Delivering Influenza Vaccine to Pregnant Women

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Pregnant women have an increased risk of influenza infection and complications. The Advisory Committee on Immunization Practices currently recommends vaccination for women who are pregnant during influenza season. The authors review the literature concerning influenza vaccine safety, effectiveness, and coverage rates during pregnancy, as well as opportunities to improve vaccination rates during pregnancy. No study has demonstrated an increased risk of maternal complications or adverse fetal outcomes associated with inactivated influenza vaccine. Few studies have examined the effectiveness of vaccination during pregnancy, and the results from these studies are inconsistent, with some showing a protective effect and others showing no effect. Despite the proven safety of vaccination and the possible benefits to women and their infants, reported vaccination rates during pregnancy are generally less than 10%. Mothers frequently cite concerns about vaccine safety as a barrier to vaccination. Lack of adequate information about the risks and benefits of vaccination is reported by both patients and obstetric care providers. Organizational factors such as lack of vaccine storage facilities may also limit vaccination during pregnancy. Effective interventions should target factors pertaining to patients or providers, or they should address organizational or logistic barriers. The Advisory Committee on Immunization Practices currently recommends standing orders programs or reminders for patients and providers as strategies to improve vaccination rates.

influenza, human; pregnancy; vaccination

Abbreviations: ACIP, Advisory Committee on Immunization Practices.

INTRODUCTION

Influenza is a significant cause of morbidity and mortality in the United States, resulting in an average of 200,000 hospitalizations and 36,000 deaths each year (1, 2). Typical influenza illness is characterized by abrupt onset of fever, myalgia, sore throat, and nonproductive cough. Unlike other common respiratory illnesses, influenza can cause severe malaise lasting several days. More severe illness can result from primary influenza pneumonia or secondary bacterial pneumonia.

Young children and the elderly, as well as persons with such chronic medical conditions as asthma or diabetes, are at increased risk for influenza and its complications. The Advisory Committee on Immunization Practices (ACIP) annually reviews the available scientific evidence and recommends target populations for vaccination. Vaccination is currently recommended for persons over the age of 49 years; children 6–23 months of age; persons with asthma, diabetes, heart disease, or an immunosuppressive condition; and persons in close contact with these high-risk groups (3).

In addition to these populations, women who are pregnant during influenza season also have an increased risk of infection and complications. The ACIP currently recommends vaccination for women who are pregnant during influenza season (3). Most providers administer influenza vaccine during the second and third trimesters (4), but influenza vaccine is also administered during the first trimester, especially for women with an underlying high-risk medical condition, such as asthma. Pregnant women should be immunized with the inactivated influenza vaccine; the live attenuated intranasal vaccine is not indicated during pregnancy (3).
INFLUENZA DURING PREGNANCY

A woman’s risk for influenza-related complications increases during pregnancy because of the physiologic changes associated with pregnancy, including heart rate and stroke volume increase, lung capacity decrease, and attenuation of cell-mediated immune responses (5, 6). Several epidemiologic studies have shown that pregnant women have an increased risk of influenza infection, morbidity, and mortality relative to nonpregnant women of the same age. Excess mortality was noted among pregnant women in both the 1918 and 1957 influenza pandemics (7–9). During the 1918 pandemic, the mortality rate from pneumonia and influenza was 50 percent among pregnant women (7). During the 1957 pandemic, influenza was the leading cause of maternal mortality, accounting for 20 percent of all maternal deaths (8), and pregnant women accounted for nearly one fourth of all influenza deaths among persons less than 50 years of age during the period (9). In both pandemics, mortality rates were higher for the later stages of pregnancy relative to the first trimester.

