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Case Study

FATAL PROGNOSIS OF H1N1 INFLUENZA IN LATE TRIMESTER OF PREGNANCY: DESCRIPTIVE ANALYSIS OF FOUR CASES

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ABSTRACT

Influenza infection in late trimester associated with complications is attributable risk factors for critical illness among pregnant women. We have analyzed the medical records of four pregnant women retrospectively who were admitted in a medical intensive care unit of tertiary care center with influenza-like symptoms of breathlessness, fever, headache, myalgia and cough. Their mean age was 26.5 (19-30). They were confirmed to have H1N1infection by real-time reverse transcriptase polymerase chain reaction assay. Chest x-ray of all patients showed abnormalities like pulmonary edema and suggestive of acute respiratory distress syndrome. Arterial blood gas analysis of all four patients shown severe hypoxia and all of them was mechanically ventilated. Oseltemivir was started for all four from the day of admission. Pipracillin-tazobactum combination along with other antibiotics was given as prophylaxis and treatment of different infections. Midazolam and morphine were given together to reduce the restlessness and ventilator-associated distress. Furosemide was given to all for breathing problems and pulmonary edema. Despite of all the management provided none of the patients survived due to the progression of H1N1 into septic shock and multiple organs dysfunction syndromes.

Keywords: Viral infections, Swine flu, Septic shock, Multiple organs dysfunction, Acute respiratory distress syndrome

INTRODUCTION

World Health Organization (WHO) has declared that the new strain of virus is more likely to cause infection in pregnant women. Hence Influenza A-H1N1 (Hemagglutinin-H-neuroaminidase-N) infection is a severe cause of illness and mortality in pregnant women. Admission of pregnant women with H1N1 infection and the associated mortality is increased when compared with non-pregnant women [1]; mostly death occurs in the late trimester of pregnant women. The real-time reverse transcriptase-polymerase chain reaction (RT-PCR) technique is widely used to confirm H1N1 infection. The increased risk of H1N1infection in pregnant women is due to the occurrence of several physiological, mechanical and hormonal alterations. Cardiovascular and respiratory systems changes (increased heart rate, stroke volume, oxygen consumption and decreased lung capacity) are other factors associated with mortality in pregnant women [2-4]. Here we are reporting 4 cases diagnosed with HIN1 in the third trimester of pregnancy with clinical characteristics, risk factors and management. Permission from institutional ethical committee (IEC) was taken for the same. The main reason came out with the high mortality rate in pregnant women is the delayed treatment with antiviral therapy, severity of the symptoms, other associated infections and resistant of antibiotic therapy [5]. According to Centers for Disease Control and Prevention (CDC) recommendations, antiviral therapy should initiate immediately if the pregnant woman in suspected to have H1N1 infection. The patient started on antivirals after 48 h have 4 times more risk of intensive care unit (ICU) admission or fatal outcomes. Co-morbidities also worsen the outcome. This case series enlighten the fatal prognosis of H1N1 in pregnant women in a late trimester.

Case presentation

Case 1

A 30 y old pregnant woman admitted to a tertiary care hospital with chief complaints of pedal edema, fever, breathlessness when she was primigravida at 25 w. The patient had influenza type symptoms and yet on oseltemivir 150 mg twice daily for 2 d from the local hospital with no other co-morbidities. Her blood pressure was 160/100 mmHg, SPO_2 of 72 % on room air and started on non-invasive ventilation (NIV) with FiO_2 = 100 %. Her arterial blood gas (ABG) analysis showed a predominant decrease in pH (7.052), PaO_2 (83.2 mmHg) and increase in the $PaCO_2$ (50.3 mmHg). On admission her blood reports showed serum creatinine (5.9 mg/dl), hemoglobin 10 g/l, total leucocytes count 10,700 cells/mm^3 and absolute neutrophil count 36,960/mm^3. Urine analysis showed high protein (15 mg/dl), the presence of uric acid crystals and WBC (12-15 cells/ml). To confirm the H1N1 infection patient's throat swab was taken which came out to be positive by RT-PCR technique. She has started on azithromycin 400 mg daily for 5 d, tazobactam and piperacillin 4.5 g twice daily for a week and continuation of oseltemivir 150 mg twice daily with methylprednisolone 80 mg at every 8 h as supportive care. As the patient was on ventilation support; midazolam IV infusion 4 mg/h was given for 5 d, for ventilator-associated stress and restlessness. Furosemide 20 mg twice daily given for 2 d, intravenously as the patient had pedal edema.

