Original Article

Maternal and Perinatal Outcomes of Influenza in Pregnancy after Treatment with Oseltamivir

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Abstract

Context: Influenza infection in pregnancy causes 4%–8% case fatality and five times more perinatal mortality. Influenza is a major contributor to mortality in developing countries; however, the morbidity has largely been underestimated. Public health interventions for prevention are also lacking. **Aims:** This study aimed to determine the seasonality of influenza in pregnant Indian women and to estimate the maternal and perinatal morbidity after treatment with oseltamivir. **Settings and Design:** This was a prospective observational cohort study, conducted in a tertiary hospital. **Subjects and Methods:** Pregnant women with ILI (influenza-like illness) were recruited into Cohort 1 (polymerase chain reaction [PCR] positive) and Cohort 2 (PCR negative). Gestational age-matched asymptomatic controls formed Cohort 3. Women in Cohort 1 received oseltamivir for 5 days. The incidence of small-for-gestational age (SGA) and preterm birth were the primary outcomes. Maternal and neonatal morbidity formed the secondary outcomes. **Statistical Analysis:** Unmatched (Cohort 1 and 2) and matched analysis (Cohort 1 and 3) were done. Student's *t*-test and Chi-square test were used to compare between variables. **Results:** Year-round incidence of influenza was recorded. Severe illness was more in Cohort 1 compared to Cohort 2 (36.2% vs. 6.3%; $P < 0.001$). SGA was comparable in all the cohorts (13%). Preterm birth (7.8% vs. 3.3%; $P < 0.08$; relative risk-2.75) was considerably high in Cohort 1. Secondary maternal and neonatal outcomes were similar between the groups. **Conclusion:** Influenza in pregnancy showed year-round incidence and increased maternal and neonatal morbidity despite treatment with oseltamivir. We suggest the need for newer interventions to curtail the illness in pregnancy.

Keywords: Influenza, influenza like illness, pregnancy, preterm birth, small for gestational age

Introduction

Influenza virus is an important respiratory pathogen that causes increased morbidity and mortality among pregnant women, a risk well documented in the 1918 global influenza pandemic and 2009 H1N1 pandemic.[1] Severe maternal illness has also been associated with low birth weight and increased risk of preterm birth.[2]

South East Asia[3] and equatorial regions have been implicated as the source of many new strains of influenza that circulate globally.[4] The virus is a major contributor to mortality in these low-income countries; however, the morbidity has largely been underestimated. Awareness campaigns and health interventions to curtail influenza infections are also lacking. Continued and enhanced surveillance in the tropics is hence warranted to monitor both the disease load and the impact of interventions.

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_157_20

The WHO Strategic Advisory Group of Experts on immunization has given highest priority for pregnant women to receive influenza immunization.[5] However, in India, vaccine uptake among these women is extremely poor.[6] In addition, the lack of disease burden data among pregnant Indian women has reduced the attention toward influenza prevention as a public health priority. Hence, the objectives of our study were to determine the seasonality

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How to cite this article: Abraham K, Abraham A, Regi A, Lionel J, Thomas E, Vijayaselvi R, *et al*. Maternal and perinatal outcomes of influenza in pregnancy after treatment with oseltamivir. J Global Infect Dis 2021;13:20-6.

Received: 31 May 2020 **Revised:** 15 July 2020
Accepted: 18 August 2020 **Published:** 29 January 2021

of influenza and to estimate its influence on maternal and perinatal morbidity after treatment with oseltamivir. The data would be valuable for planning further preventive strategies.

