

H1N1-LIKE INFECTIONS IN PREGNANT WOMEN

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ABSTRACT. The Pandemic H1N1/09 virus is a swine origin Influenza A virus subtype H1N1 virus strain responsible for the 2009 flu pandemic. While only mild symptoms are experienced by the majority of people, some patients, who in the following article will be considered as coming from risk groups, can develop more severe complications, even leading to death. Risk groups being considered: asthmatics, diabetics, obese or immune compromised patients, children with neurodevelopmental conditions, and most important from our point of view, pregnant women. In the next lines we are going to present two clinical cases of pregnant women, both presented in our hospital, supposed to have AH1N1 viral infection and treated in consequence, but unfortunately both ended malevolent as result of the severe and very rapid deterioration of their status. Although the two cases were similar as evolution and ending, there were also important differences between them, which can guide us for the future in investigating and treating this kind of pathology.

Keywords: AH1N1 virus, pregnancy, respiratory distress, differential diagnose

INTRODUCTION

Pandemic H1N1 2009 influenza virus has been identified as the cause of a widespread outbreak of febrile respiratory infection worldwide. Although the severity of this illness has ranged from mild to severe, little has been reported about how this outbreak has affected pregnant women.

2009 H1N1 influenza virus appears to be transmitted from person to person through close contact in ways similar to seasonal influenza viruses. In general population, the symptoms are alike in any other flu, represented mainly by fever, sore throat, cough, headache, muscle or joint pains, nausea, vomiting, diarrhea.

A significant difference of the discussed infection was observed soon after patients were admitted in hospitals, or sometimes they were even not able to get to hospitalization units, supporting a very fast deterioration of the general status, developing acute respiratory distress syndrome, manifested as increased breathing difficulty, typically occurring 3–6 days after initial onset of flu symptoms.

Deterioration is rapid, with many patients progressing to respiratory failure within 24 hours, requiring immediate admission to an intensive care unit. Upon admission, most patients need immediate respiratory support with mechanical ventilation.

Pregnant women infected with H1N1 influenza virus have been more likely to suffer severe complications than other population groups. The epidemiology and spectrum of maternal illness in the immediate postpartum period are not yet fully understood and are under investigation.

Most likely, the increased severity of H1N1 viral infection at pregnant is due to the physiologic immunological depression during pregnancies, an indeed very important aspect of maternal

accommodation to the half-allogenic implant represented by the embryo at the beginning. Although this is needed to be able to keep the pregnancy, later on, when the patient has to confront external antigenic stimuli, such as bacteria, viruses or any other kind of infectious agents, the immune response of her body will be lowered, and as a result, all infectious diseases have more rapid and more severe course than at non-pregnant women.

MATERIALS AND METHODS

Our study, although the number of cases we discuss is only 2, had some important aspects to prove. First, we meant to demonstrate the severity of influenza H1N1 viral infection when speaking about pregnant women and nevertheless the fact that definitively they do belong to high risk groups when speaking about infectious diseases.

Another aspect we followed during the studied cases was that of the differential diagnose, which was very difficult to set in the course of the pathology, as one can see, in our case the only proof for the differential diagnose was given after the autopsy and microbiological exams.

One more, maybe the most important facet of the discussed cases, was the very rapidly deteriorating status of the patients, overcalling the medical assistance's possibilities of intervention, underlined also by the lack of protocols to follow.

In order to follow our goals, we are going to present two clinical cases appeared in the Obstetrics-Gynecology Hospital of Oradea, a few month after the first influenza H1N1 reported cases, at the beginning of 2009 autumn, period when, unfortunately, we were not prepared theoretically nor practical or treatment related, to confront or even to diagnose such cases.

The first appeared case in our hospital, suspected to be swine flu, was a controversial case, in which not even the hospital's committee didn't agree upon the epidemiology of the infection, so the treatment was delayed on administrative behalf. As we found out later on, a soon induced antiviral treatment wouldn't have helped, because the infection was not determined by H1N1 virus, but we were not sure of this until the pathology results.

By the appearance of the second case, learning well from the previous unfortunate death, the hospital was better prepared to admit, diagnose and treat a swine flu case, but this time, due to other causes than administrative ones, we were also not able to save the mother's or the child's life.

CASE REPORTS

The first case had a relatively quick evolution. A 29 years old pregnant woman showed up the emergency department with severe respiratory complaints, shown as dyspnea, cough with no sputum, fever and a severe general alteration of her status.

As general data, the patient was coming from urban environment, good social and familial background.

Familial history showed no relevant issues, as well as her personal physiologic and pathological antecedents. From obstetrical point of view, she was at her 2nd gestation at moment of admittance, with a 32 weeks old healthy and normally developed pregnancy, no pathology or treatment needed along the gestation.