Pregnant women also have an increased risk of medical visits and hospitalizations for influenza-related illness during interpandemic periods relative to women of the same age. In an analysis of acute respiratory illness visits within a managed-care organization, nonpregnant women had 10 excess such visits per 1,000 compared with 23.7 excess visits per 1,000 among pregnant women (10). A large study of Medicaid-enrolled women during 17 influenza seasons demonstrated that pregnancy increased the risk of hospitalization for cardiopulmonary conditions (11). The rate of hospitalization among pregnant women was 12.0 per 10,000 women-months compared with a rate of 6.8 per 10,000 women-months among nonpregnant and postpartum women. The risk of hospitalization increased during the later stages of pregnancy; the hospitalization rate increased from 6.5 per 10,000 women-months in the first trimester to 21.7 per 10,000 women-months in the third trimester (11).

Pregnant women with a chronic high-risk medical condition, such as asthma or diabetes, are even more likely to be hospitalized than healthy pregnant women are (11, 12). Among high-risk women, 31, 16, and 21 influenza-attributable hospitalizations per 10,000 women-months were observed for women in the first, second, and third trimesters, respectively; comparative numbers for healthy pregnant women were 3, 6, and 10 events per 10,000 women-months (11). Hartert et al. (12) report that women with asthma represented 50 percent of hospitalizations for influenza-related illness in their cohort of pregnant women.

Although the risk to pregnant women is clear, the relation between influenza infection during pregnancy and adverse health effects in the fetus is less clear. During the 1918 pandemic, 52 percent of influenza and pneumonia cases during pregnancy were associated with spontaneous abortion or premature delivery (7). A rate of pregnancy interruption this extreme, however, has not been observed since the 1918 pandemic, and only a few case reports of stillbirths and neonatal deaths following maternal infection have since been published (13, 14).

In 1974, MacKenzie and Houghton (15) published an exhaustive review of influenza and congenital anomalies. The authors concluded that the available scientific evidence did not support an association between maternal influenza and congenital anomalies. The authors further state that most of the prospective studies they reviewed were limited by small sample sizes, and the retrospective studies were limited by their definitions of influenza infection. Most of the studies relied on self-reported histories of respiratory illness during pregnancy, which are likely to misclassify true influenza infection and to introduce selective recall bias into a study. The authors suggest that serologically confirmed influenza infection would be a better exposure measure for these types of studies.

Two studies have since evaluated the neonatal effects of serologically confirmed influenza infections during pregnancy. In one study of 1,595 pregnancies in which influenza infection was serologically confirmed, no difference in birth weight was noted among infants born to infected mothers relative to controls (16). This study also reported a small, but not statistically significant, increase in congenital anomalies among infants born to mothers infected during pregnancy. The other study of 1,659 pregnancies found no differences in birth weight, Apgar scores, head circumference, or congenital anomalies (17). To fully investigate the relations between maternal infections and neonatal outcomes, a large prospective epidemiologic study is needed with the ability to adjust for potential confounders, such as the medications used during pregnancy, smoking, and high-risk medical conditions.

INFLUENZA VACCINATION DURING PREGNANCY

Vaccine effectiveness during pregnancy

Few studies have evaluated the effectiveness of influenza vaccination during pregnancy. Vaccine effectiveness estimates vary year to year and are highest when the vaccine antigens are well-matched to the influenza strains circulating in the community each season. In a large managed-care organization, women who received influenza vaccine during pregnancy had the same risk of influenza-like illness over several influenza seasons as did women who were not vaccinated (hazard ratio = 1.00; p = 0.99) (18). In another study, 19.2 percent of unvaccinated women had an acute respiratory illness visit during the influenza season compared with 9.8 percent of women vaccinated during pregnancy (19). An ideal addition to the literature would be a study examining the effectiveness of influenza vaccine in pregnant women using laboratory-confirmed influenza, rather than influenza-like illness or acute respiratory illness, as the outcome measure. Serologic studies have demonstrated, however, that pregnant women are able to mount a sufficient and protective immune response to influenza vaccine (20, 21). Based on this immune response, influenza-like illness and acute respiratory illness outcomes data, and vaccine effectiveness estimates in other high-risk populations, vaccination seems to be the best way to decrease a woman’s risk of influenza and complications during pregnancy.

