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Influenza and pregnancy: Impact of infection and benefits of vaccination

Influenza y embarazo: Impacto de la infección y beneficios de la vacuna

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ABSTRACT

The influenza virus causes acute respiratory infections seasonally every year and has historically been responsible for pandemics that have resulted in high morbidity and mortality in various periods. Pregnant women and women in the postpartum period constitute an important risk group for complications arising from influenza infection. These complications can occur in the mother (pneumonia, hospitalization), the fetus (congenital anomalies), or represent adverse pregnancy outcomes (fetal death, premature birth, low birth weight). Inactivated influenza vaccines have proven to be an effective and safe tool in preventing influenza-related complications in pregnant women and infants, with their main benefit being the prevention of infections and reduction in hospitalization rates for pregnant women and infants during the first months of life. These benefits are greater when vaccination occurs during the third trimester of pregnancy and appear to be restricted to the first 4 months of the infant's life. It is recommended that pregnant women be vaccinated before the start of the peak influenza season, regardless of the trimester of pregnancy.
Keywords: Influenza, Pregnancy, Vaccine, Efficacy, Safety.

RESUMEN

El virus de influenza causa infecciones respiratorias agudas de forma estacional todos los años e históricamente ha sido responsable de pandemias que han producido alta morbilidad y mortalidad en diversos periodos. Las mujeres embarazadas o en puerperio constituyen un grupo importante de riesgo para complicaciones derivadas de la infección por influenza. Dichas complicaciones pueden ocurrir en la madre (neumonía, hospitalización), el feto (anomalías congénitas) o representar resultados adversos del embarazo (muerte fetal, parto prematuro, bajo peso al nacer). Las vacunas inactivadas contra influenza han demostrado ser una herramienta eficaz y segura en la prevención de complicaciones asociadas a influenza en gestantes y lactantes, siendo su principal beneficio el prevenir las infecciones y reducir las tasas de hospitalización de gestantes y lactantes durante los primeros meses de vida. Estos beneficios son mayores cuando la vacunación ocurre durante el tercer trimestre del embarazo y parecen estar restringidos a los primeros 4 meses de vida del lactante. Se recomienda que las gestantes se vacunen antes del inicio del periodo de mayor actividad de influenza del año, independientemente del trimestre del embarazo en el que se encuentren.
Palabras clave: Influenza, Embarazo, Vacuna, Eficacia, Seguridad

Introduction

The flu is an acute respiratory infection caused by the influenza virus, which circulates worldwide. Influenza A and B viruses cause seasonal outbreaks, while only the influenza A virus has been the causative agent of pandemics throughout history. In temperate climates, annual outbreaks of seasonal influenza occur during periods of low temperatures, while in tropical and subtropical climates, peaks in influenza activity are observed throughout the year. Respiratory infection with the influenza virus has a clinical spectrum ranging from asymptomatic infection to severe infection and death. It is estimated that 1 billion people contract influenza each year, of whom 3 to 5 million develop severe forms of the disease[1, 2]. The estimated annual mortality rate from influenza-associated respiratory infections worldwide is 4.0 to 8.8 per 100,000 people[3].

Risk groups for developing severe forms of influenza infection or death include children under 5 years of age, adults aged 65 years and older, pregnant women or women who have recently given birth, people

with certain chronic medical conditions, people with immunosuppression, and people who are obese, among others[1, 4-6].

Impact of influenza infection during pregnancy

Several studies have reported an increased risk of complications from influenza infection during pregnancy or the postpartum period, including pneumonia, hospitalization, admission to intensive care, and death[7-9]. The mechanisms underlying this increased risk of complications are not fully understood, but it is thought that they may be related to anatomical, physiological, and immunological changes that occur during pregnancy and that may predispose women to acquiring infections, developing respiratory failure, and making it difficult to manage[10, 11]. Pregnant women with comorbidities (chronic lung disease, cardiovascular disease, immunosuppression, among others) have a higher risk of hospitalization, admission to intensive care ICU, and death from influenza[12].

