AMJ Australasian Medical Journal [AMJ 2016;9(12):519–525]

Clinical profile and outcome of critically ill pregnant females with H1N1 influenza

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RESEARCH

Please cite this paper as: Shastri M, Kansara T, Shringarpure K. Clinical profile and outcome of critically ill pregnant females with H1N1 influenza. AMJ 2016;9(12):519–525. https://doi.org/10.21767/AMJ.2016.2769

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ABSTRACT

Background

Record based review of the 2009 H1N1 Influenza pandemic suggests that pregnant women are at higher risk for hospitalization and death due to H1N1 Influenza.

Aims

To study the clinical profile and outcome of critically ill pregnant females admitted in intensive care unit (ICU) with real-time recombinant polymerase chain reaction (rRT-PCR) proven positive H1N1 cases.

Methods

A retrospective record-review based study was conducted at Sir SayajiRao General Hospital (SSGH) and Medical College, Vadodara on data of confirmed rRT-PCR H1N1 pregnant females admitted during the pandemics of 2010and 2015. Demographics, clinical profile and laboratory investigations were recorded and outcomes (survived or expired) were analysed.

Results

There were a total of 20 H1N1 positive pregnant females requiring ICU admission. With equal demographic distribution among rural and urban population, cough and fever were the most common presenting complaints. 65 per cent were in third trimester, the subgroup which also had the highest mortality. Mean days from onset until presentation was 5.05 days. 12 (60 per cent) patients' required invasive mode of ventilation and all died. Average hospital stay was 7 days. Foetus had favourable outcome in patients who recovered from H1N1 acute illness.

Conclusion

Pregnant females in our study had 60 per cent mortality. Thus, awareness, early diagnosis and treatment should be provided to them. Guidelines, policy changes and government protocols are required specifically for pregnant females with H1N1 Influenza A infection. Our study was an observational study and comparisons with non-pregnant females were not done, conclusions applicable to entire pregnant population was not derived.

Key Words
H1N1, pregnancy, clinical profile

What this study adds:

1. What is known about this subject?
Pregnant females are at higher risk of infection and severe disease with H1N1 Influenza A infection.

2. What new information is offered in this study?
An attempt is made to provide clinical characteristics of critically ill pregnant females with H1N1 Influenza, which is most often seasonal and unpredictable pandemic, for future references, as literature does not describe it exclusively.

3. What are the implications for research, policy, or practice?
Prevention (e.g., immunisation, isolation), guidelines for

prompt detection and treatment are necessary as pregnant females are vulnerable to H1N1 influenza.

Background

The 2009 influenza A (H1N1) epidemic which started in Mexico had rapidly spread worldwide.[1–3] In India, the number of confirmed cases in 2009 and 2010 were 27,236 and 20,604 respectively.[4] The 2015 epidemic in India had a total of 31,974 confirmed cases with 1,895 deaths.[4] In 2015, Gujarat was among the most affected states in India with 6,495 reported cases and 428 deaths.[4] Studies show that health conditions typically associated with risk of seasonal influenza cases admitted to an intensive care unit (ICU) are chronic lung disease, neurological disorders, diabetes and pregnancy.[5]

Due to changes in the immune, cardiac and respiratory system, pregnant women are at increased risk for severe illness with influenza.[6] The impact of pandemic H1N1 influenza A on disease severity in pregnant women was illustrated in a California based study which included 18 pregnant and 4 postpartum females requiring intensive care.[7] Six of eight women who died had some underlying medical conditions including hypothyroidism, asthma, gestational diabetes, or a history of Hodgkin's lymphoma. For the 2009 H1N1 pandemic, influenza-specific maternal mortality ratio (number of maternal deaths per 100,000 live births) was 4.3.[7]

To our knowledge, very few studies have looked at clinical profile and outcome of H1N1 in pregnant females. This study will be among the first of its kind; given the lesser numbers of pregnant females in such pandemics. However, this high-risk group needs to be highlighted; and clinical factors associated with risk of poor outcomes, if known, can help in giving specific treatment or intensive care to such females. Hence, the aim was to study the clinical profile and outcome of critically ill pregnant females with H1N1 Influenza.

Method

Settings

A retrospective record-review based study was conducted in Sir SayajiRao General Hospital, Vadodara after taking due permission from Institutional Ethics Committee. Total 417 rRT-PCR proven H1N1 positive patients were admitted during the 2010 and 2015 pandemic in the hospital. From this data, we shortlisted those pregnant females who required Intensive Care Unit (ICU) admissions. There were a total of 20 such pregnant females during the two epidemics of 2010 and 2015, who satisfied our inclusion criteria (pregnancy, H1N1 rRT-PCR positivity, critically ill and ICU admission). We used the following definitions given by Centre for Disease Control (CDC) for including H1N1 positive females in our study.

