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ASPECTOS CLÍNICOS E IMUNOLÓGICOS DA ADAPTAÇÃO DO RECÉM-NASCIDO DE MÃE COM INFECÇÃO INTRAUTERINA

CLINICAL AND IMMUNOLOGICAL ASPECTS OF NEWBORN ADAPTATION BORN FROM MOTHERS WITH INTRAUTERINE INFECTION

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ АСПЕКТЫ АДАПТАЦИИ НОВОРОЖДЕННОГО ОТ МАТЕРЕЙ С ВНУТРИУТРОБНОЙ ИНФЕКЦИЕЙ

ZHUMALINA, Akmaral K.[1*]; TUSUPKALIEV, Balash T.[2]; ZAME, Yuliya A.[3]; VOLOSHINA, Lyudmila V.[4]; DARZHANOVA, Klara B.[5]

[1,2,4] West Kazakhstan Marat Ospanov Medical University, Department of Children`s Deseases, Aktobe – Republic of Kazakhstan

[3] West Kazakhstan Marat Ospanov Medical University, Center for Continuing Professional Development, Aktobe – Republic of Kazakhstan

[5] West Kazakhstan Marat Ospanov Medical University, Department of Normal and Topographic Anatomy with Operative Surgery, Aktobe – Republic of Kazakhstan

** Correspondence author*
e-mail: Zumalina@mail.ru

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RESUMO

Hoje, cerca de 40% das crianças estão infectadas com infecções congênitas. As condições imunológicas das crianças no período neonatal estão amplamente associadas à natureza da gravidez em suas mães. O objetivo deste trabalho foi estudar as características clínicas e imunológicas em recém-nascidos de mães com infecção congênita. 48 bebês foram observados. Os recém-nascidos foram divididos em dois grupos: grupo 1 – 33 recém-nascidos de mães infectadas com infecção por citomegalovírus, grupo 2 – 15 recém-nascidos de mães saudáveis. O diagnóstico de infecção congênita é verificado com base em um questionário para mulheres grávidas, dados ambulatoriais de mulheres grávidas e recém-nascidos, testes sorológicos, reação em cadeia da polimerase (PCR), imunoensaio enzimático (IEE), bem como imunidade celular e imunidade humoral. A história somática e obstétrico-ginecológica das mães foi cuidadosamente coletada e avaliados os fatores de risco para o desenvolvimento de complicações no período inicial de adaptação. Como resultado do estudo, verificou-se que na estrutura dos fatores de risco em gestantes com infecções congênitas, são de grande importância a idade de 30 anos, patologia dos órgãos genitais e período extragenital durante a gravidez, abortos espontâneos e gravidez não desenvolvida, os abortos. As infecções virais associadas (CMV, citomegalovirus) predominam na estrutura da infecção congênita. A análise indica uma carga significativa da história perinatal em crianças com fatores infecciosos e fatores de hipóxia perinatal. Os principais sintomas clínicos de infecções congênitas entre as crianças examinadas são o período neonatal precoce, asfixia prematura, sintomas urinários, período neonatal tardio, que diferem no polimorfismo dos sintomas. Durante esse período, um órgão específico do sistema nervoso central é detectado. Em recém-nascidos com infecções congênitas, os parâmetros imunológicos são inibidos (CD4+, Cd8+, Cd19+).

Palavras-chave: imunidade, parâmetros imunológicos, história perinatal, infecção, sintomas clínicos.

ABSTRACT

Today about 40 % of babies are infected with intrauterine infections. The immune statuses of children during the neonatal period are largely associated with the patterns of pregnancies in their mothers. This work aimed to study clinical and immunological features in newborns of mothers with intrauterine infection. 48 infants were observed. Neonates were divided into two groups: group 1 – 33 newborns from mothers infected with cytomegalovirus infection, group 2 – 15 children from healthy mothers. The diagnosis of intrauterine infection verifizierung the basis of survey questionnaire for pregnant women, outpatient data of pregnant women and neonates, serologic study, PCR, ELISA, and the cellular immunity and humoral immunity. Somatic and obstetric and gynecological history of mothers was thoroughly collected and the risk factors for the development of complications

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in the early period of adaptation were assessed. The result of the study revealed that the structure of risk factors in pregnant women with intrauterine infections is of great importance the age of 30 years, genital and extragenital pathology during pregnancy, spontaneous abortions and non-developing pregnancy, abortion. Associated viral infections (CMV, Cytomegalovirus) predominate in the structure of congenital infection. The analysis indicates significantly burdened perinatal anamnesis in children infectious factors and factors of perinatal hypoxia. The leading clinical symptoms for intrauterine infections among the examined children are in the early neonatal period prematurity asphyxia, urinary symptoms, late neonatal period differ polymorphism symptomatic. In this period reveals a specific organ of the Central nervous system. In newborns with intrauterine infections observed inhibition of immunological indicators (CD4+, Cd8+, Cd 19+).

