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RESEARCH ARTICLE

OBSTRETIC CARE AND MANAGEMENT OF H1N1 PATIENTS: CLINICO-EPIDEMIOLOGICAL CONTEMPORARY CASE ANALYSIS

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ABSTRACT

Background: Influenza like illness caused by influenza A (H1N1), a quadruple reasserted influenza virus. It is an orthomyxovirus responsible for outbreak that occurred in state, Gujarat, India in year 2017. During the 2009 H1N1 pandemic, pregnant women had higher morbidity and mortality comparing to non-pregnant women.

Aim: To study the Obstetric care and Management of H1N1 pregnant women during an outbreak of H1N1 influenza.

Methods: Retrospective data of 11 pregnant women with signs & symptoms corresponding to influenza like illness was collected and subjected to throat swab testing for H1N1. Epidemiological characteristics were analyzed in terms of clinical presentation and outcome.

Results: 6 (45%) patients out of total 11 patients were confirmed (positive) for H1N1. Maximum 3 (60 %) patients were in third trimester of pregnancy and 2 (40%) patient was in second trimester of pregnancy. Fever (100%) and cough (100%) were common presenting symptoms. 1 (20 %) patient was put on mechanical ventilator but unfortunately she didn't survive.

Conclusion: Pregnant women might be at increased risk for complications from outbreak of H1N1 virus infection. Fever and cough were the most common symptoms in these pregnant women. Severe acute respiratory distress syndrome (ARDS) and late presentation were a poor prognostic indicator in these patients. Early treatment with effective antiviral drugs like oseltamivir will decrease the mortality in H1N1 patients

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INTRODUCTION

H1N1 Influenza causes annual epidemics of varied severity and high mortality. Human infection with the novel H1N1 strain of the influenza a virus (formerly called swine flu) was first reported from Mexico on 18th March 2009, and spreads rapidly to neighboring states. India reported its 1st case on 13th May 2009 in Hyderabad (Centers for Disease Control and Prevention Web site). There is a high risk of infection of H1N1 Influenza A in pregnant women (Amanda Carlson *et al.,* 2009). Therefore, physicians should be well equipped to manage the infection in order to decrease the morbidity, mortality and pregnancy-related complications (including spontaneous miscarriage and preterm birth) faced by pregnant women during an influenza pandemic (Centers for Disease Control and Prevention Web site). During pregnancy, healthy women have a 4- to 5-fold increased rate of serious illness and hospitalization with influenza (Mak *et al.,* 2008). For this reason, it is critical that all physicians be familiar with the symptoms, treatment, and prevention of H1N1 infection in pregnant women. The 1918 pandemic was associated with a high maternal mortality rate of 27% and also associated with high rates of spontaneous miscarriage and preterm labour. In the 1957 pandemic, a 20% maternal mortality rate was reported and increased incidences of birth defects such as neural tube defects and cardiac abnormalities were reported (Lim Boon, 2009).

Clinical Manifestations

Infection with influenza viruses can give rise to a wide range of clinical presentations, ranging from asymptomatic infection to severe illness and death depending on the characteristics of both the virus and the infected person. For purposes of clinical management, influenza disease can be categorized as follows:

- **Uncomplicated influenza:** Patient may present with fever, cough, sore throat, coryza, headache, malaise, myalgia, arthralgia and sometimes gastrointestinal symptoms, like loos motion vomiting but without any features of complicated influenza.

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- **Complicated/severe influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxemia, dyspnea, tachypnea, lower chest wall in drawing and inability to feed), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

Risk groups for severe/complicated influenza disease include:

- Pregnant women (including the post-partum period)
- HIV–infected individuals
- Individuals with tuberculosis
- Persons of any age with chronic disease, including.

