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A review of influenza virus infection during pregnancy

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ABSTRACT

Respiratory influenza infection is one of the leading causes of global morbidity and mortality, affecting approximately 10-20% of the world's population annually. According to recent estimates, influenza respiratory infections are associated with about 398,000 deaths per year, accounting for a mortality rate of 2% among viral respiratory infections. During seasonal and pandemic influenza outbreaks, it has been found that pregnant women are more likely to develop severe influenza-related complications compared to the general population. During pregnancy, immunological and physiological changes affecting the respiratory, cardiovascular, and other systems put women at greater risk of developing certain infections and related complications. In this review study, at first, the characteristics of influenza virus infection and its epidemiology were briefly discussed, and then the clinical aspects of influenza virus infection in pregnant women and fetuses were explained.

Keywords: Review, Influenza virus, Pregnancy, Mortality

Introduction of influenza virus: features, epidemiology, and history

Influenza virus (IFV) consists of an eight-segment single-stranded RNA genome with negative polarity and reassortment ability. Influenza virus is generally divided into four types, including A, B, C, and D; the first three types cause disease in humans, but so far no evidence of Group D disease has been reported in humans (1). Influenza A viruses are divided into different serotypes based on their surface proteins anchored on the envelope, including hemagglutinin (HA) and neuraminidase (NA). At least 16 different HA glycoproteins (HA1-HA16) and nine different NA serotypes (NA1-NA9) have been identified, which differentiate viral serotypes. In fact, surface glycoproteins are named based on their ability to agglutinate red blood cells and break down neuraminic acid and involved in cellular entry of the virus and then its release from the human respiratory tract epithelial cells, respectively. They are also the main targets of the human immune response to IFV infection. Currently, only H1N1 and H3N2 subtypes as well as two species of Victoria and Yamagata belonging to Group B are common as endemic viruses in the human population; thus, most existing vaccines are derived from these two types (2).

Respiratory infections caused by IFV affect humans in the form of seasonal and pandemic diseases which have a significant impact on health and the annual economy. The highest IFV-related death rate recorded for the first time could be traced back to the Spanish flu pandemic of 1918-1919 with 50 million deaths. After that, IFV was considered as one of the life-threatening infections in human societies. Influenza pandemics occur following seasonal infections. In fact, seasonal viruses spread around the world, evolving by making point mutations in the genetic sequence of their two surface glycoproteins (HA and NA), which is called the antigen drift phenomenon. Therefore, the use of influenza vaccine is recommended annually (3). Also, following genomic reassortment due to the segmentation of the viral genome, another unique phenomenon called antigen shift occurs, which may cause pandemics (4). Influenza A virus is known as a pandemic-causing virus. Altogether, the world papulation has so far been affected by four major influenza virus pandemics. Based on phylogenetic studies, the Spanish influenza pandemic of 1918 was found to be caused by H1N1 virus which was more similar to mammalian viruses, especially swine or human H1N1 viruses, causing 50 to 80 million deaths worldwide (5). The Asian H2N2 influenza pandemic of 1957 was associated with the reassortment of H2N2 low-pathogenic avian influenza (LPAI) virus and H1N1 seasonal influenza virus, leading to the mortality of 1.5 million people. The 1968 Hong Kong H3N2 pandemic was caused by the reassortment of LPAI H3N2 and H2N2 of the 1957 epidemic, leading to the mortality of one million people globally. Finally, in influenza A (H1N1) virus appeared in 2009, most of the genes were closely related to H3N2 and H1N2 originated from pigs, while its neuraminidase gene was completely derived from avian influenza, leading to the lowest mortality rate of about 300,000 deaths worldwide (6, 7). A study on 70,000 pregnant women with H1N1 influenza in 2009 found that 17.4% of patients were hospitalized, 15% were transferred to the intensive care unit (ICU), and 6.9% died. However, accurate information about the vaccination status of these individuals is not available (8). Due to the fact that following the outbreaks of seasonal and pandemic influenza, pregnant women are more likely to suffer from severe influenza-related complications compared to the general population; therefore, this review article aimed to explain the clinical aspects of IFV infection in pregnant women and fetuses. It also aimed to discuss why the flu virus is more risky for pregnant women. In this regard, studies were identified by searching PubMed and Google Scholar databases using the following search terms: ‘maternal’, ‘pregnancy’, ‘pregnant’, ‘mother’, ‘pregnant women’, ‘fetus’, or ‘neonate’ as well as ‘influenza’ or ‘influenza virus’. Relevant review studies, original articles, and case reports were screened in English. Articles written in other languages were excluded.

