

## INFLUENZA A/H1N1 2009 IN PREGNANCY- EXPERIENCE IN TAMILNADU, INDIA

GUNASEKARAN PALANI<sup>a</sup>, KAVERI KRISHNASAMY<sup>b1</sup>, KAVITA ARUNAGIRI<sup>c</sup>, MOHANA SAMBASIVAM<sup>d</sup>, KIRUBA RAMESH<sup>e</sup>, SURESH BABU BOMMALA<sup>f</sup>, SARAN NATARAJAN <sup>g</sup>AND SENTHIL RAJA RAMALINGAM<sup>h</sup>

Department of Virology, King Institute of Preventive Medicine & Research, Chennai, India.

<sup>a</sup>E-mail: Gunzking@gmail.com

<sup>b</sup>E-mail: kaveri\_raj1967@yahoo.com

<sup>c</sup>E-mail: kavita\_77@gmail.com

<sup>d</sup>E-mail: Mohanas@yahoo.com

<sup>e</sup>E-mail: kirubarv@yahoo.com

<sup>f</sup>E-mail: barv@gmail.com

<sup>g</sup>E-mail: saran69@gmail.com

<sup>h</sup>E-mail: serratiasenthil@gmail.com

### ABSTRACT

Infection with influenza A/ H1N1 2009 has been reported worldwide following initial identification of the virus in April 2009. The groups at highest risk for infection and influenza-related complications include pregnant women and children. We have analyzed H1N1 2009 positives among pregnant women in Tamilnadu during and after the outbreak. After initial reports of infection in pregnant women, we began systematically collecting additional information about pregnant women with H1N1 2009 virus infection as part of enhanced surveillance. A total of 126 antenatal women were screened during this period, of this 27 (21.4%) were positive for H1N1 2009 and 14 (11.1%) were positive for Seasonal flu (12 A/H3 and 2 Flu B). Fifteen of the H1N1 2009 positive women had crossed 29 weeks of gestation. It was the 18-30 age group which was highly affected by both H1N1 2009 and seasonal Flu. Among the non pregnant women population, 206 (2.7%) patients were H1N1 2009 positive and 106 (1.4%) were positive for seasonal Flu. It was observed that pregnant women were at increased risk for acquiring H1N1 2009 infection than the non pregnant population. These data lend support to the present recommendation to promptly treat pregnant women with anti-influenza drugs and to initiate vaccination.

**KEYWORDS:** H1N1 2009, RT PCR, pregnant women, Influenza Like Illness (ILI)

With the advent of H1N1 2009 pandemic, foremost was the concern that the virus could be more life threatening than its seasonal peers (Garten et al., 2009) as evidenced by its unusual clinical burden in young adults (Chowel et al., 2009). who experienced more than half of Intensive Care Unit (ICU) stays and deaths (Zarychanski et al., 2009). Data from previous influenza pandemics have indicated that pregnant women have a higher risk for morbidity and mortality than the non-pregnant women (Freeman and Barno, 1959). It is also known that pregnant women and children are at increased risk for acquiring infection and influenza-related complications (CDC, 2009). However, the virus appears to have a predilection for infection of the lower respiratory tract in some cases producing severe acute respiratory distress syndrome, which is difficult to manage despite advanced ventilatory techniques. In this study we did a retrospective analysis of the cumulative prevalence of H1N1 2009 influenza among pregnant and postpartum women in Tamilnadu during September 2009 May 2011 of the

pandemic and post pandemic period.

### MATERIALS AND METHODS

The Influenza Regional Reference Centre at King Institute of Preventive Medicine and Research has been screening for H1N1 2009 in samples referred from all over Tamilnadu and tertiary care referral institutions in Chennai. The first case in Tamilnadu appeared on 1<sup>st</sup> June 2009 followed by its epidemic spread into the community by July 2009. All H1N1 2009 suspected pregnant/postpartum women (delivered within 2 weeks), with signs and symptoms of ILI/SARI referred to us during June 2009 to May 2011 were tested by r RTPCR. As per case definition, Influenza Like Illness (ILI) is defined as when a person presents with sudden onset of fever >38C or history of sudden onset of fever in the recent past, cough, sore throat, and/or rhinorrhea in absence of other diagnosis. Severe Acute Respiratory Illness (SARI) is defined as a person presenting with sudden onset of fever >38C or history of sudden onset of fever in the recent past, cough, sore throat, and/or rhinorrhea and in addition to having breathlessness

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<sup>1</sup>Corresponding author

or difficulty in breathing and clinically suspected pneumonia.

