Rev. Med. Virol. 2013; **23**: 3–14.
Published online 13 March 2012 in Wiley Online Library
(wileyonlinelibrary.com)
DOI: 10.1002/rmv.1712

REVIEW

Pandemic influenza A(H1N1) 2009 virus in pregnancy

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SUMMARY

Two hundred fourteen abstracts and 87 full texts regarding pregnant women infected with pandemic influenza A(H1N1) 2009 virus were systematically reviewed by using a PubMed search and assessing pandemic, clinical, laboratory test, vaccine, and control experiences. Both policy and health education were excluded. This review counted the total number of pregnant cases from different countries and analyzed their epidemic features, including trimester distribution, morbidity, hospitalization, intensive care unit admissions, maternal mortality, underlying diseases, complications, high-risk factors for death, pregnancy outcome, and clinical symptoms compared with the previous pandemic seasonal influenza A/H1N1 as compared with the general population. Early identification and treatment were the most important factors in different countries and areas examined. The vaccine and antiviral drugs that have been the most efficient means to control the novel virus appear to be safe but require more extensive study. In the future, the focus should be placed on understanding vertical transmission and the severe mechanisms.

Received: 30 September 2011; Revised: 5 February 2012; Accepted: 8 February 2012

INTRODUCTION

Influenza virus type A, B, or C can infect many species, including humans, pigs, horses, mink, and a wide variety of domestic and wild birds. Of these, A is the predominant subtype in human populations. Thus far, it has been classified into 16 HA (Hemagglutinin) and nine NA (Neuraminidase) subtypes on the basis of its antigenic properties [1]. The influenza virus A genome consists of eight RNA segments. The virus has the special capabilities of antigenic shift and antigenic drift. Through the re-assortment or exchange of genetic material among influenza viruses from different animal, human, and bird sources, novel strains may emerge, causing unstable and unpredictable outbreaks. In the past 100 years, there have been four pandemics: 1918 (Spanish A/H1N1), 1957 (Asian A/H2N2), 1968 (Hong Kong A/H3N2), and 1977 (Russian A/H1N1) [2].

In March 2009, another influenza pandemic was caused by a novel virus strain, designated as triple reassortant pandemic influenza A(H1N1) 2009 virus (A(H1N1)pdm09). A(H1N1)pdm09 quickly spread

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Abbreviations used;
A(H1N1)pdm09, pandemic influenza A(H1N1) 2009 virus; ARDS, acute respiratory distress syndrome; HA, hemagglutinin; ICU, admission to an intensive care unit; NA, neuraminidase; RNA, ribonucleic acid; RR, the relative risk; TB, tuberculosis; WHO, World Health Organization.

to all continents and caused considerable human suffering since the first case emerged in Mexico [3–5]. According to the World Health Organization (WHO) data, as of 1 August 2010, worldwide more than 214 countries and areas have reported laboratory-confirmed cases of A(H1N1)pdm09, including over 18,449 deaths [6]. It was noted that pregnant women, especially those with comorbidities, were at increased risk for complications from A(H1N1)pdm09. Compared with non-pregnant individuals, pregnant women are approximately 4~5 times more likely to develop severe disease, with the highest risk occurring in the third trimester. Infection with influenza while pregnant is associated with an increased risk of adverse outcomes, such as spontaneous abortion, preterm birth, and fetal distress. At the same time, infants, children less than 2 years of age, and children with underlying chronic medical conditions have the highest rates of influenza-associated hospitalizations [7].

Although there were many pregnant women included in the data from the USA, France, Japan, Austria, South India, and other countries, the information is very fragmented. Therefore, a systematic review of the currently available literature, with an attempt to better understand the effects of A(H1N1)pdm09 on pregnant women and their fetuses, was performed. These data will be of benefit for the prevention and control of novel A(H1N1)pdm09 and seasonal influenza in pregnant women and therefore improve the outcome of their fetuses.

LITERATURE SEARCH STRATEGY

A PubMed search was performed on April 5, 2011 to find all publications in the medical literature discussing A(H1N1)pdm09 and pregnancy, using the following search terms: "Influenza H1N1" or "Swine" and "Pregnancy" or "Pregnant women." We did not limit searches to the English language. Of the resulting 214 abstracts, we then screened 87 of the full texts associated with the abstracts, on the basis of epidemiology, clinical, testing, vaccine immunology, and control characteristics. Policy and health education papers were excluded. However, cross-referenced papers were included as a source of data. The review of these articles on influenza associated with pregnancy was used to count total cases, hospitalizations, admission to an intensive care unit (ICU), and deaths. The following regions were represented with varying degrees within the reports: North America, Europe, Asia, and the Southern Hemisphere.

