European Journal of Clinical Microbiology & Infectious Diseases (2020) 39:1279–1286
https://doi.org/10.1007/s10096-020-03841-8

ORIGINAL ARTICLE

Evaluation of respiratory syncytial virus IgG antibody dynamics in mother-infant pairs cohort

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Received: 25 December 2019 / Accepted: 5 February 2020 / Published online: 14 February 2020

Abstract

RSV is one of the most important agents of lower respiratory infections in childhood. In this study, anti-RSV antibody levels in mother-infant pairs and factors related to antibody transfer ratio were investigated. One hundred and twenty-seven women that had term babies and their babies and 84 mother-infant pairs of them who continued the study after 6 months were enrolled. Anti-RSV IgG antibodies of the mothers and infants were positive in 46.5% and 61.5%, respectively. At the sixth month, anti-RSV antibodies were negative in all infants. Median of the anti-RSV antibody levels of the mothers and infants at birth were 12.08 IU/ml (1.21–119.27) and 13.78 IU/ml (3.99–108.6), respectively. There was a significant correlation between anti-RSV antibody levels of mothers and infants at birth (p: 0.0001, r: 0.667) and anti-RSV antibody levels of infants at birth and at 6th month (p: 0.0001, r: 0.343). Median ratio of infant and mother antibody levels was 1.22 (0.14–6.05). Median ratio that was detected in appropriate for gestational age infants was significantly higher than in small for gestational age or large for gestational age infants. In this study, the significant positive correlation between maternal antibody levels and infants' antibody levels at birth suggests that maternal vaccination strategies may be logical. We showed that antibody transfer rate was highest in appropriate for gestational age infants. It should be kept in mind that maternal vaccination strategies may be less effective in small for gestational age and large for gestational age infants.

Keywords Respiratory syncytial virus · Maternal antibodies · Passive immunization · Transplacental antibody transfer

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Abbreviations

RSV	Respiratory syncytial virus
LRTI	Lower respiratory tract infection
SGA	Small for gestational age
AGA	Appropriate for gestational age
LGA	Large for gestational age

Introduction

Lower respiratory tract infections (LRTI) are one of the major causes of morbidity and mortality in children in the preschool age group all over the world, especially in developing countries [1]. In a meta-analysis conducted in 2013, the incidence of pneumonia in children under 5 years was 0.22 episodes per child per year [2]. One hundred and fifty million new cases of pneumonia occur all over the world per year; 7–13% of these cases require hospitalization and LRTIs caused 19% of children deaths under 5 years [3]. In the light of these data, LRTIs are

particularly have been striking as a significant public problem due to its high mortality and morbidity rates in children under 5 years of age.

In children, LRTIs can be caused by various microorganisms. The most frequent viral causes of LRTIs, especially in children under 2 years, are respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, and adenovirus [4]. RSV is the most common viral agent in childhood LRTIs [5]. There is no proven treatment option other than adequate hydration and oxygenation for RSV infections [6]. Therefore, protection from RSV infections is crucial. In recent years, efforts to develop vaccines against RSV infections have gained momentum. Vaccine development efforts focus on early childhood vaccination or protection of babies by antibodies that are transplacentally transported to babies from immunized mothers. While vaccine development studies are ongoing, it is important to understand RSV immunity to determine RSV Ig G antibody seropositivity rates in mother-infant pairs and to evaluate the transplacental antibody transfer kinetics.

For this purpose, we investigated RSV antibody levels at birth and 6th month (only infant's antibody levels) of age and evaluated the factors related to antibody transfer ratio in 84 mother-infant pairs.

Material and methods

Study population, definitions

The patients who were admitted to Istanbul Faculty of Medicine, Department of Obstetrics and Gynecology for delivery between January 2016 and April 2016 were informed in detail for the study.

Written consent was obtained from the families who were interviewed and agreed to participate in the study. Family contact information, gestation week, type of delivery, gravidity, parity, number of school-aged siblings, household members, and smokers at home were asked to parents.

Infants that were born between 37 + 0/7 and 38 + 6/7 weeks of gestation were defined as *early term*, those that were born between 39 + 0/7 and 40 + 6/7 weeks of gestation were defined as *full term*, and that those were born between 41+ 0/7 and 41 6/7 weeks of gestation were defined as *late term* [7].

