

Maternofetal transfer of antibodies and the influence of maternal atopic status on the neonate

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ABSTRACT

Background: Epidemiologic evidence has shown that sensitization of allergic diseases develops early in life, even before birth. The gestational environment, including maternal atopic status and transplacentally transferred antibodies to allergens, may be of importance in the sensitization process.

Objective: To investigate maternofetal transfer of antibodies and the influence of maternal atopic status on the neonatal immune response.

Methods: Fifty-seven healthy pregnant women who underwent elective cesarean section (ECS) were recruited. Total and specific IgE (Phadiatop) levels in cord blood (CB) and maternal blood (MB) were determined using the ImmunoCAP assay. MB- and CB-specific IgG1 and IgA1 antibodies against ovalbumin and house dust mite were analyzed by enzyme linked immunosorbent assay. The cytokines, interleukin (IL)-13, interferon (IFN)- γ , and IL-10 in the supernatant of cultured CB mononuclear cells were quantified by enzyme linked immunosorbent assay. Two subgroups were defined based on the maternal levels of specific IgE (atopic group, Phadiatop IgE more than or equal to 0.35 kilo international units of allergen-specific antibody (KUA)/L; nonatopic group, Phadiatop IgE less than 0.35 KUA/L).

Results: Although total IgE was detectable in all MB samples, it could only be detected in 7% (4/57) of the CB samples. Specific IgE was detectable in all MB samples but undetectable in all CB samples. There was no correlation of total IgE between mothers and their neonates. The concentrations of IL-10, IL-13, and allergen-specific IgG1 and IgA1 in the CB samples did not differ significantly between the atopic and nonatopic groups. IFN- γ was undetectable in the CB samples.

Conclusions: Maternal IgE cannot be transferred to the child in utero. Maternal atopic status has no significant effect on neonatal immune responses.

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Allergic rhinitis has become a global health problem with a high prevalence (10%–25%) at the present time.¹ The high incidence of allergic rhinitis in children indicates that immunologic changes leading to atopy can develop early in life, even in utero.^{2,3} The prenatal influence of the maternal immune system on the development of neonatal immune response is therefore the interest of our research.

The level of IgE and Th1/Th2 cytokines in cord blood (CB) are often used to reflect neonatal immune response at birth. However, there is less information about the relationship between other immunoglobulins (IgG and IgA) and atopic phenotypes in early life. Several previous studies have indicated that cord IgG and IgA may be considered as factors among early life that regulate infant atopic programming.^{4–9} CB IgE is an early marker of atopy, because IgE can be produced by the fetus after intrauterine sensitization.^{10,11} However, some studies have shown that IgE is derived from maternofetal

transfer.^{12,13} Contamination of CB by maternal blood (MB) that occurs during CB sampling or after small placental bleeding may account for the previously mentioned disparate conclusions. Other studies have investigated the influence of maternal atopic status on the immune response of CB cells, although the conclusions were inconsistent.^{4,5,14–16} These different conclusions may be affected by the experimental design, in particular the inclusion criteria of subjects as multiple maternal factors can affect the immune response of the neonate.^{16–22}

The purpose of the current study was to determine maternofetal transfer of antibodies and the influence of maternal atopic status on neonates. In this study, we have adhered to strict inclusion criteria to reduce the interference of confounding factors.

METHODS

Study Design

Pregnant women paired with their neonates were recruited in Wuhan City between July and September of 2011, which was during the summer. To control the quality of the study, we established very strict inclusion and exclusion criteria. Specifically, we have only selected healthy pregnant women who underwent elective cesarean section (ECS). Written informed consent was obtained from every pregnant woman before their enrollment in the study. Relevant information was obtained from their medical records and a directed questionnaire. The inclusion and exclusion criteria of the pregnant women and neonates are shown in Table 1. The study was approved by the Huazhong University of Science and Technology Medical Ethics Committee. Z.Y. and J.C. contributed equally to this work and should be considered cofirst authors.

The study population was divided into atopic and nonatopic groups according to the concentration of IgE antibodies (Phadiatop) against common food and inhalant allergens (ovalbumin [OVA] and house dust mite [HDM]) in the MB serum, in the next order: atopic group, Phadiatop IgE more than or equal to 0.35 kilo international units of allergen-specific antibody (KUA)/L; and nonatopic group, Phadiatop IgE less than 0.35 KUA/L.^{22–25}

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Table 1 Inclusion and exclusion criteria for study objects

	Inclusion Criteria	Exclusion Criteria
Mother	18–35 years old Single birth Primipara Elective cesarean section* Operated between July and September Han nationality** (including husband) Long-term residence in Wuhan city (beyond 2 years)	Placenta previa Smoking or alcohol abuse Systemic diseases Emergency surgery Suffering infectious diseases Received corticosteroids or blood-derived product transfusion Using antibiotics (pre- or intraoperative)
Neonate	37 w $\leq$ gestational age <42 w 2.5 kg $\leq$ birth weight <4 kg	Congenital diseases Apgar score <8

* = all healthy pregnant women who underwent elective cesarean section had no contractions before cord blood sampling was completed.