Keywords: *immunity, immunological indicators, perinatal history, infection, clinical symptoms.*

АННОТАЦИЯ

Актуальность данного исследования заключается в том, что сегодня около 40 % детей заражены внутриутробными инфекциями. Иммунные состояния детей в неонатальном периоде в значительной степени связаны с характером беременности у их матерей. Целью данного исследования является изучение клинических и иммунологических особенностей у новорожденных матерей с внутриутробной инфекцией. Под нашим наблюдением было 48 младенцев. Новорожденные были разделены на две группы: группа 1 – 33 новорожденных от матерей, инфицированных цитомегаловирусной инфекцией, группа 2 – 15 детей от здоровых матерей. Диагноз внутриутробной инфекции верифицируется на основе опросного листа для беременных, амбулаторных данных беременных и новорожденных, серологического исследования, ПЦР, ИФА, а также клеточного иммунитета и гуморального иммунитета. Соматический и акушерско-гинекологический анамнез матерей был тщательно собран и оценены факторы риска развития осложнений в раннем периоде адаптации. В результате проведенного исследования выяснилось, что в структуре факторов риска у беременных с внутриутробными инфекциями большое значение имеет возраст 30 лет, патология половых органов и экстрагенитальный период при беременности, самопроизвольные аборты и неразвивающаяся беременность, аборты. В структуре ВУИ преобладают связанные вирусные инфекции (ЦМВ, вирус простого вируса). Анализ свидетельствует о значительном отягощении перинатального анамнеза у детей инфекционными факторами и факторами перинатальной гипоксии. Ведущими клиническими симптомами внутриутробных инфекций раннего неонатального периода являются недоношенность, асфиксия, мочевой синдромы; поздний неонатальный период отличается полиморфизмом симптоматики: гипертензионно-гидроцефальный, судорожный и желтушный синдромы. У новорожденных при внутриутробных инфекциях наблюдается угнетение иммунологических показателей (CD4+, Cd8+, Cd19+).

Ключевые слова: *иммунитет, иммунологические показатели, перинатальный анамнез, инфекция, клинические симптомы*

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1. INTRODUCTION:

According to many authors, the prevalence of intrauterine infections in the human population can reach 10 to 22 % (Shabalov, 2006; Hwang *et al*., 2019; Stagno *et al*., 1981; Helmo *et al*., 2018; Schleiss and Marsh, 2018; Redko, 2015; Ashorn *et al*., 2018; Britt, 2018; Mamyrbayeva *et al*., 2017; Bocharova *et al*., 2019; Wang *et al*., 2011). Unfortunately, now only 60 % of children are born healthy. Subsequently the number of healthy children aged up to one year is reduced to 29 % (Makarov *et al*., 2004). It is intrauterine infection (IUI) that largely determines the rates of stillbirth, early neonatal mortality, and morbidity in newborns and infants (Dolgushina *et al*., 2017). According to various authors, the early neonatal morbidity associated with IUI is 5.3–27.4 %, stillbirth 14.9–16.8 % (Zile *et al*., 2019), and IUI-related perinatal mortality reaches 65.6 % (Stetsyuk and Andreeva, 2006; Isakov *et al*., 2006; Perepelitsa, 2018). Specific antibodies to CMV in pregnant women are detected in 40 % in developed countries and in 100 % of cases in developing countries (Kitsak, 2005; Sial and Patel, 2000; Zhukova *et al*., 2018; Damato and Winnen, 2002).

It has been proven that the intrauterine infectious agents include more than 27 types of bacteria, many viruses, parasites, 6 species of fungi, 4 species of protozoa, etc. Mycoplasmas (17-50 %) and viruses (herpes simplex virus 7-47 %, enteroviruses 8-17 %, cytomegalovirus 28-91.6 %) are considered to be the predominant antenatal pathogens, and intranatal infections are caused by chlamydia (2-25 %), group B streptococcus (3-12 %), listeria (1-9 %), conditionally pathogenic microorganisms (9- 14.7 %) (Polucci *et al.,* 2009). An intrauterine infection contamination shall mean the supposed

fact of intrauterine microbial fetal penetration without signs of infectious fetal disease, and IUI is the established fact of intrauterine microbial fetal penetration, in which the pathophysiological changes which are specific for the infectious disease occurred in the fetus and newborn prenatally or shortly after birth (Bonaros *et al.*, 2008; Kemp, 2014).