Influenza infection during pregnancy

According to data reported following the outbreaks of seasonal and pandemic influenza, pregnant women are more likely to suffer from severe influenza-related complications than the general population. During pregnancy, immunological and physiological changes affecting the respiratory, cardiovascular, and other systems put women at greater risk of developing certain infections and related complications. Pregnancy increases the risk of hospitalization of pregnant women with IFV infection by up to 2.4 times compared to non-pregnant women. In a study, the highest rate of hospitalization was observed in the third trimester of pregnancy; during this period, pregnant women were 3-4 times more likely to be hospitalized due to an underlying disease such as chronic heart disease, chronic lung disease, diabetes, chronic kidney disease, malignancy, and suppressive disorders of the immune system in the influenza season compared to postpartum women (9).

Influenza is primarily a febrile respiratory illness characterized by a sudden onset of fever, followed by chills, myalgia, headache, nasal congestion, cough, and sore throat. The interval between the onset of the infection and the appearance of respiratory symptoms is 1 to 4 days. In most patients, influenza infection is a mild self-limiting illness that resolves in approximately 3-4 days (10). Pregnant women are one of the few populations suffering from more severe complications of influenza, including pneumonia and other sever diseases. Influenza-related pneumonia could be primarily viral and could also be accompanied or followed by a secondary bacterial infection, mainly due to *Staphylococcus aureus* and *Streptococcus pneumoniae* (11).

Effect of influenza infection on the fetus

Few pathogens could be transmitted through the maternal-fetal barrier, including TORCH, HIV, varicella zoster, plasmodium malaria, B19 parvovirus, rubella, zika virus, cytomegalovirus (CMV), herpes simplex virus (HSV-1), and HSV-2. There is little information on the transmission of IFV through the placenta to the fetus, which has been reported sporadically (13).

However, the adverse effects of IFV indirectly affect the fetus and cause problems such as neural tube defects, encephalitis, congenital heart defects in the first trimester, as well as preterm delivery and spontaneous abortion (14).

Anatomical, hormonal, and immunological changes in pregnant women with influenza

During pregnancy, immunological, hormonal and hemodynamic changes are necessary for a successful pregnancy. Reproduction in women is mainly regulated by the estrogen, progesterone, luteinizing (LH), and follicle-stimulating (FSH) hormones. Pregnant women have unique immunological properties that are regulated by the sex hormones estrogen and progesterone. The role of these hormones in the coordination of maternal and fetal uterine tissue has been extensively studied (15). Sex hormones also play vital roles in regulating granular lymphocytes in the innermost epithelial layer of the uterus, uterine natural killer (NK) cells, dendritic cells (DC), macrophages, and memory and regulatory T cells. During pregnancy, uterine progesterone induces the production of interleukin 4 (IL-4), IL-5 and IL-6 to promote T helper 0 cells evolution into Th2 cells to detect antigens. Th2 cells play a role in the development of immune tolerance between the mother and the fetal placenta, prevent the activation of NK cells against fetal trophoblasts, stimulate B cells, and suppress cytotoxic T cells. Increased expression of IL-4 and IL-6 causes the secretion of human chorionic gonadotropin (HCG) from the corpus luteum, which in turn causes the production of progesterone, providing positive feedback on boosting Th2 production. All of these steps prevent recurrent miscarriage and provide immune tolerance by overcoming Th1 cells in endometrium. Progesterone also regulates regulatory T cells (Treg) activity in the uterus, which suppresses the inflammatory system by suppressing NK cells and macrophages in the endometrium (16). Estrogen plays a vital role in the induction of CD4 and CD25 to maintain maternal-fetal tolerance (17). Thus, estrogen and

progesterone create a coordinated environment in the uterine epithelial cells and innate immune cells for the stability and growth of the fetus.