** = the main nationality in China.

Table 2 Characteristics of the study population

	Atopic (n = 17)	Nonatopic (n = 40)	p Value
Mother			
Age, years	29 (26.5–31)	28 (27–31)	0.67
Total IgE, KU/L	87.8 (66.85–140.0)	20.9 (12.68–59.8)	0.000
Specific IgE, KUA/L	1.45 (0.48–2.06)	—	0.000
Neonate			
Gestational age, weeks	39 (38–40)	39 (38–40)	0.68
Weight, kg	3.5 (3.2–3.65)	3.3 (3.1–3.6)	0.20
Gender, male/female	7/10	22/18	0.34
Apgar score	9 (8.5–9)	9 (9–9)	0.54

Data represent median values and interquartile range (shown in parenthesis). $p < 0.05$ is considered as statistically significant.

MB and CB Collection

MB was collected within three days before surgery. The serum was stored at -80°C until analyzed. CB sampling was performed by experienced obstetricians. The recruited pregnant women would first undergo epidural anesthesia during surgery. The puncture points on the cord were cleaned with normal saline, then 15 mL of CB were collected using a needle from the placental side of the umbilical vein after delivery of the neonate but before delivery of the placenta. A total of 10-mL aliquot of CB was then transferred into a heparin anticoagulation tube for cell culture. Another 5-mL aliquot of CB was placed into a serum tube. The serum was then separated and stored at -80°C until the antibodies were analyzed. All pregnant women were contraction free before CB sampling was completed.

Antibody Measurements

The levels of total and specific IgE antibodies in the serum from MB and CB were determined by using the ImmunoCAP assay (Pharmacia, Uppsala, Sweden). Detection limitations for total and specific IgE (Phadiatop) were 2 KU/L and 0.35 KUA/L, respectively. The determination of specific IgG1 and IgA1 antibodies against OVA (a food allergen) and HDM (an inhalant allergen) in CB and MB was performed by enzyme linked immunosorbent assay (Sigma, St. Louis, MO) as described in detail elsewhere.¹⁵

Cytokine Measurements

CB mononuclear cells were isolated and stimulated with phytohemagglutinin (Sigma, St. Louis, MO) at $10\text{ }\mu\text{g/mL}$, then incubated at 37°C in 5% CO_2 . Cell supernatants were harvested 24 hours after the stimulation and stored at -80°C until analysis. The concentrations of

interleukin (IL)-10, IL-13, and interferon (IFN)- γ in the supernatants were then measured by enzyme linked immunosorbent assay according to the manufacturer's instructions (eBioscience, San Diego, CA). The sensitivities of the assays were less than 1.6 pg/mL for IFN- γ , less than 4.5 pg/mL for IL-13, and less than 1.9 pg/mL for IL-10.

Statistics

Statistical analyses were performed with the Statistical Package for Social Sciences (version 13.0; SPSS, Inc, Chicago, IL). The correlation coefficients of antibody levels in MB versus CB were determined by Pearson tests because most data held to normal distribution. The differences in the level of CB cytokines and antibodies between the atopic and nonatopic groups were examined with the Mann-Whitney U -test. In addition, we also compared some other characteristics of the two study groups using the Mann-Whitney U -test. A χ^2 test was used to examine differences between the gender. $p < 0.05$ was considered statistically significant for all tests.

RESULTS

Characteristics of the Study Population

There were 57 pairs of women and neonates included in the study. The study population was divided into two groups according to maternal atopic status (atopic and nonatopic). Total and specific IgE concentrations in blood samples from the atopic mothers ($n = 17$) were significantly higher than the nonatopic mothers ($n = 40$). The basic characteristics of the two groups were similar, such as maternal age, neonatal weight, gestational age, Apgar score, and male-to-female ratio (Table 2).

