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THE EFFECT OF INTRAUTERINE TRANSFUSION TO THE FETUS ON THE INDICATORS OF THE NEWBORN'S INNATE HUMORAL IMMUNITY

***U. Jabborov*[1], *K. Salimova, F. Jabborova*[2]**

Republican perinatal center of the ministry of health of the republic of Uzbekistan[1]
(Tashkent, Uzbekistan),
Bukhara State Medical Institute named after Abu Ali ibn Sino[2]
(Bukhara, Uzbekistan)

Summary

Fetal hemolytic disease is caused by the transplacental passage of maternal antibodies that target and destroy fetal red blood cells. These antibodies are produced following maternal exposure to fetal erythrocytes, typically occurring around 16-18 weeks of gestation, upon recognition of fetal red blood cell antigens. At the turn of the millennium, hemolytic disease of the fetus and newborn (HDFN) was still largely equated with Rh incompatibility. However, the introduction of active postpartum immunoprophylaxis in the 1970s led to a decrease in maternal Rh sensitization rates from 14% to 1-2%. The subsequent implementation of antenatal immunoprophylaxis in Rh-negative pregnant women has further reduced this incidence to approximately 0.1%.

The aim of the study: *to investigate parameters of innate humoral immunity – specifically immunoglobulins G, M, and A – in the umbilical cord blood of newborns with hemolytic disease who underwent advanced fetal surgical intervention during gestation.*

Study materials. *A total of 60 newborns were enrolled and categorized into three groups. The first (main) group included 20 newborns diagnosed with hemolytic disease who underwent intrauterine intravascular fetal blood transfusion during the antenatal period. The second (comparison) group consisted of 20 newborns with hemolytic disease who did not receive any fetal surgical intervention prenatally. The third (control) group comprised 20 healthy newborns.*

Immunologic methods of research: evaluation of the immune status of newborns was performed on umbilical cord blood collected on the first day of life, in the Laboratory of Fundamental Immunology at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. Statistical analysis of the data was performed using both parametric and non-parametric methods. Data collection, correction, systematization, and visualization were conducted using Microsoft Office Excel 2018 spreadsheets. The statistical computations were carried out using IBM SPSS Statistics v.26 (IBM Corporation).

All investigations were conducted at the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.

Conclusions. *Intrauterine transfusion has demonstrated a beneficial effect on fetal hematological parameters and on the humoral immune status of the neonate after birth. Notably, it has been associated with a reduction in immunoglobulin G, A, and M levels. These findings suggest a diminished inflammatory potential and indicate a preventative effect against the development of immunodeficiency at birth.*

Keywords: *Immunoglobulins G, M, A Rhesus Immunization; Hemolytic Disease of the Newborn (HDN); Intrauterine Intravascular Blood Transfusion (IVPC).*

Introduction

In our country, the issue of Rh alloimmunization remains relevant and necessitates proactive measures for its resolution. The implementation of prenatal immunoprophylaxis has led to a slight increase in the incidence of hemolytic disease of the fetus and newborn (HDFN) due to non-Rh erythrocyte antigens [1]. The pathogenesis of HDFN involves extravascular hemolysis of fetal and neonatal erythrocytes caused by damage to their membranes by maternal antibodies. During the breakdown of these erythrocytes, hemoglobin is converted into bilirubin (1 g of hemoglobin yields approximately 35 mg of bilirubin) [2]. Rh alloimmunization most commonly becomes active during the third trimester or at delivery. However, HDFN develops in the first trimester in approximately 3% of cases, in the second trimester in 12%, and in the third trimester in 45%, with 90% of cases occurring after 28 weeks of gestation [3]. In subsequent pregnancies, HDFN tends to be more severe than in the first due to a more rapid and pronounced alloimmune response [4, 5]. The inheritance of maternal immune system features by the fetus during gestation is referred to as epigenetic maternal immune imprinting [6, 7]. Persistent maternal immune dysregulation is frequently transmitted to the fetus via this imprinting mechanism [8]. In the fetus, as in adults, natural killer (NK) cells are a principal component of immunobiological defense, assessed by the expression of CD16 and CD56 surface markers [9, 10, 11]. It is important to recognize that any disruption of the bidirectional immunological adaptation between mother and fetus poses a threat to placental development, fetal growth, and viability at any stage of pregnancy. This is particularly relevant in cases of HDFN arising in the second or third trimesters [11, 12, 13]. In light of the above, we sought to examine in greater detail the key parameters of innate cellular immunity in newborns diagnosed with hemolytic disease.