Subjects and Methods

Procedure

This prospective observational cohort study was conducted in Christian Medical College (CMC), Vellore, a 2700-bedded tertiary referral center in South India from November 1, 2015, to October 31, 2017. All pregnant women who attended the antenatal clinic or admitted to the obstetric wards with influenza-like illness (ILI) were eligible for participation. Enrollment was done after obtaining written informed consent. ILI was defined as fever ≥38°C in the presence of either cough or sore throat reported by women. Women with gestational hypertension, pregestational diabetes, hyperthyroidism, and severe anemia were excluded. Gestational age was confirmed from antenatal ultrasound reports. After clinical examination (included recordings of pulse rate, respiratory rate, blood pressure, oxygen saturation, and auscultation of lung fields), nasal and oropharyngeal swabs were collected, transported appropriately in cold containers, and tested for influenza virus using a standardized polymerase chain reaction (PCR) for all women with ILI. Because the clinical picture was strongly suggestive of respiratory illness, investigations (blood and urine cultures) to rule out other causes of fever were done only for patients requiring admission. PCR results were obtained within 3 days based on which pregnant women with ILI were grouped into two cohorts – influenza PCR positive cohort and PCR negative ILI cohort. In addition, one gestational-age matched asymptomatic pregnant woman seen in the same week was selected as control for every woman who presented with PCR-positive influenza. The group with PCR negative ILI was considered the first control group (Cohort 2), while the healthy pregnant women constituted the second control group (Cohort 3). Antitussives, gargles, bronchodilators, or antibiotics, as needed, were given to all women with signs of ILI. In addition, women with PCR positive influenza were started on oral antiviral drug oseltamivir (75 mg twice daily for 5 days) within 72 h of presentation.[7] Those who were admitted to the wards/intensive care unit (ICU) were considered to have severe illness.[8] After discharge, they were provided routine clinic based antenatal care. All participants were followed up through pregnancy, childbirth, and the postnatal period. The infant's weight, length, head circumference, Apgar scores, and perinatal complications were recorded immediately after birth. The infants were followed up at 2 and 4 weeks after birth either through postnatal checks or telephonic interviews to assess their health status. The primary outcomes were the incidence of small-for-gestational age (SGA) and preterm births. The secondary outcomes assessed were obstetric complications in the mother and perinatal morbidity.

Definition of outcomes

SGA was defined as an infant with birth weight lower than the tenth centile of the sex-specific and gestational age-specific INTERGROWTH-21st birth weight standard.[9] Preterm delivery was defined as birth before 37 weeks of gestation. The secondary perinatal outcomes included Apgar score < 6 at 5 min, blood culture-positive neonatal sepsis, respiratory distress syndrome (RDS), admission to neonatal ICU (NICU) for preterm care and pregnancy loss defined as any abortion or birth of a nonviable fetus after 22 weeks of gestation. Perinatal data of twins and those who did not give birth in our institution were excluded from the analysis. Maternal data [Tables 1 and 2] from all women at the time of infection were included to assess the morbidity. However, data on obstetric complications could be collected only from women who gave birth in our hospital.

Sample size calculation

The expected SGA rates were 25% in the influenza group and 10% in the noninfluenza group. To show a 15% statistically significant difference in proportions with unequal allocation of 1:2, $\alpha = 0.01$, $\beta = 0.1$, and dropout rate of 20%, the required sample sizes were 166 women with influenza and 332 women with ILI, respectively. To compare the SGA rates of women with influenza and healthy controls (8% SGA rate), with equal allocation of 1:1, the required sample size was 166.

Ethical approval was obtained from the Institutional Review Boards of CMC, Vellore on August 27, 2014 (IRB No. 9014[OBSERVE]), and Cincinnati Children's Medical Centre, USA (Study ID: 2014-7670), who funded the study and developed the study protocol.

Statistical methods

The data were abstracted in a predesigned case report form and entered in EpiData software, version 3.1, Odense, Denmark. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean (standard deviation) or median (interquartile range) as appropriate. Continuous variables were compared between groups using Student's *t*-test and categorical variables were compared using Chi-square test. Unmatched analysis (Cohorts 1 and 2) and matched analysis (Cohorts 1 and 3) were done as appropriate to compare between the cohorts. Relative risks (RRs) with 95% confidence interval (CI) were calculated. The significance level was fixed at 5% level.

Results

During the study period, on an average, 8455 women attended the antenatal clinics every month. A total of 29,635 live births were registered during the same period, with an average of 1234 births per month. Figure 1 describes the flow of participants into the study. A total of 650 pregnant women were included in the study. Of the 476 women with ILI, 174 were influenza PCR positive (Cohort 1) and 302 were influenza PCR negative (Cohort 2).174 gestational age-matched healthy pregnant women were recruited into Cohort 3. Among the 174 women with influenza, 49 (28%) were positive for human influenza virus Type

