



## Pandemic Influenza and Pregnant Women: An Overview on Influenza Vaccination during Pregnancy and its Impact on Pregnancy Outcomes

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### Abstract

**Background:** Evidence of the effectiveness and safety of the influenza vaccine in pregnancy is necessary for the decision-making process of healthcare providers. The present study aims to review the available evidence on the effectiveness and safety of influenza vaccination during pregnancy and its impact on pregnancy outcomes.

**Materials and Methods:** In this overview, two independent researchers have selected articles reporting on the effectiveness and safety of influenza vaccination for pregnant women and their fetuses in the Scopus, EMBASE, Cochrane Library, Web of Science, CINAHL, Medline databases and Google Scholar search engine, without time restrictions up to January 2023.

**Results:** Based on the available evidence, pregnant women are at a higher risk of serious illness due to influenza than non-pregnant women. The influenza vaccine is the best way to protect pregnant women and their infants against influenza and to prevent possible influenza-associated pregnancy complications. Vaccination during pregnancy is a safe and cost-effective method and also provides neonatal protection against influenza due to the partial transplacental transfer of protective antibodies. There is no evidence of associations between influenza vaccination administered at any time in pregnancy and adverse pregnancy or fetal outcomes, including premature birth, spontaneous abortion, congenital anomalies, shortened gestation, gestational diabetes, chorioamnionitis or gestational hypertensive disorders, and fetal death. In addition, influenza vaccination during pregnancy reduced pregnant women's risk of pre-delivery hospitalization with influenza-like illness by approximately 39%.

**Conclusion:** The administration of an inactivated influenza vaccine during pregnancy is safe for both the mother and the fetus and is recommended for all pregnant women. There is no evidence of associations between influenza vaccination and maternal complications or adverse fetal outcomes.

**Key Words:** Adverse events, Influenza vaccination, Pregnant women, Outcomes.

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## 1- INTRODUCTION

Influenza (commonly known as the flu) is an infectious disease caused by influenza viruses. There are four types of influenza viruses, termed A, B, C, and D. Aquatic birds are the primary sources of influenza A virus (IAV), which is also widespread in various mammals, including humans and pigs. Influenza B virus (IBV) and influenza C virus (ICV) primarily infect humans, and Influenza D virus (IDV) is found in cattle and pigs. IAV and IBV circulate in humans and cause seasonal epidemics. ICV causes mild infection, primarily in children, and IDV can infect humans but is not known to cause illness (1-10). Influenza affects different population groups disproportionately, with pregnant women, the very young, the very old, and people with certain health conditions being at the highest risk of serious complications. Since the 1918 influenza pandemic (11), pregnant women and their babies (up to six months of age) have been recognized as the two important groups at high risk of disease and serious complications (12-20).

Influenza can be severe in pregnant women and newborns. Changes in the immune system, heart, and lungs during pregnancy make pregnant women more likely to suffer complications from influenza than women of childbearing age who are not pregnant. Influenza can cause life-threatening illnesses like pneumonia and damage to the heart, brain, and other parts of the body. These complications can lead to hospitalization and even death. Evidence suggests that pregnant women are more vulnerable during pandemics (15-19). Evidence from the last influenza pandemic (2009/H1N1) showed that pregnant women were particularly vulnerable to severe infection (15-19), resulting in increases in maternal and perinatal mortality alike (21, 22). The best way to protect pregnant women against influenza is by vaccinating against it (23).

The World Health Organization (WHO) recommends influenza vaccination for pregnant women at any stage of pregnancy (24). It has been found that influenza vaccination for pregnant women at any stage of pregnancy is highly effective in preventing the disease and its complications in mothers and newborns during pregnancy and up to six months after birth by the passive protection passed on to the baby in utero through the placenta (25, 26). Therefore, protecting pregnant women and infants from influenza is a priority, as seen in the 2009 influenza A (H1N1) pandemic, where pregnant women developed severe complications from influenza infection. However, it is considered an expensive public health measure, and a large amount of new evidence is now available following the pandemic influenza A (H1N1) 2009 outbreak. A rapid study of this group (pregnant women) is needed to assess all available studies (reviews, systematic reviews, and cohort studies) to provide clarity on the effectiveness and safety of influenza vaccination during pregnancy and the impact on pregnancy outcomes.

## 2- MATERIALS AND METHODS

This overview considered all reviews, cohort studies (prospective or retrospective clinical observational studies), systematic reviews, and meta-analyses available in full and in Persian or English inclusion. The search included articles from the inception of each database up to January 2023. The following databases were searched: Scopus, EMBASE, Cochrane Library, Web of Science, CINAHL, and Medline (via PubMed), and Google Scholar search engine. This overview focused on pregnant women with or without risk factors for complications from influenza infection and their fetuses and infants up to the age of six months. Two

independent researchers conducted the search process, and a supervisor resolved possible discrepancies. The following steps were taken to develop this review: (1) identifying the research question; (2) identifying the relevant studies; (3) selecting studies; and (4) summarizing and reporting the data.

