

REPUBLIC OF AZERBAIJAN

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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**COMPLEX EVALUATION OF THE HEALTH
OF EARLY AGE CHILDREN BORN WITH
INTRAUTERINE INFECTION**

Specialty: 3220.01- Pediatrics

Field of scientific: Medicine

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BAKU - 2022

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GENERAL DESCRIPTION OF THE WORK

Relevance of the theme: The development of healthcare, which is one of the priorities of the healthcare system of the Republic of Azerbaijan, and the improvement of the quality of medical services provided to the population are always relevant. One of the most complex and important medical and social problems of neonatology and pediatrics is children born with congenital infectious pathology. The exact incidence of intrauterine infections has not been determined, but some authors estimate that it can be as high as 10%. For this reason, intrauterine infection not only causes perinatal and postnatal losses, but can also lead to serious changes in children's health at a later age, which can lead to a decrease in the child's quality of life and social maladaptation^{1,2,3}. Intrauterine infections in most young children lead to the development of diseases that cause disability, such as psychomotor retardation, cerebral palsy, chronic somatic diseases, congenital malformations^{4,5}.

¹ Сеидбекова Ф.О. Intrauterine infections as a risk factor for the development of congenital malformations // Family medicine, -2012. No.3, - с.124-126.

² Lanzieri TM, Dollard SC, Bialek SR, Grosse SD. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. Int J Infect Dis. -2014. 22:44-48. doi:10.1016/j.ijid.2013.12.010.

³ Qarayeva S.Z. Learning the structure of diseases in the first 3 years of life of children born with intrauterine growth retardation // Azerbaijan Journal Medicine, -2015. No.3, -s.64-70.

⁴ Hayashida K. Promoting factors of physical and mental development in early infancy: a comparison of preterm delivery/low birth weight infants and term infants / K. Hayashida, M. Nakatsuka // J Spec PediatrNurs. - 2014.- Nov. 7.

⁵ Dreher A.M. Spectrum of Disease and Outcome in Children with Symptomatic Congenital Cytomegalovirus Infection / A.M.Dreher, N.Arora, K.B.Fowler et al. // The Journal of Pediatrics. - 2014. - Vol. 164, no 4. – P.855–859.

Many factors affect the formation of health in the perinatal period - genetic characteristics, unfavorable antenatal period, severe and long-term disorders that lead to multiorgan changes^{6,7}. The study of the characteristics of the formation of the health of these children, the regularities of the development of diseases can help to carry out adequate early treatment and rehabilitation measures. In order to reduce the incidence of neonatal diseases, infant mortality and childhood disabilities, it is important to develop a comprehensive action plan to prevent intrauterine infections among women of childbearing age, pregnant women and young children^{8,9}.

Over the past 10 years, many studies have been conducted to study the consequences of intrauterine infections affecting the central nervous system, internal organs, and the immune system.

The data in the world literature on comprehensive assessment of the health of children with intrauterine infections at an early age are contradictory and in most cases based on few observations. Therefore, there is a great need for both scientific and experimental research on the developmental characteristics of children with intrauterine infections, the etiology and structure of their pathologies, the immune response, the study of the recovery of mental functions.

Object of research: children born at different gestational age (0-3 years) with intrauterine infection.

The study involved 234 children born at 27-42 weeks of gestation. The main group involved 158 children born with intrauterine infection.

⁶ Ito Y., Kimura H., Torii Y. et al. Risk factors for poor outcome in congenital cytomegalovirus infection and neonatal herpes on the basis of a nationwide survey in Japan. // *Pediatr. Int.* - 2013. - Vol. 55. № 5. - P. 566-570.

⁷Цинзерлинг В.А. *Внутриутробные инфекции: современный взгляд на проблему.* Журнал инфектологии,- 2014;6(4):13-18.

⁸ Pinninti S.G., Kimberlin D.W. Preventing herpes simplex virus in the newborn//*ClinPerinatol.*,- Dec,- 2014. -41(4) . -P. 945-55.

⁹ Pass RF, Anderson B. Mother-to-Child Transmission of Cytomegalovirus and Prevention of Congenital Infection. *J Pediatric Infect Dis Soc.*- 2014. 3 Suppl 1(Suppl 1):S2-S6. doi:10.1093/jpids/piu069.

Depending on the age of gestation, the main group is divided into 2 subgroups: 110 term children - group 2A, 48 preterm children - group 2B.

The control group included 76 practically healthy children with no clinical or laboratory signs of intrauterine infection and was divided into 2 (1A and 1B) subgroups depending on the gestational age.

Aim of the study: research of complex assesment of health condition of early age children born with intrauterine infection and improvement of dispanser monitoring.

Research objectives:

1. Learning the impact of perinatal risk factors to the clinical progress and severeness of intrauterine infections in children.
2. Learning clinical, functional and etiological features of health condition of children during neonatal period who born on time and prematurely with intrauterine infections.
3. Define clinical-diagnostic factors of blood parameters and sitocin status during neonatal period in the children born on time and prematurely with intrauterine infection and learning the prognostic importance of neurospecific proteins during CNS damages.
4. Complex evaluation of health condition of children born with intrauterine infection during the first 3 years of life depending on gestation age.
5. Prepare prognostic model for dynamic clinical observation of children born with intrauterine infection.

Research methods. anamnestic, clinic, laboratory methods and clinical observations.

Clinical-anamnestic, laboratory-instrumental examinations of children involved in the study were conducted for 3 years. All children included in the study underwent clinical and laboratory examination methods: general and biochemical examination of blood, urine, feces. Immunochemical, bacteriological and serological methods were used in laboratory examination. All figures obtained in the course of the study were performed using the methods of variation, discriminant, variance, correlation and ROC-analysis.

