



Original Article

H1N1 Infection in Pregnancy; A Retrospective Study of Feto-Maternal Outcome and Impact of the Timing of Antiviral Therapy

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Abstract. Background and Objective: H1N1 infection carries an increased risk in pregnancy. Our aim was to study the feto-maternal outcome and the effect of early initiation of therapy.

Methods: This is a retrospective descriptive study. Confirmed infected cases were included. Maternal age, parity, gestational age at diagnosis, presenting symptoms, the time between presentation and starting therapy, ICU admission, and maternal and perinatal outcome were evaluated.

Results: Nineteen confirmed patients were included. Most patients are 31 years old or more. Multiparous patients were 73.68%, and 57.89% were in the third trimester. Most of our patients presented with cough, fever, and chills. Two patients were admitted to the ICU. One of them was a case of maternal mortality. 42.10% of patients were started on therapy only one day after the clinical onset of symptoms. 26.31% delivered before 37 completed weeks. 73.68% delivered beyond term. Around one third delivered vaginally. 45% of babies weighed more than 3 kg. Four babies weighed less than 2 kg. Ninety percent had APGAR scores more than 8 at 1 and 5 minutes after delivery. Twenty-five percent were admitted to the NICU with no neonatal mortalities.

Conclusions: H1N1 influenza A infection in pregnancy is associated with adverse maternal and perinatal outcomes. Medical and public awareness, low threshold for testing suspected pregnant patients, very early initiation of antiviral therapy, and a multidisciplinary approach in our series decreased the overall adverse effects of this infection.

Keywords: Influenza A; H1N1; Neuraminidase inhibitors; Pregnancy; Perinatal; Outcome.

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Introduction. Influenza A viruses are classified based on the viral surface proteins, hemagglutinin (HA or H) and neuraminidase (NA or N) such as H1N1, H5N1. Influenza-like illness caused by a new H1N1 strain (Swine flu) was reported from Mexico in April 2009 and

rapidly spread to all the continents. It appeared to be associated with high mortality. By May 2009, data from the USA and elsewhere showed that its virulence was considerably less than that initially reported in Mexico.¹

There are confirmed cases in Jordan during most seasons both in pregnant and non-pregnant patients.

Data obtained from many countries revealed that old patients seemed to be relatively protected from getting infected. There are, however, certain other vulnerable groups of patients.^{2,3,4,5} They are the same groups that are more vulnerable during seasonal influenza—those with underlying heart disease, lung disease, etc. The unexpected, much higher risk group was pregnancy. Pregnant women had a hospitalization and death rate up to 10 times higher compared to other females in the same age group.^{3,5,6} These data lend support to the present recommendation to promptly treat pregnant women with H1N1 influenza virus infection with anti-influenza drugs.⁵

Reports from the past pandemics (1918-1919) and 2009 outbreaks showed that pregnant women are at risk of complications from the disease.⁷ Pregnancy stage also modified the association between influenza activity and influenza-like illness episodes. Findings estimate that 20-43 pregnant/postpartum women need to be vaccinated with an 80% effective vaccine to prevent one influenza-like illness episode.⁷ In addition, pregnant women are prone to complications such as pneumonia and adult respiratory distress syndrome (ARDS) because the maternal immune system is modified to accommodate the developing fetus, the gravid uterus elevates the diaphragm, and they have congestion and local edema.⁸

There was a 4- times higher rate of hospital admissions in pregnant women compared to the general population.⁵ Among patients with H1N1 virus infection, pregnant women accounted for 6-9% of the intensive care unit (ICU) admissions and 6-10% of patients who died. The risk of death is particularly increased in infected women during the third trimester.^{5,9,10} The excess risk may be limited to women infected in the third trimester and the first four weeks postpartum; however, available data are of low quality.¹¹

Our study is a retrospective descriptive case series that evaluates the clinical course, the effects of various maternal characteristics, and the impact of the timing of antiviral therapy on feto-maternal outcome in H1N1 infected pregnant patients.