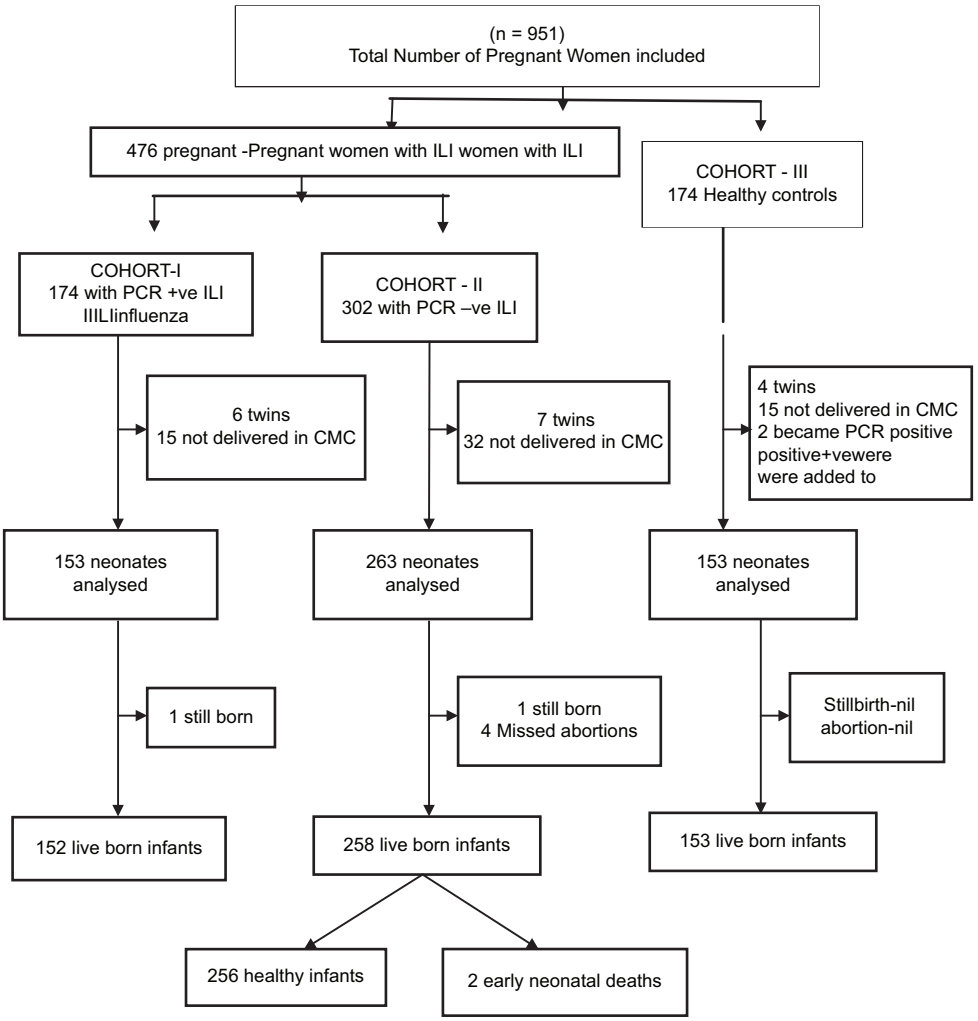

Figure 1: Influenza study flow chart

A (H1N1), 93 (54%) for A (H3N2), and 32 (18%) for influenza B. After excluding 6 sets of twins and 14 infants who were born elsewhere, Cohort 1 had 153 live born infants. In Cohort 2, data from 7 sets of twins and 32 infants born elsewhere were excluded. Among the 263 pregnancy outcomes, there were four missed abortions, one stillbirth, and 258 live births. Among the 174 gestational age-matched healthy pregnant women recruited into Cohort 3, two later developed influenza. They were removed from Cohort 3 and added to Cohort 1. In their place, two new gestational age-matched controls were enrolled in Cohort 3 but not at the same time as the recruitment of cases. In Cohort 3, data from 4 sets of twins and 15 born elsewhere were excluded from the analysis. One hundred and fifty-three infants were born healthy in this cohort. The data from a total of 570 birth outcomes registered in our hospital have been included in the analysis.

Figure 2 shows the incidence rate of PCR-positive influenza during the study period from November 2015 to October 2017. The peak incidence has occurred during late monsoon and winter months. An epidemic range incidence had been recorded during September–October 2017. During the summer months (March–August), the reports of influenza were very low though there was year-round incidence. AH3 showed peak infection rates during the winters of 2015 and 2017, whereas AH1 and B subtypes had prevailed from 2016 November to February 2017 [Figure 3].