The main provisions of dissertation to be defended:

- Neonatal adaptation period in the children in different gestation age with intrauterine infection is characterized with the progress of different clinical variants of pathological process and this contributes formation of damages and chronic diseases.
- Disbalance of citocin status shows itself with increase of pre-inflammatory citocins yield (IL-8, ŞNA- α) and decrease of the level of anti-inflammatory citocins (IL-10) depending on gestation age of intrauterine infections and newborns.
- The intense displacement towards the yields of intrauterine infections, neurospecific proteins in newborns (GFAP, S100B) is considered as one of the most important factors defining formation of CNS diseases.
- Prognostic model and revealing risk groups that worked out on the basis of information about the number of pathologies and unsuitable factors and impact character in the children born with intrauterine infections opens new opportunities to select the most optimal prophylactic measures. This kind of approach is important to minimize formation risk of severe pathologies and applying preventive methods of their correction.

Scientific innovation of the research:

Early age health condition of the children born in different gestation age with intrauterine infection has been involved into the complex evaluation for the first time. Clinical, functional features and etiological structure of pathological conditions of neonatal period have been learned depending on the risk factors of the children born in different gestation age and intrauterine infection.

Clinic-diagnostic importance of disbalance (IL8, IL10, ŞNA- α) of blood parameters and revealed citocin status during neonatal period of the children having intrauterine infection who born with the different gestation age has been defined and prognostic-diagnostic importance of neurospecific proteins (GFAP, S100B) in the formation of pathologies during CNS damages has been learned.

A prognosing model has been prepared on the basis of prognosing diseases at the early age depending on antenatal and

neonatal period with the purpose of optimizing dynamic clinic observation of the children born with intrauterine infection.

Practical significance of the research

1. Disbalance of citocin status in blood can be used as an additional criterion in early diagnostics of pathological process by evaluating the severeness level of pathology during the complex clinical-functional inspections of the children born with the intrauterine infection.
2. Learning the neurospecific proteins concentration in blood and evaluating as prognostic marker is important during the central nervous system damages in the children born with intrauterine infection.
3. Depending on antenatal, neonatal period of the children born with intrauterine infection, prognostic model has been worked out allowing complex evaluation of health condition of early aged children on the basis of clinical, laboratory and statistic data.

Application the results of dissertation work in practice.

Conclusions of the work are applied at the departments of anesthesiology reanimation and intensive therapy, newborns pathology, premature infants' pathology of the Scientific-Research Pediatrics Institution and consultative-polyclinics departments.

Research approbation. Main provisions of the dissertation. Abstracts of XI Congress of Pediatrists of Eurasian Countries (2011, Dushanbe), the 4th Conference of Azerbaijani Neurologists by the attendance of the International specialists (Baku 2010), the International scientific-practical conference in the subject of "Contemporary aspects of allergic diseases in the children" (Baku-2011), 2nd International Scientific Confererense "Theoretical and Applied Sciences in the USA" (2015), the International scientific-practical conference "Science and education in the life of modern society" (Tambov 2016), 20th congress of the pediatricians of Russia with the International participation "Actual pediatric problems" (Moscow 2018), V the International Scientific Conference "Medicine: The present day's challenge" (St.Petersburg, July 2018), 4thInternational Conference on Biology and Medical Sciences:

Innovations and practice (New York, June 2018), conference materials in the subject of “Modern achievements in Medicine” (Baku, 2018), Scientific conference devoted for the anniversary of D.Hajiyev(Baku 2019), Conference devoted for 80 years anniversary of the chair of child surgery (2019), 21st congress of the pediatricians in Russia with an international participation “Actual problems of pediatrics” (Moscow February 2019), 15 Uludağpediatricswinter congress (Turkey, March2019), Conference devoted to 90 years anniversary of prof. HS.D.V.Hajiyev associated professor of ANSA (Baku, 2019)”,the international scientific-practical conference devoted to the actual problems of X-ray diagnostics on the subject of “Viewing eyes of medicine” (Baku, 2019), the international scientific-practical conference devoted to the 100 years anniversary of the establishment of Medical faculty under BSU, Actual problems of medicine (Baku, 2019), scientific conference devoted to 90 years anniversary of the professor HS.Z.T.Guliyeva (Baku, 2019), 17.UNPSTR-EurasianCongress (Baku, 2019), scientific conference devoted to 75 years of anniversary of the doctor of medicine. A.T.Aghayev (Baku, 2019), World Congress of Perinatal Medicine (Turkey, Istanbul, 11-14 September, 2019), Abstracts of the XVIII International Eurasian congress of surgery and hepatogastroenterology (Baku, 11-14 September, 2019).

The initial discussion of the dissertation was held at the meeting of the Scientific Council of the Scientific-Research Institute of Pediatric named after K.Y. Farajova (protocol No.1 at 30.04.2019). Approbation of the dissertation was discussed at the meeting of the Approbation Council (protocol №7, 15.10.2021), conducting scientific workshops within the Dissertation Council ED 2.27 on the specialty 3220.01 - "Pediatrics" of the Azerbaijan Medical University.

Name of the organization of realization the dissertation: The Research work is included into the planned work of Scientific-Research Pediatric Institution by K.Y. Farajov for 2014-2018 years.

Published works: 36 scientific works are published concerning to the dissertation subject (17 journal articles and 19 thesis).

Volume and structure of the dissertation. Dissertation has been written in 161 pages (201.869 symbols) typed in computer and described with 38 tables and 12 photos. It is worked out according to the traditional planning: it consists of introduction, table of contents, materials and methods of research work, 4 chapters about personal researches, conclusion, findings, practical recommendatins and literature list (211 resourses).

