

Original Article

Influenza infections in the 2014–2015 season and pregnancy outcomes

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Introduction: The most recent influenza season saw a prominent infectious burden over a period of six months in the Turkish capital, reminding observers of the pandemic in 2009 year. The aim of the present study was to investigate the consequences of seasonal outbreaks in pregnant women during the 2014–2015 influenza season.

Methodology: Forty-seven pregnant female patients with symptoms of influenza-like illness who were admitted to tertiary perinatal care center in Ankara, Turkey, between October 2014 and May 2015 were included in this case-control study. The subtype determination of influenza was performed with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing. Clinical observations and pregnancy outcomes were compared with respect to subtypes.

Results: Classifications were available for 35 patients, of whom 12 were determined to have influenza A infection, while 10 had influenza B infection. The remaining 13 patients were influenza-negative. Eight of the 22 (36.4%) influenza-positive patients delivered their babies in the preterm period (< 37 weeks). The corresponding rate was 8.3% (1/12) in the influenza-negative group. This difference was not statistically significant ($p = 0.077$).

Conclusions: Preterm deliveries in pregnant women did not differ significantly among influenza-positive and influenza-negative pregnant women in non-vaccinated study population. Further studies with larger sample sizes may provide more supporting results.

Key words: Communicable disease; influenza; outbreak; pregnancy; pregnancy outcome; preterm birth.

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Introduction

Influenza virus, a member of the Orthomyxoviridae family, is a negative-stranded RNA virus containing eight genes that code 16 different proteins. Influenza typing is based on its two surface glycoproteins, located on the envelope: hemagglutinin (HA; 17 types), and neuraminidase (NA; 10 types). The superficial HA protein binds to sialic acid receptor proteins located in the respiratory tract epithelium. After replication is completed, NA is used to release new virions from the host cell to infect more respiratory cells [1].

Influenza infection may lead to medical complications that can become very serious, especially in older people, children, and pregnant women, who are vulnerable to respiratory infections. Therefore, vaccination has become more popular over the last decade in these high-risk groups [2].

Influenza infections (especially H₁N₁, or influenza A) may clinically present as pneumonia in pregnant women, and greater clinical severity leads to more

pregnancy complications. Intensive care unit referrals increased during the most recent influenza seasons [3]. The aim of the present study was to investigate the consequences of seasonal outbreaks during the 2014–2015 influenza season and to review the current literature that refers to this important communicable disease.

Methodology

This case-control study included 47 pregnant Caucasian women who presented to Zekai Tahir Burak Women's Healthcare Training and Research Hospital (a tertiary care center for maternal-fetal medicine and perinatology) between October 2014 and May 2015 with influenza-like illnesses. The Institutional Review Board approved the study. The inclusion criteria were at least one antenatal care visit and the presence of influenza-like illness. The exclusion criteria were as follows: unavailable medical data; bacteria-positive throat, blood, urinary, or cervical cultures; any

influenza-like illness before pregnancy; or any chronic systemic disease, such as hypertension, diabetes, or asthma.

The diagnosis of influenza-like illness depended on the presence of a cough, sore throat, myalgia, symptoms of upper and/or lower airway infection such as dyspnea, fever of >39 °C, and decreased arterial oxygen saturation. The latter three symptoms were previously evaluated to determine the severity and prognosis of the disease [4].

All of the participants were closely followed in high-risk pregnancy clinic and their medical records were evaluated. All of the hospitalized patients gave informed consent for participation in the study, and detailed anamnesis was obtained from each patient.

The subtype determination of influenza was performed using nasopharyngeal swab samples for real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing before any medication was administered. The determination of viral subtype could not be performed in 12 of 47 patients, as they presented to the hospital on weekend days when laboratory staff was not available to perform the analysis. Twelve of the remaining 35 women were determined to have influenza A, 10 had influenza B, and 13 had no influenza infection. After excluding patients who had undetermined subtypes, the following three groups were defined: influenza A, influenza B, and influenza-negative.