Data from Cohort 1 were compared separately with Cohort 2 and Cohort 3. Demographic features [Table 1] of the mothers in the three groups were comparable with respect to age, body mass index, gravidity, place of residence, and previous adverse pregnancy outcomes. Annual income was significantly lower among women with influenza compared to the negative group ($P = 0.004$) and healthy controls ($P < 0.001$). The influenza infection rates steadily increased with advancing gestational age.

The symptoms of ILI included fever, coryza, and dyspnea. The incidence of tachycardia (pulse rate > 100 beats/min), tachypnea (respiratory rate > 20 breaths/min), and hypoxia (oxygen saturation < 90%), assessed as per our hospital protocol, was significantly more ($P < 0{\cdot}001$) among women with influenza [Table 2]. Significantly higher proportion of women in Cohort 1 had severe illness requiring inpatient and ICU care compared to PCR-negative women (36.2% vs. 6.3%, $P < 0.001$). The expenditure toward treatment, ₹15,432 (~$ 216) for an average of 5 days, was three times higher

for women with severe illness compared to women who had outpatient-based care. On an average, each woman who had outpatient care had to spend ₹4392 (~$ 62). This included the cost of influenza PCR, antiviral drugs, and physician fees.

Mean birth weight, head circumference, and length of the neonate were comparable between the cohorts [Table 3]. The primary neonatal outcomes analyzed are listed in Table 4. The incidence of SGA was similar between the cohorts. Twenty babies (13·1%) in the influenza PCR-positive group were SGA compared to 33 (12.8%, $P = 0.9$, RR – 1.01) in the PCR-negative ILI group and 20 (13%, $P = 0.9$, RR– 1.12) among the healthy controls. The incidence of preterm birth was also similar among the women with acute respiratory infection (7.8% vs. 8·9%, $P = 0.72$). However, there was a trend toward more preterm births in Cohort 1 compared to the healthy controls in Cohort 3 (7.8% vs. 3.3%; $P = 0.08$), but the difference was not statistically significant.

There was one unexplained term stillbirth in Cohort 1 3 weeks after the mother had recovered from influenza infection. Cohort 2 also had a stillbirth due to abruption at 24 weeks of gestation which occurred 4 weeks after the mother had recovered from ILI. The overall pregnancy loss (including miscarriage) was lower among women with influenza (0.6%) compared to PCR-negative ILI (1.9%). No birth defects or neonatal deaths occurred in Cohort 1. The secondary neonatal outcomes are listed in Table 5. Cohort 1 had one baby with Apgar score < 6 at 5 min, four cases of neonatal sepsis and five babies with RDS. There was a trend toward increased preterm care requirement in this group compared to healthy controls (RR 2.75; $P = 0.1$). Obstetrical complications such as polyhydramnios (0.7% vs. 1%; $P = 1.0$; RR-0.74) and oligohydramnios (3.3% vs. 1.9%;

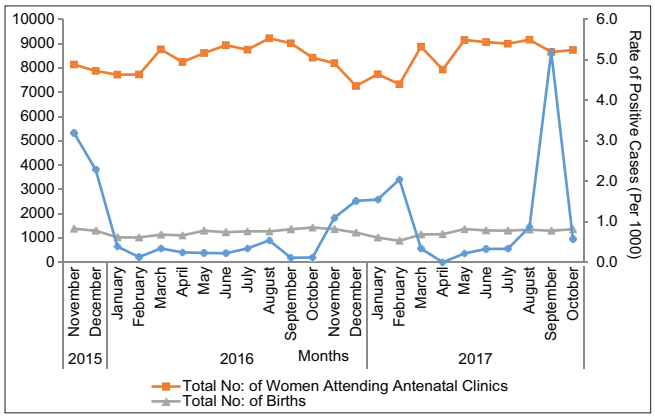

Figure 2: Line diagram plotting total number of women attending antenatal clinics, total number of births (primary axis), and incidence rate of influenza (secondary axis)

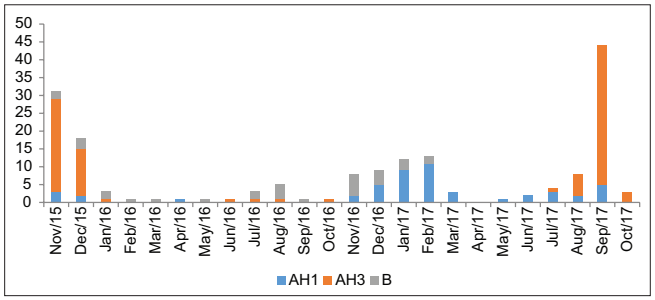

Figure 3: Strains of influenza viruses detected by polymerase chain reaction over the study period

