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Cytomegaloviral Infection in Children: Intrauterine Infection and the Process of Early Postnatal Adaptation

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Abstract.
Cytomegalovirus infection acquired in utero or during childbirth significantly affects neonatal mortality and, to a large extent, is responsible for early and late childhood morbidity. Of great interest are prospective observations of infected but clinically healthy children at the time of birth. The study of the frequency of infection of mothers (419) and their newborns (220) children with cytomegalovirus, followed by analysis of the process of early postnatal adaptation during intrauterine infection with the pathogen showed a high frequency of infection with pathogens TORCH in women in labor (according to the results of PCR for CMV, HSV types 1, 2, Ch.trachomatis and Ur. urealyticum, respectively, 51.9% and 44.7%, 13.6% and 6.8%) and their children (18.5%, 14.8%, 9.2% and 0.5%). Detection of the CMV genome in blood and urine samples and a high viral load in a blood sample of mothers were significant factors of a high risk of intrauterine infection of children with the pathogen. All children infected intrauterinely with CMV at the time of birth and in the early neonatal period did not have specific manifestations of the infectious process, however, its influence led to the development of asphyxia (OR = 1.2), the birth of premature and immature babies (OR = 2.7), intrauterine malnutrition (OR = 7.3), small developmental anomalies (OR = 4.3).

Keywords:newborn children; cytomegalovirus infection; intrauterine infection; early postnatal adaptation.

Introduction. Cytomegalovirus infection (CMVI) occupies one of the first places in the study of infections of the TORCH complex. Currently, there is an increase in the incidence of CMVI in all countries of the world. This is due to the improvement in the quality of diagnosis and a true increase in the incidence. According to the WHO, the incidence of congenital CMVI among newborns ranges from 0.3% to 3% in different countries. In the United States, 20,000-40,000 children are born annually with congenital CMVI, which is 0.6 - 0.7% [1-7]. In the Russian Federation - 0.2 -5%. 15-30% of them die [8-10].

In our country, the incidence of congenital CMVI in newborns is not recorded.

Transmission of cytomegalovirus (CMV) from mother to fetus is possible throughout pregnancy. Acute primary CMVI in pregnant women poses a particular danger to the fetus: the probability of fetal infection increases to 40% [11-13]. Fetal damage can also occur with a secondary infection: upon reactivation (in 10-30% of cases) of a latent virus, re-infection with a new CMV strain, or in the presence of both factors [5, 14, 15] In this case, the risk of fetal infection is significantly lower (from 0 , 1 to 3%), intrauterine infection usually leads to an asymptomatic course. A state of weak viral reproduction or persistence can continue in a child

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infected with CMV for a long time without pronounced clinical manifestations [16-18].

Congenital CMVI has a rather varied constellation of clinical symptoms from their complete absence to fulminant dysfunction of end organs [17, 18]. Approximately 90% of babies with congenital CMVI are asymptomatic at birth. However, between 0.5% and 15% of these children are at risk of developing psychomotor, auditory, neurological, ocular and dental abnormalities during the first few years of life. In particular, sensory-neural hearing loss is manifested in 5-10% of cases and can affect the ability to learn [19, 20]. At the same time, it is still unclear in what cases in the fetus and newborns the disease becomes severe [21].

One of the features of CMVI in children is the delayed nature of the CNS lesion, a decrease in mental development by 5-6 years of age in 20-30% of intrauterine infected children [22, 23]. This phenomenon is called "latent cytomegalovirus syndrome". 95% of these children belong to the “conditionally healthy” group. In such "healthy" children at birth, in the long-term period, neurological disorders (low IQ, behavioral disorders), poor school performance, defects in vision, hearing, speech, and chronic liver pathology can be detected. Sudden death syndrome in children is associated with asymptomatic forms of infection [24-26].

In 50% of symptomatic children, there is a syndrome of cytomegalic inclusion disease, consisting of jaundice (67%), hepatosplenomegaly (60%), petechial rash (76%), multi-organ damage (microcephaly, motor disorders, chorioretinitis, cerebral calcifications, lethargy, respiratory distress , convulsions). Mortality can range from 20 to 30% in fulminant syndrome and occurs within a few days or weeks [27, 28].