The aim of the study. To investigate parameters of innate humoral immunity – specifically immunoglobulins G, M, and A – in the umbilical cord blood of newborns with hemolytic disease who underwent advanced fetal surgical intervention during gestation.

Research materials and methods

Immunologic methods of research: evaluation of the immune status of newborns was performed on umbilical cord blood collected on the first day of life, in the Laboratory of Fundamental Immunology at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. The

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concentrations of principal immunoglobulins and cytokines in biological fluids were determined by enzyme-linked immunosorbent assay (ELISA), utilizing commercial Human ELISA kits (Germany). These test systems employ the solid-phase sandwich ELISA method, using horseradish peroxidase as the indicator enzyme. The reagent kits comprise monoclonal antibodies (MCATs) specific to the target cytokines, immobilized on the surfaces of wells in detachable polystyrene microplates. These kits are designed for the quantitative determination of human cytokines in peripheral blood serum and other biological fluids. Optical density in each well was measured at a wavelength of 450 nm using an automated microplate photometer (Stat-Fax analyzer, USA).

Statistical analysis of the data was performed using both parametric and non-parametric methods. Data collection, correction, systematization, and visualization were conducted using Microsoft Office Excel 2018 spreadsheets. The statistical computations were carried out using IBM SPSS Statistics v.26 (IBM Corporation). For normally distributed quantitative data sets, comparisons of means were made using Student's t-test. The resulting *t*-values were interpreted by comparison with critical values. Differences were considered statistically significant at a *p*-value of less than 0.05.

Results and Discussion

The primary objective was to conduct an immunological evaluation and assess the effectiveness of intrauterine intravascular fetal hemotransfusion by analyzing humoral immunity in newborns who underwent fetal surgery. For this purpose, immunological studies were conducted on umbilical cord blood samples from newborns with hemolytic disease of the newborn (HDN), both those who received intrauterine hemotransfusion and those who did not. The results of these analyses are summarized in Table 1.

Table 1

THE MAIN HUMORAL PARAMETERS OF NEWBORN IMMUNITY (UMBILICAL CORD BLOOD), (M±m, g/l)

Parameters	The main group (n-20)	Comparison Group (n-20)	The control group (n-20)
Immunoglobulin G	7,33 ± 0,75 ^	8,51 ± 1,21 *	6,36 ± 0,35
Immunoglobulin A	1,53 ± 0,32 ^	2,95 ± 0,24 *	1,28 ± 0,44
Immunoglobulin M	1,64 ± 0,50 * ^	2,26 ± 0,45 *	1,05 ± 0,45

*Note: * – the significance of differences with the control group is p<0.05; – the reliability of differences between the studied groups*

IgG class antibodies are known to possess the capacity for transplacental transport, enabling continuous immunological interaction between the maternal and fetal systems. In the postnatal period, IgG is rightly considered the predominant immunoglobulin, prevailing in the serum of both fetuses and newborns. In contrast, the concentrations of IgM, IgE, and IgA remain relatively low, although maternal IgE can enter the fetal circulation as part of an IgG/IgE complex. During gestation, IgG levels gradually increase throughout the first and second trimesters, reaching a peak in the third trimester. Typically, full-term newborns exhibit IgG concentrations of approximately 1000 g/dl – equivalent to 125% of the maternal serum level – reflecting active antibody transfer mediated indirectly by Fc receptors (FcRn) of the placenta [12].