Infants were divided into 3 groups according to their birth weights: *small for gestational age* (SGA), *appropriate for gestational age* (AGA), and *large for gestational age* (LGA). According to the fetal birth weight percentiles, infants were defined as SGA if their birth weight were less than 10th percentile, AGA if their birth weight were between 10 and 90 percentile, and LGA if their birth weight were above 90th percentile [8].

Sampling

Before delivery, when vascular access was opening, 2-mL blood sample was taken from the mothers. Babies' blood samples (2 ml) were taken via umbilical cord immediately after birth. Blood samples were stored at – 70 °C until

Table 1 Sociodemographic characteristics of the cases

Characteristics of mothers	*n* (%) or mean ± SD
Mean age	30.4 ± 5.4
Gravidity	
≤ 2	75 (59.1)
2–4	26 (20.5)
≥ 4	26 (20.5)
Parity	
≤ 2	113 (89)
2–4	9 (7.1)
≥ 4	5 (3.9)
Delivery type	
Vaginal	26 (20.5)
Cesarean section	101 (79.5)
Number of household members	
≤ 2	25 (19.7)
2–4	29 (22.8)
≥ 4	73 (57.5)
Smoking by household members	66 (52)
Characteristics of infants	*n* (%) or mean ± SD
Gender	
Male	62 (48.8)
Female	65 (51.2)
Weeks of Gestation	
Early term	72 (56.7)
Full term	47 (37.0)
Late term	8 (6.3)
Birth weight	
Small for gestational age	8 (6.3)
Appropriate for gestational age	93 (73.2)
Large for gestational age	26 (20.5)
Exclusive breastfeeding	46 (54.7)
Bronchiolitis history	24 (28.5)
Number of siblings	
≤ 2	107 (84.3)
2–4	13 (10.2)
≥ 4	7 (5.5)
Number of school-aged siblings	
≤ 2	118 (92.9)
2–4	7 (5.5)
≥ 4	2 (1.6)

processing after they were rapidly centrifuged at 3000–3500 rpm for 15 min.

Six months after birth, the parents whom could be reached were reinterviewed. And control blood samples were taken after informed consents were obtained. Blood samples were stored at – 70 °C until processing after they were rapidly centrifuged at 3000–3500 rpm for 15 min, and 2 mL of blood samples were taken from infants.

Detection of RSV antibody levels in serum samples

In our study, anti-RSV Ig G antibody levels in serum samples were determined by ELISA method in the Department of Virology and Basic Immunology of Istanbul University Istanbul Medical Faculty. The ELISA test was performed automatically on a Triturus (Grifols, Spain, Serial No. 053-195-1484) instrument using the Serion ELISA classic (Viron/Serion, Germany, Catalog No. 13.13 / 09-1) kit.

Serum samples were thawed at − 70 °C to + 4 °C the day before the testing began. Patient specimens and control sera were identified in the Triturus analyzer. At the end of the study, the optical densimeter values obtained for the blank, control sera, and patient samples were manually entered into the "Serion activity 11" program. The values of the quality control certificate were used for the standard curve of the program. Patient results from the Serion activity 11 program were quantified as "IU/mL." This program interprets the quantitative measurements as negative, intermediate, and positive according to the cut-off values given in the certificate.

Statistical analysis

Statistical analysis was performed with SPSS version 21.0 (IBM, Armonk, NY).The Kolmogorov-Smirnov test was used for analyzing the distributions of variables. Categorical variables were reported as numbers and percentages. Continuous variables with normal distribution were given as mean ± standard deviation (SD) while those with non-normal distribution were presented as median (minimum-maximum). Categorical data were compared by the $\chi 2$ test and Fisher's exact test. Normally distributed continuous variables were compared by Student's T test. Mann-Whitney U test or Kruskal Wallis test were used for continuous variables, which are not normally distributed according to number of groups. Relations between quantitative variables were evaluated by

