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VACCINES IN PREGNANT WOMEN & INFANTS (D SCHWARTZ AND C KRUBINER, SECTION EDITORS)

Current Perspectives on Maternal Influenza Immunization

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Abstract

Purpose of Review Pregnant women and young infants are more likely to experience severe complications associated with influenza infection and are at increased risk of hospitalization. Influenza vaccination during pregnancy produces antibodies which protect the mother against infection, and due to transplacental transfer of maternal antibodies before birth, it also protects the infant in the first few months of life.

Recent Findings In many countries, influenza vaccination is recommended during pregnancy to protect mothers and their infants. In fact, influenza vaccine is the most widely used vaccine in pregnancy globally. When administered during pregnancy, the vaccine has been shown to be safe and effective for both mothers and their infants. Despite the health benefits, acceptance of influenza vaccine is low during pregnancy, indicating many women and infants are not protected against influenza.

Summary Concerted efforts are needed globally to improve the proportion of women and young infants who receive the health benefits of influenza vaccination.

Keywords Influenza vaccines · Influenza · Maternal vaccination · Pregnant women · Infant health

Introduction

Influenza is a potentially serious respiratory illness, resulting in an estimated 291–645,000 deaths worldwide every year [1]. Although infection typically results in a self-limiting illness, severe cases can result in potentially life-threatening complications requiring hospitalization and intensive treatment. Such complications can include pneumonia, myocarditis, encephalitis, acute respiratory distress syndrome, respiratory failure, sepsis, or death [2]. Certain individuals, in particular pregnant women and young infants, are at higher risk of developing serious complications including death.

This article is part of the Topical Collection on *Vaccines in Pregnant Women*

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Burden of Influenza in Pregnant Women and Young Infants

Numerous studies have observed a higher risk of morbidity and mortality among pregnant women compared with the nonpregnant adult population during influenza pandemics and seasonal epidemics [3, 4]. Immunological, anatomical, and hemodynamic changes induced by pregnancy are believed to predispose pregnant women to a higher risk of severe illness [5]. The anatomical and physiological changes in pregnancy present challenges to clearing viral infections, including a shift from cell-mediated immunity to humoral immunity, increased progesterone and glucocorticoids, increased heart rate, stroke volume, and oxygen consumption, as well as deceased lung capacity [4, 6]. Animal studies have shown that altered inflammatory responses in response to influenza infection can lead to increased maternal morbidity, as well as increased risk of preterm labor, impaired fetal growth, and fetal mortality [7].

Several studies employing self-controlled methods have demonstrated greater severity of influenza illness during pregnancy. Ohfuji et al. [8] showed that across four influenza seasons, pregnant women were 2 to 4 times more likely to be hospitalized with respiratory illness during the influenza season compared with nonpregnant women. Similar estimates were reported in a previous Canadian study by Dodds et al. [9] that showed risk of respiratory hospitalization increases as pregnancy progresses, with the greatest increase in risk occurring in the third trimester. Among women with chronic medical conditions, the risk of hospitalization in the third trimester was 7 times greater compared with nonpregnant women [9]. Recent data from Spain indicate that influenza infection is also associated with increased rates of outpatient visits during the first or second trimester and the highest rates of hospitalization occur during the third trimester [10]. Estimates of the incidence of hospitalization with laboratory-confirmed influenza infection range from 0.04 to 7.7 cases per 10,000 pregnancies, with incidence of infection ranging from 487 to 1097 cases per 10,000 pregnancies [11]. Early initiation of antiviral treatment has been shown to reduce length of stay in hospital for pregnant women with laboratory-confirmed influenza during pandemics [12] and seasonal epidemics [13].

In addition to directly impacting maternal health, severe influenza illness is also associated with an increased risk of pregnancy complications [6, 12] and adverse fetal outcomes [14, 15]. A recent systematic review concluded that severe 2009 pandemic A/H1N1 influenza illness (i.e., influenza illness requiring hospitalization) was associated with increased risk of preterm birth and fetal death [14]. A Canadian study showed that women with chronic medical conditions who were infected with 2009 pandemic A/H1N1 influenza experienced higher rates of spontaneous preterm birth [16]. During previous pandemics, several studies highlighted an increased risk of fetal death and other adverse events including preterm birth and low birthweight associated with pandemic infection during pregnancy [4, 15]. In the most recent pandemic, the risk of fetal death was increased 2-fold for women who were infected with pandemic influenza A/H1N1 during pregnancy [15]. Additional studies have also suggested women infected with pandemic influenza may be at higher risk of having a small-for-gestational-age infant [17]. The severity of maternal illness is likely to play an important role in the impact on fetal health, with more severe illnesses more likely to have adverse impacts [14]. While increased risk of severe illness and adverse outcomes has been observed during all trimesters of pregnancy, risk seems to be most pronounced in the third trimester of pregnancy [6, 12].