According to some authors, the reliability of the diagnosis of cytomegalovirus infection, in particular, based on clinical data alone, does not exceed 10%. Therefore, the diagnosis of CMVI cannot be established without appropriate laboratory confirmation [29].

Isolation of the virus from culture or organs, or within the first three weeks of life, is necessary to diagnose congenital CMV infection. CMV usually takes two weeks or more to grow on tissue culture. Polymerase chain reaction (PCR) can be used on urine, saliva, cerebrospinal fluid and biopsy samples to confirm the diagnosis. Although serologic tests are inconclusive, umbilical cord serum IgM antibody detection may be confirmatory and should be continued in viral cultures. There are many methods with different sensitivity and specificity for the determination of IgM [8, 10, 19, 20, 27].

A number of researchers note that the diagnostic value of routine serological methods based on the assessment of humoral immunity to CMV (determination of antibodies to CMV of IgM and IgG classes), especially in the period of early neonatal adaptation, is low [14, 19]. The use of special serological methods (immunoblotting, avidity) provides additional information, but only in some cases allows assessing the prognosis of the development of the infectious process [27-29].

The morphological method with the detection of cytomegal cells during histological studies of materials from patients (saliva, urine, breast milk), autopsy materials and biopsies of parenchymal organs allows the diagnosis of CMVI only in 50% of cases, and the absence of cytomegalic inclusions does not exclude the presence of infection [10, 26] ...

Thus, CMVI acquired in utero or during childbirth significantly affects neonatal mortality and is largely responsible for early and late childhood morbidity. Of great interest are prospective

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observations of infected but clinically healthy children at the time of birth. Most of the observed children in the postnatal period are among the frequently ill, have a somatic pathology, an unfavorable allergic background. If we take into account that most of these children have combined disorders (movement disorders, mental impairment, defects of vision, hearing and speech, seizures, etc.), then it becomes clear how dramatic the fate of these children and their parents is, and how great social "burden" for society. In the consensus recommendations of 2017, developed following the results of the 5th International Conference on Congenital CMVI (2015), it was noted that neonatal screening for CMV is necessary for the early detection of active and asymptomatic congenital CMVI [30]. Currently, no country in the world has developed a universal screening of newborn children for CMV, although its value is an increasingly debated issue.

Purpose of the study. To study the frequency of infection of mothers and their newborns with cytomegalovirus, followed by analysis of the process of early postnatal adaptation in intrauterine infection with the pathogen.

Material and research methods. We examined 216 newborns, followed by observation in the early neonatal period (88), born to mothers with chronic latent persistent TORCH infections and aggravated obstetric and gynecological anamnesis for the period 2006-2012. The studies were carried out on the basis of the Republican Specialized Scientific and Practical Medical Center for Obstetrics and Gynecology of the Ministry of Health of the Republic of Uzbekistan, based on a prospective study of 130 cases of delivery of women aged 18 to 42 years, selected by a randomized study.

The selection criterion for women was a burdened obstetric and gynecological history and positive markers for TORCH antibodies (ELISA-IgG). Children born to these mothers were tested for cytomegalovirus (CMV): 130 mother-child pairs were included in the study. The study also included the results of examinations of 86 newborn children who applied to the city medical children's consultative and diagnostic center.

General clinical examination of mothers and newborns was carried out according to standard methods:

- assessment of the characteristics of the somatic, obstetric and gynecological anamnesis of mothers, the course of pregnancy and childbirth, the state of health of mothers (examination, complete blood count, urine, biochemical blood test, ELISA for the detection of specific antibodies of classes M and G for Toxoplasmosisgondii (T), Rubella, Cytomegalovirus, Herpes Simple Virus type 1, 2 (HSV 1, 2types), Chlamydia trachomatis (C) , Ureaplasmosisurealyticum (Ur); genome detection of the above mentioned infections in a venous blood sample; instrumental research methods - ultrasound of internal organs, ECG). The functional state of the fetoplacental system was studied according to the data of fetometry and dopplerometry of the uteroplacental-fetal vessels.

- assessment of the health status of newborns (examination, Apgar scale, anthropometric data, neurological status), the nature of the course of early neonatal adaptation, feeding, vaccination, complete blood count, urine analysis, biochemical blood test. For this, we used maps of pregnant women, birth histories, newborn development histories and our own clinical

observation.

Assessment of gestational age and neuromuscular maturity of newborns was carried out according to J. Bollard et al [31].