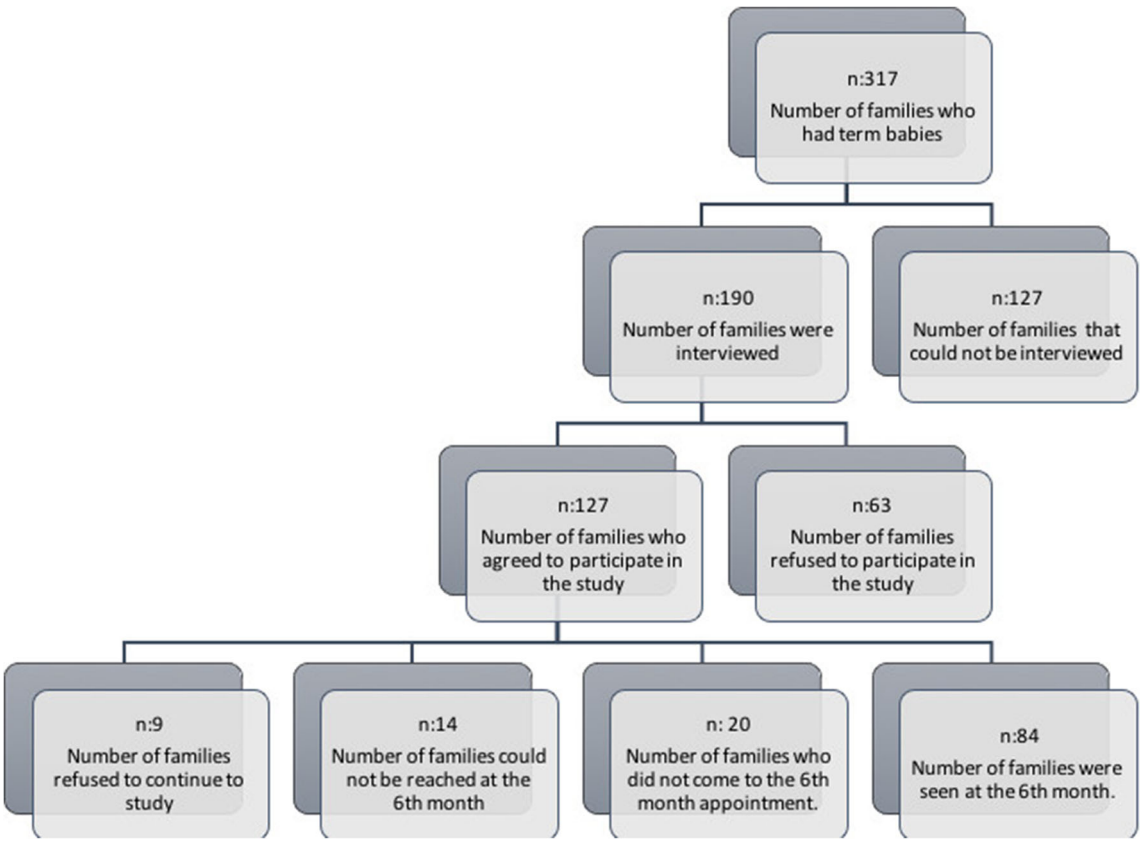

Fig. 1 Flowchart diagram. Schematic representation of patient group

Table 2 Anti-RSV antibody positivity rates and levels of mothers and infants

	n (%)
Positivity rates of anti-RSV antibody levels of mothers	
Positive	59 (%46.5)
Borderline	10 (%7.9)
Negative	58 (%45.7)
Positivity rates of anti-RSV antibody levels of infants (at birth)	
Positive	78 (%61.5)
Borderline	4 (%3.1)
Negative	45 (%35.4)
Positivity rates of anti-RSV antibody levels of infants (6th month)	
Positive	0
Borderline	0
Negative	84 (%100)
	Anti-RSV antibody level
Anti-RSV antibody levels of mothers *(median, range)*	12.08 IU/ml (1.21–119.27)
Anti-RSV antibody levels of infants	
At birth *(median, range)*	13.78 IU/ml (3.99–108.6)
6th month *(mean ± SD)*	3.42 ± 0.43 IU/ml

Spearman's correlation coefficient. In all analyses, a value of $p < 0.05$ was considered as statistically significant.