During the waiting period for subtype detection, oseltamivir (a neuraminidase enzyme inhibitor) was empirically prescribed in doses of one 75-mg tablet orally every 12 hours for subjects who manifested symptoms of influenza, based on the recommendations of the United States Centers for Disease Control and Prevention (CDC) [5].

Maternal adverse outcomes were defined as admission to the maternal intensive care unit (MICU) or a clinical diagnosis of pneumonia. Neonatal adverse outcomes were defined as admission to the neonatal intensive care unit (NICU), a need for mechanical ventilation, birth weight of < 2500 g (low birth weight), and gestational age at birth of < 37 weeks (preterm birth).

Statistical analyses and data compilations were performed using Statistical package for the Social sciences (SPSS) for Windows version 16.0 (SPSS, Inc., Chicago, USA). Distributions of variables were determined with the Kolmogorov-Smirnov test and histogram curves. Continuous variables were expressed as mean±standard deviation (SD) or median (range), and dual comparisons were performed using the

independent-sample t-test or the Mann-Whitney U-test. One-way ANOVA and Kruskal-Wallis analyses of variance were used for multi-group comparisons of continuous variables. Categorical variables were expressed as numbers (percentages), and compared using the Chi-square (χ^2) or Fisher's exact test. Pearson's correlation coefficients were calculated for normally distributed continuous variables, and Spearman's correlation coefficients were calculated for non-normally distributed continuous variables. For all tests, a two-tailed *p*-value of <0.05 was considered as significant.

Results

None of the patients had previously received vaccinations for influenza A (H₁N₁) or any other type. Two of the patients had anemia, both with hemoglobin values of 8 g/dL. The distribution of the participants' individual characteristics is shown in Table 1, and a comparison of individual characteristics among the three groups is shown in Table 2.

One of the patients who had a negative PCR test was diagnosed at 5 weeks of gestation, but the embryo spontaneously aborted at 7 weeks. None of the women required mechanical ventilation. The distribution of admissions to the MICU is shown in Table 3. The patients who required admission to the MICU were all diagnosed with pneumonia. The preterm birth rates were similar among the three groups (Table 3). The maximum leukocyte counts in the whole influenza

Table 1. Distribution of individual characteristics of the 47 subjects with influenza-like illness.

Variable	Distribution
Age (years)*	30.06 ± 5.85
BMI (kg/m ²)*	26.60 ± 4.84
GW at admission (weeks)**	27.57 (5 – 39.57)
Maximum leukocyte count (per mL)**	10,800 (4,600 – 27,500)
Hemoglobin (g/dL)*	11.85 ± 1.4
Gravidity**	3 (1 – 11)
Parity**	1 (0 – 9)
Abortus**	0 (0 – 3)
GW that pregnancy ended (weeks)**	38 (7 – 41)
Birth weight (g)*	3033.47 ± 529.95
Apgar1**	7 (5 – 9)
Apgar5**	9 (7 – 10)
LOS - first hospitalization (hours)**	120 (48 – 280)
LOS - final hospitalization (hours)**	47 (24 – 143)

*Mean ± standard deviation; ** Median (range); Abbreviations: Apgar1, Apgar score at 1 min; Apgar5, Apgar score at 5 min.; BMI, body mass index; GW, gestational week; LOS, length of stay.

Table 2. Comparison of individual characteristics among groups (according to influenza subtype).