The present pathology symptoms appeared about a week ago, first with mild cough and feverish state, but her status deteriorated fast and her family had to call ambulance. The out coming doctor decided that she needs no admittance to hospital, diagnosing the patient as having respiratory virosis and recommending bed rest and symptomatic treatment with antipyretics and vitamins.

The next days, because she was not getting better, the patient went to her family doctor for a consult, which decided the need of antibiotics, administering her Penicillin. After 3 days of antibiotics, the gravida got even worse, her respiratory issues got more severe, with sudden respiratory distress, so she came to our emergency department and she was immediately admitted to the Intensive Care Unit. During all the process, her status was deteriorating every minute, the only positive part was that the pregnancy she was carrying was not affected yet. The fetus had good biometric and circulatory parameters, no signs of fetal suffering.

General examination showed modified general status, multiple episodes of fainting, severe sweating, with very pale skin and perioral cyanosis. The frequency of breath showed tachypnea (22/minute), diminished vesicular sounds and confusing and disseminated pulmonary sounds, similar as in an interstitial pneumonia.

After admittance she was given i.v. Cefort for the supposed pneumonia, Miofilin to free the respiratory

tract, HHC, vitamins, Algocalmin for the fever and rehydration, but in spite of all ICU efforts, her FiO₂ level remained between 52-60%, with arising and decreasing blood pressure, from 90/140mmHg to 60/95mmHg and tachycardia of 118-126/minute.

Laboratory findings were the followings: WBC-4300/mm³, RBC-3,03 mil/mm³, HGB-9,5g/dL, PLT-114.000/mm³, glycemia-92mg%, all coagulation and renal probes in normal range, only the liver tests were higher, TGO-109iu and TGP-79iu. The urinary and vaginal discharge probes were negative, as well as the testing of the faringian secretion and the sputum, and also the haemoculture came back sterile.

The next day an infections specialist was called to consult, which made the supposition that the patient could be infected with the new type of respiratory virus, AH1N1(swine flu), reason why she decided that the patient should be transferred to the County Hospital Isolation ICU, where the tests for H1N1 were performed and specific treatment for this kind of pathology was given, with Tamiflu antiviral, not knowing the precise effect of the drug or of the present pathology upon the fetus.

After some a few doses of Tamiflu, the situation seemed to be in control, the respiratory problems got better. The patient was breathing spontaneously, only with the help of an oxygen mask, her blood oxygenation parameters got to 64-70%. The good response to antiviral treatment underlined the supposition of "Swine Flu", diagnosis set in the given circumstances.

Next day the status of the pregnant woman worsened very fast, so the gynecological committee decided to perform an emergency Caesarian section, in order to save at least the unborn child's life. The operation went relatively well, obtaining a female newborn in weight of 1600gr, with no specific signs of fetal suffering, so at first glance the new-born was safe.

Meanwhile the results of immunological serology came back negative, infirming the "Swine Flu" diagnose. Because of not finding any other pathology and the case was still going bad, the medical team decided to maintain the treatment and repeated the laboratory analysis for the specific viral infection, which came negative for the second time, too.

The worst fear of gynecological team got real. After CS the patient was not able to breathe on her own, anesthesiologists and intensive care medical team could not take her off mechanical ventilation, so she remained on assisted respiration further on. Two days after intervention, the patient died of respiratory failure.

Anatomic and histo-pathological examinations were performed and the finally set diagnosis said bronchopneumonia with multiple pulmonary infarctions and abscesses and confirmed sepsis with *Pseudomonas aeruginosa*.

The new-born was transferred to Preterm Intensive Care Unit, where she got the best assistance, and after multiple investigations she was declared healthy and in good conditions, relatively well adapted to

environment, if we consider the prematurity and the mother's pathology. She was released from hospital a month later, with a weight of 2400 g, no associated pathology and negative H1N1 serology.

The second case we confronted, supposed from the beginning to have H1N1 infection, had a more rapid evolution, but she was much more affected the time she came.

First pregnant woman of 15 years old, with a chronological uncertain pregnancy came to our emergency department with respiratory complains: dyspnea, tahipnea, cough with no spit, fever, severe general alteration of her status, and what was very important, she didn't feel the fetal movement for a couple of days.

As general data, the young girl was coming from rural environment, from an unorganized and unfavorable familial background, very low educational and social level. No reliable information about her familial or personal history was found out.

She was at her first pregnancy, as far as we were able to do a pertinent anamnesis, but she was never seen by any doctor during the last months, so we were not able to be eloquent regarding her obstetrical past. From her telling, the pregnancy went well till the last few days, when she felt no fetal movement at all.

An obstetrical ultrasound was performed, showing that the fetus was of about 30/31 weeks old, but already dead for at least a few days, with values of about 30 weeks fetal biometry, mild hydrops fetalis and low amniotic fluid level.