Pulmonary diseases (e.g. asthma, COPD), Immunosuppression (e.g. persons on immunosuppressive medication, malignancy), Cardiac diseases (e.g. congestive cardiac failure), Metabolic disorders (e.g. diabetes), Renal disease , Hepatic disease, Certain neurologic and neurodevelopmental conditions, including: disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy; epilepsy(seizure disorders); stroke; mental retardation; moderate to severe developmental delay; muscular dystrophy; or spinal cord injury. Haemoglobinopathies (e.g. sickle cell disease)

- Persons aged ≥65 years
- Persons ≤18 years receiving chronic aspirin therapy
- Persons who are morbidly obese (i.e. BMI ≥40)
- Young children (particularlyage < 2years) (Influenza Guidelines, 2017)

All individuals seeking consultations for flu like symptoms are screened at healthcare facilities both Government and private or examined by a doctor and these will be categorized as under:

1. Category- A

Patients with mild fever plus cough / sore throat with or without body ache, headache, diarrhoea and vomiting will be categorized as Category-A. They do not require Oseltamivir and should be treated for the symptoms mentioned above. The patients should be monitored for their progress and reassessed at 24 to 48 hours by the doctor. No testing of the patient for Influenza is required. Patients should confine themselves at home and avoid mixing up with public and high risk members in the family.

2. Category-B

- In addition to all the signs and symptoms mentioned under Category-A, if the patient has high grade fever and severe sore throat, may require home isolation and Oseltamivir;
- In addition to all the signs and symptoms mentioned under Category-A, individuals having one or more of the following high risk conditions shall be treated with Oseltamivir: Children with mild illness but with predisposing risk factors. Pregnant women; Persons aged 65 years or older; Patients with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS; Patients on long term cortisone therapy.

No tests for Influenza is required for Category-B (i) and (ii). All patients of Category-B (i) and (ii) should confine themselves at home and avoid mixing with public and high risk members in the family. Broad Spectrum antibiotics as per the Guideline for Communityacquired pneumonia (CAP) may be prescribed.

3. Category-C

In addition to the above signs and symptoms of Category-A and B, if the patient has one or more of the following: Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discolouration of nails; Children with influenza like illness who had a severe disease as manifested by the red flag signs (Somnolence, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc). Worsening of underlying chronic conditions. All these patients mentioned above in Category-C require testing, immediate hospitalization and treatment.

Confirmation of seasonal influenza (including HIN1) infection is through:

- Real time RTPCR or
- Isolation of the virus in culture or
- Four-fold rise in virus specific neutralizing antibodies.

For confirmation of diagnosis, clinical specimens such as nasopharyngeal swab, throat swab, nasal swab, wash or aspirate, and tracheal aspirate (for intubated patients) are to be obtained. The sample should be collected by a trained physician/microbiologist/technical or nursing staff, preferably before administration of the anti-viral drug. Keep specimens at 40^{o}C in viral transport media until transported for testing. The samples should be transported to designated laboratories within 24 hours. If they cannot be transported then it needs to be stored at -70^{o}C. Paired blood samples at an interval of 14 days for serological testing may also be collected, if required.[7] Oseltamivir is the recommended drug for treatment (75 mg BD for 5 days) (Clinical Management Protocol for Seasonal Influenza, 2016).

Effects of Pregnancy on H1N1 Influenza

It is commonly thought that a pregnant woman's immunity is suppressed. In pregnancy, there is modification of the immune system to prevent rejection of the fetus and placenta. It is thought that the cell mediated immunity is modified by an increased in the production of T-helper cells as opposed to T-killer cells to reduce the risk of rejection. There appears to be a tendency towards humoral immunity. As the virus replicates intracellularly, the ability to fight off an infection is reduced. It is known that infections such as chicken pox get worse in pregnancy, particularly in the latter half of pregnancy, but this is due to the risk of pneumonitis from local spread to the respiratory system of the virus and also the mechanical effects of the enlarged uterus on the diaphragm and the respiratory system. There is no evidence that Human Immunodefi- ciency Virus (HIV) or tuberculosis get worse in pregnancy. Hence, there is no evidence to suggest that pregnant women are at increased susceptibility of catching the flu virus (Stirrat, 1994). However, due to the modification in their immune systems to accommodate their developing fetus and adaptations in their body as a result of the hormonal and physical changes, they are

at greater risk of developing complications should they acquire the illness. The enlarging uterus presses on the diaphragm and together with changes in the lungs such as reduced tidal volume, congestion and localized oedema, make the woman more prone to complications such as pneumonia and Adult Respiratory Distress Syndrome (ARDS) (Siston, 2009).

