

## Original Article

Pandemic influenza H1N1 2009 virus infection in pregnancy in Turkey<sup>☆</sup>

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**Abstract**

**Objectives:** To describe the clinical characteristics of the pregnant women who were hospitalized in a tertiary referral hospital with pandemic influenza H1N1 2009 virus infection and neonatal outcomes from October 2009 to December 2009 during which the pandemic influenza cases peaked in Turkey.

**Materials and Methods:** Twenty-five pregnant women who were hospitalized with influenza-like illness and who had laboratory confirmation for pandemic influenza H1N1 virus infection were evaluated prospectively.

**Results:** Of the 25 patients, 4 (16%) were in the first trimester, 8 (32%) were in the second trimester, and 13 (52%) were in the third trimester. The median time from the onset of symptoms to the initiation of antiviral therapy was 1 day (range 1–9 days). Nineteen (76%) patients received oseltamivir treatment. It took 1.6 days on the average for the fever defervescence after the initiation of treatment or hospitalization. Of the 14 patients who underwent chest radiography, three had findings consistent with pneumonia. The mean duration of hospitalization was 4.8 days. Four women (16%) were admitted to an intensive care unit, but there were no maternal or neonatal deaths in this series. At the time of their H1N1 hospitalization, seven women delivered by cesarean at 33–40 weeks gestation, two vaginally at 38 weeks gestation, and two had an abortion at 10 weeks and 16 weeks of gestation, respectively. None of the infants had any evidence of influenza infection.

**Conclusion:** Pregnant women are at increased risk for complications from pandemic influenza H1N1 virus infection. Timely medical attention with early recourse to antiviral therapy is associated with a better outcome in H1N1-affected pregnant women.

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**Keywords:** H1N1; Influenza; Neonatal outcomes; Pregnancy

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**Introduction**

Pandemic influenza H1N1 2009 virus infection caused a widespread outbreak of respiratory infection. The virus, which originated in Mexico, has spread to nearly 191 countries and territories worldwide. On April 15 and April 17, 2009, Centers for Disease Control and Prevention (CDC) identified the first two cases of infection in the United States [1]. The

novel virus contained a unique combination of gene segments that had not been identified before [2,3].

The cases of the current pandemic presents with mild symptoms, such as body aches, fatigue, chills, rhinorrhea, conjunctivitis, shortness of breath, headache, and gastrointestinal (GI) symptoms. Unlike seasonal influenza, GI symptoms, such as diarrhea and vomiting, appear more frequently [2]. Besides these symptoms, pregnant women tend to present with fever, cough, and/or sore throat [4]. Pregnant women experience shortness of breath more often than nonpregnant cases.

During both interpandemic seasonal influenza and previous pandemics, it is found that pregnant women and fetus are at increased risk for complications [5]. During the period of April 15, 2009–June 16, 2009, CDC reported 45 deaths from H1N1 infection; 6 (13%) of these individuals were pregnant

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<sup>☆</sup> There are no potential conflicts of interest.

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[6]. Of these six deaths, one died during her first trimester, one during the second, and the remaining four during the third trimester. All of them were previously healthy pregnant women. They developed viral pneumonia and subsequently acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. The CDC has implemented enhanced surveillance for infection with H1N1 in pregnant women because of the concerns about the severity of the disease during pregnancy [4].

This report summarizes the cases of pandemic H1N1 influenza virus infection in pregnant women who were hospitalized in a tertiary referral hospital from October 2009 to December 2009, during which the pandemic influenza cases peaked in our country.

## Materials and methods

The study was conducted in a tertiary referral hospital and was approved by the institutional review board. We describe 25 pregnant women who were hospitalized in the perinatology department for at least 24 hours with an influenza-like illness (fever, cough, and/or sore throat) from October 2009 to December 2009. All cases had laboratory confirmation for pandemic H1N1 virus infection by real-time reverse transcriptase polymerase chain reaction. The symptomatic patients were isolated from other pregnant women during hospitalization. The demographic data, information about the current pregnancy, clinical signs, symptoms, laboratory tests, radiographic findings, treatment courses, the time from onset of symptoms to initiation

of treatment, the duration of fever, and maternal and fetal outcomes were noted.