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TABLE 1. Influenza vaccination rates during pregnancy, Canada and United States, 1974–2003

<table>
<thead>
<tr>
<th>Authors, year (reference)</th>
<th>Population</th>
<th>Study period</th>
<th>Source of vaccine data</th>
<th>Vaccination rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuzil et al., 1998 (11)</td>
<td>Medicaid population, United States</td>
<td>1974–1993</td>
<td>Medicaid database</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Mullooly et al., 1986 (10)</td>
<td>Managed care organization, United States</td>
<td>1975–1979</td>
<td>Medical record review</td>
<td>&lt;1*</td>
</tr>
<tr>
<td>Black et al., 2004 (18)</td>
<td>Managed care organization, United States</td>
<td>1997–2002</td>
<td>Vaccine registry</td>
<td>7.5</td>
</tr>
<tr>
<td>Munoz et al., 2005 (19)</td>
<td>Clinic population, United States</td>
<td>1998–2003</td>
<td>Clinical database</td>
<td>3.5</td>
</tr>
<tr>
<td>Silverman and Greif, 2001 (35)</td>
<td>Hospital-based survey of postpartum women, United States</td>
<td>2000</td>
<td>Self-report</td>
<td>8</td>
</tr>
<tr>
<td>Tuyishime et al., 2003 (44)</td>
<td>Hospital-based survey of postpartum women, Canada</td>
<td>2002</td>
<td>Self-report</td>
<td>2</td>
</tr>
<tr>
<td>NHIS,† 2003 (34)</td>
<td>Population-based telephone survey, United States</td>
<td>2003</td>
<td>Self-report</td>
<td>12.8</td>
</tr>
</tbody>
</table>

* Vaccination rate was 6% during the 1976 swine flu vaccination campaign.
† NHIS, National Health Interview Survey.

In addition to protecting mothers, vaccination during pregnancy has the potential added benefit of protecting infants from infection. Infants are particularly vulnerable to influenza infections and complications (22–24). Vaccination is currently recommended for infants 6–23 months of age but is not recommended for younger infants because they often fail to mount a sufficient and protective immune response to vaccination (25, 26). The best strategy for reducing the risk of infection in neonates is to provide them with passive immunity by vaccinating their mothers during the later stages of pregnancy (3, 20). Data suggest that protective antibodies to influenza are transmitted from the vaccinated mother to the fetus across the placenta (20, 21, 27, 28). These antibodies may confer protection to the neonate for an average of 2–3 months after birth when mothers are vaccinated during the second or third trimester (20, 21, 27). Only one published study has examined the effectiveness of maternal vaccination in infants. Maternal vaccination was not associated with a reduced risk of influenza and pneumonia hospitalizations or influenza-like illness clinic visits in infants in this study (18).

Vaccine safety during pregnancy

Influenza vaccine has been administered to pregnant women in the United States since 1957 (26, 29). Over 2,000 pregnant women received inactivated influenza vaccine as part of the Collaborative Perinatal Project, a longitudinal population-based study conducted in the 1960s. Maternal vaccination during pregnancy was not associated with fetal malformations, cognitive or neurologic disabilities, or childhood cancers during 7 years of follow-up with this cohort (30, 31). A total of 650 women in this study were vaccinated during the first 4 months of their pregnancy. Additional studies have further evaluated the safety of vaccination during the second and third trimesters. The mothers in these studies have not reported any significant vaccine reactions, and no associations between vaccination and delivery complications (e.g., cesarean section, preterm delivery) or poor fetal outcomes (e.g., low birth weight) have been observed (18, 19, 21, 32, 33).

BARRIERS TO VACCINATION

Although inactivated influenza vaccine is considered safe and effective for both mother and fetus, the rates of influenza vaccination during pregnancy are generally low (table 1). In an analysis of the Tennessee Medicaid population, less than 1 percent of all pregnant women and less than 3 percent of those with high-risk conditions received influenza vaccine during the 1974 through 1993 vaccination seasons (11). Only 3.5 percent of 7,183 pregnant women seen at a Houston, Texas, clinic between 1998 and 2003 were vaccinated (19), and only 7.5 percent of pregnant women enrolled in a large managed-care organization were vaccinated during influenza seasons from 1997 through 2002 (18). In the latter study, coverage rates ranged from a low of 4.7 percent in 2000–2001 to 11.9 percent in 1999–2000 (18). Twelve percent of pregnant women who participated in the 2003 National Health Interview Survey reported receiving influenza vaccination during pregnancy (34).