The physical development of children was assessed according to the calculated indicators of the ratio of the head circumference to the chest (PS), body weight and length for a given age, as well as according to the indicators of weight - height index (MRI).

Detection of the CMV genome in venous blood and urine of women in labor and mothers (n = 103), as well as in a sample of umbilical cord, venous blood, in the urine of newborns was carried out by the polymerase chain reaction (PCR) method using a test system from Sigma, USA, with primers specific for the CMV virus gene. Test formulation and interpretation of the results obtained were carried out strictly in accordance with the instructions of the manufacturer of the test system. In addition, in 35 women in labor, the CMV genome was quantitatively detected in a venous blood sample by real-time PCR using the AmpliSens® CMV-FL reagent kit using the iQiCycler device (USA) at the Gentox laboratory.

Detection of specific (anti - IgG) antibodies to the pathogen TORCH (Toxoplasma, CMV, HSV 1, 2 types, Ch.trachomatis, Ur.urealyticum) in the blood serum of mothers, newborns and children over a year old was carried out using the test system of JSC "Vector- Best "(Novosibirsk) on the ELISA analyzer" Hospitex Diagnostics "(Italy).

The avidity index (IA) of specific IgG to CMV in the blood serum was determined using the DS-IFA-ANTI-G Avidity test systems (NPO Diagnostic Systems, Nizhny Novgorod) on the LabsystemMultiscan MCC / 340 apparatus (Finland) on the basis of the laboratory of the scientific and diagnostic center "IMMUNOGEN-TEST" at the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Statistical processing of the material was carried out by calculating the mean values (M), their standard error (m), confidence interval (CI), Student's t criteria, while the difference was considered significant at $p < 0.05$. The case-control method was used to assess the frequency of exposure to risk factors by calculating the odds ratio(OR)[32]. The analysis of the relationship of variables was carried out with the calculation of the Spearman correlation coefficient (r) [33].

Research results and discussion.A retrospective analysis of screening ELISA diagnostics for TORCH markers of pathogens based on data from maps of pregnancy management, birth histories (n = 130) and interviews of 419 mothers, revealed the highest percentage of positive results for CMV (n = 353, 84.2 ± 1.9% with CI: 80.3- 88.1) and HSV types 1, 2 (n = 314, 74.9 ± 2.4%, CI: 70.0-79.8), which is consistent with literature data. The vast majority of women (77.3 ± 2.4%, CI: 72.6 - 82.2) were infected with a mixed infection: "CMV + HSV 1, 2types " - 52.3 ± 2.4%, CI: 47.5-57.1; "CMV + HSV 1, 2 types + C" - 6.7 ± 1.2%, CI: 4.3-9.1; "CMV + HSV 1, 2 types + T" - 6.0 ± 1.2%, CI: 3.6-8.4; "CMV + C" - 4.5 ± 1.0%, CI: 2.5-5.5); “CMV + Ur"- 1.9 ± 0.7%, CI <95%. Monoinfection of CMV was noted in 9.8 ± 1.4%, CI - 7.0-12.6 cases; HSV 1, 2 types - 6.7 ± 1.2%, CI - 4.3-9.1. Moreover, only 41 women were seropositive for T.gondii, which amounted to 9.8 ± 1.5%, with CI - 6.8 -12.8. Data are presented in table 1.

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Table 1
Results of examination of mothers by ELISA and PCR methods for the complex of infectious pathogens TORCH - complexResults of examination of mothers by ELISA and PCR methods for the complex of infectious pathogens TORCH - complex

