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H1N1 IN PREGNANCY- AN OVERVIEW OF CASES IN PATIENTS ADMITTED AT A TERTIARY CARE HOSPITAL

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Abstract- Background & Objectives: The Influenza A *H1N1* is a novel strain of the influenza A virus. The risk of morbidity from *H1N1* is higher among pregnant women, specifically in second and third trimester. Pregnant women, because of their altered immunity and physiological adaptations, are at higher risk of developing pulmonary complications. This study was done to observe pattern and severity of *H1N1* cases in pregnant women. Objective was to know the prevalence of *H1N1* cases and risk factors associated with it in pregnancy.
Methods: This study was conducted over a period of 3 months from January to March 2015. The following inclusion criteria were used: Pregnancy confirmed via beta human chorionic gonadotropin test or ultrasound, Suspected or confirmed infection with *H1N1* virus, Infection requiring hospitalisation, Admitted at Civil Hospital, Ahmedabad.
Results: Out of 39-suspected antenatal women, 29 were tested positive for pandemic novel *H1N1*. (74.3%) out of which 27 patients had normal delivery (93.1%). One case was emergency caesarean section (3.4%); one case was of a preterm delivery (3.4%). With reference to maternal outcome, 15 women survived (51.7%) and 14 women died (48.3%).
Interpretation &Conclusion: *H1N1* infection in pregnancy may lead to fatal outcome both maternally and perinatally. Proper antenatal management as per symptoms and early diagnosis may help reducing mortality.

Keywords: *H1N1* infection, Pregnancy, rRT PCR

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Introduction

Although outbreak of influenza A *H1N1* 2009 appeared first in Mexico in April 2009, this was followed by a growing number of cases reported across the globe. The outbreak of the novel A *H1N1* virus was declared a global pandemic by World Health Organisation (WHO). The Influenza A *H1N1* is a novel strain of the influenza A virus. The risk of morbidity from *H1N1* is higher among pregnant women, especially in second and third trimester. Pregnant women, because of their altered immunity and physiological adaptations, are at higher risk of developing pulmonary complications [1].

The pregnancy outcomes are also generally poor for women affected with *H1N1*. It may lead to increased perinatal mortality rate and increased preterm delivery rate. There may be complications such as fetal distress or even still birth. This may be associated with increased incidences of birth defects such as neural tube defects [2].

Various physiologic changes that occur during pregnancy may lead to complications due to *H1N1* infection. There is a significant fall in oncotic pressure in 3rd trimester in healthy pregnant women, therefore pregnant women if infected with *H1N1*, can rapidly suffer from a haemodynamic imbalance, which acutely affects lung function and facilitates the development of pneumonia, acute pulmonary oedema, and other serious respiratory illnesses. Pregnancy also reduces the ability of women to tolerate hypoxic stress, and thus increases the risk of maternal and perinatal mortality. All these complications lead to disproportionately increased incidence of hospitalisations and ICU admissions in pregnant women with *H1N1* [3].

Aims and Objectives

The aim of this study was to observe pattern and severity of *H1N1* cases in pregnant women. Objectives were to know the prevalence of *H1N1* cases and risk factors associated with it in pregnancy and to study maternal and perinatal outcome of *H1N1* infection in pregnant women.

Materials and Methods

This study was conducted over a period of 3 months from January to March 2015. The following inclusion criteria were used: Pregnancy confirmed via beta human chorionic gonadotropin test or ultrasound, Suspected or confirmed infection with *H1N1* virus, Infection requiring hospitalisation and Admitted at Civil Hospital, Ahmedabad. Pregnant women with following symptoms at presentation were taken into consideration: Cough, Fever, Sore throat, Myalgia, Shortness of breath, Chest pain, Headache, Nausea, Vomiting, Diarrhoea. They were then categorised according to signs & symptoms into 3 categories:

Category- A: Patients with mild fever plus cough/ sore throat with or without body ache, headache, diarrhea and vomiting are categorised as Category- A. They should be monitored for their progress & reassessed every 24-48 hours by the doctor.

Category- B: In addition to all signs & symptoms mentioned in category A, if the patient has high grade fever and severe sore throat they are included in category-B. In high risk patients, signs & symptoms of Category- A, should be managed as Category- B which includes the following: Children less than 5 years old; 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;
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, they are included in category-C, Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discolouration of nails ;Worsening of underlying chronic conditions.
For this study following parameters were taken into consideration: Maternal Age, Maternal signs and symptoms, Need for mechanical ventilation, Test result for Pandemic Novel *H1N1* tested by real time Reverse Transcriptase Polymerase Chain Reaction (rRT PCR) at Department of Microbiology, Civil Hospital, Ahmedabad, Gestational age of Antenatal woman, Maternal and Perinatal outcome of all included antenatal women.