## Results

Population of Turkey was 72,561,312 on December 31, 2009 [7]. The number of pregnant women was estimated by using the following formula [6]: the fertility rate (76 per 1000 women of reproductive age) was multiplied by nine-twelfths of the population of women of reproductive age (15–49 years of age), which is 19,493,140 [7] because pregnancy lasts roughly 9 months. The abortion rate (20 per 1000 women of reproductive age) was also multiplied by a sixth of the population of women of reproductive age because these pregnancies last an average of 2 months. These numbers are added together to estimate the number of women who are pregnant, which gives the number of 1,176,085. It was reported that 3% of hospital admissions were because of influenza-like illness during the study period [8]. From October 22 to December 31, 2009, a total of 605 deaths occurred because of H1N1 influenza virus infection (mortality rate 8.3 per million) [9]. Among these deaths, 36 of them were pregnant and postpartum women (30.6 per million) [10]. Mortality rate is reported to be three times more in pregnant and postpartum women. This report describes the pregnant women who were hospitalized with H1N1 influenza virus infection in a tertiary referral hospital in Turkey. From October 1, 2009 to the end of December 2009, 10,755 pregnant women were admitted to the hospital. Among these pregnant women, 1031 had the

Table 1  
Patients' age, gestational age, pregnancy, and labor characteristics

Case	Age	Gestational age at hospital admission	Additional complications at hospital admission	Pregnancy outcome	Neonatal outcome
1	28	23	Preterm labor	—	—
2	22	10	—	—	—
3	24	22	—	—	—
4	17	8	Threatened abortion	—	—
5	23	40	—	Delivered by cesarean	3680 g, Apgar 7/9
6	27	35	Fetal tachycardia	—	—
7	18	32	Twin-preterm labor	—	—
8	22	39	Fetal tachycardia	Delivered by cesarean	3550 g, Apgar 7/9
9	23	17	—	—	—
10	31	17	—	—	—
11	22	16	Threatened abortion	Abortion	—
12	26	38	—	Delivered vaginally	2770 g, Apgar 7/9
13	25	7	Emesis gravidarum	—	—
14	24	37	—	Delivered by cesarean	3250 g, Apgar 7/9
15	34	36	Oligohydramnios	Delivered by cesarean	2320 g, Apgar 8/10
16	27	30	—	—	—
17	28	31	—	—	—
18	27	38	Oligohydramnios	Delivered vaginally	2920 g, Apgar 7/9
19	37	36	Asthma, HT	Delivered by cesarean	3000 g, Apgar 7/9
20	21	29	Preterm labor	—	—
21	36	10	—	Dilatation and curettage	—
22	22	27	Preterm labor	—	—
23	33	33	Thrombocytopenia	Delivered by cesarean	2060 g, Apgar 7/9
24	26	36	Fetal tachycardia	Delivered by cesarean	2740 g, Apgar 7/9
25	33	22	—	—	—

HT = hypertension.

Table 2  
Presenting manifestations in pregnant cases with pandemic H1N1 influenza virus infection

Symptom	Pregnant women (n = 25), n (%)
Fever	23 (92)
Cough	22 (88)
Sore throat	20 (80)
Myalgia	19 (76)
Dehydration	16 (64)
Vomiting	3 (12)
Dyspnea/tachypnea	2 (8)
Diarrhea	1 (4)

symptoms of influenza. In 61 of them, 2009 H1N1 influenza virus infection was confirmed with real-time reverse transcriptase polymerase chain reaction. A total of 25 pregnant women were hospitalized during this study period. The mean age of the patients was 26.2 years (range, 17–37 years). Nine (36%) women were primigravidas and 16 (64%) women were multigravidas. There were eleven (44%) nulliparous and 14 (56%) multiparous women. Of the 25 patients, 4 (16%) were in the first trimester, 8 (32%) were in the second trimester, and 13 (52%) were in the third trimester. The mean gestational age at admission was 26.7 weeks (range, 7–40 weeks) (Table 1). All of the patients were nonsmokers. Only one patient had underlying medical condition of asthma and hypertension. Eight (32%) women reported close contact with a family

member with influenza-like illness or pneumonia. None of the women reported a recent travel abroad. Common symptoms at presentation included fever, cough, sore throat, myalgia, vomiting, diarrhea, dyspnea, tachypnea, and dehydration. Fever more than 37.5°C was reported in 92% (n = 23), cough in 88% (n = 22), sore throat in 80% (n = 20), myalgia in 76% (n = 19), dehydration in 64% (n = 16), vomiting in 12% (n = 3), dyspnea and tachypnea in 8% (n = 2), and diarrhea in 4% (n = 1) of the patients (Table 2). On admission, eight (32%) of the patients had anemia and four (16%) had leukopenia. The median oxygen saturation level on admission was 97% (range, 92–99%) (Table 3).