COUNTRIES IN THE TEMPERATE ZONE OF THE NORTHERN HEMISPHERE

North America

In the USA, the total number of pregnant women accounted for 1.0% of the general population, but 5.8% (28/484) of the deaths were attributed to pregnant women infected with A(H1N1)pdm09 (on the basis of the report from the Center for Disease Control and Prevention (CDC) in the USA in August 21, 2009) [8,9]. Jamieson *et al*. [10] reported that there were 34 confirmed or probable cases of A(H1N1)pdm09 in pregnant women from April 15 to May 18, 2009. The infections occurred in all three trimesters: first, 8.8% (3/34); second, 55.9% (19/34); third, 26.5 (9/34); and unknown, 8.8% (3/34). Eleven of the these women (32.4%, 11/34) were hospitalized, and six died (6/45, 13.3% of total) from the A(H1N1)pdm09. About 50.0% (3/6) of the patients who died had other medical diseases such as mild asthma, obesity, or factor V Leiden deficiency and developed primary viral pneumonia with subsequent acute respiratory distress syndrome (ARDS), requiring mechanical ventilation. Pregnancy outcomes among the six deaths included five infants delivered by cesarean section at 27–36 weeks gestation (three of these infants were placed in the ICU or the emergency department) and one fetal loss at 11 weeks. The length of time from symptom onset to receipt of antiviral medication was 6–15 days (median 9.0 days). The length of time from presentation for medical care until receipt of antiviral treatment was 2–14 days (median 4.5 days).

Another small case study covering the state of California from April 23 through August 11, 2009 reported 94 pregnant women hospitalized with A(H1N1)pdm09; of these women, 94.7% (89/94) were in the second or third trimester. Eight postpartum and 137 non-pregnant women of reproductive age were also included in the study. Approximately one-third (34.4%, 32/93) had established risk factors other than pregnancy for complications from influenza. Eighteen pregnant women and four postpartum women (21.6%, 22/102) required intensive care, and eight (7.8%, 8/102) died. Six deliveries occurred in the ICU, including four emergency cesarean deliveries. As compared with early antiviral treatment (administered ≤2 days after symptom onset) in pregnant women, later treatment

DOI: 10.1002/rmv

was associated with admission to ICU or death; the relative risk (RR) was 4.3. In all, the A(H1N1) pdm09-specific maternal mortality ratio was 4.3 (the number of maternal deaths per 100,000 live births) [11,12]. The high A(H1N1)pdm09-specific maternal mortality suggests that this pandemic had the potential to notably increase overall maternal mortality in the USA in 2009.

Another paper reported 788 pregnant women in the USA with A(H1N1)pdm09 from April through August 2009 [9]. Among 509 hospitalized women, 115 (22.6%, 115/509) were admitted to an ICU. Pregnant women who received treatment more than 4 days (56.9%, 37/65) after symptom onset were more likely to be admitted to an ICU (RR 6.0) compared with those treated within 2 days after symptom onset (9.4%, 13/138). Thirty patients died (5.0% of all reported deaths in this period). Updating these data with the CDC's continued surveillance of ICU admissions and deaths among pregnant women with symptom onset through December 31, 2009, we found that an additional 165 women were admitted to ICUs; a total of 280 pregnant women were infected, 56 of whom died. Among the deaths, four occurred in the first trimester (7.1%, 4/56), 15 in the second (26.8%, 15/56), and 36 in the third (64.3%, 36/56). Pregnant women had a disproportionately high risk of mortality due to A(H1N1)pdm09. Among pregnant women with A(H1N1)pdm09 reported to the CDC, early antiviral treatment appeared to be associated with fewer ICU admissions and fewer deaths.

From Canada, Salaheddin *et al*. reported that the cumulative incidence of A(H1N1)pdm09 among pregnant women in Manitoba until August of 2009 was 8.6%. The rate was 20.8% in the northern regions of the province according to HA IgG antibody testing (more than serum antibody titer 1:40 is positive). It has been proposed that the uniformity of the patterns of A(H1N1)pdm09 among aboriginal communities across the globe, despite their genetic diversities, suggests a role for socio-economic and environmental factors. These may include over-crowding, poor housing, and limited access to health care services [13].

Europe

Several European countries, such as France, Spain, and Greece, reported occurrences of pregnant women with A(H1N1)pdm09 infection. In France, there were 315 cases of laboratory-confirmed A (H1N1)pdm09 in pregnant women from 46 hospitals, including 40 ICU cases, 111 hospitalized in obstetric or medical wards (moderate outcomes), and 164 outpatients. The occurrence of infection appeared across all trimesters, but most women (54.0%, 170/315), notably the most severe patients (70.0%, 28/40), were in the third trimester. Twenty (50.0%, 20/40) of the 40 severe patients underwent mechanical ventilation, and 11 (27.5%, 11/40) were treated with extracorporeal membrane oxygenation. Three women died [14]. The scientists found strong associations between severe outcomes and co-existing illnesses and the delay in Oseltamivir treatment after the onset of symptoms (>3 or 5 days). Among the 140 deliveries, 19 neonates (13.6%, 19/140) were admitted to a neonatal intensive care unit, mainly for preterm delivery (22 weeks gestation), and two neonates died. None of these neonates developed A(H1N1)pdm09 infection. According to Maraví-Poma *et al*. [15], in Spain, from April 23, 2009 to February 15, 2010, 234 women of reproductive age were admitted to intensive care units; 50 (21.4%) of these women were pregnant. Seven deaths were recorded among the pregnant women and 22 in the non-pregnant women. Viral pneumonia was more frequent in the pregnant women than in the non-pregnant women. The development of primary viral pneumonia in women of reproductive age appeared to be related to the time of commencement of antiviral treatment.