Available treatment guideline for HINI in pregnant women

- There is no evidence to suggest that pregnant women are at increased susceptibility of catching the flu virus[8]. However, due to the modification in their immune systems to accommodate their developing fetus and adaptations in their body as a result of the hormonal and physical changes, they are at greater risk of developing complications (Siston, 2009).
- Pregnant women who meet the current case definition for uncomplicated illness with confirmed or suspected pandemic (H1N1) 2009 virus should be treated early with the antiviral medications oseltamivir or zanamivir. The regimen is the same as the regimen for other adults. Treatment is for five days.
- Treatment with antiviral medications should begin as soon as possible and without waiting for results of diagnostic testing. A negative laboratory test should not stop treatment in a patient with clinical suspicion of influenza.
- Patients who have severe or progressive clinical illness should be treated with oseltamivir. This recommendation applies to all patient groups, including pregnant women. Currently, there are no data supporting administration of oseltamivir in doses higher than 75 mg twice daily for pregnant women.
- Danger signs that can signal progression to more severe disease in pregnant women are the same as in other patients (i.e. shortness of breath either during physical activity or while resting, difficulty in breathing, turning blue, bloody or coloured sputum, chest pain, altered mental state, high fever that persists beyond three days, and low blood pressure).
- Fever (>38° C) in early pregnancy is associated with increased risk of fetal anomalies and, in late pregnancy, with adverse perinatal outcomes. Treat fever associated with pandemic (H1N1) 2009 virus infection in pregnant women or women in labour or breastfeeding with paracetamol (acetaminophen).
- Explain the importance of adequate nutrition and fluid intake to the woman and her family.
- Prophylactic antibiotics are not recommended. Co-infections must be treated early. Ensure that antimicrobials for treating any co-infections are safe for use during pregnancy and lactation.
- If oxygen is required for severe pneumonia, ensure that oxygen saturation (SaO2) remains above 92-95% (Influenza Guidelines, 2017).

Indications of Hospitalization in pregnant Women

- Pregnant women with swine flu are four times more likely to be hospitalized. There is three times increase risk of preterm delivery, five times increase in still birth rate and increased risk of maternal death.
- Risk factors: Younger maternal age, Obesity, Asthmatic, other co-morbidities including Diabetes and heart disease, Black or other ethnic minorities, Delay in start of treatment with Anti-viral treatment.
- Risk factors for ICU admission: High fever 38^{o}C, Dyspnoea (Respiratory rate(30/min), Requirement of supplemental oxygen, Pneumonia on admission, Tachycardia, Altered conscious levels (Lim Boon *et al.,* 2009).

Special Care

Antepartum: Hospitalize in a private room. A single-patient room whenever possible Use of face mask by patients when outside the room. Standard precautions for all patient care. Diagnostic testing and empirical antiviral therapy immediately. Do not delay antiviral treatment. Healthy attendants may be allowed inside the room

Intrapartum: Protect the infant from exposure to respiratory secretions during or immediately after delivery. Mother should use face mask throughout labor, as tolerated. Adhere to current infection control guidance. During delivery all persons should face mask, gloves and gown. Immediately separate newborn to an open warmer by a distance of >6ft. Bathe infant as soon as the temperature is stable.

Postpartum: Temporary separation of the infected mother from the newborn within her room OR in a separate room until the risk of infection transmission is reduced, which is when ALL of the following criteria are met: The mother has received Antiviral Medications for at least 48hrs. The mother is without fever for 24hrs without antipyretics. The mother can control cough and respiratory secretions, Once these criteria are met, the mother and the newborn can initiate close contact throughout the postpartum period with droplet precautions and mother can start breast feeds (Gupte *et al.,* 2014).