Immunological changes in pregnant women

In order to have a safe and successful pregnancy, in addition to hormonal changes, major changes occur in the immune system, which include increasing the activity of humoral immunity compared to cellular immunity, thereby reducing the ratio of Th1 to Th2. During the first and second trimesters of pregnancy, inflammatory reactions occur in the mother's body, and then during the rapid growth of the fetus, hormonal changes and contact with fetal immune antigens lead to anti-inflammatory reactions. These immunological changes are essential for a successful pregnancy but provide the basis for some infections (18, 19). Elevation of Th2 cells promotes the humoral immunity against antigens but jeopardizes cellular immunity by suppressing the cytotoxic T cell response. These changes may be clinically observed in patients with autoimmune disorders during pregnancy. While 70% of women with rheumatoid arthritis may experience temporary improvement during pregnancy, those with systemic lupus erythematosus may experience relapse due to over production of antibodies (Abs); in general, these immunological and systemic changes increase the mother's susceptibility to various infections such as influenza, malaria, and hepatitis E (20-22).

A study on peripheral blood mononuclear cells (PBMCs) culture showed that IFV H1N1 in pregnant women significantly reduced interferon-alpha (IFN-α) and interferon-gamma (IFN-γ) responses, resulting in more susceptibility of pregnant women to viral infections (23).

Another study found that although the amount of cellular immunity and NK cells decreased during pregnancy, they increased when pregnant women were exposed to the influenza virus as an intracellular pathogen compared to non-pregnant women. Influenza is the cause of pulmonary inflammation, which is one of the leading causes of death in this patient group (24). In addition, elevated levels of pro-inflammatory cytokines and chemokines, including tumor necrosis factor (TNF-α), IL-1β, IL-6, IL-10, CXCL8, and CXCL10, were found to be associated with increased NK and T cell responses in pregnant women with influenza A (H1N1) (25). Influenza virus was shown to cause cytokine storm and consequently pneumonia or respiratory distress syndrome during the influenza pandemic in 2009 (26).

Physiological changes in pregnant women

Cardiovascular changes during this period include increased blood volume along with increased cardiac output and decreased vascular resistance. Also, diastolic and systolic blood pressure of the heart decreases, which causes cardiac output and thus diastolic blood pressure to increase, but not systolic blood pressure (27).

The increase in blood volume starts in the first trimester and increases by 30 to 45%, reaches its maximum level in the second trimester, and slowly increases again in the third trimester (28). Respiratory function is altered due to increased progesterone as well as changes in chest size and chorionic B gonadotropin levels; as maternal oxygen consumption increases, the volume of inhalation and exhalation increases by 15-20% and 40-30%, respectively. However, respiration rate and vital capacity remain unchanged, which in turn reduces the lungs' ability to compensate for respiratory stressors during pregnancy (27).

Cytokine Storm

Respiratory epithelial cells are the main targets of IFV during infection, they induce cytokine production during infection. At the beginning of each infection, tissue damage increases blood flow to induce inflammation in order to recruit leukocytes and macrophages into the area, causing the temperature to rise. In general, the acute inflammatory response is characterized by the activation of cytokines or pro-inflammatory chemokines, which ultimately stimulate inflammatory cells and their proliferation, during which the expression of inflammatory, antiviral,

and apoptotic genes is accompanied by the infiltration of immune cells, probably leading to extensive tissue damage (29, 30).

