

H1N1 Influenza Virus Infection in Pregnancy: A Study of 32 Cases

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ABSTRACT

Reports from the past pandemics (1918-1919) and the 2009 outbreak have shown that pregnant mothers are at risk of complications from the H1N1 influenza virus infection. This study was undertaken to analyze the clinical course of H1N1 infection in pregnancy, the maternal and perinatal outcome and the treatment efficacy of oseltamivir in H1N1 infected mothers. This is a descriptive study from the Institute of Obstetrics and Gynaecology and the case series were collected from September 2009 to December 2010. Influenza like illness (ILI) was suspected in 207 pregnant women, and the 32 cases who were positive for H1N1 influenza infection by RT PCR test were taken for this study. 90.6% were in the age group between 21 and 29 years of age and 34.4% were multigravid women. The most common presenting symptoms were fever and cough. Co-morbid conditions such as gestational hypertension, bronchial asthma and others were seen in 9 cases. In 53% of cases treatment was initiated with oseltamivir within 48 hours of onset of symptoms. All the patients recovered completely at the end of 5 days of treatment. There were no maternal or perinatal deaths.

Keywords: Pregnancy, H1N1 infection, Course of disease, Morbidity.

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INTRODUCTION

Influenza like illness caused by influenza A (H1N1), a quadruple reassorted influenza virus (Swine flu), was reported from Mexico on the 18th March, 2009 and spread rapidly to neighboring United States and Canada.¹ India reported its first case on 13th of May 2009 in Hyderabad.

This virus affects humans and contains segments of genes from pig, bird and human influenza virus. It is transmitted by droplet inhalation, contact with infected objects and surfaces and direct contact with an infected person. On June 11th 2009, the World Health Organization (WHO) signalled that a global pandemic of novel influenza A infection (H1N1) was underway by raising the world wide pandemic alert level to Phase 6. Phase 6 or global pandemic is declared when the infection is characterized by human to human spread of the virus with community level outbreaks in at least two WHO regions – meaning that there is widespread global transmission. The earlier H1N1 influenza pandemic caused high morbidity and mortality among pregnant women compared to the general population. The 1918 pandemic was associated with a high maternal mortality rate of 27% and was also associated with high rates of spontaneous miscarriages and preterm labour. In the 1957 pandemic, a 20% maternal mortality rate was reported and increased incidence of birth defects was also noted.² In the H1N1 /2009 pandemic Jamieson et al reported a four times higher rate of hospital admissions in pregnant women compared to the general population.³ Among patients with H1N1 virus infection, pregnant women accounted for 6 to 9% of ICU admissions and 6 to 10% of patients who died.^{4,5} There appears to be a particularly increased risk of death among infected women during the third trimester.³

This study was undertaken to analyze the maternal and perinatal outcome in 32 antenatal mothers who suffered from H1N1 infection and to analyze the clinical course and the treatment efficacy of oseltamivir in H1N1 infected mothers.

MATERIALS AND METHODS

This is a descriptive study from the Institute of Obstetrics and Gynaecology, a tertiary care hospital in Chennai with 18,000 deliveries a year. The case series were collected from September 2009 to December 2010. Influenza like illness (ILI) was suspected when the pregnant woman presented with fever of $>37.8^{\circ}\text{C}$, myalgia cough, sore throat and breathlessness in the absence of other causes of fever. During the study period 207 pregnant women presented with symptoms suggestive of influenza like illness. In all these 207 suspected cases, throat swabs were taken and laboratory testing by RT PCR was carried out at the King Institute Laboratory, Guindy, Chennai. In 32 cases, RT PCR

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was positive and the diagnosis of H1N1 influenza virus was confirmed. All laboratory confirmed cases were nursed in isolation ward and were further investigated with complete hemogram, renal function test and liver function test. Patients were carefully monitored with temperature chart, pulse and BP chart and routine surveillance was done. All the 32 confirmed swine flu cases were treated with Oseltamivir 75 mg twice daily for 5 days. The demographic data was collected for each patient and the following details were noted and analyzed: contact history, time taken from the onset of symptoms to admission, gestational age at diagnosis, co-morbid conditions, clinical findings, investigation results, course in the hospital, response to treatment, mode of delivery and neonatal outcome.