Influenza-like illness (ILI) is defined as fever (temperature of 100 F [37.8°C] or greater) with cough or sore throat in the absence of a known cause other than influenza.[8] A confirmed case of pandemic H1N1 influenza A is defined as an individual with an ILI with laboratory-confirmed H1N1 influenza A virus detection by rRT–PCR or culture.[8] A severe case of H1N1 Influenza A (H1N1 influenza category C) is defined as sudden onset of fever >38°C and cough or sore throat in the absence of other diagnosis and shortness of breath or difficulty in breathing and requiring hospital admission.[8] Gestational age was provided for month of pregnancy.

Data Collection

Data entry was done in a standardized case report form and symptoms, signs, laboratory investigations, treatment and outcome of patients were acquired. This case report form included demographics, gestational age, underlying conditions and co-morbidities, clinical presentation, duration of onset of symptoms before admission, detailed respiratory system examination, chest X-ray report of patients, laboratory investigations including haemoglobin, total white blood cell counts and lymphocyte counts, liver and renal function tests, arterial blood gas analysis on admission, duration of ventilator therapy, total ICU days, and maternal and foetal outcomes. Maternal outcomes were classified as survived or expired. Based on these case reports, data was extracted in our data sheet.

All patients were treated with tablet oseltamivir as per Government of India guidelines (150mg twice daily for a minimum of 5 days).[9] Treatment was started immediately after admission, following nasopharyngeal swab for rRT-PCR.

Analysis

The pregnant females' demographic profile, symptoms, examination findings, laboratory investigations and outcomes were analyzed and described. Parameters like mean, median and standard deviation were derived wherever possible. Microsoft Excel was used for data entry and calculations.

Results

Earliest date of reporting of pregnant female with H1N1 Influenza A in the Sir SayajiRao General Hospital (SSGH),

Vadodara, Gujarat, India, was 20th August, 2010 while the latest date was 19th March, 2015. The 2010 pandemic data records spread from 20th August, 2010 to 30th September, 2010. The 2015 pandemic data records spread from 05th February, 2015 to 19th March, 2015. A total 417 positive cases were listed. Out of these, 138 females were admitted in isolation facility of SSGH. Out of them, 20 (4.8 per cent) were pregnant cases who required Intensive care. Thirteen critically ill pregnant females of 2010 pandemic (warm and humid climate) and seven critically ill pregnant female of 2015 pandemic (winter season) were included.

Who were the women affected?

Among the pregnant females, 9 (45 per cent) were from rural areas while the rest 11 (55 per cent) were from urban areas. The average age of presentation was 24.55 ± 4.26 years. Among the pregnant females, one was in first trimester (5 per cent), six (30 per cent) in second trimester and thirteen (65 per cent) in third trimester. 40 per cent were nulliparous while the rest 60 per cent were multiparous. The average (mean) days since onset of symptoms were 5.05 ± 1.94 days. Only two out of twenty patients had hypertension, while one out of twenty had rheumatic mitral stenosis. All other pregnant females seventeen out of twenty had no co-morbidities (apart from being pregnant).

Clinical symptoms **[Figure 1]**

Cough was the most common symptom present in all the 20 patients, with average duration to presentation being 4.40 ± 2.32 days. Fever was present in 18/20 (90 per cent) patients, with average duration of presentation being 4.39 ± 2.50 days. Expectoration was present in five out of twenty (25 per cent) patients with average days to presentation of four days, while the rest 15 (75 per cent) patients had dry cough. Nasal stuffiness and rhinorrhoea was present in five out of twenty (25 per cent) patients; average duration to presentation being four days. Sore throat was the symptom present in seven out of twenty (35 per cent) patients with average duration to presentation of 4.57 days. Dyspnoea at presentation was seen in 18/20 (80 per cent) patients, with average duration of 3.44 days. In our study, chest pain in one out of twenty (5 per cent) patient with an onset 3 days before presentation. One patient was drowsy for 2 days prior to presentation. Pedal edema was present in 2 (10 per cent) patients with average time to presentation of 3 days. Drowsiness, chest pain, maculo-papular rash and abdominal pain with vomiting was present in one patient each 2, 3, 2 and 4 days respectively prior to presentation. Average time between onset of the first symptom and development of dyspnoea was 2 days.

Examination findings on admission

At the time of presentation, temperature was recorded to be above 37.77°C (100°F) in two (10 per cent) patients, while less than 35.27°C (95.5°F) in one (5 per cent) patient. Other patients had normal temperature on admission. This was due to widespread use of antipyretics. Pulse of more than 100 was present in 14 (70 per cent) of the patients, while none of them had bradycardia. Systolic blood pressure of less than 100 mm Hg was present in one (5 per cent) patient while more than 140 mm Hg was present in four (20 per cent) patients of the study. Tachypnoea (respiratory rate of more than 20 beats per minute) was recorded in 14 (70 per cent) of patients. Oxygen saturation of less than 90 per cent was present in 10 (50 per cent) patients.

