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Registration certificate SMI PI № FS 77 – 69379 from 6<sup>th</sup> of April 2017, issued by the Federal Service for Supervision of Communications, Information Technology, and Mass Media

Russian version ISSN 2541-8475

English version ISSN 2542-1336

### **Founder and publisher**

Federal State Budgetary Educational Institution of Higher Education “Altai State Medical University” of the Ministry of Health of the Russian Federation (FSBEI HE ASMU of the Ministry of Health of the Russian Federation), 656038, RF, Altai Krai, Barnaul, Lenina Prospect, 40

www.asmu.ru

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**Print.** LLC “AZBUKA”. RF, Altai Krai, Barnaul, Merzlikina Street, 10.

Format: 60x90 1/8. Conventional printed sheets – 9. Circulation – 500 copies. Open price.

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UDC 613.86:612.821-053.2(571.15)

## HYGIENIC ASPECTS OF INFLUENCE OF SUMMER HOLIDAYS IN THE TERRITORY OF THE ALTAI BIOSPHERE RESERVE ON THE PSYCHOPHYSIOLOGICAL STATE OF CHILDREN AND TEENAGERS

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*There was assessed the psychophysiological status of children during the stay in the Reserve and the emotional state before and after book reading sessions in conditions of different natural landscapes. The psychoemotional state of children, according to the results of testing, showed the most favorable level of the studied indicators after staying in the Reserve, which indicates the significant health-saving potential of such organization of children's recreation. Changes in the emotional state of children under the influence of reading sessions confirm the sensitivity of the valuation method used, and also show the potential opportunities for a favorable change in the emotional status of children through familiarizing them with reading books.*

**Key words:** psychophysiological status, health-saving potential, book reading.

One of the most important focus areas of children's hygienists is the overall assessment of various factors of external environment from the point of view of their influence on the child's health. From these points essential is not only the research of the educational process organization, its evaluation and expertise, but also extra-curricular activities, in particular, holiday organization.

The analysis of the health status of children and teenagers in Russia indicates, that at the present time there holds the trend to the growth of the incidence rate, spread of chronic pathology, reduction of the number of healthy children in all age-sex groups. Since the major part of child-teenage population of Russia are the children visiting school, it is obvious that a series of negative factors directly affect the situation. It is the expressed intensification of the educational process (the increase of the learning material amount by the deficiency of time for its digestion) numerous innovational reforms at schools not taking into account the peculiarities of perception and processing of information by pupils of different age-sex groups, inconsistency of sanitary and hygienic conditions of children's stay at the educational institution with the standards, irrational organization of nutrition, lack of physical activity, incompetence of the teaching staff in the issues of health protection, low-quality medical service.

Unfortunately, the same factors can potentially make the same negative influence on the children's health during the holidays. This issue requires our focused attention and hygienic assessment.

**The objective** of the current research work was the assessment of the psychophysiological status of children during the stay in the Reserve, and also the determination of peculiarities of the emotional

state before and after book reading sessions in conditions of different natural landscapes.

To reach the stated goal there were necessary to solve the following **tasks**:

1. To evaluate the initial level of children's neurotization.
2. To reveal and assess the character of changes of the psychophysiological status of children in the beginning and in the end of the period (shift) of stay in the Reserve.
3. To determine and evaluate the peculiarities of the emotional state of children before and after book reading sessions in conditions of different natural landscapes, and also to check the sensitivity of the used method.

### Materials and methods

Testing of the neurotization level by means of a special questionnaire, monitoring of the psychoemotional state in dynamics by means of WAM (wellbeing, activity, mood) checklist, study of the emotional state in dynamics by means of "color-writing" according to Lutoshkin.

### Results and discussion

At the first stage, we evaluated the initial level of neurotization among the children of the shift. It was stated, that the main neurotizing factor for children is the school. Even during the period of summer holidays children experience anxiety about school problems (57%), feeling of shyness (50%), are afraid of making mistakes (74%), have difficulties with concentration (50%) and decision-making (70%). Besides, the majority of children complain about tiredness and apathy during the day (60%), and also sleep disorders (53%). At the same time, half of the respondents evaluate their level of health as average and below the average (53%).

At the second stage there was registered the psychoemotional state of children in dynamics (in the beginning and in the end of the shift) using the WAM checklist. Thus, initially the indexes of "wellbeing" and "mood" in the majority of children (82% and 85% respectively) were in the most favorable scale range. However, high level of the "activity" index was registered only in 41% of respondents. By the end of the shift, practically all indexes reached their maximum values, which totally indicates the expressed positive influence of the organized rest in the reserve on the psychoemotional state of children. The index of activity increased most significantly – from 41% to 74%. It turned out, that the positive reaction of boys to the influence of the complex of natural and social factors (organized rest in the territory of the Reserve) was more intensive than in the girls.

Third stage of study – determination and evaluation of the peculiarities of the emotional state of children before and after book reading sessions (reading aloud) in conditions of various natural landscapes.

According to the questionnaire, more than a half of the children prefer computer games instead of reading real books in the free time. In order to develop the interest of the younger generation to reading one of the forms of prevention of high computer activity and addiction included "real" reading (reading aloud). The assessment of emotional reactions to such activity was performed by means of "Color-writing" test (according to Lutoshkin). Such method allows to reveal the participants with comfortable emotional state (CES), balanced emotional state (BES) and discomfort emotional state (DES) at the moment of examination.

Totally, there were organized six different areas for such reading activities. Depending on the character of emotional reactions, these areas can be nominally divided into two groups. The first group included area 1 (among the friends), area 2 (with the view on Lake Teletskoye), area 3 (besides the fire), and also the area "Chachilgan Mull". The current study revealed a significant increase of children undergoing CES (for example, areas 1

and 3 – from 5 to 10 persons, Chachilgan Mull – from 2 to 10 persons) due to the obvious decrease of children with DES (for example, Chachilgan Mull – from 8 to 3 persons). The second group included the areas "Cave of pokemons" and "Vas'kina Mountain". The "Cave of pokemons" did not show any changes in the emotional state. In the area "Vas'kina Mountain" the number of children with CES did not change, however, the number of participants with emotional discomfort reduced, apparently, due to the joining of children with balanced emotional status to the group, which can also be considered a positive result.

### Conclusion

Consequently, the participants of the pilot project were the children with average health level exposed to the considerable neurotizing influence of school. The testing of the psychoemotional state showed the most favorable level of studied parameters (wellbeing, activity, mood) in the end of stay in the Reserve, which indicates a considerable health-preserving potential of such children's holiday organization. The changes of indexes of the emotional state of children under the influence of reading sessions prove the sensitivity of the used method of evaluation, and also show the existing potential abilities of the favorable change of the emotional status of children by means of involving them into reading process. Moreover, the influence of various landscapes on the emotional state of participants is obvious.

For more deep study of the issue, it is planned to continue the research in the current direction implementing more specialized psychophysical methods.

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UDC 613.15:616.831-005.1

## THE ROLE OF AIR POLLUTING SUBSTANCES IN THE DEVELOPMENT OF STROKE IN THE CONDITIONS OF THE LARGE INDUSTRIAL CITY

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*The results of examination of 538 patients with stroke are presented in the article - 280 men (52.0%), 258 women (48.0%); and the structure of seasonal incidence of stroke is studied. At the same time, there was assessed the influence of atmospheric environmental factors on the level of the given morbidity in the conditions of the industrial city of Western Siberia. According to the results of the study, the incidence of stroke is the leader in spring (during the period of high atmospheric pollution). A strong direct correlation was found between the number of stroke disease patients and the concentration of nitrogen dioxide and suspended solids in the air in certain months of a year.*

**Key words:** stroke, seasonality, nitrogen dioxide.

Stroke still presents an important medical and social problem both in the world and in Russia, which is conditioned by high indexes of morbidity, lethality and invalidization. According to the statistical analysis [4], about 0,5 million people in Russia suffer from stroke every year with the morbidity rate 3 per 1000 people. Mortality rate due to stroke holds the stable second position in the stricter of total population mortality trailing only the cardiac pathology [4].

It is considered, that the contribution of the external environment (ecological factors) to the deterioration of health and main forms of pathology in Russia ranges within 40-60%. One of the environmental factors mostly influencing the state of health of the majority of the Russian Federation population is the quality of air.

The climate of Novosibirsk and its surroundings is continental. A distinctive feature of the city climate is a great number of inversions, which considerably reduce the ability of the atmosphere to dissipate contaminating substances.

**Research objective:** to evaluate the influence of atmospheric ecological factors on the level of stroke morbidity in the conditions of the industrial city of Western Siberia.

### Materials and methods

There were analyzed hospital medical histories, medical certificates of death, forensic medical reports, ambulance calls, out-patient medical records including all new and recurrent stroke cases (in-patient and out-patient), lethal and not lethal, having been developing in the permanent residents of one of Novosibirsk districts during 3 years. The age of patients constituted from 25 to 74 years. All studies were performed according to the protocol including a standard questionnaire "Register of stroke and its risk factors".

The study considered daily average concentrations of contaminating substances during the year in the air of the studied district according to the data of the Department of social-hygienic monitoring of the city center of Rosbotrebnadzor (suspended materials, carbon oxide, sulphur dioxide, carbon, nitrogen dioxide, formaldehyde, ammonia, benzopyrene). The monitoring of the city atmosphere air is performed by the Novosibirsk Center of Hydrometeorology and Monitoring of Environment with Functions of Regional Specialized Meteorological Center of World Service of Weather at 10 fixed monitoring stations. The studied district contains two fixed stations.

### Results and discussion

There were examined 538 patients with stroke: 280 men (52,0%), 258 women (48,0%). According to the WHO classification, the patients were divided into age groups: young age (from 25 to 44) – 24 people (4,2%), middle age (from 45 to 59) – 185 people (34,8%), elderly age (from 60 to 74) – 329 people (61%).

The study of the seasonal structure of stroke revealed the following frequency: winter period – 115 people (21,4%), spring period – 161 people (29,9%), summer period – 120 people (22,3%), autumn period – 142 people (26,4%).

The peculiar feature of the ecological situation is the concentration of the industrial potential of the region in the city. The highest level of contamination is registered in the studied district on a number of parameters (basic contaminating substances and specific ingredients) being detrimental to the cardio-vascular and nervous systems. Novosibirsk is characterized by increased concentrations of suspended materials during the warm period of the year when the air is dominated by natural substances (soil dust) in combination with suspended substances of industrial origin.

The excess of maximum permissible concentration (MPC) of carbon oxide is registered at the “auto stations”. The level of air contamination is mainly formed as a result of emissions of low uniform sources (mainly automobile transport), thus, there are observed comparatively gradual changes of nitrogen dioxide concentration month-over-month. During the cold period due to the load of the heating system, monthly concentrations of nitrogen dioxide are a bit higher. The increased concentration of formaldehyde is observed during the warm period of the year, which is connected, with the rise of daily temperature and photochemical transformations. The growth of carbon content in the air is usually observed during the cold half of the year, which is conditioned by increased emissions of boiler and electric stations.

To evaluate the influence of the air contamination level on the rate of morbidity there was determined the correlation coefficient. There were stated positive correlations for two contaminating substances.

A strong direct correlation is observed ( $r=0,72$ ) between the number of stroke patients and the level of nitrogen dioxide concentration during particular months of the year (Figure 1). The changes of both parameters are parallel: increase during winter till May, decrease in July, the peak of increase in August and September.

The exiting correlation can be explained by the proved influence of nitrogen dioxide on the state of brain blood circulation due to the appearance of hypoxic effect and changes of blood rheological properties, which, in its turn, leads to thrombi formation.

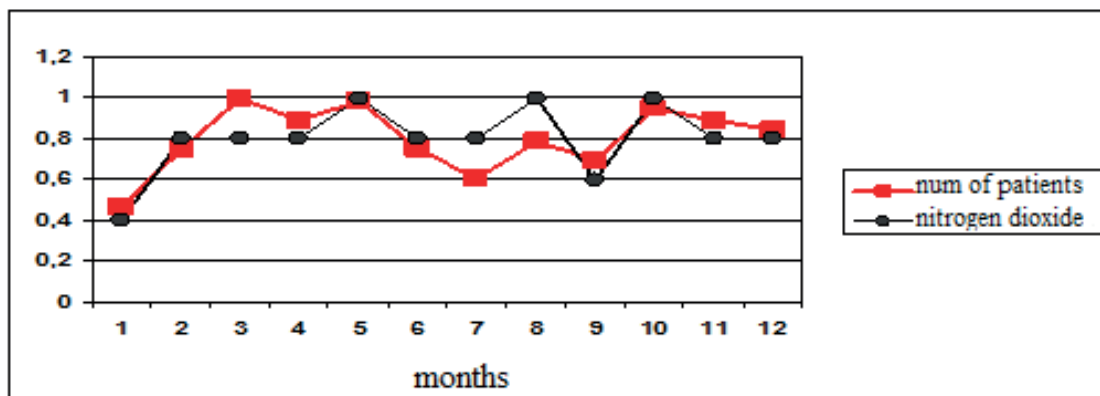


Figure 1. Correlation of relative number of patients and relative concentration of nitrogen dioxide

The average direct correlation ( $r=0,31$ ) is revealed between the number of stroke patients and the level of suspended materials concentration (Figure 2). The parallel changes of pa-

rameters are observed during the first months of the year (gradual growth from January till May) and during the autumn period (reduction of both parameters).

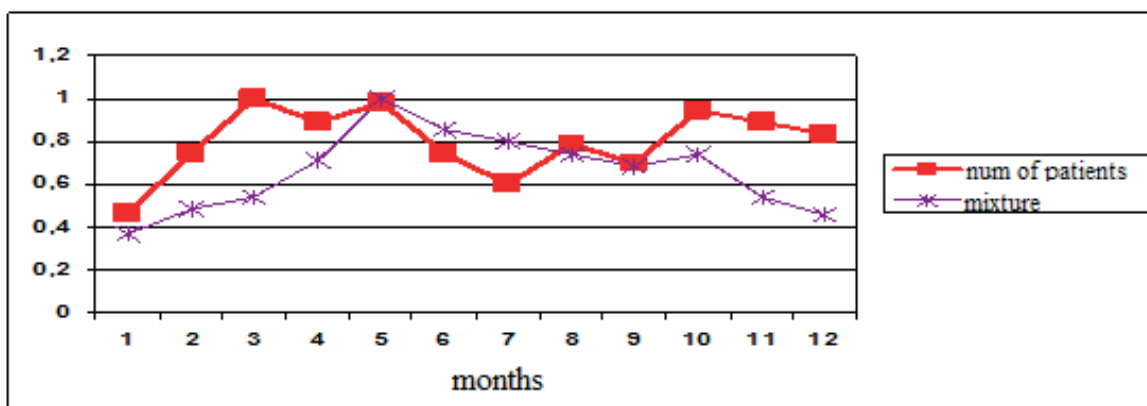


Figure 2. Correlation of relative number of patients and relative concentration of suspended materials

It is known, that suspended materials stimulate the development of phagocytosis leading to peroxide stress, which causes membrane pathological effect, and specifically in cardiomyocytes. Moreover, there is proved the correlation

of the development of cardio-vascular pathology (arterial hypertension and ischemic heart disease) in persons with long-term exposure to dust –  $r=0,71$  (Vavilova V.A., 2005). Arterial hyperten-

sion and ischemic heart disease are the risk factors of stroke development.

To evaluate the effect of the air contamination level on the disease outcome there were calculated the average number of lethal cases every month and further their relative values. The average cor-

relation ( $r=0,48$ ) was determined between the number of dead patients and the level of nitrogen dioxide concentration (Figure 3). Figure 3 shows that the changes of these parameters and the overall number of stroke patients are parallel.

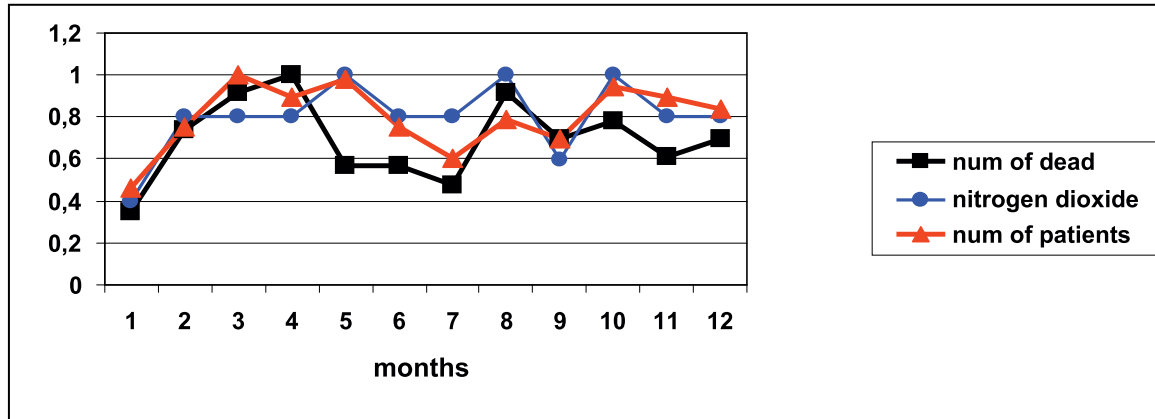


Figure 3.  
Correlation of average number of stroke patients, dead patients and relative concentration of nitrogen dioxide

For the other contaminating substances (benzopyrene, sulphur dioxide, carbon, ammonia, formaldehyde and carbon oxide) there was revealed a slight and negative correlation with the level of stroke morbidity and lethality.

The obtained data on the correlation of stroke morbidity level and air contamination can be explained both by the direct influence of chemical substances on neurons, nerve fibers and synaptic connections, and by the effect on the cardio-vascular system (blood rheological properties, vascular endothelium, change of peripheral circulation, heart rhythm disorder). Furthermore, it should be taken into consideration, that in the zone of industrial discharge can appear patients with chronic diseases (arterial hypertension, ischemic heart disease, atherosclerosis, diabetes mellitus), the course of which is worsened. In some cases, the chemical substances themselves can lead to the development of pathology.

The stated correlations between the number of stroke patients and the level of contaminating substance concentration in the air of Novosibirsk corresponds to the results of standardized epidemiological research conducted in terms of the international program MONICA which revealed an expressed dependence of the growth of cardio-vascular disease cases on the increase of CO, SO<sub>2</sub> and dust particle concentration in the air.

### Conclusion

The seasonal structure of stroke morbidity in the conditions of the large industrial city of Western Siberia is prevailed by the spring period. During the period of increased atmosphere con-

tamination, there is revealed the growth of stroke morbidity level. The obtained data are the background for making organizational and management solutions: improvement of environment monitoring during the period of maximum pollution, reduction of concentration of such substances as nitrogen dioxide, suspended materials.

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UDC 614.777:612.462.1-053.2-055.1

## THE ANALYSIS OF KIDNEY FUNCTION IN BOYS OF 10-11 YEARS IN THE CONDITIONS OF CONSUMING DRINKING WATER WITH HIGH CATION CONCENTRATION

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*The article presents the results of study of kidney function of 10-11 years old students in conditions of consumption of drinking water with an increased content of sodium, calcium and magnesium. Analysis of the water and ion-releasing function of this contingent indicates adaptive changes in the renal response, depending on the ionic composition of drinking water, which reflects the ability of the body and mechanisms of regulation of the homeostatic functions of kidneys to adaptive reconstructions. However, prolonged intervention into the system can probably cause its stress and lead to the development of renal pathology.*

**Key words:** cations, diuresis, kidney pathology.

One of the global problems of the present time is providing the population with qualitative drinking water the content and amount of which influence the state of human health. According to the sanitary and hygienic researches performed in the FBHI "Center of hygiene and epidemiology of the Novosibirsk Oblast" of Rospotrebnadzor, by 2016 in the territory of the Novosibirsk Oblast, Vengerovsky and Kyshtovsky districts are presented as unfavorable in terms of mineralization and hardness of drinking water (Table 1).

The imbalance of chemical elements in the objects of the external environment contributes to the dis-

orders of the chemical composition of organisms and deviations in their functioning [1].

To study electrolytic homeostasis and ion-regulating kidney function under the influence of particular environmental conditions experimental researches successfully implement various salt-water exercise stress tests the diagnostic effectiveness and informative value of which is now generally acknowledged [2].

**The research objective** was to study the kidney function in the pupils of 10-11 years of age in the conditions of consuming drinking water with high concentration of sodium, calcium and magnesium.

Table 1

Quality indicators of drinking water in the settlements of the Novosibirsk Oblast by 2016 (mg/dm<sup>3</sup>)

№ p/p	Indicators	Settlements		
		Verkh-Irmen	Vengerovo	Kyshtovka
1	Sodium	61,17±6,12	224,6±22,5*	57,60±5,80
2	Potassium	≤0,50	≤0,50	≤0,50
3	Calcium	65,93±4,35	80,76±5,29*	107,82±6,99*
4	Magnesium	37,54	55,08	40,74
5	Ferrum	0,12±0,30	1,65±0,29*	3,70±0,60
6	Mineralization	493,00±59,20	1114,00±111,40	663,00±66,30
7	Total hardness	6,38±0,96	8,56±1,28	8,73±1,31

Note: \* - significant differences by  $p \leq 0,05$  between concentrations of ions in the villages Verkh-Irmen and Vengerovo/Kyshtovka.

### Materials and methods

In order to study the reaction of kidneys to the loads in the conditions of drinking water with high hardness conditioned by the content of calcium and magnesium and also with high concentration of sodium in the water of Vengerovo village, there was performed the examination of children for the evaluation of peculiarities of kidney functions and spare capacities of the system of wa-

ter-electrolytic balance regulation. The level of basic ions and salts in the drinking water of Verkh-Irmen village stays within the range of maximum allowable concentration (MAC) (Table 1) which allows to determine the obtained data as control.

The study included healthy boys at the age of 10-11 (19 persons in Verkh-Irmen, 25 and 11 persons in Vengerovo and Kyshtovka respectively) with normal parameters of physical development.



The water exercise testing was performed in the morning, in the fasted state, after 10-12 hours of water deprivation (night hours). After the baseline urine sampling within the period of one hour, the examined persons drank 10ml/kg water in minimal time which did not cause any uncomfortable conditions. During two hours after the water load every hour there was collected urine to determine the concentration of basic electrolytes and osmotically active substances.

The concentration of Na<sup>+</sup> and K<sup>+</sup> electrolytes in the urine was determined by means of flame photometry (BWB-XP FlamePhotometer, Great

Britain); the concentration of Ca<sup>2+</sup>, Mg<sup>2+</sup> ions – by means of the biochemical analysis (analyzer “BS-200E”, China). The statistical analysis of the results was conducted by means of variation statistics using the parametric t-Student test, and also standard MicrosoftOffice programs; the differences were considered significant by p≤0,05.

### Results and discussion

Table 2 shows the basic indexes of the diuretic kidney function in the conditions of relative rest in the morning in the fasted state (baseline) and after 1% water load.

Table 2

*The change of indicators of kidney function in the conditions of relative rest in the morning in the fasted state after 1% water load in children at the age of 10-11 in villages Verkh-Irmen (n=19), Vengerovo (n=25) and Kyshtovka (n=11).*

Indicators		Verkh-Irmen	Vengerovo	Kyshtovka
V, ml/min*m <sup>2</sup>	Фон	0,59±0,03	1,43±0,15 <sup>▲</sup>	0,47±0,12 <sup>•</sup>
	1 час	1,47±0,09*	2,28±0,16* <sup>▲</sup>	1,82±0,33*
	2 час	1,67±0,13*	2,00±0,22*	2,99±0,46*
GRF, ml/min*m <sup>2</sup>	Фон	52,09±2,76	113,38±15,39 <sup>▲</sup>	41,55±7,00 <sup>•</sup>
	1 час	43,53±1,91*	32,21±1,97* <sup>▲</sup>	27,44±4,08* <sup>▲</sup>
	2 час	36,02±1,62*	40,41±2,25*	62,64±9,64* <sup>▲•</sup>
%RH <sub>2</sub> O,%	Фон	98,82±0,17	98,61±0,15	98,95±0,12
	1 час	96,57±0,61*	92,39±0,65* <sup>▲</sup>	92,45±1,12* <sup>▲•</sup>
	2 час	95,16±0,39	95,14±0,43*	95,10±0,55*
% water load excretion		65,62±2,54	79,00±6,00 <sup>▲</sup>	93,50±13,68 <sup>▲•</sup>

Note: here and in the following tables significant differences by p≤0,05. \* – significant differences between 1, 2 hours in relation to baseline urine samples; ▲ – the significance of indicators between Verkh-Irmen and Vengerovo/Kyshtovka; • – the significance of indicators between Vengerovo and Kyshtovka.

According to the obtained data, the average indicator of the baseline diuresis in children of Vengerovo village exceeds the same parameter in Verkh-Irmen and Kyshtovka nearly two times, consequently, the background level of glomerular filtration rate in the stated group of examined by the same level of liquid reabsorption is exceeded twice. Apparently, it can be conditioned by the high concentration of sodium in drinking water.

In the examined children of the mentioned regions after 1% water load there was observed high output renal reaction. The exceeded reactivity of renal response in children living in the regions with high concentration of cations in drinking water appeared due to the deeper retardation of liquid reabsorption. High reactivity of renal response is also determined by the percent of liquid excretion during 2 hours, which was significantly higher than the control value both in the villages of Vengerovo and Kyshtovka. In consequence, in one and two hours after the water intake there was registered a significant increase of diuresis in comparison with the control group. Moreover, during one hour after the load there was observed a considerable reduction of liquid reabsorption in relation to the control and baseline values, but by the sec-

ond hour the level of reabsorption became nearly equal in all groups.

To evaluate the state of the electrolyte metabolism there was conducted the analysis of the ion urine content. Table 3 presents the basic indicators of the ion-uretic kidney function in the children of examined regions.

The background excretion of ions of calcium, magnesium, uric acid and urea in Kyshtovka nearly corresponded to the control data and did not have significant differences by slightly decreased 'excretion of sodium and potassium. However, in Vengerovo the baseline level of excretion for all cations several times exceeded the indicators of the examined persons both in Verkh-Irmen and Kyshtovka.

In the background of 1% water load in Vengerovo in relation to other regions there was registered a more expressed growth of sodium, calcium and urea excretion which can indicate the exceeded reactivity of osmoregulatory mechanisms. It should be also noted, that in the mentioned group even by the overall decrease of ionouresis after water load, the level of sodium, calcium and urea excretion was significantly higher in relation to the same values in Verkh-Irmen. The excretion of basic ions by the second hour after water load reduced like in the examined persons of Verkh-Irmen. The chil-

dren of Kyshtovka showed a two-stage reaction, namely the reduction of ion and urea excretion level during the first hour, as well as in the control group, and rapid increase during the second hour. Apparently, the content of drinking water

in these regions sensibilized the mechanisms of regulation of ion-osmotichomeostasis, which lead to the growth of the excretion of basic cations in relation to the control group.