Causative agents	Number of studies					
	In mothers by ELISA (n = 419; IgG)		У матерей (n=103)			
			Blood test by PCR (n = 103)		PCR (n = 103) study urine sediment	
	abs	%	abs	%	abs	%
Positive results: Total monoinfection:	95	22,7	53	51,5	67	65,0*
CMV	41	9,8	24	23,3	29	28,2
HSV 1, 2 types	28	6,7	29	28,2	17	16,5
Toxoplasma gondii (T)	13	3,1	-	-	-	-
Chlamidia trachomatis (C)	10	2,1	-	-	14	13,6
Ureaplasma urealyticum (Ur)	3	0,7	-	-	7	6,8
Mixed infection (total):	324	77,3	11	10,7	23	22,3*
CMV + HSV	219	52,3	2	1,9	3	2,9
CMV + C	19	4,5	4	3,9	9	8,7
CMV + Ur	8	1,9	-	-	-	-
CMV + HSV + C	28	6,7	-	-	-	-
CMV + HSV + Ur	2	0,5	-	-	-	-
CMV + HSV + Rubella	5	1,2	-	-	-	-
CMV + HSV + T	25	6,0	-	-	-	-
CMV + T	3	0,7	-	-	-	-
HSV + T	-	-	2	1,9	-	-
CMV + HSV + C + Ur	3	0,7	-	-	-	-
HSV + C	4	0,95	3	2,9	8	7,8
C + Ur	8	1,9	-	-	3	2,9
Total positive results:	419	100	64	62,1	90	87,4***

Note: reliability of differences * - $p < 0.05$, *** - $p < 0.001$

Detection of the genome of TORCH pathogens in venous blood and in the urine of women in labor (n = 103) by PCR showed the most frequent detection of CMV DNA(deoxyribonucleic acid) in urine (28.2 ± 4.4%) and somewhat less frequently in blood (23.3 ± 4.2%). In total, CMV DNA was detected in both biological media in 51.5 ± 4.9% (n = 53) cases. In 21 (20.4 ± 3.9%) women in labor, CMV DNA was present in the blood and urine. CMV reactivation, like re-infection, can occur at any stage of pregnancy [5-9].

Analysis of the frequency of detection of TORCH pathogens in newborns by PCR in

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umbilical cord samples (n = 134, at the time of birth) and venous blood (n = 86, at the third week of life) is presented in Table 2.

Table2

Results of examination of newborns by PCR method for the complex of infectious pathogens TORCH

Causative agents	Number of PCR studies					
	Blood test (n = 220)		Study urine sediment (n = 209)		Study epithelial mucus of the nasopharynx (n = 78)	
	abs	%	abs	%	abs	%
Positive results: Total monoinfection:	36	16,7	45	15,5	2	2,6***
CMV	19	8,8	21	10,0	-	-
HSV 1, 2 types	17	7,9	15	7,2	-	-
Chlamidia trachomatis (C)	-	-	8	3,8	2	2,6
Ureaplasma urealyticum (Ur)	-	-	1	0,5	-	-
Mixed infection (total):	5	2,3	15	7,2*	3	3,8
CMV + HSV	-	-	3	1,4	-	-
CMV + C	2	0,9	5	2,4	1	1,3
HSV + C	1	0,5	5	2,4	1	1,3
C + Ur	-	-	2	0,9	1	1,3
HSV + T	2	0,9	-	-	-	-
Total positive results:	41	19,0	60	28,7	5	6,4***
Total negative results:	175	81,0	149	71,3	73	93,6

Note: reliability of differences * - p <0.05, ** - p <0.01, *** - p <0.001

A newborn was considered “infected in utero” if pathogen markers were found in at least one of the samples of clinical material obtained no later than four weeks of age.

Among positive PCR results, monoinfection was found significantly more often in 37.5 ± 3.3%, (n = 81) cases compared with mixed infection in various associations, which totaled 7.9 ± 1.8% (n = 17, p <0.001). Markers of CMV and HSV in blood were determined in 8.8 ± 1.9% and 7.9 ± 1.8% of cases, respectively, without a significant difference in indicators in urine sediment (10.0 ± 2.1% and 7.2 ± 1, 8% of cases, respectively). A combination of pathogens was found in only three cases in urine sediment samples. Monoinfection of newborns Ch. trachomatis was confirmed by positive PCR results in urine sediment samples in 8 (3.8 ± 1.3%) cases and simultaneously in one case in a nasopharyngeal mucus sample. Only in one urine sediment sample was the Ur gene verified.

Genomes of 2 pathogens were detected significantly more often in urine sediment (7.2 ± 1.8%) compared to the frequency of their detection in blood samples (2.3 ± 1.0%, p <0.05). In case of combined infection with “CMV + C”CMV DNA was detected in 2 cases in blood, in 3

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cases in blood and urine, in 2 cases only in urine sediment, in one case in nasopharyngeal mucus. Genome Ch. trachomatis was found in 5 cases in urine sediment cells and in one case both in a urine sample and in nasopharyngeal mucus. Similar dynamics of detection of HSV types 1, 2 and Ch. trachomatis was detected in mixed infection with "HSV types 1, 2 + C"in 5 newborns.