Even though the effects of the flu on pregnancy have been observed for many years, it's important to note that the evidence that most strongly supports the impact of influenza infection on pregnant women comes mostly from studies conducted during or after the 2009 influenza A H1N1 pandemic. A systematic review of the literature related to influenza infection in pregnant women during the 2009 influenza A H1N1 pandemic revealed that pregnant women had an increased risk of hospitalization, admission to intensive care ICU, and death, compared to women of reproductive age of similar ages or compared to the general population[7].

Similarly, a surveillance study in the US reported that during the 2009-2010 influenza pandemic season, 12% of deaths in pregnant women were attributed to confirmed or suspected infection with influenza A H1N1 pdm09[8], representing a much higher number than the 0.8% estimated for the period 1998-2005[13]. On the other hand, a systematic review and meta-analysis of observational studies, not limited to the 2009 pandemic, confirmed an increased risk of hospitalization for influenza in pregnant women compared to non-pregnant patients (OR 2.44; 95% CI 1.22–4.8), but did not find an increased risk of death (OR 1.04; 95% CI 0.81–1.33) (14). Similar findings were reported in a meta-analysis published in 2019, showing a sevenfold increased risk of hospitalization in pregnant women (OR 6.80, 95% CI 6.02–7.68), but no increased risk of death (OR 1.00, 95% CI 0.75–1.34)[15].

The increased risk of hospitalization in pregnant women appears to be higher in later stages of pregnancy. A cohort study conducted in New Zealand, which followed women of reproductive age during the period 2012-2015, found that pregnant women had a 3.4 times higher rate of hospitalization associated with influenza than non-pregnant women (RR 3.4; 95% CI 2.4-4.7)[9]. This risk of hospitalization increased as pregnancy progressed, with rates 2.5, 3.9, and 4.8 times higher for the first, second, and third trimesters, respectively. Among pregnant women hospitalized for influenza, the association was greater with influenza A virus, RR 5.3 (95% CI 3.2-8.7) for the H1N1 subtype and RR 3.0 for the H3N2 subtype (95% CI 1.8-5.0).

An increase in obstetric complications associated with influenza infection has also been reported, including miscarriage, stillbirth, premature birth, and low birth weight[16-19]. Similar to the maternal effects, most of the evidence regarding the impact of influenza infection on obstetric complications comes from studies conducted during or after the 2009 influenza A H1N1 pandemic.

An analysis conducted by the US CDC to evaluate clinical outcomes in pregnant and postpartum women during the 2009 influenza A H1N1 pandemic found that during the 2009-2010 period, pregnant women hospitalized with severe influenza who gave birth during that hospitalization had a higher risk of giving birth to premature and low birth weight infants[16]. Similarly, a study conducted in the United Kingdom found that pregnant women hospitalized with influenza A H1N1 infection during the 2009 pandemic had a threefold increased risk of preterm delivery (OR 3.1; 95% CI 2.1-4.5)[17]. Another study conducted during the 2009 pandemic in Norway found an increased risk of fetal death in pregnant women with influenza (HR 1.91; 95% CI 1.07-3.41)[18].

Additionally, a systematic review and meta-analysis of cohort studies found an association between influenza and the risk of stillbirth (RR 3.62; 95% CI 1.6–8.2), but did not identify a sig-

nificant association with preterm birth (RR 1.17; 95% CI 0.95–1.45), fetal death (RR 0.93; 95% CI 0.73–1.18), small for gestational age (RR 1.10; 95% CI 0.98–1.24), and low birth weight (RR 1.88; 95% CI 0.46–7.66). However, subgroup analysis did identify an association with low birth weight for studies conducted during the 2009 H1N1 pandemic (RR 2.28; 95% CI 1.81–2.87)[19].