### 3- RESULTS

A total of 16 related studies were selected (systematic reviews and meta-analysis=5, reviews=5, and cohort studies=6). The general specifications and data of the selected articles are presented below:

**1.** A systematic review and meta-analysis (of ten studies) aimed to investigate risk factors of influenza virus infection during pregnancy and to analyze its impact on pregnancy outcomes, especially birth weight. Results study showed that anemia, asthma, and obesity during pregnancy are risk factors for influenza A virus infection during pregnancy. Regarding birth outcomes, influenza A virus infection did not affect the likelihood of cesarean section. Mothers with influenza had a higher rate of stillbirth, and their offspring had lower five-minute Apgar scores ( $P<0.05$ ). Also, the rate for a birth weight lower than 2500g ( $P=0.04$ ,  $RR=1.71$ , 95% CI: 1.03-2.84) was increased (27).

**2.** A systematic review (of 40 studies) aimed to investigate the safety of inactivated influenza vaccination (IIV) in pregnancy. The results confirmed the safety of influenza vaccination in pregnancy and affirmed that there was no evidence of an increased risk of adverse pregnancy outcomes following influenza vaccination (28).

**3.** A systematic review (of 46 studies) aimed to synthesize the best available evidence on the effectiveness and safety of influenza vaccination during pregnancy, fetuses, and infants. Results showed that

the influenza vaccine administered during pregnancy was effective and provided a similar reduction in influenza-like illnesses as in the healthy adult population. However, there is no evidence of the effectiveness of the influenza vaccine in reducing severe illness or hospitalization in pregnant women. Infants of pregnant women vaccinated during their second or third trimester could have reduced rates of influenza and influenza-related hospitalization for their first six months of life. Also, influenza vaccination during pregnancy had no association with adverse outcomes for the fetus, including premature birth, small size for gestational age, congenital malformations, spontaneous abortion, and fetal death (29).

**4.** A systematic review and meta-analysis (of 18 studies) aimed to determine the impact of maternal vaccination on the rates of preterm (PTB), small for gestational age (SGA), and low birth weight (LBW) births. The results showed that receiving the influenza vaccine during pregnancy was associated with a decreased risk of PTB and LBW (30).

**5.** A systematic review and meta-analysis (of 17 studies) aimed to assess the effect of influenza infection on pregnancy outcomes. The results showed that influenza infection was associated with a higher risk of stillbirth. The effect of infection on preterm birth, fetal death, and small for gestational age, and low birth weight remains uncertain (31).

**6.** A review aimed to examine the Indian studies on influenza among pregnant women. The results showed that in most studies, influenza A (pH1N1) was associated with increased maternal mortality (25–75%), greater disease severity, and adverse fetal outcomes as compared to non-pregnant women (32).

**7.** In a review, inactive influenza vaccination was recommended for pregnant women. All women who are

pregnant or about to deliver during influenza season should be vaccinated with trivalent or quadrivalent influenza vaccine regardless of the trimester of pregnancy. Vaccination during pregnancy is a safe and cost-effective method and also provides neonatal protection against influenza due to the partial transplacental transfer of protective antibodies (33).

**8.** A review aimed to provide information on the influence of influenza virus infection during pregnancy on maternal health and pregnancy outcomes and on the effects of treatment and vaccination. The results showed that pregnant women might be at an increased risk of complications of influenza virus infection, especially during the third trimester. For hospitalized patients, increased rates of preterm birth and fetal/neonatal death were reported. Vaccination of pregnant women is safe and reduces maternal and neonatal morbidity (34).

**9.** A review aimed to investigate the literature on influenza vaccine safety, effectiveness, and coverage rates during pregnancy, and opportunities to improve vaccination rates. The results showed that no study demonstrated an increased risk of maternal complications or adverse fetal outcomes associated with the inactivated influenza vaccine. The influenza vaccine can be safely and effectively administered during any trimester of pregnancy (35).

**10.** A review aimed to briefly discuss the data collected before and after the 2009 pandemic regarding the impact of influenza on pregnant women and their fetuses/newborns. The results indicated the benefits and a history of safety of vaccination for pregnant women. Prevention of influenza infection in pregnant women and their newborns begins with efforts to limit exposures, including hand washing, respiratory hygiene, and cough etiquette, and implementation of infection control precautions and environmental procedures

in the healthcare settings frequented by these individuals. It has also been documented that risks increase as the pregnancy progresses, with influenza-associated hospitalization rates being up to five times higher in women infected with influenza during the third trimester (36).

