ORIGINAL ARTICLE

The Risk of Intrauterine Infections in Newborns in Aktobe Region of Kazakhstan

Marzya Abdramanovna Mamyrbayeva[1], Galina Dautovna Zhumagaliyeva[2], Natalia Anatolevna Altynnik[3], Aleksey Alekseevich Dmitrashchenko[3]

[1]Department of General Practice, West Kazakhstan Marat Ospanov State Medical University, Aktobe 030019, The Republic of Kazakhstan, [2]Department of Infectious Diseases and Children's Infections, West Kazakhstan Marat Ospanov State Medical University, Aktobe 030019, The Republic of Kazakhstan, [3]Department of Ultrasound and Prenatal Diagnostics, The Institute of Advanced Training of Federal Medical-biological Agency", 91,Volokolamskoe Sh., Moscow 125371, Russia

Abstract

Background: The aim of the study was to assess the risk of intrauterine infections (IUIs) in newborns in Aktobe region of Kazakhstan. **Materials and Methods:** The aggregate data of neonatal mortality in the Republic of Kazakhstan for 2010-2014 years and the rate of neonatal mortality in Aktobe region were analyzed. The retrospective analysis of medical records of 231 mothers was conducted and 938 blood serums probes of infected newborns were analyzed. **Results:** In the obstetric history of mothers, the most important factors were the following: The spontaneous abortion and non-developing pregnancy, with which the appearance of the liver lesions of the newborn. In somatic status of women, the most frequent pathologies during pregnancy were anemia, chronic foci of infection: Chronic gastritis, chronic pyelonephritis in the exacerbation phase, and chronic adnexitis. However, the violations of fat metabolism in the form of obesity – 9.76% ($P = 0.05$) and allergic diseases in the form of hay fever – of 19.52% ($P = 0.05$) were revealed significantly more often in the group of mothers who gave birth to neonates with liver injury. In newborns, the most important factor is the IUI (43.05%) of children. In the neonatal period, 81.6% of infants were diagnosed the central nervous system (CNS) lesion in the form of syndrome of vegetative – visceral dysfunction and the syndrome of depression: A support reflex – 22.2%, a step reflex – 23.6%, the Robinson's reflex – 18.05%, and others. The conducted ultrasound examination of the brain revealed an increased echogenicity in the region of the thalamus of neonates, which had developed in conditions of hypoxia (chronic placental insufficiency and chronic fetal hypoxia) – 23.6% or with acute intrapartum hypoxia, and the expansion of the cavity of transparent partitions is typical for premature babies – 9.72%. **Conclusion:** Aktobe is a region with average neonatal mortality rates due to the late mortality, despite the low rate of early neonatal mortality. From all the diseases that took place during pregnancy, that are affecting the manifestation of IUI, there should be noted acute respiratory viral infections (ARVIs), which were registered in 20% cases. Between the event of ARVI and the development of fetal hepatitis were observed an average correlation ($r = 0.48$). In newborns, the most important factor is the IUI (43.05%) with the CNS lesion of children.

Key words: Intrauterine infection, newborn, neonatal period

INTRODUCTION

Despite the progress of innovative technologies of diagnostics and treatment in medicine worldwide, the problems of perinatal pathology remain extremely challenging and complicated. According to the WHO, 40-60% of children that are dying in the 1st year of life, will die during the 1st month of life, and of the total number of children who are dead during the 1st month of life 70-75% of children die in the early neonatal period. The proportion of stillbirths in the perinatal mortality rate is from 55% to 65%. One-third of perinatal deaths are due to the intrauterine infection (IUI) and its prevalence ranges from 1:3000 to 1:100. 63% of children with IUI are born with no signs of infection, 24% - with questionable signs of infection and

Address for correspondence:
Marzya Abdramanovna Mamyrbayeva, West Kazakhstan Marat Ospanov State Medical University, 68, Maresiev Street, Aktobe 030019, The Republic of Kazakhstan.
E-mail: mamyrbayeva@list.ru

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only 13% - with clinical manifestations.[1] The central place is occupied by IUI. Their frequency ranges from 6% to 53%, achieving 70% among preterm infants.[2] This is due to the fact that the epidemic process at the present stage is characterized by the prevalence of perinatal infection because of the growth of the infection in women of childbearing age due to the widespread herpes viruses, and there are also the possibilities (4-10%) of perinatal infection from mother to infant.[3] Is expanding the etiologic spectrum of congenital infections of TORCH–complex, which is characterized by the veiled and effacement of clinical manifestations, and sometimes with a variety of clinical syndromes.[4] The frequency of detecting of viral infections in children, who died in the early neonatal period and during the 1st year of life, increases to 88-92%.