During IFV infection, cytokine response is induced in two stages: IFV infection in epithelial cells, endothelial cells, and alveolar macrophages leads to an early wave of cytokine production, especially type I IFN, by stimulating the production of interferon-producing genes. Endothelial cells expressing the Sphingosine-1-phosphate (S1P1) receptor have been shown to be the major regulators of cytokine storms. Following the release of type I IFN, the expression of interferon-stimulated genes (ISG) increases, and antiviral responses and inflammatory cytokine production occur. Subsequently, innate immune cells, such as DCs (macrophages, neutrophils, and monocytes), are activated (31). In the second step of response to the virus, T cells and lymphocytes of innate immunity are activated and regulated to secrete secondary cytokines to maintain lung tissue homeostasis. During the initial cytokine storm, more than 15 cytokines are produced, the most important of which include: type I and III IFN, IL-1β, IL-18, TNF-α, IL-6, and IL-33.

The cells then secrete a second wave of cytokines to facilitate the virus clearance process, modulate inflammation, and restore lung tissue, in which IFN-γ, IL5, and IL10 are effective (32). IFN-γ secreted by T and NK cells has several functions during influenza infection, including promoting viral clearance, inducing humoral and cellular immunity, and improving disease outcomes (33). High levels of IL10 indicate a host attempt to regulate inflammatory damage caused by cytokine storms. In general, IL10 shows an index of uncontrolled inflammation (34).

Why IFV is more risky for pregnant women?

The data show that sialic acid levels in serum and possibly in cell surfaces are elevated during pregnancy, especially at the end of the second trimester (19–14 weeks) and in the third trimester (40–29 weeks). Relative changes in the amount of sialic acid in the amniotic fluid have also been observed. Sialic acid content has also been shown to increase in saliva (35). It is not known whether sex hormones affect the activity of the enzymes sialyltransferases or sialidases that control serum sialic acid levels. Increased total serum sialic acid levels may reflect increased sialylation of glycoproteins or glycolipids, suggesting an increase in sialyltransferase activity. Thus, increased serum sialic acid levels and possibly cellular receptors increase the binding capacity and the number of interactions between human IFV and the cell surface, thereby increasing viral attachment and accelerating infection. Consequently, this feature could support the hypothesis that changes in sialic acid levels during pregnancy could be an important factor in increasing the risk of developing severe complications in pregnant women infected with IFV (36, 37).

Influenza vaccine during pregnancy and its safety

The influenza vaccine is the most effective means to prevent IFV infection and its severe consequences. Given the safety of the influenza vaccine and the risks of influenza virus, many studies have recommended that pregnant women or those intending to become pregnant be vaccinated before or during the influenza season (8).

The use of seasonal and endemic vaccines at any stage of pregnancy period is safe. The attenuated live influenza vaccine is not recommended for use in pregnant women, but could be administered after delivery. In general, the use of quadrivalent influenza vaccine is recommended to prevent both types of IFV A and B, and its use is not prohibited during any semester of pregnancy (38). Unfortunately, given the importance of maternal influenza vaccination, only 49% of pregnant women in the United States received the vaccine in 2017-2018 (38). Extensive studies have been conducted on the vaccine safety, and no side effects such as fetal death, fetal defects, and birth defects or long-term complications such as teratogenicity and neurological complications have been reported even in the first trimester of pregnancy (39).

In addition, pregnant women do not experience complications such as gestational diabetes, eclampsia, preeclampsia, and other vaccination-related complications. Maternal influenza vaccination not only reduces the hospitalization of their infants due to flu by up to 72%, but is also effective for the mother herself up to 44% (40). Newborns under 6 months could not get the influenza vaccine because they do not have an evolved immune system. After vaccination, the induced immunity in the mother's body is transmitted to the fetus through the umbilical cord and protects the fetus and newborn from infection (41).

Fetal immunity

In humans, protective IgG Abs are transferred from the mother to the fetus through the placenta, and IgA Abs are transmitted from breast milk to the baby. The degree and duration of embryonic protection depends directly on the maternal Ab titer and effective transmission through the umbilical cord (42). The results of the 2009 IFV pandemic showed that 90% of mothers receiving the influenza vaccine had under-6-month infants who were more immune and 50% less likely to be hospitalized due to flu compared to unvaccinated mothers. Women who receive the influenza vaccine 15 days before delivery could not provide effective immunity for the fetus; thus, the interval between vaccination and delivery must be over 15 days to provide effective immunity for the fetus. The rate of anti-influenza antibody decreases by 63% after 6 months, indicating that the half-life of congenital Abs is 42-50 days (43, 44). Due to changes during pregnancy and immune progression to Th2, Ab isotypes also alter.