MATERIAL AND METHODS OF RESEARCH

Clinical laboratory inspections of the research work were conducted at the scientific-diagnoststic laboratory of Scinetific-Research Pediatrics Institution by K.Y.Farajova and at the laboratory of Biological chemistry chair of the Azerbaijan Medical University and at the private medical center according to the targeted obligations. Dynamic observation of the health condition in the early age was conducted at the Baku city polyclinics No. 4, 5, 7, 8, 9, 10, 11, 12, 13, 17, 19, 21 and at Xirdalan city children polyclinic.

234 children born in their 27-42 gestational week were involved into the research work and clinical-anamnestic, laboratory-instrumental dynamic observation of this children was carried out during 3 years. The main group involved 158 children born with intrauterine infection of different etiology. These children born from mothers having complicated obstetric-gynecological history were transferred at 0-7 day of their life to the SRPI by K.Y. Farajov from different maternity hospitals of Baku city and regions and received inpatient treatment at the reanimatoriy and intentsive therapy departments, pathology departments of premature and newborns. Children included into the main group were splited into 2 sub-groups depending on their gestation age: 110 children born on time in the group 2A and 48 premature (27-36 week) in the subgroup 2B. Supervision group included 76 children being practically healthy and not having clinical-laboratory symptoms and splited into subgroups 1A (37-42 gestation week) and 1B (27-36 gestation week). Main group included 98 boys and 60 girls, while supervision group included 42 boys and 34 girls.

Factors of involving into research in the main group:

- intrauterine infection confirmed with main clinical diagnosis-laboratory inspection methods (PZR, İFA, bacteriological method);
- entering newborns to the anesthesiology reanimation and intensive therapy department and entering newborns to pathological department during the early neonatal period (first 0-7 days of their life) and into the prematures pathological department with diagnosis of intrauterine infections;
- 27-42 weeks gestation age;
- Body weight being more than 1000 gr.

Special neonatal medical card and catamnestic cards were prepared reflecting anamnesis, clinical diagnosis (dynamics and result of disease), results of inspection and treatment for every children involved into the inspection. PZR (chain polymeraza reaction) and Ig M,G immunoenzymes analysis method was used with the purpose of verification of the causative agents of intrauterine infections together with anamnestic, clinical-laboratory and instrumental inspections (biochemical and serological inspection of blood, inspection of urine and feces) in all children included into the main group.

ŞNA- α , İL-8, İL-10 indexes of 3 chains of neurospesific proteins (GFAP and S100B) and cytokines were conducted by using monoclonal antibodies with fluorecence method in the blood of children in their 1-2nd week of life.

Clinical inspection, analysis of ambulatory cards, laboratory and functional inspections were carried out of children in 3-6-9-12-18-24-36 months of their life and results of pathologies were analysed with the purpose of solution of targeted duties. All children involved into the researched swere inspected by pediatrician, neurologist, ophthalmologist, orthopedist and haemathologist, surgeon and other specialists according to the instruction. Health condition of the children has been evaluated by splitting them into health groups: I group were practically healthy children, the 2nd group were children included into risk group having functional changes and for their pathological development and frequency of morbidity, III, IV and V

groups were the children having chronic pathologies in compensation, subcompensation and decompensation condition.

Statistical working of results. All figured indexes obtained during the progress of research were conducted by applying variation, discriminant, dispersion, correlation and ROC analysis methods. All calculations were conducted in electronic table of EXCEL-2013 and SPSS-20 package program, conclusions were summarized in schemes and tables.

RESULTS OF THE RESEARCH AND DISCUSSION

Assesment of antenatal and intranatal period. Blood and hematopoietic diseases ($60.8 \pm 3.9\%$) and respiratory diseases ($43.7 \pm 1.1\%$) are more common in mothers with intrauterine infection than in the control group ($p < 0,001$). Other pathologies were as digestive diseases $8,2 \pm 2,2\%$, sexually transferred diseases $11,4 \pm 2,5\%$, endocrine diseases $3,2 \pm 1,4\%$. During the pregnancy of mothers having intrauterine infections vomiting during pregnancy ($67,1 \pm 3,7\%$) preeclampsia ($23,4 \pm 3,4\%$) in the first half of pregnancy, pathology of amnion liquid ($13,3 \pm 2,7\%$), placental impairment ($6,3 \pm 1,9\%$) in the 2nd trimester of pregnancy were recorded with statistically accuracy ($p < 0,001$). Percentage of surgical births were $32,9 \pm 3,7\%$ in the main group and $18,4 \pm 4,4\%$ in the supervision group ($\chi^2 = 5,32$, $p < 0,05$). It was obvious from anamnestic data that abortions ($7 \pm 2,0\%$), miscarriages ($17,7 \pm 3,0\%$) and stillbirths $10,1 \pm 2,4\%$ were recorded ($p < 0,05$).

The characteristics of obstetric-gynecological anamnesis in mothers showed that complicated obstetric anamnesis shows high level of stillbirths and miscarriages, diseases of blood and blood, hematopoietic organs and respiratory diseases and sexually transmitted diseases.

Assesment of total condition of children born with intrauterine infection. Average body weight of term boys and girls with IUI were $3,1 \pm 0,1$ kg, average body length is $50,8 \pm 0,2$ cm in boys and $50,2 \pm 0,5$ cm in girls. Average weight were $2,1 \pm 0,1$ kg for boys and $1,9 \pm 0,1$ kg for girls and average body length were $42,8 \pm 0,8$ cm

and $42,8 \pm 1,0$ cm accordingly for boys and girls who born premature and having intrauterine infections.