Asia

In China, 41 cases of infected pregnant women were reported, accounting for 7.6% (41/543) of 543 severe A(H1N1)pdm09 cases till November 10, 2009 [16]. There were three cases in the first trimester, six in the second trimester, and 31 in the third trimester; one occurred postpartum. Of the deaths from severe cases, 8.1% (6/74) were associated with pregnancy, including five deaths in the third trimester and one death in the second trimester; yet all deaths did not have chronic underlying diseases. Nakai *et al*. [17] reported 181 cases of infected pregnant women in Japan; 74.6% (132/177) of the hospitalized women were in the third trimester. In Japan, from May 2009 to March 2010, 0.2‰ (181/1,080,000) of the births were associated with A(H1N1)pdm09-infected mothers. That is, one in 6000 pregnant women required hospitalization for treatment of A(H1N1) pdm09. This represented 1.0% (181/17,646) of the total population requiring hospitalization. Thus, pregnant Japanese women did not have an

DOI: 10.1002/rmv

increased risk of severe complications, which is inconsistent with other countries. Seventeen (9.4%, 17/181) cases developed viral pneumonitis, two of which required admission to an ICU. However, all 181 women recovered completely; there were 178 live births and three abortions. Pramanick *et al*. reported a small case–control study in India [18], in which there were 20 pregnant women infected with A(H1N1)pdm09, and 144 non-pregnant women were also included in the study. The results showed that five pregnant and three postpartum women required admission to the ICU. Five (25.0%, 5/20) pregnant/postpartum women died from A(H1N1) pdm09 infection, whereas 12 women (8.3%, 12/144) who died were in the non-pregnant group ($p = 0.04$). One woman (5.0%, 1/20) delivered twins. Eleven women (55.0%, 11/20) delivered vaginally, six (30.0%, 6/20) delivered by cesarean, two (10%, 2/20) delivered prenatally, and one (5%, 1/20) evacuated by suction.

COUNTRIES IN THE TEMPERATE ZONE OF THE SOUTHERN HEMISPHERE

Australia reported 43 cases of pregnant women infected with A(H1N1)pdm09 in the state of Victoria from May 20, 2009 through July 31, 2009 [19]. The incidence of hospitalization was estimated at 0.5% (28/6094) of all 6094 pregnant women in the third trimester, but it was estimated at 0.2% (13/6094) in the second trimester. Of the cases, 35.7% (15/42) delivered during their hospitalization; there were eight ICU admissions, one maternal death, two fetal deaths, and one neonatal death. A large proportion (33/43, 76.7%) of women received antiviral treatment, and 55.8% (24/43) received antibiotics. Archer *et al*. [20] reported that in South Africa, a total of 91 women including pregnant women died from laboratory-confirmed A(H1N1)pdm09 as of October 12, 2009. Twenty-five of the 88 pregnant or puerperal women and 25 of the 45 women of reproductive age died. Among 21 deaths associated with pregnancy, 18, one, and two deaths occurred in the third, second, and puerperium trimesters, respectively. Ten of the 14 pregnant or puerperal women tested for A(H1N1)pdm09 were also infected with HIV, and four of 21 women had active pulmonary tuberculosis (TB). Schout *et al*. [21] reported that there were 9249 confirmed cases of A(H1N1)pdm09 in Brazil, including 699 deaths until September 16, 2009. Eight hundred and fifty-six pregnant women were infected, of whom 91 died, resulting in a mortality rate of 10.6% (91/856).

GEOGRAPHIC AND TRIMESTER DISTRIBUTIONS

Up to March, 2011, a total of 1490 cases of pregnant women infected with A(H1N1)pdm09 were reported (USA, 788 [9]; California, 102 [11]; France, 315 [14]; China, 41 [16]; Japan, 181 [17]; India, 20 [18]; and Australia, 43 [19]). These reports were taken from seven studies in different countries and areas; 9.1% (136/1490) of the cases occurred in the first trimester (≤12 weeks), 29.8% (444/1490) in the second trimester (13–27 weeks), and 47.0% (701/1490) in the third trimester (28–40 weeks), and 0.9% (13/1490) happened in the postpartum period (≤2 weeks). Of the cases, 13.2% (196/1490) were not clear regarding the stage of pregnancy while infected. The proportion of cases infected in the first, second, third, postpartum, and unknown trimesters were as follows: California (April 23 to August 11, 2009): 4.9% (5/102), 34.3% (35/102), 52.9% (54/102), 7.8% (8/102), and 0.0% (0/102); USA (April to August, 2009): 8.5% (67/788), 31.7% (250/788), 34.9% (275/788), 0.0% (0/788), and 24.9% (196/788); France (August 1 to December 31, 2009): 11.4% (36 /315), 34.6% (109/315), 54.0% (170/315), 0.0% (0/315), and 0.0%(0/315); China (as of November 10, 2009): 7.3% (3/41), 14.6% (6/41), 75.6% (31/41), 2.4% (1/41), and 0.0% (0/41); Japan (May 2009 to March 2010): 12.7% (23/181), 14.4% (26/181), 72.9% (132/181), 0.0% (0/181), and 0.0% (0/181); India (August 5, 2009 to January 31, 2010): 0.0% (0/20), 25.0% (5/20), 55.0% (11/20), 20.0% (4/20), and 0.0% (0/20); Australia (by July 31, 2009): 4.7% (2/43), 30.2% (13/43), 65.1% (28/43), 0.0% (0/43), and 0.0% (0/43), respectively. Comparing the data across countries and areas relative to gestational age, we found that they are consistent in that the majority of women were infected in the middle-late gestational periods. The percentages by trimester are shown in Figure 1.