Several studies have evaluated patient- and provider-perceived barriers to vaccination during pregnancy (4, 33, 35–37). These barriers can best be described within the framework of the Systems Model of Clinical Preventive Care proposed by Walsh and McPhee (38). This model describes the interaction between patient and provider and the factors influencing each to either promote or inhibit preventive care (figure 1).

Demographics, beliefs, attitudes, perceptions, motivations, and expectations are all factors that predispose patients to seek preventive care, such as vaccinations (38). Concern about the safety of influenza vaccine is one of the major barriers to vaccination during pregnancy for many mothers (33, 35, 39). Forty-four percent of women interviewed during the postpartum period said they believed...
that all vaccines should be avoided during pregnancy (35). In one study, women were more likely to be vaccinated during pregnancy if they either had experienced influenza or had been vaccinated against it in the past (35). Vaccinated women were also 30 percent more likely to believe that influenza infection during pregnancy presented a higher risk of complications than infection during nonpregnant periods (35). Age, medication use, and chronic medical conditions did not influence vaccination rates during pregnancy (35). Some studies report that fear of needles and cultural beliefs are associated with decreased vaccine acceptance during pregnancy (33, 35, 39).

Within Walsh and McPhee’s model, patient-enabling factors include education, knowledge, physician advice, skills, income, and logistic factors (38). Lack of patient-oriented information about vaccine risks and benefits during pregnancy has been cited as a barrier to vaccination (33, 35, 39). Advice from a health-care provider also plays an important role in a woman’s decision to be vaccinated during pregnancy; 56 percent of women surveyed during the postpartum period said they would have accepted influenza vaccine during pregnancy if their physician had recommended it to them (35).

Age, gender, ethnicity, beliefs, attitudes, prior clinical experiences, and personal health practices represent physician-predisposing factors in the model (38). In one survey of obstetrician-gynecologists, providers who had been vaccinated themselves were more likely to offer influenza vaccine to their pregnant patients than were their unvaccinated peers (85 percent vs. 45 percent; \( p < 0.001 \)) (35). These providers were also more likely to offer vaccine to their patients if they believed pregnant women had an increased risk of influenza, or if they believed that vaccination during pregnancy also protected infants (35). On the other hand, 12 percent of providers surveyed said they believed all vaccines should be avoided during pregnancy (35).

Some obstetric care providers may not recognize the important role that they play in delivering influenza vaccine to pregnant women. Obstetrician-gynecologists frequently provide other types of preventive health care, such as breast and cervical cancer screening to women, and they are often a woman’s sole provider of health care (36). However, 41
percent of obstetrician-gynecologists recently surveyed said they believed that influenza vaccine should be administered by an internist, family practitioner, or public health nurse rather than by a provider from their specialty (4). These responses may be related to provider age, as younger clinicians are more likely to self-identify as primary care providers than are older clinicians, perhaps reflecting the increasing emphasis on preventive care in obstetrics and gynecology training programs (40). Within the model, factors that enable a provider to promote a behavior include training in preventive care, knowledge of current recommendations, and availability of educational materials (38). Silverman and Greif (35) report that providers who were more knowledgeable about influenza vaccine were more likely to initiate discussions about vaccination with their pregnant patients than were providers with less knowledge about the vaccine. Several surveys suggest that many providers are not adequately informed about current vaccine recommendations and the risks and benefits of vaccination. Twenty percent of the obstetrician-gynecologists surveyed did not know that pregnant women have an increased risk of influenza morbidity, and 55 percent did not know that passive immunity could be conferred to the infant through maternal immunization (35). Sixty-five percent of respondents incorrectly identified the first trimester as a contraindication to influenza vaccination (37).