Throat and nasal swabs were taken from the referred patients. A standard laboratory request form which included demographic data, history, underlying medical condition, clinical signs and symptoms and treatment course were filled in and informed consent obtained from the individuals or from the guardian. A positive case was defined as a pregnant /postpartum woman with symptoms of ILI/SARI, testing positive by rRT PCR. A fatal case is one with symptoms of ILI/SARI, positive rRT PCR test in whom H1N1 2009 is the attributable cause of death. Demographic and clinical data were obtained from the performa filled in by the referral institution. Daily reports were sent to the state and central health authorities on a day to day basis. A total of 6245 samples were analyzed by the rRT-PCR assay. All samples were subjected to RNA extraction using viral RNA kit (Qiagen) and rRT- PCR was performed as per CDC protocol, wherein four sets of primers and probes were used. Each sample was subjected to primers against Pan A, Swine A, Swine H1 and RNase P. Ambion super script one-step RT PCR kit was used for performing Real time RT- PCR. The CDC supplied all primers and probes.

#### Statistical Analysis

The data presented was analyzed using Chi-square test for proportion and the Chi- square test for linear trend using Graph pad prism 5.02 program. Results were considered statistically significant when  $p < 0.05$ .

#### RESULTS

During the period, testing was performed for 126 pregnant and 7512 non pregnant women presenting with signs and symptoms of ILI/SARI based on the national pandemic response plan. During the initial phase of the pandemic all suspected cases were referred to us for testing, later during the course, as per the directive of the Health and Family Welfare Department, cases belonging to category C, based on case definition were subjected to testing. Of the 126 antenatal women screened, 27(21.4%) were positive for H1N1 2009 and 14(11.1%) were positive for Seasonal flu (12 A/H3 and 2 Flu B). Out of the 27 H1N1 2009 positive

cases, 12 had antenatal onset and 15 had post partum onset. Eighty five of the pregnant patients were negative for H1N12009. It was the 18-30 age group which was more affected by both H1N1 2009 and seasonal Flu. Fifteen of the H1N1 2009 positives had crossed 29 gestational weeks and 8 patients positive for seasonal Flu were between 14-28 weeks of gestation. One asthmatic antenatal patient tested positive for H1N1 2009. During this period a total of 7512 non pregnant women were screened and 206 (2.7%) patients were positive for H1N12009. 107 (1.4%) of patients were positive for seasonal influenza (A/H3-86 and Flu B-21). Nulliparous women were more affected by H1N1 2009 and by seasonal Influenza. Majority of H1N1 2009 positives. In 2009 were diagnosed during the monsoon months of September 09 to December 09. In the year 2010, positives were observed between July 10 to January 2011. In the year 2009 the pandemic strain was predominant replacing the circulating seasonal strains.

#### DISCUSSION

The antenatal cases tested were from different districts of Tamilnadu, as well as cases referred from tertiary care centres in Chennai, thus reflecting the patterns and effects of pandemic H1N1 2009 on antenatal cases in the state. During this period 126 pregnant women were screened, of these 27 (21%) were positive for H1N1 2009 and 14 (11.1%) for seasonal flu. This was found to be statistically insignificant with a  $P=1.0$ . Eighty five cases (65%) tested flu negative. It is known that pregnant women are at high risk for not only acquiring the infection but also have a propensity to develop complications in and during the inter pandemic periods (US Department of Health and Human Services 2007; Neuzil, 1998). Among the 27 cases positive for H1N1 2009, 25 were ILI cases and 2 were SARI cases. All positive patients were kept under observation in isolation wards as per the directive of the Health Department and Oseltamivir was administered. It was observed that 12 of them had antenatal onset and 15 had post partum onset. As with most drugs, information about the safety and effectiveness of the anti-influenza drugs during pregnancy is scarce (Freund et al., 1999; Tanaka et al., 2009). Based upon the CDC guidance antiviral treatment

with Oseltamivir was initiated considering the high risk for influenza related complications from infection with H1N1 2009 virus.

The non pregnant women population had H1N1 2009 positivity of 206 (2.7%) when compared to seasonal Flu 106 (1.4%) and this was found to be statistically insignificant where else in a study in south Reunion island H1N1 2009 positivity was 3.6% and seasonal Influenza positivity was 12.8% among non pregnant women. This could be as a result of the pandemic strain displacing the circulating seasonal Influenza strains in Tamilnadu. Our observation showed pregnant women were more vulnerable to H1N1 2009 (21%) compared to non pregnant women (2.7%) and this was found to be statistically significant with  $P < 0.0001$ . We also observed a decline in the incidence of seasonal flu during the pandemic period in both pregnant and non pregnant women, implicating the predominance of H1N1 2009 strain. It was the 18-30 age group which was predominantly affected by both H1N1 2009 and seasonal Flu compared to the other age groups among the pregnant women and this was found to be statistically significant ( $P > 0.05$ ). In the non pregnant women also it was the 18-30 age group which was more affected and this was found to be statistically significant. ( $P > 0.05$ ). This could be because majority of the antenatal cases referred were from this younger age group and it was also observed that H1N1 2009 during the pandemic, affected young adults more than children and infirm. This is very similar to the study done in Reunion Island (Gerardin et al., 2009). Nulliparous women were found to be more affected by H1N1 2009 ( $p = 0.99$ ) and by seasonal Flu, than multiparous women ( $p = 1.00$ ). It was observed that H1N1 2009 predominantly affected pregnant women who had crossed 29 weeks of gestation with an insignificant P value. ( $p = 0.2$ ) whereas seasonal flu was detected at relatively higher level in the 14-28 gestational week. Among the pregnant women, seven of them were asthmatics, among them 1 tested positive for H1N1 2009 and 3 were positive for seasonal flu. of the 27 pregnant women with H1N1 2009 viral infection, 98% of women presented with a febrile illness and 94% of women had fever plus either cough or sore throat. Other than fever, the most common symptoms were headache, breathlessness and myalgia, with vomiting and diarrhea. This is similar to