Co-infection "C + Ur"was recorded in 2 newborns with positive PCR results in a urine sediment sample (in 2 cases) and simultaneously in a sample of nasopharyngeal mucus (in 1 case) for Ch. trachomatis and Ur. urealyticum. Positive urine PCR results for Ch. trachomatis and Ur. urealyticum indirectly confirm the favorite localization of these pathogens in the urogenital tract.

The results obtained are comparable with the literature indicators of screening for the genome of chlamydia and indicate a high degree of detection of Ch. trachomatis and associated CMVI, HSV types 1, 2 and Ur. urealyticum in the general population of newborns in 20 newborns out of 216, which amounted to 9.3 ± 1.9% of cases.

In 3 cases (1.4 ± 0.8%), perinatal losses were recorded: in two cases (stillbirth) - with detection of the genome of Toxoplasma and HSV types 1, 2 (0.93 ± 0.6%), where it had place the presence of multiple concomitant malformations incompatible with life. In one case, there was a lethal outcome on the 5th day of life with a positive PCR marker for HSV types 1, 2 (0.5 ± 0.4%) and congenital heart disease (pronounced stenosis of the mitral atrioventricular foramen with hypoplasia of the left ventricle of the heart). When examining umbilical cord blood samples from 3 deceased children and biological environments of their mothers, soon after childbirth, 100% coincidence of pathogen genomes was noted: detection of HSV + T.gondii in blood samples from 2 mothers and HSV types 1, 2 in both environments one mother. Apparently, in both cases, HSV types 1 and 2 had a dominant dangerous teratogenic effect, possessing a specific mechanism of action [1, 14-16], but the joint action of microorganisms in a mixed parasitocenosis is not excluded.

The genome of the studied pathogens was not detected in any biological fluid in 117 (54.6 ± 3.4%, CI: 47.8 - 61.4) newborns (control group).

Thus, detection of CMV DNA was positive in 40 (18.5 ± 2.6%, CI: 13.3 -23.7) newborn children (main group), HSV genome 1, 2 types - in 32 (14.8 ± 2.4%, CI: 10.0-19.6), in one case with a fatal outcome and in 20 (9.0 ± 1.9%, CI: 5.2-12.8) a positive PCR result for Ch. trachomatis (as a monoinfect in 8 children - 3.7 ± 1.2%, CI: 1.3-6.1) and an associated infection (in 12 children - 5.5 ± 1.5%, CI: 2 , 5 - 8.5; 10 of them had an equal number of mixed "CMV + Ch. Trachomatis" and "HSV types 1, 2 + C" and only 2 children had a combination of "C+ Ur.") The genome of Toxoplasma was detected in the blood sample of stillborn fetuses in 2 cases. Newborns infected with Ur. urealyticum (in one case) and "CMV + HSV types 1, 2" (in 3 cases) were not included in the groups for further study. A comparative analysis of the results of examination of newborn children and their mothers by the PCR method for the TORCH pathogen complex was carried out (Table 3).

The highest value of the coincidence criterion (χ^2 = 95.1) was established at the level of verification of the genomes of TORCH pathogens in the urine sediment of newborns and their mothers. When the genomes of pathogens were found in the blood, this indicator was χ^2= 58.8.

With mono-infection of newborns, the highest coincidence rate was noted with positive PCR results in blood samples for HSV types 1, 2 –χ^2 = 23.3, versus χ^2 = 7.1 when the genome of

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HSV types 1, 2 was detected in urine sediment. A diametrically opposite picture was observed in newborns with CMV infection: when the CMV genome was detected in the urine sediment, the coincidence criterion was χ^2 = 16.8, versus χ^2 = 12.6 - in the blood. A high coincidence rate was set at the Ch. trachomatis and Ur. urealyticum in urine sediment samples (χ^2 = 10.04 and χ^2 = 10.9, respectively). A similar trend can be traced in the case of mixed infection of newborn babies with “CMV + C"and "HSV + C".