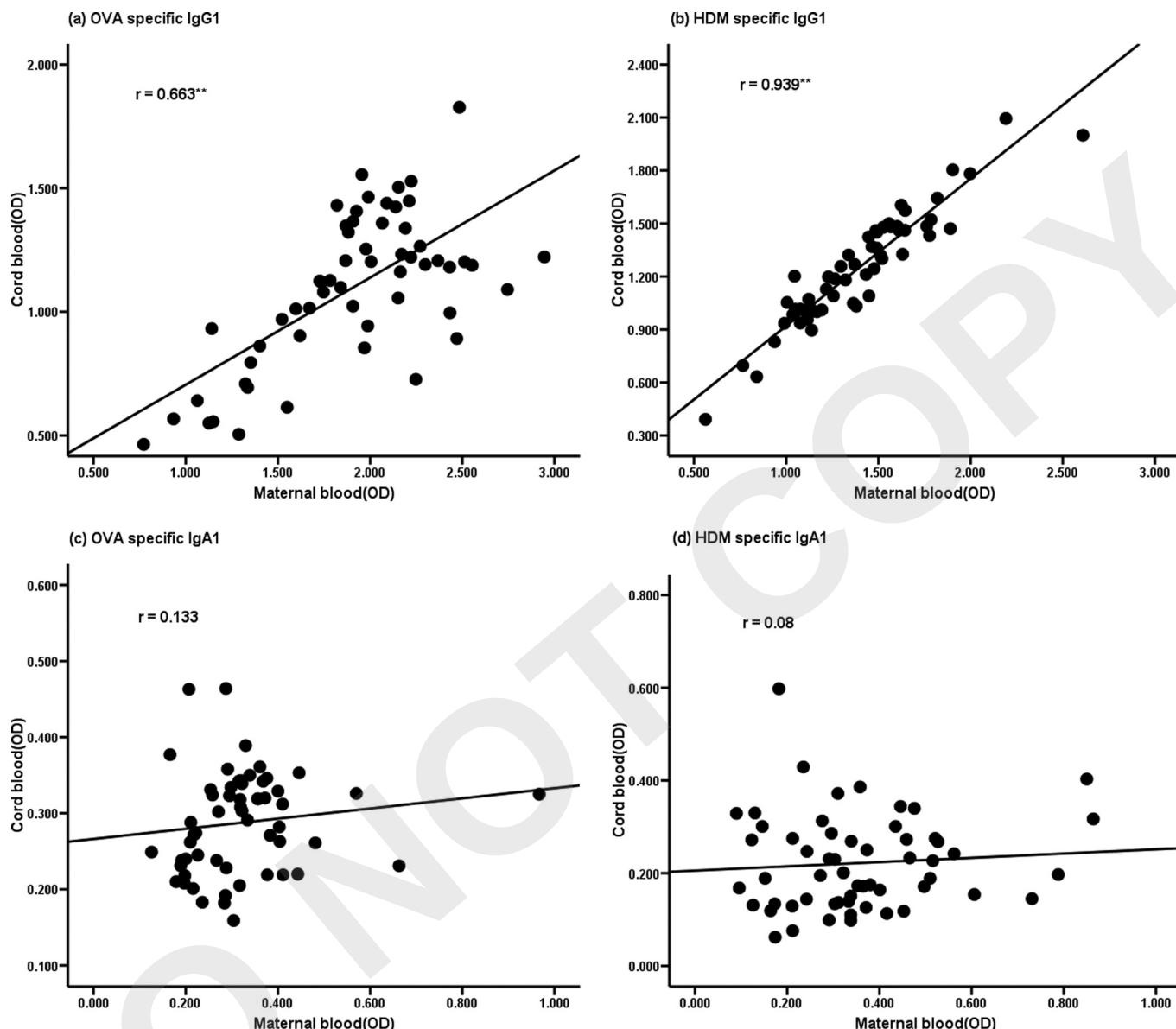


Figure 1. The concentration of specific IgG1 and IgA1 between CB and MB. The levels of IgG1 and IgA1 antibodies are shown as optical density (OD). The specific IgG1 concentrations against OVA (A) and HDM (B), as well as IgA1 concentrations against OVA (C) and HDM (D) obtained in CB of all 57 neonates, are correlated with concentrations in respective MB by Pearson test. **, correlation is significant at the 0.01 level (A and B).

Correlation of MB and CB Immunoglobulins

Specific IgE (Phadiatop) could be detected in all MB samples but was undetectable in all CB samples. Total IgE was detectable in all MB samples but could only be detected in 7% (4/57) of the CB samples (total IgE, CB/MB in these four positive samples, KU/L: 10.5/3.04, 5.78/69.5, 3.78/53.4, 2.29/206). Thus, we found that CB total IgE levels had no correlation with the corresponding MB total IgE levels ($r = -0.804$, $p = .20$). The OVA-specific IgG1 and IgA1, and HDM-specific IgG1 and IgA1 in all MB and CB samples were detectable. The concentration of specific IgG1 between the CB and MB samples were significantly correlated (OVA-specific IgG1: $r = 0.663$, $p < 0.001$; HDM-specific IgG1: $r = 0.939$, $p < 0.001$) (Fig. 1). There was no significant correlation of specific IgA1 between CB and MB (OVA-specific IgA1: $r = 0.133$, $p = .33$; HDM-specific IgA1: $r = 0.08$, $p = .56$) (Fig. 1). No significant difference was detected in the concentrations of specific IgG1 and specific IgA1 in CB between the atopic and nonatopic groups (Table 3).