Ethics statement

Our study was found to be ethically acceptable by Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (2015/1816). Written informed consent was obtained from all of the participants' parents.

Results

Sociodemographic characteristics of the cases and schematic representation of patient group are shown in Table 1 and Figure 1. Anti-RSV IgG antibodies of the mothers were positive in 46.5%, negative in 45.7%, and borderline in 7.9%. Anti-RSV IgG antibodies of infants at birth were positive in 61.5%, negative in 35.4%, and borderline in 3.1%. At the sixth month, anti-RSV antibodies were negative in all infants. Median of the anti-RSV antibody levels of the mothers and infants at birth were 12.08 IU/ml (1.21–119.27) and 13.78 IU/ml (3.99–108.6), respectively. Mean anti-RSV antibody levels of infants at 6th month were 3.42 ± 0.43 IU/ml (Table 2). Anti-RSV IgG antibody levels of the mothers and infants (at birth and 6th month) are shown in Figure 2.

Median ratio of cord antibody level to maternal antibody level was 1.22 (0.14–6.05).In order to investigate the affecting factors to the transfer of antibodies from mother to baby, "*the ratio of cord antibody level to maternal antibody level*" was compared

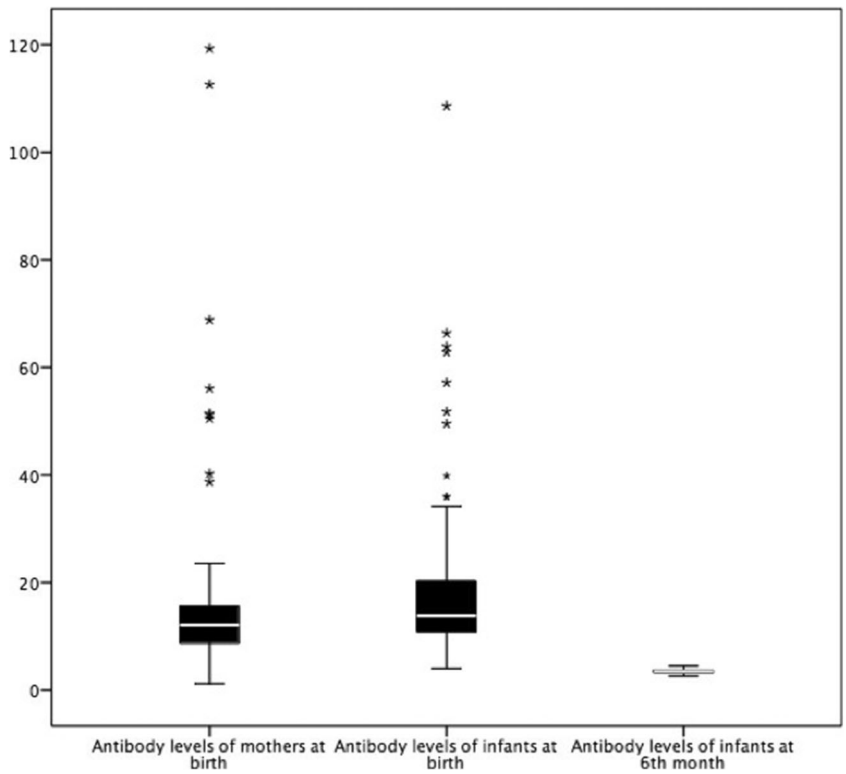

Fig. 2 Anti-RSV IgG antibody levels of the mothers at birth and infants at birth and 6th month

according to gender, type of delivery, gestation week, birth weight, and the number of gravidity and parity. Median ratio that was detected in AGA infants was statistically higher than the median ratio detected in SGA or LGA infants (Table 3).

Anti-RSV antibody levels of infants at birth and 6th month were compared according to factors may affect the antibody levels. There were no significant differences at birth and at 6th month between groups for each factor (Tables 4 and 5).

There was a statistically significant and strong correlation between anti-RSV antibody levels of mothers and infants at birth (p: 0.0001, r: 0.667) and anti-RSV antibody levels of infants at birth and at 6 months of age (p: 0.0001, r: 0.343) (Fig. 3 a and b).