Table3

Comparative analysis of the results of examination of newborn children and their mothers by the PCR method for the TORCH pathogen complex

PCR results	CMV		H		C	U	CMV+C		H+C		C+U	Total	
	1	2	1	2	2	2	1	2	1	2	2	1	2
Mothers in labor (n = 103) abs.	24	29	29	17	14	7	4	9	3	8	3	64	90
Newborns (n = 216) abs.	19	21	17	15	8	1	2	5	1	5	2	41	60
Conformity criteria (χ2)	12,6	16,8	23,3	7,1	10,0	10,9	3,3	6,5	3,4	5,0	1,7	58,8	95,1

Примечание:*1- in blood, 2- in urine sediment, CMV, H - HSV types 1, 2, C - Ch. trachomatis, U- Ur. urealyticu.*

According to the available data, the spectrum of antibodies and their avidity most fully characterize the body's immune response to a viral infection than the routine determination of the presence of antibodies in the blood and allow judging the activity of the infectious process and its duration [1, 2, 3, 29].

The results of determining the avidity index of specific antibodies of class G to CMV are presented in Table 4.

Table4

Results of serological diagnostics of newborns using enzyme immunoassay

Groups of children	IgG antibodies avidity Anti CMV- IgG	
	<0,5	>0,5
Main group (n = 40)	29/ 72,5%	5/ 12,5%
Counter. gr. (n = 75)	2/ 4,1%	47/ 95,9%

The overwhelming majority of children in the main group had low avidity class G antibodies to CMV (72.5%). A similar trend is observed in children of the control group in

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relation to the content of highly avid class G antibodies to CMV in 95.9% of cases.

In the intervals of 3-6 and 12-22 months, repeated PCR studies on the CMV genome were carried out. When re-examined in 5 out of 40 children with primary positive results for CMV, the virus genome was not detected, which explains the presence of highly avid anti-CMV-IgG antibodies in the neonatal period. In 35 children, CMV DNA was re-identified (Table 5).

Table5
Results of detecting CMV markers by PCR in the studied children during the first year of life

Results	Main group (n = 40)		Control group (n = 75)	
	3-6 months	12-22 months	3-6months	12-22 months.
Negative (abs /%)	3/ 7,5	2/ 5,4	49/ 65,3	25/ 33,3
Positive (abs /%)	37/ 92,5	35/ 87,5	26/ 34,7	50/ 66,7

It is important to note that in 11 children, CMV DNA was detected in venous blood, in 15 children - in urine sediment samples. In the group of uninfected children 3-6 months after birth, 26 out of 75 were first detected CMV genomes. It should be emphasized that for a period of 12-22 months, direct markers of CMV reappeared in 24 children and 26 children (54.7%). And only 25 children remained uninfected. It is possible that detection of CMV in some children after 3 months is a delayed manifestation of asymptomatic intrauterine infection, which explains the presence of low-avidity antibodies G to CMV in the control group [18-21]. It is known that low avidity antibodies circulate in the peripheral blood for approximately 20 weeks after the initial infection, then the avidity increases and remains high throughout life [18. 21]. It is also possible that the infection of these newborns occurred already in the neonatal period, in particular when the infants were fed with infected breast milk and / or if the mother and the medical worker did not observe hygiene [16, 23, 27].

Thus, the incidence of infected children with CMV by 22 months was 55.3% of cases, which is 1.7 times more often than during the neonatal period. The study showed that a single study of clinical materials is not enough for the detection of CMV genomes in newborns. In children, by 22 months, in 12.5 ± 5.2% (n = 5) cases, CMV was eliminated, which corresponds to negative ELISA results for specific antibodies of class G to CMV in the neonatal period. Apparently, the elimination of viruses was accompanied by the appearance of their own antiviral-IgG antibodies and an increase in their activity. With the preserved immune reactivity, the virus is gradually inactivated and eliminated, while cell metamorphosis does not occur [28, 29]. In some children (34.7 ± 5.5%), viral genomes were detected only by 3-6 months after birth, and at the age of 12-22 months they were isolated in 32.0 ± 5.4% of children. This means that repeated examination of the child can help differentiate the transient shedding of viruses from the disease and, in time, make a decision on the appointment of adequate treatment [17-22].