When entering into clinic the condition of 27 premature children from group 2B evaluated as very severe ($56,3 \pm 7,2\%$) and 14 children ($29,2 \pm 6,6\%$) was severe. The health condition of the majority of children born on time from group 2A was – severe (54 uşaq ($49,1 \pm 4,8\%$) and verysevere in 45 children ($40,9 \pm 4,7\%$). There were 7 premature children ($14,6 \pm 5,1\%$) and 9 children ($8,2 \pm 2,6\%$) born on time were entered in preagonal condition. The disease reflected by damaging all organs and systems in the form of generalized ceptic process in this group of patients. 4 organs damage at the same time recorded in most of newborns: $57,3 \pm 4,7\%$ in group 2A and $66,7 \pm 6,8\%$ in group 2B. 1-3 organ damage observed as $42,7 \pm 4,7\%$ and $33,3 \pm 6,8\%$ accordingly in children born on time and premature children having intrauterine infections. Stationary treatment for the inspection groups was averagly $14,3 \pm 0,9$ days in group 2A and $18,3 \pm 2,2$ days in group 2B.

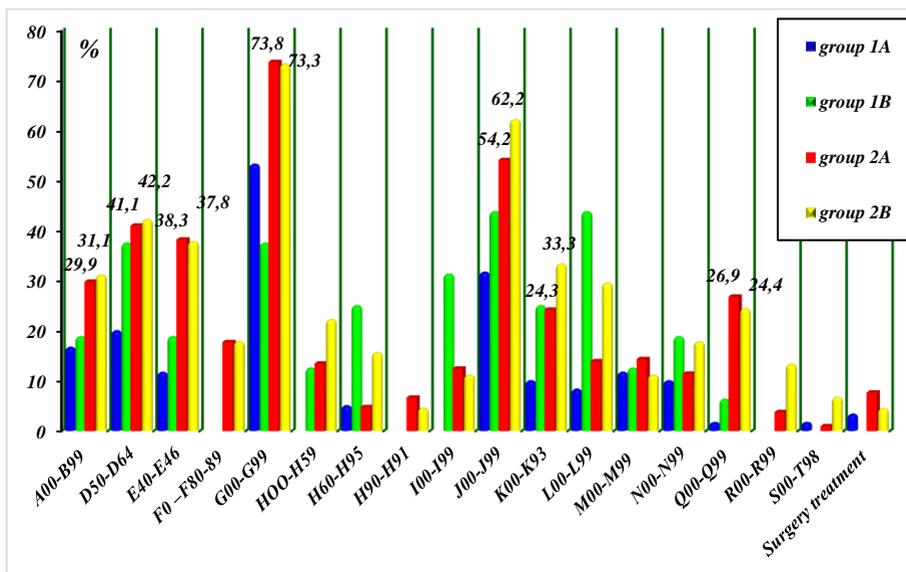
Analysis of progress features of neonatal period showed that severe condition if typical for premature children born with intrauterine infections. So, $14,6 \pm 5,1\%$ premature children and $5,5 \pm 2,2\%$ children born in time had asphyxia. Middle level respiratory imparment in premature newborns in the main group gradually transferred into the severe respiratory impairment in the first 1-2nd hour of their life. Artificial respiration apparatus for lungs were necessary for $10,4 \pm 4,4\%$ prematures having generalized intrauterus infections and $11,8 \pm 3,1\%$ in children born in time. Oxygenotherapy conducted with the purpose of correction of arterial hypoxemia conducted $47,9 \pm 7,2\%$ in prematures and $52,7 \pm 4,8\%$ in children born in time in the main group. Non-invasive ventilation of lungs with CPAP method was carried out in cases $15,5 \pm 3,4\%$ from the group 2A and $29,2 \pm 6,6\%$ from group 2B.

So, newborns having complicated generalized form of intrauterine infections born in asphyxia condition and require intensive therapy and reanimation beginning from the first minutes of life, and majority face with different cerebral and respiratory disorders

and this makes necessary to apply respiratory support methods starting from first minutes of life and during all neonatal period.

Neonatal morbidity of newborns having intrauterine infection. The frequency of central nervous system damages is $98,2\pm 1,3\%$ in newborns on time and $100,0\pm 0,0\%$ in premature newborns, though no any CNS damages occurred in both supervision group.

Birth traumas were $10,0\pm 2,9\%$ in the disease structure of children born on time and $8,3\pm 4,0\%$ in premature children both having intrauterine infections. Haematological and haemorrhagic disorders in newborns occurred $75,5\pm 2,5\%$ in children born on time and $85,4\pm 5,1\%$ in premature children. Respiratory and cardiovascular disorders being typical for perinatal period occurred as $62,7\pm 4,6\%$ in group 2A, while $72,9\pm 6,4\%$ in group 2B (pic.1).



Picture 1. Neonatal morbidity

Disorders in connection with the fetus development (P05-P08), e.g. intrauterine growth restriction and malnutrition observed in $7,3\pm 2,5\%$ case in group 2A and $8,3\pm 4,0\%$ case in group 2B.

Analysis of newborns disease found that increase of newborns disease mainly caused from the intrauterine hypoxia and apnea. It should be also mentioned that, more severe symptoms of intrauterine infections noticed the group of premature diseased children among the proper differences matched with the clinical facts among the main inspected groups.

Assessment of functional parameters. Results from neurosonographic inspections showed that intraventricular haemorrhages, cerebral circulatory disorders, enlargement of the subarachnoid area, ventriculomegalia etc. mostly from cerebral pathologies with the help of echographoc method in newborns having Intrauterine infections. Intracranial hemorrhages is $44,5\pm 4,7\%$ vs $66,7\pm 6,8\%$ in children born on time and prematures having intrauterine infections ($p<0,001$). In children born on time and prematures having intrauterine infections mostly observed 1st level intraventricular haemorrhages (subependymal hemorrhages not spreaded into the brain ventricles) ($38,2\pm 4,6\%$; $50,0\pm 7,2\%$), cerebral circulation disorder ($42,7\pm 4,7\%$; $52,1\pm 7,2\%$, $p<0,05$), dilatation of lateral ventricles ($10,9\pm 3,0\%$; $22,9\pm 6,1\%$) and expansion of the subarachnoid area ($26,4\pm 4,2\%$, $37,5\pm 7,0\%$, $p<0,001$) etc. observed mostly in premature children in the structure of Intracranial hemorrhage.