Thus, the analysis showed that the levels of immunoglobulin G in the umbilical cord blood of newborns in the comparison group were significantly elevated – by a factor of 1.4-compared to the control group, whereas IgG levels in the umbilical cord blood of newborns in the main group were not significantly elevated relative to the control group. A comparison between the two study groups revealed that, following hemotransfusion, the IgG level in the main group decreased slightly but significantly compared to the comparison group, with a difference of 1.2 times.

The level of immunoglobulin A in the umbilical cord blood of newborns who did not undergo intrauterine hemotransfusion was significantly increased – by 2.3 times – compared to the control group. In contrast, immunoglobulin A levels in the umbilical cord blood of newborns following intrauterine hemotransfusion were not significantly elevated relative to the control group. A comparison between the two study groups showed that the IgA level in the main group was 1.9 times lower than that in the comparison group.

IgM is the first class of immunoglobulins synthesized by the fetus, beginning at 18-20 weeks of gestation. During initial antigen exposure, IgM is produced first, and although it also appears upon repeated exposure, the levels are lower IgM does not cross the placental barrier. According to some authors, changes in IgM concentration in HDN have limited diagnostic significance; however, the complex «proliferation of mononuclear cells stimulated by ConA, anti-CD3 monoclonal antibodies and IgM» demonstrates high specificity, sensitivity and informativeness, i.e., indicates fetal immune pathology with a high probability (26:1) [13].

The levels of immunoglobulin M in the umbilical cord blood of newborns in the comparison group, i.e., where pregnancies were carried out conventionally, were significantly increased by 2.2 times compared to the control group. Meanwhile, IdM levels in the umbilical cord blood of newborns taken after fetal surgery, that is, in the main group was significantly increased by 1.6 times compared to the control group control. As can be seen, following intrauterine hemotransfusion, immunoglobulin M levels slightly decrease in the main group, with a significant difference of 1.4 times relative to the comparison group.

Based on the obtained results, it can be concluded that intrauterine and intravascular hemotransfusion to the fetus during the antenatal period leads to an improvement in humoral immunity parameters in the newborn, as evidenced by our research findings. It should be emphasized that following intrauterine hemotransfusion, there is a normalization of the concentrations of the studied

immunoglobulins in the newborn after birth. Specifically, a decrease in the levels of immunoglobulins G, A, and M was observed. These findings indicate a reduction in the inflammatory potential following hemotransfusion.

Conclusions

1. In newborns in the main group who underwent fetal interventions during the antenatal period, the IgG index in umbilical cord blood was not significantly elevated compared to the group of healthy newborns.

2. In umbilical cord blood samples obtained from newborns who did not undergo intrauterine hemotransfusion during the antenatal period, IgA levels were significantly increased by 2.3 times compared to the control group, whereas IgA levels in the main group were not elevated.

3. IgM levels in the umbilical cord blood of newborns in the comparison group – i.e., those whose pregnancies proceeded without fetal intervention – were significantly increased by 2.2 times relative to the control group.

4. Intrauterine transfusion has been shown to have a beneficial effect on the hematological parameters of fetal blood and on the humoral immunity of the newborn after birth. In particular, it contributes to a reduction in IgG, IgA, and IgM levels. These changes indicate a decrease in inflammatory potential and help prevent the development of immunodeficiency at birth.

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ВПЛИВ ВНУТРІШНЬОУТРОБНОЇ ТРАНСФУЗІЇ ПЛОДУ НА ПОКАЗНИКИ ВНУТРІШНЬОГО ГУМОРАЛЬНОГО ІМУНІТЕТУ НОВОНАРОДЖЕНОГО

***У. У. Джабборов*[1], *К. А. Салімова*[1], *Ф. У. Джабборова*[2]**

Республіканський перинатальний центр Міністерства охорони здоров'я республіки Узбекистан[1]
(м. Ташкент, Узбекистан),
Бухарський державний медичний інститут ім. Абу Алі ібн Сіно[2]
(м. Бухара, Узбекистан)

Резюме.