Discussion

In this prospective study, we reported an effective anti-RSV antibody transfer from mother to infant. In addition, we have showed that the antibody transmission rate is optimal in AGA infants. To our best knowledge, it is the first study reporting that anti-RSV antibody transmission rate may be negatively affected in SGA and LGA infants.

In accordance with our results, Chu et al. [9] found the median ratio of cord antibody level to maternal antibody level to be 1.01 and baseline demographic features like age and gender had no effect on it. In another study, it is reported that increasing number of maternal parity and female gender were related with increased antibody transfer [10]. Furthermore, Okoko et al. [11] suggested that low birth weight and prematurity were associated with lower antibody transfer rate for various viruses including RSV.

There are a limited number of studies investigating the effect of weight for gestational age on antibody transfer rate. Yeung et al. [12] reported that IgG levels were lower in "small for dates" infants. It has been reported that transfer rate of all IgG subtypes was negatively affected in premature AGA infants and term SGA infants. In contrast, Addy et al. [13] reported that AGA and SGA infants had similar IgG levels. The conflicting results found in the studies may be related to underlying conditions of the inappropriate birth weights for gestational age. The inappropriate birth weight for gestational age

Table 3 Comparison of ratio of cord antibody level to maternal antibody level according to gender, type of delivery, gestation week, birth weight, and the number of gravidity and parity

	Ratio of cord antibody level to maternal antibody level *median (min-max)*	p
Gender		
Male	1.14 (0.36–6.05)	0.17*
Female	1.33 (0.14–2.6)	
Delivery type		
Vaginal	1.34 (0.22–2.28)	0.44*
Cesarean section	1.21 (0.14–6.05)	
Gestation week		
Early term	1.26 (0.63–6.05)	0.19†
Full term	1.14 (0.14–4.5)	
Late term	1.32 (0.96–2.35)	
Birth weight		
Small for gestational age	1.25 (0,87–2.34)	0.04†
Appropriate for gestational age	1.29 (0.14–6.05)‡	
Large for gestational age	1.10 (0.36–1.72)	
Number of gravidity		
≤ 2	1.22(0.22–6.05)	0.30†
2–4	1.31 (0.63–4.5)	
≥ 4	1.15 (0.14–2.34)	
Number of parity		
≤ 2	1.22 (0.22–6.05)	0.84†
2–4	1.22 (0.14–1.82)	
≥ 4	1.15 (0.95–2.25)	

*Mann-Whitney U

†Kruskal Wallis (Mann-Whitney U)

‡Significantly higher than other groups

Table 4 Comparison of anti- RSV antibody levels of infants at birth according to gender, gravidity, parity, type of delivery, gestation week, and birth weight

	Anti-RSV antibody levels of infants at birth (IU/ml) *median (min-max)*	*p*
Gender		
Male	13.86 (4.48–108.6)	0.96*
Female	13.7 (3.99–62.8)	
Gravidity		
≤ 2	13.7 (4.48–108.6)	0.15†
2–4	16.6 (7.2–66.3)	
≥ 4	13.1 (3.99–27.2)	
Parity		
≤ 2	13.7 (3.99–108.6)	0.82†
2–4	16.2 (8.03–21.3)	
≥ 4	11.5 (10–27.2)	
Delivery type		
Vaginal	15.1 (4.97–108.6)	0.42*
Cesarean section	13.7 (3.99–66.3)	
Gestation week		
Early term	14.2 (3.99–63.8)	0.79†
Full term	12.5 (4.48–66.3)	
Late term	14.4 (9.89–108.6)	
Birth weight		
Small for gestational age	13.6 (8.15–57.1)	0.25†
Appropriate for gestational age	14.2 (4.48–108.6)	
Large for gestational age	12.9 (3.99–24.7)	

*Mann-Whitney U

†Kruskal Wallis (Mann-Whitney U)

can be caused by many conditions associated with the fetus, placenta, or mother, such as hypertension, diabetes, and various placental pathologies. In order to be able to make more accurate statements about this subject, prospective studies are needed by evaluating the conditions causing inappropriate birth weights for gestational age.