Despite the improvement of the basic parameters which characterize the specific weight of infections (Sukhanova and Sklyar, 2007) in the structure of perinatal and gynecological morbidity (Orekhov, 2002; Volodin, 2001), herpes infection remains the main cause of neonatal morbidity and mortality (Lutoshin, 2005; Subramaniam and Britt, 2018). Herpes virus infections are opportunistic infections, when a virus can exist for a long time in the human body, it may not reveal itself and cause any pathological phenomena, but when the body protective functions decrease, the virus begins to multiply intensely and impair various organs and systems (Ovchinnikova *et al*., 2018).

The immune systems of newborns are physiologically depressed. According to the WHO, herpes infection is considered one of the most common congenital viral diseases (Volodin, 2002). Herpes infection is an infection that causes spontaneous miscarriage, premature birth, missed abortion, congenital malformations of newborns, fetopathy. The study of the timely early detection of herpes virus infection in women of reproductive age and pregnant women can help to prevent intrauterine fetal viral infections and reduce the number of overt forms of infection in newborns and reduce deaths (Zhumalina *et al*., 2014; Orekhov, 2002; Borovkova, 2005). In addition, the prognosis of intrauterine transmission depends on the gestational age at which the infection occurred, the characteristics of the pathogen (its pathogenic and immunogenic properties), the type of maternal infection (primary or secondary), the functional state of the mother's immune system (Coppola *et al*., 2019; Tyutyunnik *et al*., 2014), the integrity of the uteroplacental barrier, etc.

Due to the incompetent immune system of infants, the basic protective functions are performed by passively acquired serum and secretory antibodies (Kadieva, 2007; Fowler *et al*., 1992). Functional immaturity of lymphocytes, incompetent cell cooperation in the formation of the immune response, and physiological immunosuppression highly predispose newborns to infection (Carbone, 2016). This is the reason of fundamental study of pathology and development of treatment management and prognosis. Therefore, the purpose of this study was to analyse the clinical and immunological characteristics of children born from mothers with intrauterine infection.

2. MATERIALS AND METHODS:

Retrospective and prospective studies of women observed in antenatal care, maternal care departments, and clinics and their newborns were conducted. 48 newborns were followed.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (Local Ethics Committee No. WHC-72(23)) of the West Kazakhstan Marat Ospanov Medical University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

According to the research policy of this university, the committee does not require any official supporting document, therefore, informed consent, in which the research and its outcomes are clearly and well explained, was obtained from all individual participants included in the study. The obtained research data will be used for study clinical and immunological features in newborns of mothers with intrauterine infection.

Newborns were divided into two groups: Group 1 included 33 children born from mothers infected with cytomegalovirus infection, Group 2 had 15 children born from healthy mothers (conditionally healthy children). Inclusion criteria: children aged up to 1 month; with positive markers for CMV; hepatitis B vaccination in the first 24 hours of age. Exclusion criteria: children with established causes of jaundice (current overt infection process, breast milk jaundice, etc.); children with congenital malformations; children with physiological jaundice.

Somatic and obstetric and gynecological history of mothers was thoroughly collected, clinical observation was performed. The laboratory test material was venous and capillary blood. Blood was sampled upon the informed consent of parents (mother and father) with the study explained. Blood of newborns was taken in the morning before feeding: 1 ml of venous blood for polymerase chain reaction (PCR), 2 ml of venous blood in the first 7-8 days of age for the cellular and humoral immunity state (determination of T, B-lymphocytes and their subpopulations).

The diagnosis of intrauterine infection was verified on the basis of a questionnaire for pregnant women, outpatient data for pregnant

women and newborns, serological studies, PCR, ELISA and the state of cellular and humoral immunity (determination of T, B-lymphocytes and their subpopulations). Statistical data were processed using:

1. nonparametric Mann-Whitney U-test. The Mann-Whitney test assumes that the studied variables are measured, at least in an ordinal scale (ranked). U-test is calculated as the sum of indicators of pairwise comparison of the first sample elements with the second sample elements. U-test is the most powerful (sensitive) nonparametric method for independent samples. Together with the U-test, z-value (for the normal distribution) and the corresponding p-value are shown
2. descriptive statistics of quantitative data in groups,
3. comparison of groups on PC using MS Excel, EpiData database,
4. licensed statistical program SAS 9.2.