Materials and Methods. This is a retrospective descriptive study at the maternal unit in Jordan University Hospital, which is a tertiary referral hospital in Amman, Jordan. We studied positive cases of H1N1 infection in pregnancy and up to 6 weeks postpartum in the period January 2017 to January 2018. All patients who presented to the emergency obstetric unit or the antenatal clinics suspected of having the H1N1 infection were tested by taking throat (pharyngeal) or nasal swabs (special H1N1 swabs), or tracheal aspirate for intubated patients and sent to the laboratory. The indications for H1N1 testing were fever (oral temperature of more than

38°C), cough, sore throat, and shortness of breath. Our laboratory used real time reverse transcriptase polymerase chain reaction (RT PCR) for testing H1N1. During the study period, 68 pregnant patients were tested. 19 patients were confirmed to have H1N1 infection (wherein a confirmed case was defined as an acute respiratory illness with laboratory-confirmed H1N1 virus infection by RT PCR). Once a positive diagnosis was obtained, patients were admitted and isolated. All persons who enter the patients' room put on effective masks, protective surgical gowns, gloves, head caps and shoe covers. The number of visitors allowed was restricted. Waste products were considered biohazards and were disposed of as per hospital policy. All infected patients were further investigated with complete blood count (CBC), kidney function test (KFT), urinalysis and culture, blood culture, and liver function test (LFT). All patients were evaluated for fetal wellbeing using an ultrasound scan (U/S) &/or cardiotocography (CTG) according to their gestational age. All patients were evaluated by the respiratory and infection teams at our hospital. Chest radiograph (CXR) was only performed in selected critical cases as judged by the respiratory consultants. Patients were then closely monitored by vital signs and pulse oximeters. All but one confirmed cases were given neuraminidase inhibitor, Oseltamivir, 75 mg twice daily for 5 days in addition to several other supportive medications (bronchodilators, nasal decongestants, and oxygen therapy). All patients were also started on antibiotics, oral or intra-venous, as dictated by their clinical condition. Data was collected using our hospital's electronic and paper-based systems. The demographic data were obtained for these patients. The following details were noted and studied: maternal age, parity, gestational age at presentation and diagnosis, coexisting medical diseases, presenting symptoms, signs, chest radiographs, time between presentation and starting therapy, need for oxygen, ICU admission, gestational age at delivery, mode of delivery, birth weight, APGAR score, premature delivery, stillbirth, neonatal ICU (NICU) admission and maternal mortality.

Results. Jordan University Hospital is a tertiary teaching hospital in the capital of Jordan, Amman. It has an annual delivery rate of 4,600. These cases were collected between January 2017 and January 2018.

A total of 243 non-pregnant patients and a total of 68 pregnant patients were tested for H1N1 influenza A based on their presenting symptoms. Among the pregnant population, 27 patients (39.70%) were found to be positive for the H1N1.

None of the confirmed cases received the seasonal flu vaccine or specific A/H1N1 2009 influenza vaccine that season (starting September 2017). There were five patients who missed their antenatal care and/or did not

deliver at our unit. Every effort was done to obtain further information about their antenatal course, delivery and neonatal outcome, including telephone calls. Besides, there were three patients who, after obtaining the positive result for H1N1 infection in the second trimester, denied and refused admission and treatment. We could not obtain any further data concerning their pregnancy and delivery.

A total of nine of our patients (47.37%) are of age 31 years or older. Only one patient was less than 20 years of age. The vast majority (14 patients, 73.68%) were multiparous patients. There was one case of twin pregnancy. Eleven patients (57.89%) were infected in the third trimester (57.89%), six patients (31.6%) in the second trimester, one patient (5.3%) in the first trimester and one (5.3%) in the postpartum period. (**Table 1**).

Most of our patients presented with cough, fever, and chills; 17, 16 and 13 patients, respectively. Other causes of fever were excluded by urinalysis and urine and blood cultures. There were also a variety of symptoms including a runny nose, generalized fatigue, shortness of breath, sore throat, sputum, headache, myalgia, and vomiting. Documented fever at presentation was a prominent sign in our patients (14 patients, 73.68%). There are also other physical signs including tachycardia, pharyngitis, wheezes, hypoxia and decreased air entry. One patient had sinus bradycardia (at a rate of 36-40 beats/minute with normal echocardiogram and thyroid function) which was relieved two days after starting antiviral therapy,

Table 1. Patients' characteristics, maternal age, parity and gestational age at diagnosis and presentation.