Clinically, distinct forms of intrauterine cytomegalovirus infection (CMVI) can cause severe pathology, until the death of the child. Are well-known facts that even in the asymptomatic forms of 5-15% of children in the next 1-2 years and at a later date would be registered: The disorders of the central nervous system (CNS) (from 60% to 100%), diseases of the respiratory tract (from 15.4% to 69.2%), liver (15.4%), and other forms of embryo and fetopathy.[5-8]

Among the most important agents of perinatal infections can be mentioned the following bacteria (*Listeria*, Chlamydia, *Treponema*, *Mycobacterium tuberculosis*, *Escherichia coli*, *Streptococci*, *Staphylococci*, *Klebsiella*, *Mycoplasma*), viruses (rubella, CMV, Herpes simplex virus [HSV], enteroviruses, adenovirus of type No. 7 and No. 32, HIV, hepatitis B and C, parvovirus, influenza virus, and measles), fungi (*Candida*), protozoa (toxoplasma, trichomonas, *Plasmodium* and ureaplasma).[9,10]

Asymptomatic and persistent viral infections of the mother are capable for the activation during pregnancy; later, they can get into the placenta and fetus to have a damaging effect. According to the international center European Registration of Congenital Abnormalities and Twins, which unites more than 20 countries of the European economic community, the total frequency of congenital malformations varies from 10.3 to 32.3 per 1000 of live births. Still now are not well studied the risks of manifestation of the latent and persistent infections in the system of "mother-fetus," there are no differential diagnostic criteria for the prediction of IUI in newborns and catamnesis in the further development of the child.[11] The implications of fetal infection for the future are varying in gravity and nosological manifestations, ranging from CNS lesion to schizophrenia. In children without clinical symptoms of IUI in the neonatal period are most likely to develop serious complications up to cerebral palsy, delayed mental and physical development with sensory impairments, i.e., lead to a sharp decline in the quality of a child's life.[12,13] Effacement of clinical manifestations, and sometimes, on the contrary, polymorphism variants, different duration of the disease dictate the need for early diagnosis and timely adequate treatment. From these positions, the aim of the study was to study the risk of IUIs in newborns Aktobe region of Kazakhstan.

MATERIALS AND METHODS

The first stage of research were the samples taken from the aggregate data of deaths of children during the first 28 days from IUIs (P23 – a congenital pneumonia and P35-39 – infections specific to the perinatal period) in the Republic of Kazakhstan (RK) in the country and its regions for 2010-2014 years. Should be noted that the fatal cases were calculated with regard to the place where the death was registered.[14] The main method in the study of neonatal mortality was used a retrospective study using the descriptive and analytical methods of medical statistics and epidemiology. The second phase was conducted a retrospective analysis of the structure of neonatal mortality in the accounting of medical documents of the Aktobe regional Department of Health and the Municipal Children's Hospital for 2008-2013 years.

The third stage of the study was investigated the anamnestic-clinical characteristics of 231 mothers who had given birth to infants with generalized CMVI and with fetal hepatitis with positive CMV antibodies-immunoglobulin G (IgG).

At the fourth stage, the groups of children with hepatitis were analyzed to reveal the risks of developing IUI. The aim of etiological verification of IUIs was examined blood serum of 938 ill children aged from 3 days to 12 months of life who were hospitalized in city and regional children's clinical hospitals in Aktobe 2013. Antibodies IgM and IgG to the antigens of CMV, HSV, toxoplasmosis, and chlamydia were determined by enzyme immunoassay (ELISA). The authors performed a prospective analysis of 403 patients with the diagnosis "infectious viral hepatitis". Infectious viral hepatitis was diagnosed on the basis of anamnestic, clinical data, and results of laboratory tests.

The viral etiology of infectious hepatitis was verified by results of enzyme immunoassay analyzer "BioRad" with reagents from "Vector-best" (Russia), if necessary, in parallel with the determination by polymerase chain reaction (PCR) for DNA of CMV in various biological substrates (blood, urine). Clinical and laboratory indicators of liver damage were assessed by jaundice with coverage areas according to Kramer, the size of the liver and spleen. The content of total bilirubin with fractions, the activity of hepatocellular enzymes was determined with the Cobas 6000 analyzer with using of "C6000 Roche" reagents (Switzerland). The research was conducted in licensed clinical-diagnostic laboratory "OLYMP" (license №30, LP00545DM, series 0007678, was passed the international accreditation ISO 15189:2012, Astana). Statistical processing was performed using standard software package statistics 7.0.

DISCUSSION AND RESULTS

IUIs are the leading causes of stillbirth, spontaneous abortion, preterm birth, neonatal morbidity, and infant mortality. We analyzed an infant mortality. As the material, we used the summarized data of the Ministry of Health and Social Development of the RK about the children who died within the first 28 days because of the IUIs (P23-congenital pneumonia and P35-39 – infections specific to the perinatal period) in the Republic and in regions. By retrospective study with the use of descriptive and analytical methods of medical statistics and epidemiology, it was established that in the Republic for 2010-2014 were 3298 neonatal deaths due to IUIs, among which 1.373 and 1.925 were early and late neonatal deaths. Distribution by regions is presented in Table 1.

The average annual neonatal mortality because of the IUI in the Republic amounted to 1.73 ± 0.23 per 1000 births (95% confidence interval = 1.27-2.19%). The dynamics of neonatal mortality rates decreased from 2.20% (2010) to 1.10% in 2014 [Figure 1]. The alignment of this indicator also has a tendency to decrease (T = −15.3%). In general, the dynamics of neonatal mortality in almost all regions of the country tended to decrease, with the exception of Astana (T = +0.9%), East Kazakhstan (T = +2.3%) and North Kazakhstan (T = +24.5%) regions, where the trends aligned indicators tended to increase.