The differences between the groups were significant if the error probability was less than 5 % ($p<0.05$).

3. RESULTS AND DISCUSSION:

One of the effective ways to predict and diagnose IUI in newborns is to identify intrauterine infection risk factors in pregnant women (Boppana *et al*., 2011; Zavattoni *et al*., 2016; Tabata *et al*., 2016; Wagner *et al*., 2014; Revello *et al*., 2008; Stehel *et al*., 2008) Therefore, we performed a retrospective analysis of 160 outpatient medical records of pregnant women. 34 patients who were considered to be at risk of fetal infection and who had perinatal risk factors for the delivery of newborns with intrauterine infections were selected. Outpatient medical records of pregnant women were reviewed, and the perinatal risk factors that could cause fetal infection and the course of pregnancy were studied. The following data were studied: primipara, abortion, spontaneous miscarriage, missed abortion (non-developed pregnancy), maternal age (30-34 years and above), uterine scarring, aggravation of existing chronic maternal diseases, acute infectious genital diseases, CMV carrier status, acute viral diseases during pregnancy, threatened abortion, polyhydramnios, anemia, colpitis.

According to the analysis, the following premorbid factors were identified. As can be seen from Figure 1, in the group of risk factors that characterize the reproductive health of pregnant women, the share of missed abortion (30 %) was the largest followed by spontaneous miscarriage and primipara (8 %). Medical abortions and threatened miscarriage were observed in 5 % and 3 %, respectively.

In the group of risk factors that occur during pregnancy, the most intense risk is anemia (22 %). The same risk group included 18 % for acute infectious genital diseases, 9 % for colpitis, 6 % for polyhydramnios, and only 3 % for acute viral infections during pregnancy among women infected with herpes virus (Figure 2).

As for the pregnant women's somatic health, when the risk factors were graded, a larger percentage is represented by chronic inflammatory diseases (chronic gastritis, chronic cholecystitis, COPD) (6 %). CMV carrier status and uterine scarring are 5 % and 4 %, respectively (Figure 3).

The maternal age (30-34 and above) was the most interesting social factors, its specific gravity was 45 %. Other social factors, such as marital status (single, divorced), bad habits (mother's smoking), mother's age under 18, and unintended pregnancy were not considered, since there were isolated cases in outpatient cards of pregnant women. A comparative analysis of the frequency of risk factors showed that 22 mothers (62.9 %) whose children were observed had a latent persistent CMV infection. We noticed that in the late neonatal period icteric syndrome persisted in 33 (48.5 %) children, 16 (23.5 %) had hepatomegaly, and 7 (10.3 %) had splenomegaly. It can be seen that maternal infection and latent persistence of CMV with hypoxic disorders cause protracted hyperbilirubinemia.

The leading neurological syndromes in infected children in the early neonatal period were muscle hypotension, depression and hypertensive hydrocephalus syndrome. The findings in the peripheral blood test of infected children included: left deviation in WBC differential in 12 (17.6 %) children, anemia in 2 (2.9 %) children, thrombocytosis in 2 (2.9 %) children, thrombocytopenia in 1 (1.5 %) child. Urinary syndrome manifested as proteinuria and leukocyturia in 7 (10.3 %) children, microhematuria in 1 (1.5 %) (Chen *et al*., 2019). According to literature data (De la Calle *et al*., 2018; Pereira *et al*., 2014; Seidel *et al*., 2017), children with CMVI in the late neonatal period develop specific inflammatory changes in the form of meningoencephalitis, pneumonia, hepatitis, nephritis. Our analysis has confirmed these data.

The greatest specific weight among all

syndromes was caused by the nervous system disorders. They were observed in 20 (29.4 %) children and manifested as encephalopathies, various congenital malformations (hydrocephalus, microcephaly) (De Bie and Boucoiran, 2019; Ximenes *et al*., 2019). In the late neonatal period, hypertensive hydrocephalus and convulsive syndromes were significantly more common in children. We examined the immunological status, evaluated the cellular component of the immune system of newborns infected from mothers of CMVI. We determined the lymphocyte phenotype (main subpopulations) – CD3, CD4, CD8, CD19. The table shows that a significant (p-0.038044) increase in the general population of T-lymphocytes (CD3+) was found in the study and control groups: 73.8±6.9 in the study group and 67±8.1 in the control group (Tables 1 and 2).