Age (years)	Number of patients	Percentage (%)
Less than 20	1	5.3%
20-25	4	21.0%
26-30	5	26.3%
31 and above	9	47.4%
Parity		
Primigravida (PG)	5	26.3%
Multigravida (MG)	14	73.7%
Gestational age at diagnosis and presentation (weeks)		
First trimester	1	5.3%
Second trimester	6	31.6%
Third trimester	11	57.9%
Postpartum	1	5.3%

and another patient had hemoptysis (**Table 2**). Chest radiographs were deemed necessary in 3 patients dictated by their clinical situation. The first of them had mild atelectasis, the second had diffuse bilateral ground-glass opacification and pleural effusion, and was admitted to the ICU. She later underwent an urgent

cesarean section due to severe respiratory distress and hypoxia. The third patient had severe infiltration and opacification, and she passed away in the ICU.

Eight patients (42.10%) were started on Oseltamivir therapy, 75 mg twice daily, only one day after the clinical onset of symptoms and they were the patients with no fetomaternal complications. Two patients started antiviral therapy five days after the onset of symptoms (**Table 3**). Both were admitted to the ICU, and one of them passed away. The deceased patient was on Zanamivir inhalation instead of Oseltamivir because she was ventilated.

Fifteen patients (78.95%) completed a 5-day course of Oseltamivir. Two patients received six days of therapy. Another two patients received seven days of Oseltamivir. At the discretion of the respiratory and

Table 2. Presenting symptoms and signs.

Presenting symptoms	Number of patients	Percentage (%)
Cough	17	89.5
Fever	16	84.2
Chills	13	68.4
Runny nose	8	42.1
Generalized fatigue	7	36.8
Shortness of breath (SOB)	7	36.8
Sore throat	6	31.6
Sputum	5	26.3
Headache	3	15.8
Myalgia	4	21.0
Vomiting	1	5.3
Physical signs		
Fever	14	73.7
Tachycardia	5	26.3
Pharyngitis	4	21.0
Chest X-ray (CXR)	3	15.8
Wheezes	2	10.5
Hypoxia	2	10.5
Decreased air entry	2	10.5
Sinus bradycardia	1	5.3
Tachypnea	2	10.5
Hemoptysis	1	5.3

Table 3. Time between onset of symptom and starting therapy.

Time interval between onset of symptoms and starting therapy	Number of patients	Percentage (%)
1 day	8	42.1
2 days	4	21.0
3 days	4	21.0
5 days	1	5.3
More than 5 days	2	10.5

infectious consultants, one of them received the last two days as an outpatient at home.

Six patients (31.58%) needed oxygen therapy, and 2 (10.53%) were admitted to the intensive care unit (ICU).

Except the two patients who were admitted to the ICU, the earliest delivery was two weeks after the confirmed H1N1 infection.

The first ICU admission was the case of a 41-year-old lady who had essential hypertension, and a history of ICU admission due to a penicillin allergy. She had three children and one miscarriage, P3+1 (previous three caesareans). She presented at 38+1 weeks for urgent cesarean section due to a non-reassuring CTG. The cesarean section went uneventfully with the delivery of a healthy male fetus weighing 3.7 kg with 1-minute APGAR score of 8/9. On the first postoperative day, she started to complain of SOB, cough, and a fever. She was started on antibiotics and went home on the second postoperative day. She presented on the 3rd postoperative day with severe respiratory distress and hypoxia. Her chest radiograph showed severe infiltration and opacification (**chest radiographs 1-4, shown**). She was admitted to the ICU and intubated. H1N1 influenza infection was suspected, so a tracheal aspirate was taken and was positive for H1N1 (she was the first case in the hospital to be diagnosed with H1N1 infection). A total of 6 days were between the initial presentation and the initiation of therapy. She was then intubated, and over a deteriorating course of 15 days with multi-organ failure, she passed away.