The maternal antibody positivity rate in our study was lower than the literature. Up to 98% seropositivity has been reported in the literature [14, 15]. Hacımustafaoglu et al. [16] found that 83% of mothers had anti-RSV IgG antibody positivity in a study conducted in Turkey. The rate reported by Hacımustafaoglu et al. is also lower than the ones in the literature, suggesting that antibody positivity rates may be affected by geographical and climatic characteristics. Supporting to this idea, in a cohort study conducted in Gambia and the USA at the same time, a significant difference in anti-RSV IgG antibody levels was found in infants between the countries [17].

In our study group, 61.5% of infants had positive anti-RSV IgG antibodies at the time of birth. Forster et al. [18] reported that 99% anti-RSV IgG positivity was detected in cord blood in a group of infants with an allergic disease history. In another study, Hacımustafaoglu et al. [16] reported that anti-RSV IgG antibody positivity was detected in 83% of mothers and infants in their study. These high seropositivity rates reported in the literature are inconsistent with our results. The high seropositivity rate reported by Forster et al. [18] was thought to be related to their patient group's atopic characteristics. The low antibody positivity rate reported in our maternal group may have caused to the low antibody positivity rate in infant group at birth.

All blood samples we collected at sixth month had negative anti- RSV Ig G antibody levels. Arankalle et al. [19] found that only 0.7% of babies who were all positive for RSV antibodies at birth were positive for anti-RSV antibodies at the sixth month. In another study, the infants' anti-RSV IgG antibody positivity rate at sixth month was reported as 16% [20]. Cox et al. [21] found that maternal antibodies began to diminish at 2nd month and the lowest anti-RSV IgG antibody levels were detected at 6th–8th month. In a similar study, the lowest anti-RSV IgG antibody levels were detected at 5th–6th month [17]. Although there are conflicting reports about the positivity rates at 6th month in the literature, all studies agree that the lowest antibody levels are detected around 5th–7th month.

In accordance with our results, Bhattarakosol et al. [22] reported that they found no relationship between gender and RSV seropositivity. Chu et al. [9] reported that the only variable associated with antibody levels at birth was maternal education. In another study, it is reported that low birth weight and prematurity were associated with low antibody levels of infant [23]. Le Saux et al. [24] found that having at least one child at home was associated with high levels of RSV antibodies at birth.

In our study, there was a statistically significant correlation between cord and maternal antibody level and this correlation suggests that raising maternal antibody levels through maternal inoculation could be a logical strategy for protecting infants from RSV infections.

The most important limitation of our study was that the entire patient group consisted of term babies. As preterm infants are more susceptible to RSV infections, there is a particular need for studies in this population.

Table 5 Comparison of anti-RSV antibody levels of infants at 6th month according to demographic variables

	Anti-RSV antibody levels of infants at sixth months (IU/ml) *Mean* ± SD	*p*
Gender		
Male	3.41 ± 0.45	0,97*
Female	3.42 ± 0.40	
Delivery type		
Vaginal	3.56 ± 0.48	0.09*
Cesarean section	3.37 ± 0.40	
Gestation week		
Early term	3.41 ± 0.05	0.89†
Full term	3.41 ± 0.09	
Late term	3.50 ± 0.13	
Birth weight		
Small for gestational age	3.88 ± 0.53	0.26†
Appropriate for gestational age	3.42 ± 0.51	
Large for gestational age	3.35 ± 0.11	
Exclusive breastfeeding		
Yes	3.39 ± 0.47	0.57*
No	3.45 ± 0.37	
Bronchiolitis history		
Yes	3.44 ± 0.30	0.61*
No	3.40 ± 0.47	
Number of siblings		
≤ 2	3.43 ± 0.05	0.66†
2–4	3.41 ± 0.11	
≥ 4	3.26 ± 0.13	
Number of school-aged siblings		
≤ 2	3.49 ± 0.46	0.44†
2–4	3.28 ± 0.31	
≥ 4	3.29 ± 0.08	
Number of household members		
≤ 2	3.36 ± 0.33	0.32†
2–4	3.55 ± 0.43	
≥ 4	3.38 ± 0.45	
Smoking by household members		
Present	3.38 ± 0.44	0.40*
Not present	3.46 ± 0.41	