Diagnosis of Pandemic Novel *H1N1* infection: For diagnosis of Pandemic Novel *H1N1* infection, following protocol was followed. Demographic details and clinical history were obtained and recorded in laboratory request forms. Nasal swabs, nasopharyngeal swabs, or throat swabs were collected from the patients and transferred in viral transport media to the laboratory. All samples were checked for cold chain maintenance and quality of samples [4]. Samples were tested by real time reverse transcriptase PCR (rRTPCR) using CDC validated and WHO approved primers and probes sequences and rRTPCR protocols [5].
RNA extraction was performed using QIAgen Mini RNA extraction kit. Extracted RNA was subjected to one step RTPCR reaction using 4 target sequences i.e. Influenza A (InfA), swine A (SwA), swine H1 (SwH1), and ribonucleoprotein (RNP). Master Mix was prepared by using Ag-Path one-step RTPCR kit by Applied Biosystems.
Interpretation of the test results was done as follows:

InfA	SwA	SwH1	RNP	Interpretation
-	-	-	+	Negative for influenza A virus
+	+	+	+	Positive for pandemic H1N1
+	-	-	+	Positive for seasonal influenza A virus
-	-	-	-	Invalid test

- denotes no amplification
+ denotes amplification

Amplification in RNP target sequence was used as an internal quality control. A test was considered valid only if amplification in RNP was obtained. Samples are routinely stored at-70 ^{0} C after testing for a period of one year.
Clinical complications of *H1N1* infection such as admission to ICU, endotracheal intubation or death were considered as critical. In patients who delivered, parameters were recorded in the form of mode of onset, duration of labour, mode of delivery and neonatal outcome. Spontaneous abortion, preterm delivery, still birth and neonatal death were considered as indicators of adverse perinatal outcome. Pregnant women with an *H1N1* diagnosis in the 1st trimester were considered to have early-pregnancy infection, and those in the 2nd or 3rd trimester were considered to have late-pregnancy infection. Any coexisting illnesses, gravidity, parity, estimated date of delivery, plurality, miscarriage (defined as fetal loss before 22 weeks of gestation), were also considered for this study.

Results: Out of total 2084 samples, 39 were of suspected antenatal women. Results of which are shown in [Fig-1].
As shown in [Fig-1], out of total 39 suspected cases, 29 cases(74.3%) were diagnosed as positive for Pandemic Novel *H1N1* virus infection whereas 10 cases(24.7%) were diagnosed as negative for the same. From these positive cases, 15 cases were of maternal age less than 25 years (51.7%), whereas 14 cases were of maternal age more than 25 years. (48.2%) 17 cases required mechanical ventilatory support (58.6%), whereas 12 were stable (41.4%). None was in 1st trimester, whereas 7 were in 2nd trimester (24.1%) and 22 were in 3rd trimester (75.9%). There were no still births or birth defects among these cases.
Perinatal outcome of these cases is shown in [Fig-2].

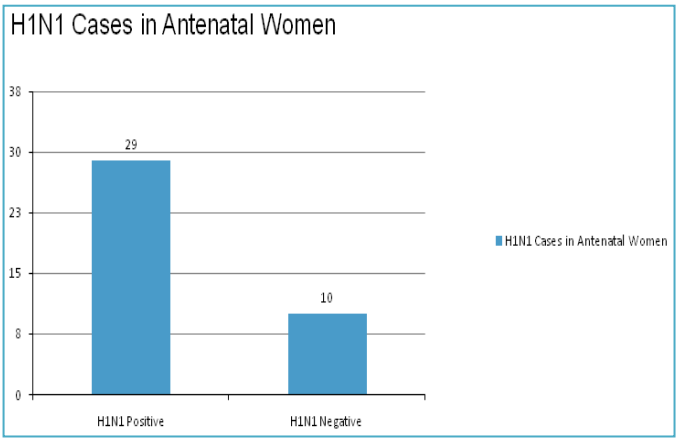

Figure-1

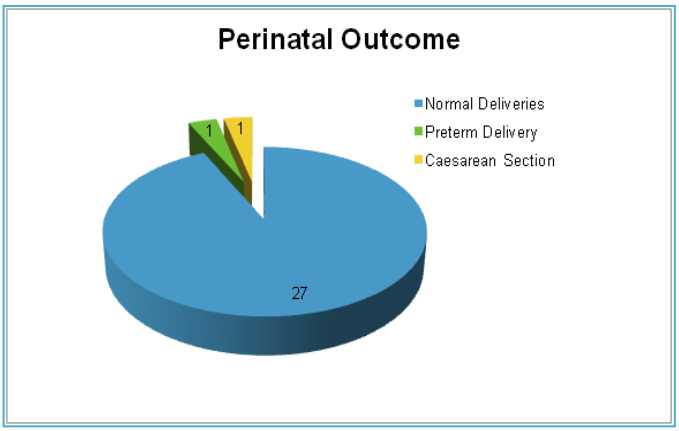

Figure- 2

As shown in [Fig-2], out of total 29 cases, 27 cases (93.1%) ended in normal delivery whereas 1 case (3.45%) ended in a preterm delivery and 1 case (3.45%) delivered by a caesarean section. With reference to maternal outcome, 15 women survived (51.7%) and 14 women died (48.3%).
The study noted that gestational age was associated with higher risk of progression to critical infection resulting in maternal deaths. The risk increased with the weeks of gestation. Influenza increases the risk of severe respiratory diseases in pregnancy. This is comparable to a study on 'Maternal mortality due to pandemic influenza A *H1N1* 2009 virus'in Colombia [6-8, 19].
In our study, the women in the second or third trimester of pregnancy had a higher rate of developing critical infection, which is similar to that reported in the USA [7]. It may be related to specific immune suppression, decreased resistance and physiological changes in pregnancy [10-12].