Cartograms neonatal mortality

One of the leading methods of scientific analysis of the epidemiological situation is the mapping,[15] which allows to conduct an analysis of the spatial distribution of the frequency of neonatal mortality. The cartography was performed on the basis of neonatal mortality rates (NMR) (general, early and late) after the preliminary determination of the average annual indicators in different medical and geographic regions. Then, the average coefficients (M) and the standard deviation (õ) were calculated. By obtained data, the scale of cartogram steps with a grouping of death rates was determined. It should be noted that the data of the Republican organizations were excluded from the calculation. On the cartogram, the neonatal mortality in general was determined the following groups of regions [Figure 2a]:

1. Regions with low rates (up to 1.28%) - South Kazakhstan (0.83%), North Kazakhstan (0.93%), West Kazakhstan (1.20%) and Pavlodar (1.21%) regions and Astana (0.93%);
2. Regions with average rates (from 1.28% to 2.12%) – Almaty (1.28%), Aktobe (1.33%), Karaganda (1.48%), Atyrau (1.50%), Zhambyl (1.53%), Kyzylorda (1.89%), Mangystau (1.96%) and East Kazakhstan (1.96%) region;
3. Regions with high rates (from 2.12% and above) – Kostanay (2.39%), Akmola (2.66%) regions and Almaty (4.18%).

Table 1: Distribution of cases of neonatal death due to the IUI by regions of Kazakhstan for 2010-2014

Area/city	Neonatal mortality, *N* (%)		
	In general	Early	Late
North Kazakhstan	39 (1.2)	21 (1.1)	18 (1.3)
West Kazakhstan	73 (2.2)	52 (2.7)	21 (1.5)
Pavlodar	76 (2.3)	32 (1.7)	44 (3.2)
Astana	97 (2.9)	69 (3.6)	28 (2.0)
Atyrau	117 (3.5)	66 (3.4)	51 (3.7)
Aktobe	122 (3.7)	68 (3.5)	54 (3.9)
Republican Organization	148 (4.5)	61 (3.2)	87 (6.3)
Kostanay	154 (4.7)	62 (3.2)	92 (6.7)
Mangystau	158 (4.8)	92 (4.8)	66 (4.8)
Akmola	161 (4.9)	128 (6.6)	33 (2.4)
Karaganda	181 (5.5)	130 (6.8)	51 (3.7)
Kyzylorda	182 (5.5)	121 (6.3)	61 (4.4)
Zhambyl	207 (6.3)	121 (6.3)	86 (6.3)
East Kazakhstan	223 (6.8)	147 (7.6)	76 (5.5)
Almaty	244 (7.4)	171 (8.9)	73 (5.3)
South Kazakhstan	322 (9.8)	148 (7.7)	174 (12.7)
Almaty	794 (24.1)	436 (22.6)	358 (26.1)
The Republic of Kazakhstan	3298 (100.0)	1925 (100.0)	1373 (100.0)

IUI: Intrauterine infections

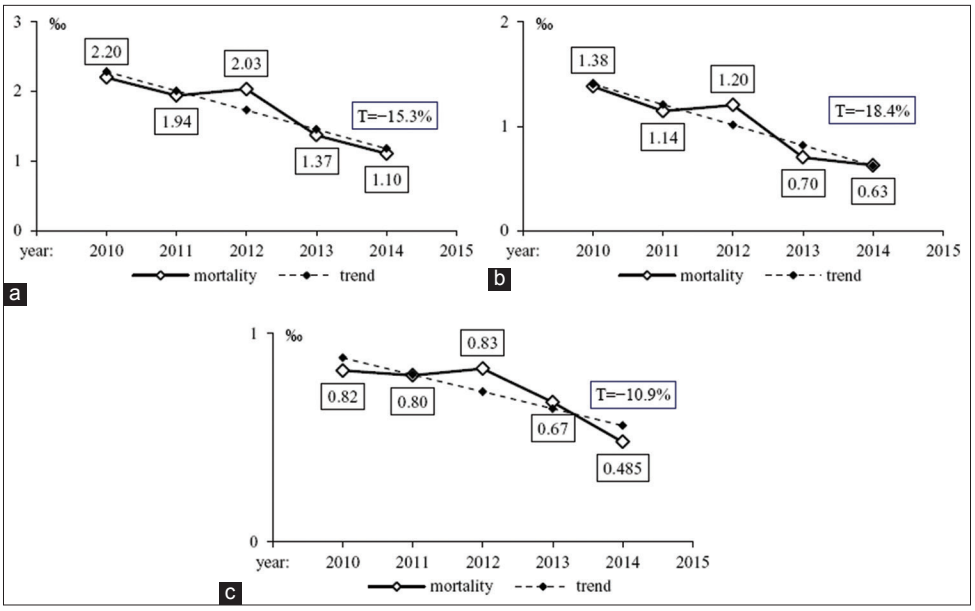

Figure 1: (a-c) Dynamics of indicators of neonatal mortality

Spatial assessment of early neonatal mortality identified regions [Figure 2b].