Table 3

*Iono-uretic kidney function in children of 10-11 years of the villages Verkh-Irmen (n=19), Vengerovo (n=25) and Kyshtovka (n=11) in the conditions of relative rest in the morning in the fasted state after 1% water load (M±m)*

Indicators		Verkh-Irmen	Vengerovo	Kyshtovka
UNa V, mkM/min*m <sup>2</sup>	ФОН	98,67±6,28	242,80±32,92 <sup>▲</sup>	37,98±4,57 <sup>▲•</sup>
	1 час	50,15±6,56*	62,37±7,44*	49,91±11,94
	2 час	40,78±4,67*	63,58±9,51* <sup>▲</sup>	95,61±16,84* <sup>▲</sup>
UK V, mkmol/min*m <sup>2</sup>	ФОН	45,94±2,42	90,59±13,03 <sup>▲</sup>	34,26±6,20 <sup>▲•</sup>
	1 час	47,16±4,48	35,83±3,39*	24,21±4,94 <sup>▲•</sup>
	2 час	38,80±3,47	41,80±4,02*	73,58±16,80* <sup>▲•</sup>
UCaV, mkM/min*m <sup>2</sup>	ФОН	0,50±0,03	3,69±0,53 <sup>▲</sup>	0,48±0,12 <sup>•</sup>
	1 час	0,26±0,03*	0,62±0,15* <sup>▲</sup>	0,32±0,20
	2 час	0,13±0,04*	0,50±0,15* <sup>▲</sup>	0,55±0,24 <sup>▲</sup>
UMgV, mkmol/min*m <sup>2</sup>	ФОН	1,26±0,08	2,77±0,32 <sup>▲</sup>	1,09±0,26 <sup>•</sup>
	1 час	0,83±0,04*	0,68±0,09*	0,71±0,13
	2 час	0,66±0,08*	0,98±0,17* <sup>▲</sup>	1,85±0,54 <sup>▲</sup>
UUa V, mkmol/min*m <sup>2</sup>	ФОН	1020,2±44,9	3081,4±392,0 <sup>▲</sup>	939,6±254,6 <sup>•</sup>
	1 час	1272,8±56,8*	1173,7±76,9*	1074,0±149,5
	2 час	982,4±71,3	1401,1±157,0* <sup>▲</sup>	2380,9±376,0* <sup>▲•</sup>
UureaV, mkM/min*m <sup>2</sup>	ФОН	90,3±4,4	1210,2±157,3 <sup>▲</sup>	86,1±18,0 <sup>•</sup>
	1 час	112,7±6,1*	394,1±51,1* <sup>▲</sup>	91,3±17,8 <sup>•</sup>
	2 час	92,1±7,5	135,4±11,7* <sup>▲</sup>	161,7±18,2* <sup>▲•</sup>
EF Na, %	ФОН	1,46±0,10	1,56±0,16	0,81±0,16 <sup>▲•</sup>
	1 час	0,83±0,09*	1,42±0,17 <sup>▲</sup>	0,42±0,19 <sup>▲•</sup>
	2 час	0,81±0,07*	1,07±0,13*	0,38±0,15 <sup>▲•</sup>
EF K, %	ФОН	23,88±1,40	19,59±2,45	21,66±2,85
	1 час	26,36±2,55	27,46±2,30*	22,57±3,88
	2 час	26,25±2,31	25,30±2,20*	26,75±4,23
EFCa, %	ФОН	0,37±0,03	1,47±0,25 <sup>▲</sup>	1,03±0,19 <sup>▲</sup>
	1 час	0,19±0,03*	0,84±0,23* <sup>▲</sup>	1,18±0,18 <sup>▲</sup>
	2 час	0,16±0,06*	0,51±0,16* <sup>▲</sup>	1,17±0,23 <sup>▲•</sup>
EFMg, %	ФОН	2,63±0,11	2,85±0,22	2,70±0,33
	1 час	1,96±0,10*	2,48±0,35	3,11±0,58 <sup>▲</sup>
	2 час	2,07±0,28*	2,60±0,38	2,96±0,60
EFUrea, %	ФОН	39,51±1,19	241,97±12,17 <sup>▲</sup>	44,76±2,57 <sup>•</sup>
	1 час	56,56±2,31*	263,00±29,12 <sup>▲</sup>	71,85±5,27* <sup>▲•</sup>
	2 час	56,57±4,34*	73,30±3,64* <sup>▲</sup>	62,26±4,81* <sup>•</sup>

Due to lower reabsorption the background level of the excreted calcium and urea fraction in the villages of Vengerovo and Kyshtovka is higher than the control values which can be conditioned by the elevated calcium level in drinking

water. The excreted sodium fraction in the examined children in Kyshtovka is also exceeding the control values by a significant level of its reduction in Kyshtovka.

After 1% water load the examined children of Vengerovo and Kyshtovka retained the lowered level of reabsorption of calcium, magnesium and urea ions in comparison with the data of Verkh-Irmen, which was indicated by the increase of the excreted fraction amount, while in Vengerovo – also by a significant increase of the excreted sodium fraction. The excreted potassium fraction after the water load did not differ significantly from the control values.

### Conclusion

Thus, the analysis of the water and ion-releasing kidney function in children living in the districts with various concentration of sodium, calcium and magnesium in drinking water indicates the adaptive changes of kidney reaction depending on the ion content of drinking water, which reflects the possibility of the organism and mechanisms of homeostatic kidney function regulation to adaptive changes. However, long-term influence on the system can, apparently, cause its tension and lead to the development of kidney pathology [3].

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UDC 614.446:616.24-002(571.15)

## CURRENT EPIDEMIOLOGICAL SITUATION OF COMMUNITY-ACQUIRED PNEUMONIA IN ALTAI KRAI

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*The aim of the study is to assess the current epidemiological situation of community-acquired pneumonia in child and adult population in Altai Krai in 2011-2015. Conducting a retrospective analysis of the incidence of community-acquired pneumonia (CAP) we found out that this disease is a significant problem for Altai Krai because since 2014 the incidence rate of CAP in Altai Krai (AK) was higher than the incidence rate of CAP in Russia. The incidence rate of CAP in children was higher than in teenagers and in adults both in AK and in the Russian Federation. According to the results of laboratory tests, we noticed the percentage increase of pneumococcal CAP.*

**Key words:** community-acquired pneumonia, pneumococcal infection, retrospective analysis.

Community-acquired pneumonia (CAP) is a common disease and a common cause of death in people of any age all over the world [1, 2]. The types of CAP causative agents vary depending on age, and respiratory viral infections more often take place in infants [2, 3]. Pneumococcus is one of the main bacterial causative agents of CAP in all age groups after neonatal period and it is often associated with complications [4, 5]. Wide occurrence of this bacterium is explained by a large number of its serotypes [6, 7]. Today there are more than 93 known pneumococcus serotypes which are characterized with long-term carriage and the development of severe forms of diseases [8]. Among all these serotypes, about 20 of them cause more than 80% of pneumococcal diseases all over the world. This problem is important today in the Russian Federation (RF) because among all children under five years old admitted to hospital with pneumonia 47% of them had *S. pneumoniae* in their nasopharyngeal swabs [9]. In risk groups, the incidence rate of diseases caused by this microorganism is 5-100 times higher than the incidence rate in the population at large. These groups consist of children under 5 years old (especially under 2 years old), people over 65 years old and patients with some chronic diseases regardless of their age [8]. This infection is not well enough studied in Altai Krai (AK) but respiratory diseases occupy a dominant position in the incidence structure in child population.

**Research objective:** the aim of this study is to assess the current epidemiological situation of community-acquired pneumonia in child and adult population in Altai Krai in 2011-2015.

### Materials and methods

The subject of the study is represented by main mechanisms of the development of the epidemic process of community-acquired pneumonia in Altai Krai. There was conducted a retrospective analysis of the incidence rate of community-acquired pneumonia. The total number of reported cases of this dis-

ease was 38663 cases during 2011-2015. In the course of our study, we conducted a retrospective analysis of the dynamics of the long-term incidence of CAP in AK and the RF. There was performed the statistical analysis of the study materials. For statistical analysis, there was used STATISTICA 10.0 and MS Excel 2010. Mean sample values for quantitative variables are specified as  $M \pm m$  ( $M$  – a sample mean and  $m$  – a standard error of the mean). A paired  $t$  test was employed for the assessment of statistical significance ( $p$ ). The level of significance for all statistical criteria was 0.05.

### Results and discussion

For the period from 2011 to 2015 the trend has been toward the increase of the incidence rate of community-acquired pneumonia in the Russian Federation and Altai Krai (Figure 1). In 2015 the incidence rate in the RF was  $337.8 \pm 0.5$  per 100,000 population being 1.1 times higher ( $p=0.0001$ ) than in 2011 ( $316.0 \pm 0.5$  per 100,000 population). The highest incidence rate was noticed in 2013 and it was  $389.9 \pm 0.5$  per 100,000 population.

In 2015 the incidence rate in Altai Krai was  $452.2 \pm 4.4$  per 100,000 population being 3.8 times higher ( $p=0.0001$ ) than in 2011 ( $118.6 \pm 2.2$  per 100,000 population). The highest incidence rate was noticed in 2014 and it was  $604.0 \pm 5.0$  per 100,000 population. Starting from 2014 the growth of the incidence rate of community-acquired pneumonia was registered in Altai Krai in comparison with the Russian Federation. It is worth mentioning that in 2014 the vaccination against pneumococcal infection was included into the National Calendar of Prophylactic Immunization. That is why we can assume that the dominance of CAP in the incidence structure in AK is associated with vaccination shortage in comparison with the RF.

However, the mean long-term incidence rate of community-acquired pneumonia in the RF over the past period was  $348.5 \pm 0.5$  per 100,000 population being 1.1 times higher than in Altai Krai ( $323.0 \pm 3.7$  per 100,000 population,  $p=0.001$ ).

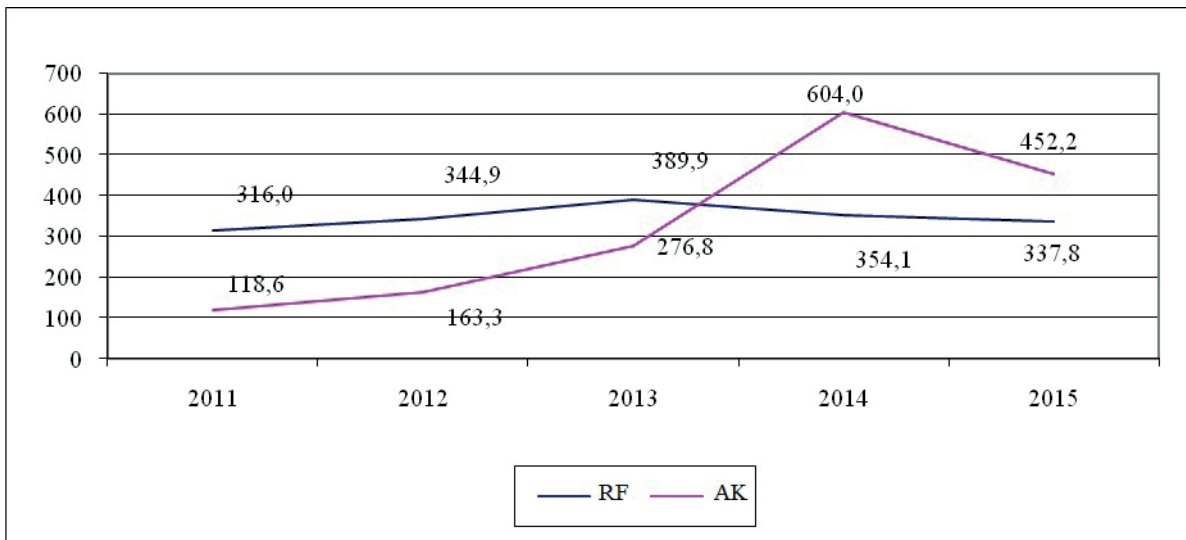


Figure 1. The dynamics of the incidence rate of community-acquired pneumonia in the Russian Federation and Altai Krai during 2011-2015 (per 100,000 population)

During the studied period the mean incidence rate of CAP in the RF in the child group (0-14 years old, child incidence rate) was  $687.3 \pm 1.7$  per 100,000 children being 2.5 times higher than mean teenager incidence rate (15-17 years old) ( $271.7 \pm 2.6$  per 100,000

teenagers,  $p=0.00001$ ) and 2.4 times higher the incidence rate in the adult group (18 and over 18 years old) ( $283.2 \pm 0.5$  per 100,000 adults,  $p=0.00001$ , Figure 2).

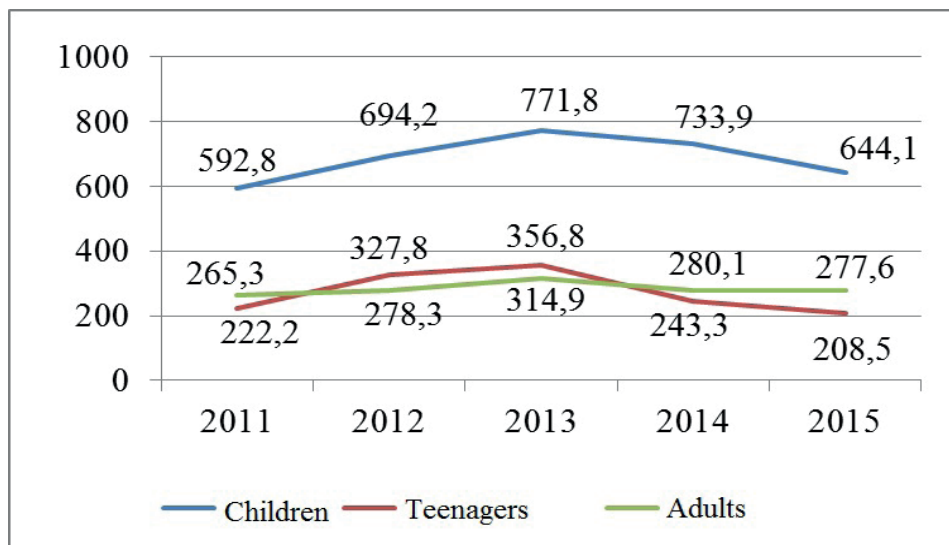


Figure 2. The dynamics of the age structure of the incidence rate of community-acquired pneumonia in the Russian Federation during 2011-2015 (per 100,000 population of the each age group)

During the period of the highest incidence rate (in 2013) its growth rate in adults was higher than in teenagers and children. The growth of the incidence rate of CAP in adult population was 13% (from  $278.3 \pm 0.5$  per 100,000 adults in 2012 to  $314.9 \pm 0.5$  per 100,000 adults in 2013,  $p=0.0001$ ). The growth of the incidence rate in children was 11% (from  $694.2 \pm 1.8$  per 100,000 children in 2012 to  $771.8 \pm 1.8$  per 100,000 children in 2013,  $p=0.0001$ ), the growth of the incidence rate in teenagers was 9% (from  $327.8 \pm 2.8$  per 100,000 teenagers in 2012 to  $356.8 \pm 3.0$  per 100,000 teenagers in 2013,  $p=0.001$ ). During the year when the decrease of the incidence rate was registered the rate of the decrease was low-

er in children than in teenagers and adults. In 2014 the decrease of the incidence rate in children was 5% (up to  $733.9 \pm 1.8^{0/0000}$  of children,  $p=0.0001$ ), in adults – 11% (up to  $280.1 \pm 0.5^{0/0000}$  of adults,  $p=0.0001$ ), in teenagers – 32% (up to  $243.3 \pm 2.5$  per 100,000 teenagers,  $p=0.0001$ ).

In AK the incidence rate in children was also higher than in teenagers and adults (Figure 3). The mean incidence rate in children was  $1027.2 \pm 16.3$  per 100,000 children being 4.2 times higher than the mean incidence rate in teenagers ( $245.6 \pm 19$  per 100,000 teenagers,  $p=0.0001$ ) and 3.7 times higher than the mean incidence rate in adults ( $280.9 \pm 3.8$  per 100,000 adults,  $p=0.0001$ ).



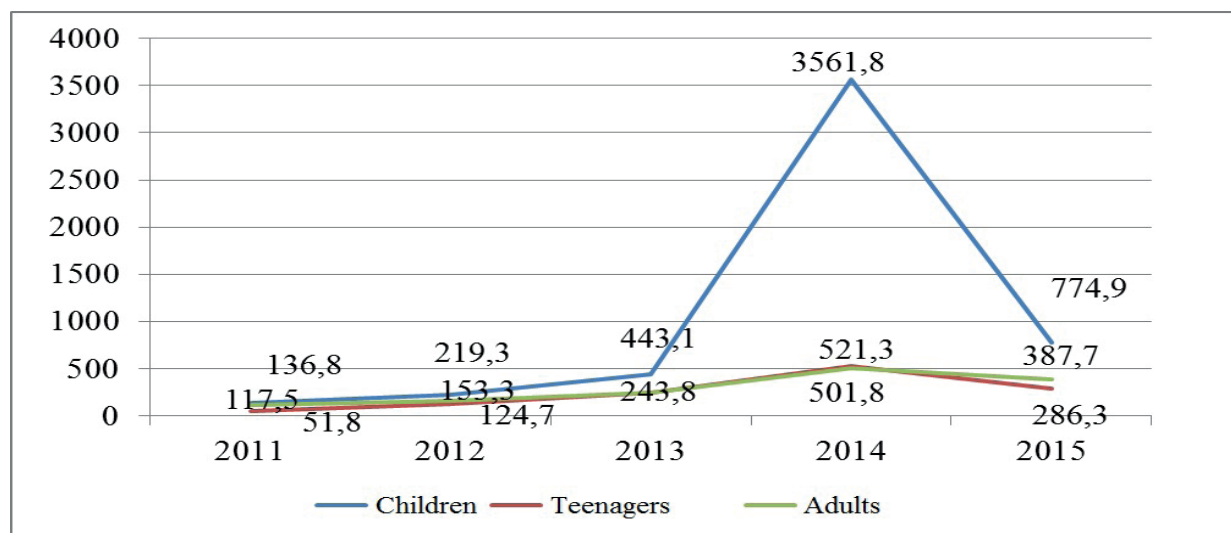


Figure 3. The dynamics of the age structure of the incidence rate of community-acquired pneumonia in the Altai Krai during 2011-2015 (per 100,000 population of the each age group)

During the period of the highest incidence rate (in 2014) its growth rate in children was higher than in teenagers and adults. The growth of the incidence rate in children was 704% (from  $443.1 \pm 10.6$  per 100,000 children in 2013 to  $3561.8 \pm 29.6$  per 100,000 children in 2014,  $p=0.00001$ ). The growth of the incidence rate in teenagers was 114% (from  $243.8 \pm 19.4$  per 100,000 teenagers in 2013 to  $521.3 \pm 28.5$  per 100,000 teenagers in 2014,  $p=0.001$ ); the growth of the incidence rate in adults was 106% (from  $243.8 \pm 3.5$  per 100,000 adults in 2013 to  $501.8 \pm 5.1$  per 100,000 adults in 2014,  $p=0.0001$ ).

During the year when the decrease of the incidence rate was registered (2015) the rate of the decrease was also higher in children than in teenagers and adults. The decrease of the incidence rate in children was 78.2% (up to  $774.9 \pm 13.7$  per 100,000 children,  $p=0.0001$ ), in adults – 22.7% (up to  $387.7 \pm 4.5$  of adults,  $p=0.0001$ ), in teenagers – 45.1% (up to  $286.3 \pm 21.1$  per 100,000 teenagers,  $p=0.001$ ).

To sum it up, during 2011-2015 the incidence rate in children was 1.5 times higher in AK than in the RF (mean incidence rates  $1027.2 \pm 16.3$  and  $687.3 \pm 1.7$  per 100,000 children respectively,  $p=0.0001$ ). The mean incidence rate of CAP in teenagers was 1.1 times higher in the RF than in AK ( $271.7 \pm 2.6$  and  $245.6 \pm 19$  per 100,000 teenagers respectively,  $p=0.061$ ). The mean incidence rate in adults has no significant difference ( $280.9 \pm 3.8$  per 100,000 adults in AK and  $283.2 \pm 0.5$  per 100,000 adults in the RF).

The age structure of community-acquired pneumonia patients was mostly represented by adults in the Russian Federation and Altai Krai. In the RF the part of adults on average for the period was  $66.3 \pm 0.1\%$ . In Altai Krai the part of adult CAP patients was 1.2 times larger ( $p=0.0001$ ):  $76.6 \pm 0.1\%$  (Figure 4, 5).

It should be mentioned that for the studied period the part of adult CAP patients in Altai Krai decreased by 12.2% (from  $80.7 \pm 0.6\%$  in 2011 to  $68.5 \pm 0.4\%$  in 2015,  $p=0.0001$ ). In the RF the similar decrease is not significant: 2.6% (from  $69 \pm 0.1\%$  in 2011 to  $66.4 \pm 0.1\%$  in 2015,  $p=0.0001$ ).

For the studied period the part of CAP patients in AK in the child group increased by 11.8% (from  $18 \pm 0.7\%$  in 2011 to  $29.8 \pm 0.4\%$  in 2015,  $p=0.0001$ ). In the RF the part of CAP patients in the child group also insignificantly increased by 3.1% (from  $28.8 \pm 0.1\%$  in 2011 to  $31.9 \pm 0.1\%$  in 2015,  $p=0.0001$ ).

The part of CAP patients in the teenager group was  $2.3 \pm 0.02\%$  in the RF and  $2.6 \pm 0.05\%$  on average. The trend has been toward the increase of the part of CAP patients in the teenager group in AK from  $1.3 \pm 0.2\%$  in 2011 to  $1.7 \pm 0.1\%$  in 2015 ( $p=0.061$ ). In the RF the part of CAP patients in this group decreased from  $2.2 \pm 0.02\%$  in 2011 to  $1.7 \pm 0.02\%$  in 2015 ( $p=0.0001$ ).

Summarizing the above, in 2015 the proportions of the age groups in the age structure of community-acquired pneumonia patients became quite similar in Russia and Altai Krai.

According to the Form No 2 of the State Statistical Reporting *Information About Infectious and Parasitic Diseases* bacterial types of community-acquired pneumonia prevailed in Altai Krai making up  $67.3 \pm 0.5\%$  of all other types of reported cases of community-acquired pneumonia during the period from 2011 to 2015 (Table 1).  $1.9 \pm 0.2\%$  of them were represented by viral types of community-acquired pneumonia. It should be noted that the number of validated diagnoses of bacterial pneumococcal community-acquired pneumonia increased every year. Thus, 3 cases of pneumococcal pneumonia were reported in 2011 and 39 cases – in 2015 (absolute numbers). This increase is explained by the growth of the number of laboratory tests for pneumococcus identification and the in-

roduction of the necessary test systems. However, this information does not show real numbers

of the incidence rate of pneumococcal infection in Altai Krai because of the underfunding.

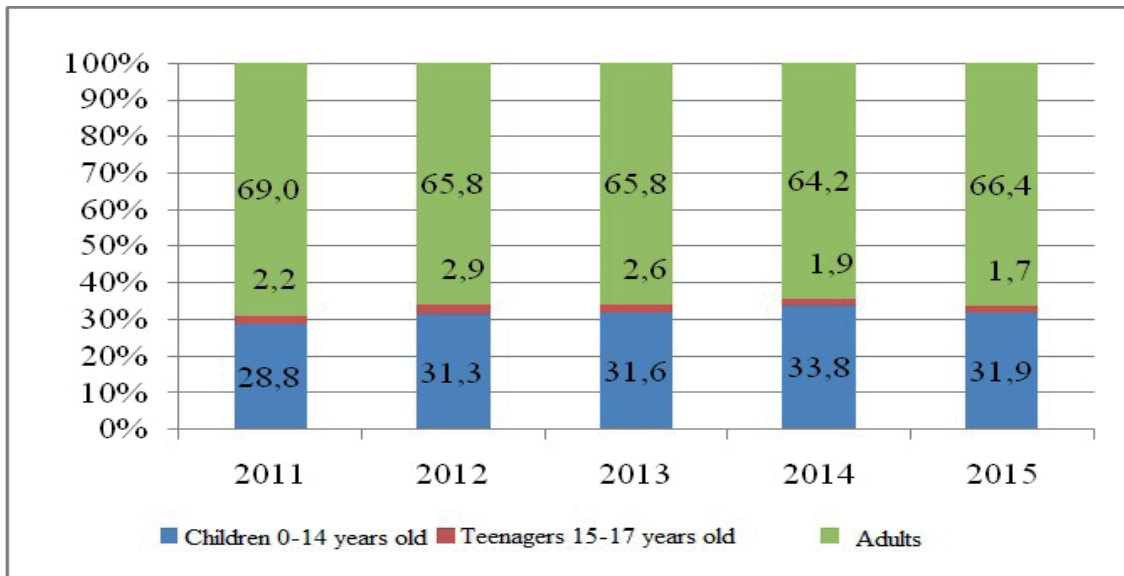


Figure 4. The age structure of community-acquired pneumonia patients in the Russian Federation during 2011-2015 (%)

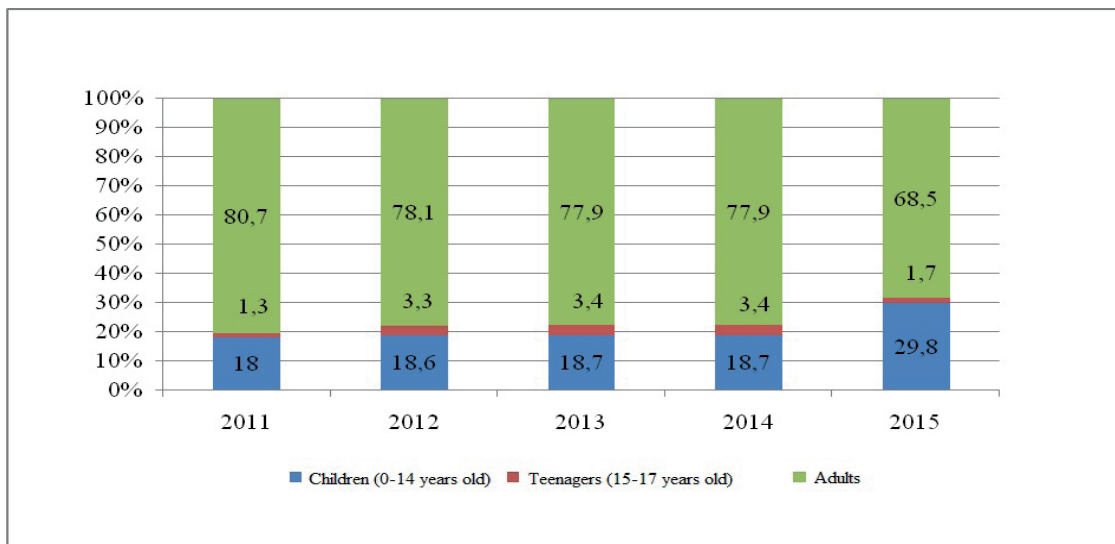


Figure 5. The age structure of community-acquired pneumonia patients in Altai Krai during 2011-2015 (%)

Table 1

*Etiological structure of community-acquired pneumonia (absolute numbers)*

Types of community-acquired pneumonia	2011	2012	2013	2014	2015
Bacterial	2738	3932	5296	10855	3206
with pneumococcus as a causative agent	3	1	1	25	39
Viral	129	0	5	476	114
All	2867	3932	6639	14440	10785

According to *Information Source Book about the Situation with Infectious Diseases and Their Prevention in Altai Krai during 2011-2015* we can note, that the part of pneumococcus found in the phlegm during these years increased from 4.40±0.2%

in 2013 to 6.59±0.2% in 2015 (p=0.001) and the part of pneumococcus found in the blood increased from 0.01±0.01% in 2013 to 0.05±0.02% (p=0.061) in 2015 (Table 2).