The median time from the onset of symptoms to the initiation of antiviral therapy was 1 day (range, 1–9 days). Nineteen (76%) patients received oseltamivir treatment 75 mg twice daily for 5 days (Tamiflu; Roche, Turkey). Three of the six patients who did not receive treatment refused to use antiviral medication. Three other patients were also not treated for the following reasons; fever resolved spontaneously on the same day in one of them, the symptoms were subtle in the other, and the third one had symptoms lasting for 9 days and the fever subsided when she was admitted. These three patients received only symptomatic treatment during hospitalization. Antibiotic treatment was given to the patients in the intensive care unit (ICU) because they had high fever (>39°C) with infiltrations on chest X-ray. It took 1.6 days on the

Table 3  
Laboratory findings, the time from symptom onset to initiation of treatment, and the duration of fever after the initiation of treatment or hospitalization

Patient	WBC ( $\times 10^6/L$ )	Hb (g/L)	ALT (IU/L)	AST (IU/L)	Temperature (°C)	O <sub>2</sub> saturation (%)	Oseltamivir (d) <sup>a</sup>	The duration of fever (d) <sup>b</sup>	Duration of hospitalization (d)
1	10.600	12.7	15	27	38	97	3	2	3
2	5.500	10.1	11	17	39.5	98	No treatment	4	7
3	15.800	13.4	10	18	38.4	97	1	1	2
4	8.200	12.4	5	19	38.7	98	5	2	6
5	10.400	12.3	18	22	37.5	98	1	1	5
6	10.500	11.9	20	20	38	96	1	1	3
7	8.000	10.9	92	28	38.2	96	No treatment	1	3
8	12.000	14	17	17	38.1	96	4	2	4
9	8.100	11.7	13	6	37.5	98	2	1	4
10	5.100	11.3	45	58	38	95	No treatment	4	8
11	9.000	11.9	30	38	39.6	95 → <80	4	3	10
12	8.000	10.8	22	14	38.2	98	2	2	3
13	6.900	12.9	29	26	38	99	4	2	7
14	8.900	8.7	32	20	38.3	94	3	2	4
15	6.800	8.1	17	40	39.2	96 → 88	1	3	10
16	8.200	10.2	10	20	38.8	98	3	1	5
17	5.600	11.2	27	26	38.7	92	2	1	4
18	10.700	11.3	6	15	39	98	1	3	7
19	7.600	11.9	18	24	37.4	92	1	1	5
20	10.800	11.2	22	31	36.8	99	No treatment	No fever	3
21	5.000	11.6	28	30	38	97	1	1	5
22	7.000	11.1	15	18	37.6	99	No treatment	1	2
23	8.000	7.4	16	34	37	98	No treatment	No fever	3
24	10.200	11.6	12	20	38.5	97	1	1	2
25	6.500	9.9	25	25	38	96	1	2	5

O<sub>2</sub> saturations are in room air values.

Patient IDs in Tables 1 and 3 matches.

<sup>a</sup> Time from symptom onset to initiation of treatment.

<sup>b</sup> The duration of fever after the initiation of treatment or hospitalization.

ALT = alanine transaminase; AST = aspartate transaminase; Hb = hemoglobin; WBC = white blood cell.

average for the fever defervescence after the initiation of treatment or hospitalization.

Of the 14 patients who underwent chest radiography, three had findings consistent with pneumonia. Two of these patients had bilateral diffuse infiltrates, one patient had infiltrate limited to lower zones.

#### *Patients admitted to ICU*

Of the 25 patients evaluated, four (16%) were admitted to an ICU. One of these patients was a 37-year-old woman at 36 weeks' gestation. She had underlying asthma and hypertension with severe dyspnea. Two patients developed pneumonia and ARDS. One of them was a 22-year-old woman at 16 weeks' gestation who presented with symptoms of fever, cough, sore throat, myalgia, dehydration, dyspnea, and tachypnea lasting for 4 days. She had bilateral diffuse infiltrates on chest X-ray. Oxygen saturation level was 95% on admission. She had vaginal bleeding, which led to abortion on the next day of hospitalization. Oxygen saturation level decreased to 80%. She was admitted to ICU with pneumonia and subsequently developed ARDS. The other woman with ARDS was 34-year-old at 36 weeks' of gestation. She was hospitalized with the diagnosis of intrauterine growth restriction; oligohydramnios; and flu-like symptoms of fever, cough, sore throat, myalgia, and dehydration. She refused to take oseltamivir at first. She delivered a 2320 g infant by caesarean section. In the post-partum period, she developed dyspnea and tachypnea. Chest X-ray demonstrated diffuse bilateral infiltrates. Oxygen saturation level decreased to 88%. Oseltamivir was initiated after the patient's approval. She was admitted to ICU. She remained intubated for 2 days in ICU. Fourth woman who was sent to ICU was 28-year-old at 31 weeks' of gestation presented with fever, cough, and sore throat. Chest X-ray showed infiltrates in the lower zone of the right lobe. Oxygen saturation level was 92%. All the patients in the ICU showed gradual improvement in their follow up and were discharged. The mean duration of hospitalization was 4.8 days. There was no maternal death.