Erythropoietin 1 ampoule (4000 IU) daily given for 6 d, as patient's hemoglobin, was low. Her condition deteriorated during the management, and she developed acute respiratory distress syndrome (ARDS) and intrauterine sepsis along with H1N1 infection. On 8th day of admission her condition worsened which leads to excessive dropping in blood pressure (60/40 mmHg) due to which dopamine 20 µg/kg/min was administered. The patient developed multiple organ dysfunction syndromes (MODS) on the 10th day and succumbed to cardiac arrest.

Case 2

A 19 y old pregnant woman was admitted with chief complaints of fever and cough for 1 w, breathlessness and sore throat for 4 d. She was primigravida at 34 w. Patient's medical history revealed that she had developed bilateral pneumonia/ARDS primarily and was on azithromycin from a local hospital. On the 2nd day of admission, lower (uterine) segment caesarean section (LSCS) was done with the delivery of twins; both babies were fine and doing well. Her SPO_2 is 82 % on room air and 97 % on NIV 60 % venture. She had tachypnea; harsh vesicular breath sounds heard in all areas with crepts. H1N1 was confirmed by PCR technique from patient's throat swab and chest x-ray showed homogenous opacity suggested of ARDS. Her ABG analysis showed abnormal $PaCO_2$ (19.1 mmHg), PaO_2 (68.4 mmHg), SO_2 (93.2 %) with low potassium of 2.5 meq/l. Blood reports showed low hemoglobin 9.1 g/dl, total leukocyte count

(TLC) 20,800 cells/mm^3, ESR 94 mm/h with normal liver function test and urine analysis showed no abnormalities. She was started on piperacillin and tazobactam in combination 4.5 g daily intravenously for 7 d, oseltemivir 75 mg twice daily for continuous and powder potassium chloride was given the first day only as the potassium level was low (3.2 mmol/l). Furosemide 20 mg IV was given on the first day; again started on the 5th day and continued till 11th day. Her condition worsened on 7th day so she was shifted to mechanical ventilation and Midazolam infusion 1 ml/h started for ventilator-associated stress. On that day ABG analysis showed pH 7.58, PaO_2 (56 mmHg), $PaCO_2$ (28 mmHg) and HCO_3 (24 meq/l). On 7th day patient also developed sepsis and piperacillin-tazobactam changed to netilmicin 150 mg daily and meropenem 1 g for every 8 h intravenously to continue. One packed cell pint was transfused on the 11th day for low hemoglobin and supported by inotropes and morphine for her deteriorated condition. Patient succumbed to bradycardia and septic shock on the same day.

Case 3

A 30 y old female admitted to a tertiary care hospital with chief complaints of a cough, fever, breathlessness, vomiting and 39 w of gestation. Patient's medical history revealed that she had upper respiratory tract infection outside before 1 w with no medication history. Her ABG analysis showed pH 7.376, $PaCO_2$ 24.2 mmHg and PaO_2 74.8 mmHg. On admission, her PaO_2 was 95 % and SPO_2 was 97 % on 60 % venturi, she also presented crepts. Other biochemical and hematological reports were normal on admission. The patient was confirmed to have H1N1 by RT-PCR technique. She was started on medication piperacillin-tazobactam in combination 4.5 g daily intravenously, oseltemivir 150 mg once daily and 5 % dextrose solution at 60 ml/h with other supportive settings.