Although transplacental transmission of the influenza virus appears to be rare[20], a possible association between influenza infection and adverse effects on the developing fetus has been reported. A meta-analysis of observational studies conducted in the United Kingdom revealed an association between exposure to influenza during the first trimester of pregnancy and an increased risk of congenital anomalies (OR 2.00; 95% CI 1.62-2.48), neural tube defects (OR 3.33; 95% CI 2.05-5.40), hydrocephalus (OR 5.74; 95% CI 1.10-30.00), cardiac malformations (OR 1.56; 95% CI 1.13-2.14), aortic valve atresia/stenosis (OR 2.59; 95% CI 1.21-5.54), ventricular septal defect (OR 1.59; 95% CI 1.24-2.14), cleft lip (OR 3.12; 95% CI 2.20-4.42), digestive system abnormalities (OR 1.72; 95% CI 1.09-2.68) and limb defects (OR 2.03; 95% CI 1.27-3.27)[21].

Flu vaccine

The World Health Organization (WHO) recommends annual vaccination against seasonal flu, which should be carried out before the start of the flu season. In tropical and subtropical areas, this activity occurs at various peaks throughout the year, and therefore the WHO recommends vaccination before the period of peak influenza activity[1]. In Peru, influenza vaccination is recommended during the months of April and May, before the start of the winter season. For pregnant women, the WHO recommends administering any of the inactivated or recombinant vaccines that are available, at any stage of pregnancy. Live attenuated vaccines are not recommended for pregnant women. In Peru, the national vaccination schedule includes inactivated influenza vaccines and recommends their administration to pregnant women at any stage of pregnancy[22].

Seasonal flu vaccines are developed in two formulations: the trivalent formulation includes two subtypes of influenza A virus (H1 and H3) and one influenza B virus (Yamagata or Victoria lineage), while the quadrivalent formulation includes two influenza A viruses and two influenza B viruses (one from each lineage)[1].

Vaccine efficacy, effectiveness, and safety

The inactivated influenza vaccine has been shown to protect against influenza infection and hospitalization in pregnant women[23-25]. A combined analysis of three clinical trials conducted in Nepal (2011-2014), Mali (2011-2014), and South Africa (2011-2013), evaluating the efficacy of the trivalent inactivated influenza vaccine against PCR-confirmed infection in pregnant women, demonstrated an efficacy of 50% (95% CI 32-63). Efficacy was 42% (95% CI 12-61) during pregnancy and 60% (95% CI 36-75) during the first 6 months postpartum. The effect was greater during the third trimester of pregnancy, with an efficacy of 30% (95% CI -2 to 52) in pregnant women vaccinated before 29 weeks, and 71% (95% CI 50-83) in pregnant women vaccinated at 29 weeks or later[23]. The authors conclude that the lack of statistical significance for efficacy in pregnant women vaccinated before week 29 could be due to insufficient study power for that group. Additionally, a combined analysis of two case-control studies conducted in the US (2010-2011 and 2011-2012 seasons) and Australia (2010 and 2011 seasons), evaluating the effectiveness of the trivalent inactivated vaccine in pregnant women, also demonstrated a protective effect against PCR-confirmed influenza infection (OR 0.37; 95% CI 0.23-0.61)[24]. A case-control study that included pregnant women from four countries (Canada, the US, Israel, and Australia) during the period 2010-2016 found that the influenza vaccine during pregnancy was 40% effective (95% CI 12-59) against hospitalization for PCR-confirmed influenza[25].

On the other hand, the inactivated influenza vaccine during pregnancy has been shown to reduce the risk of influenza infection and hospitalization in infants younger than 6 months, but this protection appears to be limited to the first 3-4 months of life[23, 26]. Considering that infants are not candidates for influenza vaccination before 6 months of age according to current recommendations, there may be a period of vulnerability to influenza between 4 and 6 months of life.