Lower respiratory system involvement was evident in 19 (95 per cent) patients. On chest X-ray 4 or more zones were involved in three (15 per cent) patients, 2 or 3 zones in 14 (70 per cent) patients, single zone was affected in 2 (10 per cent) patients and one (5 per cent) patient had clear X-ray at presentation. Diffuse involvement on X-ray was present in 15 (75 per cent) patients and localized involvement in four (20 per cent) patients. Sixteen (80 per cent) patients had bilateral involvement, and only three (15 per cent) patients had unilateral involvement.

Laboratory investigations

Reports of laboratory investigations were obtained from case records. Investigations which were available in all patients included haemogram, chest X-Ray, nasopharyngeal swab for rRT-PCR. Some investigations like transaminase, bilirubin and arterial blood gas analysis were not available in some patients. Laboratory investigations showed haemoglobin of less than 6.21mmol/L (10gm/dl) in 10 (50 per cent) patients, total white blood cell counts of more than 11,000cells/mm^3 in 11 (55 per cent) patients and less than 4000cells/mm^3 in none of the patients. Absolute lymphocytosis was not evident on admission. Aspartate transaminase (AST) was elevated in eight out of seventeen patients (47.05 per cent) and alanine transaminase (ALT) in four out of seventeen patients (23.53 per cent). Serum bilirubin of greater than 34.2µmol/L (2.0mg/dl) was present in two out of seventeen patients (11.76 per cent). On admission, arterial blood gas analysis showed pH of less than 7.35 in four out of fourteen patients (28.57 per cent). PaO_2 was less than equal to 80mm Hg in nine out of fourteen patients (34.29 per cent) on admission.

All patients were treated with tablet oseltamivir 150mg twice daily for a minimum of 5 days.

Among the 20 patients, twelve (60 per cent) required invasive mode of ventilation. Among others, four (20 per cent) patients required non-invasive ventilatory support and the rest four (20 per cent) patients required nasal oxygen. Average number of days on invasive ventilator was three days (for 12 patients). Average duration on non invasive ventilatory support was six days until outcome.

Outcome of H1N1 Influenza in pregnant females

Average hospital stay of all patients until outcome (death or discharged) was seven days. Average duration of hospital stay until death was six days, while average duration until discharge for surviving patients was nine days. Three out of six patients (50 per cent) who were in second trimester of pregnancy died and nine out of thirteen patients (69.23 per cent) of third trimester died. One patient with first trimester pregnancy survived [Figure 2].

All patients had clinical or radiological involvement of lower respiratory tract involvement of which 12 (60 per cent) eventually developed Acute Respiratory Distress Syndrome (ARDS) and mortality was 100 per cent in this subgroup. All these patients were on invasive mode of ventilation. All patients who died (12 out of 20; 60 per cent) had either intrauterine death of the foetus during the course of illness or death of the foetus when the mother expired. Among the eight (40 per cent) who survived, all had favourable outcome of pregnancy, with seven patients continuing pregnancy and one live birth during hospital stay.

Discussion

The results above summarized the clinical profile of 20 critically ill pregnant females with H1N1 Influenza A virus infection. The 2010 epidemic occurred in the months of August and September, which are hot and humid times in Western India; which goes against the usual fact that Influenza occurs in winter and cold seasons.[15] The study data clearly showed that the residential demographics did not play any role in infection with 45 per cent being from urban areas and 55 per cent from rural areas. All patients were in their early 20s (Average age at presentation: 24.55 years), findings which are similar to the study by D. Jamieson et al which included 50 per cent patients in age group of 18–29 years.[10] The majority of patients, 65 per cent were in third trimester with 30 per cent in second trimester. These findings were similar to the study by Hewagama et al. where 65 per cent patients were in third trimester[11], and in contrast to study by Jamieson et al. which had 56 per cent patients in second trimester and Lim et al. which had 46.90 per cent patients in second trimester.[12] Our study had 40 per cent nulliparous females while 60 per cent multiparous females. A study by Lim et al. had 50.70 per cent nulliparous while 49.30 per cent multiparous females. The average days of onset until presentation was 5.05 days while in a study by Creanga et al. in New York City had average days of onset 1.5 days.[13] This shows that patients in our study were late presenters compared to other geographic areas. Although it is seen that H1N1 commonly affects patients who have co-morbidities as stated in a study by Siston et al.[14] where 55.30 per cent had co-morbidities, only 15 per cent of patients in our study had co-morbidities. Among 115ICU admissions in a study by Siston et al. 30 died (mortality 26.08 per cent); however our study had a mortality of 60 per cent. This was probably because all patients were late presenters with average days until presentation of 5.05 days. In CDC continued surveillance (Siston et al.), a total of 56 out of 165ICU admission pregnant females died (mortality 33.94 per cent).

