The Significance of Transplacental Antibody Against Respiratory Syncytial Virus

Pedro A. Piedra1,2 and Flor M. Munoz1,2

1Department of Molecular Virology and Microbiology, and 2Department of Pediatrics, Baylor College of Medicine, Houston, Texas

(See the major article by Chu et al on pages 1582–9.)

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Respiratory syncytial virus (RSV) is the major respiratory virus of young children, causing substantial morbidity and mortality annually. Epidemics occur during the fall and winter months in countries in the temperate zones and year-round, with or without outbreaks tied to the rainy season, in countries in the tropical and subtropical zones. Worldwide, RSV causes >33 million cases of lower respiratory tract illnesses, 3 million hospitalizations, and 66 000–199 000 deaths per year in children <5 years of age [1]. It is the number one cause of hospitalization in infants aged <12 months in industrialized countries [2] and results in a high burden of outpatient disease in children 24–59 months of age that likely goes unrecognized by pediatric healthcare professionals [3]. Although there are no currently approved vaccines for the prevention of RSV infection in any age group, there is a large development pipeline of RSV vaccines targeting high-risk groups [4]. In adults, RSV also causes substantial morbidity and mortality. It accounts for approximately 10% of cases of community-acquired pneumonia [5] and 10 000 deaths [6] annually. Importantly, there is no information on the incidence or clinical impact of RSV infection during pregnancy. It is well known that pneumonia is the most common cause of fatal nonobstetrical infection in pregnant women [7]. Pneumonia due to influenza virus can be more severe in pregnant women than in nonpregnant women and results in an increased risk of hospitalization and death during the third trimester of pregnancy [8]. It is highly likely that RSV infection during the third trimester of gestation could also increase the risk of maternal-fetal morbidity. The significant gap in medical knowledge on the prevalence of RSV infection during pregnancy and its adverse effects on the mother-fetal pair need to be addressed.

RSV-specific neutralizing antibodies are efficiently transferred transplacentally to the newborn [9]. High levels of maternally derived RSV-specific antibody protect infants against RSV infection during the first few months of life [10]. Proof-of-concept studies have demonstrated the safety and protective effectiveness of passive administration of RSV-specific antibodies, either as immune globulin containing high titers of RSV antibodies (RSV-IG; no longer available) or as monoclonal antibody (palivizumab) that targets the fusion protein of RSV [11, 12]. The article by Chu et al in this issue of the Journal advances our understanding of the kinetics of natural RSV-specific transplacentally acquired maternal antibodies in a low-resource country. Chu et al studied 149 mother-infant pairs in Bangladesh from the third trimester of pregnancy to week 72 of the postpartum period. Although no specific diagnostic surveillance for RSV infection in mothers was established in this trial, maternal infection likely occurred in some women during the period of increased circulation of RSV. A boost in RSV-specific antibodies in the mothers after infection would have likely resulted in greater antibody transfer to the fetus, particularly toward the end of a term gestation. As in prior studies, the authors noted that maternal RSV-specific serum neutralizing antibodies were efficiently transferred transplacentally from mother to infant at a ratio of approximately 1 (95% confidence interval, 0.99–1.03). The maternal antibody half-life was 31–38 days, depending on the definition used to determine intercurrent RSV infection in infants in the first few months of life. This is consistent with the maternal antibody half-life calculated in infants born to mothers who received a purified fusion protein vaccine against RSV during their third trimester of pregnancy [9]. Of interest, Chu et al evaluated the time to reduction in serum neutralizing antibody below a putative threshold titer associated with protection, taking into consideration the possibility of acquired RSV infection...
in infants in the first few months of life. The median time to reduction below a protective titer was 17 weeks, and for every 0.5 log increase in infant antibody titer there was an estimated increase in duration of protection by 19 days. Therefore, it is possible that through maternal immunization, high concentrations of neutralizing antibodies in newborns could provide protection for at least 3–6 months, allowing the infants to improve their ability to resist RSV infection or decrease its severity during this period of high vulnerability. This is particularly important in subpopulations of mothers who have neutralizing antibody titers below the mean population titer at the time of delivery [9, 13]. Recently, a nanoparticle RSVF vaccine was evaluated in healthy adults [14]. At the 60-µg dose, there was an approximately 2-fold increase in the mean serum neutralizing antibody titer; however, adults with lower baseline titers experienced about a 5-fold increase after vaccination. This suggests that maternal immunization with an immunogenic vaccine will likely provide the greatest benefit to infants born to mothers with low baseline antibody titers prior to receiving the RSV vaccine during the third trimester of pregnancy.

Maternally derived antibody is an important component of the immune defense of neonates and young infants. Maternal immunization can provide direct benefit to mothers and to the newborn by enhancing the amount of antibody transferred transplacentally to neonates. Maternally derived antibody or passively administered antibody have not been linked to enhanced respiratory disease, a phenomenon that occurred in the 1960s in children <2 years old who were vaccinated with the Pfizer-derived [15] but not the Merck-derived [16] formalin inactivated alum precipitated RSV vaccine upon natural infection with RSV. A maternal immunization approach has already been proven to protect infants against neonatal tetanus worldwide [17], and influenza [18], and has been implemented in the United States and other industrialized countries in response to the rising number of cases and infant mortality from pertussis [19]. This immunization strategy is being considered for the prevention of severe RSV disease in term infants <6 months of age [9, 20]. There is great interest in expanding maternal immunization because of the potential to meet a significant medical need, especially when considering the costs and limitations of the current strategy based on passive administration of RSV-specific monoclonal antibodies to high-risk preterm infants and some newborns with underlying cardiopulmonary disease [20, 21]. The current approach leaves the majority of the infant population (term infants <6 months of age) vulnerable to infection and the complications associated with RSV in early life. The results in the study of Chu et al are encouraging, as the number of infants with possible RSV infection defined by serologic parameters (2- or 4-fold elevation of neutralizing antibody titers) was lower when antibody concentrations were higher in the first 6 weeks of life. These findings are supportive of maternal immunization as a potential strategy to reduce the impact of RSV in early life. Even though the results reported by Chu et al might not be generalizable to the population of the United States or other industrialized countries, given regional differences in epidemiologic characteristics and climatic conditions, the results are helpful to inform researchers and regulatory agencies of the potential beneficial effects to the newborn of boosting antibody concentrations in mothers through vaccination in the second or third trimester of gestation. Thus, the continuation of efforts to develop safe and immunogenic RSV vaccines for pregnant women with the goal to protect infants against RSV disease and its complications is warranted.

**Note**

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**References**

13. Piedra PA, Jewell AM, Cron SG, Athmar RL, Glezen WP. Correlates of immunity to respiratory syncytial virus (RSV) associated...