Influenza vaccine could neutralize viral HA by various mechanisms, including Ab-mediated activation of inflammatory cells and virus aggregation on the cell surface. The result of viral accumulation is a decrease in viral titer within the cell (45). In humans, these unique protective mechanisms are regulated by Abs that are primarily controlled by four IgG isotypes (IgG1, IgG2, IgG3, and IgG4).

IgG1 and IgG3 are mainly produced in response to viral infections, with IgG3 stimulating a strong anti-inflammatory response. The vaccine produces weaker pro-inflammatory responses compared to influenza infection, which are C-reactive protein (CRP) and TNFα produced in responses to the vaccine, similar to the body's response to viral infections. Antibody isotypes also alter due to changes during pregnancy and immune progression to Th2 (46). IgG class 1 and 3 Abs are produced in response to vaccine injection, but due to the specific conditions of pregnancy, these responses are somehow suppressed, and the reduction of these isotypes may lead to an inefficient response to the vaccination (40, 47). However, IgG-2 is produced in bacterial or fungi infection in response to their capsule, and there is no evidence showing its effects on influenza (48).

Antiviral treatment

Antiviral therapy should not be delayed even by a negative test result; otherwise, this delay could be very dangerous for people who are prone to the disease, especially pregnant women or women who are two weeks pregnant. Early initiation of treatment is associated with reduced duration, severity, and mortality of the disease, need for antibiotics, and hospitalization (49). Antiviral therapies for IFV include inhibitors of viral replication and cellular signaling and modulatory pathways in immune reaction. Neuraminidase inhibitors (including oseltamivir, zanamivir, peramivir, and laninamivir) are commonly used for treatment but may also be used for prophylaxis; however, no side effects have been reported in pregnant women or fetuses (50). At the time of the 2009 pandemic, little was known about antiviral therapy, but early treatment with oseltamivir, especially within 48 hours of the onset of symptoms, was shown to reduce mortality compared with late treatment. Therefore, treatment with oseltamivir is recommended in pregnant women, especially those with symptomatic hospitalization (51). A study on NA inhibitors reported no side effects for these drugs, including abortion, preterm delivery, stillbirth, or teratogenic effects in animal models.

Global data have shown that only about 1% of circulating strains are resistant to oseltamivir (52). Antiviral therapy for the treatment of influenza during pregnancy includes 75 mg oseltamivir twice daily for five days or 10 mg zanamivir (two inhalations) twice daily for five days (53). Both antiviral drugs used in the treatment provide acceptable safety; however, there is no adverse reaction in pregnancy or infancy. Both oseltamivir and zanamivir are usually well tolerated with minimal side effects. The most common side effect of oseltamivir is mild nausea and vomiting, which is usually self-limiting and may occur in up to 15% of patients. Zanamivir is prescribed in a dry inhaled powder and therefore is generally not recommended for people with underlying respiratory diseases such as asthma (8, 52).

Conclusion

It could be concluded that influenza vaccination is considered safe at any stage of pregnancy and could prevent possible fetal defects such as congenital heart, harelip or cleft lip, and hydrocephalus. However, it is important to note that the use of the vaccine ten days before delivery could not provide an effective immunity for the fetus. Maternal vaccination induces effective immunity in newborns up to 6 months of age. Pregnant women should also be advised to report flu-like illnesses to physicians immediately, as early diagnosis and treatment are very important. Despite the many and necessary recommendations for receiving the vaccine during pregnancy, unfortunately, not much attention is still paid to this important issue, the realization of which requires extensive training of the community and raising public awareness by health care providers and building the necessary trust.

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