The health-care delivery system and other organizational factors have also been cited as barriers to vaccination during pregnancy. From the patient’s perspective, lack of adequate health insurance or fragmented medical care may decrease their likelihood of seeking vaccination during pregnancy (19, 32, 35, 39). Munoz et al. (19) report higher vaccination rates during pregnancy among patients with health insurance compared with uninsured patients. Providers most commonly report lack of adequate reimbursement for vaccination as a barrier to vaccination (4, 37). Other reported barriers include lack of vaccine storage and handling facilities, lack of time during patient visits, and liability concerns (4, 37). Obstetric care providers working in a multispecialty practice were more likely to offer vaccination during pregnancy than were providers working in obstetrics-gynecology practices (odds ratio = 2.8, 95 percent confidence interval: 1.9, 4.3) (4).

**IMPROVING VACCINATION RATES**

Within the model described above, several opportunities exist for focused intervention efforts targeting both patients and providers. In several studies, both patients and providers said that lack of information about influenza vaccination during pregnancy was a barrier (4, 35, 39). Clinicians must have enough information about the risks and benefits of vaccination during pregnancy so that they feel comfortable in offering vaccine to their patients and can help their patients to make informed decisions. Pregnant women should also be provided with clear, easy-to-understand information about vaccination. The Centers for Disease Control and Prevention currently offers vaccine information statements that are designed for patients and providers to provide information about vaccine benefits and vaccine safety. Vaccine information statements and other educational materials for both patients and providers are available for free download on the Centers for Disease Control and Prevention website (41).

Other intervention efforts might target organizational barriers to vaccination. The ACIP currently recommends standing orders programs as a strategy to improve adult vaccination rates (42). Standing orders programs authorize nonphysician medical personnel (e.g., nurses, pharmacists) to administer vaccinations to patients according to a specified protocol without direct physician involvement. This type of program may improve vaccination rates when obstetric care providers do not have access to vaccine storage facilities or have limited time during patient encounters.

Other recommended strategies to improve vaccination rates include reminder systems for providers and patients, such as letters or telephone calls to targeted patient groups, or flags in an electronic medical record system to alert providers to vaccine-eligible patients (43). No study has evaluated the effectiveness of any of these intervention strategies in improving influenza vaccination rates during pregnancy.

**CONCLUSIONS**

Influenza infection during pregnancy is associated with increased maternal morbidity and mortality, and it may also affect the health of the fetus. These effects were most pronounced during the 1918 and 1957 influenza pandemics, but epidemiologic studies conducted during interpandemic years have consistently demonstrated an increased risk of influenza and related complications among pregnant women. Vaccination during the second and third trimesters can also provide protection to vulnerable infants. For these reasons, the ACIP currently recommends influenza vaccination during pregnancy.

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. Despite the proven safety and possible benefits of influenza vaccine, vaccination rates during pregnancy remain generally low.

Pregnant women frequently cite concerns about vaccine safety as a barrier to vaccination during pregnancy. Just as they provide other types of preventive care, obstetric care providers could help women to understand the actual vaccine risks and benefits, but these providers may need more information themselves. Many providers did not know of the increased influenza risks during pregnancy or of the infant’s benefit of passive immunity, and a majority thought that influenza vaccination was contraindicated during the first trimester. Obstetric care providers could play an important role in delivering vaccine to pregnant patients, but they often do not recognize this opportunity.

Following the Systems Model of Clinical Preventive Care, interventions should target enabling factors for both patients and obstetric care providers to increase vaccination...
rates during pregnancy. In addition to inadequate information about the vaccine, other logistic and organizational barriers limit the vaccination of pregnant women. To address these barriers, the ACIP recommends standing orders programs and reminder systems for providers and patients as strategies for improving adult vaccination rates. Future studies should assess the effectiveness of these strategies for improving rates of influenza vaccine coverage during pregnancy.

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REFERENCES