1. With low rates (up to 0.76%) - South Kazakhstan (0.38%), Pavlodar (0.51%), North Kazakhstan (0.52%) and Aktobe (0.74%) region and Astana (0.66%);
2. With average rates (0.76-1.29%) – Atyrau (0.85%), West Kazakhstan (0.85%), Zhambyl (0.90%), Almaty (0.90%), Kostanay (0.96%), Karaganda (1.07%), Mangystau (1.11%) and Kyzylorda (1.26%) regions;
3. With high levels (from 1.29% and above) – East Kazakhstan (1.29%), Akmola (2.11%) regions and Almaty (2.30%).

On the cartogram, the late neonatal mortality is represented the following regions [Figure 2c]:

1. Regions with low rates (up to 0.47%) – Astana (0.27%), West Kazakhstan (0.34%), Almaty (0.38%), Karaganda (0.42%), North Kazakhstan (0.45%) and South Kazakhstan (0.45%) region;
2. With average rates (from 0.47% to 0.89%) – Akmola (0.55%), Aktobe (0.59%), Kyzylorda (0.64%), Zhambyl (0.64%), Atyrau (0.65%), West Kazakhstan (0.67%), Pavlodar (0.70%) и Mangystau (0.80%) regions;
3. Regions with high rates (from 0.89% and above) – Kostanay (1.43%) and Almaty (1.88%).

Thus, Aktobe oblast is a region with the average neonatal mortality rates (1.33%) due to the late mortality (0.59%), despite the low rate of early neonatal mortality (0.74%). The results of the spatial assessment (map) of neonatal mortality due to the IUI demands the need for focused studies of infection and the incidence of IUIs in newborns, with the aim of reducing them.

According to the statistics Board of Aktobe region, the neonatal mortality in the region tends to decrease as in general

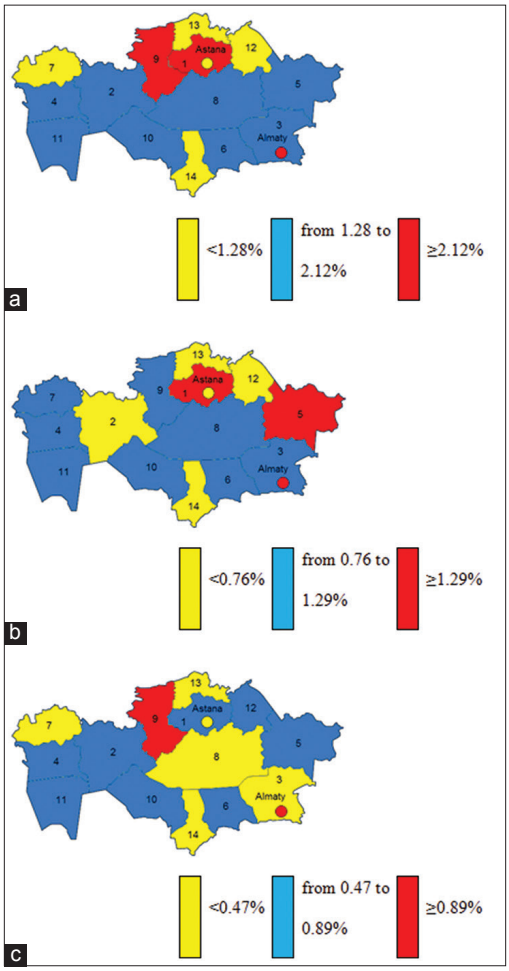

Figure 2: (a-c) Cartogram of neonatal mortality due to the intrauterine infections in Kazakhstan for 2010-2014 years. Regions: 1 - Akmola, 2 - Aktobe, 3 - Almaty, 4 - Atyrau, 5 - East Kazakhstan, 6 - Zhambyl, 7 - West Kazakhstan, 8 - Karaganda, 9 - Kostanai, 10 - Kyzylorda, 11 - Mangistau, 12 - Pavlodar, 13 - North Kazakhstan, 14 - South Kazakhstan

throughout the territory of the RK. Analysis of the structure of newborn deaths (from 0 to 28 days of life) showed that the mortality (per 10,000) due to the IUIs in the first 3 years was higher in comparison with mortality from congenital anomalies [Figure 3]. If in 2011, the neonatal losses due to the congenital anomalies exceeded in 2.5 times the mortality rate of infants with IUI, whereas in 2013, these causes of mortality played an almost equivalent role in neonatal mortality.

We studied causes of mortality in infants in the municipal children's hospital over the past 3 years. Analysis of mortality structure showed the increased ratio of deaths due to the CMVI in the overall mortality: In 2010 - 50%, 2011 - 60%, 2012 - 66.7%, 2013 - 58.7%.

To assess the risk factors of IUI with clinical manifestation of infection in newborns was conducted a study of anamnestic-clinical characteristics of mothers who give birth for children with generalized CMVI and fetal hepatitis with positive CMV antibodies-IgG.