The second patient admitted to the ICU was a 32-year-old lady, P3 (all were NVD). She has a history of seasonal allergy and angioedema. She was also admitted to the ICU and intubated ten months before her current pregnancy due to pulmonary hemorrhage, implying a probable residual lung disease or damage. She was confirmed to have H1N1 infection at 30 weeks +3 days gestation. She presented with a dry cough, shortness of breath, palpitations, headache, chills, generalized fatigue, myalgia, and hemoptysis. Her physical examination revealed tachycardia (130 beats/minute), wheezes and hypoxia. She was diagnosed to have H1N1 infection with a secondary bacterial infection and started on Oseltamivir, nebulizers, and antibiotics three days after her onset of symptoms. Her CXR showed diffuse bilateral ground-glass opacification and pleural effusion. In the ICU she developed anemia and was given a blood transfusion. She developed severe respiratory distress with hypoxia at 33 weeks and underwent urgent cesarean section under epidural anesthetic with an outcome of an alive baby weighing 2 kilograms (Kg) and an APGAR score of 8/9. The baby was admitted to the NICU due to prematurity. She was kept in the ICU. Her respiratory condition started to improve and continued improving over the postoperative course. She recovered well and was discharged with her baby in good condition.

Except these two patients, all other patients delivered 2 or more weeks after their infection; babies were not separated from them and they were encouraged to breastfeed. A total of 5 patients (26.31%) delivered before the 37 weeks were completed. Most of our patients (73.68%) delivered beyond term. 36.84% of our patients delivered vaginally while 12 patients (63.16%) were delivered by cesarean section, most of them were elective caesareans (**Table 4**).

Nine babies out of 20, (45%) weighed more than 3 kg. Four babies (20%), 2 of which were twins, weighed less than 2 kg. 18 babies (90%) had APGAR scores more than 8 at 1 and 5 minutes after delivery. Five babies (25%) were admitted to the NICU (**Table 5**).

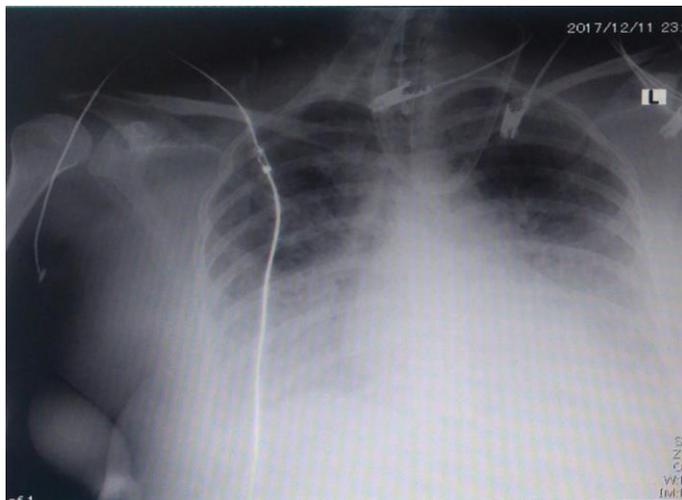
One patient was pregnant with twins and delivered three weeks after H1N1 admission (admitted at 28+6 weeks, delivered at 35+4 weeks) by cesarean section due to intra-uterine growth restriction (IUGR), decreased liquor and decreased fetal movement and spontaneous decelerations on CTG. She started therapy three days after the onset of her symptoms. The babies weighed 1.5, and 1.51 kg and both were admitted to the NICU. The 4th baby who was admitted to the NICU was delivered at 34 weeks due to fetal distress during induction of labor because of oligohydramnios. The mother was H1N1 infected at 28+3 weeks, with 2 days between onset and therapy. The baby weighed 1.7 kg and was admitted for one week. The same baby was admitted again 2 weeks after discharge due to a chest

Table 4. Gestational age at delivery and mode of delivery.

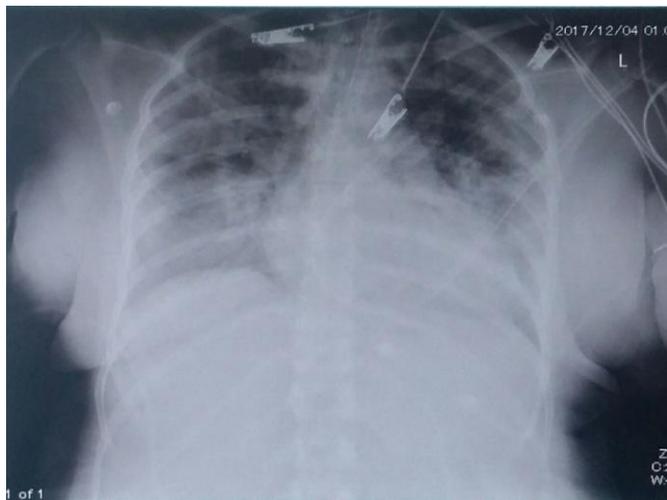
<i>Gestational age at delivery</i>	<i>Number of patients</i>	<i>Percentage (%)</i>
Less than 34 weeks	1	5.3
34-37 weeks	4	21
More than 37 weeks	14	73.7
Mode of delivery		
Caesarean section (elective)	8	42.1
Caesarean section (urgent)	4	21.0
Vaginal delivery	7	36.8
Maternal mortality	1	5.3

Table 5. Birth weight, APGAR score, preterm delivery and NICU admission.