CB Cytokine Comparison Between the Two Groups

IFN- γ in the supernatant of CB was undetectable. There was no significant difference in the concentrations of IL-10 and IL-13 in the CB between atopic and nonatopic mothers (Table 3).

DISCUSSION

In this study, we have discovered that maternal atopic status had no significant effect on the levels of cytokines and antibodies in CB. Our finding is similar to that reported by Casas *et al.*, who found no differences in IL-10, IL-13, IFN- γ , and *Felis domesticus* 1-IgG1 concentrations between allergic and nonallergic mothers.⁵ However, some other authors have suggested that maternal atopic status can affect the neonatal immune response. Specifically, Hrdý *et al.* found increased IL-10 and IL-13 and decreased IFN- γ concentrations in the CB of allergic mothers.¹⁴ Gold *et al.* detected decreased CB IL-10 concentrations in allergic mothers.¹⁶ Prescott *et al.* reported that CB HDM-specific IgG1 was increased in

Table 3 Comparison of CB cytokine and antibody concentrations between the atopic and nonatopic groups

	Atopic (n = 17)	Nonatopic (n = 40)	p Value
OVA-IgG1	1.08 (0.87–1.36)	1.17 (0.89–1.31)	0.67
HDM-IgG1	1.36 (1.05–1.48)	1.20 (1.01–1.45)	0.25
OVA-IgA1	0.30 (0.22–0.36)	0.29 (0.24–0.33)	0.87
HDM-IgA1	0.17 (0.13–0.26)	0.23 (0.14–0.31)	0.14
IL-10	6.66 (6.01–8.82)	7.65 (6.91–8.39)	0.14
IL-13	128.42 (107.67–140.14)	129.86 (115.76–143.49)	0.79
IFN- γ	Negative*	Negative*	

The levels of IgG1 and IgA1 antibodies are shown as optical density (OD). Levels of IL-10 and IL-13 are shown in pg/mL. Data represent median values and interquartile range (shown in brackets). $p < 0.05$ is considered as statistically significant. OVA = ovalbumin; HDM = house dust mite; CB = cord blood;

* = negative, IFN- γ in CB was undetectable.

allergic mothers.⁴ These conclusions are not completely consistent. As mentioned previously, differing inclusion criteria of the studies might be a very important factor that could lead to different results.

It has been reported that many factors of mothers and neonates can affect the neonatal immune response. For example, neonatal innate cytokine responses may be affected by somatic fetal growth, ethnicity, and season of birth.¹⁶ Hernández *et al.* found a positive influence on IgE detectable levels in Mexican newborns born in spring.²² Gestational age and infections in pregnancy are considered to be associated with infant wheezing.^{18,26} Davidson *et al.* reported significant associations between an increased risk of asthma and factors, including maternal smoking in pregnancy, subsequent births compared with first-born, male gender, and forceps deliveries.²⁰ Allergic eczema was more prevalent in children of younger mothers.¹⁸ CS is also associated with increased level of IL-13 in CB¹⁷ and decreased level of IFN- γ in CB.¹⁹ Among twins born by CS, evidence showed that first-born twins had a higher risk of developing asthma in comparison with second-born twins.²¹ Thus, in this study, we have rigorously screened healthy pregnant women and their neonates. We assumed that the maternal atopic status is responsible for the changes in CB cytokine and antibody concentrations.

Labor-related stress, such as fear, pain, and more physical strength, can significantly decrease the total number of neonatal T lymphocytes and the CD4 (helper) T-cell subpopulation in CB.²⁷ The impact of the mode of delivery on neonatal immune responses may be explained by absent or reduced labor in CS delivery. Moreover, forceps delivery is shown to be significantly associated with an increased risk of asthma.²⁰ We have selected mothers who underwent ECS. Only a few researchers have conducted similar studies limited to ECS. Our study criteria were based on two considerations. Firstly, labor had not ensued before surgery in the study. In other studies which also selected CS-experienced gravidas as research objects, CS may be performed at different stages of labor, thus labor-related stress may not be completely avoided. Secondly, the pregnant women who underwent ECS in this study were all healthy. Therefore, it was easy to control experimental conditions and avoid the effect of confounding factors. To avoid probable difficult births, ECS is adopted by some mothers in China because of the one child policy.