Table 1: Demographic variables

Variable	Cohort I ($n=174$), n (%) Mean±SD	Cohort II ($n=302$), n (%) Mean±SD	P^a	Cohort III ($n=174$), n (%) Mean±SD	P^b
Age (years)	25.6±4.4	25.9±4.1	0.350	25.9±4.3	0.382
BMI					
≤25	94 (54.0)	143 (47.4)	0.161	100 (57.5)	0.517
>25	80 (46.0)	159 (52.6)		74 (42.5)	
Gravidity					
Primi gravida	78 (44.8)	148 (49.0)	0.379	87 (50.0)	0.334
Multi gravida	96 (55.2)	154 (51.0)		87 (50.0)	
Previous pregnancy loss					
No	168 (966)	289 (95.7)	0.646	165 (94.8)	0.428
Yes	6 (3.4)	13 (4.3)		9 (5.2)	
Residence					
Urban	122 (70.1)	193 (63.9)	0.168	111 (63.8)	0.210
Rural	52 (29.9)	109 (36.1)		63 (36.2)	
Annual income (INR)					
Median (IQR)	120,000 (77,250-200,000)	160,000 (85,000-245,000)	0.004	180,000 (110,000-250,000)	0.001
GA at presentation with ILI (weeks)					
<13	5 (2.9)	33 (10.9)	<0.001	8 (4.6)	0.694
13-28	47 (27.0)	113 (37.4)		47 (27.0)	
>28	122 (70.1)	156 (51.7)		119 (68.4)	

BMI: Body mass index, GA: Gestational age, ILI: Influenza-like illness, SD: Standard deviation

Table 2: Clinical characteristics and severity of illness in the mothers at the time of infection/recruitment

Variable	Cohort I (*n*=174), *n* (%) Mean±SD	Cohort II (*n*=302), *n* (%) Mean±SD	*P*[a]	Cohort III (*n*=174), *n* (%) Mean±SD	*P*[b]
Pulse rate	101.9±14.5	93.6 ±11.1	<0.001	78.9±5.9	<0.001
Respiratory rate	23.1± 6.7	21.9±5.3	0.039	20.3±4.1	<0.001
Systolic BP	105·6±10.5	105.4±10.1	0.814	107.0±8.4	0.175
Diastolic BP	67.8±10.0	67.9±8.5	0.879	69.8±8.4	0.049
Oxygen saturation	98·6±0.8	98.8±0.8	0.86	99.4±1.6	<0.001
Severity of illness					
OP care	111 (63.8)	283 (93.7)	<0.001	174 (100.0)	<0.001
IP and ICU care	63 (36.2)	19 (6.3)		-	

BP: Blood pressure, OP: Outpatient, IP: Inpatient, ICU: Intensive care unit, SD: Standard deviation

Table 3: Characteristics of neonates at birth

Variable	Cohort I (*n*=153) Mean±SD, *n* (%)	Cohort II (*n*=258) Mean±SD, *n* (%)	*P*	Cohort III (*n*=153) Mean±SD, *n* (%)	*P*
Head circumference (cm)	33.5±1.30	33.7±1.40	0.135	33.6±1.2	0.324
Length (cm)	48.12±2.3	48·00±2.7	0.648	48.2±2.0	0.742
Gender					
Male	84 (54.9)	127 (49.2)	0.266	70 (45.7)	0.108
Female	69 (45.1)	131 (50.8)		83 (54.3)	
Mean birth weight (kg)	2.96±0.4	2.95±0.5	0.782	2.97± 0.43	0.817

SGA: Small for gestational age, SD: Standard deviation

Table 4: Primary outcomes

Variable	Cohort I (*n*=153), *n* (%)	Cohort II (*n*=258), *n* (%)	*P*	RR CI	Cohort III (*n*=153), *n* (%)	*P*	RR CI
SGA							
Yes	20 (13.1)	33 (12.8)	0·946	1.01	20 (13.0)	0.899	1.12
No	133 (86.9)	224 (87.2)		0.69-1.47	133 (87.0)		0.58-2.15
Preterm (<37 weeks)	12 (7.8)	23 (8.9)	0·724	0.92	5 (3.3)	0.086	2.75
Term	141 (92.2)	235 (91.0)		0.57-1.48	148 (96.7)		0.88-8.64