Variable	Influenza A (n = 12)	Influenza B (n = 10)	Influenza-negative (n = 13)	p value
Age (years)*	27.66 ± 6.82	32.7 ± 3.91	31.3 ± 5.76	0.113
BMI (kg/m ²)*	24.86 ± 2.23	26.87 ± 4.89	27.88 ± 5.13	0.220
GW at admission (weeks)**	28.5 (13.28 – 36.57)	24.07 (9 – 39.57)	25.28 (5 – 38.28)	0.915
Maximum leukocyte count (per mL)**	9300 (4600 – 17500)	9150 (5900 – 17600)	12900 (5200 – 27500)	0.060
Body temperature (°C)**	38.25 (37 – 39.5)	37.65 (37 – 39.1)	37.5 (37 – 39)	0.148
CRP _{max} (mg/L)**	23.5 (7.4 – 78)	34.15 (11 – 79)	40 (8 – 106)	0.551
Hemoglobin (g/dL)*	12.05 ± 1.74	11.95 ± 1.47	11.33 ± 1.29	0.443
Gravidity**	2.5 (1 – 4)	3 (1 – 6)	2 (1 – 4)	0.151
Parity**	1 (0 – 2)	2 (0 – 3)	1 (0 – 3)	0.093
Pr. abortion**	0 (0 – 1)	0.5 (0 – 2)	0 (0 – 1)	0.377
GW that pregnancy ended (weeks)**	37.64 (31 – 40)	38.14 (35.28 – 39.71)	38.43 (7 – 41)	0.607
Birth weight (g)*	2815 ± 713.93	3189 ± 490.11	3074.16 ± 350.67	0.261
Apgar1**	7 (6 – 9)	7 (5 – 8)	7.5 (7 – 9)	0.239
Apgar5**	9 (8 – 10)	9 (7 – 10)	9.5 (9 – 10)	0.285
LOS - first hospitalization (hours)**	144 (48 – 280)	120 (72 – 249)	96 (48 – 144)	0.146
LOS - final hospitalization(hours)**	48 (24 – 115)	30 (25 – 80)	30 (24 – 100)	0.442

*One-way ANOVA test; **Kruskal-Wallis test; Abbreviations: Apgar1, Apgar score at 1 min.; Apgar5, Apgar score at 5 min.; BMI, body mass index; CRP_{max}, maximum C-reactive protein value; GW, gestational week; LOS, length of stay; Pr., previous.

positive group (median 9,300/mL; range 4,600–17,600) were significantly lower than in the influenza-negative group (median 12,900/mL; range 5,200–27,500) (p = 0.018). Other continuous variables did not differ significantly between these two groups. Eight of the 22 influenza-positive patients (36.4%) delivered their

babies in the preterm period (<37 weeks). The corresponding rate was 8.3% in the influenza-negative group (one of 12 patients). The difference between these two groups was not statistically significant in terms of preterm birth rates ($\chi^2 = 3.134$; p = 0.077). Other categorical variables did not differ significantly

Table 3. Distribution and comparison of categorical data among groups.

Variable		Influenza A (n = 12)	Influenza B (n = 10)	Influenza-negative (n = 13)	p value
MICU	Yes	3 (25%)	1 (10%)	2 (15.4%)	NS
	No	9 (75%)	9 (90%)	11 (84.6%)	
Maternal pneumonia	Yes	3 (25%)	1 (10%)	2 (15.4%)	NS
	No	9 (75%)	9 (90%)	11 (84.6%)	
Preterm birth	Yes	5 (41.7%)	3 (30%)	1 (8.3%)	NS
	No	7 (58.3%)	7 (70%)	11 (91.7%)	
EP	S. abortion	0	0	1 (7.7%)	NS
	CS	7 (58.3%)	3 (30%)	5 (38.5%)	
Indications for CS	Vaginal delivery	5 (41.7%)	7 (70%)	7 (53.8%)	NS
	Fetal distress	2 (28.6%)	0	1 (20%)	
	Pr. utx. surgery	2 (28.6%)	1 (33.3%)	3 (60%)	
	Malpresentation	2 (28.6%)	1 (33.3%)	0	
	Mech. reasons	1 (14.3%)	0	1 (20%)	
Gender of baby	U.C. prolapse	0	1	0	NS
	Male	8 (66.7%)	4 (40%)	5 (41.7%)	
Need for NICU	Female	4 (33.3%)	6 (60%)	7 (58.3%)	NS
	Required	3 (25%)	1 (10%)	0	
Neonatal mech. V.	Not required	9 (75%)	9 (90%)	12 (100%)	NS
	Required	1 (8.3%)	0	0	
	Not required	11 (91.7%)	10 (100%)	12 (100%)	

CS, cesarean section; EP, end of pregnancy; Mech., mechanical; MICU, maternal intensive care unit; NICU, neonatal intensive care unit; NS, not significant; Pr., previous; S, spontaneously; U.C., umbilical cord; utx., uterine; V., ventilation.

between these two groups. Six of eleven preterm neonates required admission to the NICU, one of whom required mechanical ventilation. No maternal or neonatal deaths were observed in this study population.