In the first months after birth, infants are especially susceptible to severe influenza illness due to the immaturity of their immune systems. Newborns have limited antibodies to protect against influenza infection [18••]. Young infants are at increased risk of influenza-associated complications and have been shown to experience the highest rates of hospitalization [19, 20] and death [21] compared with older children. Among infants hospitalized with influenza during the first year of life, 35% will require admission to an intensive care unit, and 1 in every 350 dies [22]. Because of the immature immune system in newborns, vaccines do not trigger adequate immune response and have not been shown to be effective in preventing influenza in young infants [23]. There is currently no licensed influenza vaccine for infants younger than 6 months. Beginning in the second trimester of pregnancy, antibodies cross the placenta from mother to fetus [24, 25]. These maternal antibodies act as nature's way of protecting young infants against the disease targeted by the antibody [26]. Vaccination in pregnancy boosts the concentration of vaccine-derived antibodies in maternal sera, and as a result, increases the transplacental transfer of maternal antibodies [27]. These maternally produced antibodies can offer protection to the infant in the first 6 months of life [28•, 29, 30, 31•, 32]. In the absence of primary vaccination strategies, maternal vaccination produces antibodies against influenza which are transferred to the infant during pregnancy, offering the optimal method of protection against potentially severe illness during infancy [28•, 33].

Historical Experience

Since as early as 1960 in the United States (US), routine influenza immunization has been recommended to pregnant women [34, 35]. During the 1957 influenza A/H2N2 pandemic (also known as the "Asian Flu"), high mortality rates were observed, with 1.1 million deaths worldwide [36]. As a result of the excess deaths observed among those with chronic medical conditions, older adults, and pregnant women during the pandemic, the US Public Health Service made a recommendation to routinely immunize these priority groups [35]. To our knowledge, this was the first formal recommendation of influenza vaccines to pregnant women.

Following the 1957 pandemic, an estimated > 100,000 US pregnant women received an influenza vaccine between 1959 and 1965 [37]. The US Collaborative Perinatal Project provided the earliest insights on maternal influenza vaccination. This prospective cohort study of maternal and childhood health aimed to recruit 50,000 pregnant women across 12 US clinical sites [38]. Between 1959 and 1966, the US Collaborative Perinatal Project followed up the children of 34,846 women, 2291 (6%) of whom had received influenza vaccine during their pregnancy. After evaluating outcomes in the children, the investigators found no evidence for an increase in stillbirth, congenital malformations, or neurodevelopmental disabilities associated with influenza vaccination [39]. This was the first major report on safety of influenza vaccination during pregnancy and the largest study of vaccinated pregnant women at the time.

In 1965, after considering the limited evidence of an increased risk of severe influenza-related disease in the general obstetrical population since the 1957–1958 influenza pandemic, the US Advisory Committee on Immunization Practice (ACIP) adjusted the national influenza vaccine recommendation to include only pregnant women with comorbid conditions known to predispose them to increased risk of severe disease [40]. These guidelines did not mention at what stage of pregnancy vaccination should occur [40]. In 1995, ACIP recommended that pregnant women with comorbid conditions receive influenza vaccine at any stage of pregnancy [41]. In 2004, ACIP expanded the recommendation to include healthy pregnant women with no comorbid conditions [42]. Today, influenza immunization is considered an essential component of prenatal care in the US and many other high-income countries [43–46], although some variation to these recommendations exists. For example, several European countries recommend vaccination after the first trimester rather than during any stage of pregnancy [47]. In the years immediately following these recommendations in the US, uptake of influenza vaccine during pregnancy remained low. US estimates show that between 10 and 14% of pregnant women were vaccinated between 1997 and 2005 [48, 49]. During this time, low immunization rates were linked to limited knowledge and implementation of the ACIP recommendations—fewer than half of obstetric providers reported recommending or providing influenza vaccine to pregnant women [48, 50].

It was not until the 2009 influenza A/H1N1 pandemic that the demand for and use of influenza vaccines during pregnancy dramatically increased. As the pandemic unfolded between March and June 2009, it became apparent that pregnant women were a high-risk group for severe illness [12]. In April 2009, the US Centers for Disease Control and Prevention (CDC) first reported the identification of novel influenza A virus infection in two young children [12]. The World Health Organization (WHO) declared influenza A/H1N1 a public health emergency of international concern on April 25 [51]. By the end of May, laboratory-confirmed cases were identified in 53 countries and 99 deaths had occurred [52], and by August, all continents were affected [53]. It was noted during the early stages of the pandemic that pregnant women appeared to be at higher risk of admission to ICU and death [54, 55], and by the end of the pandemic, pregnant women ultimately accounted for 5% of the total deaths [12].