In this study, IFN- γ was undetectable in CB whether the mother was sensitized or not. This is not consistent with previous studies, although the sensitivity of the assay for IFN- γ in our study was even lower (less than 1.6 pg/mL, others: less than 10 pg/mL,¹⁴ less than 6.9 pg/mL,¹⁶ and less than 2 pg/mL¹⁷). There are two probable explanations for this finding. Firstly, the CB IFN- γ concentration was naturally low for a successful pregnancy and is dependent upon a Th2-type dominant immunologic response in gestation-associated compartments.²⁸ For example, Tadaki *et al.* found that the proportions of CB samples with detectable IFN- γ concentration was 1%.²⁶ Secondly, the low CB IFN- γ concentration may be due to ECS. It has been reported that the CB IFN- γ concentration was decreased in gravidas who underwent ECS.¹⁹

Relative to IgE and Th1/Th2 cytokines, there is less information about the relationship between other immunoglobulins (IgG and IgA) and atopic phenotypes in early life. Some previous studies suggest that maternal atopic status has certain influence on the levels of cord IgG.^{4,5} Furthermore, other studies investigated the relationship between cord IgG and atopic status in the children. Jenmalm and Björkstén reported that high levels of IgG antibodies in CB against inhalant allergens were associated with less development of atopy in the children,⁶ whereas Iikura *et al.* found that infants with high egg-specific IgG antibody levels in CB were statistically more prone to develop allergic disease.⁷ The role of IgA in allergy is mainly focused on the protection of the host. It is reported that atopic manifestations in infants may be more dependent on delayed maturation of IgA production than the overproduction of IgE.⁸ The possible mechanism is that IgA can prevent other immune active factors from binding to antigens competitively. However, Kukkonen *et al.* found that atopic children had higher sera OVA-IgA and OVA-IgG1 than nonatopic children.⁹ The later finding may be explained by the hygiene hypothesis, which is, the lack of IgA increased the risk of infection, and multiple infections in early life can promote the development of the immune system, thus reduce the susceptibility to allergic diseases. In summary, the previous findings showed that *trans*-placental maternal IgG and cord IgA may be considered to regulate infant atopic programming among early life factors.

We have discovered that maternal IgE cannot be transferred to the fetus in utero. Total IgE was detectable in all MB samples, but only 7% (4/57) of CB samples. No specific IgE in CB serum was detected. There was no correlation of total IgE between the mother and neonate. It has been reported that the source of CB IgE might be fetal in origin as a result of in utero sensitization.¹¹ However, this concept was challenged by Bønnelykke *et al.*, who suggested that maternofetal transfer might be a common cause of increased IgE levels in the CB.^{12,13} Contamination of CB by MB that takes place during CB sampling or is caused by slight placental bleeding might be the reason for the difference between the two conclusions. In our study, we used strict sampling procedures during CB sampling to avoid MB contamination, including cleaning of the umbilical cord, the usage of experienced obstetricians and needle puncture. We have excluded pregnant women with placenta previa, which could cause placental bleeding. As mentioned previously, we selected pregnant women who underwent ECS. Placental bleeding in ECS can be avoided without the onset of labor and contractions.¹³

In agreement with other studies,^{11,15} the correlations between allergen-specific (OVA and HDM) IgG1 in CB and MB were positive in the current study. This confirms the mechanism of IgG placental transfer. Generally, only IgG can be transferred through the placenta. At the same time, we did not find significant correlation of allergen-specific (OVA and HDM) IgA1 between mothers and neonates. Thus, IgA1 may not be transferred across the placenta. This indicates that the CB samples were not contaminated by MB in the process of collecting CB in this study.²⁹

We have realized several additional limitations for our findings. Firstly, due to practical reasons, it was not possible to perform this study with a larger number of participants. The small sample size limits the statistical power of the analysis. However, we have adhered to strict inclusion criteria to reduce the interference of confounding factors. Additionally, placenta, in general and the physiology of maternofetal cytokines transfer, is underresearched and underinvestigated; a lot of things are still fully unknown. Thus, the findings of the study should be interpreted as preliminary data.

In conclusion, this study suggested that IgE levels were extremely low in the neonates and supported the view that CB IgE may be fetal origin. In addition, we did not find that maternal atopic status have significant effect on the neonatal immune responses. An ongoing tracing observation of the 57 newborns in our study will investigate the relationship between these atopic markers and allergic diseases in the children.

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