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# Mucosal Immunity Of The Nasal Cavity In Premature Infants Of Different Gestational Age In The First Year Of Life.

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**ABSTRACT**

The indices of local immunity of the nasal mucosa in 47 premature infants of the first life year born at the gestational age of 28-37 weeks were studied. **Antibody (**IgA, IgG, IgE) and cytokine (TNF-α, IL-1β, IF-γ) levels in mucosal washes were determined by enzyme immunoassay. Premature infants revealed transient IgG deficiency at the age of 6 months (2.08 (0.78-6.99) mg/ml), low IgE values at the age of 12 months (0.89 (0.47-1.32) ng/ml), low IF-γ values at the age of 6 months (7.51 (4.84-13.82) PG/ml) and 12 months (8.28 (4.70-12.07) PG/ml), and hyper production of proinflammatory cytokine IL-1β during the first year of life. Extremely premature infants feature the worst antibody and intreferon protection deficiency. Indices of mucosal immunity of the nasal cavity can be used in the development of pathogenetic approaches to the prevention and treatment of infectious and inflammatory diseases of the respiratory system in premature infants.
**Keywords:** mucosal immunity, nasal cavity, premature infants

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## INTRODUCTION

Infectious and inflammatory diseases are leading in the pathology of premature infants and have remained the main cause of high incidence and death rates in the infants so far [6, 10, 13]. Premature infants demonstrate higher rates related to insufficient congenital passive immunity, dominance of Th2 immune response, increased synthesis of anti-inflammatory cytokines than mature infants [5, 7, 9, 11]. Distinctions in premature infants' immune system functioning bring about specific immune response to antigenic stimulation, abnormal physiological adaptation processes and long-lasting health problems [2, 3, 15].

The first protective barrier in respiratory tract infection is known to be the mucous membrane of the respiratory tract. Disorders of the local mucosal system lead to lower resistance to infectious and inflammatory diseases [8, 12]. There are few data on mucosal immunity of the upper respiratory tract in premature infants which lack systematic approach. There are no data on the features of the immune status of mucous membranes in premature infants of different gestational age. In this regard, the study of mucosal immunity of the upper respiratory tract in premature infants is of considerable scientific and practical interest.

**The aim of the study** was to determine the features of the mucosal immunity of the nasal cavity in premature infants of different gestational age in the first year of life.

## MATERIALS AND METHODS

The indices of local immunity of the nasal mucosa in 47 infants of the first life year born prematurely at the gestational age of 28-37 weeks (the treatment group) were studied. The studied group consisted of 23 (48.9%) boys and 24 (51.1%) girls. The average body weight at birth was 2174.7±46.2 g, the average length was 45.3±0.4 cm. During the study the infants were divided into two subgroups based on the gestational age: the first subgroup comprised15 infants (31.9%) born at the gestational age of 28-32 weeks, and 32 infants (68.1%) born at the gestational age of 33-37 weeks made up the second subgroup.

The control group included 46 mature infants of the first year of life born at the gestational age of 37-41 weeks. It consisted of 18 (39.1%) boys and 28 (60.9%) girls. Their average body weight at birth was 3511.5 ± 53.7 g, the average length was 52.8 ± 0.3 cm.

The infants were divided into control and treatment groups after obtaining the informed consent from parents to participation in a research study. At the time of examination the infants suffered from no acute or chronic somatic and (or) neurological pathology in decompensation.

Antibody and cytokine levels were determined through nasal mucosa wash procedures at the age of one month, six months and twelve months. The nasal wash specimen were collected on a cotton swab moistened with saline (isotonic 0.9% NaCl solution) within 30 seconds, then the swab was put into 0.5 ml of saline, and then frozen at a temperature of minus 86C$^{o}$, then it was centrifuged at 1500 rev/min for 10 minutes and the supernatant fluid was examined [1]. Antibody **(**secretory IgA, total IgG and total IgE) and cytokine (TNF-α, IL-1β, IF-γ) levels were determined based on enzyme immunoassay (EIA or ELISA) using the test kits produced by ZAO (CJSC)"Vector-Best" (Novosibirsk, Russia).

'STATISTICA 7.0' statistical programme operating in Windows XP environment was used to perform a statistical analysis of the obtained data. Patterns of quantitative distribution were assessed based on the Kolmogorov-Smirnov test. Median (Me) and interquartile range-values of the 25th and 75th quartiles (Q25-Q75) were determined as a measure of the Central tendency. Nonparametric Mann-Whitney (U) test was used to assess the significance of differences in the obtained indices. The Mann-Whitney test was used to assess quantitative value differences between the two groups and the Kruskal-Wallis test was used to assess differences in variables among the three groups. The results were considered as statistically relevant at $p < 0.05$. Spearman's rank correlation coefficient (r) was used to determine the correlation dependence.