The combined analysis of three clinical trials conducted in Nepal, Mali, and South Africa de-

scribed previously[23] found that the trivalent inactivated influenza vaccine administered during pregnancy had an efficacy of 35% (95% CI 19-47) against PCR-confirmed infection in infants up to 6 months of age. This significant protection was restricted to the first 4 months of life, with efficacy of 56% (95% CI 28-73) for the first 2 months of life, 39% (95% CI 11-58) between 2 and 4 months of life, and 19% (–9 to 40) between 4 and 6 months of life. Additionally, efficacy was similar in infants born to mothers vaccinated before or after 29 weeks of gestation (34% [95% CI 12-51] vs. 35% [95% CI 11-52]). In this combined analysis, no association was found between maternal vaccination and low birth weight, stillbirth, preterm delivery, or small for gestational age. Furthermore, a case-control study conducted in the US found that influenza vaccination during pregnancy was 34% effective (95% CI 12-50) against emergency visits or hospitalizations due to PCR-confirmed infection in infants younger than 6 months of age. This effectiveness was 17% (95% CI -15 to 40) when vaccination occurred during the first or second trimester of pregnancy, and 52% (95% CI 30-68) when vaccination occurred during the third trimester. Likewise, effectiveness was higher for infants younger than 3 months of age (53%; 95% CI 30-68)[26].

Studies have reported generally favorable results regarding the effect of inactivated vaccines against obstetric complications from influenza. A meta-analysis of seven studies found that pregnant women vaccinated against influenza during pregnancy had a reduced risk of stillbirth (RR 0.73; 95% CI 0.55–0.96), but found no difference in the risk of spontaneous abortion (RR 0.91; 95% CI 0.68–1.22)[27]. Other cohort studies conducted in the US and Canada have shown an association between maternal influenza vaccination during pregnancy and a lower rate of preterm birth, low birth weight, and small for gestational age[23, 28, 29].

Studies have also been conducted to determine whether influenza vaccines during pregnancy have negative effects on children before or after birth, demonstrating a favorable safety profile. A cohort study conducted in Canada during the period 2010-2016 evaluated whether influenza vaccination during pregnancy was associated with adverse health effects during early childhood. After an average follow-up of 3.6 years, the study found no significant association between maternal vaccination during pregnancy and the development of childhood asthma, neoplasms, vision or hearing loss, infections during early childhood, or increased use of emergency services or hospitalization[30]. Another cohort study conducted in Denmark evaluating infants born in the period 2009-2010 found that administration of the monovalent influenza A(H1N1) pdm09 vaccine during the first trimester was not significantly associated with congenital malformations (OR 1.21; 95% CI 0.60-2.45), preterm birth (OR 1.32; 95% CI 0.76-2.31), or small for gestational age (OR 0.79; 95% CI 0.46-1.37). Exposure to the vaccine during the second or third trimester was also not significantly associated with preterm birth (OR 1.00; 95% CI 0.84-1.17) or small for gestational age (OR 0.97; 95% CI 0.87-1.09)[31]. A systematic review and meta-analysis found no association between maternal influenza vaccination during any trimester of pregnancy and congenital malformations (OR 0.96; 95% CI 0.86-1.07). No association was observed for pregnant women vaccinated during the first trimester (OR 1.03; 95% CI 0.91-1.18)[32]. Another systematic review found a protective effect of influenza vaccination during pregnancy in relation to preterm birth (OR 0.87; 95% CI 0.78–0.96) and low birth weight (OR 0.82; 95% CI 0.76–0.89). Likewise, it found no significant association between congenital malformations (OR 1.03; 95% CI 0.99–1.07), small for gestational age (OR 0.99; 95% CI 0.94–1.04), and stillbirth (OR 0.84; 95% CI 0.65–1.08)[33].

Conclusion

Pregnancy and the postpartum period are stages of increased risk of complications associated with influenza infection, both for the mother and the unborn child. The main tool for preventing infection and its complications in this population group is the inactivated influenza vaccine. This vaccine has been shown to be effective and safe, so it is the responsibility of all health personnel to promote its use and work to achieve optimal vaccination coverage in the population.

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