Early in the pandemic, it was shown that the seasonal influenza vaccine did not offer protection against the pandemic virus [56], and a monovalent vaccine was developed and rapidly introduced. In July 2009, the US ACIP recommended that pregnant women and other high-risk groups be targeted for pandemic influenza immunization. During the pandemic in the US, it is estimated that 47% of pregnant women received a 2009 H1N1 vaccine [57]. The pandemic represented a shift in immunization acceptance, resulting in an increase in influenza vaccination rates. Several countries have reported sustained higher immunization rates among pregnant women during the post-pandemic period; however, the increase in uptake remains slow [58–62].

As of 2012, the WHO lists pregnant women as the highest priority group for countries considering initiation or expansion of their seasonal influenza vaccine campaigns [63]. At the last evaluation in 2014, it was estimated that 42% of WHO Member States had policies recommending routine immunization of pregnant women against influenza [64]. It is almost certain that the number of countries has increased since then. As the importance and awareness of the health benefits of vaccination during pregnancy continue to increase, it is likely that uptake will continue to improve.

Safety and Effectiveness

Over the past two decades, the safety and effectiveness of influenza vaccination during pregnancy have been well investigated. The safety of vaccine administration has been confirmed in randomized controlled trials [29, 31•, 65–68], observational cohort studies [15, 16, 69–86], and post-licensure safety surveillance studies [87, 88, 89•, 90, 91]. Post-licensure surveillance data have shown that pregnant women report similar or fewer adverse events following influenza immunization compared with nonpregnant women of the same age [88]. Approximately 1 in 10 pregnant women reports a common, expected adverse event (e.g., local reaction, swelling, fatigue), and fewer than 3% report fever post-vaccination [87, 89•, 91, 92]. Similar rates of adverse events are reported by nonpregnant women of the same age, indicating pregnancy does not increase the risk of adverse events following immunization [88]. Although live attenuated influenza vaccines (LAIV) are contraindicated during pregnancy due to a hypothetical risk posed to the fetus, inadvertent administration of LAIV during pregnancy occurs infrequently. Post-licensure safety monitoring studies evaluating pregnancy administration of LAIV have not observed serious adverse events [93].

A number of comparative observational studies have confirmed the safety of influenza vaccination in terms of fetal health. Since 2015, seven systematic reviews have been published evaluating the association between influenza vaccination during pregnancy and subsequent birth outcomes [92, 94–99]. These reviews summarize data from more than 100,000 pregnancies and have all shown that vaccination during pregnancy is safe in terms of preterm birth, low birthweight, small-for-gestational-age, congenital anomalies, spontaneous abortion, and stillbirth [99]. Three large retrospective cohort studies have evaluated the safety of maternal vaccination in relation to childhood health outcomes, finding no increase in the risk of pediatric hospitalization [100],

autism spectrum disorder [101], or the development of immune-related and non-immune-related pediatric outcomes [102•].

The most recent systematic review noted several gaps in our knowledge of the safety of influenza vaccination during pregnancy [99]. First, the majority of studies include women vaccinated in the second or third trimester [99, 103••]. Studies from countries recommending influenza vaccination at any time in pregnancy, including first trimester, have not found an increased risk of congenital malformations, stillbirth, neonatal death, or preterm delivery [104, 105]. However, the limited evidence on first trimester vaccination has contributed to conservative immunization guidelines in some European countries, where vaccination is recommended in the second or third trimester of pregnancy [47]. Further studies evaluating the safety and benefits of influenza vaccination during the first trimester of pregnancy would be informative to international vaccine policy. Second, relatively few studies have been able to assess the impact of influenza vaccination during pregnancy on the risk of spontaneous abortion. Despite numerous studies evaluating birth outcomes, a small number of studies (including < 7000 pregnancies) have evaluated spontaneous abortion [99]. Furthermore, the studies that have been conducted are all prone to left truncation bias [106, 107], due to pregnancy losses that occur at early gestational ages which are unrecognized or unreported. While the majority of studies that have been conducted have found no increase in the risk of spontaneous abortion associated with prenatal influenza vaccination [78, 84, 85, 108, 109], a recent case-control study identified a possible increase in the risk of spontaneous abortion, particularly among those who received a 2009 pandemic A/H1N1-containing vaccine in the season prior to becoming pregnant [110]. Although subsequent replication of this study in a different time period and with a larger sample size identified no association between influenza vaccination and spontaneous abortion [111], in combination with the biases present in existing research, this study highlights the need for more rigorous research of spontaneous abortion and maternal vaccination. Finally, with the introduction of pertussis vaccine recommendations in several countries and new vaccines on the horizon [28•], monitoring the safety of concomitant vaccine administration and repeat administration may be warranted.