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It should be considered that the risk of fetal infection and the possibility of infection in the form of a disease in newborns are due to the type of pathogen, the degree of its virulence and the massiveness of infection. In this connection, the next stage of our work was to study the relationship between the data of intrauterine infection of the fetus and the newborn and the relative amount of DNA in clinical samples of mothers obtained using the real-time PCR method (PCR - real time). Calculated threshold cycle values Ct (threshold cycle) for each sample by determining the point at which the fluorescence exceeded the background value (SD). We compared the results of the study of samples from mothers with positive PCR tests for CMV and HSV of types 1 and 2, respectively, of the 1st (n = 15), 2nd (n = 15) and control group (n = 10) newborns (Table 6)

Table6

Comparative analysis of the results of detecting the relative amount of CMV DNA in blood samples of mothers using PCR - real time

The investigated group	Real time PCR results	SD	p
Mothers of the main group of newborns with CMV (n = 25)	31,47	0,57	p<0,01
Mothers with positive results of PCR for CMV in the control group of newborn children (n = 10)	15,43	3,1	p >0,05

Application:*Threshold values of 19.1 correspond to 20,000 copies of pathogens in 1 ml of blood.*

The revealed significant differences served as additional evidence in favor of the fact of infection. The viral load in blood samples of mothers of the main group is significantly higher (p <0.01) than in samples of mothers of the control group of newborn children. Thus, the existing high viral load of CMV in the blood of mothers was an absolute risk of intrauterine infection.

The early adaptation period in newborn infants infected with CMV in utero was studied according to the state of newborns at the time of birth and in the early neonatal period.

The control group included 50 newborn children without contamination with the investigated TORCH pathogens. The main group was formed by newborn children (n = 38) contaminated with CMV.

General characteristics of newborns at the time of birth and in the early neonatal period are presented in Table 7.

As follows from the data in Table 7, premature babies were only in the main group (10.5%), which is explained by the high frequency of premature birth and placental insufficiency, as well as the complicated course of the gestational period in this group of patients.

Full-term babies born on time (38-40 weeks) were significantly less likely to be born in the main (p <0.01) group compared to the frequency of this indicator in the control group. But there was a tendency to an increase in the proportion of relatively post-term infected children (13.2%) versus 2% in the control.

The general condition of all newborns after birth was satisfactory, except for one newborn in the study group, whose condition was regarded as moderate, developing against the background

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of aspiration syndrome with unilateral cephalohematoma. All examined children were born in the anterior occipital presentation.

When analyzing the state of newborn children after birth according to the Apgar scale, no statistically significant differences were found. However, the likelihood of having children with a low Apgar score (6/7 points) was 2.03 times higher, respectively, in the group of infected children. Intrauterine growth retardation (hypotrophic variant) was significantly more often observed in the main group ($p < 0.05$, OR = 9.2) relative to the control group.

Table 7
General characteristics of newborns in the study groups

Analyzed parameters	Counter. group (n = 50), abs /%	1 - group (n = 38) abs /%
Gestational age, weeks: 35	-	2 / 5,3
36	-	2 / 5,3
37	1 /2	1 / 2,6
38-40	48 / 96	28 / 73,7
41-42	1 /2	5 / 13,2
Asphyxia during labor (I degree)	9 / 18	8 / 21,1
Aspiration syndrome	-	1 / 2,6
Assessment of newborns on the Apgar scale, point: at the 1st min. 8 b.	2 / 4	-
7 points	43 / 86	30 / 78,9
6 points	5 / 10	8 / 21,1
in the 5th minute: 9 points	1 / 2	-
8 points	44 / 88	31 / 81,6
7 points	5 / 10	7 / 18,4
ZVUR (hypotrophic variant)	1 / 2	6 / 15,8*
Birth injury (unilateral cephalohematoma)	-	1 / 2,6
CMD (pyelectasis of both sides according to Doppler data)	-	-
Stigmas of dysembryogenesis (the number of small abnormalities - up to 5-7)	5 / 10	12 / 31,5*
Body weight at birth, g, (M ± m)	3470±260,0	3320±90,0
< 2500	2 / 4	5 / 13,2
>4000	7 / 14	3 / 7,9
Body length at birth, cm, (M ± m)	53,0±0,70	52,0±0,5
< 45,0	-	4 / 10,5
Mass-growth index of Ponderal, g / cm, (M ± m)	67,03±6,60	62,8±7,80
<60	9 / 18	12 / 31,5
60-70	30 / 60	18 / 47,4
>70	11 / 22,0	8 / 21,4