MORBIDITY

Jamieson *et al*. [10] reported that pregnant women were more likely to suffer severe complications than other population groups and that the severity of illness was greater than that observed with seasonal influenza. The cumulative incidence of hospitalization was estimated at 0.5% (95.0% confidence interval, 0.3–0.7%) of all pregnant women in the

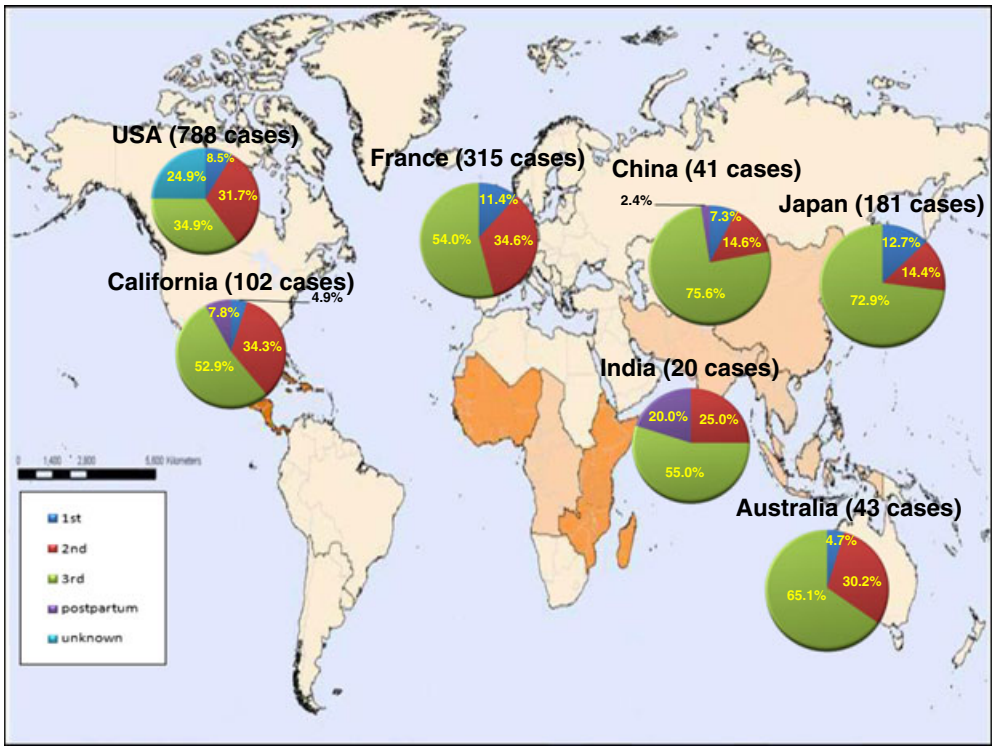

Figure 1. The trimester distribution among pregnant women infected with pandemic influenza A(H1N1) 2009 virus in different countries or areas

USA, and the incidence of hospitalization in the second trimester was estimated at 0.2% (95.0% confidence interval, 0.1–0.4%). Admission rates per 100,000 pregnant women and the general population with A(H1N1)pdm09 were 0.32 and 0.076, respectively with a RR of 4.3. Hanslik *et al*. measured the risk for admission into an intensive care unit for a pregnant woman and found an odds ratio of 5. In an Australian cohort of 64 pregnant/postpartum women with A(H1N1)pdm09 infection, the risk of ICU admission was 13-fold greater for women who developed the infection at 20 or more weeks of pregnancy. These findings indicate that the infection risk is higher in the latter part of pregnancy [22]. The Japanese results indicated that approximately one in 6000 (181/1,080,000 maternity births) pregnant women required hospitalization or treatment for A (H1N1)pdm09 annually, and one in 7200 (17,646/127 million persons) required hospitalization. Thus, pregnant Japanese women did not have an increased risk of severe complications, which is inconsistent with pregnant women being more likely to suffer severe complications than other population groups.

HOSPITALIZATION RATE

In Europe, A(H1N1)pdm09 among the general population caused a mild and self-limiting illness, with 1.0–2.0% of the cases requiring hospitalization. From the four countries studied with the available data, there were 1361 confirmed pregnancy cases, with 44.7% (608/1361) of those needing hospitalization. Because antiviral treatment was started earlier in Japan and France, their hospitalization rates were much lower than in the USA and other countries. The results are indicated in (Table 1).