An increase in the level of T-lymphocytes is seen in the figure of range (Figure 4).

The count of T-helpers (CD4+) in Group 1 (study group) is slightly lower compared to Group 2 (control group), however, the differences are not significant (p-0.910538), we can suggest immunological deficiency (Figure 5).

The depression of CD4+ subpopulation of T-lymphocytes may be the result of the direct selective action of intrauterine infections on these cells or serve as the background on which infection occurs. The relationship of the level of lymphocyte subpopulations with infection contamination of the newborns can be established. A more pronounced decrease in Group 1 (study) compared with Group 2 (control) of newborns (p-0.000004) when the data of T-cytotoxic lymphocyte count (CD8 +) is interpreted (Figure 6).

In Group 1 (study) group and Group 2 (control), a decrease in B-lymphocyte count (CD19+) was observed, but lower in the study group (8.37±2.5) than in the control group (9.81±3.5) (Figure 7).

Thus, in our study, specific immune system disorders were identified in Group 1 (study), which are characterized by an increase in CD3+, a decrease in CD4+, CD8+, and a decrease in CD19+ proving the impact of intrauterine infections on the immune system of infected newborns; a decrease in T-lymphocytes (CD4+, CD8+) indicates that the fetus was infected antenatally and as a result of exposure to the infection in utero.

4. CONCLUSIONS:

1. In the structure of risk factors, the age above 30 years, extragenital and genital pathologies during pregnancy, spontaneous miscarriages and missed abortion, pregnancy termination are of great importance in pregnant women with intrauterine infections (herpes viruses and CMV). Associated viral infections (CMV, herpes simplex virus) are prevailed in the IUI structure.

2. The analysis indicates a significantly aggravated perinatal history in children by infectious and perinatal hypoxia factors. The leading clinical manifestations of intrauterine infections in the children examined were as follows:

- prematurity, asphyxia, urinary syndromes in the early neonatal period.
- the late neonatal period is characterized by the symptom polymorphism: hypertensive hydrocephalus syndrome, convulsive and icteric syndromes. In the same period, specific central nervous system disorders, urinary and respiratory system disorders, and gastrointestinal disorders are detected.

3. Intrauterine exposure to factors may result in impaired formation of immunocompetent structures and be accompanied by activation of the fetal immune system and early synthesis of antibodies, which can be regarded as a complex of protective reactions or premature overstrain.

The obtained data on the clinical and immunological characteristics of newborns which were born from mothers with intrauterine infection will give deeper understanding of the intrauterine process pathogenesis. They can also be used when antiviral drugs are prescribed and can be used in the prevention of congenital cytomegalovirus and herpes infections in newborns.

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***Table 1**. Parameters of Cellular Immunity in Newborns*

	Group 1 (study group)	Group 2 (control group)
CD3+	73.8 ±6.9	67±8.1
CD4+	37.1 ±4.2	38.6±4.4
CD8+	17.5±4.2	25.7±1.6
CD19+	8.37 ±2.5	16.4±0.3

***Table 2.** Values of the General Population of T-lymphocytes in Newborns*

Variable	Mann-Whitney U-test (complete blood test and CD) Group by variables Specified criteria are significant at p <0.05000								
	Total ranks Group 1	Total ranks Group 2	U	Z	p-level	Z adjusted	p-level	N Group 1	N Group 2
CD3+	902.0000	274.0000	154.0000	2.06858	0.038586	2.07439	0.038044	33	15
CD4+	814.0000	362.0000	242.0000	0.11121	0.911447	0.11236	0.910538	33	15
CD8+	601.5000	574.5000	40.5000	-4.59314	0.000004	-4.62756	0.000004	33	15
CD19+	767.5000	408.5000	206.5000	-0.90083	0.367677	-0.92111	0.356996	33	15