In addition to the evidence supporting safety, influenza vaccination during pregnancy has been shown to be effective, both in terms of preventing maternal and infant infection. Effectiveness estimates vary, depending on the influenza season of the investigation and the study methods employed. The strongest evidence has been generated by the "Mother's Gift" randomized clinical trial conducted in 2004 in Bangladesh [29] and subsequent trials in Nepal, Mali, and South Africa [28•, 30, 31•, 32]. The initial trial, including 164 infants, showed that influenza vaccination during pregnancy was 63% efficacious in preventing laboratory-confirmed influenza in infants [29]. The subsequent trials showed that maternal vaccination was between 30% (Nepal) [31•] and 49% (South Africa) [32] efficacious against laboratory-confirmed infant influenza compared with controls. Several of these same trials also indicated that vaccination during pregnancy was between 50 and 70% efficacious in preventing laboratory-confirmed infection among pregnant women [30, 32].

Observational studies of laboratory-confirmed influenza have supported the effectiveness of influenza vaccine in preventing influenza for both mothers and infants. Between 2000 and 2009, a matched case-control study by Benowitz et al. [112] estimated that influenza vaccination during pregnancy was 91% effective in reducing the risk of laboratory-confirmed influenza hospitalization among infants. A subsequent UK population-based study showed that influenza vaccination was 71% effective in preventing infant infection and 64% effective in preventing infant hospitalization [113]. More recently, a Danish study reported seasonal influenza vaccine was 57% effective in preventing laboratory-confirmed influenza in infants < 6-month old during the 2010 through 2016 influenza seasons [114]. Estimates have been slightly lower for maternal protection associated with vaccination. A case-control study in two US states showed that influenza vaccination during pregnancy was associated with a 27–57% reduction in laboratory-confirmed influenza during pregnancy during the 2010–2011 and 2011–2012 influenza seasons [115]. A recent international cohort study which included data from four high-income countries showed that influenza vaccines were 40% effective in preventing laboratory-confirmed influenza hospitalization of pregnant women between 2010 and 2016 [116].

Several other studies with non-specific outcomes, such as all-cause acute respiratory infections, have also demonstrated the effectiveness of influenza vaccination during pregnancy. Two Australian studies have shown that maternal vaccination was associated with a 65% reduction in maternal hospitalization with acute respiratory infection [117] and a 25% reduction in infant hospitalization [118]. In Japan, a study of self-reported influenza diagnosis showed that vaccination was 61% effective in preventing infant infection [119]. These estimates align with the 43% reduction in all-cause acute lower respiratory infections observed in some clinical trials [120]. However, it is worth mentioning that several observational studies have failed to identify measurable effectiveness of maternal vaccination [121–123].

In many countries, influenza vaccination is recommended during any trimester of pregnancy; however, limited data have evaluated the effectiveness of influenza vaccination by the trimester of vaccination. A recently published systematic review of immunological studies reported a 1.3-fold greater geometric mean fold increase in maternal sera and 1.2-fold greater geometric mean titer (GMT) in cord blood among women vaccinated in the third trimester when compared with

the second trimester [103••]. There were insufficient data to perform comparisons of the immunogenicity of vaccination during the first trimester [103••]. Despite this difference in immunogenicity, a recently published clinical trial found that vaccine efficacy against maternal and infant disease does not vary by gestational age at vaccination [18••]. Several observational studies have considered the effectiveness of influenza vaccination by trimester of pregnancy at vaccine administration. A recent CDC-led study estimated that influenza vaccination during pregnancy was 55% effective in preventing severe laboratory-confirmed maternal illness when the vaccine was administered in the first or second trimester, and offered no significant effectiveness when administered in the third trimester [116]. An observational study from Australia compared vaccine effectiveness by trimester of vaccination and identified a 33% reduction in all-cause acute respiratory infection hospitalization of infants for vaccination in the third trimester, but no significant reduction when the vaccine was administered earlier in pregnancy [118]. Further evaluation of the effectiveness of vaccination by trimester with respect to both maternal and infant protection is warranted.