INTENSIVE CARE UNIT ADMISSIONS

According to the data from the different countries and areas, there were 1533 pregnant women infected with A(H1N1)pdm09. Of the cases, 16.8% (258/1533) required ICU admission. The lowest rates of ICU admissions were found in Japan (1.1%, 2/181), whereas the highest (40.0%, 8/20) was that of India. The rates were different in different areas and periods in the USA (Table 2).

DOI: 10.1002/rmv

Table 1. Comparison of the hospitalization rate for pregnant women infected with pandemic influenza A(H1N1) 2009 virus in different countries or areas

Countries or areas	Hospitalization cases (*n*)	Total confirmed pregnancy cases (*n*)	Hospitalization rate (%)	References
USA (April 15 to May 18, 2009)	11	34	32.4	Jamieson *et al*. [10]
USA (April to August, 2009)	509	788	64.6	Alicia *et al*. [9]
France (August 1 to December 31, 2009)	46	315	14.6	Dubar *et al*. [14]
Japan (May 2009 to March 2010)	17	181	9.4	Nakai *et al*. [17]
Australia (by July 31, 2009)	25	43	58.1	Hewagama *et al*. [19]
Total	608	1361	44.7	

Table 2. Comparison of the ICU rate for pregnant women infected with pandemic influenza A (H1N1) 2009 virus in different countries or areas

Countries or areas	ICU Admission (*n*)	Total confirmed pregnancy cases (*n*)	ICU rate (%)	References
USA (April 15 to May 18, 2009)	3	34	8.8	Jamieson *et al*. [10]
California (April 23 to August 11, 2009)	22	102	21.6	Louie JK *et al*. [11]
USA (April to August, 2009)	165	788	20.9	Alicia *et al*. [9]
France (August 1 to December 31, 2009)	40	315	12.7	Dubar *et al*. [14]
Japan (May 2009 to March 2010)	2	181	1.1	Nakai *et al*. [17]
India (August 5, 2009 to January 31, 2010)	8	20	40.0	Pramanick *et al*. [18]
Australia (by July 31, 2009)	8	43	18.6	Hewagama *et al*. [19]
Spain (April 23, 2009 to February 15, 2010)	10	50	20.0	Maraví-Poma *et al*. [15]
Total	258	1533	16.8	

MATERNAL MORTALITY

In the 1918 seasonal influenza A/H1N1 pandemic, overall mortality of infected pregnant women was 27.0%, reaching 60.0% for those in the last month of pregnancy. Mortality in pregnant women in the 1957 pandemic was greater than that in non-pregnant women, and greater than 50.0% of young women who died with pneumonia were pregnant. In the USA, pregnant women infected with A (H1N1)pdm09 had a sixfold higher mortality rate than that for non-pregnant women. The maternal mortality ratio (number of maternal deaths per 100,000 live births) attributed to A(H1N1)pdm09 was 4.3. The case fatality rates in the USA and the UK in normal populations have been in the range of 0.3–0.4%. In 10 studies reporting 2441 pregnant women infected with A(H1N1)pdm09 in different countries, 157 patients died, a mortality rate of 6.4% (157/2441). Considering these reports, which included countries where medical and nutritional conditions differ, the mortality rates for pregnant women from lowest to highest were found as follows: Japan (0.0%, 0/181); France (1.0%, 3/315); Australia (2.3%, 1/43); USA (April to August 2009, 3.8%, 30/788); California (April 23 to August 11, 7.8%, 8/102); Brazil (10.6%, 91/856); USA (April 15 to May 18, 2009, 13.3%, 6/45); Spain (14.0%,7/50); China (14.6%, 6/41); India (25.0%, 5/20) (Figure 2).

UNDERLYING DISEASES

There were five countries or areas (California, USA, Australia, India, and France) that reported a total of

DOI: 10.1002/rmv

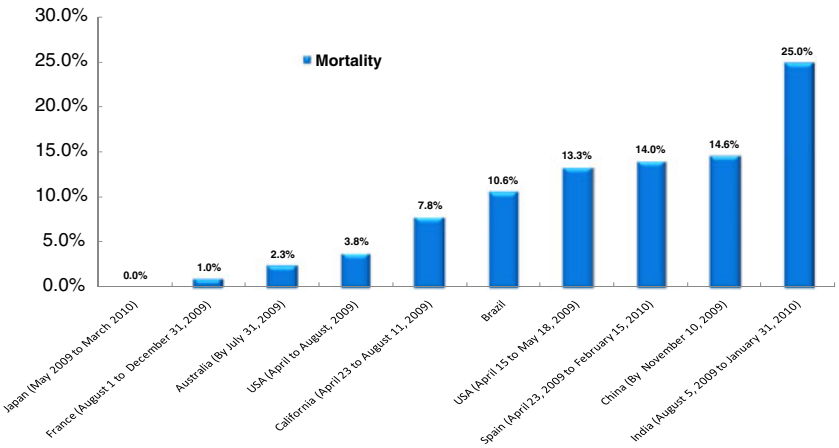

Figure 2. Mortality of pregnant women infected with pandemic influenza A(H1N1) 2009 virus in different countries and areas

1268 pregnant women infected with A(H1N1) pdm09. The number with underlying diseases was 725 (57.2%, 725/1268). It was the highest (72.2%, 569/788) in the USA, and it was the lowest in India (5.0%, 1/20), although India had a 25.0% (5/20) mortality rate. The rates of underlying diseases were 33.3% (34/102), 31.4% (99/315), and 51.2% (22/43) in California (April 23 to August 11, 2009), France, and Australia respectively. These results are shown in Table 3.

