

Respiratory Virus Infection During Pregnancy: Does It Matter?

Janet A. Englund¹ and Helen Y. Chu²

¹Department of Pediatrics, Seattle Children's Hospital/University of Washington, and ²Department of Medicine, University of Washington, Seattle

(See the Major Article by Hause et al, on pages 528–35.)

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Respiratory illnesses during pregnancy are well recognized and are anecdotally considered to be common by pregnant women and healthcare providers alike. However, data describing the incidence and impact of common respiratory viruses other than influenza virus in pregnant women are extremely limited. The article by Hause et al in this issue of *The Journal of Infectious Diseases* provides a prospective description of respiratory viral disease in women seen at an outpatient obstetrical clinic during their second or third trimesters of pregnancy, based on symptoms noted by the women themselves [1]. The authors evaluated women from a large urban outpatient clinic for viral causes of acute respiratory symptoms and the clinical extent of disease when participants presented for medical care. Although the study did not evaluate the incidence of respiratory disease in this population by prospective enrollment of a pregnant cohort, this information provides a relevant end point for future epidemiology studies, as well as vaccine trials. The most significant finding of their study was that over one third

of women with symptoms of acute respiratory illness had disease consistent with lower respiratory tract disease, which the authors defined as difficulty breathing or shortness of breath, wheezing, or cyanosis. Morbidity associated with these symptoms and signs was considerable and associated with a variety of respiratory viruses. Of note, this study evaluated asymptomatic pregnant women as well, allowing for comparisons of respiratory viruses detected in women with and without symptoms. The study population reflected the contemporary make-up of pregnant women in the United States, with a median age of 31 years and a broad representation of racial and ethnic backgrounds. Common viruses detected included rhinovirus (27%), coronavirus (17%), and respiratory syncytial virus (RSV; 10%)—all well-known respiratory viruses with high attack rates in both adults and children but not well-described in pregnant women.

Prior studies of respiratory viral illness during pregnancy have focused primarily—and usually exclusively—on influenza. Starting with the 1918 pandemic, pregnant women have been identified to be at higher risk for severe morbidity and mortality due to influenza, compared with nonpregnant adults [2]. In the 2009 influenza A(H1N1) pandemic, pregnant women with influenza, particularly during the third trimester, were demonstrated to have increased disease severity, as well as higher rates of secondary bacterial pneumonia and increased risks of

inpatient and intensive care unit admissions, compared with nonpregnant adults [3]. These risks extended to the fetus, with higher rates of stillbirth, miscarriage, and preterm birth observed with influenza virus infection during pregnancy [4]. Overall, inactivated influenza vaccination has been found to be safe, immunogenic, and effective in prevention of influenza in pregnant women [5]. Despite concerns about a relatively immunocompromised state during pregnancy, pregnant women were shown to achieve serologic protection rates generally comparable to those for nonpregnant adults [5]. The recorded epidemiologic data from the early part of the 2009 pandemic resulted in pregnant women receiving priority for vaccination in the United States and other countries, and international prioritization of influenza vaccination during pregnancy by the World Health Organization [5–7]. This recommendation was based mainly on the benefits for the pregnant women themselves. Recently, 3 large prospective controlled clinical trials again demonstrated the effectiveness of maternal influenza immunization to prevent disease in pregnant women [8–10]. These studies also demonstrated reduction of influenza incidence among infants born to vaccinated women, another important benefit of maternal immunization. Potential benefit of influenza vaccine to the fetus was only documented in Nepal, 1 of 3 clinical trials sites, where influenza was present nearly year-round and the prevalence of low birth weight and

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Correspondence: J. Englund, MD, Department of Pediatrics, Seattle Children's Hospital/University of Washington, Seattle, WA (janet.englund@seattlechildrens.org).

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preterm birth was high, representative of the South Asian population [9, 11]. In that study, the frequency of low birth weight was significantly lower among infants born to vaccinated women. This birth-weight effect was more pronounced during periods of high influenza virus circulation and when matching of circulating virus to the vaccine strain was present [12]. This study, as well as a previous randomized controlled trial of maternal influenza immunization in Bangladesh, showed an effect of influenza vaccination on improvement of fetal outcomes [13].

Respiratory viruses are increasingly recognized as an etiologic agent of community-acquired pneumonia in adults, with a recent population-based active surveillance study identifying rhinovirus and influenza virus as the most common pathogens in adults requiring hospitalization [14]. Few studies have evaluated the role of respiratory viruses other than influenza virus during pregnancy. RSV infection in pregnancy remains poorly characterized, reflecting a major gap in our epidemiological understanding that should be addressed before introduction of an RSV vaccine [15]. In healthy adult populations aged 18–60 years, RSV has been shown to be a commonly acquired cause of symptomatic respiratory illness, with increased symptom duration and less fever as compared to influenza [16]. In that US study, 26% of adults with RSV had lower respiratory tract symptoms, defined as tracheobronchitis, bronchitis, or wheezing. The proportion of symptomatic RSV infection is likely to be even higher among pregnant women, as evidenced in this study, owing to an increased risk of exposure to young children and decreased cardiopulmonary reserve.