## RESULTS

The study revealed features of antibody protection in the nasal mucosa in premature infants. IgG antibodies prevailed in nasal mucosa in both premature and mature infants in their first year of life (table 1).

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IgG levels fell down twice in premature infants by the age of 6 months (p>0.05) and rose up to the standard levels by the age of 12 months. Despite the improved IgE indices (p=0.029) by the end of the first half of life IgE indices by the end of the year proved lower in premature infants than in full-term infants. Infants born at the gestational age of 28-32 weeks demonstrated lower IgE values of 0.65 (0.47-0.99) ng/ml at the age of 12 months compared to 1.91 (1.68-2.52) ng/ml (p=0.002).

**Table 1: Indices of sIgA, AgG, IgE on the nasal mucosa in premature infants**

| Immunoglobulins | Age, months | Premature infants n=47 | Mature Infants n=46 | P |
|---|---|---|---|---|
| sIgA, mg / ml | 1 | 1.40 (0.39-2.92) | 0.84 (0.54-2.44) | >0.05 |
| | 6 | 1.13 (0.47-2.46) | 1.79 (0.36-3.09) | >0.05 |
| | 12 | 1.90 (0.87-2.38) | 2.36 (1.09-2.94) | >0.05 |
| IgG, mg / ml | 1 | 4.11 (1.27-8.23) | 2.37 (1.04-7.95) | >0.05 |
| | 6 | 2.08 (0.78-6.99) | 4.21 (2.38-9.35) | >0.05 |
| | 12 | 6.13 (2.29-11.27) | 5.54 (1.34-12.33) | >0.05 |
| IgE, ng / ml | 1 | 0.54 (0.40-0.74) | 0.53 (0.32-1.26) | >0.05 |
| | 6 | 0.97 (0.46-1.91) | 0.87 (0.42-1.80) | >0.05 |
| | 12 | 0.89 (0.47-1.32) | 1.91 (1.68-2.52) | **0.003** |

The study revealed features of cytokine regulation on the nasal mucosa in premature infants. IL-1β и IF-γ cytokines prevailed on nasal mucosa both in premature and mature infants (table 2). By 12 months of life IL-1β level (p>0.05) rose three-fold which was two times higher in premature infants than in mature infants (p>0.05) of the specified age. TNF-α level proved lower in premature infants than in mature infants at the age of 6 months, but by the end of the first year of life TNF-α values reached the age standards. IF-γ values proved lower in premature infants than in full-term infants in the second half of their year of life. The group of infants born at the gestational age of 28-32 weeks demonstrated lower IF-γ values of 6.32 (5.26-8.00) pg/ml at the age of 12 months compared to 14.49 (11.75-19.87) pg/ml, (p<0.001).

**Table 2: Indices of TNFa, IL-1β, IF-γ on nasal mucosa in premature infants**

| Cytokines | Age, months | Premature infants n=47 | Mature infants infants n=46 | P |
|---|---|---|---|---|
| TNF-α, pg / ml | 1 | 1.86 (1.34-3.02) | 2.61 (1.69-4.06) | >0.05 |
| | 6 | 1.86 (1.64-2.72) | 3.99 (2.87-6.30) | **<0.001** |
| | 12 | 2.63 (1.94-3.88) | 2.27 (1.01-2.97) | >0.05 |
| IL - 1β, pg / ml | 1 | 7.36 (1.59-43.86) | 13.14 (6.51-75.5) | >0.05 |
| | 6 | 9,94 (3,99-28,91) | 11.61 (6.75-22.93) | >0.05 |
| | 12 | 20.21(10.41-54.8) | 10.14 (3.31-28.51) | >0.05 |
| IF-γ, pg/ ml | 1 | 8.25 (4.28-9.96) | 10.46 (5.54-18.26) | >0.05 |
| | 6 | 7.51 (4.84-13.82) | 17.45 (8.19-27.5) | **<0.001** |
| | 12 | 8.28 (4.70-12.07) | 14.49 (11.75-19.87) | **0.012** |

Correlation analysis showed that there was a moderate statistically significant relationship between the antibody protection of the nasal mucosa and maternal factors (pregnancy interruption risks, smoking), neonatal indicators (gestational age, birth weight, intrauterine growth retardation), weight-growth parameters in the first half of life, respiratory infectious diseases severity and incidence rates (table 3).

