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Review Article (Pages: 61-72)

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

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Abstract

Background: Evidence regarding the effectiveness and safety of the influenza vaccine during pregnancy is crucial for healthcare providers' decision-making processes. This study aims to review the existing evidence on the effectiveness and safety of influenza vaccination in pregnant women and its impact on pregnancy outcomes.

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

Results: Based on the available evidence, pregnant women are at a higher risk of serious illness from influenza compared to non-pregnant women. The influenza vaccine is the most effective way to protect both pregnant women and their infants against influenza, as well as to prevent potential complications associated with the virus during pregnancy. Vaccination during pregnancy is safe, cost-effective, and provides neonatal protection against influenza through the partial transplacental transfer of protective antibodies. There is no evidence linking influenza vaccination administered at any stage of pregnancy to adverse outcomes such as premature birth, spontaneous abortion, congenital anomalies, shortened gestation, gestational diabetes, chorioamnionitis, gestational hypertensive disorders, or fetal death. Furthermore, influenza vaccination during pregnancy has been shown to reduce the risk of pre-delivery hospitalization due to 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 linking influenza vaccination to maternal complications or adverse fetal outcomes.

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

*Please cite this article as: Tafazoli A, Sorouri Sh, Vafi sani F, Soleimani Houni M, Nosratabadi I, Saadat S. Pandemic Influenza and Pregnant Women: An Overview of Influenza Vaccination during Pregnancy and Impact on Pregnancy Outcomes. Health Provid 2023; 3(1): 61-72. doi: **10.22034/HP.2022.370519.1027**

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Received date: Feb. 17, 2023; Accepted date: Jun.12, 2023

1- INTRODUCTION

Influenza, commonly known as the flu, is an infectious disease caused by influenza viruses. There are four types of influenza viruses: A, B, C, and D. Aquatic birds are the primary reservoirs for the influenza A virus (IAV), which is also prevalent in various mammals, including humans and pigs. The influenza B virus (IBV) and influenza C virus (ICV) primarily infect humans, while the influenza D virus (IDV) is found mainly in cattle and pigs. IAV and IBV circulate among humans and are responsible for seasonal epidemics. ICV typically causes mild infections, predominantly in children, whereas IDV can infect humans but is not known to cause illness (1-10).

Influenza affects different population groups disproportionately, with pregnant women, young children, the elderly, and individuals with certain health conditions being at the highest risk for serious complications. Since the 1918 influenza pandemic (11), pregnant women and their infants (up to six months of age) have been recognized as two critical groups at high risk for severe disease and complications (12-20).

Influenza can be particularly severe in pregnant women and newborns. Changes in the immune system, heart, and lungs during pregnancy increase the likelihood of complications from influenza compared to non-pregnant women of childbearing age. Influenza can lead to life-threatening illnesses, such as pneumonia, and can cause damage to the heart, brain, and other organs. These complications may result in hospitalization and even death. Evidence suggests that pregnant women are more vulnerable during pandemics (15-19).

During the last influenza pandemic (2009/H1N1), data indicated that pregnant women were especially susceptible to severe infection (15-19), leading to increases in both maternal and perinatal mortality (21, 22). The most effective way to protect pregnant women against influenza is through vaccination (23). The World Health Organization (WHO) recommends influenza vaccination for pregnant women at any stage of pregnancy (24).

Research has shown that influenza vaccination during pregnancy is highly effective in preventing the disease and its complications for both mothers and newborns, providing passive protection to the baby in utero through the placenta for up to six months after birth (25, 26). Therefore, protecting pregnant women and infants from influenza is a priority, particularly highlighted during the 2009 influenza A (H1N1) pandemic when pregnant women experienced severe complications from influenza infection (15-17).