**11.** A retrospective cohort study (of 86779 pregnancies during the influenza season in 2012–2014) aimed to measure the epidemiological characteristics of seasonal influenza infection among pregnant women and its impact on infant health. The results showed no difference in the infection cases admitted to hospitals regarding the trimester or subtype of infection. Influenza B infections were more likely to occur in the second trimester compared with A/H3N2 and A/H1N1 infections (41.3%, 23.6%, and 33.3%, respectively). On average, infants born to women with influenza B during pregnancy had 4.0% (95% CI 0.3–7.6%) lower birth weights than the optimal compared with infants born to uninfected women ( $P = 0.03$ ) (37).

**12.** A retrospective cohort study used a birth registry from health administrative data containing all live births in Nova Scotia, Canada, between 2010 and 2014 to assess the association between maternal influenza vaccination during pregnancy and early childhood health outcomes. The results showed that maternal influenza vaccination during pregnancy was not associated with immune-related adverse health outcomes (e.g., asthma, infections), non-immune-related health outcomes (e.g., neoplasms, sensory impairment), or nonspecific health service utilization (e.g., emergency department visits and hospitalizations) in young children (38).

**13.** A national, prospective, observational cohort study used the UK Obstetric Surveillance System (UKOSS) to identify all pregnant women admitted to hospitals between 2016 and 2018 with laboratory-confirmed influenza at any gestation age

up to two days after giving birth. The study aimed to describe the characteristics and outcomes of pregnant women hospitalized with seasonal influenza and found that influenza immunization reduced the risk of hospitalization with influenza in pregnancy. Higher awareness of the safety and effectiveness of immunization in pregnancy and vaccine provision within antenatal care settings, especially for high-risk groups, are required (39).

**14.** A prospective, longitudinal cohort study of pregnant women in three middle-income countries (Thailand, Peru, and India) evaluated the effect of laboratory-confirmed influenza on pregnancy and perinatal outcomes. The results showed that pregnant women were at an increased risk for influenza-associated hospitalizations, but little was known about the incidence of influenza and influenza-associated complications during pregnancy. There were no published studies from low- or middle-income countries on the effect of seasonal influenza during pregnancy on birth outcomes, even though pregnancies in these countries accounted for > 90% of births globally (40).

**15.** A retrospective cohort study on 1253 healthy nulliparous pregnant women in South Australia between 2015 and 2018 aimed to assess the safety and protective effect of maternal influenza vaccination on pregnancy and birth outcomes. The results supported the safety of maternal influenza vaccination and suggested a positive effect on reducing low birth weight rates and small for gestational age births. There was no evidence of associations between influenza vaccination administered at any time in pregnancy and adverse pregnancy or fetal outcomes, including spontaneous abortion, congenital anomalies, shortened gestation, gestational diabetes, chorioamnionitis, or gestational hypertensive disorders, consistent with the literature. In addition, the study found that

influenza vaccination during pregnancy reduced a pregnant woman's risk of pre-delivery hospitalization with influenza-like illnesses by approximately 39% (41).

**16.** A prospective cohort study on more than 11,000 pregnant women from three middle-income countries (India, Peru, and Thailand) aimed to assess the effect of antenatal influenza on pregnancy outcomes. The results showed that influenza was not associated with preterm birth but was associated with a decrease in birth weight of singleton, full-term, and live-born infants. Also, women had a 0.7–0.9% risk of influenza for each month of pregnancy spent in the influenza season (42).

#### 4- DISCUSSION

This overview aimed to review the best available evidence on the effectiveness and safety of influenza vaccination during pregnancy and its impact on pregnancy outcomes. Based on the results, maternal vaccination is a safe and cost-effective method during pregnancy and the best way to protect pregnant women and their infants from influenza and possible influenza-associated pregnancy complications. There was no evidence of associations between influenza vaccination and maternal complications or adverse fetal outcomes.

Influenza typically involves symptoms such as fatigue, headache, muscle aches, and pains, and patients usually have a fever. This winter (2022/2023), COVID-19 and influenza continue to circulate and can be difficult to distinguish based on their symptoms alone without a laboratory test. This fact should be considered in clinical assessments. The most effective way to avoid influenza infection is through vaccination.

There are four types of influenza viruses: A, B, C, and D. Human influenza A and B viruses cause seasonal epidemics of the

disease (known as the flu season) almost every winter. Influenza A viruses are the only influenza viruses known to cause flu pandemics. A pandemic can occur when a new and different influenza A virus emerges that has the ability to infect and spread efficiently among people. Influenza C virus infections generally cause mild illness and are not thought to cause human epidemics. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people (10, 43-46).