Analysis of obstetric-gynecologic history of 231 women revealed that 101 (43.5%) of the 231 women had comorbidities [Table 2]. The most important factor was a spontaneous miscarriage and non-developing pregnancy (76%). With this conditions, the appearance of the liver lesions of newborn is observed an average correlation, equal to $r = 0.55$. In the study of somatic status of women, it was revealed that most of the women had a chronic pathology of one or more systems. Such pathologies were frequent during pregnancy, like anemia – 19.52%, chronic foci of infection: Chronic gastritis - 2.44%, chronic pyelonephritis in the exacerbation phase - 4.88%, and chronic adnexitis - 2.44%. However, significantly more often in the group of mothers who gave birth to neonates with liver injury were diagnosed the violations of fat metabolism, like obesity - 9.76% ($P = 0.05$) and allergic diseases in the form of hay fever – of 19.52% ($P = 0.05$).

A special role is played by the disease during pregnancy [Table 2]. Among all the diseases that were during the pregnancy that affected the manifestation of IUI, it should be noted an acute respiratory viral infections (ARVIs), registered in 44 (20%) cases.

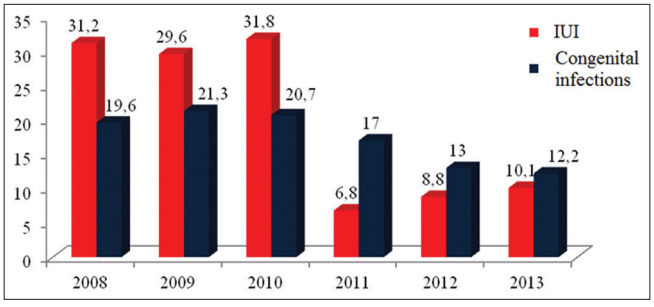

Figure 3: Structure of neonatal mortality of newborns in Aktobe region (rate per 10,000 of newborns)

Between the event of ARVI and the development of fetal hepatitis are observed an average correlation ($r = 0.48$).

It is known that the physiological course of pregnancy contributes to the harmonious morphological and functional development of the fetus, normal childbirth, to the subsequent development of the baby. During the pregnancy, those or other deviations lead to birth with pathological changes. Hence, the percentage of women with pregnancy complicated by threatened abortion and preeclampsia is often mentioned in conjunction with bad obstetric history [Table 2]. In this category of the studied quality parameters, the anemia in pregnant women attracts the attention. Anemia is associated with the revealed average correlation between the occurrence of IUI in children in the neonatal period and within the 1st year of life.

The analysis of the flow of birth found no significant association with qualitative variables. Was only observed a weak correlation ($r = 0.38$) between birth characteristics and prediction of IUI in newborns.

As one would expect, a survey of 253 women during pregnancy with markers of IUI has implications for the prediction of IUI, such as Identification of the mother during pregnancy seroconversion to CMV and the markers of active replication of CMV - anti-CMV IgG of low avidity and anti-CMV IgM.

While good correlation ($r = 0.68$) is recorded in the presence of CMV antibodies in the ELISA results.

Thus, taking into account an obstetric history and the history of the life of the mother, the most important risk factors for IUI are as follows:

- Spontaneous abortion in the obstetric history of the mother;
- A pathological course of pregnancy, including the development of anemia in pregnant women;
- Infectious diseases of any organs and systems of the mother during pregnancy, especially ARVI;
- Diseases of the genitourinary system of the mother;
- Violation of lipid metabolism in obesity;
- Allergic diseases in the form of hay fever;
- Immunocompromised condition, causing the activation of latent infections current and contributes to the appearance of CMV antibodies in the ELISA results.

Therefore, on the basis of the most significant risk factors for IUI indications for newborn screening are:

History:

- A disease of mother with mononucleotide disease during pregnancy;
- Identification in mother during pregnancy of seroconversion to CMV;
- Identification in mother during pregnancy the markers of active replication of CMV;

Table 2: Risk factors of IUIs in newborns

Risk factors for IUI	Frequency (%)	Accumulated frequency (%)	Correlation
History of mother (*N*=231)			
Spontaneous miscarriage	72 (76.00)	24 (50.00	*r*=0.55
Stillbirths	2 (4.17)	26 (54.17	-
Not developing pregnancy	72 (76.00)	24 (50	*r*=0.55
Infection by viruses	11 (9.17)	36 (75.00	-
Infection by bacteria	13 (10.83)	48 (100.00)	-
The diseases in past (*N*=220)			
Diseases of the urinary-excretory system	16 (18.82)	16 (27.59)	-
Diseases of the reproductive system	20 (23.8)	36 (62.07)	-
ARVI	44 (52.38)	54 (93.10)	*r*=0.48
Diseases of the endocrine system	4 (5)	58 (100.00)	-
Course of pregnancy (*N*=204)			
Physiological	68 (33)	68 (41.46)	-
Operative deliveries	3 (4)	51 (97)	-
Pregnancy burdened by pre-eclampsia	8 (4.01)	77 (46.34)	-
Pregnancy burdened by the threat of termination	38 (18.87)	115 (69.51)	-
Anemia in pregnant women	90 (44.12)	165 (100.00)	*r*=0.58

ARVI: Acute respiratory viral infection, IUI: Intrauterine infection

- Burdened the obstetric history maternal (miscarriages, stillbirths, non-developing pregnancy, etc.).