RESULTS

Our cohort consisted of 32 hospitalized pregnant women with laboratory confirmed H1N1 infection. Twenty-nine

patients (90.6%) were in the age group between 21 and 29 years, two cases were less than 20 years of age and one case was 34 years old. Twenty one (65.6%) were primigravidae and 11 (34.4%) were multigravid women. Gestational age at diagnosis was first trimester in one case, second trimester in three cases and third trimester in 28 cases (Table 1). Looking at the month wise distribution of H1N1 infection, though the cases were distributed throughout the year, 20 of the 32 cases occurred between the months of July and November. The median time from symptoms onset to hospitalization was 1 day in 17 cases, 3 days in 10 cases and 5 days in 5 cases. The most frequent presenting symptoms were: fever > 37.8° C in 28 cases (87.5%), cough in 20 cases (62.5%), myalgia in 10 cases (31.25%), breathlessness in 7 cases (21.9%), rhinorrhea and sore throat in two cases each and vomiting and diarrhea in four cases each (Table 2). Co-morbid conditions were seen in 9 patients. Gestational hypertension was seen in four cases, bronchial asthma in one case. One

Table 1: Characteristics of patients

	No.	%
<i>Age distribution in years</i>		
<20	2	6.25
21-29	29	90.6
30 and more	1	3.1
Median age	25	
<i>Parity</i>		
Primigravidae	21	65.6
Multigravidae	11	34.4
<i>Gestational age</i>		
First trimester	1	3.1
Second trimester	3	9.3
Third trimester	28	87.5
<i>Comorbid conditions</i>		
Gestational hypertension	4/32	12.5
Bronchial asthma	1/32	3.1
Idiopathic thrombocytopenic purpura	1/32	3.1
Leptospirosis	2/32	6.2
Typhoid	1/32	3.1

Table 2: Clinical presentation and course of the disease

	No.	%
<i>Presenting symptoms</i>		
Fever	28	87.5
Cough	20	62.5
Myalgia	10	31.25
Breathlessness	7	21.9
Sore throat	2	6.2
Rhinorrhea	2	6.2
Vomiting	4	12.5
Diarrhea	4	12.5
<i>Median time from symptom onset to hospitalization</i>		
1 day	17	53
3 days	10	31
5 days	5	16
<i>Initiation of treatment after symptom onset</i>		
<2 days	17	53
3-4 days	10	31
5-7 days	5	15.6

patient suffered from idiopathic thrombocytopenic purpura for which she had undergone splenectomy earlier and was on long-term corticosteroids. There was also concomitant infection with leptospirosis in two cases and typhoid fever in one case (Table 1). None of the patients gave history of contact with persons suffering from influenza like illness within the 7 days prior to the onset of symptoms. None of the women have received seasonal flu vaccine or specific A/H1N1 2009 influenza vaccine. All investigation results were normal except in two cases where there was mild anemia with hemoglobin of 9 gm%. Among the 32 cases, treatment was started within 2 days of onset of symptoms in 17 (53%), within 3 to 4 days in 10 cases (31%) and within 5 to 7 days in 5 cases (Table 2). The first symptom to subside after starting oseltamivir was fever and the response was seen in 2 days. Cough disappeared in 3 to 4 days time. None of the patients worsened after starting the treatment. All patients recovered completely at the end of 5 days treatment. None of the patients were admitted in the intensive care unit and none required mechanical ventilation. There was no maternal death in this series.