*Pneumococcus found in clinical samples in Altai Krai during 2013-2015 (absolute numbers)*

	2013			2014			2015		
	Clinical samples (pcs)	Result +	%	Clinical samples (pcs)	Result +	%	Clinical samples (pcs)	Result +	%
Phlegm	11989	528	4,40	11958	689	5,76	11178	737	6,59
Pleural fluid	4907	105	2,14	5051	92	1,82	4159	65	1,56
Ear secretion	3553	44	1,24	3114	22	0,71	3506	13	0,37
Blood	21123	2	0,01	19255	7	0,04	22207	12	0,05
CSF	1250	6	0,48	3407	9	0,26	1511	0	0,00

### Conclusion

1. The conducted retrospective analysis of the incidence rate of community-acquired pneumonia during 2011-2015 showed that this disease is a significant problem for Altai Krai because since 2014 the incidence rate of CAP in AK was higher than the incidence rate of CAP in the RF.
2. In 2011-2015, the incidence rate of CAP in children was higher than in teenagers and in adults both in AK and in the RF. In AK it was 1.5 times higher than in the RF. The mean incidence rate of CAP in the teenager group in the RF was 1.1 times higher than in AK. The mean incidence rate of CAP in adults had no significant difference.
3. The age structure of community-acquired pneumonia patients was mostly represented by adults. The part of adult community-acquired pneumonia patients was 76.6% of all community-acquired pneumonia patients in AK being 1.2 times larger than in the RF (66.3%). For the studied period in AK the part of CAP patients in the adult group decreased by 12.2%, the part of CAP patients in the child group increased by 11.8% and the part of CAP patients in the teenager group increased by 0.4%.
4. Bacterial types of community-acquired pneumonia dominated over viral types and made up 67.7% of all CAP types for the studied period of time.
5. According to the results of laboratory tests, we noticed the percentage increase of pneumococcal CAP.

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UDC 613.99:616-053.32

## REPRODUCTIVE PICTURE OF ADOLESCENT GIRLS BORN PREMATURELY

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*The aim of the study was to assess the reproductive system of adolescent girls born prematurely at the gestational age of 28-32 weeks and full-term ones (their somatic health, physical, sexual development, menstrual function, pelvic size, basic ultrasound parameters of the uterus and appendages were assessed). The object of the study was 200 teenage girls (15-16 years of age) who were born prematurely at the gestational age of 28-32 weeks and full-term ones, examined by general clinical, gynecological, instrumental, ultrasound, and statistical methods. There were established statistically significant differences in the main indicators characterizing the reproductive system in adolescent prematurely born girls to full-term born girls, namely, the difference in sexual development, menstrual function, pelvic size, ultrasound parameters of the uterus and appendages. The miscarriage of pregnancy makes a change in the formation of the reproductive system in the postnatal period and contributes to the emergence of its pathology.*

**Key words:** adolescent girls born prematurely full-term ones, indicators of the reproductive system.

During the period of fetal development there is formed the basis of human reproductive health, and often – ill health. The “perinatal trace” of reproductive system pathology, apparently, takes place more often than we imagine. It is connected with the fact that the realization of pathology is postponed until puberty or even later [1, 2]. The problem of pregnancy miscarriage is one of the topical issues of obstetrics. Numerous researches implying morphological material show that by miscarriage organometric parameters and histological structure of reproductive organs are exposed to changes [3, 4, 5, 6]. In this regard, the study of the reproductive health adolescent girls born prematurely is important.

**Research objective:** to determine the basic parameters of the reproductive system of adolescent girls born prematurely at the gestational age of 28-32 weeks and full-term ones (physical, sexual development, menstrual function, pelvic size, basic ultrasound parameters of the uterus and appendages).

### Materials and methods

The study was performed by the informed consent of adolescent girls on the basis of Regional Children Clinical Hospital, Kemerovo. The research was approved by the Ethics and medical investigation evidence committee of FSBEI HE KemSMU of the Ministry of Health of the Russian Federation and corresponded to the ethical standards of the bioethical committee elaborated in accordance with the WHO Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects amended in 2013 and in accordance with the Rules for clinical practice in Russian Federation approved by the Decree of the Ministry of Health of Russia of 19.06.2013 № 266. All adolescent girls provided written informed consent to participate in the study.

Research design: retrospective analytical study “case-control”. The study included 200 adolescent girls of 15-16 years. I group – 100 adolescent girls born prematurely at the gestational age of 28-32 weeks. II group - 100 adolescent girls born full-term. Criteria of inclusion into group I - adolescent girls born prematurely at the gestational age of 28-32 weeks by practically health mothers without somatic diseases or being at the stage of compensation by the time of delivery residing in Kemerovo Oblast. Criteria of exclusion from group I: adolescent girls born full-term by mothers with somatic pathology at the stage of decompensation by the time of delivery, non resident. Criteria of inclusion into group II: adolescent girls born full-term by practically health mothers without somatic diseases or being at the stage of compensation by the time of delivery residing in Kemerovo Oblast. Criteria of exclusion from group II: adolescent girls born full-term by mothers with somatic pathology at the stage of decompensation by the time of delivery, non resident.

The group were comparable by the age of women-mothers, the average age was 26,21±5,31 and 26,81±4,72 years respectively (p=0,9201). However, the pregnancy of mothers of adolescent girls born prematurely was more often first (p=0,0388), was threatened miscarriage (p=0,0002). The duration of gestation of prematurely born adolescent girls was determined according to the anamnestic data and also data of medical records (maternal discharge summary). There were studied the basic parameters of the reproductive system state: somatic health, physical, sexual development, menstrual function, pelvic size, basic ultrasound parameters of the uterus and appendages. The analysis of the health state was performed on the basis of incidence of outpatient visits, periodic health examination, periodic and ad hoc examinations



of specialists: pediatrician, ENT specialist, neurologist, ophthalmologist, surgeon, gynecologist. The overall medical report on the girl's health was made by the pediatrician.

The assessment of physiological development was conducted according to the unified methods using anthropometric measurements: height and body weight. The menstrual function was evaluated according to the age at menarche, establishment and duration of menstrual cycle, duration and painfulness of menstruation. The examination of sexual development was based on the basic pelvic measurements, dynamics of appearance and degree of manifestation of secondary sexual characteristics. The level of sexual development was studied by the rate of development of mammary glands ( $Ma_0-Ma_3$ ), pubic pilosis ( $P_0-P_3$ ), auxiliary pilosis ( $Ax_0-Ax_3$ ), state of menstrual function ( $Me_0-Me_3$ ). The rate of development of secondary sexual characteristics was integrated into the sexual formula ( $Ma, P, Ax, Me$ ) [7]. The pelvic inlet was characterized according to the measurements of its basic sizes d. spinarum, d. cristarum, d. trochanterica, c. externa. The ultrasound parameters of uterus and appendages were assessed by means of «Aloka 630» (Japan) using a transabdominal detector. There was carried a comparative analysis in the parallel groups of adolescent girls born prematurely and full-term.

The statistical data analysis was conducted by means of Microsoft Office Excel 2003 (license 74017-640-0000106-57177) and StatSoftStatistica 6.1 (license BXXR006D092218FAN11). The charac-

ter of data distribution was evaluated by means of Shapiro-Wilk test. Depending on the type of distribution there were used various algorithms of statistical analysis. Qualitative characteristics were presented by relative indicators (rates, %). Quantitative data were presented by central tendencies and dispersion: mean value (M) and standard deviation (s) of characteristics having approximately normal distribution, median (Me) and interquartile range (25<sup>th</sup> and 75<sup>th</sup> percentiles) in case of value distribution different from the normal one.

The comparison of two independent groups by one or several characteristics having nonnormal distribution at least in one of the groups or if the type distribution was not analyzed, was conducted by means of testing of statistical hypothesis for the equality of mean ranks by means of Mann-Whitney U-test. The difference of relative values was assessed by the analysis of contingency table ( $\chi^2$ ). By frequencies under 5, there was used Fisher exact test p. The comparison of relative frequencies in both groups was performed by comparing 95% CI of relative frequencies. If CI are not covered, the differences of frequencies can be considered statistically significant (by significance level 0,05). If intervals are covered, differences are not statistically significant.

### Results and discussion

The somatic health of adolescent girls born prematurely and full-term is presented in Table 1.

Table 1

Somatic health of adolescent girls born prematurely and full-term

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
	case number	case number	
Urinary system diseases	25	24	0,0911
Respiratory system diseases (bronchial asthma)	13	12	0,8515
Respiratory system diseases (chronic bronchitis)	32	22	0,1214
Cardio-vascular diseases (mitral valve prolapse)	19	5	0,0025
Endocrine system diseases (thyroid gland diseases)	35	30	0,8515
Endocrine system diseases (adiposis)	4	11	0,0653
Nervous system diseases (hypertensive type vegeto-vascular dysfunction)	13	16	0,5279
Nervous system diseases (hypotensive type vegeto-vascular dysfunction)	25	25	0,9676
Nervous system diseases (asthenoneurotic syndrome)	31	21	0,1166
Gastrointestinal diseases (chronic gastritis)	24	31	0,2498
Ophthalmological diseases (myopia)	31	8	0,0000
Musculoskeletal disorders (scoliosis)	25	12	0,0440

Note: p – reached level of significance of differences between the indicators of adolescent girls born prematurely and full-time.



The somatic health of adolescent girls born prematurely and full-term did not have statistically significant differences in basic diseases: urinary, respiratory, gastro-intestinal, endocrine and nervous systems. However, adolescent girls born prematurely more often had mitral valve pro-

lapse ( $p=0,0025$ ), scoliosis ( $p=0,0440$ ) and myopia ( $p=0,0000$ ).

Anthropometric parameters of adolescent girls born prematurely and full-term are shown in Table 2.

Table 2

*Anthropometric parameters of adolescent girls born prematurely and full-term*

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
Height, sm	160,0 [156,0-163,0]	160,0 [156,0-163,0]	0,7766
Weight, kg	56,0 [56,0-60,0]	56,0 [52,0-58,5]	0,7507

Note: p – reached level of significance of differences between indicators of adolescent girls born prematurely and full-term.

Anthropometric parameters of adolescent girls born prematurely and full-term did not have statistically significant differences.

The characteristic of menstrual function of adolescent girls born prematurely and full-term is presented in Table 3.

Table 3

*Menstrual function of adolescent girls born prematurely and full-term*

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
	case number	case number	
Menstrual cycle established at once	24	76	0,0000
Duration of menstrual cycle:			
28 days	17	28	0,0033
from 29 to 35 days	36	47	0,0033
over 35 days	48	25	0,0033
Duration of menstruation:			
3-4 days	40	18	0,0000
5-7 days	30	76	0,0000
8 and more	31	6	0,0000
Painful menstruations	52	26	0,0002

Note: p - reached level of significance of differences between indicators of adolescent girls born prematurely and full-term.

The age of menarche in adolescent girls born prematurely and full-term did not have statistically significant differences  $12,6\pm 0,15$  and  $12,47\pm 0,06$  ( $p=0,9201$ ).

However, adolescent girls born prematurely more often than the ones born full-term had irregular ( $p=0,0000$ ) and prolonged (over 35 days) menstrual cycle ( $p=0,0033$ ), duration of menstruation over 8 days ( $p=0,0000$ ), dysmenorrhea ( $p=0,0002$ ).

Sexual development of adolescent girls born prematurely and full-term also differed. The sexual formula of adolescent girls born prematurely was  $Ma_2, P_3, Ax_3, Me_2$ ; adolescent girls born full-term

-  $Ma_3, P_3, Ax_3, Me_3$ . Differences were statistically significant for the development of mammary glands ( $p=0,0041$ ) and menstrual function ( $p=0,0015$ ).

The pelvic measurements of adolescent girls born prematurely and full-term are presented in Table 4.

Pelvic measurements of adolescent girls born prematurely and full-term had statistically significant differences in all cross parameters. Pelvic measurements of adolescent girls born prematurely are smaller than of full-term born girls.

Ultrasound parameters of uterus and appendages are shown in Tables 5, 6, 7.

Table 4

*Pelvic measurements of adolescent girls born prematurely and full-term*

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
d. spinarum, sm	22,0 [21,0-22,0]	23,0 [22,0-23,0]	0,0000
d. cristarum, sm	24,0 [23,0-25,0]	26,0 [26,0-27,0]	0,0000
d. trochanterica, sm	27,0 [26,0-28,0]	28,0 [27,0-29,0]	0,0000
c externa, sm	18,0 [17,0-19,0]	18,0 [17,0-18,0]	0,3032

Note: p - reached level of significance of differences between indicators of adolescent girls born prematurely and full-term.

Table 5

*Ultrasound parameters of uterus of adolescent girls born prematurely and full-term*

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
Cervical length, mm	22,0 [21,0-23,0]	19,0 [16,0-22,0]	0,0001
Endometrial thickness, mm	7,0 [5,0-8,0]	7,0 [6,0-8,0]	0,4598
Midline echo, mm	6,0 [6,0-7,0]	9,0 [7,0-10,0]	0,0000
Length of uterus, mm	40,0 [39,0-42,0]	44,0 [42,0-45,0]	0,0000
Width of uterus, mm	39,0 [38,0-40,0]	41,0 [40,0-42,0]	0,0000
Thickness of uterus, mm	30,0 [29,0-31,0]	32,0 [31,0-32,9]	0,0000

Note: p - reached level of significance of differences between indicators of adolescent girls born prematurely and full-term.

Table 6

*Ultrasound parameters of the right ovary of adolescent girls born prematurely and full-term*

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
Length of ovary, mm	30,0 [29,0-31,0]	31,0 [30,0-32,0]	0,0015
Thickness of ovary, mm	21,0 [20,0-23,0]	22,0 [21,0-23,0]	0,0168
Width of ovary, mm	22,0 [21,0-24,0]	23,0 [21,0-24,0]	0,6190
Follicle size in ovary, mm	5,0 [4,0-6,0]	6,0 [5,0-7,0]	0,0000
Follicle number in ovary	5 [4-5]	5 [5-6]	0,0039

Note: p - reached level of significance of differences between indicators of adolescent girls born prematurely and full-term.

Table 7

*Ultrasound parameters of the left ovary of adolescent girls born prematurely and full-term*

Indicator	adolescent girls		p
	born prematurely (n=100)	born full-term (n=100)	
Length of ovary, mm	31,0 [30,0-31,0]	32,0 [31,0-33,5]	0,0000
Thickness of ovary, mm	21,0 [20,0-22,0]	20,0 [19,0-21,0]	0,0003
Width of ovary, mm	22,0 [20,0-23,0]	22,0 [19,0-24,0]	0,4528
Follicle size in ovary, mm	5,0 [5,0-6,0]	5,5 [5,0-6,0]	0,0698
Follicle number in ovary	5 [4-5]	8 [7-9,0]	0,0000

Note: p - reached level of significance of differences between indicators of adolescent girls born prematurely and full-term.

The majority of ultrasound parameters of uterus and appendages of adolescent girls born prematurely and full-term had statistically significant differences. Adolescent girls born prematurely were characterized by a longer cervix, smaller midline echo, length, thickness and width of uterus, ovaries (length and thickness) and smaller number of follicles.

### Conclusion

Consequently, there was conducted the evaluation of reproductive system of adolescent girls born prematurely and full-term. Pregnancy miscarriage changes the process of establishment of reproductive system during postnatal period.

The structure of gynecological pathology of adolescent girls in the Russian Federation is led by disorders of menstrual function which constitute 4925,2 per 100 000 girls. The frequency and structure of gynecological diseases of adolescent girls have regional peculiarities [8, 9]. In Kemerovo Oblast gynecological morbidity of adolescent girls in 2016 constituted 18,1%. The structure of overall gynecological morbidity is prevailed by inflammatory diseases of external genital organs (41,3%), disorders of menstruation (34,0%), cystic ovaries (3,5%), disorders of sexual development (2,1%). According to the preventive examinations, disorders of menstrual function constitutes 38,3% [10].

One of the important criteria of reproductive function preservation in adolescent girls is the reduction of gynecological incidences by means of modern technologies in early diagnosis, treatment and prevention [8, 11]. On the basis of introduction of modern technologies into diagnostic and treatment process there were obtained new data on etiology and pathogenesis of neuroendocrine disorders in adolescent age, chromosomal and congenital defects [12, 13].

The formation of main elements of reproductive system of adolescent girls begins in the early fetal period. Diseases of perinatal period are risk factors for the disorders of reproductive system during the period of its establishment [14, 15, 16].

In recent years, great attention in medical literature is given to medical and social factors of reproductive health formation of adolescent girls as future mothers [17, 18, 19, 20, 21].

Pregnancy miscarriage is a topical problem of obstetrics and perinatology. Frequency of pregnancy miscarriage constitutes 10-25% of all pregnancies, 6-10% - premature delivery. In spite of its medical and social importance the state of reproductive health of adolescent girls born prematurely is studied insufficiently.

The basic researches of reproductive system of adolescent girls born full-time were the data on physical development, menstrual function, pelvic measurements, ultrasound parameters of uterus and appendages.

There were determined statistically significant differences of basic parameters characterizing reproductive system of adolescent girls born prematurely in relation to full-time born ones. Adolescent girls born prematurely more often than the ones born full-term had irregular and prolonged (over 35 days) menstrual cycle, dysmenorrhea. Pelvic measurements of adolescent girls born prematurely are smaller than of full-term born girls. Ultrasound parameters of uterus and appendages also differ. Adolescent girls born prematurely were characterized by a longer cervix, smaller midline echo, length, thickness and width of uterus, ovaries (length and thickness) and smaller number of follicles. All this indicates the existence of immaturity and diminished function of reproductive organs in adolescent girls born prematurely.

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UDC 618.39:616-084

## COMPLEX REHABILITATION OF WOMEN AFTER LATE ABORTION FOR MEDICAL GROUNDS

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*The objective was to evaluate the effectiveness of an integrated approach to the rehabilitation of women after late induced abortion. 60 women after interruption of pregnancy in terms of up to 22 weeks with congenital malformations of the fetus, incompatible with life, underwent the rehabilitation. The women were divided into 2 groups: the main group underwent the complex elaborated rehabilitation, in the comparison group the activities were limited by regulatory documents. Delayed complications were observed in 13.3% and 40.0% of women ( $p = 0.041$ ) respectively, in the study groups (in the main group, complications were 3 times less frequent than in the comparison group); long-term consequences were observed in 10% and in 53.3% respectively ( $p = 0.000$ , in the main group 5.3 times less often than in the comparison group). In the complex implementation of rehabilitation measures, the number of late complications was observed 3 times less frequently than with the traditional approach, and the number of delayed sequela - by 5.3 times. The management of patients should not include only standard therapy for the treatment of complications, but also provide for the preventive use of contraceptives, suppression of lactation, a supplementation of folic acid, physiotherapy.*

**Key words:** late abortion, rehabilitation, termination of pregnancy.

The topical issue of the reproductive health protection is the minimization of risk of possible complications of medical abortions including late termination of pregnancy for medical grounds by congenital malformations of the fetus incompatible with life. The problem of abortions stays significant due to the possibility of development of early and long-term effect forming in the future a series of pregnancy, delivery complications and gynecological diseases. These circumstances enforce to search the ways of alternative improvement of technologies of pregnancy termination and means of prevention of possible complications [1, 2]. In recent years, there has been conducted numerous researches on the elaboration of various technologies of safe abortion aimed at the reduction of risk of complications [2].

One of the modern means – medically induced abortion at early and late stages by means of prostaglandins in combination with antiprogestins [3-5]. The relative risk of complications is, apparently, higher in the II trimester, at the same time, the absolute risk is low, when the interruption of pregnancy is performed by qualified medical personnel [6]. Every year there is improved the quality of medical service by abortions at different stages. According to the Decree of the Ministry of Health of the Russian Federation 572 [7], pregnant women, depending on the term of pregnancy, indications and contra-indications, are exposed to artificial termination of pregnancy using medicamental method on the basis of informed voluntary consent of a woman.

There is also elaborated clinical protocol “Medicated termination of pregnancy in I trimester” considered by international experts as a considerable

reserve in reducing maternal lethality [8]. WHO recommend to make every possible efforts to replace curettage by vacuum aspiration and medicated methods in order to make procedure of abortion more safe [9]. Although, however attenuated the method of abortion is, it still is a serious psychological and physical trauma, hormonal stress and always present risk of serious complications including disorders of menstrual and reproductive functions [10-12].

Recently, the role of rehabilitation in practical medicine becomes more and more significant. The basic principles of rehabilitation include: early start, complexity, phasing, continuity and sequence, individual program, focus on social orientation of measures, control of effectiveness [13-15]. Postabortal rehabilitation implies a complex of measures directed, firstly, at the restoration of reproductive health.

**Research objective:** to work out and evaluate the effectiveness of complex approach to the rehabilitation of women after late stimulated abortion by congenital malformations of the fetus, incompatible with life.

### Materials and methods

60 women after interruption of pregnancy in terms of up to 22 weeks with congenital malformations of the fetus, incompatible with life, underwent the rehabilitation. The women were divided into 2 groups: the main group underwent the complex elaborated rehabilitation, in the comparison group the rehabilitation measures were limited by regulatory documents [7]. The complex approach to the rehabilitation of women after late induced abortion including the following measures:



preparation to abortion, conduction of abortion itself by means of modern attenuated methods, post-abort rehabilitation.

Before late abortion, women were provided with written objective information based on evidences. All women were exposed to artificial termination of pregnancy in terms of up to 21 weeks 6 days in the conditions of the gynecological department of obstetric hospital having the opportunity to provide specialized help.

In accordance with the introduction of regulatory documents into practice [7, 8], artificial pregnancy termination was performed by means of medicated method depending on the term of pregnancy, indications and contra-indications. In this regard, there were used medicinal drugs registered in the territory of the Russian Federation, in accordance with the instructions for medical application of drugs. The control of uterine cavity emptying was maintained by visualization of deleted tissues. On the second day after the abortion, there was performed ultrasound investigation. The decision on the evacuation of the uterus content in case of incomplete abortion was based on clinical symptoms and USI data. By the signs of incomplete abortion and (or) parts of gestational sac there was conducted vacuum aspiration. The antibiotic prevention took place at late stages by the following combined method: mifepristone orally in the dose of 200 mg once, in 24 hours luminaria were injected into the cervical canal. If elimination of fetus did not occur, in 3-4 hours – 200-400 mkg of misoprostol [18, 19].

Artificial abortion was accompanied by obligatory anesthesia, women with Rh-negative blood were exposed to the prevention of rhesus immunization, there was prescribed immunoglobulin anti-D injected to unsensitized Rh-D-negative women during 72 hours after the induced abortion.

During the consultation with every woman there were discussed symptoms of complications in case of which she has to immediately contact with the doctor; there were also provided recommendations on the regime, hygienic measures, measures for prevention of abortions and necessity of preservation and carrying of further pregnancy. The control examination by obstetrician-gynecologist by lack of complaints is performed in 9-15 days.

The elaborated complex rehabilitation included the following additional element before the pregnancy termination: the woman was provided with screening for sexually transmitted infections (STIs), all women had the opportunity to be examined for Chlamydial infection and other STIs. By the result of microscopic swab examination of IV purity level, there were additionally excluded the causative agents of basic STIs ((Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium) by means of multiplex kit

produced by the Federal State Budgetary Institution of Science Central Research Institute of Epidemiology, Russian Federal Consumer Rights Protection and Human Health Control Service, Moscow. For the extended characteristics of the state of vaginal flora there were used reactive kits of "FloroTsenoz" series based on multiplex PCR in real time ("AmpliSens® FloroTsenoz Bacterial vaginosis-FL"). The results of the mentioned test allowed to quantitatively characterize the content of bacteria and also the content of lactobacillus, *G. vaginalis*, *A. vaginae*.

By the diagnosis of "bacterial vaginosis", "non-specific vaginitis", "vulvovaginal candidiasis", the pregnant women received gel "Metrogil plyus" intravaginally. The recommended dose constituted 5 g (I full applicator) 2 times a day (in the morning and in the evening). The cycle of treatment – 5 days. One gram of gel contains: 10 mg of metronidazole and 20 mg of clotrimazole. By STI verification, there was performed the treatment of infections according to the existing clinical recommendations and international standards [20, 21].

For the group of comparison by the presence of risk factors there was necessary the prescription of broad-spectrum antibiotics. For women not examined for Chlamydial infection – inclusion of 100 mg of doxycycline orally 2 times a day during seven days beginning from the day of abortion, and also 800 mg of metronidazole orally before and during the abortion.

Taking into consideration that the late abortion was conducted for medical grounds, all women were motivated for further realization of their reproductive function, the observation was performed with the transition to preconception preparation with the choice of the optimum pause between pregnancies. The best period for the occurrence of pregnancy after the miscarriage of the previous one are considered the first six months [22, 23]. All women were provided with information on all existing modern contraceptive methods. The discussion and the choice of methods were performed before the procedure. The chosen contraceptive method started to be used right after the abortion. In the early period after the abortion, the implementation of combined oral contraceptives (COCs) assures reduction of intensity (elimination) of bleeding; suppression of proliferative processes; anti-inflammatory and regenerative effect on the level of endometrium; decrease of irritation of pituitary-hypothalamic-ovarian system (PHOS) and reduction of gonadotrophic activity; and, finally, interception [11, 12].

Suppression of lactation after late abortion is a significant component of the rehabilitation of women's reproductive system, as the termination of pregnancy is one of the main causes of mammary gland diseases development. Late abortions are absolute indications for suppression

of lactation, thus, there was prescribed the inhibitor of prolactin secretion (dostinex). To prevent lactation the medication was prescribed in the dose of 1 mg (two pills) once on the first day after the abortion [24].

On account of planning further realization of reproductive function the women received folic acid (daily dose 400-800 mkg) not less than three months before the occurrence of pregnancy and during the whole I trimester (up to 12 weeks of pregnancy) [25].

The complex of rehabilitation including physical factors. Physical factors used for the rehabilitation after abortion has a specific and non-specific effect, cause total and local effect, thus, there were considered contraindications. In the postabortal period, there were used preformed possessing expressed anti-inflammatory, antiedemic, analgetic, uterotonic, desensitizing, immunomodulating and sedative effects aimed at restoration. Influencing receptive fields, functionally active zones, centers of nervous, endocrine and immune regulation, physical conductors of energy restore natural processes of homeostatic regulation of organism functional systems. The success of such regulation is determined by the functional state of organism, correct choice of the factor, regime, localization and parameters of its action.

Physical factors were implied in the early post-abortal period for the preventive purpose, in case of complications – with the treatment purpose in complex with antibacterial or other therapy, and in the late period – with the purpose of the menstrual cycle restoration and preservation of the reproductive health. The method of physical therapy was chosen according to the concomitant pathology: intensity of the inflammatory process, presence of myomatous nodules, adhesive process. Upon indications there was implied the combined method – daily amplipulse phoresis with copper sulphate or sodium thiosulfate solution (“Aplipuls-7”, then low intensity laser therapy of the projection of uterus and appendages and lumbosacral spine (“Rikta-04”, “Milta”, “UZOR-A-2K”, “Lazmik”).