Echocardiographic inspection has been conducted in all children of the main group that included into our inspections. Inability of the fetus to close the areterial flow, which is very important in the bloodstream, after birth under the influence of various factors, keeps open and causes the heart defect, so, comprised the proper difference by observing $12,5\pm 4,8\%$ in prematures and $11,8\pm 3,1\%$ in the children born on time ($p<0,05$). Congenital heart defect observed as $9,1\pm 2,7\%$ in group 2A and $8,3\pm 4,0\%$ in group 2B ($p<0,05$), $7,0\%$ of these was intraventricular, $7,6\%$ defect of atrium and $1,9\%$ transposition of magistral veins.

The etiological importance in the main group of children showed that, IgG $99,1\pm 0,9\%$ and $100,0\%$ case predominated in children born on time and premature accordingly in this group. In toxoplasmosis high levels of IgG in the serum in group 2B were

recorded at $75.0 \pm 6.3\%$, and in group 2A - $50.9 \pm 4.8\%$, which differed statistically from each other ($\chi^2 = 7, 97; p < 0.01$). Antiviral IgG for herpes virus is $30.9 \pm 4.4\%$ and $29.2 \pm 6.6\%$, respectively, and the high titers of chlamydia class immunoglobulins are almost the same, $6.4 \pm 2.3\%$ and $6.3 \pm 3.5\%$. was found. Specific IgG immunoglobulins against rubella virus were $0.9 \pm 0.9\%$ and $2.1 \pm 2.1\%$, respectively, in the main group.

Serological markers IgM of persistent SMV-infection activation were $39.1 \pm 4.7\%$ and $31.3 \pm 6.7\%$ in 2A and 2B groups, and $19.1 \pm 3.7\%$ and $22.9 \pm 6.1\%$ in toxoplasmosis were found. The frequency of anti-HSV detection of class M immunoglobulins is $10.9 \pm 3.0\%$ in group 2A, $4.2 \pm 2.9\%$ in group 2B, IgM against chlamydia trachomatis was detected in $0.9 \pm 0.9\%$ in group 2A and $2.1 \pm 2.1\%$ in group 2B.

In preterm infants in group 2A using PCR (polymerase chain reaction), one of the most accurate methods of laboratory diagnosis of infectious diseases, the DNA of SMVI is $45.7 \pm 4.7\%$, the DNA of toxoplasmosis is $20.0 \pm 3.8\%$, SHV DNA - was determined in $11.4 \pm 3.0\%$ of cases. In group 2B premature births, SMV DNA was detected in $50.0 \pm 7.2\%$ of half of those examined, and SHV and toxoplasmosis DNA in each case at the same frequency of $12.5 \pm 4.8\%$.

Different pathogens were set by bacteriological method from different locuses in the inspected children during the progress of the research work: Staphylococcus aureus vø Streptococcus B. Staphylococcus infection was found as $19,1 \pm 3,7\%$ in children born on time and $25,0 \pm 6,3\%$ in prematures. Streptococcus infection recorded less- $6,4 \pm 2,3\%$ vø $4,2 \pm 2,9\%$ accordingly, in groups 2A and 2B.

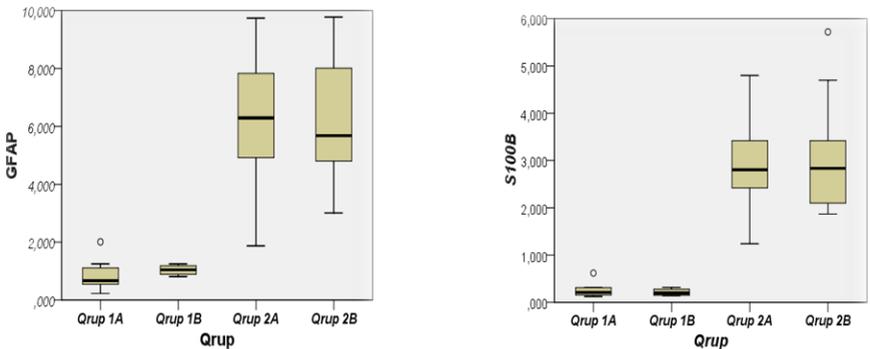
One of the features of the modern etiological structure of intrauterine infections is that they occur in the form of common infections, so in our research mono infection was $30,0 \pm 4,4\%$ (33) in children born on time and $14,6 \pm 5,1\%$ in prematures, (7), and mixt infection was $70,0 \pm 4,4\%$ (77) in children born on time and $85,4 \pm 5,1\%$ (41) in prematures.

Significant change in various parameters of the hemogram in children with intrauterine infection: acute anemia, neutropenia, lymphocytosis, monocytopenia, eosinophilia, accelerated SRE, which indicates the presence of an inflammatory processes in children with a

acute decrease in immunoreactivity. Hypocalcemia, hypomagniemia, hypoproteinemia, hypoalbuminemia were recorded in the newborn children having intrauterine infection. Intrauterine infections are accompanied with the hyperbilirubinemia together with the predominance of direct bilirubin, the reason of this is higher amount of bilirubin in blood in connection with disorder of dynamic balance between its creation and excretion. Excessive activity of the liver enzymes observed during intrauterine infections. It can be conditioned with the increased erythrocyte hemolysis, liver damage, cholestasis, or a combination of these factors.

Levels of interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor (a) (ŞNA-a) were defined with the purpose of evaluating the level of immune response mediators in blood serum of umbilical cord after birth of fetus.

Results of the obtained data show the tendency increase of the level of preinflammatorycytocins (İL-8, ŞNA-a) both in children born on time and premature with perinatal infections. Chane of İL-10 level is of different character. Depending on preinflammatory cytokines, İL-10 amount in children born on time and prematures having SMVİ and mixed infections reduces comparing with the children in supervision group.