A linear regression analysis was performed to determine the predictive values of the independent variables for maternal adverse outcomes in the influenza-positive group. This analysis showed no significant colinearity (Table 4).

Discussion

The influenza outbreak during the 2014–2015 season was similar to the 2009 H₁N₁ pandemic, as the occurrence of upper airway infections requiring hospitalization increased again after being lower during the intervening years. In the present study, the preterm birth rate was 36.4% in the influenza-positive group, higher than in the influenza-negative group (8.3%). The general preterm birth rate in Turkey was reported as 12% in a worldwide study, although the difference between the influenza-positive and -negative groups was not significant [6]. Results of the present study are consistent with those of a study by Naresh *et al.* on the perinatal outcomes of influenza infection, which showed a preterm delivery rate of 25% in the influenza group versus 11.6% in the control group [7].

A study on the 2009 H₁N₁ pandemic in Singapore by Lim *et al.* concluded that pregnant women were more likely to require hospitalization than their non-pregnant counterparts [8]. The increased vulnerability of pregnant women can be attributed to physiologic changes of the respiratory and immunological systems during pregnancy. These changes include an altered form of the thoracic space, dyspnea, increased oxygen consumption and tidal volume, decreased functional residual capacity, decreased cellular immunity that is crucial for the survival of the fetus, and increased vulnerability to all respiratory pathogens, including

influenza [9,10]. In seriously ill pregnant women, symptoms related to viral upper-airway infections (fever, cough, sore throat, and myalgia) may be exaggerated, and a fever of >39 °C and decreased arterial oxygen saturation may be present.

Most of hospitalized patients in the present study were in their late second or early third trimester of pregnancy, while only a few were in the first trimester. The population of a multicenter observational cohort study by Varner *et al.* was similar to ours in terms of gestational stage at the time of hospital admission [3].

Vulnerability to congenital abnormalities in babies whose mothers experience an influenza-like illness during pregnancy was highlighted in a recent meta-analysis by Luteijn *et al.* According to that study, neural tube defects, hydrocephaly, congenital heart defects (predominantly aortic valve atresia/stenosis), cleft lip, and limb-reduction defects were more frequently seen in this infant population compared to those whose mothers did not experience influenza-like illnesses [11]. Moreover, studies from Denmark [12] and California [13] reported that the offspring of mothers with influenza infections during pregnancy had an increased risk of schizophrenia later in life. No congenital malformations were detected in the present study population; however, long-term effects may be expressed in late-onset diseases.

Sokolow *et al.* demonstrated that influenza infections cause more severe clinical symptoms and complications than non-influenza acute respiratory illnesses [14]. The clinical importance of this is obvious. Although influenza B was reported to cause milder disease than influenza A [15], some studies have found similar severities between influenza A and B infections [14,16]. The present study also identified no difference between the clinical severities of influenza A versus B.

Table 4. Linear regression analysis showing predictive values of independent variables for maternal adverse outcomes in influenza-positive pregnant patients.

Model (maternal adverse outcomes)	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. error	Beta		
Age (years)	-0.024	0.027	-0.296	-0.877	0.406
Gravidity	-0.087	0.072	-0.393	-1.209	0.261
BMI (kg/m ²)	-0.029	0.020	-0.444	-1.401	0.199
Maximum leukocyte count (per mL)	-2.942	0.000	-0.031	-0.089	0.932
Hemoglobin (g/dL)	0.048	0.074	0.226	0.655	0.531
CRP _{max} (mg/L)	-0.007	0.004	-0.518	-1.712	0.125
Body temperature (°C)	-0.039	0.144	-0.096	-0.272	0.793
GW at admission (weeks)	-0.012	0.010	-0.388	-1.189	0.268
GW that pregnancy ended (weeks)	-0.048	0.063	-0.261	-0.765	0.466

Abbreviations: BMI, body mass index; CRP_{max}, maximum C-reactive protein value; GW, gestational week.