Medical abortion also presents a psycho-traumatic, stressful factor, thus, the course of rehabilitation treatment included also psycho-relaxing methods. The patients subject to such methods were exposed to cranial electrotherapy stimulation or electrosleep therapy, individual sessions with psychologist. Women were directed by the obstetrician-gynaecologist to the room of medical and social help of the women’s consultation clinic (Center of medical and social of pregnant women in a difficult situation) for the consultations with psychologist (medical psychologist, when required - social work specialist). The consultation was conducted by a medical worker with higher medical education upon the woman’s informed voluntary consent.

## Results and discussion

The average age of patients constituted 29,8±3,9 in the main group and 30,1±4,3 in the comparison group. The conducted examination of the vaginal biotope by means of system “Florotsentoz” in the main group showed, that bacterial vaginosis and non-specific vaginitis were observed in 46,6%, in the comparison group disorders of the vaginal biotope were registered only in 26,7%. In terms of research, there were analyzed delayed and long-term consequences. Complications of late abortion developed during the 1<sup>st</sup> month after the operation were observed in both groups. Endometritis in the postabortal period was registered in 1 (3,3%) patient of the main group and in 3 (10%; p=0,605) patients of the comparison group. Subinvolution of uterus was observed in 1 (3,3%) women and in 4 (13,3%; p=0,350) women respectively. Hematometra was diagnosed in 1 (4,0%) patient of the main group and in 2 (6,7%; p=1,0) patients of the comparison group. Inflammatory diseases of appendages or aggravation of chronic inflammatory process were registered in 1 patient of the main group and in 3 patients of the comparison group (p=0,605). Totally, delayed complications of late induced abortion were observed in 4 (13,3%) of women and 12 (40,0%; p=0,041) respectively, thus, in the main group complications were met three times rarer than in the group of comparison.

Long-term effects were connected with menstrual cycle disorders, dysfunction of the pituitary-hypothalamic-ovarian system (PHOS), psychogenic disorders. Disorders of menstrual cycle were observed in 1 (3,3%) patient of the main group and 4 (13,3%; p=0,350) patients of the comparison group. PHOS dysfunction was revealed in 1 (3,3%) woman and 4 (13,3%; p=0,350) women respectively. Mastopathy manifesting itself as mastalgia and galactorrhea was observed only in patients of the comparison group (5 women – 16,7%; p=0,062). Psychogenic disorders are detected in 1 (3,3%) patient of the main group and 3 (10%; p=0,605) patients of the group of comparison. Totally, long-term consequences were registered in 3 (10%) patients of the main group and 16 (53,3%; p=0,000) patients of the comparison group, h.e. in the main group complications were met 5,3 times rare than in the group of comparison.

## Conclusion

Supplement to the Decree of the Ministry of Health of the Russia Federation [7] allowed to adjust the regulatory structure in accordance with imperatives within the shortest possible time and introduce modern methods aimed at the improvement of quality of medical service for women by stimulated abortion at late stages. The introduction of clinical protocol “Medicated termination of pregnancy” also allows to efficiently use the experience of foreign countries and specialized

societies of safe abortions in the II trimester upon medical indications.

By the complex conduction of rehabilitation measures the number of delayed complications (endometritis, subinvolution of uterus, hematometra, inflammatory diseases of appendages or aggravation of chronic inflammatory process) in the main group was registered 3 times rarer than in the group of comparison, the number of long-term complications (menstrual cycle disorders, dysfunction of the pituitary-hypothalamic-ovarian system, mastopathy, psychogenic disorders) – 5,3 times rarer. The tactics of patients' management after artificial termination of pregnancy, especially in late terms, should not include only standard therapy of complications treatment, but also preventive implementation of combined oral contraceptives, suppression of lactation, supplement of folic acid, physiotherapeutic treatment aimed at prevention of negative consequences for woman's health.

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UDC 615.38:618.3+616-053.3

## PREVENTION OF RHESUS IMMUNIZATION IN PREGNANT WOMEN WITH POTENTIALLY SENSITIZING EVENTS

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*The incidence of hemolytic disease of the fetus and the effectiveness of its prevention has been studied. 56 pregnant women with Rh-negative blood without antirhesus- antibodies titers were observed; they had a complication of gestation in the form of threat of termination of pregnancy, accompanied by bloody discharge from the genital tract, some of whom (the main group consisted of 29 women) had an unplanned prophylaxis of Rhesus immunization together with preventive measures in the decreed period. The comparison group consisted of 27 women with the threat of abortion, accompanied by bloody discharge from the genital tract, for whom preventive measures were not performed in full because of the development of immunization or their refusal to participate. The best results were obtained in the main group, where it was possible to prevent the development of Rh- immunization in 100% of cases. In the comparison group, the proportion of immunized pregnant women who did not receive an unscheduled prophylactic dose of immunoglobulin due to complications of gestation was 7.4%, with an abstinence from prenatal prophylaxis at 28-30 weeks – 11,1%. With the development of complications of gestation in the form of the threat of termination of pregnancy, accompanied by bloody discharge from the genital tract in women with Rh-negative blood, the method of choice is to carry out unscheduled prevention of Rh-immunization along with preventive measures in the prescribed time.*

**Key words:** Rh-immunization, preventive measures, threat of abortion.

According to statistics, the frequency of hemolytic disease of the fetus and newborns in the Russian federation ranges from 0,1 to 2,5%, has not changed during the recent 10 years and constitutes 9,9% and 1,46% of all born in the structure of perinatal morbidity and lethality [1, 2]. The results of epidemiological researches conducted in various regions of the country considerably differ from the data of foreign authors. In Russia, the rate of rhesus-immunized women reaches 1,2% [3]. The conduction of preventive measures for women with rhesus-negative blood is an extremely important issue. Preventive measures include planned injection of anti-Rh (D) immunoglobulin G to non-immunized women with rhesus-negative blood (28-30 weeks of pregnancy, first 72 hours in the postpartum period) and by potentially sensitizing events, which is the gold standard for prevention of immunization in women, and, consequently, hemolytic disease of the fetus [4, 5, 6].

The list of potentially sensitizing events requiring prevention of rh-immunization: invasive prenatal diagnosis, reduction of one of the embryos, intrauterine treatment of the fetus (shunting, blood transfusion), stomach trauma, intrauterine fetal demise, termination of pregnancy (regardless of the method), prenatal bleeding, spontaneous miscarriage, extra-uterine pregnancy [7, 8]. Preventive measures by the occurrence of potentially sensitizing event include the injection of preventive dose of anti-Rh (D) immunoglobulin depending on the time of occurrence of potentially sensitizing events and period of drug half-life.

**Research objective:** to study the incidence of hemolytic disease of the fetus and effectiveness of its prevention.

### Materials and methods

The study included 56 pregnant women at the age of 27-35 years with rh-negative blood without antibody titers receiving medical treatment in the obstetrics department of the City clinical perinatal center, Omsk, during the period of 2012-2016. All examined women referred to the category of recurrently pregnant, underwent examination and treatment for threatened preterm labor (threatened late spontaneous miscarriage). Criteria of inclusion into the research group were: Rh-negative blood without antibody titer, Rh-positive blood of the partner, threatened miscarriage accompanied by bloody discharge from genital tracts, lack of symptoms of hemolytic disease of the fetus and newborns and/or hemotransfusions, intrauterine fetal death of hemolytic disease; lack of severe extragenital pathology.

The main group consisted of 29 pregnant women with threatened miscarriage accompanied by bloody discharge from genital tracts having been exposed to prenatal unplanned prevention of Rh-immunization by human immunoglobulin anti-Rh<sub>0</sub> [D] (Rezonativ, LSR-000970/10, Oktafarma AB, Sweden) in the dose of 250 mkg (1250 IU) and also prevention of Rh-immunization in the decreed terms of 28-32th weeks of gestation and during 72 hours after the delivery. The group of comparison included 27 pregnant women with threatened miscarriage accompanied by bloody



discharge from genital tracts having rejected to undergo prenatal unplanned prevention of Rh-immunization. In terms of the current study there were examined pregnant women (n=56) from the moment of admission to the hospital pathologic pregnancy department till the delivery by means of the laboratory method of diagnosis of Rh-immunization. The titer of anti-Rh antibodies was determined in one laboratory by helium cards (DG Gel® Anti-IgG, №210322). The effectiveness of the conducted prevention was evaluated by the lack of appearance of complete or incomplete anti-Rh<sub>0</sub> (D) antibodies in blood in 10 days, 1 and 3 months after the drug injection in the postpartum period (obstetric patients the titer dynamics of whom was impossible to follow were excluded from the research group).

The clinical study of the course of pregnancy and labor outcome required the search of standard criteria of group homogeneity. The basic feature uniting the groups of pregnant women were: parity of labor, threatened miscarriage accompanied by bloody discharge from genital tracts, with rh-negative blood without antibody titers, Rh-positive blood of the partner or Rh-positive blood of the fetus. The registered group features were

characterized by high significance ( $p < 0,05$ ) which is acceptable for medico-biological studies.

The statistical data processing was performed by "Statistica" program, version Exel 3, OSPPS v. 12. There were implied standard methods of descriptive statistics; the data are presented in the form of median (Me) and interquartile range (25 and 75% percentiles). The comparison of data was performed by non-parametric Mann-Whitney test. The null hypothesis was checked by Wilcoxon signed-rank test. For categorical variables the data were presented as rates (percentage), comparison was conducted by means of  $\chi^2$  criterion. Differences were considered statistically significant by  $p < 0,05$ .

### Results and discussion

The average age of patients in groups constituted  $28,5 \pm 3$  years. The somatic anamnesis of 11 pregnant patients (19,6%) was aggravated by cardio-vascular pathology (vegetovascular dystonia, gestational arterial hypertension); in 13 patients (23,2%) – gastro-intestinal diseases, in 7 patients (12,5%) – renal diseases, other extragenital pathology was registered in 4,3% of cases. The obstetric-gynecologic anamnesis was assessed in the traditional representation (Table 1).

Table 1

Parameters of reproductive function of patients of main and comparison groups

Parameters of reproductive function	Groups(M±m)		p
	I(n=29)	II (n=27)	
Number of pregnancies	3,1±0,03	3,3±0,03	$p > 0,05$
Parity	0,6±0,06	0,5±0,04	$p > 0,05$
Caesarean section	0,1±0,02	0,2±0,05	$p > 0,05$
Medical abortion	0,2±0,1	0,7±0,01	$p > 0,05$
Spontaneous miscarriage	0,2±0,03	0,3±0,02	$p > 0,05$
Extra-uterine pregnancy	0,01±0,03	0,02±0,02	$p > 0,05$
Non-developing pregnancy	0,01±0,04	0,03±0,01	$p > 0,05$

Prenatal unplanned prevention of Rh-immunization in patients of the main group included i.m. injection of human immunoglobulin anti-Rh<sub>0</sub> [D] in the dose of 250 mkg (1250 IU) to all patients with threatened spontaneous miscarriage and bloody discharge during 48 hours since the moment of hospital admission. In case of recurrent threatened spontaneous miscarriage with bloody discharge the drug was injected again in the dose of 250 mkg (1250 IU) if the time interval since the previous injection did not exceed 6 weeks (n=1). All pregnant patients of the main group received preventive dose of human immunoglobulin anti-Rh<sub>0</sub> [D] on the 28-32th week of gestation (conduction of prevention of Rh-immunization depended on the terms of unplanned prevention and was carried since 6 weeks with compulsory pre-test for presence of anti-Rh<sub>0</sub> (D)-antibodies in blood and in the postpartum

period. The titer of anti-Rh<sub>0</sub> (D)-antibodies up to 1:8 not tended to increase was considered as residual in case of prenatal unplanned prevention of Rh-immunization and did not affect the decision on the necessity of Rh-immunization prevention conduction.

The complications occurred after the injection of immunoglobulin included infiltration and local painfulness in 5% of cases. In the postpartum period, all pregnant women were exposed to the prevention of Rh-immunization by human immunoglobulin anti-Rh<sub>0</sub> [D] in the dose of 250 mkg (1250 IU) i.m.

The effectiveness of performed prevention was evaluated by the presence of anti-Rh<sub>0</sub> (D)-antibodies in blood during 10 days, 1 and 3 months after the delivery. The absence of anti-Rh<sub>0</sub> (D)-antibodies titers since 1 and 3 months after the de-

livery and also remaining anti-Rh<sub>0</sub> (D)-antibodies titers not exceeding 1:8 up to 10 days with further disappearance were considered a positive effect of Rh-immunization prevention. Gestational terms

and number of pregnant women having received the preventive dose of human immunoglobulin anti-Rh<sub>0</sub> [D] are shown in Table 2.

Table 2

*Gestational terms of human immunoglobulin anti-Rh<sub>0</sub> [D] injection*

Prenatal unplanned prevention		Prenatal planned prevention	
20-21weeks	n = 7	28 weeks	n = 14
22-23weeks	n = 8	29 weeks	n = 5
23weeks	n = 5	30 weeks	n = 5
24-25weeks	n = 5	32 weeks	n = 5
26-27weeks	n = 4	-	-

In 2 (6,8%) patients with performed prenatal unplanned prevention of Rh-immunization in the term of 25-26 weeks and in 1 patients in the term of 26-27 weeks further there was registered threatened miscarriage accompanied by bloody discharge occurred during 3 weeks since the 1<sup>st</sup> injection of unplanned preventive dose of human immunoglobulin anti-Rh<sub>0</sub> [D], they did not need its recurrent injection. One patient with recurrent threatened miscarriage occurred since 6 weeks after the 1<sup>st</sup> injection of unplanned preventive dose of human immunoglobulin anti-Rh<sub>0</sub> [D] in the term of 26-27 weeks of pregnancy was injected with the recurrent preventive dose.

In all patients of the main group before the planned prevention by human immunoglobulin anti-Rh<sub>0</sub> [D] there was determined the titer of anti-Rh<sub>0</sub> (D)-antibodies: 10 patients (34,40%) had the titer 1:4; 7 patients (24,1%) – 1:2; 12 patients lacked the titer. Considering the period of drug half-life, the current titer was determined as residual.

All pregnant women of the main group performed delivery in the term of 37-40 weeks. The titer of anti-Rh<sub>0</sub> (D)-antibodies 1:2 before the delivery was observed in 13,7% (4 patients) women and was revealed in patients exposed to the planned prevention on the 32<sup>nd</sup> week of gestation. The stated titer was considered as residual and did not affect the decision on the necessity of Rh-immunization prevention conduction. In the study group incomplete anti-Rh<sub>0</sub> (D)-antibodies in the titer 1:2 in 10 days were registered in 2 out of 29 patients due to their incomplete clearance. In the following period of observation, none of the examined patients had antibodies in blood, which indicates the effective performance of prevention of Rh-immunization.

The dynamic observation of patients of the comparison group revealed appearance of anti-Rh<sub>0</sub> (D)-antibodies in the blood of 2 pregnant women (7,4%) in the term of gestation up to 28 weeks; 12 patients were not exposed to Rh-immunization on the 28<sup>th</sup> week due to rejection: 13 patients re-

ceived the preventive dose of drug on the 28-30<sup>th</sup> week. In 2 patients of the group not receiving the preventive drug dose there appeared anti-Rh<sub>0</sub> (D)-antibodies in titer 1:32 (in dynamics 1:64) after 32 weeks. All non-immunized patients underwent postpartum prevention (n=23). The blood of 1 patient contained anti-Rh<sub>0</sub> (D)-antibodies in the postpartum period in titer 1:16 on the 10<sup>th</sup> day after the drug injection. The dynamic observation of the mentioned patient showed the presence of titer 1:4 in the 1<sup>st</sup> and 3<sup>rd</sup> months which allows to conclude on the inefficiency of the prevention. Thus, the rate of immunized pregnant women having not received the preventive dose of immunoglobulin due for gestation complications constituted 7,4% (n=2); the number of immunized pregnant women having not received the preventive dose of immunoglobulin due for gestation complications and rejected prenatal prevention on the 28-30<sup>th</sup> week of gestation constituted 11,1%.

### Conclusion

The main objective of the antenatal fetal health protection in Rh-negative pregnant women are the measures aimed at the prevention of immunization development on non-sensitized patients. The treat of pregnancy miscarriage accompanied by bloody discharge from genital tracts is a risk factor of the development of mother's immunization for erythrocytic antigens. The performance of planned prevention of Rh-immunization in the given category of patients together with decreed antenatal and postpartum prevention precludes the development of Rh-D-antigen immunization.

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UDC 618.179

## PECULIARITIES OF CONTRACEPTION OF WOMEN OF REPRODUCTIVE AGE LIVING IN OMSK

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*Using the questionnaire of 321 patients, the most frequently used methods of contraception after abortion and the reasons for refusing to prevent the unwanted pregnancy of women of fertile age in Omsk were analyzed. The overwhelming majority of women of childbearing age refuse contraception in connection with mastalgia (75%), the second most important reason is headache and increased blood pressure (13%) with the self-institution of combined oral contraceptives. Most often, after an abortion, women of childbearing age use an intrauterine device (26.8%), a vaginal ring (21.2%), ethinyl estradiol in combination with desogestrel (12.1%).*

**Key words:** *contraception, reproductive age, combined oral contraceptives.*

One of the main ways to improve the demographic situation in the country is to strengthen reproductive health and preserve the genital function of women, which is directly related to the reduction in the number of abortions. Undoubtedly, a big role in this was played by the promotion of the use of modern contraceptives and the selection of the optimal method of preventing unwanted pregnancies for every woman who turned to the doctor with this question. It should be noted that the prevention of abortion is directly related to the use of modern methods of contraception to prevent unwanted pregnancies [1]. Contraception is as old as humanity itself. For millennia, people have been using contraception to protect themselves from unwanted pregnancies. The need for birth control led to the creation of a variety of methods of contraception, which were used in the primitive society and go on to exist at the present time. At present, there is no doubt that contraceptives do not reduce fertility, but are an effective method of preserving the reproductive health of women [2, 3]. Despite the wide experience of using hormonal contraceptives to protect against unwanted pregnancies, up to now, some aspects of the safety of their use remain a subject of discussion. In the Russian Federation, hormonal contraception is not the main method of birth control [4]. The risk of side effects and complications of hormonal contraception does not exclude the need for monitoring the childbearing of people suffering from diseases and conditions that pose a threat to life and health in the event of an unplanned pregnancy [5].

**Research objective:** to analyze the most frequently used methods of contraception and the reasons for refusal to protect the onset of unwanted pregnancy in women of fertile age in Omsk.

### Materials and methods

In 2016-2017 within the framework of the preventive examination, there was conducted a questionnaire for 321 patients at OOO «Center for Contemporary Medicine «DoktorSash Clinic». When collecting anamnesis, special attention was paid

to age, sexual function (age of onset of sexual activity), features of reproductive function (course and outcomes of previous pregnancies), contraceptive methods used after abortion, history of pelvic organs, including cervical disease. All patients after the questionnaire were divided into the main group and the comparison group, each of which was divided according to age into three subgroups. The main group consisted of women of reproductive age ( $n = 89$ ) who used combined oral contraceptives (COCs). Criteria for inclusion in the main group were the following: women of childbearing age (18-49 years old) who took COCs. Exclusion criteria from the main group were the following: women of fertile age who use other methods of contraception; age younger than 18 and over 49; women who have contraindications to taking COC. The subgroup IA included women aged 18-30; in subgroup I B - 31-45 years old, in the subgroup IC - 46-49 years old.

The comparison group consisted of women of reproductive age ( $n = 232$ ), using other methods of contraception or having contraindications to taking COC. The comparison subgroup IIA included women of 18-30 years old; subgroup IIB consisted of 31-45 years old women; subgroup IIC included women of 46-49 years.

The questionnaire for women consisted of 30 questions, where the most attention was paid to obstetric-gynecological anamnesis. Each person was informed that the survey was anonymous; the results of the survey and the answers to the questions, the name and other personal data would not be disclosed. The performed work did not infringe the rights, did not endanger the patients examined and was carried out with their informed prior consent to use medical documentation in research work.

### Results and discussion

When analyzing the data it was found out that the average age of the onset of menstruation in the main group was  $13.5 \pm 1.1$  years, in the comparison group -  $15 \pm 1.5$  years. The onset of sex-

ual activity in the main group is  $18 \pm 2.1$  years, in the comparison group -  $16 \pm 1.2$  years. All women had an obstetric-gynecologic history: the number of births, abortions, and miscarriages was analyzed.

Most women of reproductive age in the history have one, two or more births, and the older the age group, the greater the number of births is observed (Table 1).

Table 1

*Parity of births in women of fertile age in the study groups*

Births	group IA n=25	group IB n=48	group IC n=16	group IIA n=98	group IIB n=117	group IIC n=17
0	4 (16%)	7 (14,6%)	0 (0%)	23 (23,5%)	7 (60%)	1 (5,8%)
1	18 (72%)	17 (35,4%)	7 (43,8%)	59 (60,2%)	52 (44,4%)	2 (11,8%)
2 and more	3 (12%)	24 (50%)	9 (56,2%)	16 (16,3%)	58 (49,6%)	14 (82,4%)
Comparison of the groups	$\chi^2=1,2$ ; df = 2; $p = 0,55$	$\chi^2=20,4$ ; df = 2; $p < 0,0001^*$	$\chi^2=4,8$ ; df = 2; $p = 0,09$	$\chi^2=1,2$ ; df = 2; $p = 0,55$	$\chi^2=20,4$ ; df = 2; $p < 0,0001^*$	$\chi^2=4,8$ ; df = 2; $p = 0,09$
Comparison among subgroupми within the group	$\chi^2=14,2$ ; df = 4; $p = 0,007^*$			$\chi^2=45,9$ ; df = 4; $p < 0,0001^*$		
Comparison of all subgroups: $\chi^2=60,3$ ; df = 10; $p < 0,0001^*$						

When analyzing the number of abortions in anamnesis, it was found out that the majority of the women studied (53.4%) have 1 abortion; 2 or more abortions were more frequent in group IIB

(Table 2, 3). Most often, unwanted pregnancy occurs when women use the method of contraception «interrupted sexual intercourse» (64%).

Table 2

*Characteristics of obstetric anamnesis (abortion) in women of reproductive age in the study groups*

abortion	group IA n=25	group IB n=48	group IC n=16	group IIA n=98	group IIB n=117	group IIC n=17
0	5 (20%)	3 (6,3%)	2 (12,5%)	54 (55,1%)	21 (17,9%)	4 (23,5%)
1	17 (68%)	31 (64,6%)	11 (68,8%)	41 (41,8%)	56 (47,9%)	1 (5,9%)
2 and more	3 (12%)	14 (29,1%)	3 (18,7%)	3 (3,1%)	40 (34,2%)	12 (70,6%)
Comparison of the groups	$\chi^2=11,3$ ; df = 2; $p = 0,004^*$	$\chi^2=5,3$ ; df = 2; $p = 0,07$	$\chi^2=14,4$ ; df = 2; $p = 0,001^*$	$\chi^2=11,3$ ; df = 2; $p = 0,004^*$	$\chi^2=5,3$ ; df = 2; $p = 0,07$	$\chi^2=14,4$ ; df = 2; $p = 0,001^*$
Comparison among subgroupми within the group	$\chi^2=5,1$ ; df = 4; $p = 0,28$			$\chi^2=67,2$ ; df = 4; $p < 0,0001^*$		
Comparison of all subgroups: $\chi^2=95,1$ ; df = 10; $p < 0,0001^*$						

Based on the data obtained in Table 2, it can be seen that the largest number of women in the main study group have a history of one abortion. Most often, this situation occurs when the intake of combined oral contraceptives is impaired. In agreement with the data of the comparison group it can be seen that the majority of 31-45-year-old women in the comparison group have one abortion, it happens more often when they use an interrupted sexual intercourse as a contraceptive. The prevailing number of women aged 18-31 had no abortions, and the majority of women over 45 years old have two or more abortions in the history, more often when using the calendar method of contraception.

Spontaneous miscarriages in the anamnesis were observed more often in group I C – in women over the age of 45 years who have an anamnesis of inflammatory diseases of the pelvic organs.

Due to the fact that almost every woman of childbearing age has at least one medical abortion, contraceptive methods used after the interruption of unwanted pregnancy were analyzed (Table 4).

18-30-year-old women (group I, II A) most frequently used a vaginal ring as a contraceptive method after abortion, those of 31-45 years old (group I, IIB) used the intrauterine device more often, women of late reproductive age (45 -49 years old) (group I, II C) prioritized the barrier method of contraception.

The gynecological anamnesis of the studied groups of women of the reproductive period is examined in detail. In all groups, inflammatory diseases of the pelvic organs occupy a prime place, especially in groups IA, IB and IIB (Figure 2).



Table 3

Characteristics of obstetric anamnesis (spontaneous abortions) in women of reproductive age in the study groups

Miscarriage	group IA n=25	group IB n=48	group IC n=16	group IIA n=98	group IIB n=117	group IIC n=17
0	18 (72%)	32 (66,7%)	3 (18,7%)	71 (72,4%)	97 (83%)	12 (70,6%)
1	5 (20%)	13 (27,1%)	2 (12,5%)	24 (24,5%)	11 (9,4%)	4 (23,5%)
2 and more	2 (8%)	3 (6,2%)	11 (68,8%)	3 (3,1%)	9 (7,6%)	1 (5,9%)
Comparison of the groups	$\chi^2= 1,4; df = 2; p = 0,50$	$\chi^2= 8,6; df = 2; p = 0,014^*$	$\chi^2= 14,4; df = 2; p = 0,001^*$	$\chi^2= 1,4; df = 2; p = 0,50$	$\chi^2= 8,6; df = 2; p = 0,014^*$	$\chi^2= 14,4; df = 2; p = 0,001^*$
Comparison among subgroups within the group	$\chi^2= 34,8; df = 4; p < 0,0001^*$			$\chi^2= 10,6; df = 4; p = 0,031^*$		
Comparison of all subgroups: $\chi^2= 85,9; df = 10; p < 0,0001^*$						

Table 4

Methods of contraception used by women of reproductive age after medical abortion

Methods of contraception	group IA n=25	group IB n=48	group IC n=16	group IIA n=98	group IIB n=117	group IIC n=17
IUD	1 (5%)	27 (60%)	0 (0%)	5 (11,4%)	51 (53,1%)	2 (15,4%)
vaginal ring	16 (25%)	11 (24,4%)	2 (14,3%)	26 (59,1%)	12 (12,5%)	1 (7,7%)
COC: ethinyl-oestradiol with desogestrel	1 (5%)	7 (15,6%)	0 (0%)	11 (25%)	28 (29,2%)	2 (15,4%)
barrier contraception	0 (0%)	0 (0%)	12 (85,7%)	2 (4,5%)	5 (5,2%)	8 (61,5%)
Rigevidon	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Silhouette	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Comparison of the groups	$c^2= 9,8; df = 4; p = 0,045^*$	$c^2= 7,6; df = 3; p = 0,055$	$c^2= 5,1; df = 3; p = 0,16$	$c^2= 9,8; df = 4; p = 0,045^*$	$c^2= 7,6; df = 3; p = 0,055$	$c^2= 5,1; df = 3; p = 0,16$
Comparison among subgroups	$c^2= 96,7; df = 8; p < 0,0001^*$			$c^2= 82,9; df = 6; p < 0,0001^*$		
Comparison of all subgroups: $c^2= 214,4; df = 20; p < 0,0001^*$						

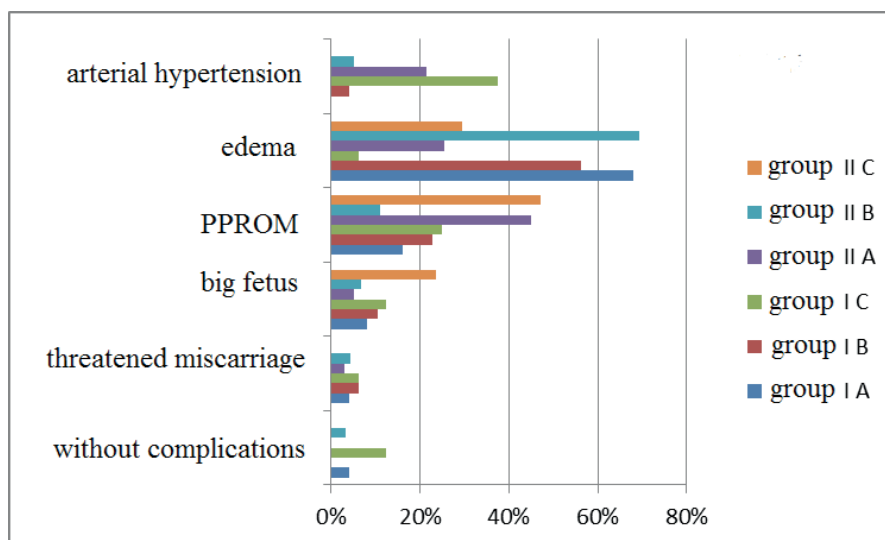


Figure 1.