However, vaccination is often perceived as an expensive public health measure, and a significant amount of new evidence has emerged following the 2009 outbreak of influenza A (H1N1) (15, 16, 21, 22). The aim of this rapid review is to assess all available studies—including reviews, systematic reviews, and cohort studies—to clarify the effectiveness and safety of influenza vaccination during pregnancy and its impact on pregnancy outcomes.

2- MATERIALS AND METHODS

This overview included all reviews, cohort studies (both prospective and retrospective clinical observational studies), systematic reviews, and meta-analyses available in full text in Persian or English. The search covered articles from the inception of each database up to January 2023. The databases searched included Scopus, EMBASE, Cochrane Library, Web of Science, CINAHL, Medline (via PubMed), and Google Scholar. This study focused on pregnant women with or without risk factors for complications from influenza infection, as

well as their fetuses and infants up to six months of age.

The aim of this overview was to comprehensively assess the effectiveness and safety of influenza vaccination during pregnancy and its impact on maternal, fetal, and neonatal outcomes. Two independent researchers conducted the search process to ensure methodological rigor, with a supervisor resolving any discrepancies.

The steps taken to develop this review included:

- Identifying the research question.
- Identifying relevant studies through systematic database searches.
- Selecting eligible studies based on predefined inclusion criteria.
- Summarizing and reporting the data to provide a comprehensive synthesis of findings.

This study did not require ethics committee approval because it exclusively analyzed publicly accessible articles. Nonetheless, ethical standards were upheld by adhering to copyright regulations and providing transparent documentation of methods and sources.

3- RESULTS

A total of 16 relevant studies were selected, including 5 systematic reviews and meta-analyses, 5 reviews, and 6 cohort studies. The general specifications and data from the selected articles are presented below:

1. A systematic review and meta-analysis of ten studies aimed to investigate the risk factors for influenza virus infection during pregnancy and analyze its impact on pregnancy outcomes, particularly birth weight. The results indicated that anemia, asthma, and obesity during pregnancy are significant risk factors for influenza A virus infection. Regarding birth outcomes, influenza A virus infection did not affect the likelihood of cesarean section. However, mothers with influenza had a higher rate of stillbirth, and their offspring had lower five-minute Apgar scores ($P < 0.05$). Additionally, the rate of birth weight below 2500 g was increased ($P = 0.04$, Relative Risk (RR) = 1.71, 95% Confidence Interval (CI): 1.03-2.84) (27).

2. A systematic review of 40 studies aimed to investigate the safety of inactivated influenza vaccination (IIV) during pregnancy. The results confirmed the safety of influenza vaccination in this population and indicated that there is 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 for mothers, fetuses, and infants. The results indicated that the influenza vaccine administered during pregnancy was effective and provided a similar reduction in influenza-like illnesses as observed in the healthy adult population. However, there is no evidence supporting the effectiveness of the influenza vaccine in reducing severe illness or hospitalization in pregnant women. Infants born to vaccinated mothers during their second or third trimester showed reduced rates of influenza and influenza-related hospitalization during their first six months of life. Additionally, influenza vaccination during pregnancy was not associated with adverse outcomes for the fetus, including premature birth, small size for gestational age, congenital malformations, spontaneous abortion, or 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 births (PTB), small for gestational age (SGA), and low birth weight (LBW). The results indicated that

receiving the influenza vaccine during pregnancy was associated with a decreased risk of both 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 indicated that influenza infection was associated with a higher risk of stillbirth. However, the impact of infection on preterm birth, fetal death, small for gestational age, and low birth weight remains uncertain (31).