Previous studies of RSV in pregnancy have been primarily case reports and secondary analyses of influenza vaccine trials [17–20]. Use of data from influenza vaccine trials to determine the incidence of infections due to RSV and other respiratory viruses has multiple limitations, including the use of influenza-like illness

(ILI) criteria for respiratory illness and surveillance only during the influenza season. ILI criteria are traditionally based on the presence of fever and cough and/or sore throat, and it is known that the majority of cases of RSV infections in adults are afebrile [16]. Additionally, influenza and RSV seasons often do not overlap, likely leading to underestimation of the RSV infection burden when sampling is ongoing only during periods of influenza virus circulation [21]. Two of the recent maternal influenza studies, from Nepal and South Africa, evaluated the incidence of maternal respiratory disease due to RSV during pregnancy [9, 10]. In Nepal, where women with a fever and respiratory symptoms had a nasal swab specimen collected, the RSV infection prevalence was 0.2%, with an incidence of 3.9 cases/1000 person-years overall. In South Africa, the RSV infection prevalence based on the presence of respiratory symptoms was much higher, at 2%, with an overall incidence of 14.4–48.0 cases/1000 person-years [19]. Importantly, none of the maternal cases of RSV infection in the South Africa trial were associated with fever [16, 22, 23]. RSV infection was not associated with an increased risk of low birth weight or preterm birth in either the South Africa or Nepal studies, although numbers of women in both studies with RSV were small.

Other respiratory viruses, including rhinovirus, coronavirus, parainfluenza viruses 1–4, and human metapneumovirus, have recently been identified as causes of febrile respiratory viral infections in pregnant women [24, 25]. Rhinovirus has been identified as a common cause of ILI in pregnant women, and Middle Eastern respiratory syndrome and severe acute respiratory syndrome coronaviruses have been described to cause severe disease in pregnant women [26, 27]. Other respiratory viruses were commonly detected in the maternal influenza vaccine trial in Nepal in women with fever and respiratory symptoms, with a virus detected in the majority of 767 febrile respiratory illness

episodes in 3693 pregnant women [19, 20]. The frequency of care seeking from a physician or hospital for these illness episodes ranged from 0% to 33% of all illness episodes, based on the virus, a significant finding in a region of the world where medical care is extremely limited and difficult to access. Febrile rhinovirus and human metapneumovirus infections were both associated with an increased risk of fetal growth restriction in this study. This suggests that the deleterious effect of maternal viral infections on the fetus may not be restricted to pregnant women with influenza.

Maternal immunization is increasingly recognized as a safe and effective intervention to boost antibody levels during pregnancy and increase levels of transplacental antibody transferred to the fetus [28]. Until infants are several months old, they are generally unable to mount an effective immune response to vaccination or infection or they require several doses of vaccine, leaving a window of vulnerability for serious infections. Maternal vaccination may increase maternal and subsequently fetal antibody titers above potential protective levels, thereby protecting infants during this critical window. Multiple RSV vaccine candidates are already in clinical trials, including an RSV nanoparticle vaccine with an alum adjuvant under evaluation in a large clinical trial involving pregnant women vaccinated during their third trimester of pregnancy (ClinicalTrials.gov identifier: NCT02624947). Other RSV vaccine candidates are also intended for use in pregnant women. The World Health Organization estimates that an RSV vaccine will be licensed in the next 5–10 years [29]. As these studies progress, findings from the study reported in this issue will provide important background data in understanding the potential effect of maternal vaccination in protection of pregnant women and fetuses. Investigation into the impact of these respiratory viruses during pregnancy in other settings is worthy of

further study, as sensitive molecular diagnostic testing becomes more widely available and the development of new vaccines, antivirals, and monoclonal antibodies for respiratory viruses grows.