The course of pregnancy in women of childbearing age (n =321)

Note. \* Here and in the remaining graphs, the null hypothesis was rejected at  $p < 0,05$  (критерий  $\chi^2$ ). Comparison of all subgroups:  $\chi^2=109,8; df=25; p < 0,0001^*$ . Comparison among subgroups within the group I:  $\chi^2=32,4; df=10; p=0,0003^*$ . Comparison among subgroups within the group II:  $\chi^2=72,6; df=10; p < 0,0001^*$ . Comparison between subgroups IA and IIA:  $\chi^2=24,4; df=5; p=0,0002^*$ .

Comparison between subgroups IB and IIB:  $\chi^2=6,7; df=5; p=0,24$ .

Comparison between subgroups IC and IIC:  $\chi^2=13,7; df=5; p=0,018^*$ .

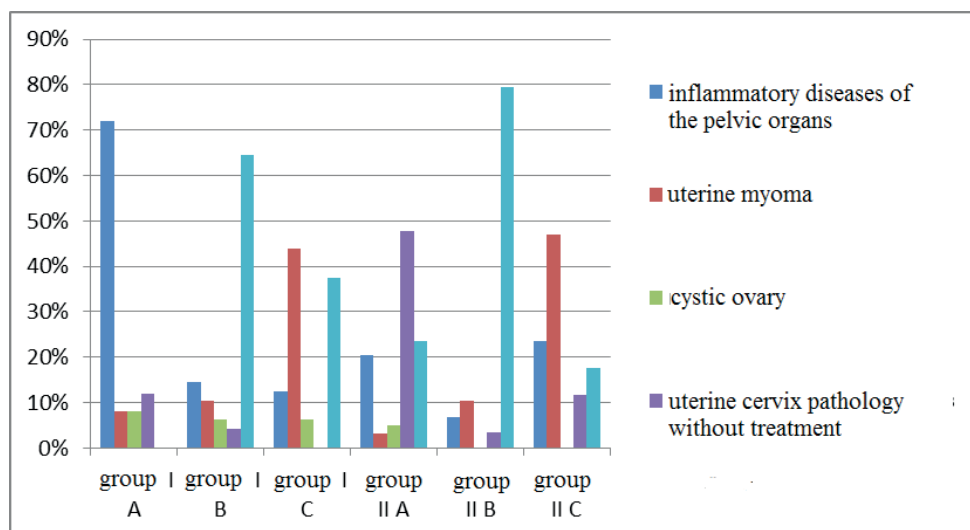


Figure 2.  
Gynecological anamnesis in women in the study groups

Note. \* Here and in the remaining graphs, the null hypothesis was rejected at  $p < 0,05$  (criterion  $\chi^2$ ). Comparison of all groups:  $\chi^2=222,2$ ;  $df=20$ ;  $p < 0,0001^*$ . Comparison among subgroups within the group I:  $\chi^2=49,2$ ;  $df=8$ ;  $p < 0,0001^*$ . Comparison among subgroups within the group II:  $\chi^2=127,5$ ;  $df=8$ ;  $p < 0,0001^*$ . Comparison among subgroups IA и IIA:  $\chi^2=30,9$ ;  $df=4$ ;  $p < 0,0001^*$ . Comparison between subgroups IB and IIB:  $\chi^2=10,6$ ;  $df=4$ ;  $p=0,03^*$ . Comparison between subgroups IC and IIC:  $\chi^2=4,7$ ;  $df=4$ ;  $p=0,32$ .

Among women of comparison groups using other methods of contraception, the reasons for abandoning the COC were analyzed, and in most cases, the woman prescribed a combined oral contraceptive quite individually: in 75% of cases there appeared pain in the mammary glands, 13% suffered from headache and increase in blood pressure, in 7% intermenstrual secretions occurred, in 5% – weight gain. The most common contraindications to taking COC were smoking – 23%, pregnancy – 3%, and diabetes mellitus with angiopathy – 1%.

### Conclusions

1. The overwhelming majority of women of fertile age refuse contraception in view of mastalgia (75%), the second most important cause is headache and increased blood pressure (13%) with the self-administration of combined oral contraceptives.

2. On average, women of reproductive age had one abortion in an anamnesis. Most often, after an abortion, women of childbearing age use an intrauterine device (26.8%), a vaginal ring (21.2%), ethinyl estradiol in combination with desogestrel (12.1%).

3. When analyzing the course of previous pregnancies, it was revealed that both in the main and in the comparison group they were most often complicated by edema during pregnancy and premature rupture of the membranes, especially in groups II C, II A, the patients of which used the natural method of contraception and interrupted sexual intercourse.

4. When analyzing a gynecological anamnesis, it was found out that the prevailing majority

of the subjects had a history of cervical pathology (49.5%), and pelvic inflammatory disease (19%).

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UDC 618.14-007.66-089.844

## AMBULATORY RECONSTRUCTIVE SURGERY BY INTRAUTERINE SEPTUM (TECHNIQUE)

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*Anomalies in the development of female genital organs account for 4% of all congenital malformations. They can cause disorders of the menstrual cycle, infertility and complicated course of pregnancy.*

*One of the abnormalities of the development of the uterus is the intrauterine septum. When this pathology is combined with infertility or miscarriage, there appear a question of the need to conduct and choose the method of operative correction. The article presents a procedure for reconstructive and plastic surgery on the uterus using an office rigid hysteroscope with a diameter of 4-5 mm and a surgical laser.*

**Key words:** *intrautous septum, office hysteroscopy, metroplasty, surgical laser.*

Congenital abnormalities of female genital organs, according to different literature sources, constitute 4% of all congenital disorders. In recent years, there has been observed the tendency of increase of frequency of detection of genital organs development defects which is, apparently, conditioned both by the growth of morbidity and by the improvement of diagnosis methods [1, 2].

One of the types of uterus development abnormalities is the intrauterine septum. Its presence can cause early and late spontaneous miscarriage, pre-term deliveries [3, 4].

In case of combination of this pathology with infertility or pregnancy miscarriage there often arises the necessity of surgical treatment [5].

The choice of most effective reconstructive surgeries by genital development defects remains a complicated task [5]. The implementation of hysteroscopic resectoscope and incision scissors is accompanied by the risk of penetration of uterus in the fundus, as these instruments do not allow to dissect the septum to the stated depth.

**Research objective:** to evaluate the effectiveness of the elaborated minimal invasive ambulatory technique of intrauterine septum dissection.

### Materials and methods

To evaluate the effectiveness of the elaborated method of ambulatory metroplasty there was performed the analysis of 15 ambulatory hysteroscopic operations.

The dissection of intrauterine septum was conducted by means of Russian junction laser "Latus-K" (Saint-Petersburg) with optical output power from 0 to 30 W, endoscopic scissors and office hard hysteroscope 4-5 mm in diameter having channels for irrigation of uterine cavity and instrumental channel 5 Fr for semi-hard instruments (K.STORZ). The broadening of cavity was made by the physiological solution of sodium chloride and hysteron-pump. The laser energy was brought to tissues by means of optic fiber 600 mkm in diameter.

The operations were performed in ambulatory conditions, without cervical canal broadening, under intravenous anesthesia.

For metroplasty in ambulatory conditions there was used the introduced method (patent for the invention №2610542 of 13.02.2017). Before the surgery there was conducted ultrasound investigation with 3d reconstruction of uterine cavity. In terms of study there was measured the length of the whole septum and part of the septum subject to dissection (in millimeters). For the operation there was prepared optic fiber: the laser fiber consisting of quartz and covered with polymeric enclosure was uncovered. As a result, the working element of the optic fiber was formed (5 mm). The optic fiber was introduced into the cavity of the uterus through the instrument channel of the hysteroscope and was brought to the most outstanding part of the septum. The working laser element was immersed into this part of the septum and there was formed a vaporization channel 5 mm deep. Then, with the interval of 1-2 mm on the left and right there were made additional vaporization channels. The tissue of the septum between the channel was dissected by endoscopic scissors 5 Fr. Thus, the septum was dissected to the strictly stated depth – 5 mm. The described manipulations were repeated in case of further dissection need.

For the sake of control of effectiveness of the conducted metroplasty in 2 months there was made ultrasound and hysteroscopy research.

The statistical data processing was performed by means of IBM SPSS Statistics 19. Quantitative parameters are presented by mean value and standard deviation.

### Results and discussion

The age of operated patients constituted  $31,85 \pm 3,55$  (from 25 to 38 years). The indication for surgery in 12 patients was aggravated obstetric and gynecological anamnesis: in 5 (33,33%) patients the anamnesis included two spontaneous miscarriages, in 4 (26,67%) patients – one spontaneous

miscarriage at the term of 16 weeks of pregnancy, in 3 (20%) patients – pre-term delivery at the term up to 34 weeks of pregnancy. # patients (20%) were directed to the hysteroscopic metroplasty before assisted reproductive treatment.

The analysis of duration of surgery showed that the average duration of operation constituted  $15,3 \pm 3,22$  minutes, blood loss -  $3,92 \pm 2,33$  ml.

The control ultrasound investigation conducted in 2 months revealed sufficient depth of the septum dissection, and the hysteroscopic examination showed full restoration of the endometrium structure and lack of vulnerary substrate in all patients.

### Conclusion

The elaborated hysteroscopic technique of reconstructive surgery on uterus allows to totally dissect the intrauterine septum without complications, especially, to avoid the uterine penetration. The use of hard office hysteroscope does not require the cervical channel broadening which is important from the point of view of prevention of cervical insufficiency. The implementation of laser prevents the development of complications connected with electric surgery. The combined use of surgical laser and endoscopic scissors prevents the formation of vulnerary substrate in the uterine cavity and contributes to quick restoration of endometrium. Consequently, the current technique of surgery is effective, safe and can be recommended for use in ambulatory conditions.

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UDC 618.14-002: 615.322

## COMPARATIVE EVALUATION OF EFFICIENCY OF DIFFERENT HERBAL MEDICINAL PRODUCTS CONTAINING ORTHILIA SECÚNDA IN TREATMENT OF CHRONIC

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*A comparative analysis of the effectiveness of phytopreparations containing orthilia secúnda was carried out in the treatment of chronic endometritis in 87 patients of reproductive age with chronic endometritis. For therapy there were selected three herbal medicinal products of Altai manufacturers: "Malavit-Ona", "Ortilida", and an extract of orthília secúnda. At the end of treatment, regardless of the choice of phytopreparation, all patients noted improvement in overall health, disappearance of symptoms of premenstrual tension, normalization of menstrual function. Clinical effects of phytotherapy are confirmed by echoscopic data: normalization of the M-echo, improvement of the endometrium structure.*

**Key words:** *orthília secúnda, phytotherapy, chronic endometritis.*

Phytotherapy as a method of treatment of various human diseases has been officially used since the XVIth century. The effectiveness of many medicinal plants has been proved experimentally and clinically, which allowed to consider phytotherapy as a medical specialty of official medicine [1, 2]. Flora of Altai Krai is rich in medicinal plants with proven healing properties. One of such plants is the orthilia secúnda. Anti-inflammatory, immunomodulating, anticoagulant properties of dry extract of orthilia secúnda have been proved by the experiment [3]. The antimicrobial activity of decoction of leaves of orthilia against enterobacteria, pseudomonads, staphylococci, fungi of the genus Candida [4] has been confirmed. On the basis of Altai State Medical University, we previously conducted clinical studies on the efficacy and safety of use of various phytocomplexes, which included orthilia secúnda [5].

The **research objective** was to perform a comparative analysis of the effectiveness of various herbal medicinal products of Altai producers containing orthilia secúnda in the treatment of chronic endometritis in patients of reproductive age.

### Materials and methods

The study involved 87 patients of reproductive age, diagnosed with «chronic endometritis,» which was confirmed by histological examination. Previously, taking into account the sensitivity of the detected infectious agent, all patients received antibacterial therapy according to the standards of management of patients, but at the time of their inclusion in the study, they had clinical, echoscopic and histological markers of chronic endometritis, which served as the basis for the second stage of treatment – rehabilitation.

Inclusion criteria:

- age of women – under 35 years old;

- patients who received a course of complex therapy of endometritis (antibacterial, antiviral and immunomodulating therapy) for three months before the study;
- patients with histologically confirmed chronic endometritis;
- informed consent of patients to participate in the study.

Exclusion criteria:

- uterine myoma requiring surgical treatment;
- adenomyosis 2-3 stage;
- adhesive process of the pelvis 2-3 stage;
- exacerbation of chronic or acute endometritis;
- somatic pathology in the stage of decompensation.

For the rehabilitation course of therapy of patients with chronic endometritis, three phytopreparations of Altai producers were selected, the main component of which was *Orthilia secúnda*:

“Malavit-Ona” (OOO (Limited Liability Company) “Malavit”, Barnaul). Contains herbal extracts *orthilia secúnda* 100.0 mg, *Rhodiola quadrifida* 50.0 mg, dry milfoil 50.0 mg, copper sulphate pentahydrate 0.1 mg, excipients (food lactose, calcium stearate) up to a weight of 500 mg. 2 capsules (500 mg) are taken 2 times in the morning with meals. Course of administration – 1-3 months.

“Ortilida. Formula 1 and 2” (CJSC “Balsam”, Biysk). Formula 1 contains: *orthília secúnda*, rhizomes and roots of *sulla* (red root), herbs and roots of marsh cinquefoil, rhizome and roots of *elecampa*, yarrow extract, vitamins B1 and B6. Formula 2 contains: *orthília secúnda*, burdock roots, *calendula* flowers, avian mountain herb, oregano herb, St. John’s wort extract, vitamins E and C. both formulas include microcrystalline cellulose (MCC) as the auxiliary component. Usage: formula 1 - from the 1st day of the sexual cycle to 2 tablets 2 times



a day during meals for 2 weeks; formula 2 - from 12-15th day of the sexual cycle to 2 tablets 2 times a day for the next 2 weeks. Course of administration - 1-3 months.

Instructions for use: formula 1 - 2 tablets 2 times a day during meals from the 1st day of the ovary cycle for 2 weeks; formula 2 - 2 tablets 2 times a day for the next 2 weeks from the 12th to 15th day of the sexual cycle.

"Orthilia secunda extract (HARMS, Barnaul)" - 2.5 mg / day, as an aqueous extract once a day with meals. Course of administration - 3-5 months.

By random sampling, all patients were divided into three equivalent groups. Patients of the first group (n = 29) received the phytopreparation "Malavit-Ona", the second group (n = 28) - the vitaminized phytocomplex "Ortilida", the third group (n = 30) - ortilia extract. The course of therapy was three months.

Before and after the end of the course of therapy, all patients underwent a complete clinical examination including assessment of somatic and gynecological status, bacterioscopic examination of the separated cervical canal on the flora

and sensitivity to antibiotics, PCR-based diagnostics of STIs, and ultrasound examination of pelvic organs. Clinical and echoscopic signs of endometritis are confirmed hysteroscopically and histologically once before the course of herbal medicine, since it is inadvisable to double the histological study to evaluate the effectiveness of the rehabilitation course of therapy [1].

Statistical processing of the obtained results was carried out with the help of the program Statistic 10, the values of the qualitative characteristics are represented in the form of frequencies and in percent, for comparison, the chi-square criterion was used with the Yates correction for continuity (at a frequency of fewer than 10 cases). Differences at a value of  $p < 0.05$  were accepted as statistically significant.

#### Results and discussion

The mean age of patients of all comparison groups was almost identical ( $27 \pm 1.2$ ;  $30 \pm 2.3$ ; and  $31.1 \pm 3.5$ ,  $p > 0.05$ ). The structure and frequency of extragenital pathology in the patients of the comparison groups did not significantly differ and is presented in Table 1.

Table 1

Structure and frequency of extragenital pathology in patients of the comparison groups

parameters	Malavit-Ona n=29 abs. (%)	Ortilida 1,2 n=28 abs. (%)	Orthilia extract n=30 abs. (%)	P Malavit/ Ortilida Malavit/ extract Ortilida / extract
vegetative-vascular dystonia by hypotonic type	7 (24)	10 (35,7)	6 (20)	0,3/0,7/0,1
arterial hypertension	3 (10,3)	5 (17,9)	4 (13,3)	0,3/ 0,7/ 0,6
chronic pyelonephritis	10 (34,5)	6 (21,4)	10 (33,3)	0,2/0,8/0,3
chronic cystitis	3 (10,3)	4 (14,3)	4 (13,3)	0,6/ 0,7/ 0,9
AIT, euthyroidism	7 (24,1)	12 (42,8)	10 (33,3)	0,1/0,4/ 0,4

When assessing the obstetric-gynecological history of the patients of the comparison groups, it was established that all of them had a high incidence of reproductive losses and medical abortions in the anamnesis (Table 2).

In addition to inflammatory diseases of the endometrium, they more often than in the population had hormone-dependent diseases of the genitals. Thus, the patients of the first group (24.1%) had an adenomyosis of the 1-2 degree somewhat more often than the patients of the second group (17.9%) and the third group (6.6%). In turn, the patients of the third group (23.3%) had uterine fibroids of a smaller size more often than the patients of the first group (13.8%) and the second group (5.6%). Both diseases are related to hormone-dependent (estrogen-dependent) pathology.

Patients of the second group had a history of not

only chronic endometritis but also chronic adnexitis (34.5%, 53.6% and 23.3%), which can indirectly speak of their low immune status. On the other hand, this may be a consequence of a higher incidence of induced abortions in patients in this group (10.3%, 17.9%, and 6.7% respectively).

At the time of enrollment, most patients in the comparison groups had complaints of menstrual dysfunction in the form of hyperpolymenorrhea or hypomenstrual syndrome and / or pain syndrome during the second phase of the cycle (Table 3). Echoscopic signs of chronic endometritis were established in all patients of the comparison groups.

After the end of treatment, all patients noted improvement in overall health (questionnaire SF-36), disappearance of symptoms of premenstrual tension and normalization of the menstrual cycle.

Table 2

*Frequency and structure of obstetric-gynecological pathology in patients of comparison groups*

parameters	Malavit-Ona n=29 abs. (%)	Ortilida 1,2 n=28 abs. (%)	Orthilia extract n=30 abs. (%)	P Malavit/ Ortilida Malavit/ Extract Ortilida / Extract
Term birth in time	15 (51,7)	17 (60,7)	11 (36,7)	0,8/ 1,3/ 1,7
Artificial abortions	3 (10,3)	5(17,9)	2 (6,7)	0,7/ 1,2/ 1,6
Reproductive losses	17(58,6)	15 (53,6)	21 (70)	1,1/0,8/ 0,7
Chronic adnexitis	10 (34,5)	15 (53,6)*	7 (23,3)	0,7/ 1,3/1,9
uterine fibroids of a small size	4 (13,8)	2 (5,6)	7 (23,3)	1,4/0,7/ 0,4
Adenomyosis 1-2 stage	7 (24,1)*	5 (17,9)	2(6,6)	1,1/1,7 /1,6

Table 3

*Clinical characteristics of the patients of the comparison groups before and after the course of phytotherapy*

parameters	Malavit-Ona n=29 abs./%			Ortilida 1,2 n=28 abs./%			Orthilia extract n=30 abs./%		
	before	after	p	before	after	p	before	after	p
premenstrual syndrome	28 /100	1/3,4	0,03	15/53,6	1/3,5	0,03	10/33,3	2/6,7	0,04
Hyperpolymenorrhea	14/48,3	1/3,4	0,048	7/25	4/14,3	0,046	4/13,3	1/3,3	0,047
Hypomenorrhea	3/10,3	1/3,4	0,5	7/25	3/10,7	0,46	18/60	2/6,7	0,3
Pain syndrome	9/31,3	3/10,3	0,43	7/25	1/3,5	0,44	3/10	2/6,7	0,49

Clinical improvement was confirmed by echoscopic data (ultrasound with CDC on the 21-25th day of the cycle): a tendency to normalize the M-echo

was established, an improvement in the structure of the endometrium was established (Table 4).

Table 4

*Echoscopic characteristics of patients in comparison groups before and after the course of phytotherapy*

parameters	Malavit-Ona n=29 abs./%			Ortilida 1,2 n=28 abs./%			Orthilia extract n=30 abs./%		
	before	after	p	before	after	p	before	after	p
M-echo, mm (21-23d day of cycle)	7,3±1,2	9,1±1,1	0,05	5,4±1,3	7,9±2,3	0,05	6,3±2,2	8,5±1,2	0,07
Inhomogeneity of the structure and uneven contours of the endometrium	29/100	14/48,2	0,03	28/100	17/60,7	0,04	24/80	16/53,3	0,06
Hyperechoic inclusions of the basal layer	29/100	25/86,2	0,8	28/100	26/92,8	0,8	30/100	23/76,7	0,7

All patients noted good drug tolerance; side effects in the course of the study were not established.

Thus, the conducted research demonstrated the high effectiveness of herbal medical products of Altai producers, containing orthilia secúnda, in the rehabilitation of patients with chronic endometritis.

In the course of the study, additional positive clinical effects of phytopreparations containing orthilia secúnda were recorded: reduction of pre-

menstrual tension, normalization of the menstrual cycle.

Complex herbal medical products "Malavit-Ona" and "Ortilida 1,2" are comparable in clinical efficacy with Orthilia secúnda extract, but more convenient for use in practice.

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UDC 618.333-091

## INTRANATAL FETAL DEATH IN TERM DELIVERY: CLINICAL AND PATHOMORPHOLOGICAL CORRELATIONS

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*Cases of death of a full-term fetus in term deliveries require in-depth analysis, since they are most often associated with an underestimation of the degree of obstetric risk of the mother and the choice of irrational tactics for labor management. Risk factors for intranatal death of a full-term fetus in term deliveries in Altai Krai were identified in this study: the patients were multipara women of different professions, with epilepsy and syphilis prevailing in the structure of the somatic pathology. Pregnancy of women who had full-term intranatal losses is complicated by the threat of interruption at a later date, preeclampsia, anemia, gestational pyelonephritis, delayed fetal growth, which indicates the presence of chronic secondary placental insufficiency, often an infectious genesis, confirmed by histological investigation of the placenta. The course of urgent labor in women with intranatal losses is complicated by the weakness of labor, progressive intranatal distress of the fetus, which determines the fatal outcome for the newborn. The intranatal death of a full-term fetus is due to preventable causes - asphyxia in childbirth and / or its combination with intrauterine infection.*

**Key words:** causes of intranatal mortality, full fetus, risk factors.

According to the Russian Federal State Statistics Service, since 2006, there has been marked positive dynamics of basic demographic parameters in the Russian Federation. However, Altai Krai refers to the number of regions with negative natural increase [1]. Due to the reduction of the region's reproductive potential connected with the demographic crisis of 1990s, the problem of perinatal losses remains topical [2]. In spite of the transition to new criteria of life birth, during the recent 10 years the rate of perinatal death in the region is considered stable (2006 – 9,5 promille, 2016 – 9,6 promille) due to the obstetrics and neonatal services [3]. Nevertheless, in Altai Krai since 2009 there has been registered the increase of the perinatal death rate over the average Russian value. The overwhelming majority of perinatal death cases in the region traditionally accounts for early neonatal and antenatal losses. The rate of intranatal losses in the structure of perinatal death is always minimal (2016 – 7,9%, absolute index – 22 cases).

However, cases of death of a full-term fetus in term deliveries require in-depth analysis, since they are most often associated with an underestimation of the degree of obstetric risk of the mother and the choice of irrational tactics for labor management [4]. Supposedly, an obvious solution of problem of death of a full-term fetus in term deliveries is the elimination of its preventable causes by means of compulsory monitoring of the fetal state, but two review of Cochrane Collaboration in 2013 and 2015 proved that the routine use of fetal cardiotocography (CTG) in antenatal and intranatal periods does not improve the perinatal outcome, but only contributes to the growth of number of caesarean sections and instrumental

deliveries [5, 6]. All existing methods of antenatal observation (CTG, sonography) does not possess prognostic potential in terms of various gestational complications, as they are quite informative but not specific, and allow to register only hypoxia and academia of the fetus preventing the fetal outcome conditioned by only these reasons [7, 8]. For this very reason, in the conditions of limited possibilities of means of diagnosis of fetal state, it is necessary to reveal the basic causes of full-term fetus death, to form the risk groups among women bearing intranatal losses specific for the given region aimed at a thorough fetal monitoring in these groups, to eliminate the controlled reasons of full-term fetus death and conduct a differentiated pre-conception preparation.

**Research objective:** to reveal the risk factors and basic causes of full-term fetus death.

**Tasks:** to study clinical anamnestic features of women having perinatal losses; to analyze the informational value of paraclinic methods of diagnosis of the fetal state shortly before and in the process of term labor; pathomorphological evaluation of fetuses and afterbirths.

**Subject of research:** cases of intranatal death of full-term fetus in districts of Altai Krai.

### Materials and methods

There was performed a clinic-statistical analysis of medical documentation on 252 cases "mother – full-term newborn" for the period of 2006-2015 in cities and districts of Altai Krai which were divided into two groups. The main group included 52 women at the age from 17 to 40 years whose term delivery resulted in the death of full-term fetus. The control group was formed by the lottery meth-

od and included 200 women at the age from 17 to 40 who had given birth to alive full-term newborns. In the compared groups there was performed a clinic-statistical analysis of age, social status, somatic, obstetrics and gynecological anamnesis, peculiarities of pregnancy course, delivery, functional characteristic of the fetoplacental complex by the third ultrasound screening, data of cardiocography during labor, pathomorphological characteristics of the fetus and afterbirth. The statistical significance was confirmed by the analysis of fourfold tables using Pearson's chi-square test  $\chi^2$ .

The study took into consideration: labor and delivery medical record (form №096/u), individual medical history (form №111/u), exchange notifying record (form №113/u), protocols of afterbirth histological characteristics and post-mortem examination of the fetus (form №013-1/u).