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

7. A review recommended inactivated influenza vaccination for pregnant women. All women who are pregnant or about to deliver during the influenza season should receive either the trivalent or quadrivalent influenza vaccine, regardless of their trimester. Vaccination during pregnancy is a safe and cost-effective method that also provides neonatal protection against influenza through 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, as well as the effects of treatment and vaccination. The results indicated that pregnant women may be at an increased risk of complications from influenza virus infection, particularly during the third trimester. For hospitalized patients, higher 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 the safety, effectiveness, and coverage rates of the influenza vaccine during pregnancy, as well as opportunities to improve vaccination rates. The results indicated 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 highlighted the benefits and established safety record of vaccination for pregnant women. Preventing influenza infection in pregnant women and their newborns begins with efforts to limit exposure, including handwashing, respiratory hygiene, cough etiquette, and the implementation of infection control precautions and environmental procedures in healthcare settings frequented by these individuals. It has also been documented that risks increase as pregnancy progresses, with influenza-associated hospitalization rates being up to five times higher in women infected during the third trimester (36).

11. A retrospective cohort study involving 86,779 pregnancies during the influenza season from 2012 to 2014 aimed to measure the epidemiological characteristics of seasonal influenza infection among pregnant women and its impact on infant health. The results indicated no differences in the number of infection cases admitted to hospitals based on trimester or subtype of infection. Influenza B infections were more likely to occur in the second trimester compared to A/H3N2 and A/H1N1 infections, with rates of 41.3%, 23.6%, and 33.3%, respectively. On average, infants born to women with influenza B during pregnancy had birth weights that were 4.0% (95% CI:

0.3–7.6%) lower than those of infants born to uninfected women (P = 0.03) (37).

12. A retrospective cohort study utilized a birth registry from health administrative data encompassing 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 indicated 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 utilized the UK Obstetric Surveillance System (UKOSS) to identify all pregnant women admitted to hospitals between 2016 and 2018 with laboratory-confirmed influenza at any gestational 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 due to influenza during pregnancy. Increased awareness of the safety and effectiveness of immunization during pregnancy, along with improved vaccine provision within antenatal care settings—especially for high-risk groups—is necessary (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 indicated that pregnant women were at an increased risk for influenza-associated hospitalizations; however, little was known about the incidence of influenza and its associated complications during pregnancy. There were no published studies from low- or middle-income countries regarding the effect of seasonal influenza during pregnancy on birth outcomes, despite the fact that pregnancies in these regions accounted for over 90% of global births (40).

15. A retrospective cohort study involving 1,253 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 rates of low birth weight and small-for-gestational-age births. There was no evidence of associations between influenza vaccination administered at any time during pregnancy and adverse pregnancy or fetal outcomes, including spontaneous abortion, congenital anomalies, shortened gestation, gestational diabetes, chorioamnionitis, or gestational hypertensive disorders, consistent with existing literature. Additionally, the study found that influenza vaccination during pregnancy reduced a woman's risk of pre-delivery hospitalization due to influenza-like illnesses by approximately 39% (41).

16. A prospective cohort study involving 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 indicated that influenza was not associated with preterm birth but was linked to a decrease in birth weight for singleton, full-term, live-born infants. Additionally, women faced a 0.7–0.9% risk of influenza for each month of pregnancy spent during 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. The studies reviewed underscore the significant effects of influenza infection and vaccination during pregnancy on maternal and infant health. Pregnant women face increased risks of complications from influenza, particularly in the later stages of pregnancy. Vaccination has been shown to be safe and effective, reducing hospitalization rates and adverse outcomes such as low birth weight and small-for-gestational-age births, without increasing the risk of complications.

Influenza typically presents with symptoms such as fatigue, headache, muscle aches, and fever. This winter (2022/2023), both COVID-19 and influenza continue to circulate, making it challenging to distinguish between them based solely on symptoms without laboratory testing. This consideration is crucial in clinical assessments. The most effective way to prevent influenza infection is through vaccination (20, 24).

There are four types of influenza viruses: A, B, C, and D. Human influenza A and B viruses cause seasonal epidemics of the disease, commonly referred to as the flu season, almost every winter. Influenza A viruses are the only type known to cause flu pandemics, which can occur when a new and distinct influenza A virus emerges that can efficiently infect and spread among people. Influenza C virus infections generally result in mild illness and are not considered responsible for human epidemics. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in humans (10, 43-46).