Notes

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References

1. Hause A, Avadhanula V, Maccato M, et al. A cross-sectional surveillance of the frequency and etiology of acute respiratory illness among pregnant women. *J Infect Dis* **2018**; 218:528–35.
2. Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions. *Vaccine* **2011**; 29:4439–52.
3. Siston AM, Rasmussen SA, Honein MA, et al.; Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA* **2010**; 303:1517–25.
4. Centers for Disease Control and Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)—United States, April 2009–August 2010. *MMWR Morb Mortal Wkly Rep* **2011**; 60:1193–6.
5. Jackson LA, Patel SM, Swamy GK, et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. *J Infect Dis* **2011**; 204:854–63.
6. Vaccines against influenza WHO position paper—November 2012. *Wkly Epidemiol Rec* **2012**; 87:461–76.
7. Madhi S, Cutland C, Hugo A, et al, eds. Efficacy and immunogenicity of inactivated influenza vaccine in pregnant women: a randomized, double-blind, placebo controlled trial [abstract 63.003]. Presented at: 16th International Congress on Infectious Diseases, Cape Town, South Africa, 5 April **2014**.
8. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *Lancet Infect Dis* **2016**; 16:1026–35.
9. Steinhoff MC, Katz J, Englund JA, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. *Lancet Infect Dis* **2017**; doi: 10.1016/S1473-3099(17)30252-9.
10. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med* **2014**; 371:918–31.
11. Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health* **2013**; 1:e26–36.
12. Kozuki N, Katz J, Englund JA, et al. Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal. *Int J Gynaecol Obstet* **2018**; 140:65–72.
13. Jamieson DJ, Honein MA, Rasmussen SA, et al.; Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* **2009**; 374:451–8.
14. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* **2015**; 373:415–27.
15. Kim L, Rha B, Abramson JS, et al. Identifying gaps in respiratory syncytial virus disease epidemiology in the United States prior to the introduction of vaccines. *Clin Infect Dis* **2017**; 65:1020–5.
16. Hall CB, Long CE, Schnabel KC. Respiratory syncytial virus infections in previously healthy working adults. *Clin Infect Dis* **2001**; 33:792–6.
17. Wheeler SM, Dotters-Katz S, Heine RP, Grotegut CA, Swamy GK. Maternal effects of respiratory syncytial virus infection during pregnancy. *Emerg Infect Dis* **2015**; 21:1951–5.
18. Chaw L, Kamigaki T, Burmaa A, et al. Burden of influenza and respiratory syncytial virus infection in pregnant women and infants under 6 months in Mongolia: a prospective cohort study. *PLoS One* **2016**; 11:e0148421.
19. Madhi SA, Cutland CL, Downs S, Jones S, van Niekerk N, Simoes EAF, Nunes MC. Burden of respiratory syncytial virus infection in South African HIV-infected and HIV-uninfected pregnant and post-partum women: a longitudinal cohort study. *Clin Infect Dis* **2018**; 66:1658–65.
20. Chu HY, Katz J, Tielsch J, et al. Clinical presentation and birth outcomes associated with respiratory syncytial virus infection in pregnancy. *PLoS One* **2016**; 11:e0152015.
21. Datta S, Walsh EE, Peterson DR, Falsey AR. Can analysis of routine viral testing provide accurate estimates of respiratory syncytial virus disease burden in adults? *J Infect Dis* **2017**; 215:1706–10.
22. Falsey AR, Formica MA, Walsh EE. Diagnosis of respiratory syncytial

- virus infection: comparison of reverse transcription-PCR to viral culture and serology in adults with respiratory illness. *J Clin Microbiol* **2002**; 40:817–20.
23. O'Shea MK, Ryan MAK, Hawksworth AW, Alsip BJ, Gray GC. Symptomatic respiratory syncytial virus infection in previously healthy young adults living in a crowded military environment. *Clin Infect Dis* **2005**; 41:311–7.
24. Lenahan JL, Englund JA, Katz J, et al. Human metapneumovirus and other respiratory viral infections during pregnancy and birth, Nepal. *Emerg Infect Dis* **2017**; 23:doi: 10.3201/eid2308.161358.
25. Philpott EK, Englund JA, Katz J, et al. Febrile rhinovirus illness during pregnancy is associated with low birth weight in Nepal. *Open Forum Infect Dis* **2017**; 4:ofx073.
26. Assiri A, Abedi GR, Al Masri M, Bin Saeed A, Gerber SI, Watson JT. Middle east respiratory syndrome coronavirus infection during pregnancy: a report of 5 cases from Saudi Arabia. *Clin Infect Dis* **2016**; 63:951–3.
27. Pilorge L, Chartier M, Meritet JF, et al. Rhinoviruses as an underestimated cause of influenza-like illness in pregnancy during the 2009–2010 influenza pandemic. *J Med Virol* **2013**; 85:1473–7.
28. Chu HY, Englund JA. Maternal immunization. *Clin Infect Dis* **2014**; 59:560–8.
29. Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS; WHO RSV Vaccine Consultation Expert Group. WHO consultation on respiratory syncytial virus vaccine development report from a World Health Organization meeting held on 23–24 March 2015. *Vaccine* **2016**; 34:190–7.