### Results and discussion

The average age of women in the main group constituted  $26,7 \pm 5,7$  years, in the control group -  $25,2 \pm 4,8$  years ( $p > 0,05$ ). The analysis of social status showed that patients of the main group had working occupations (34,6%) and significantly rarer were clerks (19,2%) in relation to women of the control group (12,5% and 55,0% respectively;  $p < 0,05$ ). The somatic anamnesis is significantly more aggravated in women of the main group in terms of frequency of organic brain disease - epilepsy (8,0%) and chronic specific infections including syphilis (21,0%) than in patients of the control group (0,5% and 1,5% of cases respectively;  $p < 0,05$ ). The frequency of detection of cardio-vascular pathology (45,0%) and urinary system diseases (19,0%) in both groups did not differ significantly ( $p > 0,05$ ). The majority of women of the main group were multiparous with aggravated obstetric anamnesis (AOA) (50,0%), while the control group was

significantly prevailed by primigravida women (38,5%) and multiparous patients with AOA were registered in 31,0% of cases ( $p < 0,05$ ).

There were revealed no differences of the features of obstetric anamnesis in the compared groups ( $p > 0,05$ ). It should be noted, that patients with intranatal losses (61,5%) turned out to be gynecological healthy more often than patients of the control group (44,4%,  $p < 0,05$ ). The evaluation of pregnancy course revealed that in women of the main group pregnancy was rarer complicated by threatened miscarriage at early stages (25,0%) and more often - during the whole 2<sup>nd</sup>-3<sup>rd</sup> trimester (50,0%) in relation to the control group (62,5% and 15,0% respectively;  $p < 0,05$ ). Preeclampsia developed only in women who had suffered intranatal losses (1,9%). Moreover, anemia of pregnancy, being one of the leading factors aggravating the severity of placental insufficiency, was observed in every second woman with fetal death in term delivery, while in the control group, it was diagnosed in every fifth case (21,0%) [9].

During pregnancy, patients of the main group had a significantly higher total infectious index than the women who had given birth to alive full-term newborns. Thus, infectious complications of pregnancy in the main group were registered in 59,6% cases against 35,0% in the control group ( $p < 0,05$ ). The leading infectious disease manifesting itself during pregnancy having ended in the death of the fetus in delivery was gestational pyelonephritis (17,3%). In the control group the manifestation of pyelonephritis accounted for only 4,0% of pregnancies ( $p < 0,05$ ). The echoscopic characteristic of the fetoplacental complex in the 3<sup>rd</sup> trimester showed that the significant marker of placental insufficiency - intrauterine growth restriction (IGR) - was revealed only in women who had lost the fetus in term delivery (7,7%) (Figure 1) [10].

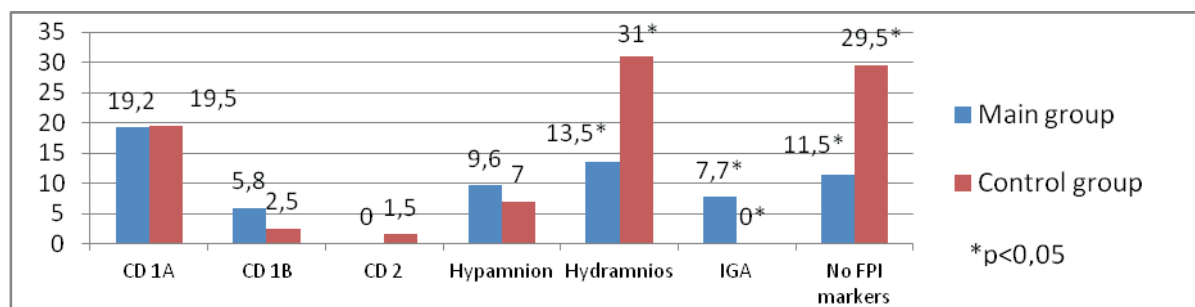


Figure 1.

Echoscopic characteristic of the fetoplacental complex in patients with intranatal losses by the 3<sup>rd</sup> ultrasound screening (%)

Horizontal axis: CD 1A, 1B, 2 - circulatory deficiency 1A, 1B, 2 degree; IGR - intrauterine growth restriction; no marker of FPI - no markers of fetoplacental insufficiency.

Vertical axis: percentage (%).

Columns: blue - main group; red - control group.

\* $p < 0,05$  - confidence interval of error probability.

There were revealed no significant differences in the frequency of circulatory deficiency (CD) of the fetoplacental complex among the pa-

tients of compared groups: CD 1A were revealed in the main and control groups in 19% of cases, CD 1B - 5,8% in the main and 2,5% in the control



group, CD 2 – only in the control group in 1,5% of cases (0,05). In women of the main group hydramnios was observed significantly rarer than in the control group (13,5% and 31,0% respectively;  $p < 0,05$ ). Generally, echoscopic markers of placental insufficiency lacked in patients having intranatal losses (11,5%) significantly higher in relation to women who had given birth to alive full-term children (29,5%;  $p < 0,05$ ). All women of the main group had obstructed labour. Poor uterine contraction strength was registered significantly more often in women of the main group (62,9%) compared to women of the control group (14,5%;  $p < 0,05$ ).

Only in women having intranatal losses there was registered umbilical cord prolapse (11,5%;  $p < 0,05$ ). Only by intranatal losses in every fifth case (21,1%) there was diagnosed expressed disorder of the heart rhythm of the fetus according to CTG

accompanied by meconium coloring of amniotic fluid in every third woman in labor (30,8%) which in 7,7% of cases lead to the necessity of assisted vaginal delivery - vacuum extraction of the fetus. Meconium coloring of amniotic fluid in women who had given birth to alive full-term newborns was observed significantly rarer – in every tenth case (12,0%;  $p < 0,05$ ). By the analysis of intranatal CTG decompensated (21,1%) and compensated disorders (44,2%) of cardio-vascular activity of the fetus were registered significantly more often in fetuses of the main group in relation to fetuses of the control group where disorders of cardio-vascular activity of the fetus had only compensated character (7,5% of cases;  $p < 0,05$ ) (Figure 2).

Results of the pathomorphological fetal autopsy are shown in Figure 3.

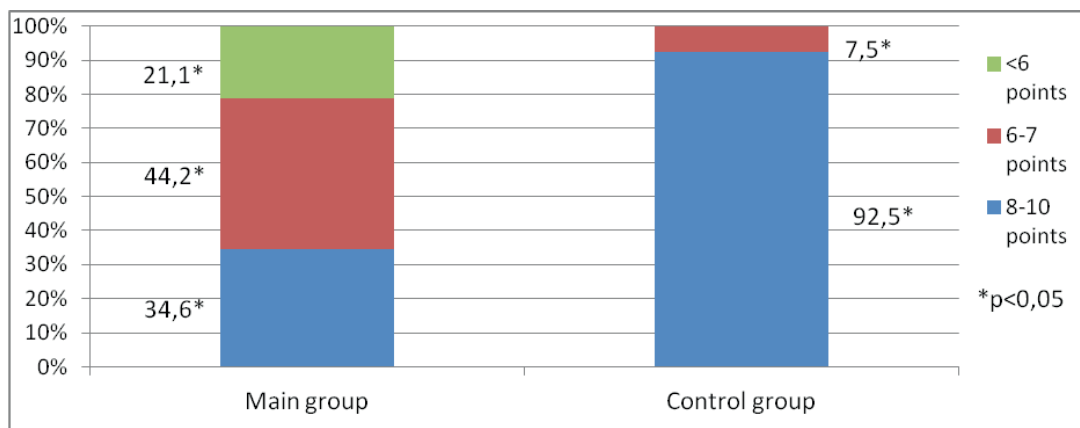


Figure 2.

Frequency of disorders of the intrauterine state of the fetus according to intranatal cardiotachography in points according to Fisher's scale (%)

Columns: №1 – main group; №2 – control group.

Vertical axis – percentage (%).

Green - <6 points according to Fisher's scale; red – 6-7 points according to Fisher's scale; blue – 8-10 points according to Fisher's scale.

\* $p < 0,05$  - confidence interval of error probability.

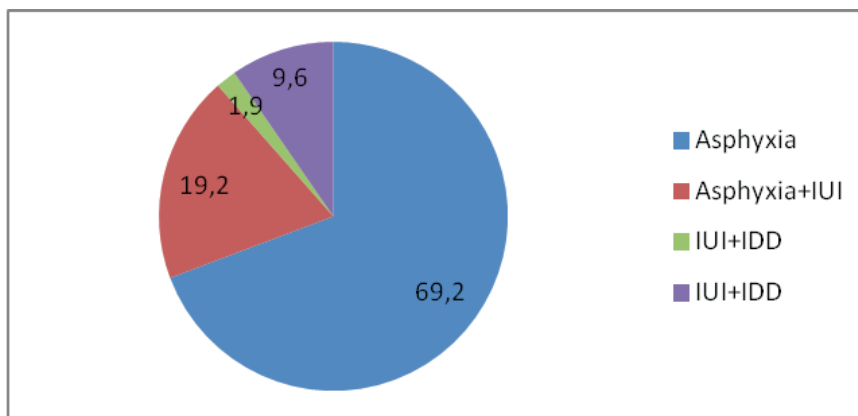


Figure 3.

Basic reasons of the intranatal fetal death according to the pathomorphological study (%)

Blue – asphyxia; red – asphyxia + intrauterine infection; green - intrauterine infection + intrauterine development disorder; purple - intrauterine infection.

The figure demonstrates that in the overwhelming majority of cases intranatal losses were determined by fetal asphyxia in labor (69,2%), including cases in combination with intrauterine infection (IUI) (19,2%). In every tenth case, pathologists considered IUI as the main cause of death and in 2% of cases – combination of IUI with fetal congenital anomalies (FCA). The morphological ground

for asphyxia in more than 70% of cases was placental insufficiency (PI), both isolated acute (7,0%) and its combination with chronic (40,0%) and inflammatory afterbirth changes (34,0%). The results of the histological examination of afterbirths showed histological markers of placental insufficiency in all afterbirths of the main group (Figures 4, 5).

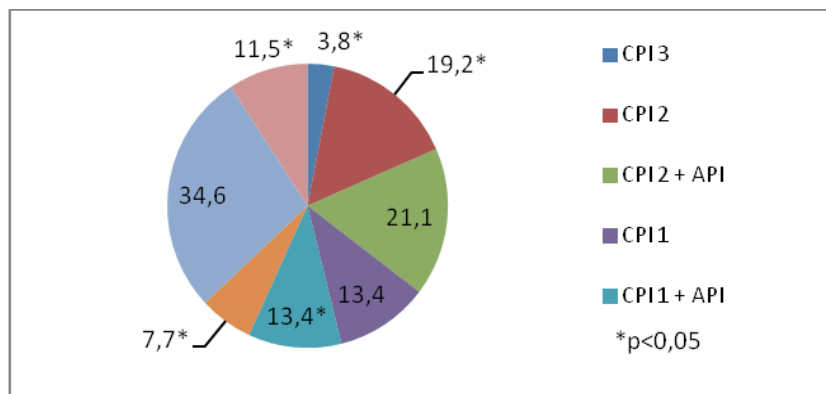


Figure 4.

Histological examination of afterbirths in women of the main group (%)

CPI 1,2,3 – chronic placental insufficiency compensated, subcompensated, decompensated.

CPI 2 + API – acute placental insufficiency in combination with chronic subcompensated placental insufficiency.

CPI 1 + API – acute placental insufficiency in combination with chronic compensated placental insufficiency.

\*p<0,05 – confidence interval of error probability.

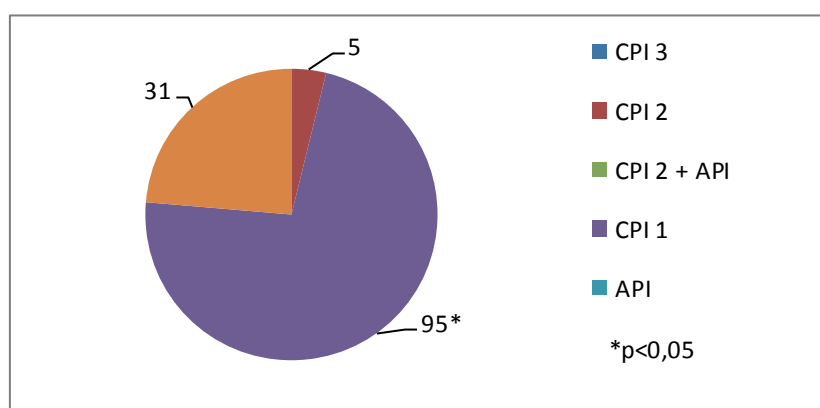


Figure 5.

Histological examination of afterbirths in women of the control group (%)

CPI 1,2,3 – chronic placental insufficiency compensated, subcompensated, decompensated.

CPI 2 + API – acute placental insufficiency in combination with chronic subcompensated placental insufficiency.

Chronic decompensated placental insufficiency (CPI 3) was revealed only in patients of the main group in 3,8% of cases, subcompensated (CPI 2) – in 19,2% of cases in the main group and in 5,0% in the control group (p<0,05). Acute placental insufficiency (API) (7,0%), its combination with chronic compensated (CPI 1) (13,4%) and subcompensated forms (21,1%) was observed only in women of the main group. Cases of thrombosis of umbilical vessels were registered only by intranatal losses (11,5%, p<0,05).

### Conclusion

The preformed clinic-statistical study in Altai Krai revealed that intranatal death of a full-term fetus is more often observed in multiparous women of working occupations whose structure of somatic pathology is significantly dominated by epilepsy and chronic specific infections, particularly, syphilis. The pregnancy of women with full-term intranatal losses is aggravated by threatened miscarriage at late stages, preeclampsia, anemia, gestational pyelonephritis, delayed fetal growth, which indicates the presence of chronic secondary placental insufficiency, often an infectious genesis, confirmed by histological investigation of the placenta.

The course of urgent labor in women with intranatal losses is complicated by the weakness of labor, progressive intranatal distress of the fetus, which determines the fatal outcome for the newborn. The intranatal death of a full-term fetus is due to preventable causes - asphyxia in childbirth and / or its combination with intrauterine infection.

Thus, in 2/3 of cases, the intranatal fetal death in term delivery (of asphyxia) is considered preventable from obstetric point by the choice of sustainable tactics of labor management on the background of hardware monitoring of the fetal state. The majority of risk factors connected with unfavorable perinatal outcome are also modified (somatic pathology, occupational hazards). The issues of prevention of perinatal losses due to intrauterine infection non-verified by the etiological factor are still unsolved, which presents further scientific concern.

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UDC 618.2:614.876

## PRINCIPLES OF FORMATION OF RISK GROUPS OF LATE RADIATION EFFECTS ON THE DESCENDANTS WHOSE GRANDPARENTS HAD BEEN EXPOSED TO RADIATION

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*The prediction of the reproductive health of the descendants of persons, whose grandparents had been exposed to radiation, is one of the primary objectives of not only medical but also social and economical profiles. The research objective was to determine the risk groups, primarily, high risk groups of late radiation effects for the reproductive health of the descendants. The study included 112 women of the second generation of descendants, whose grandparents had been exposed to radiation, and 53 women, whose parents and grandparents lived outside the radiation zone of the Semipalatinsk Test Site. The determination of risk groups was based on the results of clinical and paraclinic methods of investigation including the study of immune and hemostasiological systems. On the basis of the revealed risk factors there was created the "Prognostic scale of risk of reproductive health disorders in women of the second generation of descendants" with the corresponding software. The current program allows to determine the high degree of risk (29 points and higher) of the reproductive health disorder and low degree (less than 29 points), which, consequently, allowed to justify and implement the program of rehabilitation according to the risk degree.*

**Key words:** radiation effect, descendants, reproductive health.

At the present time, the state of reproductive health of women in Altai Krai has considerably deteriorated, especially in its south-west districts, which is conditioned by the overall reduction of health of parents and grandparents [1, 2]. One of the causes is the influence of radiation factor on grandparents in consequence of the nuclear tests at Semipalatinsk test site on the 29<sup>th</sup> of August 1949. The study of negative consequences of tests in Altai Krai showed a considerable decrease of the health state, including the reproductive one [3].

The prognosis of reproductive health disorders of descendants allows to perform modern research and choose targeted rehabilitation measures depending on the degree of risk. The informational approach to the prognosis of reproductive pathology will allow to determine basic principles of risk group formation which is a priority task for the present day, considering social and economic significance of rehabilitation of descendants whose grandparents had been exposed to radiation.

**The research objective** was to determine risk groups of late radiation effects on the basis of a prognostic scale of risk of reproductive health disorders by means of mathematical modelling in women whose grandparents had been exposed to radiation.

### Materials and methods

The qualifying scientific work is approved at the session of the Regional Ethics Committee of FSBEI HE Altai State Medical University of the Ministry of Health of the Russian Federation (protocol №12 of 08.11.12). At the stage of cross-sectional study conducted in 2011-2014 there was performed the enhanced study of the health state

of 165 women of fertile age. The main group consisted of 112 women presenting the second generation of descendants of persons who had been in the zone of radiation of Semipalatinsk test site. The control group included 53 women whose parents, grandparents and the women themselves had not been exposed to radiation.

Risk factors were determined by means of inquiry, questionnaire, clinical and paraclinic examination and also the data of medical documents: exchange notifying record (form №113/u), labor and delivery medical record (form №096/u), hospital neonatal record (form №097/u), outpatient medical record (025/u-87). The state of immune system of descendants was studied by means of laboratory tests evaluating T-cellular component of immune system: common T-cells (CD 3+), T-helpers (CD3+ CD4+), cytotoxic T-cells (CD8+), ratio CD4/CD8. There was examined the concentration of B-lymphocytes in blood, phagocytic index as the indicator of phagocytic activity of neutrophils. There were determined anti-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) by means of Procon test systems (OOO Proteinovy Kontur, Saint-Petersburg). The hemostasiological study additionally included the determination of D-dimers, prothrombogenic polymorphisms (inhibiting gene of plasminogen activator (PAI 1)) and mutations (FV Leiden, FII prothrombin gene) which implied the system "SNP-ekspres" (Litekh, Moscow).

There was evaluated the hormone profile of examined persons: thyroid-stimulating hormone (TSH), thyroxin (T4), triiodothyronine (T3), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and ovarian hormone (progesterone) by means of automatic im-

munochemiluminiscent analyzer IMMULITE 2000 DPC-SIEMENS.

The basic risk factors (predictors) of reproductive health disorders in women of second generation were determined by means of mathematical modelling. On the matrix of the obtained data there was elaborated the "Prognostic scale of risk of reproductive health disorders in women of the second generation of descendants". To determine differences and the degree of differentiation of studied factors there was performed a dispersion analysis (ANOVA). The variable significance was conducted by means of comparing the observed and critical values of F-statistics of Fisher-Snedecor [4].

The statistical significance of the research results was evaluated by various methods considering the feature and distribution type. The comparison of quantitative features having been checked for normality was conducted by means of unpaired t-test with identical or different dispersions depending on the situation after the unpaired F-test. Qualitative features having failed the normality test were compared by means of non-parametric method - Mann-Whitney U test. The comparative analysis of qualitative variables was performed by means of building contingency table 2x2. By the sum of all frequencies in the table under 20 and/or by the presence of expected frequencies under 5 there was used Fisher's two-tailed test. By the sum of frequencies over 20 - chi-square test ( $\chi^2$ ) with Yates' correction [5]. The statistical processing of obtained data was performed by means of STATISTICA 7.0 (StatSoft Inc., USA), statistical processor IBM SPSS 21.

### Results and discussion

Initially there was evaluated the degree of manifestation of influence of each reproductive health disorder risk factor revealed in women of the second generation of descendants.

Most significant risk factors effecting the reproductive health are the lineage ( $F=5,678$ ,  $p=0,0001$ ) showing who of the grandparents was exposed to radiation (grandmother, grandfather, both grandparents), aggravated reproductive medical history of mother ( $F=5,042$ ,  $p=0,01$ ), menarche (at the age of 14 and older) ( $F=5,042$ ,  $p=0,01$ ), chronic endometritis ( $F=7,264$ ,  $p=0,01$ ), menstrual disorders ( $F=13,370$ ,  $p=0,0001$ ), complicated course of previous pregnancies ( $F=13,705$ ,  $p=0,0001$ ), inevitable miscarriage in the 1<sup>st</sup> trimester ( $F=3,530$ ,  $p=0,003$ ) and pre-term delivery ( $F=3,428$ ;  $p=0,01$ ) in the anamnesis.

The function of thyroid gland in women of the second generation is closely connected with the functioning of pituitary-hypothalamic system manifesting itself through menstrual disorders, late menarche. There was revealed the increase of TSH up to  $5,4 \pm 1,8$  mIU/L ( $p=0,023$ ), in this regard there is proved the influence of increased TSH ( $F=6,319$ ;  $p=0,001$ ) on the reproductive health

of women of the second generation of descendants which confirms the presence of subclinical hypothyrosis as the manifestation of radiation late effects. One of its causes is autoimmune thyroiditis the frequency of which is considerably higher than in the control group (11,6%;  $p=0,039$ ). The median of thyroperoxidase antibodies constituted 93,0 [ $V_{0,25} 46,9$ ;  $V_{0,75} 995,0$ ], and there was revealed correlation between the TSH level and thyroperoxidase antibodies ( $r=0,377$ ,  $p=0,002$ ). Consequently, the pathology of thyroid gland is one of reproductive risk factors.

The additional risk factors with proved effect on the reproductive system are immune disorders. The leading factors of immune disorders as long-term effects of radiation influencing the health of descendants include reduced level of cytotoxic T-cells ( $F=9,218$ ;  $p=0,001$ ), increased level of anti-inflammatory cytokines ( $F=12,380$ ;  $p=0,0001$ ), primarily of interleukin-6.

The disorder of cell chain of immunity functional activity, suppression of anti-infectious organism protection, cytokine imbalance predetermine higher frequency of gynecological diseases, primarily, inflammatory diseases of female genital organs (64,3%;  $p=0,0001$ ), which can be one of the causes of menstrual disorders (27,7%;  $p=0,0002$ ). Another risk factor affecting the reproductive health is the hemostatic pathology, chiefly, PAI-1 gene polymorphism ( $F=8,777$ ;  $p=0,001$ ).

The role of each factor in the reproductive health disorder is different. To evaluate the degree of manifestation of influence of each reproductive health disorder risk factor in generations there was introduced a point system the calculation of which implied mathematical modelling method. The main factor predetermining reproductive health disorder is the lineage. Thus, the risk of reproductive health disorder was 3,0 times higher (4,8 p.) in women of the second generation of descendants, if the grandmother had been exposed to radiation, lower risk (1,6 p.) was observed in descendants whose grandfather had been exposed to radiation (Table 1). More substantial factors influencing the reproductive health of descendants are indexes characterizing the state of immune and hemostatic systems, such as the immunoregulatory index (32,2 p.) and T-killers/suppressors (11,3 p.) and also interleukin 6 (5,9 p.), homozygotic form of polymorphism PAI-I (4,7 p.), once again proving the influence of immune dysfunction and hemostatic disorders on the state of reproductive health of women of the second generation of descendants. The point evaluation of each predictor with calculated adjustment factor is presented in Table 1.

To determine risk groups there was calculated the border of point separation into low and high risk. In this regard, there was previously conducted the test calculation of risk degree in women of the main group. The scattering diagram (Figure 1) built according to the calculated degree of risk



of women of the second generation of grandparents shows the separation of the group into two sub-groups, thus, the border is the median

of points equal to 29,4 [ $V_{0,25}$  16,2;  $V_{0,75}$  62,0]. Consequently, there is determined the limit of low risk from 0 to 29 points and of high risk by 29 and more.

Table 1

*Prognostic scale of risk of reproductive health disorders in women of the second generation of descendants whose grandparents had been exposed to radiation*

Risk factors	Points
Anamnestic data	
Lineage	4,820 (grandmother) 3,213 (grandmother and grandfather) 1,607 (grandfather)
Aggravated reproductive medical history of mothers and grandmothers	7,114
Menarche (at the age of 14 and older)	0,793
Chronic endometritis	7,380
Menstrual disorders	6,258
Inevitable miscarriage in the 1 <sup>st</sup> trimester	3,001
Lack of complicated course of previous pregnancies	-0,662
Lack of pre-term delivery in the anamnesis	-0,356
Laboratory criteria	
immunoregulatory index	32,062
T-killers/suppressors	11,257
Interleukin 6	5,884
LH/FSH ratio	7,223
Follicle-stimulating hormone in blood corresponds to norm	-4,848
Thyroid-stimulating hormone	5,290
Homozygote PAI	4,657
Adjustment factor	4,26

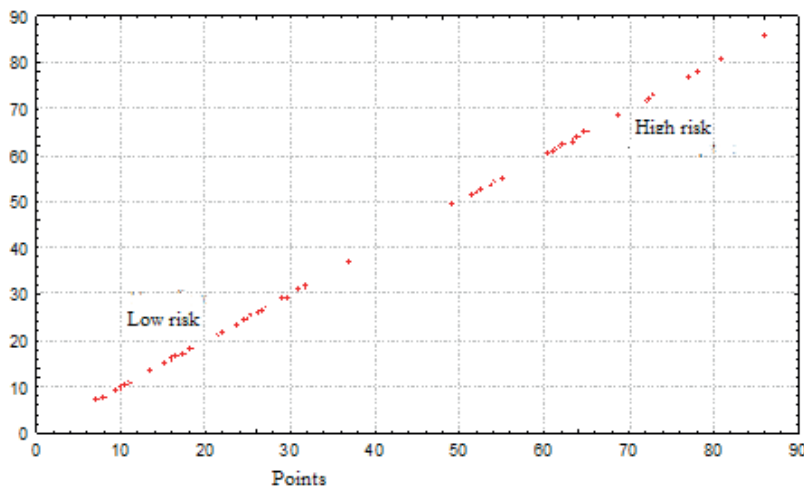


Figure 1. Scattering diagram of scores of women of the second generation of descendants

On the basis of risk gradation among women of the second generation of descendants, the group of high risk of reproductive health disorder included more than the half (53,7±1,5%) of women of the second generation of descendants whose grandparents had been exposed to radi-

ation, the group of low risk included 46,3±1,5%. In the control group none of the women corresponded to the high risk degree ( $p=0,0001$ ) of reproductive health disorder, all are traced to the group of low risk (100%;  $p=0,0001$ ).

To evaluate the effectiveness of the suggested risk scale there was determined the sensitivity and specificity. Initially, the assessment of accuracy of prognostic scale was performed on the data of the main group (n=67). Further there was conducted external validation of the scale on the test group of women of the second generation of descendants (n=30) not included into the main group which allowed to reduce the likelihood of accuracy upward bias due to the implementation of the sample. The diagnostic evaluation of the prognostic scale showed its high sensitivity – 83,9%, while the prognostic value of positive risk evaluation

(PRE) constituted 86,7%, thus, the reproductive function disorder is predicted practically in 87% of cases by the risk over 29 points.

The prognostic value of the negative risk (PVN) of test result is also high – 84,8%. The specificity of prognostic scale – 90,3%, h.e. it possible to predict the lack of reproductive function disorder with practically 90,0% accuracy by the calculated risk under 29 points.

As it is shown in Table 2, the effectiveness of the elaborated program checked on the test sample practically does not differ from the one obtained during the first evaluation.