Гемолітична хвороба плода пов'язана з проникненням через плацентарний бар'єр антитіл вагітної жінки, які руйнують еритроцити плода, що утворилися після її контакту з еритроцитами плода на 16-18 тижні гестації і виявлення їх антигенів. На рубежі тисячоліть затримка внутрішньоутробного розвитку (ЗВУР) все ще вважалася майже синонімом резус-конфлікту, але активна післяпологова імунопрофілактика, що проводиться з 1970 року, знизила материнську резус-імунізацію з 14% до 1-2%, а пренатальна імунопрофілактика вагітних з резус-конфліктом крові ще більше нівелювала проблему до 0,1%.

Мета дослідження: вивчити показники вродженого гуморального імунітету – імуноглобуліни G, M та A в пуповинній крові новонароджених з гемолітичною хворобою, які перенесли високотехнологічні операції на плоді під час вагітності.

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Матеріали дослідження. Всього в дослідженнях взяли участь 60 новонароджених, які були розділені на 3 групи. 1-у основну групу склали 20 новонароджених з гемолітичною хворобою, яким в антенатальному періоді була проведена операція «внутрішньоутробна внутрішньосудинна гемотрансфузія плоду», 2-у групу порівняння склали 20 новонароджених з гемолітичною хворобою, яким в антенатальному періоді не проводилися операції на плоді, 3-ю контрольну групу склали 20 здорових новонароджених. Імунологічні методи дослідження: оцінка імунного статусу новонароджених проводилася на основі аналізу пуповинної крові, зібраної в перший день життя, у Лабораторії фундаментальної імунології Інституту імунології та геноміки людини Академії наук Республіки Узбекистан. Статистичний аналіз даних проводився з використанням як параметричних, так і непараметричних методів. Збір, корекція, систематизація та візуалізація даних проводилися за допомогою електронних таблиць Microsoft Office Excel 2018. Статистичні обчислення проводилися за допомогою IBM SPSS Statistics v.26 (IBM Corporation). Всі дослідження були виконані в Інституті імунології Академії наук Республіки Узбекистан.

Висновки. Внутрішньоутробна трансфузія не тільки покращує гематологічні показники крові плода, але і покращує гуморальний імунітет новонародженого після народження, зокрема, сприяє зниженню рівня IgG, A і M. Все це свідчить про зниження запального потенціалу та запобігає формуванню імунодефіцитного стану при народженні.

Ключові слова: імуноглобуліни G, M, A; резус-імунізація; гемолітична хвороба новонароджених; внутрішньоутробне внутрішньосудинне переливання крові.

Contact information:
Ulugbek Jabborov – MD, Associate professor, Obstetrician-Gynecologist of the Republican Perinatal Center (Tashkent, Republic of Uzbekistan)
e-mail: uljab@mail.ru
ORCID: https://orcid.org/0009-0005-8706-3964

Kamola Salimova – Independent researcher of Bukhara State Medical Institute named after Abu Ali ibn Sino (Bukhara, Republic of Uzbekistan)
e-mail: karifdjanovna@mail.ru
ORCID: https://orcid.org/0009-0008-7046-7614

Feruza Jabborova – Associate professor of the Department of therapeutic Dentistry of Bukhara State Medical Institute named after Abu Ali ibn Sino (Bukhara, Republic of Uzbekistan)
e-mail: jabborova82@mail.ru
ORCID: https://orcid.org/0009-0002-8802-1158

Контактна інформація:
У. У. Джабборов – доктор медичних наук, доцент, акушер-гінеколог Республіканського перинатального центру (Ташкент, Республіка Узбекистан)
e-mail: uljab@mail.ru
ORCID: https://orcid.org/0009-0005-8706-3964

К. А. Салімова – незалежний науковий співробітник Бухарського державного медичного інституту імені Абу Алі ібн Сіно (Бухара, Республіка Узбекистан)
e-mail: karifdjanovna@mail.ru
ORCID: https://orcid.org/0009-0008-7046-7614

Ф. У. Джабборова – доцент кафедри терапевтичної стоматології Бухарського державного медичного інституту імені Абу Алі ібн Сіно (Бухара, Республіка Узбекистан)
e-mail: jabborova82@mail.ru
ORCID: https://orcid.org/0009-0002-8802-1158

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