Challenges to Widescale Implementation

Despite the evidence supporting the benefits of maternal vaccination to mother and infant, challenges remain on widescale implementation. Coverage of influenza vaccines among pregnant women has continued to increase in high-income countries [58–60, 124]; however, no country is currently meeting the US Healthy People 2020 goal of 80% coverage [125]. Major barriers to influenza immunization cited by pregnant women include concerns regarding the safety of vaccine administration [126–129], a perception that vaccination is not necessary during pregnancy [127–129], and lack of recommendation by a healthcare provider [127, 129]. In fact, several studies have identified a healthcare provider recommendation as the strongest and most consistent predictor of receipt of influenza vaccine during pregnancy [130]. As a result, recent interventions for improving vaccine uptake have targeted not only pregnant women but also their healthcare providers [131].

Safety concerns impact community acceptance of vaccines during pregnancy [129] and complicate the implementation of clinical trials for the development of vaccines for pregnant women [132]. Historically, pregnant women and their offspring have been excluded from vaccine research; several studies have reported reluctance on the part of regulators, healthcare providers, and participants to include pregnant women in vaccine clinical trials [132, 133]. For example, while 75% of women are willing to accept the recently developed respiratory syncytial virus (RSV) vaccine during pregnancy if it is approved and routinely recommended, just 29% of pregnant women are willing to accept the candidate RSV vaccine as part of a trial [134]. Because clinical trials form the basis for the safety information included with vaccine packaging, the limited availability of clinical trial data results in language in the package insert which contradicts clinical recommendations can lead to hesitancy on the part of health care providers to recommend vaccination to their pregnant patients [135]. Limited dissemination of clear information regarding vaccine safety for some vaccines has been identified as barriers to expanding maternal immunization programs [136, 137]. The hesitancy to include pregnant women in clinical trials may be changing, as several recent surveys have shown that women are willing to consider participating in new vaccine trials for group B *streptococcus* and Zika virus vaccines [138–140].

Several strategies have been proposed for encouraging improved implementation of maternal influenza vaccination programs in high-income settings. These include developing and executing provider-based interventions to encourage patient-provider interaction and communication about maternal vaccination, providing nudge-based interventions such as provider prompts to recommend vaccination, reducing or removing financial barriers to vaccination, and increasing access to vaccines during pregnancy at point of prenatal care [141]. However, limited high-quality evidence from randomized controlled trials is available [142] and the few trials that have been conducted provide conflicting results [143–145]. Additional high-quality investigations are needed to further evaluate interventions for improving influenza vaccination rates among pregnant women.

In a more global context, there are additional challenges facing the implementation of maternal influenza vaccination programs. Widescale implementation requires strong health information systems to routinely monitor vaccine safety [137]. Population-based local data to document baseline rates of adverse perinatal events and passive and active vaccine safety surveillance systems are needed. This can be a particular challenge in low and middle-income countries (LMICs), where population-based data and routine surveillance systems may be more limited [146, 147]. In addition, definitions and ascertainment of perinatal outcomes vary dramatically in different parts of the world [133]. To address this heterogeneity, recent efforts by the Brighton Collaboration's Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project have resulted in the development of global standards for case definitions of adverse events following immunization during pregnancy. Recent evidence suggests these case definitions are both feasible and reliable in LMIC settings [148].

In addition to vaccine promotion and acceptance, more practical challenges exist, including seasonal vaccine procurement, expansion of immunization services to antenatal care settings, and financial barriers to widescale vaccine purchasing. Access to vaccines in LMICs is a major challenge, with

more variation in access to antenatal care and greater obstacles to obtaining funding, ensuring cold chain and managing vaccine distribution and storage [149]. Routine vaccination recording and infectious disease surveillance data are needed to establish the local burden of infant and maternal influenza [149], and to provide data for studies of vaccine effectiveness and safety. Such information is rarely available in LMICs, which makes requisite economic evaluation and subsequent funding decisions difficult. Despite global evidence supporting the benefits to mother and infant, lack of available country-level data leads to the underestimation of burden and poor awareness of the need for maternal influenza vaccination in LMICs [150].

Conclusions

Influenza vaccination during pregnancy protects the mother and infant from influenza, severe complications, and death. Maternal immunization with influenza vaccine is recommended globally, with many countries currently implementing policies to promote vaccines to pregnant women. Although there are challenges to widescale implementation of these policies, these challenges can be addressed through informed and coordinated vaccine promotion. Given the evidence supporting the safety and effectiveness of maternal influenza vaccination, concerted effort to expand the use of influenza vaccines during pregnancy over the next decade is likely to have major health benefits for mothers and infants globally.

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Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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