Tramadol 50 mg intramuscular was given thrice daily for 2 d followed by propofol 20 mg IV stat on 3rd day. Midazolam 20 mg and morphine 30 mg daily intravenously were given the 4th day to continue. By 5th day clinician started meropenem 1 g IV at every 8 h and teicoplanin 400 mg IV twice daily and stopped piperacillin and tazobactam in combination because no symptomatic improvement noticed. On 7th day of admission, the patient has developed metabolic acidosis (pH 7.28, $PaCO_2$ 87.0 mmHg, PaO_2 47.2 mmHg and SO_2 74 %) and ventilator-associated pneumonia; chest x-ray showed pulmonary edema and homogenous opacity which suggested having ARDS. Furosemide 20 mg IV was given for one day for pulmonary edema. On 9th day total leucocyte count was seen high as 23,900 cells/mm^3 so blood culture was sent for microbiological testing. After 24 h blood culture report shown multidrug-resistant acinobactor and antibiotics (meropenem and teicoplanin) changed to colistimethate (colistin) 1 million IU at every 8 h continue. Same day patient showed symptoms of deep vein thrombosis hence enoxaperin 0.4 ml (40 mg) daily was started. On 14th day, she developed the symptoms of restlessness, shallow breathing and succumbed to respiratory acidosis and septic shock.

Case 4

A 27 y old female was admitted with chief complaints of a cough for 2 w, breathlessness and fever for 5 d and she was primigravida at 26 w. The patient had nil medical history. On admission, she had tachypnea, bronchial breathing in the left intra-scapular area, reduced breath sounds in the right intra-scapular and intra axillary area with positive crepts. Her SPO_2 was 70 % on 60 % venturi and she was severely hypoxic with grade 3 diastolic dysfunction. ABG analysis showed pH 7.26, $PaCO_2$ 47.2 mmHg, PaO_2 48.8 mmHg and SO_2 was 77 %. H1N1influenza has confirmed from her throat swab sample by RT-PCR technique and chest x-ray showed fluffy bilateral shadows sparing the left upper zone. Her biochemical, hematological reports were normal except high TLC; 11200 cells/mm^3 and low hemoglobin 11.8 g/dl. She was started on azithromycin 500 mg IV, nebulizer salbutamol-ipratropium bromide combination at every 8 h, injection piperacillin-tazobactam 4.5 g intravenously and oseltemivir 150 mg twice daily with other supportive care as 5 % dextrose solution 50 ml/h. The patient condition was worsening so azithromycin, nebulizer salbutamol-ipratropium bromide and piperacillin-tazobactam were stopped and she switched to meropenem 1g IV daily, clarithromycin 500 mg twice daily oral and hydrocortisone 100 mg IV daily intravenously for 2 d followed by same for continue. Morphine 30 mg daily has started with midazolam 20 mg daily for sedative effect as the patient was on mechanical ventilation from admission. On 3rd day patient had unusual vaginal bleeding so UFH 5000 U was given subcutaneously continue. On 5th day she developed ARDS and biochemical investigations showed abnormality; blood urea 49 mg/dl, serum creatinine 2.8 mg/dl, sodium 155 meq/l and potassium 5.6 meq/l. ABG analysis showed pH 7.01, $PaCO_2$ 78.0 mmHg, PaO_2 46.8 mmHg and SO_2 82 %, these all suggestive of respiratory acidosis. Ventilation settings were changed according to patient need. On 5th day condition worsened with blood urea 124 mg/dl, serum creatinine 4.7 mg/dl, sodium 156 meq/l and potassium 5.7 meq/l and ABG analysis showed pH 7.36, $PaCO_2$ 44.0 mmHg, PaO_2 45.2 mmHg and SO_2 80 %. During the course of treatment, a patient condition exacerbated on 6th day morning and succumbed to MODS and septic shock.

DISCUSSION

A number of studies have been carried out related to mortality and morbidity in female patients with H1N1 infection, but there is no sufficient data that proves the association of mortality and pregnancy clearly. According to CDC in 2009 pandemic influenza the rate of hospitalization was 4 times higher in pregnant women than the rest of population. Hereby we have presented the 4 female patients in their late trimesters with high-risk factors associated with mortality. In view of the discussion, we found that complications in H1N1 infection in pregnant females [table 1] are more towards the mortality. The need of immediate hospitalization in pregnant females is increased due to H1N1 infection and its complications.

Table 1: Detailed course of all 4 cases of H1N1 infection, succumbed in late trimesters.

