SHORT REPORT

The progression of maternal RSV antibodies in the offspring

M Hacimustafaoglu, S Celebi, E Aynaci, M Sinirtas, N Koksal, A Kucukerdogan, I Ercan, G Goral, I Ildirim

....

The concentrations of maternal anti-RSV IgG antibodies were followed in 49 healthy newborns over the first six months of life.

At birth, 41 mothers (83%) tested positive for anti-RSV IgG and all of their babies carried maternal anti-RSV IgG. Anti-RSV IgG positivity dropped to 73% at 1 month, 6% at 3 months, and 2% at 6 months.

Between 3 and 6 months, 8% did acquire RSV infection, half of them as acute bronchiolitis and half as non-specific respiratory infection. All of the patients who acquired clinical RSV disease had an antibody concentration of <20 RU/ml which may be the cut off value for protection.

A cute bronchiolitis (AB) is one of the most common reasons for hospitalisation before 1 year of age. Maternal neutralising antibodies may protect the baby and the infection may be more mild, but this protection is not complete.[1][2] No study has been performed to investigate the progression of maternal anti-RSV antibodies in Turkey. The only study in the world literature that evaluated the progression of maternal antibodies has shown that maternal antibodies disappear before 6 months of age.[3] The presence and progression of maternal antibodies is important for the health of the infant. Protection against RSV infection in early infancy is correlated with the level of maternal antibodies. In addition, infants with more severe illness have lower levels of antibodies in their sera collected near onset of illness than infants with milder illness.[1] However, the presence of these antibodies may render serological diagnosis of the RSV infection more difficult. In addition, it may potentially affect seroconversion after vaccination which is anticipated to be available in the future. Therefore, its natural progression is important for determining the rational timing for vaccination. In this prospective study, we aimed to follow the concentrations of maternal anti-RSV IgG antibodies in healthy newborns over the first six months of life.

METHODS

A total of 49 pregnant women and their full term babies born in the Zubeyde Hanim Maternity Hospital of Bursa were randomly selected, beginning in November. The aim of the study and the tests that would be done were explained to each family and written consent was obtained. Blood was drawn at birth from the mothers and their babies. The infants were seen again at 1, 3, and 6 months of age, when a history of past infections were taken, a physical examination was performed, and a blood sample was drawn. In our region, RSV infections usually present between October and April (92%) (M Hacimustafaoglu, unpublished data).

Blood samples were centrifuged at 3000 rpm for five minutes and the sera were frozen at −20℃ until they were tested by enzyme linked immunosorbent assay (ELISA). In those patients who presented with clinical AB, RSV antigens in nasopharyngeal secretion were tested (Test Pack Abbott). Euroimmune kits were utilised to measure anti-RSV IgG and anti-RSV IgM antibodies in sera. In these tests, specific antibodies will bind to the reagent antigens in the wells after incubation. To detect the bound antibodies, a second incubation is carried out using an enzyme labelled anti-human IgG (enzyme conjugate). The intensity of the formed colour is measured photometrically at a wavelength of 450 nm. The detection limit of the anti-RSV IgG is approximately 1 RU/ml. Anti-RSV IgG concentrations above 20 RU (relative units)/ml were considered positive.

The data were analysed by standard statistical methods (paired t test, McNemar test, Pearson correlation test). The study was approved by the Committee of Ethics of Uludag University Faculty of Medicine.

RESULTS

The infants consisted of 33 (67.3%) males and 16 (32.6%) females. Forty one (83.6%) were full term, five (10.2%) had a gestational age of 35–38 weeks, and three (6%) had a gestational age of 32–35 weeks. Mean gestational age was 39.2 (SD 1.86) (range 33–41) weeks; mean birth weight was 3230 (SD 542) (range 1500–4476) g. Table 1 presents the serological test results.

Although there was not a strong correlation ($r = 0.45$) between individual maternal infant paired sera, the mean antibody levels in the two groups were not significantly different ($p > 0.05$).

At 1 and 3 months of age, no infant had an increasing anti-RSV IgG positivity and none of the previously negative cases acquired antibody positivity. The mean antibody titre from birth to 1 month decreased by 38% ($p < 0.01$), and from 1 month to 3 months by 30% ($p < 0.01$).

At 6 months of age, four infants (8%) had positive anti-RSV IgG. Three of these infants had a negative result at 3 months of age and the positivity at 6 months was interpreted as acquired infection. There was a history of upper respiratory infection in two and AB in one of these patients; the antibody titres of these infants were 46, 60, and 110 RU/ml respectively. When acquired infections were excluded, the maternal antibody positivity at 6 months of age was 2%.

During the clinical follow up for six months, four (8%) infants had AB and RSV was detected in half of them. Three of these four infants were male and one female. Two acquired AB at 3 months and two at 5 months of age. The patients who had AB did not have a different maternal IgG concentration or a different titre at 0, 1, 3, or 6 months of life compared to the other healthy infants ($p > 0.05$).

DISCUSSION

Utilising anti-RSV IgG for the diagnosis of acute infection in young infants may cause difficulties in interpretation because

....