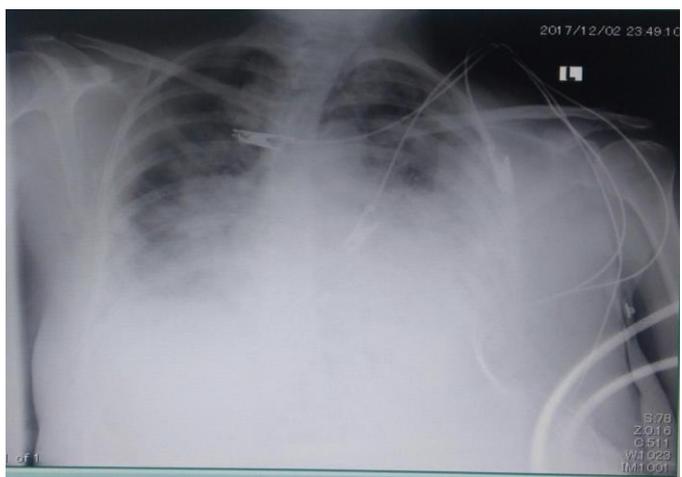
<i>Birth weight</i>	<i>Number of babies (20)</i>	<i>Percentage (%)</i>
Less than 2 kilogram (kg)	4	20.0
2-3 kg	7	35.0
More than 3 kg	9	45.0
APGAR score		
8 or more	18	90.0
5-8	1	5.0
Less than 5	1	5.0
NICU admission	5	25



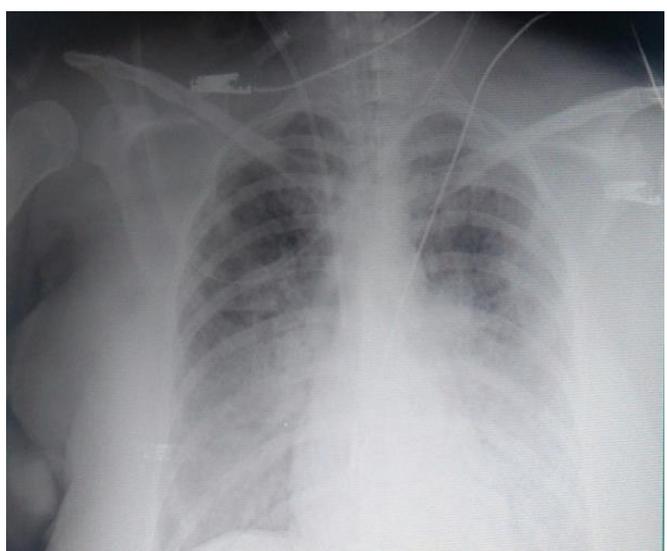
Chest radiograph 1 of the deceased patient.



Chest radiograph 2 of the deceased patient.



Chest radiograph 3 of the deceased patient.



Chest radiograph 4 of the deceased patient.

infection. One term baby, who was delivered at 38 weeks, vaginally, in a private hospital, weighing 2.6 kg with an APGAR score of 5, was admitted to the NICU for 5 days due to hypoxia and wheezes. The detailed diagnostic workup is not available. The baby was discharged and now is doing very well. The mother was infected at 19 +2 weeks, with 3 days between onset and therapy.

Discussion. Around half of our patients were above 31 years old, and more than half of them were infected in the second trimester. Prabhu,¹² however, found that 90.6% of H1N1 infected pregnant patients in the series were in the age group between 21 and 29 years, 65.6% were primigravidae, and 87.5% were diagnosed in the third trimester. According to Siston AM et al.,²³ third-trimester infection was associated with the highest death compared with first and second trimesters.