The present respiratory pathology started 3 days ago, with cough with no spit, dyspnea a certain degree of fever, but never measured.

At admittance her general status was very severe, much more altered then in the previous case, with obnubilation, generalized cyanosis, almost no perceptible pulse, immeasurable blood pressure, cold and cyanotic extremities. At respiratory examination besides tahipnea and dyspnea, we found diminished vesicular sounds and disseminated pulmonary sounds, similar as in an interstitial pneumonia. The blood oxygen saturation level was 14,8% which is practically incompatible with life or spontaneous breathing and EKG sings of myocardial ischemia were seen. She was admitted to ICU department, where she was intubated and set on mechanical ventilation with 100% oxygen, after which the saturation remained the same. Repeated resuscitation maneuvers were performed, associating also Efedrine, Atropine, Adrenaline, Miofilin, HHC and antibiotics, but after 1 hour whit no response, the death of the patient was pronounced.

The pathological and histological examinations performed demonstrated that the pregnant woman has severe cerebral edema, acute pulmonary edema, bronchopneumonia and intrauterine demise of a 30 weeks old fetus, with not respired lungs, ascites and increased liver, first degree of fetal maceration, female gender, weight of about 1700 g.

Later on from the biological probes from the pregnant woman immunological tests were performed and the confirmation of a H1N1 viral infection was positive.

RESULTS AND DISSCUTIONS

If we consider appreciating the results of the two related cases, we would have to consider them disastrous. Of course, excuses can be made in both cases, and in fact, well founded and real excuses, which didn't permit us to take our chance of treatment in front of such a horrible disease.

Even so, by the death of both patients, the results should have a single, but huge importance: to show us that any respiratory, moreover, that any kind of infectious disease presented at a pregnant should instantly arise our attention, in order to diagnose and treat it as soon as possible and always to remember the fact that an infection to any pregnant could be lethal.

The pregnant from the first presented case died because we were not able to diagnose in effective time the cause of her systemic infection. Her illness was very severe when she came, probably already with no possibility of turning it backwards.

The correct intensive care she underwent was able to maintain her vitals long enough to perform the CS and save the infant, but as expected, doctors couldn't recover her after anesthesia.

At that time, in our country, but not even abroad, no protocols whatsoever were available to follow in cases suspected to be infections with H1N1 Influenza virus, the reported infections at preganats were just a few, most of them with very fast deterioration and no possibility of treatment. The serologic diagnose that time was possible only in higher specialized infectious medical centers, not in our city, so the serology samples from the patient, and later on, from the recovered child, were sent in Bucharest to be identified.

This also slowed down the process of a correct diagnose. Meanwhile, the antiviral treatment was given to the patient, and seemed to have good results, but only for a short period of time, after which she went in respiratory distress and never recovered.

Probably the only positive issue of the case was that the child was saved, being out taken by CS in time.

The results of the second case were even worse, but due to the patient's or the family's limited capacity of understanding the symptoms or the severity of the case. When she arrived to hospital, with all the preparing and wish of help of the medical team, it was too late to do anything for her or for the child, as it was dead some days before and the infection, this time real with H1N1 virus did already irreversibly compromise the respiratory function of the patient.

No intensive care helped, she died of respiratory failure soon, under 1 hour after admission. The conclusion, which can be drawn, in order to be useful, is that every pregnancy should be followed much better, and we have to teach every pregnant woman to ask for specific medical help as soon as she notices any

kind of estate alteration. Pregnancies, and infections in pregnancy, should be more strictly observed, diagnosed and treated, with definitive seriousness.

Before the present worldwide outbreak, published work of influenza virus of swine origin in pregnant women was limited to a single case in 1988: a 32-year-old previously healthy pregnant woman at 36 weeks' gestation was infected with a swine influenza virus, contracted through exposure to pigs, and later died of complications related to primary viral pneumonia.

On the basis of our investigation, pregnant women seem to be at increased risk for complications from pandemic H1N1 virus infection, with a higher estimated rate of hospital admission than in the general population. The decision to admit a pregnant woman is difficult and might include considerations more than simply the severity of disease, should include well set differential diagnose issues and ask the opinion of related specialties, such as Infectious Diseases, Intensive Care, Epidemiology, Pathology.

A study showed that women were more likely to be admitted to the hospital for respiratory illness during influenza season during pregnancy than during the year before pregnancy. In pregnant women with associated comorbidities (defined as pre-existing diabetes, pulmonary disease, heart disease, renal disease, anemia), hospitalization for influenza-like symptoms was more than five times higher.

