Influenza Vaccination, Pregnancy Safety, and Risk of Early Pregnancy Loss

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Since 2004, the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists have recommended routine influenza vaccination for all pregnant women in any trimester. Maternal influenza vaccination has been shown to decrease the risk of influenza and its complications among pregnant women and their infants in the first 6 months of life. In a recent article published in *Vaccine*, Donahue and colleagues reported a possible association between influenza vaccination when given very early in the first trimester and spontaneous abortion. There are limited conclusions that should be drawn from this study given the case–control design as well as the small number of patients included in the subanalysis that is the basis for the report. A prior first-trimester safety study from this group, using a similar study design, had not observed any association with spontaneous abortion, and other reports of first-trimester vaccine safety have not observed an association. The lack of a biologically plausible mechanism for the suggested association between previous influenza vaccination and early pregnancy loss is of concern. The study's reported observation is not definitive and needs be replicated in appropriately designed studies before changing clinical practice. Pregnant women are at high risk for severe influenza-related complications, including death, and health care providers have an obligation to their patients to continue to recommend and provide influenza vaccinations.

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Since 2004, the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG) have recommended routine influenza vaccination for all pregnant women in any trimester.[1] This recommendation is supported by a robust body of literature. Pregnant women are at high risk for complications of influenza including serious illness, hospitalization, and death.[2,3] Maternal influenza vaccination has been shown to decrease the risk of influenza and its complications among pregnant women and their infants in the first 6 months of life.[4,5]

Despite these clear recommendations, rates of maternal influenza vaccination remain suboptimal.[6] We are concerned that misconceptions about influenza vaccine effectiveness and skepticism about influenza vaccine safety may be contributing to lukewarm endorsements by health care providers and poor uptake by patients. Endorsement by the health care provider is the single most important factor in determining vaccine uptake.[7,8]

Influenza vaccine effectiveness in disease prevention varies from season to season, depending on host characteristics (such as age and presence of comorbidities) and how well circulating influenza viruses match the viruses contained in the vaccine. Although preventing infection is ideal, mitigating the severity of disease is also important. Recent studies support that influenza vaccination provides protection against severe disease (including death) among persons who become infected despite vaccination.[9] This is important information to share with pregnant women who are at high risk for severe disease.

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The Immunization and Emerging Infections Expert Work Group Roster is in Appendix 1, available online at http://links.lww.com/AOG/B78.

Each author has indicated that she has met the journal's requirements for authorship.

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In a recent article published in *Vaccine*, Donahue et al[10] reported a possible association between influenza vaccination when given very early in the first trimester and spontaneous abortion. Researchers compared 485 women aged 18–44 years who miscarried (cases) with 485 pregnant women aged 18–44 years who did not miscarry (controls) to determine whether the women who had miscarriages were more or less likely to have received the 2010–2011 or 2011–2012 flu vaccine (both of which included a 2009 pandemic H1N1 component). For the analysis, women were subdivided into smaller cohorts based on whether they were vaccinated the previous season and also the time between vaccination and miscarriage (1–28 days, 29–56 days, or greater than 56 days). Women who experienced miscarriage in early pregnancy had an increased odds ratio of having received influenza vaccine in the preceding 28 days when they had also received two consecutive seasonal flu vaccinations. Importantly, in the subgroup analysis, there were only 18 women (14 women in the case group and 4 women in the control group) who had spontaneous abortions within the 28-day exposure window who had also received a pandemic H1N1-containing vaccine in the previous season making it difficult to draw any conclusions from these small numbers. There was no association with spontaneous abortion if vaccination occurred more than 28 days before the pregnancy loss or, even within the 28-day window, if vaccination was not received 2 years in a row. Data for this analysis were obtained from the Vaccine Safety Datalink, a collaborative of the CDC's Immunization Safety Office and several integrated health care systems in the United States.[10] A prior first-trimester safety study from this group, utilizing a similar study design, had not observed any association with spontaneous abortion[11] and other reports of first-trimester vaccine safety also have not observed an association.[12–14] There is an ongoing investigation from the same research group utilizing data from women who were pregnant and eligible to receive the flu vaccine in the 2012–2013, 2013–2014, and 2014–2015 flu seasons. Results are expected in late 2018 or 2019.

What should be done with this information from a single study? How do we explain this study to pregnant women to alleviate concerns raised by media reports? Does this warrant a change in ACOG recommendations? A critical evaluation of the merits and limitations of the current study design is needed to inform these decisions.

Our group (the ACOG Immunization and Emerging Infections Work Group) has responded to the *Vaccine* publication with a letter to the editor outlining the flaws of the Donohue study (Ault KA, Riley LE. Response to Donahue et al. 2017 in press article [letter]. *Vaccine* 2018. [epub ahead of print].). The CDC, which funded the study, has posted information on their website, which details the limited conclusions that can be drawn from this study given the small number of patients in the subanalyses and the case–control study design.[15] Only an association, not a causal link, can be inferred from a case–control design. In addition, despite matching, the study groups were dissimilar in their risks for spontaneous abortion. Among the described patient characteristics, four factors (older age, high body mass index, smoking during pregnancy, and having a history of two or more previous spontaneous abortions) are potential risk factors for spontaneous abortion and were present more frequently in the women in the case group than in the women in the control group. Nine percent of women in the case group and 5% of women in the control group had a history of two or more spontaneous abortions; prior miscarriage is the single greatest risk factor for subsequent spontaneous abortion.[16] This imbalance between women in the case group and those in the control group biases the findings to overestimate a potentially harmful relationship between vaccination and spontaneous abortion.

The lack of a biologically plausible mechanism for the suggested association between previous influenza vaccination and early pregnancy loss is concerning. The association was only significant among women vaccinated in two consecutive seasons and not among women vaccinated for the first time with a pandemic H1N1 virus strain.[10] The authors hypothesize that spontaneous abortion was somehow linked to an enhanced or altered inflammatory response after repeat vaccination with a new pandemic strain. This hypothesis is unproven.[10] There has been limited published literature addressing the immunologic and inflammatory responses to repeat influenza vaccination during pregnancy. Prior influenza vaccination has been linked to diminished immune responses (as judged by lower antibody responses and lower seroconversion rates)[17,18] presumably as a result of the presence of neutralizing antibodies (from either past vaccination with identical or similar strains and also past flu infection). This effect was seen in all trimesters. Inflammatory (serum proinflammatory cytokine) responses to seasonal influenza vaccination were evaluated in both pregnant and nonpregnant women and the observed changes in cytokine levels were mild, transient (lasting 2–3 days), and generally similar in both groups.[19,20] Inflammatory responses did not

vary by prior vaccination status. Furthermore, the inflammatory responses elicited by vaccination were substantially milder and more transient than seen with influenza illness.[19]

Ongoing surveillance of pregnancy-related risks and benefits is essential to maintain patient and health care provider confidence in vaccines as well as the current ACOG vaccine recommendations. Through the process of safety monitoring (pharmacovigilance surveillance), we expect to identify potential risks that warrant further investigation.[21] After vaccination in pregnancy, adverse events that are monitored include risks for birth defects, miscarriage, chorioamnionitis, preterm birth, and small-for-gestational-age infants.

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