Three influenza pandemics occurred have occurred in the 20th century: Spanish influenza in 1918 (~50 million deaths), Asian influenza in 1957 (two million deaths), and Hong Kong influenza in 1968 (one million deaths) (47). The World Health Organization declared the outbreak of a new type of influenza A (H1N1) as a pandemic in June 2009 (48). Influenza may also affect other animals, including pigs, horses, and birds (49).

Most people recover from fever and other symptoms within a week without requiring medical attention. However, influenza can cause severe illness or death, particularly among high-risk groups, including the very young, the elderly, pregnant women, health workers, and those with serious medical conditions. Most women who catch influenza during pregnancy develop a relatively mild illness, but the risk of becoming seriously ill or dying is greater for pregnant women than for other, otherwise healthy people (43, 46). Pregnant women are 2.5 times more likely to be admitted to hospital with influenza than other women (50). Influenza infection during pregnancy can lead to other complications, such as premature delivery and even neonatal and perinatal death (51). Vaccination is the most effective method for preventing severe influenza illness and its sequelae (27-42, 52-55). Inactivated influenza vaccine is used for pregnant women in most countries, and based on most evidence, there are no concerns about

the safety of influenza vaccination during any trimester of pregnancy (20, 25, 26, 36, 43-63). In humans, influenza viruses are primarily transmitted through respiratory droplets via coughing and sneezing. Transmission through aerosols and intermediate objects and surfaces contaminated by the virus also occurs (64, 65). In a typical year, 5–15% of the population contracts influenza (66, 67).

Changes in the immune system, heart, and lungs during pregnancy make pregnant women more susceptible to severe influenza illness, pneumonia, and hospitalization (68). Reducing morbidity and mortality from influenza in pregnancy is an important public health priority, requiring a comprehensive effort on the part of public health officials, health educators, researchers, and the healthcare system. Influenza immunization during pregnancy helps protect both the mother and the baby from the disease and its complications (69-71). Infants cannot receive their first dose of influenza vaccine until six months of age, and maternal vaccination helps protect the youngest infants from influenza. Infants of mothers immunized during pregnancy are less likely to be hospitalized for acute respiratory illnesses (72-74).

The best way to protect young infants from pertussis and influenza is by immunizing their mothers during pregnancy. The American College of Obstetricians and Gynecologists (ACOG), the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), and the Centers for Disease Control and Prevention (CDC) recommend that all pregnant women receive Tdap (tetanus, diphtheria, and pertussis) and influenza immunizations (75, 76). The World Health Organization states that pregnant women are among the highest priority groups for seasonal influenza vaccination (77). The CDC recommends that all women who are, will, or could be

pregnant during influenza season should receive an influenza vaccine during any trimester (78, 79). The composition of the influenza vaccine typically changes each year to accommodate the strain(s) of the virus that are expected to be the most prevalent that year, making it critical to receive an influenza vaccine annually (80). The expected adverse events following influenza vaccines occur as frequently in pregnant women as others. Local reactions (e.g., redness, swelling, and pain) occur in about one in ten adults who receive the vaccine, and systemic reactions (e.g., fever, tiredness, and myalgia) occur in fewer people. Serious adverse events like Guillain-Barré syndrome are very rare, occurring in about one in a million vaccinated people (81).

Reducing morbidity and mortality from influenza in pregnancy is an important public health priority, which requires extensive effort. Frequent hand washing with soap and water, avoiding touching eyes, nose, or mouth, wearing masks, staying home, and limiting contact with others, especially sick people, are important hygiene measures to prevent the spread of influenza (82-85).

## 5- CONCLUSION

Although influenza vaccine effectiveness may seasonally vary, vaccination continues to be the best available way to prevent influenza infection and its complications. Influenza vaccination can also reduce symptom severity and the risk of hospitalization and death. Pregnant women are more at risk of serious illness due to influenza compared to non-pregnant women. Available studies demonstrated that the administration of an inactivated influenza vaccine during pregnancy is safe for both the mother and the fetus. The influenza vaccine is the best way to protect pregnant women and their infants from influenza and to prevent possible influenza-associated pregnancy

complications. Influenza vaccination during pregnancy had no association with adverse outcomes for the fetus, including premature birth, spontaneous abortion, congenital anomalies, shortened gestation, gestational diabetes, chorioamnionitis or gestational hypertensive disorders, and fetal death. Infants of women who were vaccinated during pregnancy are expected to have reduced rates of influenza and influenza-related hospitalization for their first six months of life. In addition, influenza vaccination during pregnancy reduces a pregnant woman's risk of pre-delivery hospitalization with influenza-like illnesses by approximately 39%. Nevertheless, more experimental studies are recommended to confirm these findings.

**6- CONFLICT OF INTEREST:** None.

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