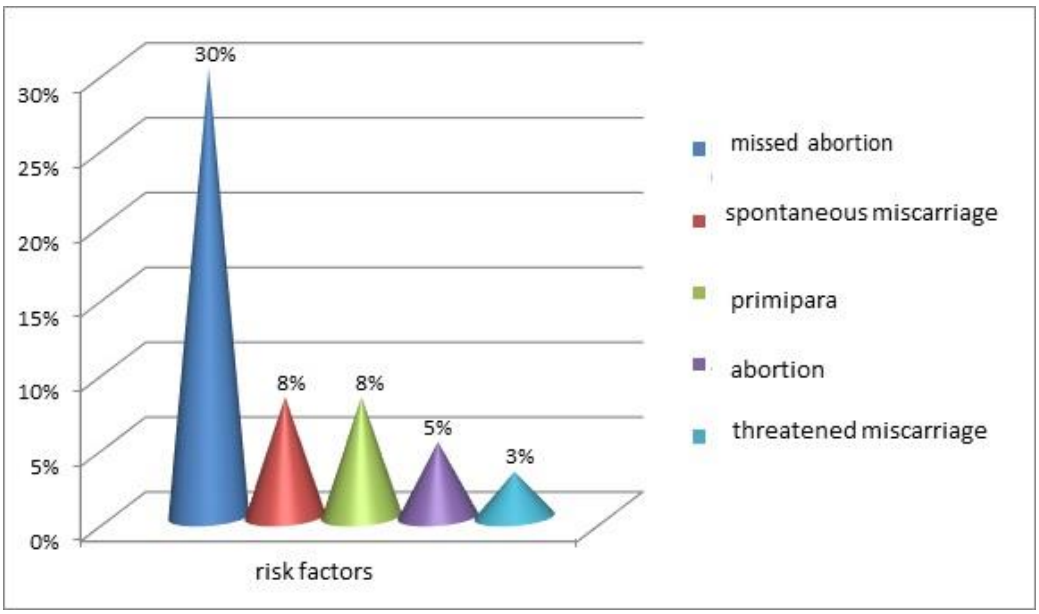

***Figure 1.** Pregnant Reproductive Health*

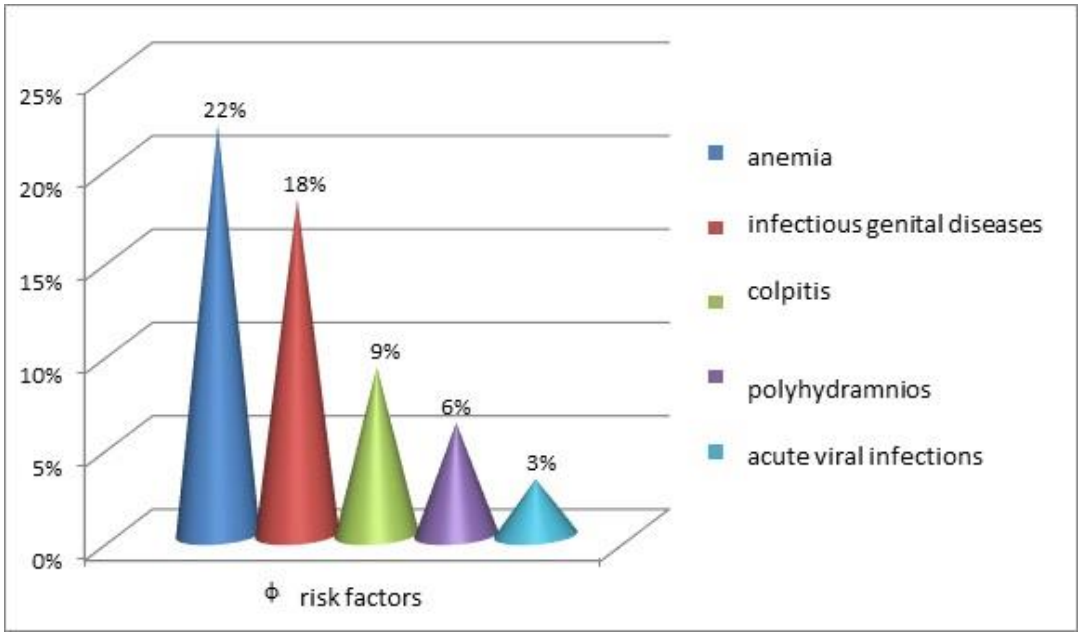

Figure 2. *Risk Factors during Pregnancy*

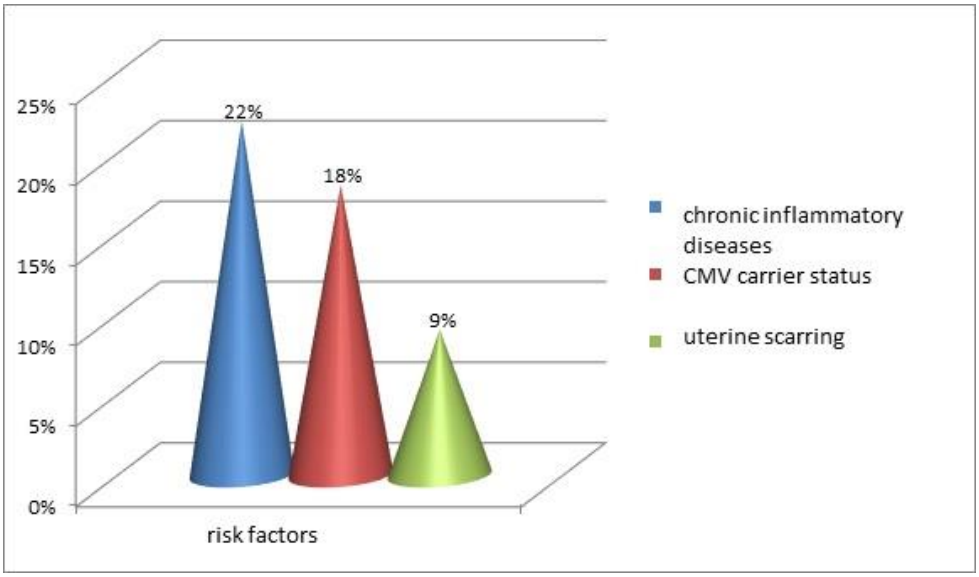