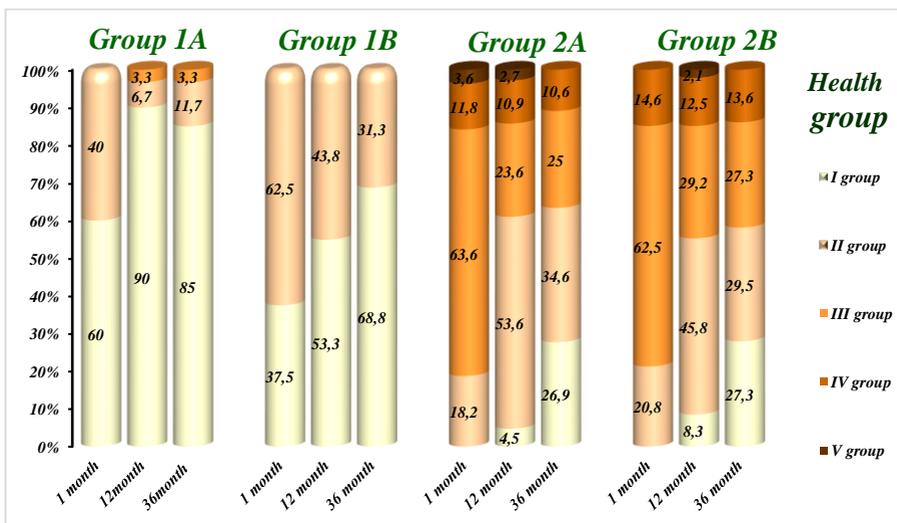
Picture 2. Average structural index of neurospecific proteins according to the gestational age

Immunochemical examination of neurospecific antigens is used to assess the permeability of the hematoencephalic barrier and the neurodegenerative process, so the level of S100B protein and glial fibrillar acid protein (GFAP- glial fibrillary acidic protein) was studied (Fig.2). Statistically significant elevations of S100B and GFAP, which are fractions of brain proteins, were recorded. In the main group of children with IUI, S100B protein increased to 2.9 ± 0.1 and 2.97 ± 0.21 in groups 2A and 2B, respectively, whereas in the control group 1A and 1B this indicator was 0.26 ± 0.06 and was 0.22 ± 0.04 ($p < 0.001$). GFAP levels are significantly higher in neonates in the main group: 6.4 ± 0.3 and 6.23 ± 0.45 in groups 2A and 2B, respectively; in control groups 1A and 1B - 0.86 ± 0.20 and 1.04 ± 0.09 ($p < 0.001$).

Health condition of early age children born with intrauterine infection. A prospective observation of children's health was conducted, during which morbidity rates were analyzed, as well as physical, psychomotor condition, speech and developmental levels were assessed.

Children with IUI have a high incidence of diseases of the nervous system, respiratory system, endocrine system, eating and metabolic disorders during one year old. The prevalence of neurological, respiratory, endocrine, nutritional, and metabolic disorders, congenital malformations, and chromosomal disorders in children with BDI increased significantly from 1 month to 12 months of age compared with the control group.

Learning of disease level of early age children born with intrauterine infection that is generalized in our research shows that, prevalence level of respiratory diseases ($56,3 \pm 4,9\%$ v $62,8 \pm 7,4\%$), blood and hematopoietic organs diseases ($34,0 \pm 4,7\%$ v $30,2 \pm 7,0\%$), infectious diseases ($35,0 \pm 4,7\%$ v $23,3 \pm 6,4\%$), nervous system diseases $24,3 \pm 4,2\%$, $27,9 \pm 6,8\%$ are statistically shown properly in term and preterm children ($p < 0,001$). Cerebral palsy in children is found in $8,2 \pm 2,6\%$ case in group 2A and $10,4 \pm 4,4\%$ case in group 2B (pic.3).



Picture 3. Health groups of children with intrauterine infection according to the gestational age

The high pathological effect of severe forms of IUI on the CNS is confirmed by the diagnosis of cerebral palsy, which was recorded in $8.2 \pm 2.6\%$ in group 2A and $10.4 \pm 4.4\%$ in group 2B. Mortality cases $8.2 \pm 2.2\%$ (13) are observed in our research. It was $7.3 \pm 2.5\%$ (8) in children born on time and $10.4 \pm 4.4\%$ (5) in preterm children.

Thus, it is found while deep analysis of the obtained quantity of information that respiratory pathologies, blood and hematopoietic organs pathologies, infectious and parasitary diseases, diseases of nervous system, endocrine system, digestic disorder, disease of skin and subcutaneous tissue, congenital development abnormalities and psychological development disorders are mostly observed in early ages of the children born with intrauterine infections.

Assesment of children born with intrauterine infection according to the health groups. Complex evaluation of newborns health condition in the first month of life in the main group showed that 4 children - $3.6 \pm 1.8\%$ are included from group 2A who was born on time into the 5th health group (decompensated diseases are included), however, no children is registered for 5th group from the premature children in their first month of lime in the main group. It is obvious that this was because of lethal result of intrauterine infections.

Majority of children in the main groups 2A and 2B included into the third health group – accordingly, $11,8 \pm 3,1\%$ vø $14,6 \pm 5,1\%$.

Children with IUI at 1 month in group II were 2A- $18,2 \pm 3,7\%$ and 2B- $20,8 \pm 5,9\%$, respectively; In group IV-2A was $63,6 \pm 4,6\%$ and 2B was $62,5 \pm 7,0\%$.

The majority of term infants in control group 1A belong to health group I - $60,0 \pm 6,3\%$, and the majority of preterm in group 1B belong to health group II - $62,5 \pm 12,1\%$.