Severe generalized forms of IUIs lead to the development of multiple organ failure and adverse outcomes. Unfortunately, mortality from IUIs in official statistics reflects only among newborns, and almost not logged in infancy (from 1 month to 1 year of life). In our practice, we meet the registration of IUI in 2-3 months of a child's life, and also we faced their long-term complications.[16] Therefore, the official data do not always reflect the accuracy of the statistics. Moreover, congenital infections of TORCH–complex are characterized by veiled and effacement of clinical manifestations, and sometimes they have a variety of clinical syndromes.[17] According to the academic literature, the hepatic injury is typical for 40-63.3% of patients and the gastrointestinal tract injury is noticed for 48% infected children. The respiratory system was diagnosed in 30-40,6% cases. The damage of the cardiovascular system was diagnosed in 27.9% of patients.[6]

According to the protocols of congenital infection, they should be suspected in any newborn, the examination of which revealed the following clinical or instrumental signs: Intrauterine growth retardation (IUGR), low weight at birth, non-immune hydrops of the fetus, visible defects and/or stigmas of dysembryogenesis; skin exanthema at birth, early and/or prolonged jaundice, fever in the first days of life; eye disease (keratoconjunctivitis, cataract, glaucoma), neurologic disorders in the first days of life (especially seizures), hepatosplenomegaly, and changes in the internal organs (interstitial pneumonia, myocarditis, congenital abnormalities of heart, great vessels hepatobiliary system, kidneys and urinary tract, gastrointestinal tract), and malformations of the brain (cysts diffuse and periventricular calcifications).

Identification of two or more of these signs allows determination a newborn as one of the high-risk groups for IUI and requires etiological verification.[18] According to the delayed formation of organic pathology due to the infection in the system of "mother-fetus" in relation to IUIs of herpetic etiology it is difficult to determine the risk factors for the development of the pathological process. On example of CMV disease, there could be considered different clinical manifestations of IUI, depending on the mechanism of infection of the fetus in different gestational ages. Transplacental infection of the fetus could be found in both cases: In primary infection of the mother, and in reactivation of chronic infection. IUI of the fetus by CMV in women with primary infection reaches up to 30%-50%. In secondary infection (reactivation of latent persistent infection) the risk of a fetal infection and a development of severe forms of CMVI are much lower and does not exceed 2%. Protal cytomegalovirus is mostly asymptomatic in infected children. This is due to the fact that in women, who have undergone a primary infection, is formed an anti-CMV immunity, which protects fetuses from the development of severe CMVI. During childbirth, the fetus may aspirate infected amniotic fluid. Furthermore, the penetration of CMV is possible through the damaged skin of the child from the vaginal secretions of the mother. CMVI is one of the most common diseases that can be transmitted as transplacental route. The frequency of fetal CMV infection ranges from 1% to 3%. During and after giving birth are infected another

5-30% of newborns. Infants often become infected by breast milk. CMV excretes out from milk in 30-40% of HIV-positive mothers, and 30-70% of children who drink this milk would be infected.[18]

We examined 112,352 preterm and full-term newborns, who were in the Department of Pathology of newborns of the municipal clinical hospital for children with clinical manifestations of congenital hepatitis. Among all the children of this group, the immunological RH factor conflict and ABO system conflict were excluded. According to gender, the examined children were allocated as follows: Boys – 68.5%, girls - 31.5%; full-term babies amounted to 75.8%, premature - 24.2%. Age of children of the main group at the time of admission to the hospital was - 15.3 ± 0.37 days. Vaccination for hepatitis B was conducted in 100% of cases. Analysis of case histories of newborns was carried out according to the following criteria: Health status of the mother during pregnancy and childbirth, the child's condition at birth according to Apgar score, time of the first initiation of breastfeeding, time of the appearance of jaundice, its duration. A full examination of the newborn was conducted according to the protocol of the clinical trial. Treatment was complex. Children were discharged from the hospital with clinical and laboratory improvement. Further, follow-up study was conducted on an outpatient basis, ranging from 1.5 to 2 months and later during the year. Analysis of the physical characteristics of the newborn found a decrease in body weight and growth of patients with congenital CMVI, compared with conjugational newborn (neonatal) jaundice [Table 3].

The child's condition at birth and during the neonatal period is an important component in the formation of the subsequent health of the child. To this end, we compared the condition of infants with CMV hepatitis as infants, the neonatal period which was uneventful [Table 4].

Most of the children in the main group with CMV hepatitis were born from the first, from the second, or from the third pregnancies, with Apgar score of 7-8 points in 87.85%, and of 5-6 points in 12.15% of children.

The findings suggest that children with deviations in the health condition were observed already in the intra- and neonatal periods. Most often in children were manifested IUI (43.05%). In 81.6% of them were diagnosed CNS lesions in the form of syndrome of vegetative – visceral dysfunction and the syndrome of oppression. Neurological impairment was evident in a decreased support reflex – 22.2%, a step reflex – 23.6% Robinson's reflex – of 18.05%, and others. A conducted ultrasound examination of the brain revealed increased echogenicity in the region of the thalamus of neonates, which developed under conditions of hypoxia (chronic placental insufficiency, chronic fetal hypoxia) – the 23.6% or with acute intrapartum hypoxia, and expansion of the cavity is transparent partitions and typical for premature babies in 9.72%.