Head circumference, cm, (M ± m)	35,7±0,35	34,3±0,38
Chest circumference, cm, (M ± m)	34,8±0,37	33,7±0,39
PS (head to chest ratio), <1.0	3 / 6	6 / 15,8
Maximum loss of initial body weight,%, (M ± m)	4,92±0,09	5,2±0,10
General symptoms (lethargy, decreased cerebral and motor activity)	4 / 8	7 / 18,4
Microcirculation disorder (acrocyanosis, pastiness, marbling)	3 / 6	8 / 21,1
Transient neurological changes (syndrome of hyperexcitability, depression, muscular dystonia syndrome)	2 / 4	5 / 13,2

Small developmental anomalies were also significantly more frequent in the group of infected children ($p < 0.05$) relative to the control group. The study with the subsequent analysis of anthropometric data at the birth of children of the compared groups did not reveal statistically significant differences. However, the distribution of low (<60), medium (60-70) and high (> 70) values of the Ponderala index showed that children infected in utero are characterized by lower variants of assessments and, as a consequence, a high frequency of registration of intrauterine malnutrition. Thus, the likelihood of the occurrence of low Ponderala index values is 2.1 (OR = 2.1) times higher in the main group than in uninfected children with more frequent registration of high values.

Analysis of indicators of the ratio of the head circumference to chest (PS) in children revealed low PS values (<1.0) in 10.4% (OR = 1.3), versus 6% in uninfected children. The highest probability of the frequency of low PS values was recorded in children infected with CMV in utero, which was OR = 2.94. Probably, insufficient nutrition of the fetus disrupts the processes of myelination, causing permanent loss of brain weight and slowing of the growth of the skull bones. This hypothesis is confirmed by a close, direct correlation between the parameters of the Ponderala index and PS ($r = + 0.561$, $p < 0.001$) in children of the main group.

There is evidence that pathological processes leading to impaired intrauterine brain growth in infants negatively affect the cognitive functions of the child in the future. The deficit in the rate of prenatal head growth, as well as head growth within 12 months after birth, can no longer be compensated for at an older age [22].

All examined children were attached to the breast in the delivery room and were further breastfed. The maximum loss of initial body weight in newborns occurred on average on 3.3 days of life in the main group and on 3.14 days of life in the control group. There were no statistically significant differences between the groups in terms of this indicator, as well as the dynamics of recovery of the initial body weight of newborns. The greatest value of the maximum loss of the initial body weight (7.9%) was noted in a newborn in the main group with cephalohematoma of the left parietal bone.

The course of the early neonatal period was satisfactory in 63 (81.8%) infected infants in utero, versus 46 (92%) uninfected infants. In 14 (18.2%) infected and 4 (8%) uninfected children, signs of maladjustment were observed. The likelihood of developing maladjustment symptoms

was 2.03 times higher in children infected with CMV. Transient physiological changes in neurological status (transient neurological dysfunction of newborns) were identified: transient strabismus, episodic floating eye movements, decreased response to examination, unstable tremor, a slight change in the amplitude of periosteal reflexes, a slight increase or decrease in muscle tone, decreased reflexes of Moro, Galant, stepper and supports. The revealed violations were short-term, and on the 4th-5th day the neurological status was restored. There were no statistically significant differences at the time of discharge from the maternity hospital in the study groups. All children were routinely vaccinated and discharged home.

Conclusions. 1. A high frequency of infection with TORCH pathogens in women in labor was revealed (according to the results of PCR for CMV, HSV types 1, 2, Ch.trachomatis and Ur. Urealyticum, respectively, 51.9% and 44.7%, 13.6% and 6.8 %) and their children (18.5%, 14.8%, 9.2% and 0.5%).

2. Detection of the CMV genome in blood and urine samples and a high viral load in a blood sample of mothers were reliable factors of a high risk of intrauterine infection of children with the pathogen.

3. All children infected intrauterinely with CMV at the time of birth and in the early neonatal period did not have specific manifestations of the infectious process, however, its influence led to the development of asphyxia (OR = 1.2), the birth of premature and immature children (OR = 2.7), intrauterine malnutrition (OR = 7.3), minor developmental anomalies (OR = 4.3). Clinical "silence" of intrauterine infection with the analyzed pathogen is characteristic of the subclinical form of infection.

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