



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

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Abstract

Background: Evidence of the Influenza vaccine's effectiveness and safety in pregnancy is critical to the decision making process of health care providers. We aimed to review the available evidence on the effectiveness and safety of influenza vaccination during pregnancy and the impact on pregnancy outcomes.

Materials and Methods: In this overview, two independent researchers have selected articles that reported the effectiveness and safety of influenza vaccination during pregnancy for pregnant women and their fetus in the Scopus, EMBASE, Cochrane library, Web of Science, CINAHL, Medline databases, and Google Scholar search engine, without time restrictions up to September 2022.

Results: Based on the available evidences, pregnant women are more at risk of serious illness due to influenza compared to non-pregnant women. Influenza vaccine is the best way to protect pregnant women and their infants from influenza and prevent possible influenza-associated pregnancy complications. While vaccination during pregnancy is a safe and cost-effective method, it also provides neonatal protection against influenza due to the partial transplacental transfer of protective antibodies. There was 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 a pregnant woman's risk of pre-delivery hospitalisation with influenza-like illness by around 39%.

Conclusion: Administration of an inactivated influenza vaccine during pregnancy is safe for both the mother and their fetus, and is recommended for all pregnant women. There was 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 virus, termed influenza viruses A, B, C, and D. Aquatic birds are the primary source 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, and ICV causes a mild infection, primarily in children. 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 at highest risk of serious complications. Two important groups at high risk of disease and serious complications have been recognised since the 1918 influenza pandemic (11), they are pregnant women and their babies (up to 6 months of age) (12-20).

Influenza can be very serious in pregnant women and their newborn babies. Changes in the immune system, heart and lungs during pregnancy make pregnant women more likely to suffer complications from the flu 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 hospitalisation and even death. Evidence suggests that pregnant women are even 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 both maternal and perinatal mortality (21, 22). The best way to protect pregnant women against flu is

by vaccinating against it (23). The World Health Organization recommends influenza vaccination of pregnant women at any stage of pregnancy (24). Influenza vaccination of pregnant women during any stage of pregnancy has been found to be highly effective in preventing influenza and its complications in the woman and her baby, during pregnancy and for up to six months after birth by the passive protection passed on to the baby in utero, through the placenta (25, 26). So, 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 to be 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) will be important to assess all available studies (reviews, systematic review and cohort studies) in an attempt to provide clarity on the effectiveness and safety of influenza vaccination during pregnancy and the impact on pregnancy outcomes.

2- MATERIALS AND METHODS

In this overview, all reviews, cohort studies (prospective studies or retrospective clinical observational studies), systematic reviews, and meta-analyses, available in full, in Persian or in English were considered for inclusion in this review. The search included articles from the inception of each database up to September 2022. The databases searched included: Scopus, EMBASE, Cochrane library, Web of Science, CIVILICA, CINAHL, and Medline (via PubMed). This overview focused on pregnant women with or without risk factors for complications from influenza infection, their fetus and infants up to the age of six months. Two independent researchers conducted the search process, and one

supervisor resolved any discrepancies on this issue. The following steps were taken to develop this review: (1) identify the research question; (2) identify the relevant studies; (3) selection of studies; and (4) summarize and report the data.

3- RESULTS

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

1. A systematic review and meta-analysis (10 studies) aimed to investigate risk factors of influenza virus infection during pregnancy, and to analyze the impact of influenza virus infection on pregnancy outcome, especially birth weight. Results of this study showed that anemia, asthma and obesity during pregnancy are risk factors of influenza A virus infection during pregnancy. Regarding birth outcomes, influenza A virus infection did not affect the likelihood for cesarean section. Mothers with influenza had a higher rate of stillbirth, and their offspring had low 5-minute APGR Scores ($p < 0.05$). Furthermore, the rate for birth weight $< 2500\text{g}$ ($P = 0.04$, $RR = 1.71$, $95\% \text{ CI: } 1.03\text{--}2.84$) was increased (27).
2. In a systematic review (40 studies) which aimed to review the safety of inactivated influenza vaccination (IIV) in pregnancy, results confirmed the safety of influenza vaccination in pregnancy and affirmed that there is no evidence of an increased risk of adverse pregnancy outcomes following influenza vaccination in pregnancy (28).
3. In a systematic review (46 studies) aimed to synthesize the best available evidence on the effectiveness and safety of influenza vaccination during pregnancy for pregnant women, their fetus and infant, results showed that Influenza vaccine