The lack of specific clinical signs, clear criteria for the laboratory diagnosis and features of immune response in children of the 1st year of life impede the recognition of the time of infection and of the chronicity of congenital infections. Analysis of the etiological structure of congenital infectious hepatitis in 978 infants and young children showed that a congenital hepatitis was caused as a mono-infection only by herpesviruses: CMV in 466 (47.6%) and HSV – in 7 (0.7%) newborns.

The hepatitis was observed mostly as coinfection, caused by association of two pathogens in 41.8% (CMV + HSV, CMV + chlamydia, CMV + mycoplasma, CMV + TOXO (Toxoplasma gondii), CMV + listeria); caused by association of three pathogenes in 9.1% (CMV + HSV + chlamydia, CMV + HSV + TOXO, CMV + TOXO + chlamydia, CMV + chlamydia + listeria, CMV + chlamydia + mycoplasma) and in 8 cases out of 4 micro-organisms [Figure 4].

As a comparison group were 240 infants with neonatal jaundice with hyperbilirubinemia due to indirect fractions with no evidence of cholestasis and cytolysis in the biochemical analysis of blood. Neonatal jaundice due to infection is characterized by hyperbilirubinemia of different degrees due to its indirect faction without cholestasis and cytolysis. Different violations of fetal development in newborns were identified. Among these, violations are the IUH first-degree hypotrophy (IUH) (18.6%), low body weight at birth (LBWB) (10.5%), a very low body mass at birth (VLBW) (1.4%), and the intrauterine growth retardation (IUGR) (6.9%) [Figure 5].

Determination of body mass index (BMI) according to WHO guidelines in contrast to the traditional calculation of BMI,

Table 3: Physical characteristics of newborns with congenital CMV hepatitis

Indicators	Neonatal jaundice		CMVI	
	Premature *N*=104	Mature *N*=136	Premature *N*=112	Mature *N*=352
Gestational age	35.06±0.39	38.90±0.11	34.54±0.43	39.01±0.06
Weight	2485.0±109.4	3335.0±63.03	2342.0±100.1	3338.0±46.19
Growth	48.35±0.59	53.0±0.36	46.253±0.82	53.01±0.22
BMI	10.52±0.28	11.74±0.18	10.75±0.24	11.76±0.132

BMI: Body mass index, CMVI: Cytomegalovirus infection

Table 4: Pathological condition in newborns in the early neonatal period

Diseases	The absolute number (%)	
	The comparison group *N*=240	The main group *N*=464
Asphyxia	10 (4.55)	54 (11.6)
IUGR	14 (5.8)	149 (32.1)
Respiratory distress syndrome	15 (6.25)	14 (3.0)
IUI	10 (4.55)	464 (100)*
Pneumonia	-	12 (2.5)
Intraventricular hemorrhage	10 (4.55)	37 (79.7)*
Pathology of the central nervous system	77 (32.0)	378 (81.6)*
Prematurity	104 (43.3)	112 (24.1)

*P<0.05. IUGR: Intrauterine growth retardation, IUI: Intrauterine infection

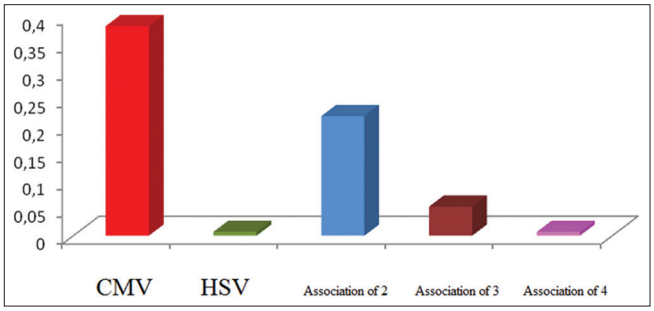

Figure 4: Distribution of newborns with congenital hepatitis

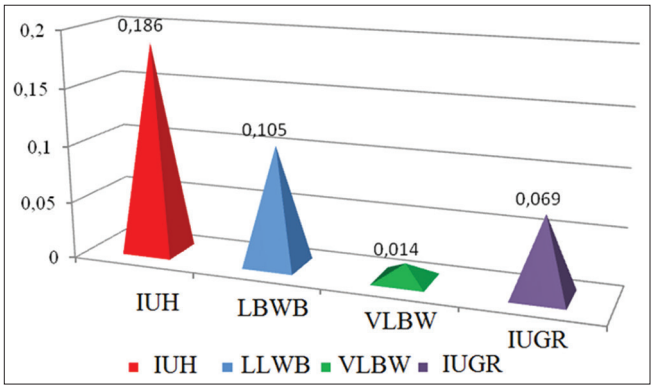

Figure 5: Violations of fetal development in newborns

when calculated a ratio of body weight of the newborn in kilograms by the square of body length in meters, revealed a decrease of this index below the norm in 100% of cases and is 11.77 ± 2.08.