	Case 1	Case 2	Case 3	Case 4
Age	30 y	19 y	30 y	27 y
Pregnancy status	25 w	34 w	39 w	26 w
Medical history	Nil	Pneumonia/ARDS	URTI	Nil
SPO_2 level on Admission	72 % on room air	82 % on room air	97 % on 60 % venturi	70 % on 60 % venturi
Intubated/Ventilation support	Yes	Yes	Yes	Yes
Hemoglobin	10 g/dl	9.1 g/dl	12.6 g/dl	11.8 g/dl
Total leucocytes count	10700 cells/mm^3	20800 cells/mm^3	8800 cells/mm^3	11,200 cells/mm^3
Duration of stay	10 d	11 d	14 d	6 d
Antibiotic Resistance	No	Yes	Yes	Yes
Complications during hospitalization	ARDS, MODS, Cardiac arrest	Sepsis	ARDS, Septic shock, Respiratory acidosis	ARDS, MODS, Septic shock
Outcome	Expired	Expired	Expired	Expired

(URTI, upper respiratory tract infection; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; SPO_2, saturation of oxygen)

Various physiological, mechanical and hormonal alterations are the leading cause of severe outcomes and high mortality rates in pregnant women. Heart rate, stroke volume, oxygen consumption and decrease lung capacity are the changes in the cardiovascular and respiratory system during pregnancy. Immunological changes in pregnancy showed a shift from cell-mediated immunity to hormonal immunity that also increased the risk of getting an infection and fatal outcomes [2-5]. Pregnant females have similar influenza-like symptoms such as a cough, sore throat, fever and breathlessness. Among these females with similar symptoms few of them rapidly deteriorate to ARDS and various other complications hence becomes critical and shift to mechanical ventilation. This generally occurs in the later phase of pregnancy due to shift from the cell-mediated immunity [6].

We have assessed the 4 cases during 2013 and 2014 with age range of 19-30 y. The RT-PCR technique is used to confirm the H1N1influenza infection. All 4 were mechanically ventilated on the basis of disease severity. As per the WHO guidelines and various studies were done for sepsis-induced ARDS are brought into consideration for the management therapy [7]. Females admitted in the late phase of pregnancy are at major risk so the pre-term delivery can reduce the risk of mortality for baby and mother both and can increase the survival chances. Catanzarite and Willms 1997 reviewed 83 similar cases which showed timing delivery is necessary for sepsis-associated ARDS patients. As soon as the delivery is extubated the condition improves dramatically within 24 h. Pre-term delivery is basically performed to reduce the risk of mortality and to increase the therapeutic option for the mother [1, 8].

In the above-studied cases only 1 female underwent delivery and gave birth to normal and healthy twins, but other 3 didn't have a suitable condition to undergo delivery. The cause of death in the female who underwent caesarian is sudden bradycardia and multiple organ dysfunction syndromes. In all four patients, oseltemivir is started as soon as they got confirmed for H1N1infection. They all started with various antibiotic combinations as prophylaxis or treatment for suspected and confirmed infections. Based on their severity and low SPO2 levels, they were put on ventilation support and were started with morphine and midazolam together to reduce the mechanical distress and restlessness. They were also given with diuretics due to pulmonary edema and breathing problems. Due to the advancement of the clinical condition females developed resistance to antibiotics which deteriorate their condition further and they developed ARDS and multiple organ failures [8, 9]. There is not much study or literature available on pregnant females with H1N1, ARDS, MODS and not responding on mechanical ventilation. Such female has to go under proper guidelines of management with their timely onset of action. The mortality can be reduced if the adjuvant therapy would be initiated timely [10].

It is really important to focus on the emergency requirements/needs in such critical situations, or cases have a chance to get critical. The various factors should remain in focus such as early detection of diseases, commencement of antiviral therapy, resistance towards antibiotics, the hypoxic condition of the patients along with fetus delivery in infected pregnant females.

CONCLUSION

The study showed that pregnant women are at more risk when compared with the normal population. They are more prone to get infected and hence high mortality rate. In the study, we found out various mortality factors that lead to death in pregnant females. We found out that pregnant females in their late trimester develop ARDS, sepsis, MODS those shifts the risk towards a fatal outcome.

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CONFLICT OF INTERESTS

Declared none

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