*Student's T test

†One-way Anova

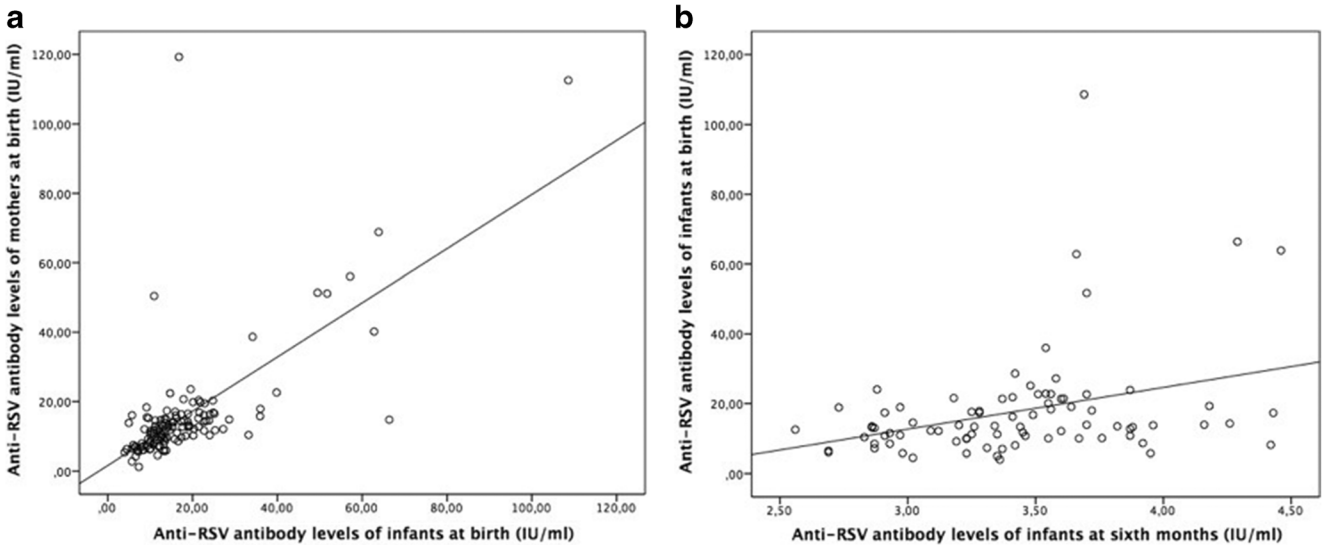

Fig. 3 **a** Correlation graph of maternal antibody levels and babies' antibody levels at birth. **b** Correlation graph of antibody levels of infants at birth and 6th month

Conclusions

The vaccine development efforts against RSV have accelerated in recent years because of its important effect on public health. A significant positive correlation between maternal antibody levels and infants' antibody levels at birth that we have reported in this study suggests that maternal vaccination strategies may be logical. We have pointed out that antibody transfer rate was highest in AGA infants. It should be kept in mind that maternal vaccination strategies may be less effective in LGA and SGA infants. Further prospective studies are needed to investigate the effect of birth weight on antibody transfer rate.

Authors' contribution Dr. Unuvar conceptualized and designed the study. Dr. Somer, Dr. Coban, and Dr. Torun drafted the initial manuscript and reviewed and revised the manuscript. Dr. Agacfidan, Dr. Mese, and Demircili carried out the analyses. Dr. Yıldız, Dr. Kara, Dr. Sivrikoz, and Dr. Sutcu designed the data collection instruments, collected data, and reviewed and revised the manuscript.

Funding information This work was supported by Scientific Research Projects Coordination Unit of Istanbul University. Project number TTU-2016-23288″.

Compliance with ethical standards

Ethical approval This study was found to be ethically acceptable by Istanbul University Istanbul Medical Faculty Clinical Research Ethics Committee (2015/1816).

Statement of informed consent Written informed consent was obtained from all of the participants' parents.

Financial disclosure All of the authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of interest All of the authors have indicated they have no potential conflicts of interest to disclose.

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