Table 2

*Evaluation of the effectiveness of the prognostic scale of risk of the reproductive health disorders in descendants of persons, whose grandparents had been exposed to radiation*

Indexes	Main group (n=67)	Test group (n=30)	p
Sensitivity ( $S_s$ ), %	83,9	83,3	>0,05
Specificity ( $S_p$ ), %	90,3	91,7	>0,05
PVN, %	86,7	93,6	>0,05
PVP, %	84,8	78,6	>0,05

The visual evaluation of dependence of true-positive results of risk evaluation on false-negative results was performed by means of ROC-curve (Receive Operative Curve). The expert evaluation of the prognostic scale was conducted by means of AUC (Area Under Curve) constituting 0,84 (CI 95%: 0,74; 0,94) which proves a very high quality of the scale according to the expert scale for AUC values [4]. Consequently, the calculation of risk according to the present scale allows to predict the reproductive health disorders practically in 86,7% of cases.

On the basis of the suggested “Prognostic scale of risk of reproductive health disorders in women of the second generation of descendants” there was elaborated an ECM program.

### Conclusion

The principle of formation of risk groups of late radiation effects according to the revealed influencing factor after the corresponding examination is based on the calculation of scores indicating high or low risk of reproductive disorders. By the sum of points over 29 women of the second generation of descendants are traced to the high risk group, under 29 – to the low risk group. In case of inclusion into the high risk group, women are exposed to personified rehabilitation program aimed at the correction of revealed disorders. By the low risk, in a certain period of time there is need a re-evaluation of risk in case of appearance of additional unfavorable influencing factors.

The current model of prediction of late radiation effects on the reproductive health and the principle of formation of risk groups can be also used

for the determination of risk of effects of other unfavorable ecological factors.

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UDC 618.177-089.888.11

## PREDICTORS OF IVF PROGRAM FAILURES IN PATIENTS INFERTILITY AND BODY WEIGHT SURPLUS

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*In order to identify the predictors of failures in IVF programs in patients with body weight surplus, a retrospective analysis of 145 histories and protocols of superovulation stimulation for 135 factors was conducted. During the study, two comparison groups were formed. The first group (n = 99) is patients whose pregnancy has not occurred. The second group (n = 46) is patients whose pregnancy has occurred. The comparative analysis of the two groups showed no significant statistical differences, with the exception of the tubal peritoneal infertility factor (82.8% and 65.2% p = 0.03), which prevailed in the group of patients with an unsuccessful outcome in the IVF program. On the grounds of the work carried out, it can be concluded that it is necessary to further search for predictors of failures in this group of patients.*

**Key words:** overweight, obesity, IVF, infertility, pregnancy.

In conditions of modern socio-economical situation one of the key priorities of Russian state policy is the strengthening of the institution of the family and increase of birth rate. This socially important priorities are settled by the Presidential Decree №1351 of 9<sup>th</sup> October, 2007 [1]. In Altai Krai, in terms of realization of the program on the increase of birth rate in 2016 medical help regarding infertility implying assisted reproductive technologies (ART) was provided to 1215 couples, pregnancy happened in 30% of cases [2]. One of the socially significant problems of modern time is the problem of excess weight. Obesity is not only the risk of cardio-vascular pathology and oncology, but also the risk of infertility, maternal and perinatal incidence and lethality [3, 4]. It is reported that patients with weight surplus are included into the risk group of ART inefficiency [5]. However, for a number of female patients excessive weight is not a barrier for the realization of reproductive function in IVF programs. It is not strictly stated yet which factors in patients with weight surplus determine the effectiveness of ART programs and which are predictors of failure.

**Research objective:** to determine the factors conditioning the outcome of ART (IVF) in patients with weight surplus and obesity.

### Materials and methods

To solve the stated goal there was conducted a retrospective analysis of 145 medical histories and protocols of superovulation stimulation. The research was conducted on the basis of Siberian Institute of Human Reproduction and Genetics (Head physician, Candidate of Medical Science Vostrikov V.V.). Criteria of inclusion: overweight and obesity (BMI $\geq$ 25), age from 18 to 35, infertility of endocrine, tuboperitoneal, idiopathic or mixed genesis, 1 trial of IVF. Criteria of exclusion: female

patients of elder reproductive age, necessity of other types of ART (use of donated oocytes, surrogate maternity), male infertility factor, reduction of ovarian reserve, congenital disorder or acquired uterine cavity deformities, endometriosis of 3-4 stage, uterine myoma of large size, heavy forms of extragenital pathology, cancellation of embryo transfer.

In terms of study, there were formed two groups of comparison. First group (n=99) – patients in which pregnancy did not occur. Second group (n=46) – patients in which pregnancy did occur. There were assessed 135 factors including social characteristics, somatic and gynecological anamnesis, data of protocols of superovulation stimulation, evaluation of endometrium and embryos for transfer, and also the outcomes of occurred pregnancies.

The statistical processing of obtained results was conducted on the personal computer by means of Statistica 10.0 program package. In cases of normal distribution and also the equality of dispersion by F-criterion, there was used Student t-test to compare the mean values. In case of distributions not corresponding to the normal law and also by the inequality of dispersions, there was implied the non-parametric Mann-Whitney U-test. For the comparison of qualitative features, there was used  $\chi^2$  criterion with Yates' correction.

### Results and discussion

Patients of the comparison groups were comparable by age, region of residence, social status, somatic load and BMI. In both groups of comparison there dominated secondary infertility (63,6% and 65,2%; p=0,99). However, the tuboperitoneal factor of infertility was registered much rarer in patients with negative result of IVF program (82,8% and 65,2% p=0,03). The rate of occurrence of infertility of endocrine (46,5% and 58,7%; p=0,23),

mixed (39,4% and 32,6%;  $p=0,54$ ) and idiopathic (2% and 4,3%;  $p=0,8$ ) genesis in the compared groups did not differ significantly. The assessment of gynecological anamnesis showed that in the 1<sup>st</sup> group of patients (ineffective IVF), the frequency of spontaneous miscarriage (21,2% and 13%;  $p=0,34$ ) and extra-uterine pregnancy (40,4% and 26,1%;  $p=0,13$ ) was higher than in the second group (effective IVF). The same group of patients was characterized by more frequent occurrence of such diagnoses as polycystic ovarian syndrome (21,2% and 15,2%;  $p=0,53$ ), pelvic inflammatory diseases (82,8% and 73,9%;  $p=0,3$ ), uterine myoma (19,2% and 10,9%;  $p=0,31$ ), adenomyosis (8,1% and 2,2%;  $p=0,31$ ). The presence of Chlamydial infection in the anamnesis was associated with the IVF failure (20,2% and 6,5%  $p=0,064$ ).

In the majority of cases (75,8% and 76,1%;  $p=0,86$ ) in two groups of comparison there was used the long protocol. The protocol with antagonists held the second position (21,2% and 21,7%;  $p=0,88$ ), the short protocol of ovulation stimulation was rarely used (3% and 2%;  $p=0,80$ ). The average duration of stimulation in two groups was averagely identical ( $12,5\pm 0,2$  and  $12,2\pm 0,3$ ). Upon the end of stimulation protocol there were calculated the follicles suitable for puncture. The average rate of follicles with diameter over 16 mm in the first group constituted  $11,1\pm 0,8$ , in the second group -  $8,5\pm 0,7$ . The evaluation of embryos quality for transfer was characterized by the following indicators: embryos of perfect quality (57,6% и 56,5%;  $p=0,95$ ), embryos of good quality (57,6% and 56,5%;  $p=0,95$ ), embryos of satisfactory quality (15,2% и 6,5%;  $p=0,23$ ). The thickness of endometrium for transfer averagely constituted  $12\pm 0,5$  mm in both groups. A dangerous complication of ovulation stimulation program is the Ovarian Hyperstimulation Syndrome. In terms of this criterion there were no significant differences stated (15,2% and 10,9%;  $p=0,66$ ).

Occurrence of pregnancy is not the solvation of infertility problem. The analysis of outcomes of occurred pregnancies in patients of the second group showed that term births took place only in 55,3% of cases. The rate of early losses constituted 18,4%, preterm deliveries – 26,3%, which exceeds the overall population indexes.

## Conclusion

The assessment of groups of female patients with weight surplus for 135 factors did not show significant difference, except for the prevalence of tuboperitoneal factor of infertility in patients with IVF failure. According to the obtained data, it is possible to conclude that it is necessary to search for further factors associated with IVF failures in patients with weight surplus and obesity.

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UDC 618.16-002: 616.594.171.2

**ACUTE VULVOVAGINAL CANDIDIASIS: NEW TREATMENT OPTIONS**

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*There was studied the effectiveness of the azole medication of fenticonazole in terms of local therapy for acute vulvovaginal candidiasis in 111 patients of reproductive age. At the first stage of the study, 54 patients received 600 mg fenticonazole in a vaginal capsule once. 47 (100%) patients with acute uncomplicated candidiasis ascertained clinical and etiologic recovery on the 4th day. 7 patients with acute complicated VVC who had inflammatory symptoms on the control of cure and microscopic elements of yeast-like fungi were detected, were given a second capsule of fenticonazole on the fourth day, and on the 10th day clinical and etiological recovery was noted. At the second stage of the study 57 patients with acute complicated VVC received 2 capsules of fenticonazole intravaginally: on the first and fourth days of treatment. Clinical and etiological efficacy in acute complicated process was 96.9%. 106 patients had no side effects during the treatment, only 5 (4.5%) had slight itching and burning, regressed independently for 1.5-3 hours and did not require withdrawal of the drug. A conclusion is made about the high efficiency and good tolerability of fenticonazole in the form of vaginal capsules of 600 mg with acute VVC.*

**Key words:** yeast-like fungi of the genus *Candida*, acute vulvovaginal candidiasis, local azoles, fenticonazole.

Vulvovaginal candidiasis (VVC) continues to be one of the most serious problems of recent decades. In spite of modern fundamental scientific researches and new trends in etiology and pathogenesis of the disease, the approaches to diagnosis and treatment of VVC remain traditional.

VVC still ranks first in the structure of inflammatory diseases of female genital organs, for example, 30-45% of all infectious vaginal diseases [1]. Regardless of the termination of its official registration since 1999, the data on the increase of frequency of occurrence and the growth of its rate in the overall structure of gynecological pathology are actively discussed and do not encourage optimism [2].

At the present time, there are known quite many various factors predisposing to the development of the given disease, both endo- and exogenous: metabolic disorders, primarily carbohydrate and lipid; concomitant endocrine pathology; chronic inflammatory diseases of female genital sphere; hematological diseases; HIV infection; long-term uncontrolled intake of antibiotic, cytostatic, glucocorticosteroid drugs, hormonal contraceptives, chemical and radiation therapy; wearing of tight synthetic under-clothes; use of daily pantyshield, various vaginal syringes, deodorants; smoking, alcohol and drug abuse, etc. [3].

The development of acute VVC is always accompanied by expressed subjective symptoms (painful itching, frequently – intense burning, painful urination, painful sexual transactions) which, apparently, decreases the quality of life of a woman and her working ability. An important clinical feature of the disease is a more repeated in recent times combination of candidiasis of lower female genitals with urethritis, urethrocystitis, pelvic organ diseases and pyelonephritis [4,5].

It is known, that the VVC structure gradually begins to be prevailed by chronic forms of the disease, while the role of *Candida non-albicans* in its development is growing [6]. In the literature there is discussed the probability of haematogenous dissemination of fungi *Candida* by their deep penetration into the sub mucous membrane and vessels [7]. Due to the presence of common antigens with kidneys, skin, vaginal and gastro-intestinal mucous membrane in *Candida albicans* a particular category of patients are exposed to the development of an autoimmune process [8].

At the present time, there arises another important problem connected with the reduction of sensitivity of *Candida* fungi to antimycotic agents, particularly, to azole antifungal agents which are most widely prescribed medications by VVC and hold first positions in all recommendations for VVC treatment [2, 9, 10]. Nevertheless, at this time, the sensitivity of *Candida* fungi to azole drugs grows [11]. Thus, the search of new drugs with more improved mechanism of action is quite topical, as it allows to broaden the range of therapeutic means in a complicated situation of antimycotic activity reduction.

A respectively new medication for Russia is fenticonazole – an imidazole derivative acting against *Candida* fungi and dermatophytes [12, 13]. Fenticonazole has been authorized for use by BBC treatment since 1986. In Europe it has been clinically used by VVC for 30 years. In Russia the drug is registered in the form of 2% cream and vaginal capsules containing 600 and 1000 mg of the drug. Several randomized studies conducted in Europe show the advantages and higher therapeutic effectiveness of fenticonazole in relation to clotrimazole in patients with VVC [14, 15].



The studies conducted with 72 women with VVC demonstrated high (92%) therapeutic and microbiological effectiveness of one vaginal capsule of fenticonazole 600 mg in 1 week after the intake, and also revealed high tolerability of the drug: no systemic and local side effects were observed [16].

In recent times, the given medication has been actively studied also in Russia. According to P.R. Abakarova et al., the therapeutic effectiveness of fenticonazole by acute VVC taken in the dose of 600 mg intravaginally two times with the interval of 3 days constituted 96,7% [17]. The results of the study of effectiveness of fenticonazole in the form of 2% vaginal cream by acute VVC in 30 women of reproductive age conducted by L.S. Logutova et al. also demonstrated clinical and etiologic recovery in 96,7% [18].

The scientific research of fenticonazole mechanism of activity earlier performed in Europe showed that the drug inhibits synthesis of ergosterol increasing the permeability of fungal cell walls, destroying lysosomes and releasing lysosomal enzymes which leads to the self-destruction of the fungal cell. This is the activity of all imidazoles. However, in the fenticonazole mechanism of activity there was revealed another pathogenically important moment: the inhibiting of acid proteinase aspartate synthesis playing the basic role in the adhesion of fungi to the vaginal epithelium, their penetration into epithelial cells and further invasion. This fenticonazole mechanism of activity is unique and not typical for any of imidazole drugs [19]. The optimal environment for the adequate antimycotic activity of fenticonazole is acid, which corresponds to the condition of genuine VVC development. Moreover, fenticonazole is characterized by long-term inhibiting activity (during 48-72 h after application) and low level of systemic absorption, and also high tolerability and safety [14, 15, 20].

**Research objective:** to determine the effectiveness of fenticonazole by the treatment of patients with acute vulvovaginal candidiasis.

### Materials and methods

The study of fenticonazole (Lomexin, Recordat) effectiveness by the treatment of patients with acute vulvovaginal candidiasis was carried on the clinical base of the Department of dermatovenerology of the Advanced Training Faculty and teaching staff of FSBEI HE Irkutsk State Medical University of the Ministry of Health of the Russian Federation.

There were observed 111 female patients with acute VVC. Their clinical examination included: complaints for the moment of first examination; anamnesis of the disease and life, previous diseases, concomitant pathology. In every patient there were analyzed factors predisposing to VVC development. The objective study of patients included

the examination of external genital organs, observation of uterine cervix and vagina in the mirrors, palpation of genital organs, pH determination, aminotest and also clinical material sampling for laboratory testing.

The stage of laboratory examination included microscopy of native, methylene-blue and Gram-stained preparations from vaginal, urethral and cervical secretions. The STD causative agents (*T.vaginalis*, *N.gonorrhoeae*, *C.trachomatis*, *M.genitalium*, *Herpes Simplex Virus*, *Human Papilloma Virus*) were revealed by means of PCR-based diagnostics. The examination for syphilis was conducted by means of micro precipitation test. 14 patients with symptoms of cervicitis accompanied by low fluor zervikalis were exposed to the cultural study of cervical secretions aimed at the microbiocenosis study.

The main criteria of inclusion of patients into the study group was the proven diagnosis of acute vulvovaginal candidiasis, lack of chronic VVC, decompensated diabetes mellitus, oncological and hematological diseases and also other severe concomitant pathology requiring continuous intake of antibiotic, immunosuppressive, chemical or radiation therapy, lack of pregnancy, lack of pathogenic and other opportunistic pathogens.

The female patients were divided into two groups. At the first stage of study 54 patients with acute VVC (group 1) received 600 mg of fenticonazole in the form of vaginal capsule once before bed. After the analysis of treatment results, and, particularly, its failures, there was performed the second stage during which 57 patients with acute complicated VVC (group 2) received 600 mg of fenticonazole intravaginally twice: on the 1<sup>st</sup> and 4<sup>th</sup> day (before bed).

The control of recovery was performed in the 1<sup>st</sup> group of patients on the 4<sup>th</sup> and 10<sup>th</sup> day after the end of treatment, in patients of the 2<sup>nd</sup> group – in 10 days after the end of treatment by means of clinical examination and microscopy of urogenital secretions. By the preservation of clinical symptoms of inflammation in the urogenital tract by the control of recovery there were prescribed systemic antimycotic agents.

### Results and discussion

111 women with acute VVC (from 15 to 51 years) had the following age groups: under 20 – 14 patients, from 21 to 30 – 49 patients, from 31 to 40 – 34 patients, from 41 – 14 patients. The majority were 83 women at the age from 21 to 40 (74,8%).

Among the factors predisposing to the development of VVC prevailed: in the first group - use of daily pantyshields – in 33 (61,1%) women, wearing of tight synthetic under-clothes – in 21 (38,8%), recent administration of antibiotics against concomitant diseases – in 15 (27,7%), long-term administration of oral contraceptives - 12 (22,2%), smok-

ing – in 15 (27,8%) women; in the second group – use of daily pantyshields and wearing of tight synthetic under-clothes – in 44 (77,2%), smoking – in 27 (47,4%), long-term administration of oral contraceptives – in 12 (21,1%), recent administration of antibiotics against concomitant diseases – in 3 (5,3%), alcohol abuse – in 1 (1,8%).

From the concomitant pathology in 7 patients of the first group there were revealed chronic inflammatory diseases, in the majority of them – in various combinations: urinary diseases – in 3 (5,6%), gastro-intestinal diseases – in 3 (5,6%), respiratory diseases – in 2 (3,7%). In 3 women there was revealed cystic ovary, in 2 – endocrine pathology.

In 18 (31,6%) patients of the second group there were revealed chronic gynecological diseases: endometriosis – in 14,1%, cervicitis – in 8,8%, cervical erosion – in 3,5%, polycystosis, cystic ovary and uterine myoma – in 1,8%. Menstrual disorders were observed in 13 women (22,8%). Various endocrine disorders were registered in 4 (7,0%) patients, gastro-intestinal diseases – in 4 (7,0%), HIV infection – in 3 (5,3%).

The age of the inflammatory process in the area of external genital organs ranged from 2 to 7 days. Subjective symptoms were traditional for acute VVC and were characterized by intensive itching – in 84 (75,7%), burning – in 69 (62,2%), dyspareunia – in 56 (50,5%), excessive secretions from genital tracts – in 54 (48,6%) patients, expressed painfulness by urination – in 16 (14,4%), dull lower abdominal pain – in 6 (5,4%).

The objective examination of all 111 patients revealed symptoms of vulvitis apparently being secondary in nature: edema, hyperemia of labia minora, rarer – of labia majora, of vaginal orifice, clitoris, epithalamic commissure, and also layering of secretions of caseous type. The vaginal examination revealed: intense hyperemia – in 101 (91,0%) patients and expressed edema of vaginal walls – in 96 (86,5%), more often – intensive (in 57 – 51,4%) or moderate (in 54 – 48,6%) secretions from vagina; the secretions were primarily caseous – in 61 (55,0%) patients. Objective symptoms of urethritis in more than the half of patients were characterized by hyperemia (in 66 – 59,5%), accompanied by edema (in 54 – 48,6%) of urethral sponges. 31 (27,9%) had stated symptoms of cervicitis with hyperemia and slight edema of the vaginal part of uterine cervix with caseous “fur”. 14 patients had slight secretions from the cervical channel, the external os of the channel was hyperemic and edemic.

The microscopy of vaginal secretion in all patients revealed the elements of yeast-like fungi – blastospores and pseudomycelium accompanied by leukocytosis of 25-50 neutrophils per field of vision and exceeded number of epithelial cells. In 24 patients out of 66 patients with symptoms of urethritis there was revealed an exceeded number

of leucocytes – more than 10 cells - per field of vision. The PCR-test did not reveal any STD causative agents. The cultural examination of cervical secretion revealed in 14 patients with symptoms of cervicitis *E. faecalis*, *E.coli*, *St. aureus*, *St. epidermidis* in concentration over  $10^4$  cfu/ml.

The control of recovery showed clinical and etiological recovery on the 4<sup>th</sup> day after fenticonazole administration in 47 (87,0%) patients of the first group.

7 women of the first group retained inflammatory symptoms in the vaginal area on the 4<sup>th</sup> day after the start of treatment (slight hyperemia without edema, slight secretions from the posterolateral vaginal fornix of mainly creamy type, in 3 patients – recurrent moderate itching). The microscopy of vaginal secretions in all 7 patients revealed blastospores, in 3 – excessive leucocytes (up to 30 cells per field of vision). The microscopy of urethral secretion corresponded to the norm.

The analysis of anamnestic data in 7 patients showed that all patients had chronic inflammatory diseases of urogenital tract, respiratory system and gastro-intestinal tract, 6 of them had concomitant nonspecific (aerobic) cervicitis. 5 patients constantly used daily pantyshields and tight synthetic under-clothes. 4 women marked long-term administration of antibacterial medications 2-3 weeks before VVC development, in 3 patients there were revealed occupational hazards: occupation of nurse in the treatment room (in 2) and pastrycook (in 1). In all 7 women these factors were stated in various combinations, thus, every patient was characterized by complicated acute VVC. Due to the preservation of inflammatory symptoms in vagina blastospores by microscopy (on the 4<sup>th</sup> day after the first fenticonazole administration) these patients were exposed to the repeated introduction of the vaginal capsule. Six patients with revealed aerobic cervicitis together with fenticonazole received co-amoxiclav for 5 days. On the 10<sup>th</sup> day after the end of treatment the clinical laboratory control showed regression of Candida vaginitis in all patients with the absence of elements of yeast-like fungi and excessive leucocytes in vagina. 6 patients receiving co-amoxiclav showed regression of cervicitis symptoms.

According to the analysis of treatment results in patients of the first group, all 47 (100%) patients with acute uncomplicated VVC showed clinical and microbiological recovery after the intake of one capsule of fenticonazole. Seven patients with diagnosed complicated acute VVC receiving 2 capsules of fenticonazole per the course of treatment also showed clinical and microbiological recovery.

The data obtained during the first stage of study allowed to assume that it is reasonable to prescribe 2 capsules of fenticonazole per the course of treatment with 3-day break to the patients with complicated acute VVC, which was proved during

the second stage of study: clinical and etiological effectiveness of the stated course of treatment constituted 95,5% (55 patients) on the 10<sup>th</sup> day after the end of therapy.

In 2 women of the second group there remained itching and vaginal inflammatory symptoms: moderate hyperemia, secretions of creamy type. The microscopy showed blastospores and mycelium fibers.

The analysis of anamnestic data of these patients showed that constantly used tight synthetic under-clothes and one woman used daily pantyshields. Moreover, both patients had chronic inflammatory diseases of the urinary tract (cervicitis, cervical erosion), menstrual disorders, endocrine pathologies (thyroid gland nodule), long-term administration of contraceptives, violation of intimate hygiene rules. Due to the preservation of inflammatory symptoms in vagina blastospores by microscopy these patients were exposed to the systemic therapy with fluconazole.

The analysis of fenticonazole safety in 106 patients did not reveal any side effect – neither local, nor systemic. Only 5 (4,5%) patients complained for slight burning and itching by the drug administration which disappeared in 1,5-3 hours.

Consequently, two stages of our study showed that therapeutic activity of one vaginal capsule of fenticonazole 600 mg by acute uncomplicated VVC constituted 100% (71 out of 47 patients), of two capsules by complicated VVC – 96,9% (62 out of 64 patients).

### Conclusions

1. Fenticonazole in the form of vaginal capsule in the dose of 600 mg is a highly effective and safe medicine by the treatment of acute VVC possessing high compliance and allowing to reach clinical and etiological recovery in the majority of patients.

2. The indication to one-time administration of vaginal capsule of fenticonazole 600 mg is acute uncomplicated VVC, to two-time administration of fenticonazole 600 mg with 3-day break – complicated acute VVC.

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UDC 616.617-002-08-055.1

## THE DYNAMIC ANALYSIS OF URETHRAL MICROCIRCULATION INDEXES IN MEN WITH CHRONIC NON-GONOCOCCAL URETHRITIS AGAINST THE BACKGROUND OF COMPLEX THERAPY

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*The aim of the study was to assess the impact of the complex effect of vibromagnetotherapy and peloidotherapy on urethral microcirculation in patients with chronic recurrent non-gonococcal urethritis. The effectiveness of treatment was assessed by the combination of clinical, laboratory and instrumental diagnostic methods. To evaluate the microcirculation of the urethra, the laser Doppler flowmetry method was used. The obtained diagnostic data before and after treatment demonstrated more effective normalization of clinical data, urethral microcirculation indices in patients receiving complex treatment with the inclusion of vibro-magnetic therapy and peloidotherapy.*

**Key words:** chronic non-gonococcal urethritis, microcirculation, vibromagnetotherapy, peloidotherapy.

The problem of chronic non-gonococcal urethritis (NGU) has not lost its significance to a large extent due to the torpidity of this disease to the conducted therapy, high frequency of residual urethritis development and high contagiousness [1]. Urethritis is considered persistent or recurrent when the symptoms of urethritis appear in 30-90 days after the treatment of acute NGU. According to various researchers, such state is observed in 10-20% of patients [2]. NGU accounts for 60-65% of urethral inflammatory diseases. Every year in Russia there are registered about 350 thousand NGU cases [3,4]. In 90-93% of cases NGU is caused by pathogenic agents destroying cells of cylindrical epithelium: chlamydia (*Chlamydia trachomatis*), genital mycoplasmas (*Mycoplasma hominis*, *Ureaplasma urealyticum*), trichomonads, *Candida* fungi, herpes simplex virus type I and II. More detailed epidemiological characteristics of NGU are limited by the fact that a part of them lack symptoms and thus, are not registered, while mycoplasmas, acting as NGU causative agents in particular conditions, are resident microflora in 50% of men [5].

One of the important pathogenic constituents of chronic NGU are vascular disorders appearing by long-term inflammatory process. However, low effectiveness of antibacterial therapy, continuous and repeated treatment courses lead to even greater suppression of local immunity and reduction of colonizational resistance of the urogenital tract [6, 7]. Considering modern data on the main causes of NGU development, pathogenetically substantiated is the implementation of therapeutic methods aimed at the elimination of all disease chains.

**Research objective:** the dynamic assessment of urethral microcirculation state against the background of complex therapy including peloidotherapy and physiotherapy in patients with chronic non-gonococcal urethritis.

### Materials and methods

The study included 48 men with chronic non-gonococcal urethritis. Criteria of inclusion: men of reproductive age from 18 to 46 years with diagnosed urethritis and period of illness not less than 6 months, and also with laboratory confirmed urogenital infection.

Criteria of exclusion: patients administrating antibacterial drugs 2 months before the visit to doctor; patients with exacerbation of chronic somatic diseases at the moment of study; patients with syphilis, gonorrhoea, HIV infection.