At the time of discharge from the hospital 19 women (59.4%) had delivered and 13 (40.6%) were undelivered. Among those who had delivered, 13 (68.4%) women were delivered by cesarean section and 6 (31.6%) had vaginal deliveries. The indication for cesarean section was previous cesarean with mobile head in six cases, placenta previa in one case, failure to progress in labor in three cases and failed induction in three cases. Four (21%) women delivered at 36 weeks of gestation. In these four women the interval between the onset of symptoms and the delivery was ranging from 7 to 10 days. In one of them there was premature rupture of membranes, therefore labor was induced. Fifteen women (79%) had delivered at term. One case who was treated for H1N1 infection in the first trimester at 9 weeks gestation was followed up regularly in the antenatal clinic. Her anomaly scan at 20 weeks gestation was normal and her antenatal period was uneventful. She delivered a healthy female baby weighing 2.9 kg at 39 weeks of gestation. In the four women (21%) who delivered at 36 weeks of gestation, the birth weight was between 1.5 and 2 kg. In the remaining 15 women who delivered at term the birth weight was between 2.1 to 2.5 kg in 5 cases (26.3%), 2.6 to 3 kg in 8 cases (42%), and between 3.1 and 3.5 kg in 2 cases (10.5%). Three neonates had febrile illness and were evaluated and treated for other causes of fever. There were neonatal deaths.

DISCUSSION

The 2009 pandemic influenza A H1N1 virus infection resulted in wide spread out break of respiratory infection

throughout the world. The virus showed a predilection to lower respiratory tract producing acute respiratory distress. Reports from the past pandemics (1918-1919) and the current 2009 outbreak have shown that pregnant mothers are at risk of complications from the infection.⁶ Besides the modification in the immune system to accommodate the developing fetus, the enlarging uterus has mechanical effect resulting in elevation of the diaphragm, congestion and local edema, making them prone for complications such as pneumonia and ARDS.²

The typical symptoms of swine flu are a sudden fever of at least 38°C and sudden cough with one other symptom of chill, lethargy, headache, sore throat, running nose, muscle pain, diarrhea and vomiting. Our patients presented with mild to moderate symptoms. Fever was seen in 87.5% of cases, cough in 62.5% of cases and breathlessness in 21.9% of cases. Our findings are consistent with reports from USA and Australia where fever was reported in 84 to 97%, cough in 37 to 41% of women and shortness of breath in 41% of cases.^{3,5,7} Louie et al have reported that pregnant women with A/ H1N1 2009 influenza frequently presented with mild to moderate symptoms, but they had rapid clinical deterioration.⁵

The signs and symptoms of severe disease include dyspnea, chest pain on breathing, purulent or blood stained sputum, respiratory rate > 30/minute, persistent tachycardia >100 beats per minute, hypoxia with SpO₂ < 94%, shock and altered consciousness.⁵ It is important to note that the above signs and symptoms can also occur in other conditions such as acute pyelonephritis, bacterial pneumonia, cerebral malaria and chorioamnionitis. Therefore it is mandatory that, following careful clinical evaluation, patients should be investigated by urine/sputum/blood culture to look for other causes of fever also. In our case series, two patients suffered from concomitant leptospirosis and one was diagnosed with typhoid fever.

Reports have shown that 2009 pandemic was associated with severe disease and higher number of maternal deaths than expected.^{3,5,8,9} The principal clinical syndrome leading to hospitalization in intensive care unit is diffuse viral pneumonitis associated with hypoxemia, ARDS, sometimes shock and renal failure.^{4,9} None of our patients presented with symptoms of severe disease and were not admitted to intensive care unit. The possible reason could be that there was greater awareness among the public about 'swine flu' (H1N1 infection) and they reported early to the hospital before they developed severe disease. In Louie et al study, 5% were infected in the first trimester, 37% in the second trimester and 57% in the third trimester.⁵ In concordance with these reports 90.6% of our patients were infected in the second and third trimester.