The analysis of health status in the neonatal period revealed that the risk factors for the development of fetal hepatitis with hyperbilirubinemia in neonates are IUIs, mostly with perinatal CNS lesions of various origins.

Clinical:

- Respiratory distress syndrome, asphyxia;
- CNS - Focal neurological symptoms, convulsions, syndrome of depression, microcephaly, hydrocephalus;
- Neurosonographic findings - Cysts, calcifications;
- Jaundice, hepatosplenomegaly, direct hyperbilirubinemia, elevation of transaminases;
- Hemorrhagic syndrome, thrombocytopenia, anemia with reticulocytosis;
- Prematurity, IUGR.

It is known that in the system of "mother-fetus" there is a transplacental intake of not only nutrients for the fetal development but also of different infectious agents in the presence of chronic foci of infection in pregnant women.[19,20] Chronic foci of infection in pregnant women do not always lead to the development of pathological processes and depends on the state of the immune system of the woman. Immunosuppression that occurs during the pregnancy reduces the protective compensatory mechanisms of the body and favors the development of bacterial and viral infections. At the antenatal stage of the development, it is very important in which gestational period the infection occurs and the nature of infection.[16,21] The condition of full-term, premature and underweight newborns depends on the gestational age, frequency and extent of fetal infection. The highest rate of fetal infection is noted in premature and low birth weight infants.

CONCLUSION

The analysis of the spatial distribution of the rate of mortality by the method of mapping revealed regions of Kazakhstan with low, medium and high rates of neonatal, early and late neonatal mortality. Aktobe oblast is a region with the average neonatal mortality rates (1.33%) due to the late mortality (0.59%), despite the low rate of early neonatal mortality (0.74%). The infant mortality rate in the region tends to decrease, as in general throughout the territory of the RK. In Aktobe region, the mortality rate of infants (per 10,000) due to the IUIs in the first 3 years was higher (31.2; 29.6; 31.8) in comparison with mortality due to the congenital anomalies (19.6; 21.3; 20.7). In 2011, neonatal losses from congenital anomalies exceeded in 2.5 times the mortality rate of infants with IUI, whereas in 2013, these causes of mortality played an almost equivalent role in the neonatal mortality rate (10.1 and 12.2 per 10,000 newborns). In the obstetric history of a mother, the most important factors were the spontaneous miscarriage and non-developing pregnancy (76%), with which the appearance of the liver lesions of the newborn is observed an average correlation equal to $r = 0.55$. In somatic status of women, the frequent pathologies during pregnancy were anemia – 19.52%, chronic foci of infection: Chronic gastritis - 2.44%, chronic pyelonephritis in the exacerbation phase - 4.88%, and chronic adnexitis - 2.44%. However, significantly more often in the group of mothers

who gave birth to neonates with liver injury, were identified the violations of fat metabolism, like an obesity - 9.76% ($P = 0.05$) and allergic diseases, like a hay fever – of 19.52% ($P = 0.05$). Among all the diseases during pregnancy that affected the manifestation of IUI, it should be mentioned an acute respiratory viral infection, registered in 44 (20%) cases. Between the event of ARVI and the development of fetal hepatitis are observed an average correlation ($r = 0.48$). The analysis of the birth records did not find any significant association with the qualitative variables. Is only observed a weak correlation ($r = 0.38$) between birth characteristics and a prognosis of IUI in newborns.

As one would expect, a survey of 253 women during a pregnancy for the markers of IUI has implications for the prediction of IUI, such as the identification in mothers during a pregnancy of a seroconversion to CMV and the markers of active replication of CMV-the anti-CMV-IgG of low avidity and anti-CMV-IgM. While the good correlation ($r = 0.68$) is recorded in the presence of CMV antibodies in the ELISA results.

In newborns, the deviations of health status were observed already in the intra- and neonatal periods. Most often manifested the IUI (43.05%) of children. In 81.6% were diagnosed the CNS lesions in the form of syndrome of vegetative – visceral dysfunction and the syndrome of oppression. The neurological impairment was evident in a decreased support reflex – 22.2%, in a step reflex – 23.6%, and in a Robinson's reflex – 18.05% and others. The conducted ultrasound examination of the brain revealed an increased echogenicity in the region of the thalamus of neonates, which developed in conditions of hypoxia (chronic placental insufficiency, chronic fetal hypoxia) – 23.6% or with acute intrapartum hypoxia, and the expansion of the cavity of transparent partitions is typical for premature babies - 9.72%.

Thus, the leading risk factors for the mother are the burdened obstetric history in the form of miscarriages and non-developing pregnancies on the background of a somatic pathology; and for the newborn are: A prematurity, IUGR with involving of a CNS, respiratory and digestive systems.

Considering IUI as a relevant problem, because it causes the perinatal mortality, economic costs of etiotropic and pathogenetic therapies, possible disability in the further development of the child. A full examination of a woman with a questionnaire (complete history) is necessary at the stage of pregnancy planning. If the IUI development risk factors are identified, preliminary sanitation and women's immune system reinforcement are required. At birth of the newborn with risk factors for the manifestation of IUI a monitoring in the form of a dispensary with the purpose of their rehabilitation and prevention of complications should be organized.

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