Discussion: Pregnant women with pandemic *H1N1* may present with typical acute respiratory illness (fever, cough, sore throat, fatigue). Many pregnant women will go on to have a typical course of uncomplicated influenza. However, for some pregnant women, illness might progress rapidly, and might be complicated by bacterial infections including pneumonia. Fetal distress associated with severe maternal illness may occur. Pregnant women, especially those in third trimester should be instructed to seek early care if they develop influenza-like symptoms in context of pandemic *H1N1* circulating in their community- particularly if they have known contact with a case. Pregnant women who have suspected pandemic *H1N1* should be tested as described above.
If lung inflammation occurs, breathing is restricted and lung function is reduced. Blood volume increases in late pregnancy, increasing the burden on the lung, which may lead to easier deterioration [13,14]. Delayed presentation to the hospital and delayed institution of antivirus treatment have been associated with the occurrence of severe illness [15-18].

Clinical Management of Pregnant Women admitted with *H1N1* Influenza A

In all clinical settings, pregnant women should be screened for signs and symptoms of febrile respiratory illness at the initial point of contact and should be promptly segregated and assessed. Outpatient clinical settings, labour and delivery units should develop and implement procedures for handling patients with respiratory illness with flu-like symptoms.

Pregnant women admitted with respiratory complications should be managed jointly between the obstetric and medical teams. An assessment needs to be made with respect to the best place to manage the woman. There should be early involvement of obstetric anesthetists, respiratory physicians, and microbiologist and a clear management plan need to be set.

Women requiring more respiratory support may be best managed in the Respiratory Unit with input from the Respiratory team and the Obstetric team. The patient needs to be carefully monitored for excluding obstetric complications such as pre-eclampsia, venous thromboembolism and pulmonary embolism. The commonest complication of *H1N1* influenza is pneumonia. Complications must be recognised and treated appropriately. In addition, antiviral treatment should be started on clinical grounds whilst awaiting test results. It is equally important to treat maternal pyrexia as epidemiological studies have linked uncontrolled maternal pyrexia to miscarriage and fetal abnormalities such as neural tube and cardiac defects. Also Maternal pyrexia is a risk factor for preterm delivery. Antenatal Steroids in order to enhance fetal lung maturity may be considered.

Decision for delivery: In most cases, the decision to deliver will be made for an obstetric indication. In the event of critically ill woman close to term, it is not unusual to deliver by Caesarean section, to help with mechanical ventilation of the lungs to improve her recovery. This should be done once her clinical condition is stabilised and other potential complications such as coagulopathy have been excluded or corrected. The decision is made in conjunction with the obstetric, critical care and neonatal teams.

Postnatal period: Women in postnatal period are probably at lower risk of respiratory complications because the effects of the gravid uterus on the lungs have been removed. However, they may still experience similar complications if they are infected and there is a risk of transmission to the newborn infant. They should observe the same strict hygiene measures and be offered antiviral medication if clinically indicated. Mothers should be encouraged to breastfeed. Breastfeeding is important and should be continued as long as possible. The benefits of breastfeeding are significant- 1. It gives babies the most appropriate nutrition for health 2. colostrum, rich in antibodies will help to prevent infections.

Antiviral Treatment: The two types of antiviral drugs known to be effective against the swine flu virus are *oseltamivir* and *zanamir.* They are neuraminidase inhibitors and act by preventing the virus from budding and escaping from the host cells. Oseltamivir is given in the form of oral capsules and zanamivir is given as an inhaler (Diskhaler).

Prophylaxis and Vaccines: Unlike in treatment after symptoms, prophylaxis may inhibit the development of immunity and prolonged or repeated prophylaxis may predispose to development of resistance. Prophylaxis is only recommended for very high-risk individuals for whom prompt treatment may not avoid the development of a severe disease. Most pregnant women do not require prophylaxis. The swine flu vaccine contains the inactivated (killed) *H1N1* virus which will not cause any harm to the fetus or mother and active immunity will develop. The antibody response to vaccines in pregnant women has been shown to be as effective as in those who are not pregnant.

Conclusion: As pregnancy is associated with altered physiological & immunological state, *H1N1* infection in pregnancy may lead to various maternal and fetal complications. Both maternal and fetal outcomes may vary with maternal age, weeks of gestation, any deteriorating condition like asthma etc. Any antenatal woman with suggestive signs and symptoms needs to be carefully monitored clinically and to be tested for *H1N1* infection if at all needed. Early diagnosis & treatment is the key to prevent worse maternal and perinatal outcomes. Vaccination should be considered after consultation of an obstetrician and a physician both.

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