Figure 3. *Women's Somatic Health Risk Factors*

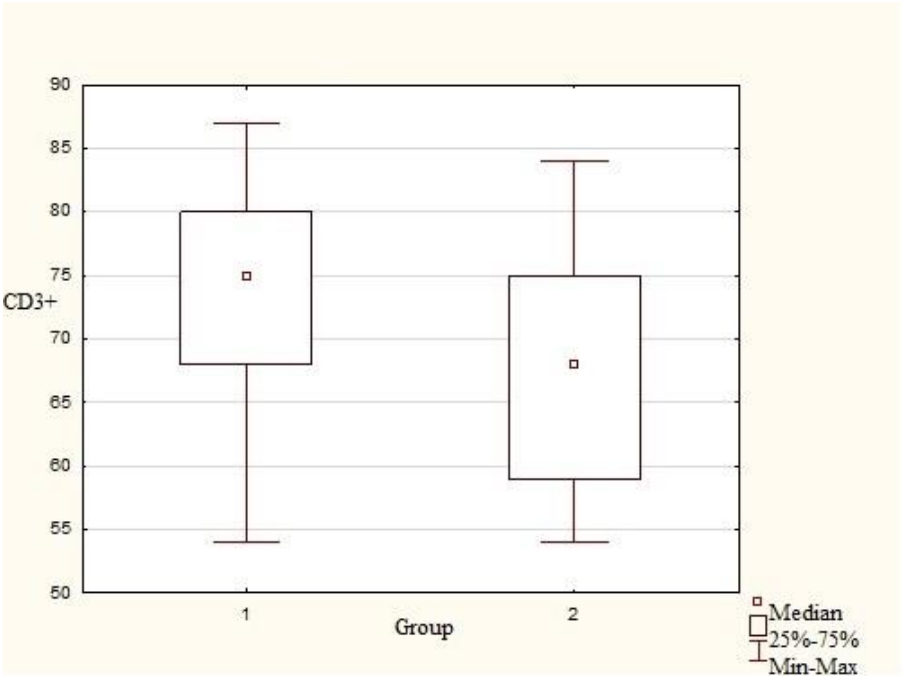

Figure 4. *Range by Groups of Variables: CD3+*

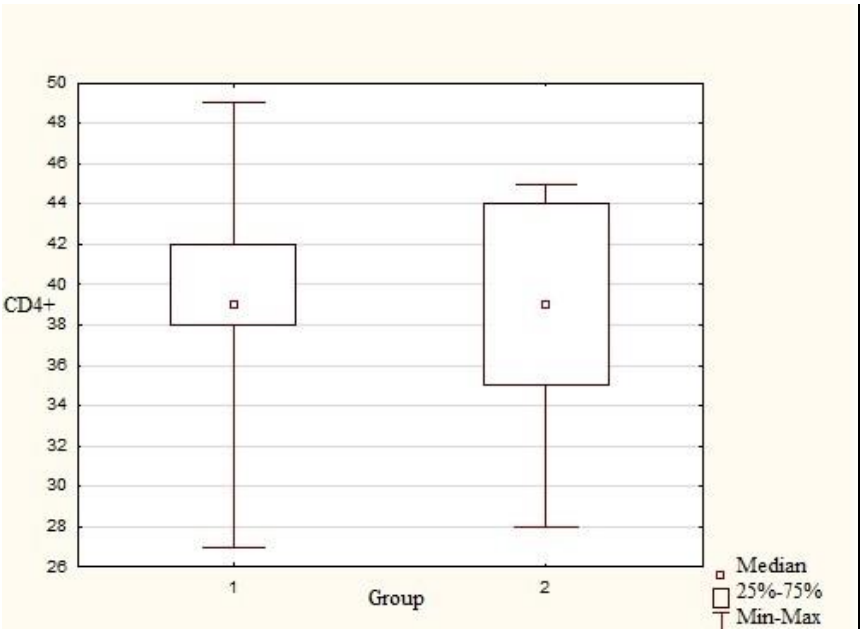