SGA: Small for gestational age, RR: Relative risks, CI: Confidence interval

Table 5: Secondary outcomes

Variable	Cohort I (*n*=153), *n* (%)	Cohort II (*n*=258), *n* (%)	*P*	RR CI	Cohort III (*n*=153), *n* (%)	*P*	RR CI
Apgar score							
<6 at 5 min	1 (0.7)	2 (0.8)	1.000	0.89	1 (0.7)	1.000	1.00
≥6 at 5 min	152 (99.3)	256 (99.2)		0.18-4.47	152 (99.3)		0.06-15.99
RDS/sepsis	9 (5.8)	11 (4.2)	0.432	0.81	6 (4.0)	0.427	1.50
No complications	144 (94.2)	247 (95.8)		0.49-1.33	147 (96.0)		0.53-4.21
Preterm care in NICU up to 4 weeks after birth							
Yes	9 (5.9)	12 (4.7)	0.573	1.17	4 (2.7)	0.167	2.25
No	144 (94.1)	246 (95.3)		0.7-1.94	149 (97.3)		0.69-7.31

RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit, RR: Relative risks, CI: Confidence interval

P = 0.3; RR – 1.44) were very few. None of these women in Cohort 1 had abruptio placentae or placenta previa, hence no tests of statistical significance could be done. Overall, there were no statistically significant differences in the secondary outcomes.

Discussion

Our study highlights the potential use of clinical data to assess the health impacts of influenza in pregnant women a target population for vaccination. We identified 174 laboratory

confirmed maternal influenza infections in Vellore (South India) during the period of 2015–2017. Influenza contributed to 36% of the acute respiratory infections in the observed pregnant women. Seventy percent were affected during the third trimester and 36% had severe illness which required inpatient care. There were more preterm births in the infected women (RR – 2.75) requiring prolonged NICU care.

The influenza viruses that contribute mainly to the disease burden in humans are influenza A and B. Currently, there are two major subtypes of influenza A in circulation among humans, A/H3N2 and A/H1N1. In India, influenza A/H3N2 was the major strain prior to the emergence of H1N1pdm09. 2013 witnessed the co-circulation of A/H3N2 with A/H1N1pdm09.[10] In Vellore, A/H1N1pdm09 prevailed in 2009, 2010, and 2012; A/H3N2 in 2011 and 2013; and influenza B in 2012. The changing trend continued during our study period with H3N2 peaks in 2015 and 2017 and H1N1 in 2016. Though earlier studies from South India have reported greater prevalence of A/H1N1pdm09 among pregnant women, later studies have attributed this to greater circulation of this strain.[11] Our findings are in concordance with Koul *et al*., with more H3N2 infections (49%) as compared to A/H1N1 (27%) and influenza B (18%).

Patterns of influenza vary in tropical and subtropical areas.[12] Countries closer to equator have year-round incidence, whereas those further away show monsoon peaks. Previous Indian studies have reported seasonal and pandemic patterns.[13] The seasonality would depend on latitude, rainfall, humidity, indoor crowding, and increased viral survival in winter months.[14] Three major patterns of circulation have been seen in India-winter peak in Srinagar (January–April); during the monsoon from June to October in Delhi, Kolkata, Nagpur, and Alappuzha; late monsoon-related peaks in Chennai and Vellore (September to December).[15] A year-round incidence of all the common strains was observed in our study with late monsoon and winter peaks (September to February). This would suggest a greater load of disease seen in this study compared to the previous studies, which have supported seasonal or pandemic patterns.[13]

The risk for infection was found to increase with advancing gestational age.[16] Liu *et al*. reported that 9.1% of the cases occurred in the first trimester, 29.8% in the second trimester, and 47% in the third trimester.[17] Previous reports from India suggest that four out of five pregnant women who developed respiratory failure were in the third trimester.[11] Our findings are consistent with 70% being infected in the third trimester. During the study period, maternal mortality in our institution ranged from 48/100,000 livebirths (2016) to 55/100,000 live births (2017). Only one death was due to H1N1 infection. This woman could not be included in our study as she was directly admitted to ICU without prior admission to obstetric ward. However, we found that influenza caused six times more maternal morbidity with a significant proportion developing severe illness ($P < 0.001$) and one-third requiring inpatient care (63 out of 174). Previous studies have reported higher morbidity with 92% hospitalization rates,[18] 73% ICU admission rates, high rates of pneumonia (75%), and maternal mortality (25%–70%).[19] However, such high rates could be an overestimation as majority were hospital-based studies and did not include community cases.[20] In addition there could have been obstetric concerns prompting hospitalization. However, a recent community-based study has reported drop in hospitalization rate to 18% and case fatality rate to 4%–8%.[21]