There were 1094 cases of infected pregnant women reported in the USA, Austria, South Africa, and France, of which 41.3% (452/1094) had other diseases including asthma (14.7%, 161/1094), obesity (9.4%, 103/1094), diabetes mellitus (2.7%, 30/1094), gestational diabetes (2.7%, 29/1094), chronic cardiac disease (2.0%, 22/1094), hypertension (1.7%, 19/1094), neurologic disorders (1.5%, 16/1094), anemia (1.4%, 15/1094), HIV (1.0%, 11/1094), other lung disease (0.8%, 9/1094), thyroid disease (0.7%, 8/1094), cancer or transplantation-related and hematologic disease (0.5%, 6/1094), renal disease (0.5%, 5/1094), TB (0.4%, 4/1094), autoimmune disease and hepatic disease (0.3%, 3/1094), and gastrointestinal disease (0.2%, 2/1094) (Figure 3).

COMPLICATIONS

The main complications were respiratory tract disease, cardiac complications, CNS complications, musculoskeletal complications, toxic shock syndrome, and exacerbation of underlying conditions, of which respiratory complication was most often found. Rapidly progressive pneumonia, respiratory failure, profound hypoxemia refractory to routine mechanical ventilation, ARDS, and secondary bacterial infections were found in 4.0% to 29.0% of the cases. Bacterial diagnoses included *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Streptococcus mitis*, and *Haemophilus influenzae*. Deaths related to pneumonia with

Table 3. The proportion of underlying diseases among the pregnant women infected with pandemic influenza A(H1N1) 2009 virus in different countries or areas

Countries or area	Underlying diseases (*n*)	Total confirmed pregnant cases (*n*)	Percentage (%)	References
California (April 23 to August 11, 2009)	34	102	33.3	Louie JK *et al*. [11]
USA (April to August 2009)	569	788	72.2	Alicia *et al*. [9]
France (August 1 to December 31, 2009)	99	315	31.4	Dubar *et al*. [14]
India (August 5, 2009 to January 31, 2010)	1	20	5.0	Pramanick *et al*. [18]
Australia (by July 31, 2009)	22	43	51.2	Hewagama *et al*. [19]
Total	725	1268	57.2	

DOI: 10.1002/rmv

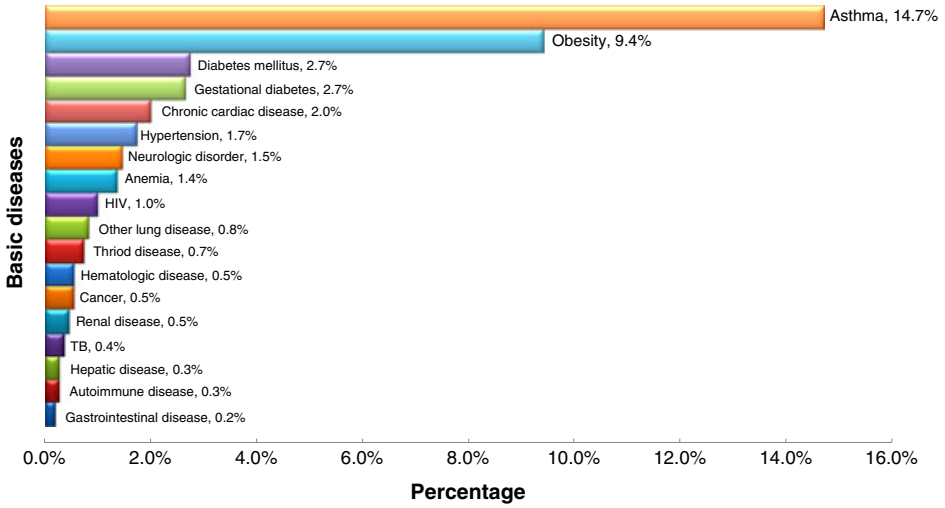

Figure 3. The percentage of the basic diseases among 1094 pregnant women infected with pandemic influenza A(H1N1) 2009 virus

subsequent ARDS had often received mechanical ventilation.

HIGH-RISK FACTORS OF DEATH

According to reports from the USA, France, Austria, Japan, and others, most of the deaths occurred in the third trimester. According to the Mosby report, 30.3% of the patients had additional risk factors (or unspecified comorbidities) for severe disease other than pregnancy. The most common additional risk factor reported was asthma, followed by obesity and diabetes mellitus of any type. Delayed Oseltamivir treatment was also a high risk in these specific populations [22–24].