The most common symptom in our study was cough, which was present in all patients, followed by fever (90 per cent) and shortness of breath (80 per cent). These findings match with various studies, like cough being present in all patients in a study by Hewagama et al.[11] and in 94 per cent patients of a study by Jamieson et al.[7] and fever in 97 per cent patients in the same study. A study by Jamieson et al. which included all serious and non serious pregnant females had dyspnoea present in 41 per cent of patients. In our study, the average duration from the onset of any symptom to the development of dyspnoea was just 2 days and the average days of onset until presentation was 5.05 days. This could be the reason that the patients had severe lower respiratory infection when they presented to us, and were already in a deteriorating condition. Tachycardia and tachypnoea were the most frequently altered vital parameters. Almost half of the patients were hypoxic with oxygen saturation less than 90 per cent. Even though fever was a common symptom, temperature on admission was high only in one-tenth of the patients due to widespread use of antipyretics.

Crepitations and bilateral involvement on chest X-ray were seen in majority of the patients. Half of the females in the study were mildly anaemic with haemoglobin below 10gm per cent. Either AST or ALT elevations were present in almost half of the patients. Bilirubin levels above 34.20µmol/L (2.00mg/dl) were seen in one-tenth of the females. Literature search does not reveal any other study describing the above findings. These clinical findings require further evidence to know if they are consistently altered in H1N1 Influenza pandemic.

All those patients who were on invasive ventilatory therapy (60 per cent) died. This showed a significant high mortality once severe respiratory failure requiring invasive ventilatory therapy sets in.

Average hospital stay for all patients was seven days. A study by Siston et al had average hospital stay of three days, but all serious and non serious pregnant females were included. Average hospital stay for survived patients was 3 days more as compared to the patients who died. All females who survived had no adverse effect on the foetus and could continue their pregnancy. Intrauterine foetal death occurred in all those patients who died. Thus recovery from H1N1 influenza had a favourable foetal outcome.

This study has several strengths. This is the first study to see the clinical features of critically ill pregnant females with H1N1 Influenza and its effect on fetomaternal outcome. Thus, it gives us an insight into clinical profile of H1N1 in pregnant females and the risk of intrauterine foetal death. A tertiary care hospital would get only the serious cases (Berkesonian effect); hence the mortality could be higher in this setting. We have a few limitations in this study. This is a record review based study; however, data can be used for giving rich information regarding H1N1 in pregnant females. Further, only 20 patients were included, so it is not possible to come to derive a conclusion for the whole population. However, this pilot data can be used for further research and when corroborated with similar data from elsewhere (other tertiary hospitals not only in Gujarat, but other states) can be extrapolated to pregnant population. It could help in identifying signs and symptoms highly suspicious of H1N1 Influenza more rapidly in pregnant females and promptly managing them. A follow up real time study in future pandemics to look into the clinical profile and outcome of pregnant females is the way forward.

Conclusion

To conclude, pregnant females in our study had a high mortality. Thus, awareness about early diagnosis and treatment of H1N1 positive pregnant females is required. Guidelines, policy changes and government protocols specific for pregnant females with H1N1 Influenza are required.

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ACKNOWLEDGEMENTS

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

ETHICS COMMITTEE APPROVAL

Institutional Ethics Committee for Human Research (IECHR& SSH Hospital, Vadodara
Dated: 09/10/2015
Protocol No: 111/Faculty/2015

Figure 1: Frequency of occurance of symptoms of critically ill pregnant females with H1N1 Influenza during pandemics of 2010 and 2015

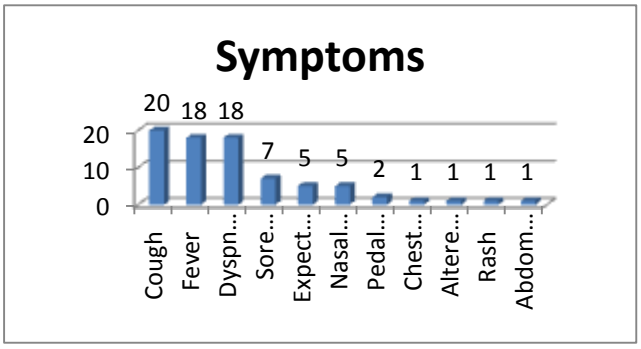

Figure 2: Outcome of H1N1 Influenza by trimester during pandemics of 2010 and 2015