The division of the remaining children having intrauterine infection in their first month of life is as following: the second group is: olaraq 2A- $18,2 \pm 3,7\%$ and 2B- $20,8 \pm 5,9\%$; 2A $63,6 \pm 4,6\%$ and 2B $62,5 \pm 7,0$ in the 4th group. The majority of those born in time in the newborns 1A supervision group are included into the 1st health group - $60,0 \pm 6,3\%$, and the majority of premature children in the group B $62,5 \pm 12,1\%$ are included into the 2nd health group.

The predominance of children born at 1 year of age with IUI was from health groups II and III. Thus, $53,6 \pm 4,8\%$ in the group 2A, - $45,8 \pm 7,2\%$ in the group 2A, - $45,8 \pm 7,2\%$ in the group 2B children were included into the 2nd health group in their 1st age. The following group is the 3rd health group: $23,6 \pm 4,1\%$ and $29,2 \pm 6,6\%$ accordingly, in the groups 2A and 2B. This group includes the children with chronic diseases. The 4th group includes the children with chronic diseases (with frequent complication periods), physical defects, limitation of functional capabilities and complication of the main disease. $10,9 \pm 3,0\%$ children in the group 2A and $12,5 \pm 4,8\%$ children in the group 2B were included in the 4th health group.

The 5th health group is the most serious group. In this group children have severe physical defects, chronic diseases (frequent complications and exacerbations). This group includes the children with limited physical capabilities: 3 children ($2,7 \pm 1,6\%$) in the group 2A and 1 child ($2,1 \pm 2,1\%$) in the group 2B. At last, practical healthy children group includes 5 children ($4,5 \pm 2,0\%$) from group 2A and 4 children ($8,3 \pm 4,0\%$) from group 2B. Thus, health condition of the children in their 1st year of life having severe form of intrauterine infection is characterized with the keeping functional capabilities, occurrence of complications of the main disease, occurrence of

physical defects (by compensating afterwards).

It was found while analyzing the health groups of early age children that majority of the children born with intrauterine infection are included into the 2nd and 1st clinical health groups. So, 34,6±4,7% and 26,9±4,3% children in group 2A are included into the 2nd and 1st health group, 29,5±6,9% v 27,3±6,7% children in the group 2B are included into the 2nd and 1stDHG. Positive dynamics of the improvement of the disease progress and neuro-psychical improvement was observed in the children with intrauterine infection and included into the 5th group before (physical capabilities severely limited in early age) owing to the long-term effective treatment and care, so children in 3 years old were included into the 4th clinical observation group as a result. Health condition of the children born with intrauterine infection differed exactly and significantly from the supervision group: accordingly, $\chi^2=50,7$; $p<0,001$ and $\chi^2=11,7$; $p<0,01$ in the groups 2A and 2B.

Thus, as a result of complex evaluation of the health condition of children it was found in their age 3 period that each 3rd child having severe form of intrauterine infection was behind the physical development, this fact increases up to 27,3% in prematures, this differs the investigated group exactly from the general child population.

Prognosing model of health of the children born with intrauterine infection for early age period. In our study, a prognosis model was developed in order to reduce the risk of complications of intrauterine infections and the formation of chronic pathologies. 19 statistical accurate differed factor among the factors that might impact on prognosis were more deeply analysed in the following stage: numbers of births of mother, congenital heart defects in children, echographic-intracranial haemorrhage, ventriculitis, dialation of lateral ventricles, hydrocephaly; laboratory indeces: GFAP, S100B, β -TNA- α , IL-8, IL-10; infectious and parasitic diseases (A00-B99), congenital abnormalities (Q00-99), diseases of endocrine system and nutrition disorder (E00-99), psychic and behavioural disorders (F00-99), ear and mammary gland diseases (H60-95), and surgical operations.

Though statistically accurate differences ($p<0,050$) were found

in the multiple indeces, some indices of statistical accurate differences in the previous researches were not confirmed in the Kruskal-Wallis test: number of birth ($p=0,634$), haemorrhage ($p=0,716$), ŞNA- α ($p=0,412$), İL-10 ($p=0,332$), ŞNA- α /İL-10 correlation ($p=0,658$) in blood serum, at the same time, E00-90 diseases ($p=0,646$) as for the IDC-10 classification within the disease facts up to 1st year.

In order not to lose "valuable" information in the planned mathematical model, the inaccurate results obtained in the Kruskal-Wallis test were specified with more specific criteria. Thus cross-tables were produced to analyse the quality indices and differences were statistically evaluated with χ^2 -Pearson criteria. It is obvious that, the higher AUC (Area Under the Curve) index is, the higher prognostic strength of model will be. Besides, as statistic accurate result could not be obtained in all KU-Kruskal-Wallis, U-Mann-Whitney and ROC analysis, other indices (ŞNA- α , İL-10, ŞNA α /İL-10) were removed from analysis in the following stage of research. "Cut of point" has been found by using the proven medical methods in the following stage on the basis of the result of ROC analysis.

Researches were continued by keeping 13 indexes removing the indexes which statistical accurate correlation relations defined on the basis of the executed correlation (numbers of births of mother, congenital heart defects in children, echographic-intracranial haemorrhage, dialation of lateral ventricles, hydrocephaly; laboratory indeces: GFAP, S100B, ŞNA- α , İL-8, infectious and parasitic diseases (A00-B99), congenital abnormalities (Q00-99), diseases of endocrine system and nutrition disorder (E00-99), psychic and behavioural disorders (F00-99), ear and mammary gland diseases (H60-95), and surgical operations.

In order to provide a comprehensive assessment of the indicators have studied, we have compiled the following prognostic card using the methods of probability theory based on the data obtained (table 1). ANOVA test has been conducted with the purpose of mathematically expressing the prognostic importance of the researched markers in the following stage, impact strength of each marker in the prognosis was calculated by the ratio of (FTG) Fişer-Snekedor and 95% approximate boundaries were evaluated.