Aim and Objectives

To study and analyze the maternal and perinatal outcome, who suffered from H1N1 infection and to analyze the clinical course and the treatment efficacy of oseltamivir in H1N1 infected mothers.

METHODS

Data of all pregnant women who were suspected to have swine flu were taken from July 2017 to December 2017 to study the clinical profile of Influenza A/ H1N1 during pregnancy. The study population included all the suspected pregnant women tested for Influenza A/H1N1. Out of 11 pregnant women, who were suspected to have Influenza A/H1N1 only 5 (45.45%) were positive. Hospital data were analyzed on the basis of signs, symptoms and final outcome. Inclusion criteria were all pregnant women irrespective of trimester who were confirmed cases for influenza A H1N1 by RT-PCR assay (TAQ MAN real time PCR CDC protocol). Exclusion criteria were non-pregnant women, Laboratory confirmed negative for influenza A H1N1by RT-PCR assay (TAQ MAN real time PCR CDC protocol) and other non-pregnant patients who were positive for influenza A H1N1. Data were analyzed using Microsoft Excel Software and basic statistical measures like mean, median derived.

RESULTS AND DISCUSSION

Total 11 patients were suspected to have the symptoms of Influenza A H1N1 swine flu, out of whom 5 (45%) patients

were positive. All the patients positive for Influenza A H1N1 were in the age group of 20-30 years. Fever and cough were the most common symptoms found in all the patients followed by sore throat, myalgia, breathlessness, nasal discharge (80%) and breathlessness in 1(20%) patient. Out of the 5 positive patients 2 (40%) patient was in her second trimester and 3 (60%) patients were in their third trimester. Out of the 5 positive patients one patient presented after 5 days of onset of symptoms of flu and 4 (63.3%) patients presented within 4 days of onset of symptoms of flu after which the treatment was started, 1 (20%) patient was kept on invasive mechanical ventilator out of the 5 patients positive for H1N1 influenza A. One patient expired out of the 5 patients who were positive for the H1N1 influenza A. Reports from the past pandemics (1918-1919) and the 2009 outbreak have shown that pregnant mothers are at risk of complications from the infection (Lindsay *et al.,* 2006). 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 (Lim Boon, 2009). Our patients presented with mild to moderate symptoms. Fever was seen in 100% of cases, cough in 100% of cases and breathlessness in 30% 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 (Denise J Jamieson *et al.,* 2009; Louie *et al.* 2010). Louie et al have reported that pregnant women with A/ H1N1 2009 influenza frequently presented with mild to mode-rate symptoms, but they had rapid clinical deterioration (Louie *et al.* 2010). 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 (Louie *et al.* 2010). Reports have shown that 2009 pandemic was associated with severe disease and higher number of maternal deaths than expected (Denise J Jamieson *et al.,* 2009; Louie *et al.* 2010).

Table 1. Characteristics of positive patients

Characteristics	No. of Patients	Percentage
Age distribution		
<20	0	0
20 to 30	5	100
>30	0	0
Median age	26	
Parity		
Primigravida	2	40
Multigravida	3	60
Gestational age		
1st trimester	0	0
2nd trimester	2	40
3rd trimester	3	60
Comorbid conditions		
Anemia	3	60
Hypertention	0	0
Diabetes mellitus	0	0
Others	0	0
Positive Result of RT-PCR OUT OF 11	5	45.45

The principal clinical syndrome leading to hospitalization in intensive care unit is diffuse viral pneumonitis associated with hypoxemia or ARDS. One of our patients presented with symptoms of severe disease and were 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. Or this study has lower numer of patients. In Louie et al study and Jamieson et al study,5% and 17% were infected in the first trimester, 37% and 56% in the second trimester and 57% and 26% in the third trimester respectively (Denise J Jamieson *et al.,* 2009; Louie *et al.* 2010). In concordance with these reports 405 and 60% of our patients were infected in the second and third trimester respectively. 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 (Denise J Jamieson *et al.,* 2009). In our study, co-morbidities such as anemia is seen in 2 (40%) 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 (Hewagama *et al.,* 2010).