The three most common clinical symptoms in our patients were cough, fever, and chills. These were moderate symptoms. Jamieson DJ et al.,⁵ Louie JK, et al.¹⁰ and Hewagama S et al.¹⁶ reported similar results.

Shortness of breath, hemoptysis, hypoxia, wheezes, tachypnea, and decreased air entry were found in

patients with severe symptoms who required chest radiographs with positive findings, oxygen therapy and intubation with intensive management. Liu L et al.,¹⁷ reported that in a general population, critical cases were associated with severe hypoxemia, multisystem organ failure, and a requirement for mechanical ventilation.

94.73% of our patients were hospitalized to complete their minimum of a 5-day course, and two patients (10.53%) were admitted to the ICU. One patient with mild symptoms declined hospitalization and completed her therapy at home with no complications. There was only one maternal death (5.26%). She deteriorated very quickly and, because of the low index of suspicion of the H1N1 infection, 6 days passed before confirming a diagnosis and starting therapy. The delay in initiating therapy, the urgent cesarean delivery due to fetal distress, and the postpartum status were the most probable contributing factors to her death, as she had only a history of essential hypertension and penicillin allergy as co-existing clinical conditions. After that case, and because of public and medical staff fear and awareness, particularly in pregnant women, the

threshold to test patients for the H1N1 was lowered, and therefore most our patients (42.10%) were diagnosed and started on therapy within one day of their disease onset. The rest of our patients started therapy within 5 days of onset of symptoms, except the maternal mortality case and the other patient who was admitted to the ICU (more than 5 days). Meijer WJ et al.¹⁸ reviewed and judged 294 reports according to the STROBE guidelines or CONSORT statement. In all, 100 studies, published between 1961 and 2015, were included and reported that, compared to the general population, pregnant women are more often hospitalized and admitted to an intensive care unit due to influenza virus infection. Our approach of early testing and initiation of therapy in confirmed cases contributed significantly to the good outcome, a lower rate of ICU admissions, less need for oxygen (only 4 excluding the ICU patients) and low complications in our series. Early treatment with Oseltamivir is associated with a reduced risk of severe disease.¹⁸ Heba V et al.¹⁹ found that initiation of oseltamivir within 48 hours of symptom onset was associated with fewer complications in patients hospitalized with 2009 influenza A (H1N1). Viasus D et al.²⁰ reported that timely oseltamivir administration has a beneficial effect on outcomes in hospitalized adults with A (H1N1), even in those who are admitted beyond 48 h after onset of symptoms. Higuera Iglesias AL et al.²¹ found that earlier initiation of Oseltamivir therapy, even when initiated more than 48 hours after the onset of symptoms, significantly reduced occurrence and severity of pneumonia and shortened hospitalization in pandemic H1N1 2009. Based on these results, patients affected by future influenza pandemics would benefit from early therapy.

In a systematic review and meta-analysis of observational studies, Dominik Mertz et al.,²² found that in influenza infection, pregnancy is associated with a higher risk of hospital admission than non-pregnant individuals with similar risk of mortality. This increased susceptibility was described for various pathogens including H1N1 influenza virus.⁵ Changes in the immune, cardiac and respiratory systems are the likely reasons that pregnant women are at increased risk for severe illness with influenza.^{14,15} These facts were taken into account during the management approach of our patients.

The only patient with significant co-existing medical diseases was the previously mentioned 2nd ICU patient. No other cases had significant medical problems. This fact could have contributed to the good outcome. Jamieson DJ et al.⁵ mentioned the reporting of six deaths in pregnant women to the CDC. All were in women who had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation.⁵ Among the 788 pregnant patients in the USA with 2009 Influenza A (H1N1) infection, 30 died (3.8%). Patients who started their therapy more than 4

days after disease onset were more likely to be admitted to an ICU. Authors concluded that early treatment was associated with fewer ICU admissions and fewer deaths.²³ Fatima S Dawood et al.²⁴ found that the estimate of respiratory and cardiovascular mortality associated with the 2009 pandemic was 15 times higher than the reported laboratory-confirmed deaths. There are several risk factors and medical conditions that increase the severity, complications, admission to the ICU and death among H1N1 infection.^{10,25,26,27}