Abbreviations: AB, acute bronchiolitis; RSV, respiratory syncytial virus

Table 1 The progression of maternal and acquired anti-RSV-IgG

Month	n	Anti-RSV IgG(+)*(n) (%)	Anti-RSV IgG (RU/ml) Range (mean, SD)
Maternal	49	41 (83%)	26–150 (71.2, 29.8)
Infants			
0	49	41 (83%)	25–150 (73.8, 26.8)
1	49	36 (73%)	24–126 (46.2, 23.6)
3	49	3 (6%)	22–37 (32.5, 7.1)
6	49	4 (8%)**	20–110 (59.0, 37.8)

*Positivity is defined as values ≥20 RU/ml.
**Three (6%) are acquired RSV infection on follow up.

it is not possible to differentiate maternal IgG and acquired IgG. In addition, false positive IgM results may be obtained without RSV infection because of maternal anti-RSV IgG during the first month of age. This situation is due to the binding of maternal IgG to the antigens used in ELISA or immunofluorescence antibody assays resulting in antigen-antibody complexes.[4] Therefore, the presence and the elimination time of maternal antibodies in young infants may influence infection rate, nature, and the diagnosis of acquired infections by serological methods.[1–4]

Brandenburg and colleagues[3] have reported that RSV infection has been shown in 32 of 38 infants with suspected infection by viral isolation, direct immunofluorescence, or RT-PCR, and only one (3%) was RSV IgM positive. Serological methods such as ELISA, viral neutralisation, RSV specific IgM and IgA, and complement fixation have yielded a range of 0–22% positivity in patients with proven RSV infections. Murphy and colleagues[5] and Meurman and colleagues[6] have shown that in younger infants, the level of maternal antibody is associated with decreased antibody responsiveness to RSV infection. Both immaturity of the immune system and antibody mediated immune suppression affect the overall response of young infants to RSV.[5] These results imply that the serological methods have a limited role and their use has disadvantages in diagnosis and seroepidemiological analyses in young infants.

Brandenburg and colleagues[3] have followed 45 healthy infants for six months by measuring RSV specific antibodies (viral neutralisation and ELISA) at birth, and 3 and 6 months of age. All infants had antibodies at birth (mean GMT 301) which decreased steadily to a mean of GMT 24 at 3 months, and GMT 10 at 6 months. The neutralising antibodies disappeared at 6 months in the majority of the infants. Two infants (4%) had increasing titres suggesting new RSV infection.

In our study, 83% of the pregnant women were anti-RSV IgG positive as well as all the babies of these mothers (≥20 RU/ml). This incidence is similar to that of Branderburg and colleagues.[3] When sensitive EIA techniques are used, all adults have RSV antibody. Thus, some mention should be made that, since only 83% of women had detectable antibody, the commercial kits used had limited sensitivity. The absence of increasing titres or new antibody positivity during the first three months suggested that there was no acquired infection during this time. The protective range for upper and lower respiratory infections of these antibodies measured by ELISA anti-RSV IgG is not known. However,

considering the rapid drop in concentration and the high frequency of negativity (94%) at 3 months of age, we may propose that these infants are sensitive to RSV infections just before 3 months of age. The fact that all of the infants who acquired RSV infections had negative IgG (<20 RU/ml) before the infection probably suggests a protective cut off concentration of 20 RU/ml. However, more studies with larger populations are needed to give a definite cut off value on this subject.

. . . .

Authors' affiliations
M Hacimustafaoglu, S Celebi, I Ildirim, Uludag University Medical Faculty, Department of Pediatrics and Pediatric Infectious Diseases, Görükle, Bursa, Turkey
E Aynaci, Uludag University Medical Faculty, Department of Pediatrics, Görükle, Bursa, Turkey
M Sinirtas, G Goral, Uludag University Medical Faculty, Department of Department of Infectious Diseases and Microbiology, Görükle, Bursa, Turkey
N Koksal, Uludag University Medical Faculty, Department of Pediatrics, Division of Neonatology, Görükle, Bursa, Turkey
A Kucukerdogan, Zubeyde Hanim Maternity Hospital, Bursa, Turkey
I Ercan, Uludag University University Medical Faculty, Department of Biostatistics, Görükle, Bursa, Turkey

Correspondence to: Dr M Hacimustafaoglu, Uludag University Medical Faculty, Department of Pediatrics and Pediatric Infectious Diseases, 16059, Görükle, Bursa, Turkey; mkemal@uludag.edu.tr

REFERENCES
1 **Glezen WP**, Paredes A, Allison JE, et al. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. J Pediatr 1981;**98**:708–15.
2 **Englund JA**. Passive protection against respiratory syncytial virus disease in infants: the role of maternal antibody. Pediatr Infect Dis J 1994;**13**:449–53.
3 **Brandenburg AH**, Groen J, van Steensel-Moll HA, et al. Respiratory syncytial virus specific serum antibodies in infants under six months of age: limited serological response upon infection. J Med Virol 1997;**52**:97–104.
4 **Tristram DA**, Weliver RC. Respiratory syncytial virus. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of clinical microbiology, 6th edn. Washington, DC: ASM Press, 1995:932–9.
5 **Murphy BR**, Alling DW, Snyder MH, et al. Effect of age and preexisting antibody on serum antibody response of infants and children to the F and G glicoproteins during respiratory syncytial virus infection. J Clin Microbiol 1986;**24**:894–8.
6 **Meurman O**, Ruuskanen O, Sarkkinen H, et al. Immunoglobulin class-specific antibody response in respiratory syncytial virus infection measured by enzyme immunoassay. J Med Virol 1984;**14**:67–72.