the disease.

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NAŠA ISKUSTVA U LEČENJU GRAVIDNIH ŽENA U EPIDEMIJI GRIPA A H1N1

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Karakteristika epidemije gripa A H1N1 je da se teške forme infekcije najčešće javljaju kod bolesnika sa prethodnim komorbiditetom, a da trudnoća predstavlja jedan od vodećih faktora rizika za razvoj težeg oblika infekcije i težeg kliničkog toka. Opisano je pet trudnica koje su lečene u jedinici za intenzivnu negu kod kojih je PCR metodom potvrđena infekcija virusom gripa A H1N1. Najteže kliničke slučajeve su prezentovale trudnice u trećem trimestru graviditeta. Nijedna od njih nije bila vakcinisana, a prosečno vreme od pojave prvih simptoma do primene Oseltamivira je 6-11 dana. Blagovremena vakcinacija je jedini siguran način prevencije gripa. Od bitnog značaja za ishod bolesti je primena terapije Oseltamivirom najkasnije 48 časova od pojave prvih simptoma bolesti. *Acta Medica Medianae 2017;56(3):25-30.*

Ključne reči: *grip, PCR, graviditet, zapaljenje pluća, mehanička ventilacija*