Co-morbidities, such as asthma, chronic lung disease, heart disease, kidney, blood and liver disorders, metabolic and endocrine conditions weaken the immune system and marked obesity can increase the risk of influenza complications.^{4,5,9} In our study, co-morbidities such as gestational hypertension, asthma and idiopathic thrombocytopenic purpura were seen in 9 (28%) cases. In Australia, Hewagama et al reported that, co-morbidities were present in 51% of pregnant women with H1N1 2009 influenza infection with asthma, obesity and diabetes being most frequently described.⁷

In our study we have included only those women who were positive by PCR test for H1N1 influenza virus infection. However, while treating cases presenting with symptoms of influenza like illness, false negative results should be kept in mind. Louie et al have reported that rapid antigen test were falsely negative in 38% of patients tested. This study has concluded that 2009 H1N1 influenza can cause severe illness and death in pregnant and postpartum women; and regardless of the results of rapid antigen testing, prompt evaluation and antiviral treatment of influenza like illness should be considered in such women.⁵ Because of the poor sensitivity of the rapid test results, CDC has alerted clinicians that the treatment of influenza should not be guided or delayed by negative results on rapid testing.¹⁰

Antiviral treatment should be commenced as early as possible, particularly within the first 48 hours of onset of symptoms. Antiviral drugs oseltamivir and Zanamivir are Neuraminidase inhibitors and they act by preventing the virus from budding and escaping from the host cells. Early initiation of treatment particularly within the first 48 hours of onset of symptoms is more important because of the possibility of rapid deterioration. Waiting for the confirmatory test will lead to delay in initiating the treatment. In our study treatment was initiated within 48 hours in 17 (53%) cases. Extensive Public health programs to create awareness among the public and orientation lectures to the medical personnel could have helped in the early initiation of treatment in these individuals. In the remaining 15 (47%) cases, the affected individuals were hospitalized 3 to 5 days after the onset of symptoms therefore treatment was delayed for more than 48 hours.

Randomized control trials have shown that oseltamivir and zanamivir will reduce the severity of seasonal influenza if commenced within 48 hours of illness onset.¹¹ The centers for disease control and prevention (CDC) recommends prompt antiviral treatment of pregnant women with suspected or confirmed 2009 H1N1 influenza, ideally within 48 hours of symptom onset.¹² In Louie et al report, the risk of admission to ICU or death was four times higher if the

treatment was received after 48 hours.⁵ The consensus from the above reports show that, regardless of the results of the rapid antigen tests, women with suspected or confirmed influenza who are pregnant or who have delivered within the previous 2 weeks should receive aggressive antiviral treatment and undergo close monitoring. No adverse effects were noted with antiviral treatment in our study. All women also received intravenous antibiotics for presumed bacterial pneumonia. Common causes of death in H1N1 infection include ARDS, viral pneumonia and secondary bacterial infection.

Regarding the pregnancy outcome, threefold increase in preterm delivery and fivefold increase in still births have been reported.² In our study, among the 19 women who delivered, four women had delivered at 36 weeks of gestation and the preterm delivery rate was 21%. In these four cases, in one case the labor was induced because of PROM. In the other three cases, there were no co-morbidities to explain the preterm labor. In these cases, as the labor had occurred within 7 to 10 days of onset of symptoms it is possible that the viremia could have resulted in preterm labor. The remaining 15 cases delivered at term. In these cases, the time interval from the onset of symptoms to delivery ranged from 10-15 days. There was no maternal or perinatal morbidity or mortality reported in this study. This may be due to the early reporting of patients to the hospital, prompt diagnosis and early initiation of treatment.

The limitation of this study is that it has included only those cases who reported to the hospital. Community based studies are required to analyze the actual impact of H1N1 infection in the community. Moreover this study has included only those cases in whom laboratory investigations have confirmed the infection.

CONCLUSION

Our experience on H1N1 infection in pregnancy suggests that the infection was mild in nature in the reported cases. This may be due to the local viral strain effect. The minimal morbidity and no mortality noted in this study may be due to the early presentation, diagnosis, public health preparedness and timely access to antiviral treatment.

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