the study in the US where 97% women with H1N1 2009 viral infection presented with a febrile illness and 94% women had influenza-like illness.

Out of the 27 positive patients, three were admitted in intensive care units severe outcome cases and five were admitted to obstetric wards and treated- moderated outcome cases. Nineteen of them were managed as outpatients with mild outcome. There was one death reported among the positive pregnant (postpartum) women. There are references stating that during the 1918 pandemic, about 50% developed pneumonia and of these women more than half died (overall case fatality rate 27%), with the highest mortality in the third trimester. During Asian influenza in 1957, it was observed that 50% of deaths occurred in pregnant women (in Minnesota) (Freeman and Barno, 1959) The comparison of severity of disease in pregnant women in previous pandemics with the present outbreak is very difficult because of the smaller number of cases screened for, case definition variability and improved public awareness and control measures. Since long term follow up was not done in our study, little is known about the effects of the H1N1 2009 virus on the fetus. Although no infections have been reported in neonates born to women with H1N1 2009 virus infection, it is probable that the infants might have had more subtle effects from maternal H1N1 2009 virus infection. In the pandemic of 1918, high rates of pregnancy loss and preterm delivery were reported and during the pandemic of 1957-58, possible increase in CNS defects and other adverse outcomes were shown. Hence follow up of outcome is definitely a limitation in our study.

Vaccines were not available during the early period of the pandemic; again vaccination with live attenuated H1N1 2009 was not given to the pregnant women in India. However in US guidelines place pregnant women in a high-priority group for receipt of pandemic influenza vaccine. However, in one study pregnant women had the lowest vaccine coverage level (4% in 2004) of all adult population groups recommended to receive influenza vaccination. The low level of use of influenza vaccine in pregnant women is disconcerting and has important implications for future pandemic vaccination planning. Our study had certain limitations, as cases tested for H1N1 2009 during the initial period of the pandemic were not based

upon the CDC case definition, hence the number of cases referred were high. Later, based upon CDC guidelines the health department had categorized the cases and had advised that only those cases belonging to the Category C and cases with co-morbid conditions need be tested and insisted upon all cases to being referred by the attending

physician and health care workers.

The pandemic had started by May 2009, with the first case appearing in Tamilnadu by June 2009. The onset of monsoon by August had augmented the spread of infection and with September to December being the seasonal Flu season, the stage was set for a full blown H1N1 2009

**Table 1. Characteristics of pregnant women (PW) and Non pregnant women with 2009 H1N12009 infection**

	PW Screened n=126	PW +ve pH1N1 n=27	PW Positive for FLU TOT n=14	p value	PW Negative for Flu n=85	NPW Screened for Flu n=7512	NPW + ve for H1N1 2009 n=206	NPW +ve Seasonal TOT n=107	p value	NPW -ve for seasonal Flu n=7199
<b>Age</b>										
<18	8	2	3	p<0.05	3	1256	26	24	p<0.05	1206
18-30	92	24	7	-	61	2704	84	34	-	2586
30-39	26	1	4	-	21	2403	56	25	-	2322
>40	0	0	0	-	0	1149	40	24	-	1085
<b>Parity</b>										
Nullipara	45	10	5	p=0.99	-	2682	74	38	p=1.00	2570
Primipara	41	9	5	-	-	2569	70	37	-	2462
Multipara	40	8	4	-	-	2261	62	32	-	2167
<b>Weeks pregnant at infection</b>										
0-13	14	3	2	p=0.2	9	1568	-	-	-	1505
14-28	38	9	8	-	21	2891	-	-	-	2760
>29	74	15	4	-	55	3053	-	-	-	2934
<b>History of current asthma</b>										
Yes, currently receiving drugs	7	1	3	-	3	15	7	6	-	2

pandemic. In 2010 increase in the number of H1N1 2009 positive cases were seen during the months of August to September and the number of patients referred as well as positivity declining by February 2011. It was observed that the number of cases positive for H1N1 2009 increased with increase in rainfall. Findings from this study will be crucial to public health planning for pregnant women, in view of this pandemic and for other novel pathogens as well. In conclusion, this report states that the pregnant women were more susceptible to H1N1 2009 pandemic when compared to the non pregnant women.

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