Although 31.58% of our patients were infected in the second trimester and 5.26% in the first trimester, only 5.26% delivered before 34 weeks. Only 21.05% delivered between 34 and 37 weeks and most patients (73.68%) delivered after 37 weeks. The increased overall prematurity rate of 26.31% could be caused by H1N1 infection. Two patients who were infected around 28 weeks (one at 28 weeks plus 3 days and the other at 28 weeks plus 6 days) developed decreased liquor and IUGR and underwent cesarean section due to fetal distress at 34 weeks and 35 weeks plus 4 days. This rate is much higher than reported in the general population.²⁸ There were no cases of intra-uterine fetal death (IUFD) or stillbirths in our cases. NICU admission in our series was 25%. Pierce M et al.,²⁹ found that perinatal mortality is increased due to an increased rate of stillbirth, increased prematurity, increased rate of NICU admission due to secondary pneumonia. Overall around two-thirds of our patients were delivered by cesarean section mostly elective obstetric indications. The mode of delivery was dictated by obstetric reasons except one patient who underwent a caesarean section because of severe respiratory compromise.

Forty-five percent of babies weighed more than 3 kg. Four babies (20%), 2 of them were twins, weighed less than 2 kg. The newborn babies were well off as indicated by an APGAR score of more than 8 at 1 and 5 minutes after delivery in 90% of babies. Fell DB et al.³⁰ in a systematic meta-analysis of comparative studies found that in the subgroup of the highest-quality studies two reported significantly increased preterm birth following severe 2009 pandemic H1N1 (pH1N1) influenza illness, whereas those assessing mild-to-moderate pH1N1 or seasonal influenza found no association. They found no association with small for gestational age (SGA). They concluded that comparative studies of preterm birth, SGA birth and fetal death following maternal influenza disease are limited in number and quality. An association between severe pH1N1 disease and preterm birth and fetal death was reported by several studies; however, these limited data do not permit firm conclusions on the magnitude of any association.³⁰ There was one case of mortality in our report. William L Callaghan et al.,³¹ found that 12 pregnancy-related deaths could be due to possible or confirmed H1N1 infection in the 2009-2010 pandemic. A CDC study of 347 pregnant women found that prompt use of antiviral

drugs during the 2009 H1N1 influenza pandemic improved survival among severely ill pregnant women.³² Neuraminidase inhibitors (NI) are likely to reduce mortality in hospitalized patients and are effective at reducing secondary symptomatic influenza transmission.³³ Because pregnancy is a high risk situation, all our patients were given NI, even with the potential significant side effects. The US Centres for Disease Control and Prevention recommend chemoprophylaxis with either Oseltamivir or Zanamivir against H1N1 influenza

For people at risk of complications, including pregnant women.³⁴ The use of NIs is reassuring to pregnant and lactating women as they aren't associated with adverse outcomes or congenital malformations even with early pregnancy exposures.^{35,36} Although cardiac side effects (1.8%) and transient neonatal hypoglycemia in the newborns were reported,^{37,38} we did not encounter such side effects in our newborns.

None of our patients had received influenza vaccination prior to or during the current pregnancy. Antenatal influenza vaccination can enhance fetal growth and can reduce preterm birthrate.^{39,40} Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants.⁴¹ Mark G. Thompson et al.,⁴² found that pregnant women vaccinated against flu had a 40% lower risk for

hospitalization if they became ill with the infection compared with unvaccinated pregnant women. We, therefore, would expect a reduction in the preterm birth rate, IUGR and NICU admissions should our patients be vaccinated. This is particularly important in our series since we had a very low threshold for testing suspected cases and early initiation of antiviral therapy.

Our one case of twin pregnancy was complicated by oligohydramnios, IUGR and urgent cesarean section due to fetal distress. Soydinc et al.,⁴³ reported that H1N1 influenza infection caused significant fetal and maternal complications and they had a maternal death of a twin pregnancy infected at 32 weeks gestation. Hein Bogers et al.,⁴⁴ reported 2 cases with severe perinatal complications, one with fetal demise at 24 weeks gestation.

Our case series are limited in number. We recommend studying all cases of H1N1 infection at a national level to reach more solid conclusions.

Conclusions. H1N1 influenza A infection in pregnancy is associated with adverse maternal and perinatal outcomes. Medical and public awareness, low threshold for testing pregnant patients, very early initiation of antiviral therapy and multidisciplinary approach in our series decreased the overall adverse effects of this infection.

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