Influenza infections may result in long-term admissions to the intensive care unit and even maternal death. When the medical complications and financial burden are taken into account, the significance of influenza is clear. Thus, underestimations based on the assumption that influenza is “a simple viral upper airway infection” should be replaced by efforts to overcome this disease and minimize the amount of suffering it causes. Seasonal vaccinations must be universalized. Influenza vaccinations have been recommended for pregnant women in any trimester as the highest-priority group by the CDC since 2004, the World Health Organization since 2005, and the American Congress of Obstetricians and Gynecologists since 2010 [17].

The historically very low use of this vaccination in Turkey (approximately 9% of pregnant women) might have led to greater suffering during the recent 2014–2015 outbreak [18]. In contrast, due to public health policy, Brazil has reached a level of H₁N₁ vaccinations in 77% of all pregnant women, higher than in many developed countries. This was achieved with an immense vaccination campaign, the participation of primary health care facilities, and the effective use of all possible media sources [19]. Healthcare policies must promote vaccinations in a timely manner and provide easy access; otherwise, non-vaccinated pregnant women may suffer from the unpredictable complications of this preventable communicable disease.

The safety of the flu vaccine was proven in a study involving a cohort of 21,087 singleton pregnant patients in Sweden [20]. The issue was recently reviewed by McMillan *et al.*, who found that maternal influenza vaccination during pregnancy does not pose a risk to fetal health [21]. Other studies have also reported fewer premature or small-for-gestational-age (SGA) newborns among mothers who were vaccinated against influenza A during pregnancy [22,23]. In a recent meta-analysis, it was reported that vaccinated pregnant women experienced stillbirths more rarely than non-vaccinated ones, and spontaneous abortion was less frequent in vaccinated pregnant women (RR=0.91; 95% CI: 0.68–1.22) compared to non-vaccinated women [2].

A recent study in animal studies with pregnant gilts revealed no evidence of viremia or transplacental transmission when viral particles were inoculated intranasally; there was no sign of fetal exposure [24]. The absence of severe neonatal adverse events in the present study could be attributed to the absence of transplacental transmission.

Another important factor is the use of oseltamivir as an antiviral therapy in the management of influenza. Animal studies on the safety of oseltamivir during pregnancy revealed no adverse fetal developmental problems [25]. The CDC recommends administration of oseltamivir within 48 hours of symptom onset at a dose of one 75-mg tablet orally every 12 hours [5]. In the present study, antiviral therapy was prescribed to each patient as soon as possible, based on the experience of the 2009 pandemic. Serious maternal complications and admissions to the intensive care unit were less frequent compared to the 2009 pandemic, and none of patients required mechanical ventilation. These observations highlight the importance of early antiviral treatment; the H₁N₁ subtype, which typically causes more severe clinical problems, probably remained quiescent due to this early prescribed therapy. The importance of early treatment with oseltamivir was similarly demonstrated in a multicenter study by Varner *et al.* [3]. General recommendations for communicable diseases should also be undertaken in patients with influenza-like illnesses, including appropriate hygiene, contact isolation, early diagnosis, and early treatment.

Possible limitations of this research include problems with the study design, sample size, and the absence of a control group with no clinical features of influenza infection. The effects of the flu vaccine on pregnant women could not be accessed as this vaccination is not widespread in Turkey because it is not covered by medical insurance and public education about its importance is scarce.

Conclusion

Individual characteristics did not differ significantly among the influenza subtypes and the influenza-negative pregnant women in non-vaccinated study population. Preterm birth was more frequent in the influenza-positive group than in the influenza-negative group, but the difference between them was not statistically significant. Nevertheless, national and worldwide vaccination campaigns against influenza should be promoted, and broad investigations should be carried out on the pathogenesis of preterm labor in pregnant women with influenza.

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