Patients underwent laboratory-instrumental examination, diagnostics of urogenital and viral infections (*C.trachomatis*, *M. genitalium*, *M.hominis*, *U.urealyticum*, HSV2) by means of polymerase chain reaction (PCR "real-time"), microscopic examination of urethral secretions in order to diagnose *Tr.vaginalis* and *Candida* fungi.

To evaluate the urethral microcirculation by means of laser Doppler flowmetry (LDF) there was used the laser analyzer of blood microcirculation LAKK-02 (NPP "LAZMA", Russia) (patent № 2605622 "Method of differential diagnosis of urethritis in men"). The helium-neon laser LGN-207B or LGN-208B with the wave length 0,63 mkm is used as a radiant. The power of laser radiation at the input of the lightguide cable constitutes not less than 0,5 mW. The patient was examined in the lying position, the endoscopic tube was introduced directly into the urethra till the transition of the anterior part into the posterior.

In order to enhance the obtaining results all measurements were performed in the same temperature regime of the room, at the same time of the day. After the tube imposition, the indications were registered during 1 minute. These researches in the stated point were evaluated after the calculation of overall average and reflected the rate of basal bloodstream. By means of hard-



ware there were processed the curves immediately after every conducted examination.

The calculation of basal bloodstream parameters was performed in two stages. At the first stage, there were calculated mean values of the perfusion change:  $M$ ,  $\sigma$  and  $C_v$ . At the second stage, there were analyzed bloodstream oscillations.

$M$  parameter – is the value of the mean bloodstream within the intervals of time of registration and the arithmetic mean value of microcirculation – is measured in perfusion units (pf. un.).

The higher  $M$  is, the bigger is the level of tissue perfusion. Moreover, the increase of its value can be connected with blood congestion in the venular chain of the microcirculatory bloodstream.

The indicator showing the stream of erythrocytes, root-mean-square deviation – RMSD – ( $\sigma$ ) – statistically significant fluctuations of the erythrocyte speed. It is also measured in perfusion units and characterizes temporal variability of microcirculation and fluctuation of the erythrocyte stream. Value  $\sigma$  is significant for the evaluation of the microcirculation state, preservation of its regulation mechanisms.

In terms of analysis of calculated parameters it is reasonable to focus on the relation of values  $M$  and  $\sigma$ , h.e. the coefficient of variation. It characterizes the relation between the tissue perfusion and the value of its variability, and is calculated according to the formula:  $C_v = \sigma / M * 100\%$ .

At the second stage, there is analyzed the amplitude-frequency spectrum (AFS) of perfusion fluctuations. The values of amplitudes of microcirculation fluctuations within particular frequency intervals allow to estimate the vascular tonus and the state of functioning of particular mechanisms of perfusion control. There is used a number of calculated rates: myogenic tonus, neurogenic tonus, rate of shunting and microcirculation efficiency index.

The neurogenic tonus (NT) of precapillary resistant microcirculation vessels is connected with the activity of  $\alpha$ -adrenoreceptors (mainly  $\alpha_1$ ) of the membrane of clue and partially adjacent smooth muscle cells, and is calculated according to the following formula:  $NT = \sigma * P_{av} / An * M$ , where  $\sigma$  – root-mean-square deviation of microcirculation rate,  $P_{av}$  – average arterial pressure,  $An$  – maximum value of the perfusion fluctuation amplitude in the neurogenic interval,  $M$  – arithmetic mean of the microcirculation rate.

The myogenic tonus (MT) of metarterioles and precapillary sphincters is determined according to the following formula:  $MT = \sigma * P_{av} / Am * M$ , where  $\sigma$  – root-mean-square deviation of microcirculation rate,  $P_{av}$  – average arterial pressure,  $Am$  – amplitude of oscillation of the myogenic interval,  $M$  – arithmetic mean of the microcirculation rate.

The shunting index (SI) is calculated according to the following formula:  $SI = MT/NT$ .

The index of microcirculation efficiency (IEM) is determined according to the following formula:

$IEM = A_{maxLF} / (A_{maxHF} + A_{maxCF})$ , it characterizes the relation between the bloodstream fluctuations in various areas of the frequency spectrum, where  $A_{maxCF}$  – amplitude of cardiac fluctuations,  $A_{maxLF}$  – amplitude of low fluctuations,  $A_{maxHF}$  – amplitude of respiratory fluctuations.

All men with NGU received standard therapy according to STD treatment recommendations aimed at the causative agent elimination. Upon determining mycoplasmal, chlamydial or ureaplasma infection there was prescribed josamycin at a dose of 500 mg orally 3 times a day during 10 days, by trichomonad infection – metronidazole at a dose of 500 mg orally 2 times a day during 7 days or ornidazole at a dose of 500 mg orally 2 times a day during 5 days [8].

At the second stage of treatment, all 48 patients received vibrational, thermal and magnetotherapy and pelotherapy. Vibrational, thermal and magnetotherapy was performed by means of "AVIM-1" apparatus (OOO "TRIMA, Saratov, RZN license No. FSR 2008/02518). The apparatus presents a disk-shaped instrument with slightly bowed work surface which can be placed on the chair. The procedures were conducted in the sitting position on the apparatus during 15-20 min daily. The vibrator places in the center of work surface was situated between the scrotum and anus. The course included 10 procedures.

The local application of mud onto the penis using sulfide silt therapeutic muds was performed 20-30 min before the procedure of vibrational, thermal and magnetotherapy. The magnetic field induction in the working zone (at the distance of 60 mm from the surface) 10 mT, vibration amplitude 2-3 mm, frequency of vibration and its character were varied and were chosen by the patient himself depending on the feeling of comfort (50 Hz with random modulation from 0,5 to 8 Hz). The temperature of the working surface 40-55 °C.

The control group consisted of 22 healthy men of reproductive age without diagnosed urogenital infection.

## Results and discussion

The efficiency of treatment was estimated on the basis of lack or reduction of pain symptoms, reduction of diuretic disorders. The elimination of causative agents was reached in 46 (95,8%) patients.

After the treatment of patients with chronic non-gonococcal urethritis pain syndrome was not observed in 47 (97,9%) patients, complaints about itching and urethral discomfort were not registered in 45 (93,7%) men, dysuric symptom was not observed in 46 (95,8%) patients.

The evaluation of urethral microcirculation state by means of LDF showed changes of basal

bloodstream parameters in all patients with NGU. The graphical image of urethral basal bloodstream

in a patient with NGU and a healthy man is shown in Figures 1, 2.

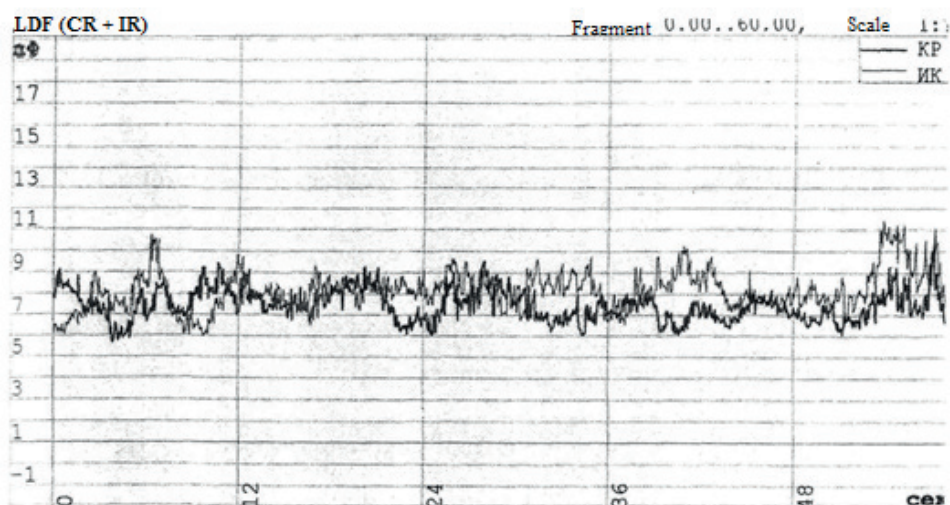


Figure 1.  
Graphical image of basal urethral bloodstream by NGU

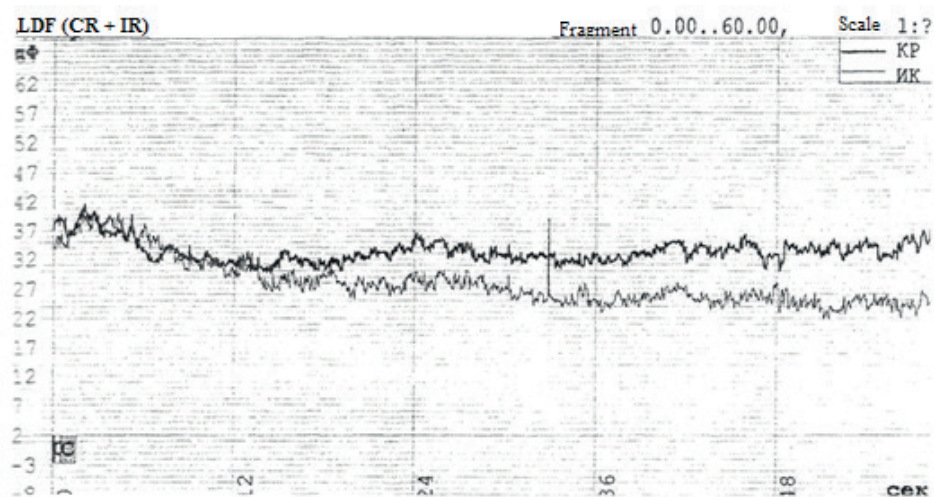


Figure 2.  
Graphical image of basal urethral bloodstream of healthy man

Disorders of microcirculation manifested itself mainly through the reduction of tissue perfusion rate, rates of myogenic ( $0,94 \pm 0,03$  rel.un.) and neurogenic ( $0,69 \pm 0,01$  rel.un.) tonus, bloodstream modulations and coefficient of variation ( $10,51 \pm 0,51\%$ ). The control study of LDF after the treatment revealed the following results: the improvement of microcirculation parameters, which approximated to the results of the control group. It happened mainly due to the increase of rates of myogenic ( $0,95 \pm 0,07$  rel.un.) and neurogenic ( $0,74 \pm 0,03$  rel.un.) tonus, coefficient of variation ( $12,4 \pm 0,87\%$ ), which indicate that combined effect of vibrational, thermal and magnetotherapy and pelotherapy leads to the normalization of urethral microcirculation parameters (Table 1).

The analysis of LDF-gram in the urethra after the treatment showed moderate increase of tissue

perfusion  $M 41,23 \pm 0,09$  pf.un (before the treatment  $M - 40,92 \pm 0,04$  pf.un.) and bloodstream modulation  $RMSD - 5,08 \pm 0,01$  pf.un. (before the treatment  $RMSD - 4,12 \pm 1,23$  pf.un.), and also the growth of variation coefficient (Cv) up to  $12,3 \pm 0,04\%$ .

The examination of urethral AFS after the treatment revealed a significant reduction of the frequency of pulse beats, amplitude of slow fluctuations. The state of bloodstream regulation factors was characterized by the reduction of the passive mechanism of microcirculation regulation and unchanged active rate in relation to the group of healthy men. There was marked a moderate decrease of intravascular resistance in all fluctuation rhythms, however, it did not reach control values. The values of NT and IEM increased, while MT and SI decreased significantly (Table 2).

Table 1

*Mechanisms of urethral bloodstream regulation in patients with chronic non-gonococcal urethritis before and after the treatment*

Microcirculation	Healthy men (n=22)	Before treatment (n=48)	After treatment (n=48)
IEM	1,24±0,11	0,95 ± 0,02*	1,12 ± 0,83**
NT	0,77±0,06	0,70 ± 0,04*	0,74 ± 0,02**
MT	0,86±0,11	0,92± 0,12*	0,85 ± 0,02**
SI	1,16±0,06	1,33± 0,05*	1,26± 0,08**

Note. \* – differences with the group of healthy men are statistically significant (p<0,05).

Note. \*\* – differences before and after the treatment are statistically significant (p<0,05).

Table 2

*Dynamics of urethral bloodstream AFS oscillations in patients with NGU in the group of comparison*

Indexes LF		Patients with NGU after treatment (n=48)			Group of comparison (n=22)		
		HF	CF	LF	HF	CF	
Fmax	(pf.un.)	3,67±0,05	13,65±0,38*	92,70±0,27*	4,41±0,73	22,76±0,69	85,80±1,03
Amax	(pf.un.)	6,91±0,07*	2,80±0,02	0,94±0,01	8,44±0,53	3,27±0,75	1,18±0,21
Amax/3y*100%	(%)	35,75±0,73*	24,01±0,70	3,62±0,20*	38,06±0,71	22,90±0,42	5,50±0,08
Amax/M*100%	(%)	19,12±0,78	8,92±0,36*	3,01±0,35	18,88±0,60	7,20±0,03	3,31±0,4

Note. \* – differences with the group of healthy men are statistically significant (p<0,05).

### Conclusion

Consequently, the combined effect of vibrational, thermal and magnetotherapy and pelotherapy in complex treatment of patients with chronic non-gonococcal urethritis leads to the elimination of causative agents in 95,8% of cases, reduction of pain symptoms and dysuric disorders, reduction of discomfort in the urethra, primarily due to the increase of blood perfusion and the bloodstream volume in arterioles, growth of blood flow into the microcirculation system and decrease of hypoxia and tissue ischemization.

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УДК 618.16: 615.849

## PHOTODYNAMIC THERAPY IN TREATMENT OF PATIENTS WITH DYSTROPHIC DISEASES OF THE VULVA

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*The article contains the results of a comparative use of two different methods for the treatment of dystrophic diseases of the vulva: photodynamic therapy and diathermocoagulation. To assess the effectiveness of therapy, patients with lichen sclerosis, hyperplastic dystrophy and combined dystrophy were divided into two clinically comparable groups. The method of photodynamic therapy consisted in irradiation of the affected areas with the Vostok-Delta-03 apparatus 3-6 hours after the external application of the photosensitizer in an amount up to 10 ml with a gel concentration of 5% without anesthetic protection. Light exposure was carried out in a pulse mode; the duration of irradiation was 20-45 min. The wavelength of radiation was 630 nm, the laser radiation power at the end of the fiber was 100 mW, and the energy density was 100-250 J / cm<sup>2</sup> for the vulva. In the comparison group with patients with hyperplastic dystrophy, the electrocoagulant was used to destroy the pathological sites with the help of the ECHVCH100 apparatus (Uzbekistan). As a result of the use of PDT, high treatment efficacy, antiviral effect, and the absence of undesirable side reactions were achieved. In this connection, the PDT method can be actively introduced into the practice of treating genital dystrophy.*

**Key words:** photodynamic therapy, lichen sclerosis, dystrophic diseases of the vulva.

The problem of dystrophic vulvar diseases (DVD) which include lichen sclerosis (syn. sclerotic), hyperplastic dystrophia, combined dystrophia and other types of dermatosis, has becoming particularly significant in recent years due to a considerable juvenation and frequent canceration [1, 12]. The risk of malignant tumour development in this category of patients, according to various data, constitutes from 9 to 49% [11, 13]. Though not always the dermal process is treated as the background one, however, it is not possible to visually predict the disease outcome without special methods of examination [2, 8]. Hyperplastic dystrophia is characterized by dermal thickening, but phimosis vaginalis is practically not registered. By lichen sclerosis the skin becomes thin, folds thicken and, as a rule, vaginal orifice shortly coarcts. Combined dystrophia occurs in 15% of cases and is characterized by the presence of symptoms of hyperplastic dystrophia and areas with lichen sclerosis [5, 9, 10]. The variety of causes leading to dystrophia make this problem interdisciplinary and complicates the process of diagnostic search and, consequently, treatment.

By the present time, there are no reliable data on the efficiency of conservative methods of the mentioned disease treatment [4, 7]. The use of hormonal ointments and creams by patients frequently leads to the tissue atrophy and formation of acquired tolerance and addiction. Later the steroid therapy becomes inefficient. Surgical treatment, in spite of higher efficiency, is characterized by high injury rate, intensive postoperative pains, high frequency of postoperative complications, unfavorable cosmetic and functional results [3, 6, 14].

**Research objective:** to study the efficiency of photodynamic therapy in treatment of patients with dystrophic diseases of the vulva in relation to traditional methods.

### Materials and methods

Totally, there were observed 31 female patients with DVD. According to the type of revealed pathology patients were divided into the following way: 22 patients (71,0%) had lichen sclerosis and 5 (16,1%) - hyperplastic vulvar dystrophia, 4 (12,9%) - combined dystrophia. As a rule, patients had been suffered from the given pathology from 3 to 22 years. The duration of postmenopause period ranged from 2 to 27 years. To specify the nature of the revealed pathology women were exposed to the examination of vulvar scrape, vulvoscopy, PCR-diagnostics to reveal cancerogenic types of human papilloma virus (HPV), and also the histology of the biopsy material from pathological areas. Pathomorphological examinations after the fixation of tissue fragments in 4% formalin solution on phosphate buffer (pH 7,6) and tissue embedding in the wax by Z.Loid (1982) were performed at the Department of pathological anatomy and forensic medicine of TashIPME (Head of the Department: Mavlyankhodzhayev R.Sh.). In 12 patients there was revealed the HPV of type 16, 18 (38,7%), in 6 patients - HPV of type 31, 33 (19,4%), in 2 (9,7%) there was revealed the carriage of low cancerogenic HPV types, in 10 (32,3%) patients HPV was not registered.

In order to reach the stated goal patients were divided into two clinically comparative groups. The main study group included 13 women with

DVD at the age from 19 to 67 years (average age  $45,6 \pm 3,2$ ). The comparison group constituted 18 women with DVD at the age from 32 to 65 years (average age  $41,8 \pm 4,1$ ).

The clinical picture of the disease was mainly presented by infiltrative plaques and also by thinning and thickening of tissues with typical white shade of skin and mucous membrane of labia minora and majora, clitoris and vaginal orifice. In some patients the process spread over the whole vulva, perinatal area and internal hips. In 8 (25,8%) patients there were registered cases of depigmentation caused by constant scratching. In the examined patients there was revealed extragenital pathology of various intensity. In half of patients (53,1%) there prevailed impaired fat metabolism, hypertensive disease, varicose vein disease of lower limbs (31%), atherosclerosis of various intensity (26%). Chronic bronchitis, gallstone disease, chronic pancreatitis were diagnosed in 7 (22,6%) patients, chronic tonsillitis and neurocirculatory dystonia – in 3 (9,7%); hepatic steatosis, kidney stone disease – in 3 (9,7%), chronic gastritis, nodular goiter, diabetes mellitus of 2<sup>nd</sup> type and chronic pyelonephritis – in 7 patients (22,6%). No significant differences between the frequency and intensity of concomitant pathology in the studied group were revealed.

All patients were exposed to the complex clinical examination including bacteriological, endovisual (colposcopy), histological and cytological methods. The morphological examination of biopsy materials of vulvar mucose membrane in patients with DVD.

The following changes of varying severity in the tissue were diagnosed in patients with DVD during the morphological examination of the biopsy materials of vulvar mucose membrane: thinning of the epidermis with the normal stratum corneum, hyper- and parakeratosis; the presence of active proliferation of the epidermis; a smoothed papillary layer; altered nuclear structures of the epidermis in the form of augmentation of the nucleus, multinucleation of cells; thickening and swelling of elastin and collagen fibers in the stroma; leukocyte infiltration; single koilocytes, lymphocytic infiltration, epithelial dysplasia of I-II degree.

Indication for the procedure of PDT was a verified diagnosis of dystrophic processes of the skin and vulvar mucosa. In the preoperative period, patients with infection of the genital tract had antimicrobial therapy and immunocorrection, followed by measures to normalize the vaginal microbiocenosis.

Laser exposure, as a rule, was performed in the first phase of the menstrual cycle, in 3-6 hours after local application of the combined photosensitizer (PS) on the basis of natural and phenothiazine photosensitizers in the form of 0.5% gel. The irradiation was carried out with the aid of the diode laser apparatus "Vostok Delta-03" (Uzbekistan).

The radiation wavelength is  $660 \pm 15$  nm, the energy density is 100-200 J / cm<sup>2</sup>, and the exposure time is from 10 to 20 minutes.

In order to select the optimal time parameters for the onset of irradiation, corresponding to the maximum accumulation of PS in the mucosa and skin, a method of estimating the local fluorescence was used with the help of the AFD-1 spectral-fluorescent diagnostic apparatus (Uzbekistan). Radiation of a wavelength of  $400 \pm 10$  nm was used for the induction of fluorescence, which made it possible to selectively excite the fluorescence of the PS. The measurements were performed prior to the administration of FS (auto-fluorescence evaluation) and 3 and 6 hours after application of PS to the skin and mucosa (induced tissue fluorescence). During spectral-fluorescent studies, it was determined that if the endogenous fluorescence of the mucosa was insignificant before the administration of PS, after injection of PS at all measurement points, the induced fluorescence was expressed with a sufficiently bright glow. The output power from the FDU-1 apparatus was up to 30 mW, the exposure time was up to 100 ms. The maximum values of fluorescence, and, consequently, the accumulation of PS, were recorded in the skin 6 hours after application to the skin. The optimal time to start treatment with PDT was the maximum value of the fluorescence of pathological tissues.

According to the procedure No.1, the irradiation session was performed by the Vostok-Delta-03 apparatus 3-6 hours after external application of FS in an amount up to 10 ml with a gel concentration of 5% without the use of anesthetic protection. Light exposure was carried out in a pulsed mode; the duration of irradiation was 20-45 min. To determine the absorption coefficient, there were made measurements of the power of the light flux at the exit from the end of the radiator, and then at the same laser power the light flux from the surface of the skin (reflected radiation) was measured as well. The degree of absorbed radiation by the tissues was determined by the difference in indices. The wavelength of the radiation was 630 nm, the laser radiation power at the end of the fiber was 100 mW, and the energy density was 100-250 J/cm<sup>2</sup> for the vulva. In the comparison group, according to the procedure No.2 the destruction of pathologic sites with an electrocoagulator was used in patients with DVD with the help of EHVCH100 apparatus (Uzbekistan).

### Results and discussion

Analysis of treatment results was conducted in 31 patients with DVD. The therapeutic effect of PDT with 13 patients was assessed visually and on the basis of indications of the presence or absence of pruritus in the vulva area; this effect was also confirmed by data of morphological examination and vulvoscopy. Thus, the disappearance



of pruritus in the vulva region was noted in 7 of 9 patients with vulvar lichen sclerosus. All patients with hyperplastic dystrophy and mixed dystrophy underwent a cytological study of vulvovaginal scraping and vulvoscopy, on the basis of which the clinical cure was reliably diagnosed. The antiviral effect of PDT was evaluated after repeated PCR with DNA typing of HPV from the vulva surface. As a result of our findings, HPV was not found in any patient. Adverse reactions consisted only in a minor pain syndrome after the procedure of PDT and body temperature rise in four patients during the first 2-3 days after the procedure, which were jugulated by the intake of non-steroidal anti-inflammatory drugs. Complete clinical remission in the 1st group was observed in 11 patients (84.6%). 2 patients (15.4%) with vulvar lichen sclerosus underwent a second session of PDT, after which a clinical cure was diagnosed. The patients were observed within 12 months after a PDT session; the relapse was observed in no case.

When analyzing the inflammatory processes of the vaginal mucosa after PDT, there was observed the formation of a thin scab in the irradiation zone 24 hours after the procedure. The beginning of marginal epithelization of the eroded surface was observed on the 5th-8th day in the absence of leukocyte infiltration. Complete epithelization was detected in 4-7 weeks, whereas in the comparison group the average epithelization completion time was 5-10 weeks. With the use of PDT in 2 patients, there was observed incomplete epithelization of the vaginal mucosa after 8 weeks, which required the repeated conduct of the PDT session, which resulted in a positive clinical effect.

The patients who underwent electrocoagulation demonstrated complications with a greater frequency. 17 patients suffered from severe pain within 3 weeks, requiring the taking of pain killers. Pregnant secretions throughout the period of repair were noted in 6 patients. Exacerbation of the inflammatory process of the uterine appendages was observed in 4 patients, exacerbation of colpitis was noticed in 6 patients, and 5 patients showed incomplete epithelization of the vaginal mucosa for 6 weeks.

According to the data of cytological and colposcopic studies, clinical effect was achieved in 17 (94.4%) patients. The antiviral effect was significant in 8 patients with antiviral and immunostimulating therapy. The study of long-term results after electrocoagulation (after 6-9 months) revealed that the pain syndrome was troubling 4 patients, 5 patients suffered scar deformity, and the recurrence of the disease was noted in 3 patients.

### Conclusion

Treatment of dystrophic diseases of female external genital organs of non-tumorous genesis by PDT method with the use of combined FS demonstrat-

ed its high therapeutic efficiency. A positive antiviral effect against HPV was achieved. Side effects and complications during treatment were minimal. The PDT method is distinguished by its selectivity, as well as by sparing effects on pathological tissues. The procedure of PDT is well tolerated, does not require the use of strong pain-relieving medications. The postoperative period goes, as a rule, without complications with a fairly rapid restoration of work capacity.

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UDC 618.16-002:616.34:616.992

## COMBINATION OF VULVOVAGINAL AND INTESTINAL CANDIDIASIS: SUBSTANTINATION OF RATIONAL APPROACH TO THERAPY

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*On the grounds of the examination and treatment of 100 patients with chronic recurrent vulvovaginal candidiasis (CRVVC) and 50 patients with a combination of CRVVC and candidal intestinal dysbiosis (CID), the article analyzes the features of clinical manifestations of the disease, the species composition and sensitivity of cultures of the Candida genus isolated from the vagina and intestine to antimycotics, as well as the results of therapy proposed on the basis of the above studies.*

**Key words:** chronic recurrent vulvovaginal candidiasis, candidal intestinal dysbiosis, fungi of the genus *Candida*, natamycin.

Chronic recurrent vulvovaginal candidiasis (CRVVC) is an important problem of modern medicine. The frequency of its occurrence, according to various authors, constitutes from 5 to 20% [1, 2].

The topicality of CRVVC problem is explained by frequent recurrence of the inflammatory process, development of complications, formation resistance of *Candida* fungi to antimycotic agents. Moreover, chronic recurrent development of VVC often complicates the course of pregnancy and can lead to early discharge of amniotic fluid, preterm delivery, development of candida infection in newborns, development of ascending urogenital infection in mothers [3].

Chronic recurrent course of VVC can be favored by numerous factors, such as endocrinopathy (diabetes mellitus, underactive thyroid gland), pregnancy, long-term uncontrolled administration of broad-spectrum antibiotics, HIV infection and intake of immunosuppressors, administration of oral contraceptives and use of intrauterine devices, frequent syringing, wearing of tight synthetic under-clothes and use of daily pantyshield [3, 4, 5, 6, 7, 8]. As a rule, CRVVC is developed by combination of several factors.

According to one of the pathogenetic hypotheses, recurrence of VVC can be caused by the presence of *Candida* fungi in the intestine [1, 9, 10]. National and foreign literature do not cover the issues of combined candidal vaginal and intestinal disease fully enough.

**Research objective:** to analyze the relation of vaginal candidiasis (VC) and candidal intestinal dysbiosis (CID), to determine clinical peculiarities of the stated combined pathology, to study the species composition and sensitivity of *Candida* fungi isolated from the vagina and intestine to antimycotics, to determine the ways of rational approach to the therapy of such patients.

### