Influenza Vaccination and Antiviral Therapy in Pregnant Women

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(See the major article by Oboho et al on pages 507–15.)

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It is well recognized that pregnant women are at increased risk of severe morbidity, maternal death, and adverse pregnancy outcomes, including pregnancy loss and preterm birth, due to seasonal and pandemic influenza [1]. In this issue, Oboho et al present the results of a US multicenter surveillance study designed to describe the characteristics and impact of antiviral therapy on influenza outcomes, including a defined composite outcome of severe influenza, and length of stay (LOS) stratified by influenza severity among pregnant women hospitalized with an influenza virus–positive test result from the 2010–2011 through the 2013–2014 influenza seasons. Eighty-five percent of the 865 pregnant women included in the analysis received antiviral treatment with oseltamivir, and two thirds had no underlying medical comorbidities. Seventy-one percent of the women received antiviral treatment within 2 days of the onset of symptoms. Severe influenza occurred in 63 (7%) and was more likely to occur earlier in pregnancy among those with comorbidities (particularly asthma). Furthermore, women with severe infection were only half as likely to have received an influenza vaccination, compared with women with nonsevere influenza (14% vs 26%), and significantly less likely to have received antiviral therapy initiated within 2 days of symptom onset (52% vs 72%; \( P = .03 \)), although the frequency of use of any antiviral therapy was similar in both groups. The authors observed a markedly shorter median LOS among women with severe influenza in the group receiving antiviral treatment within the first 2 days of symptom onset, compared with the group that received treatment after 2 days of symptoms (2.2 vs 7.8 days; \( P = .03 \)). Among women with nonsevere influenza, the median LOS differential was much smaller but still significantly lower in the group treated early, compared with the group treated late (2.4 vs 3.1 days; \( P < .01 \)). The authors conclude that antiviral treatment within the first 2 days of the onset of symptoms may reduce the LOS for pregnant women hospitalized with a positive influenza virus test result, particularly among women with severe disease.

The data for this study were captured from a variety of sources, including hospital laboratory and admission databases, infection control logs, and hospital discharge International Classification of Disease, Ninth Revision, codes. As such, this study (as do most similar epidemiological studies) suffers from potential sources of bias, such as ascertainment bias, information bias introduced by data entry errors, and potential failure to identify possible confounding variables. Nevertheless, the study includes a reasonable sample size, and the results for the most part seem internally consistent and in keeping with observations made in nonpregnant and pregnant populations. Thus, the study provides objective evidence supporting the authors’ recommendation that early antiviral therapy should be given to pregnant women with confirmed influenza or an influenza-like illness. Furthermore, the low uptake of vaccination in the population overall and the significantly lower uptake among those with severe influenza underscore the importance of adhering to national recommendations to vaccinate pregnant women at any gestational age with the inactivated trivalent or quadrivalent influenza vaccine [1].

The potential benefits of early antiviral treatment demonstrated among pregnant women should be tempered by recognizing some important limitations of the study by Oboho et al. First, the current study was not designed to assess the safety of oseltamivir in pregnancy, specifically regarding its direct effects on the fetus and particularly in the first half of pregnancy. However, the increased morbidity and mortality among pregnant women and their fetuses in cases of influenza virus infection are well known, and the available limited data do not indicate that antiviral therapy carries negative fetal consequences [2–3]. This certainly argues in favor of oseltamivir use in pregnant women, considering the maternal benefits that indirectly benefit the fetus. However, it should be acknowledged...
that the safety of oseltamivir in this context is incompletely understood.

Second, although early administration of oseltamivir treatment was associated with a lower LOS as compared to late treatment, the study does not answer the question as to whether early treatment is associated with lower rates of important adverse outcomes, such as stillbirths and maternal deaths. The study did evaluate some maternal medical and perinatal complications, including preterm delivery and fetal loss, that were more common in the severe versus nonsevere influenza groups. The association of severe cases with earlier gestational ages appears to contradict a previous report in which severe influenza was associated with later gestational ages, as well as obesity, which was not assessed in the current study [4].

Third, it would be useful to know whether outcomes in the group that received late treatment (after 2 days from symptom onset) are better if they are treated earlier as opposed to later, considering preliminary data suggesting a reduced but ongoing benefit in the general population [5]. The decision whether to give oseltamivir after 2 days have passed since the onset of symptoms is a common dilemma faced by obstetrical providers.

Overall, considering the accumulating evidence of fetal benefit and safety, influenza vaccination of pregnant and postpartum women should be a public health priority in accordance with national recommendations [1]. Prompt initiation of antiviral therapy if infection occurs, preferably within 2 days of suspected or confirmed influenza virus infection, is encouraged. Additional evaluation to assess fetal safety and to determine whether there is ongoing benefit when therapy is initiated after 2 days of symptoms are reasonable goals.

Note
Potential conflict of interest. Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References