Table 1.

**Prognosing model of early age complications
of the children born with intrauterine infection**

NN	Index	Gradation	PI
1	Number of births	> 1	-20
		1	18
2	Haemorrhage	2 nd –4 th level	-66
		None or 1 st level	7
3	Dilatation	Yes	-88
		No	15
4	Hydrocephaly	Yes	-245
		No	13
5	GFAP	> 5,5	-49
		≤ 5,5	94
6	S100B	> 2,3	-47
		≤ 2,3	261
7	Il-8	> 153	-65
		≤ 153	65
8	A00-B99 disease	Yes	-70
		No	32
9	E00-E90 disease	Yes	-21
		No	13
10	F00-F99 disease	Yes	-121
		No	26
11	H00-H95 disease	Yes	-116
		No	11
12	Q00-Q99 disease	Yes	-131
		No	48
13	Performed surgical operations	Yes	-173
		No	11

By taking into account that factors possess different impact strength, and using these risk factors in the far period dynamic monitoring is one of the important requirements for evaluating the child's condition, early diagnostics of faced complications and choosing adequate treatment tactics. Also, it must be taken into account that objective evaluation of the child's condition requires to take into account the above mentioned all risk factors, especially, factors having great impact power.

CONCLUSIONS

1. Diseases of the blood and blood-forming organs in mothers of children born with intrauterine infection $60.8 \pm 3.9\%$ ($\chi^2 = 26.26$, $P < 0.001$), respiratory diseases $43.7 \pm 1.1\%$ ($\chi^2 = 30.16$, $p < 0.001$) and sexually transmitted diseases $11.4 \pm 2.5\%$, and in the history of complicated obstetrics $10.1 \pm 2.4\%$ of stillbirths ($\chi^2 = 4.68$, $p < 0.05$) and miscarriages $17.7 \pm 3.0\%$ ($\chi^2 = 3.99$, $p < 0.05$) were more common than in the control group. Pregnancy vomiting $67.1 \pm 3.7\%$ ($\chi^2 = 24.35$, $p < 0.001$), preeclampsy $23.4 \pm 3.4\%$ ($\chi^2 = 11.70$, $p < 0.001$), pathologies of amnion liquid $13.3 \pm 2.7\%$ occurred in mothers [14,20].
2. In the neonatal period it was found statistic high level of changes in cerebral status ($98.2 \pm 1.3\%$ and $100,0\%$), haematological and haemorrhagic disorders of newborns ($75.5 \pm 2.5\%$ and $85.4 \pm 5.1\%$), respiratory and cardiovascular disorders ($62.7 \pm 4.6\%$ and $72.9 \pm 6.4\%$) in term and preterm children ($p < 0.001$) [1,9,13,15,16,21,22,36].
3. Elevated levels of pre-inflammatory cytokines (interleukin-8 and tumor necrosis factor- α) and decreased levels of anti-inflammatory cytokines (interleukin-10) were found in children born with intrauterine infection at different gestational ages, which is an informative indicator of early diagnosis. Statistically significant elevations of S100B and GFAP in the blood during polymorphic damage to the CNS are assessed as a criterion for severity [35].
4. Studying the morbidity level of the children up to 1 year born with intrauterine infection shows that accurate high morbidity level is recorded among nervous system diseases ($73.8 \pm 4.2\%$ and $73.3 \pm 6.6\%$), diseases of blood and hematopoietic organs ($41.1 \pm 4.8\%$ and $42.2 \pm 7.4\%$), respiratory diseases ($54.2 \pm 4.8\%$ and $62.2 \pm 7.2\%$), endocrine system diseases, nutrition and metabolystic disorders ($38.3 \pm 4.7\%$ and $37.8 \pm 7.2\%$) in the children born in time and premature children ($p < 0.001$) [8,10].
5. Studying the morbidity level of the early age children born with

intrauterine infection shows that prevalence level of accordingly respiratory diseases $56,3\pm 4,9\%$ and $62,8\pm 7,4\%$), diseases of blood and hematopoietic organs ($34,0\pm 4,7\%$ and $30,2\pm 7,0\%$), infectious diseases ($35,0\pm 4,7\%$ and $23,3\pm 6,4\%$), nervous system diseases $24,3\pm 4,2\%$, $27,9\pm 6,8\%$ in the children born in time and premature children increased in statistic accurate level ($p<0,001$).

6. A prognostic model of evaluation of the health condition of early age children has been prepared on the basis of statistical data from anamnestic, clinical, and laboratory indicators depending on antenatal, neonatal periods of children born with intrauterine infection[34].

PRACTICAL RECOMMENDATIONS

1. It is important to conduct complex examinations to determine the morphofunctional characteristics of the body of children born with severe intrauterine infection. Given the development of chronic pathologies in children born with intrauterine infection, these children should be registered in the dispensary.
2. The use of neurospecific proteins (GFAP, S100B) as an early prognostic criterion in CNS damage is recommended during complex clinical and functional examinations of children born with intrauterine infection.
3. In order to reduce the risk of developing chronic pathologies, the forecasting model developed as a result of personal research is recommended to identify risk groups at an early age and apply them in medical practice for the organization and implementation of preventive measures.

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The defence will be held on "02 June" 2022 at "14" at the meeting of the Dissertation Council ED 2.27 of Supreme Atestation Commission under the President of the Republic at Azerbaijan Medical University

Address: Baku city, Anvar Gasimzada str., 14, AZ1022.

Dissertation is accessible at the library of Azerbaijan Medical University.

Electronic versions of dissertation and its abstract are available on the official website of the Azerbaijan Medical University (amu.edu.az).

Abstract was sent to the required addresses on "29 April" 2022.

Signed to print: _____

Paper format: 60x84/16

Volume: 36.250 characters

Number of copies: 20