Many studies of maternal influenza reported significant impact on the fetus with 5-fold increase in perinatal mortality[22] and 3-fold increase in preterm birth.[23] Preterm birth rates reported from Western countries were lower (4%–25%)[24] compared to India (20%–33%).[13] The risk was more with severe maternal illness (odds ratio [OR] 3.2; 95% CI 2.4–4.0),[25] whereas studies based on a wider range of illness did not find any increased risk (OR 1.2; 95% CI 1.03-1.27).[26] We found a lower rate of preterm birth compared to the previous Indian studies, but it was still two times more in women with influenza (7.8% vs. 3.3%; $P = 0.08$; RR – 2.75) compared to healthy controls. Supporting evidence comes from the higher rate of NICU admission for preterm care (RR – 2.25). Incidence of SGA was similar among the three cohorts (RR – 1.1), which is again comparable to previous reports (2.8% to 15.3%; OR: 1.24)[24] However, studies on more severe illness have reported higher odds of SGA (OR: 1.66-2.35; 95% CI: 1.03–5.36).[27]

Fetal mortality reported from India ranges from 5.5% to 33%.[13] We found low fetal loss rate (0.4%) compared to an earlier study from the same hospital (5%; 1 in 20).[28] Incidence of RDS and sepsis was also comparable between the groups ($P = 0.4$). There were no neonatal deaths among the infected women. The better perinatal outcome could be attributed to less maternal morbidity after treatment with oseltamivir and higher standards of neonatal care. Lower maternal mortality could also be attributed to similar causes. Data on the effectiveness and safety of the drug are limited, though isolated reports are reassuring.[29] In addition, none of the women reported any adverse effects of oseltamivir necessitating stoppage of treatment. Still, the maternal and neonatal morbidity are higher compared to healthy women. Hence, primary prevention would be important as the next step to curtail the ailment. Our study was not designed to evaluate the effect of vaccination. However, it was estimated that a woman would spend far less for influenza vaccination (₹1239; ~$17) compared to outpatient care (₹4392; ~$62) or inpatient care (₹ 15,432; ~$216). Add on would be the costs of neonatal care. The economic burden related to the treatment of severe maternal illness (36.2% vs. 6.3%, $P < 0.001$) and advanced neonatal care (5.9% vs. 2.7%; $P = 0.1$; RR – 2.25) can prove challenging to developing nations.

The results of this study are relevant to India and other tropical countries in order to understand the burden of influenza and plan preventive strategies. The two sets of controls and matched analysis provide highly objective data. Both mild and severe cases of influenza were included, which makes the data more applicable to the general population. The study found year-round disease burden and a trend toward increased maternal and neonatal morbidity even after treatment with antiviral drug. Hence, more interventions

would be needed to curtail the disease in pregnancy. The study has the limitation of being restricted to hospital based cases which could overestimate the morbidity. Community-based studies with bigger sample sizes would give a true picture of the morbidity.

Conclusion

The study has shown year-round incidence and increased disease burden from influenza infection in India. We found reduced maternal and neonatal mortality but morbidity was comparatively higher even after treatment with oseltamivir. This study highlights the need for newer public health interventions toward primary prevention to curtail morbidity due to influenza in pregnancy. Large community-based studies are needed to evaluate the impact of the infection at the grass-root level.

Acknowledgement

We thank the patients and their families for providing consent and assisting with the present study, despite the suffering they have endured. We would also like to thank the health professional from the virology department of CMC, Vellore, for providing help in viral PCR analysis. We are extremely grateful to Matthews Mathai, Chair in Maternal and Newborn Health, Department of International Public Health, Liverpool School of Tropical Medicine, for his valuable inputs and critical revision of the manuscript. We also thank Nandhini. K and project staff Alice Rani for research assistance.

Financial support and sponsorship

The study was funded by the Cincinnati Children's Research Foundation (Study ID: 2014-7670).

Conflicts of interest

There are no conflicts of interest.

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