administered during pregnancy is effective and provides a similar reduction in influenza-like illness as it does for a healthy adult population. Despite this, there is no evidence on the effectiveness of the influenza vaccine at reducing severe illness or hospitalization in pregnant women. Infants of pregnant women vaccinated during their second or third trimester can expect to 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 for gestational age, congenital malformation, spontaneous abortion and fetal death (29).

4. In a systematic review and meta-analysis (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, results showed that receipt of influenza vaccine during pregnancy was associated with a decreased risk of PTB and LBW (30).
5. In a systematic review and meta-analysis (17 studies) which aimed to assess the effect of influenza infection on pregnancy outcomes, results showed influenza virus infection is associated with a higher risk of stillbirth among pregnant women, while the effect on preterm birth, fetal death, small for gestational age and low birth weight remains uncertain (31).
6. In a review aimed to examine the Indian studies of influenza among pregnant women, 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 by trivalent or quadrivalent influenza vaccine independent from the trimester of pregnancy. While vaccination during pregnancy is a safe and cost-effective method, it also provides neonatal protection against influenza due to the partial transplacental transfer of protective antibodies (33).

8. In a review aimed to provide information on the influence of influenza virus infection during pregnancy on maternal health and pregnancy outcome and on the effect of treatment and vaccination, results showed that the pregnant women appear to 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 are reported. Vaccination of pregnant women is safe and reduces maternal and neonatal morbidity (34).

9. In a review aimed to review the literature concerning influenza vaccine safety, effectiveness, and coverage rates during pregnancy, as well as opportunities to improve vaccination rates during pregnancy, results showed that no study has demonstrated an increased risk of maternal complications or adverse fetal outcomes associated with inactivated influenza vaccine. Influenza vaccine can be safely and effectively administered during any trimester of pregnancy. No study has demonstrated an increased risk of maternal complications or adverse fetal outcomes associated with inactivated influenza vaccine (35).

10. In a review aimed to briefly discuss the data collected both before and after the 2009 pandemic as it relates to the impact of influenza on pregnant women and their fetuses/newborns, results indicated benefits and a history of safety of pregnant

women vaccination. Also, 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 that these individuals frequent. Moreover, it has been documented that risk increases as the pregnancy progresses, with up to fivefold higher influenza-associated hospitalization rates in women infected with influenza during the third trimester (36).

11. A retrospective cohort study (a cohort of 86 779 pregnancies during the influenza season during 2012–2014), aimed to measure the epidemiological characteristics of seasonal influenza infection among pregnant women and the impact on infant health. The results showed that there was no difference in the proportion of infections admitted to hospital by trimester or subtype of infection. Influenza B infections were more likely to occur in second trimester compared with influenza A/H3N2 and influenza A/H1N1 infections (41.3%, 23.6%, and 33.3%, respectively), and on average, infants born to women with influenza B during pregnancy had 4.0% (95% CI 0.3–7.6%) lower birth weight relative to optimal compared with infants born to uninfected women ($P = 0.03$) (37).

12. In a retrospective cohort study using a birth registry linked with health administrative data. All live births in Nova Scotia, Canada, between 2010 and 2014, aimed 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

services utilization (e.g., emergency department visits and hospitalizations) in young children (38).

13. A national, prospective, observational cohort study which aimed to describe the characteristics and outcomes of pregnant women hospitalised with seasonal influenza, used the UK Obstetric Surveillance System (UKOSS) to identify all pregnant women admitted to hospital between 2016 and 2018 with laboratory confirmed influenza at any gestation and up to two days after giving birth. The results showed that influenza immunization reduces the risk of hospitalisation with influenza in pregnancy. There is a need to increase awareness of safety and effectiveness of immunization in pregnancy and provision within antenatal care settings, especially for high-risk groups (39).