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**Table 3: Correlations between clinical and anamnestic data and the nasal mucosa immunoglobulin indices**

| Clinical and anamnestic parameters | IgA | | IgG | | IgE | |
|---|---|---|---|---|---|---|
| | R | P | R | p | R | p |
| pregnancy interruption risks | -0.324 | 0.026 | -0.329 | 0.023 | - | - |
| smoking while pregnant | -0.434 | 0.024 | - | - | - | - |
| gestational age | - | - | - | - | 0.400 | 0.008 |
| body weight at birth | - | - | - | - | 0.424 | 0.005 |
| intrauterine growth retardation | - | - | - | - | -0.370 | 0.015 |
| body weight, 1 month | - | - | 0.318 | 0.029 | 0.324 | 0.036 |
| body weight, 6 months | - | - | - | - | 0.324 | 0.038 |
| Baby length, 1 month | - | - | 0.338 | 0.020 | 0.454 | 0.002 |
| Baby length, 6 months | - | - | - | - | 0.332 | 0.031 |
| respiratory infection severity | -0.310 | 0.033 | - | - | - | - |
| respiratory infection incidence rate | -0.328 | 0.033 | - | - | - | - |

The correlation analysis revealed a moderate statistically significant relationship between the level of cytokines on the nasal mucosa and the neonatal period (gestational age, birth weight, intrauterine growth retardation), weight-growth parameters in the first year of life, respiratory infectious diseases severity and incidence rates, hospital admissions (table 4).

**Table 4: Correlations between clinical and anamnestic data and the nasal mucosa cytokine indices**

| Clinical and anamnestic parameters | TNF-α | | IL-1β | | IF-γ | |
|---|---|---|---|---|---|---|
| | R | P | R | p | r | p |
| gestational age | 0.554 | 0.001 | - | - | 0.450 | 0.003 |
| body weight at birth | 0.496 | 0.001 | - | - | 0.478 | 0.001 |
| intrauterine growth retardation | - | - | -0.446 | 0.001 | -0.446 | 0.002 |
| body weight, 1 month | 0.341 | 0.020 | -0.363 | 0.021 | 0.472 | 0.001 |
| body weight, 6 months | 0.478 | 0.001 | - | - | 0.326 | 0.037 |
| body weight, 12 months | 0.435 | 0.008 | -0.350 | 0.027 | 0.439 | 0.006 |
| Baby length, 1 month | 0.395 | 0.006 | -0.315 | 0.047 | 0.473 | 0.001 |
| Baby length, 6 months | 0.362 | 0.017 | -0.313 | 0.048 | 0.314 | 0.045 |
| Baby length, 12 months | 0.447 | 0.006 | - | - | 0.345 | 0.036 |
| artificial feeding | - | - | - | - | -0.314 | 0.045 |
| respiratory infection severity | - | - | 0.544 | 0.001 | - | - |
| respiratory infection incidence rate | - | - | - | - | -0.319 | 0.041 |
| hospital admissions | -0.365 | 0.012 | 0.660 | 0.014 | | |

## DISCUSSION

The issue of local immunity of mucous membranes in children is still rather relevant, but insufficiently studied. The study could establish the features of mucosal immunity of the nasal cavity in premature infants of various gestational age in the first year of life. Adaptive immunity on the nasal mucosa features transient IgG deficiency at the age of 6 months and low IgE values in the second half of the first year. Premature infants born at the gestational age of 28-32 weeks have worse antibody protection. Low IgG values may be due to a rapid loss of maternal antibodies against their initially low potential in premature infants [14].

The study showed that premature infants at the age of 6 months lacked antiviral protection, as evidenced by low IF-γ и TNF-α cytokine values, compared to full-term infants. At the same time hyperproduction of proinflammatory cytokine IL-1β on nasal mucosa does not lead to an adequate humoral response as specified by low IgE indices. Premature infants born at the gestational age of 28-32 weeks demonstrate interferon deficiency and low IgE production during the second half of the first year.

Thus, premature infants feature mucosal immune imbalance of nasal cavity in their first year of life which makes the children highly susceptible to respiratory infections and causes severe and long lasting cases. The immune profile of nasal mucosa depends on the infant's gestational age at birth [4].

The patterns of mucosal immunity of upper respiratory tract revealed in premature infants of different gestational age in the first year of life may be used to develop pathogenic approaches to the prevention and treatment of infectious and inflammatory diseases of the respiratory system.

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