PREGNANCY OUTCOME

A(H1N1)pdm09 in pregnancy is noted by adverse pregnancy outcomes, such as spontaneous abortion, preterm birth, and fetal distress. Such outcomes increased during the pandemics of 1918 and 1957, particularly in women with pneumonia; 50.0% had high rates of spontaneous abortion and preterm birth [25–27]. From 1985 to 1993, no significant increases in adverse perinatal outcomes were associated with respiratory hospitalizations during the influenza season. In the reports from the USA, Japan, India, Austria, and France, there were 1211 pregnant women infected by A(H1N1)pdm09: 43.6% (528/1211) delivered, of which preterm births (<37 weeks) accounted for 20.2% (108/534), and 79.8% (426/534) were term births (≥37 weeks). The proportion of deliveries by abortion, vaginal, cesarean, premature, and suction were 5.1% (19/372), 50.8% (189/372), 43.3% (161/372), 0.5% (2/372), and 0.3% (1/372), respectively. The live birth rate was 94.7% (396/418) (Table 4). It is unclear if these outcomes are directly attributable to the new flu. However, in the absence of vertical transmission, adverse effects can still occur. Although respiratory droplets are the main route of virus transmission, it can be spread via contact with contaminated surfaces and by other bodily fluids [28].

THE SEVERE MECHANISMS AND CLINICAL PRESENTATIONS AMONG PREGNANT WOMEN

During pregnancy, physiological changes occur at different times; the most obvious alterations occur in the cardiovascular and respiratory systems, especially during the second and third trimesters, which can increase heart rate, stroke volume, and oxygen consumption. With the progression of pregnancy, a woman's diaphragm is pushed upward, resulting in a decreased lung capacity. This makes respiratory disease more dangerous [29]. In addition, secondary changes happen in the immune system during pregnancy. The body may shift from a cell-mediated to a humoral immune response and become immunocompromised, which increases influenza virus susceptibility and may be responsible for the severe complications of pneumonia [30,31]. These changes may have placed pregnant women at a higher risk for severe complications of influenza during previous pandemics [32–34]. Thus, they are more likely to be hospitalized from complications of influenza

DOI: 10.1002/rmv

Table 4. The pregnancy outcome among the pregnant women infected with pandemic influenza A(H1N1) 2009 virus in different countries or areas

Countries	Total pregnant women	Total delivered women	Weeks of gestation		Mode of delivery					Fetal outcome	
			Preterm (<37 weeks)	Term (≥37 weeks)	Abortion	Vaginal	Cesarean	Prenatal	Suction	Live birth	Fetal loss
USA	788	169	51	118	12	79	109	0	0	157	12
USA	34	6	6	0	1	0	5	0	0	5	1
Japan	181	178	26	152	3	–	–	–	–	178	3
India	20	20	4	16	0	11	6	2	1	19	1
Austria	42	15	6	9	–	–	–	–	–	21	3
France	146	140	15	131	3	99	41	0	0	16	2
Total	1211	528	108	426	19	189	161	2	1	396	22
Percent	–	43.6	20.2	79.8	5.1	50.8	43.3	0.5	0.3	94.7	5.3

Note: "–" indicates that no data available.

than non-pregnant women are. Dodds *et al*. reported that, compared with those of the year before, the risks of hospital admission for respiratory illness related to influenza were 1.7, 2.1, and 5.1 times higher during the first, second, and third trimesters, respectively [35]. Fever is a risk factor for some types of birth defects and other adverse outcomes such as fetal neural tube abnormalities during early pregnancy. Fever during labor may also cause neonatal seizures, hypoxic ischemic encephalopathy, cerebral palsy, neonatal deaths, and other complications. In all, the effects of A(H1N1) pdm09 on the fetus are unknown and difficult to predict. Viremia is believed to occur infrequently, and placental transmission appears to be rare in seasonal influenza; however, this was not clear for the novel influenza strains [36–39].

The clinical presentations of most confirmed cases among pregnant women were characterized by self-limited, uncomplicated febrile respiratory illnesses similar to seasonal influenza. But Yang *et al*. reported that pregnant women have a higher risk of shortness of breath compared with both non-pregnant women of reproductive age (RR 1.7) and the non-pregnant general population (RR 2.3) with influenza [40,41]. Here, 1772 confirmed cases of pregnant women infected with A(H1N1)pdm09 were analyzed and collated from the USA, France, Australia, and South India. The clinical symptoms of most cases of A (H1N1)pdm09 were typical influenza-like symptoms. The most common symptoms include fever (24.7%, 437/1772); cough (23.5%, 417/1772); muscle aches (13.7%, 242/1772); headache (8.4%, 149/1772); rhinorrhea (8.3%, 147/1772); shortness of breath (8.3%, 147/1772); sore throat (6.6%, 117/1772); nausea or vomiting (3.2%, 57/1772); diarrhea and other gastrointestinal symptoms (1.3%, 23/1772); fatigue (1.3%, 23/1772); chest pain (0.6%, 10/1772); and conjunctivitis (0.2%, 3/1772) (Figure 4).