14. A prospective, longitudinal cohort study of pregnant women in 3 middle-income countries (Thailand, Peru, and India) was done to evaluate the effect of laboratory-confirmed influenza during pregnancy on pregnancy and perinatal outcomes. The results showed that pregnant women are at an increased risk for influenza-associated hospitalizations, but little is known about the incidence of influenza and influenza-associated complications during pregnancy. There are no published studies from low- or middle-income countries of the effect of seasonal influenza during pregnancy on birth outcomes, even though pregnancies in these countries account for > 90% of births globally (40).

15. In a retrospective cohort study that comprised 1253 healthy nulliparous pregnant women in South Australia between 2015 and 2018, that aimed to assess the safety and protective effect of maternal influenza vaccination on pregnancy and birth outcomes, results support the safety of maternal influenza

vaccination and suggest a protective effect in reducing the rates of low birth weight 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 influenza vaccination during pregnancy reduced a pregnant woman's risk of pre-delivery hospitalisation with influenza-like illness by around 39% (41).

16. In a prospective cohort study including 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, results showed that Influenza was not associated with preterm birth but was associated with a decrease in birthweight of singleton, full-term, 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 the impact on pregnancy outcomes. Based on the review of the results, maternal vaccination is a safe and cost-effective method during pregnancy and is the best way to protect pregnant women and their infants from influenza and prevent 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. In addition, this winter (2022/2023), COVID-19 and influenza continue to circulate and can be difficult to distinguish from their symptoms alone without a laboratory test. This needs to be considered when a clinical assessment is being undertaken. 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 disease (known as 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 both infects people and has the ability to 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).

In the 20th century, three influenza pandemics occurred: 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 (WHO) declared an outbreak of a new type of influenza A (H1N1) to be 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 get the flu 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). Based on most evidences inactivated influenza vaccine is used for pregnant women in most countries. 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 produced from coughing and sneezing. Transmission through aerosols and intermediate objects and surfaces contaminated by the virus also occur (64, 65). In a typical year, 5–15% of the population contracts influenza (66, 67). Changes to 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, which will require a broad effort on the part of public health officials, health educators, researchers, and the healthcare system. Influenza immunization during pregnancy helps protect both mother and baby from influenza and its complications (69-71). Infants cannot receive their first dose of influenza vaccine until 6 months of age; maternal vaccination helps protect our 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 and influenza immunizations (75, 76). The World Health Organization (WHO) has stated that pregnant women are one of 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 annually to accommodate the strain(s) of the virus that are expected to be most prevalent that year, making it critical to receive an influenza vaccine each year (80). The expected adverse events following influenza vaccines occur as frequently in pregnant women as in women who are not pregnant. Local reactions (such as redness, swelling and pain) occur in about 1 in 10 adults who receive the vaccine and systemic reactions (fever, tiredness and myalgia) occur in fewer people than that. Serious adverse events like Guillain–Barré syndrome are very rare, occurring in about 1 in 1 million vaccinated people (81).

Reducing morbidity and mortality from influenza in pregnancy is an important public health priority, which requires a broad effort. Frequent hand washing with soap and water, avoiding touching eyes, nose or mouth, wearing mask, 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 can vary from season to season, 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 administration of an inactivated influenza vaccine during pregnancy is safe for both the mother and their fetus. Influenza vaccine is the best way to protect pregnant women and their infants from influenza and 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 pregnant women vaccinated during pregnancy can expect to have reduced rates of influenza and influenza related hospitalization for their first six months of life. In addition, influenza vaccination during pregnancy reduced a pregnant woman's risk of pre-delivery hospitalization with influenza-like illness by around 39%. However, more experimental studies, are needed to confirm these findings.

6- CONFLICT OF INTEREST: None.

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