Three influenza pandemics occurred in the 20th century: the Spanish influenza in 1918 (approximately 50 million deaths), the Asian influenza in 1957 (two million deaths), and the Hong Kong influenza in 1968 (one million deaths) (47). The World Health Organization declared a new type of influenza A (H1N1) outbreak a pandemic in June 2009 (48). Additionally, influenza can 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 lead to severe illness or death, particularly among high-risk groups, including the very young, the elderly, pregnant women, healthcare workers, and individuals with serious medical conditions (43, 46). Most women who contract influenza during pregnancy develop a relatively mild illness; however, the risk of becoming seriously ill or dying is greater for pregnant women than for otherwise healthy individuals (50). Pregnant women are 2.5 times more likely to be hospitalized due to influenza compared to other women (51). Influenza infection during pregnancy can result in complications such as premature delivery and even neonatal and perinatal death (52).

Vaccination is the most effective method for preventing severe influenza illness and its complications (27-42, 52-55). Inactivated influenza vaccines are administered to pregnant women in most countries, and based on available evidence, there are no significant safety concerns regarding influenza vaccination during any trimester of pregnancy (20, 25, 26, 36, 43-63). Influenza viruses are primarily transmitted through respiratory droplets produced when infected individuals cough or sneeze. Transmission can also occur via aerosols and contaminated surfaces (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 during pregnancy is an important public health priority that requires a comprehensive effort from 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 (52, 69, 70). Infants cannot receive their first dose of the influenza vaccine until they are six months old, so maternal vaccination is crucial for protecting the youngest infants from influenza. Infants of mothers who were immunized during pregnancy are less likely to be hospitalized for acute respiratory illnesses (55, 71, 72).

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 (73, 74). The World Health Organization states that pregnant women are among the highest priority groups for seasonal influenza vaccination (56). The CDC recommends that all women who are, will be, or could be pregnant during the influenza season should receive an influenza vaccine during any trimester (75, 76). The composition of the influenza vaccine typically changes each year to accommodate the strain(s) of the virus expected to be most prevalent that year, making it critical to receive an influenza vaccine annually (77).

The expected adverse events following influenza vaccines occur as frequently in pregnant women as in other populations. Local reactions (e.g., redness, swelling, and pain) occur in about one in ten adults who receive the vaccine, while systemic reactions (e.g., fever, tiredness, and myalgia) occur in fewer individuals. Serious adverse events, such as Guillain-Barré syndrome, are very rare, occurring in about one in a million vaccinated people (78).

Reducing morbidity and mortality from influenza during pregnancy is an important public health priority that requires extensive effort. Important hygiene measures to prevent the spread of influenza include frequent handwashing with soap and water, avoiding touching the eyes, nose, or mouth, wearing masks, staying home when ill, and limiting contact with others, especially those who are sick (79-82).

5- CONCLUSION

The influenza vaccine, despite seasonal variations in effectiveness, remains the best method to prevent influenza infection and its complications. It significantly reduces symptom severity and lowers the risk of hospitalization and death, especially for pregnant women, who are at greater risk of serious illness. Research shows that administering an inactivated influenza vaccine during pregnancy is safe for both mother and fetus, with no adverse outcomes such as premature birth or congenital anomalies. Infants of vaccinated mothers have lower rates of influenza and related hospitalizations in their first six months of life, and vaccination reduces a pregnant woman’s risk of pre-delivery hospitalization due to influenza-like illnesses by about 39%.

The studies highlight the critical role of influenza vaccination in improving maternal and infant health. However, there is a lack of research from low- and middle-income countries on seasonal influenza during pregnancy, indicating a need for increased awareness and vaccination efforts in these regions. Promoting influenza vaccination among pregnant women is essential for enhancing maternal and child health outcomes globally.

6- CONFLICT OF INTEREST: None.

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