ANTIVIRAL TREATMENT

The WHO recommends that pregnant women with suspected or confirmed influenza, regardless of the stage of pregnancy, should be treated with antiviral therapy. This includes women who are up to 2 weeks postpartum or at post-pregnancy loss. WHO also recommends that treatment not be delayed because of a negative rapid influenza diagnostic test result or while awaiting diagnosis [42,43]. Antivirals for post-exposure chemoprophylaxis are generally not recommended. This recommendation includes

DOI: 10.1002/rmv

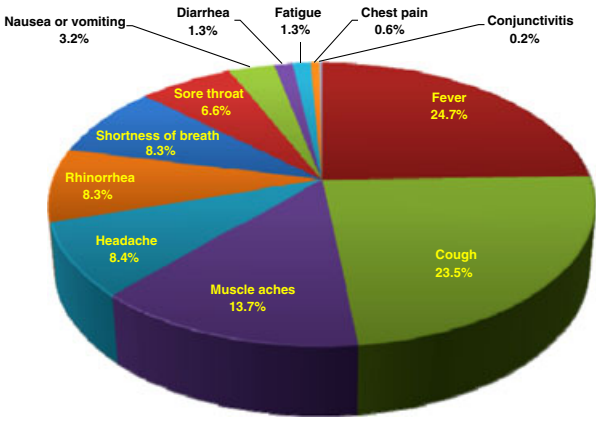

Figure 4. The percentage of the characteristic symptoms among 1772 pregnant women infected with pandemic influenza A(H1N1) 2009 virus

pregnant women and newborn infants exposed to A (H1N1)pdm09 [44,45]. Available data suggest that these are no human teratogens [46]. There are less data available on the safety aspect of Zanamivir than Oseltamivir regarding pregnancy. In *ex vivo* models, Oseltamivir is extensively metabolized by the placenta, leading to undetectable levels in the fetus even at doses above the recommended level. Although Zanamivir is less likely to be absorbed by the fetus in its inhaled form [47,48], most authors recommend Oseltamivir as the preferred treatment for pregnant women. Either Oseltamivir (Tamiflu) or Zanamivir (Relenza) can be taken to reduce the severity and length of A(H1N1)pdm09 infection, but treatment must commence within 48 h of the onset of the illness to be effective [49]. Prophylactic antibiotics are not recommended, but co-infections must be treated by appropriate antimicrobials during pregnancy and lactation as soon as possible [50].

VACCINATION

The A(H1N1)pdm09 vaccine is recommended for women who are pregnant, anticipate being pregnant, or will be pregnant during the influenza season. This includes all pregnant women in any trimester. Vaccination is also recommended even for women who have had suspected influenza. Such advice (immunization in all three trimesters) would not apply to situations where the risk of influenza is low or to live-attenuated vaccines, which in any event would not be indicated in pregnancy [51]. Few data are available on the safety of adjuvants for pandemic vaccines that could be given systematically to pregnant women. Eleven studies were published between 1964 and 2008 about the safety of seasonal influenza vaccination during pregnancy. None identified maternal or fetal problems with influenza vaccination. Reproductive toxicity studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonic/fetal development, parturition or post-natal development. The safety of the A(H1N1)pdm09 vaccine is anticipated to be similar to that of the seasonal influenza vaccine [52]. Safety information is now becoming available from the USA, Australia, Japan, China, Sweden, and Norway. The A(H1N1)pdm09 vaccine was first administered in Australia and China in September of 2009. Relatively low numbers of local and systemic reactions were reported so far. In one study, 1.3% of 189 vaccinated pregnant women had a temperature of more than 37.8 °C, which lasted between 1 and 2 days. In view of the possible teratogenic effects of hyperthermia in pregnancy on the basis of observations from animal models, there may be a theoretical risk of teratogenicity from maternal pyrexia secondary to the vaccination [53–55].

CONCLUSIONS

On the basis of the provided data from different countries, pregnant women infected with A(H1N1) pdm09 are expected to be a high-risk population with increased risk for complications, hospitalization, morbidity, and mortality. For this reason, pregnant women should be considered a population for which special considerations for prevention and treatment for A(H1N1)pdm09 are necessary. The safety of A (H1N1)pdm09 vaccines recommended for pregnant women is expected to be similar to that of the seasonal influenza vaccine. Vaccinating pregnant women and caregivers of infants less than 6 months of age is the best prevention strategy against A (H1N1)pdm09. However, the data are observational and with limitations: many studies reported only severely affected women, the numbers of which were small; follow-up times were short; and few of these cases were proven by viral diagnosis. It is not clear whether the virus distribution, molecular characteristics, virulence, and pathogenicity varied among these severe cases. In the absence of large-scale serological antibody surveys for pregnant women, the exact prevalence was not known among those populations.

This review highlights the need for understanding the transmission mechanisms underlying severe cases of maternal and fetal A(H1N1)pdm09 infection. Furthermore, it is important to perform clinical

safety studies of antiviral drugs and vaccines as these data are currently limited. Lastly, it is urgent to monitor the influenza virus (both seasonal influenza and A(H1N1)pdm09 associated with pregnancy.

CONFLICTS OF INTEREST

The authors have no competing interest.

ACKNOWLEDGEMENTS

We are grateful to Dr. Terri A Rasmussen from Tulane National Primate Research Center, USA, for proofreading the manuscript. This study was supported by grants from the Ministry of Science and Technology, China (2009ZX10004-901, 2011ZX10004-901 and 2009BAI83B01), the National Key Basic Research and Development Program of China (9732007BC109103), the CAS Innovation Program (KSCX2-YW-N-063), and the USDA/APHIS/WS-IOZ CAS joint project (0760621234).

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