At the time of their H1N1 hospitalization, seven women delivered by cesarean at 33–40 weeks gestation, two vaginally at 38 weeks gestation, and two had an abortion at 10 weeks and 16 weeks gestation, respectively. Four patients who did not deliver at the time of their H1N1 hospitalization had threaten of preterm labor with symptoms of pelvic pressure, low back pain, and uterine contractions. These patients were treated with bed rest, sedation, and hydration in the hospital. Fourteen patients had ongoing pregnancies. Neonatal outcomes are given in Table 1. None of the infants had any evidence of influenza infection.

#### **Discussion**

Influenza viruses that cause infection in mankind are classified as A, B, and C types. Although influenza A and B are associated with seasonal epidemics, only influenza A is responsible for pandemics. Influenza A virus have basic surface proteins, hemagglutinin, and neuraminidase. Minor mutations

of these proteins occur continuously. More dramatic changes in the surface proteins through either mutation of nonhuman viruses or reassortment of human and nonhuman viruses result in creation of novel human subtypes (antigenic shift) [4]. The novel H1N1 Type A influenza virus is responsible for the current pandemic. It contains a unique combination of gene segments that had not been identified before [2,3].

Respiratory droplets are the main route of transmission. It can also be transmitted via direct contact with contaminated surfaces and by other body fluids [11,12].

The clinical features of patients who were hospitalized with H1N1 2009 influenza were generally similar to those reported during peak periods of seasonal influenza and past pandemics with an acute onset of respiratory illness [13,14]. Also, the symptoms reported by the pregnant women were similar to those reported by the nonpregnant general population. Unlike seasonal influenza, the GI symptoms, such as diarrhea and vomiting, appear more frequently. More specifically, pregnant women tend to present with fever, cough, and/or sore throat. These symptoms were reported in 92%, 88%, and 80% of patients in our study, respectively.

We report the cases of hospitalized pregnant women with H1N1 2009 influenza virus infection during the 3 months, October–December, 2009. On the basis of the present studies, pregnant women seem to be at increased risk for complications from pandemic H1N1 influenza virus infection, with a higher estimated rate of hospital admission than in the general population [6]. In a large epidemiological study from 1998 evaluating the rate of influenza-related complications over 17 influenza seasons in women, it is reported that a high risk for hospitalization is for influenza-related reasons in low-risk pregnant women during the last trimester of pregnancy [15]. The decreased colloidal oncotic pressure in the third trimester of normal gravid participants when compared with normal nongravid participants supports the increased propensity for severe respiratory complications during this time [16]. Decreased oncotic pressure predisposes gravid women to develop pulmonary edema. Thirteen of the 25 patients (52%) hospitalized in our study were in the third trimester.

Eight (32%) women in the study had close contact with a family member with influenza-like illness or pneumonia. Sixty-eight percent of the women had no epidemiological link (travel or contact) with the virus.

In the previous influenza pandemics of 1918 and 1957, mortality seemed to be higher in pregnant women than in nonpregnant population. All six deaths reported in the present outbreak in healthy pregnant women is also noteworthy. Although it is expected that the effects of the infection were greatest in the women with underlying disease, in our study, only one woman admitted to ICU had a history of asthma. That patient had normal chest X-ray. Three patients who developed pneumonia and admitted to ICU were healthy pregnant women, but one of the patients in ICU had symptoms lasting for 4 days before admission to hospital and the other patient refused to take antiviral medication at first. These factors caused a delay in the initiation of the treatment and might be responsible for the rapid progression of the disease.

But most of the women exhibited a milder disease process with a stable course. In a recent study involving large series of pregnant and postpartum patients who were hospitalized with or died from 2009 H1N1 influenza, 95% of the pregnant patients were infected in the second or third trimester, and almost one-fifth required intensive care [17].