The circulating pandemic 2009 H1N1 virus was sensitive to the neuraminidase inhibitors like Oseltamivir and Zanamivir. In randomized controlled clinical trials, these drugs have reduced the severity of seasonal influenza if started within 48 h of illness onset. Recommendations for pregnant patients are that antiviral drugs should be started as soon as possible after the onset of influenza symptoms. The benefit is expected to be greatest if started within 48 h of onset.

However, neither of the pregnant women in our study was treated with either of these drugs at the time of their presentation. In the cited studies, there seem to have been delays in initiation of antiviral therapy; health-care providers might have been reluctant to treat patients with antiviral drugs because they were pregnant, or before laboratory confirmation of disease, or the pregnant woman might have been reluctant to take an antiviral drug.

As with most drugs, information about the safety and effectiveness of these anti-influenza drugs during pregnancy is scarce. In view of the expected effects of pandemic H1N1 influenza virus on the pregnant woman, the benefits of treatment with these drugs are likely to outweigh potential risks to the fetus.

In our first case, Tamiflu was given to the patient, but before laboratory confirmation of the suspected virosis was set. After finding out that in fact the infection was not due to H1N1 virus, there was no use of stopping the antiviral therapy, because the patient went into irreversible respiratory distress.

In the second case, although we already had guidelines to follow in diagnose and in therapy, the

timing was not good enough because the respiratory failure was too severe to be correctable.

Still, little is known about the effects of the pandemic H1N1 virus on the fetus. Although no infections have been reported in infants born to women with H1N1 virus infection, these infants might have had more subtle effects from maternal pandemic H1N1 virus infection. Although viremia seems to be rare in seasonal influenza and placental transmission seems not to occur in frequently, highly pathogenic strains of influenza virus, such as avian influenza A (H5N1), might be transmitted across the placenta.

Even in the absence of placental transmission, the fetus could be adversely affected by influenza or its effects. For example, fever, which often accompanies influenza, has been associated with an increased risk for neural tube defects when occurring in the first trimester and with other adverse neonatal or developmental outcomes, when occurring later in pregnancy.

Further follow-up of outcomes of pregnancy to women infected with H1N1 virus is needed to improve understanding of the possible effects of this virus.

Vaccination will be an essential component of the public health response to this influenza, and protocols should place pregnant women in a high-priority group of recipients of pandemic influenza vaccine.

Correct information about safety of influenza vaccine during pregnancy is vital, as the available data showed no evidence of adverse effects on women or their infants.

We are clearly aware of the fact that our study has many limitations. For example, because of technical limitations on laboratory possibilities in diagnosing H1N1 virus there is the likelihood that results of testing would come too late to change clinical care.

Anyhow, the purpose of our study was not that of classifications or exact results, but only to impress the reader about the seriousness of this infection among pregnant women, or about the difficulty of diagnosing it so early after first cases were reported. The small number of discussed cases in partially good, meaning that we fortunately didn't have to confront more cases like that, the pandemia stopped a few month later.

Our findings from this study will be helpful to inform public health planning for pregnant women, both for this virus and for other novel pathogens. Important would be for health-care providers to realize that pregnant women are at increased risk for severe disease and complications from pandemic H1N1 influenza virus infection, and should start treatment with anti-influenza drugs promptly.

CONCLUSIONS

Pandemic influenza type H1N1 was and it continues to be, a very serious threat, especially when speaking about certain risk groups, such as pregnant.

Being a quite new disease, but with many resemblances to other respiratory tract infections, especially in the first phases, it is difficult to

differentiate it immediately from the more common infections, this being the reason why so many cases worldwide had unfortunate ending.

At time of admittance of the first related case, we had no specific protocol to follow regarding the management of swine flu during pregnancy, no official data about usage of Tamiflu, reason why both gynecological and infectionist specialist had to confront a situation with no precedent.

When the second case appeared in our hospital, medical team was already aware about the correct management, but even so, the patient came too late to hospital, so nothing could be done in order to help her or her baby.

Even if at the end, pathologist demonstrated that the first case was not an infection with H1N1 virus, it is important to note the conclusions and remarks for differential diagnose for future incidents.

As we can see, these kinds of infectious diseases in pregnant have a very fast evolving pattern, being able to induce death in a few days or even hours, because of that, medical teams have to be well informed and prepared to treat it right away. Loosing any moment can lead to death.

The specificity of swine influenza at pregnant consists not only in being a high risk group due to the general immunological depressions during pregnancy, but also because sometimes if the illness is very advanced and the life of the gravida is in acute danger, at least the fetus can be saved.

We have to note, as always, the importance of accurate pregnancy follow-up. In the second case we knew nothing about the pregnancy, about possible associated pathology, but most probably the unfavorable familial and economic background of the gravida made her being less resistant and permitted the virosis to evolve so fast, causing her death.

When suspecting H1N1 virosis, doctors have to take action immediately to be able to save the immune compromised patient, by administrating antiviral therapy and respiratory support.

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