Figure 5. *Range by Groups of Variables: CD4+*

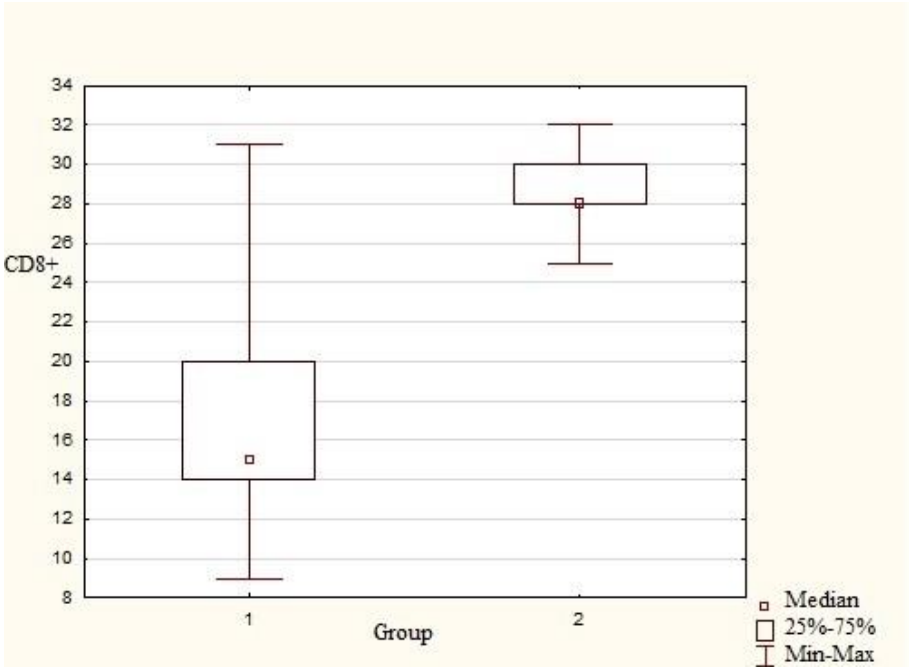

Figure 6. *Range by Groups of Variables: CD8+*

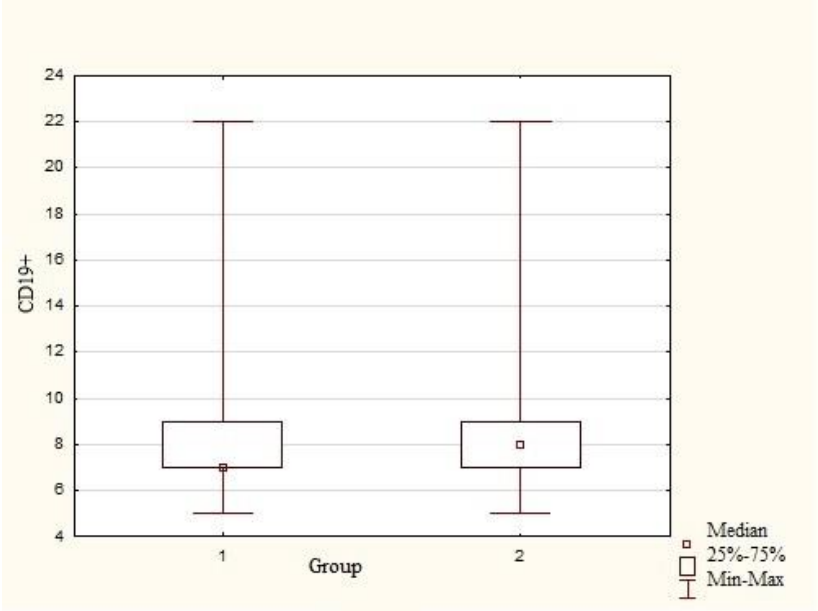

Figure 7. *Range by Groups of Variables: CD19+*