The novel H1N1 2009 influenza virus is sensitive to neuraminidase inhibitors oseltamivir and zanamivir. The benefits of treatment with these antiviral drugs outweigh its theoretical risk. Current CDC guidance suggests that antiviral treatment is recommended for groups at high risk for influenza complications from infection with H1N1 2009 influenza virus, including pregnant women. Because of its systemic activity, the drug of choice for pregnant women is oseltamivir. Ideally, it is recommended to give the treatment within the first 48 hours of symptoms. It can reduce mortality in patients even when started more than 48 hours after the onset of symptoms [6]. Nineteen of the 25 patients (76%) in our study accepted antiviral treatment, whereas only 3 patients refused to use the drug because of concerns about the fetus. The median time from the onset of symptoms to the initiation of antiviral therapy was 1 day (range, 1–9 days). In 12 (48%) patients, antiviral treatment was started within 48 hours of symptom onset. It took 1.6 days on the average for the fever to subside after the initiation of treatment or hospitalization. The mean duration of hospitalization was 4.8 days. For the patients who refused to take antiviral treatment, the mean duration of fever to subside and the mean duration of hospitalization was longer, 4 days and 6 days, respectively. For the six deaths reported by CDC from April 15 to June 16, 2009, the length of time from symptom onset to receipt of antiviral treatment ranged from 6 days to 15 days with a median of 9 days. This shows that early admission, diagnosis, and treatment of influenza gives better results in pregnant women.

The effects of maternal influenza on the fetus are not well understood. Viremia is believed to occur infrequently [18] and thus vertical transmission appears to be rare [19]. None of the fetuses born to the mothers infected with the virus have any evidence of influenza infection. Even in the absence of placental transmission, the fetus could be adversely affected by influenza and its effects. Maternal first-trimester hyperthermia is related with neural tube defects [20]; birth anomalies, such as cleft lip/palate; and congenital heart defects [21–23]. Fever during labor may cause neonatal seizures, encephalopathy, cerebral palsy, and even neonatal death [24,25]. Acute pyrexia and hypoxia can be associated with fetal tachycardia, minimal variability, and decelerations in the fetal heart rate. Thus treatment of fever with acetaminophen is recommended. Fetal complications are related to the perturbations in maternal physiology and the accompanied fetal stress response, such as preterm premature rupture of membranes, preterm labor, and preterm birth. The additional complications in the current pregnancies of the patients at admission included threaten of preterm labor in four, fetal tachycardia in three, threaten of abortion in two, nonreactivity on fetal cardiotocography in two, and oligohydramnios in two patients. This suggests that the fetuses of the ill-pregnant

patients are under risk of adverse outcomes. Because most women in the study are still pregnant, little is known about the effects of virus on the fetus.

The CDC have listed pregnant women as a priority group for vaccination [26]. The pregnant women are at a higher risk for complications and can also potentially provide protection to infants who cannot be vaccinated via the transfer of maternal antibodies to the fetus. On September 15, 2009, four influenza vaccine manufacturers received approval from the Food and Drug Administration for their novel influenza A H1N1 2009 monovalent vaccines.

Ethnic-dependent susceptibility to viral infection has been discussed in the current pandemic, which opened a new avenue for the issue. Among the racial and ethnic groups in the United States, American Indians/Alaska Natives have been hospitalized more than any other group, followed by Hispanics, and then Black, non-Hispanics, which suggests that H1N1 2009 influenza virus follows an ethnic pattern. One study from New Zealand reported ethnic-related susceptibilities to H1N1 virus infection [27]. A reasonable explanation for the extremely low case fatality ratio as well as mortality rate in China so far during the H1N1 influenza pandemic may be ethnic-dependent susceptibility, rather than the stringent strategies used in the prevention [28]. In addition to ethnic subgroups, the current H1N1 2009 influenza virus also showed age- and gender-dependent mortality rates different from other subpopulations. Young people and pregnant women have been assumed to be high-risk subpopulations, probably in any ethnic groups [6]. In the present ongoing pandemic outbreak of the H1N1, the identification of the higher susceptibility of young people and pregnant women is a reminder that more medical surveillance of these two subpopulations is required. Additionally, the assessment of susceptibilities among selected groups can help to focus on the prevention and treatment efforts in targeting ethnic groups with high susceptibility [28].

Our experience suggests that timely medical attention with early recourse to antiviral therapy is associated with a better outcome in H1N1 affected pregnant women. Fever more than 39°C and low oxygen saturation levels at admission should alert the clinician about the development of a complication, such as pneumonia, respiratory distress, and these patients should be followed in ICU. It is important to promote strategy of vaccination, basic hygienic prevention, and prompt antiviral treatment of pregnant women who develop influenza symptoms.

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