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 (Denise J Jamieson *et al.,* 2009; Louie *et al.* 2010). 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. Antiviral treatment should be commenced as early as possible, particularly within the first 48 hours of onset of symptoms (Centers for Disease Control and Prevention Web site). 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 3 days in 3 (60%) 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 2 (40%) cases, the affected individuals were hospitalized 3 to 5 days after the onset of symptoms therefore treatment was delayed for more than 48 hours.

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 (Centers for Disease Control and Prevention Web site). 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 (Louie *et al.* 2010). No adverse effects were noted with antiviral treatment in our study. Common causes of death in H1N1 infection include ARDS, viral pneumonia and secondary bacterial infection. In our study, among the 4 women who delivered, all four women had delivered at 36 weeks of gestation with no preterm or stillbirth. There was no maternal or perinatal morbidity or mortality reported in this study.

Table 2. Signs, Symptoms, and Clinical Course of the positive patients

Presenting symptoms		
Fever	5	100
Cough	5	100
Myalgia	4	80
Sore throat	4	80
Rhinorrhea	4	80
Breathlessness	3	60
Vomiting	0	0
Diarrhea	0	0
Abdominal pain	0	0
Altered sensorium	0	0
Clinical categories (A/B/C)	CAT-C: 4	80
	CAT-B2: 1	20
Median time from symptom onset to hospitalization	4	
Initiation of treatment after symptom onset		
<2 days		
2 to 4	0	0
>4 days	4	80
	1	20
Infiltrates on x-ray	4	80
History of contacts	0	0
ARDS		
Mild	2	40
Moderate	0	0
Severe	1	20
Invasive or non-invasive venti-support required.	IV-1	20
	NIV-2	40
Median hospital stay	5 days	
Death (no.)	1	20
Median time from symptom onset to death	7 days	

Table 3. Comparison with other studies

	Louie et al. (2010)	Jamieson et al. (2009)	Present Study
No. of positive patients	38/94	34	5/11
Gestational age			
1st trimester	0	0	0
2nd trimester	35%	65%	40
3rd trimester	57%	23%	60
Presenting symptoms			
Fever	91%	97%	100%
Cough	93%	94%	100%
Myalgia	41%	12%	80%
Sore throat	41%	50%	80%
Rhinorrhea	0	59%	80%
Breathlessness	41%	14%	60%
Vomiting	0	0	0
Diarrhea	0	0	0
Abdominal pain	0	0	0
Altered sensorium	0	0	0
Infiltrates on x-ray	59%	No proper data available	60%
ARDS	13%	No proper data available	60 (40%-mild, 20%- severe)
Mechanical Ventilation	14%	3%	20%
Initiation of treatment after symptom onset			
<2 days	50%	9%	0
2 to >2 days	81%	32%	100%
Median time from symptom onset to hospitalization	2 days	3.5 days	3 days
Median time of stay in hospital	3 days	No proper data available	5 days
No of deaths.	6	6	1
Median time from symptom onset to Death	20 days	12days	7 days

This may be due to the early reporting of patients to the hospital, prompt diagnosis and early initiation of treatment.

Outcome in terms of pregnancy

Out of 5 pregnant positive patients, 4 had no complications in course of pregnancy and normal progress with delivery of healthy baby, 1 patient who was 5 months of amenorrhea had severe ARDS unable to sustain her life and succumb to death with baby intrauterine.

Conclusion

Pregnant women are at increased risk of infection during outbreak of H1N1 influenza A. Fever and cough are the most common presenting complaints in these patients. Severe ARDS

and late presentation are the poor prognostic indicators of this disease. Early treatment with effective antiviral drugs like oseltamivir will decrease the mortality in H1N1 patients.

Limitation

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. Also the numbers of positive cases tested for H1N1 were limited as it was single centre study. This analysis may not reflect the actual distribution of the cases at the population level.

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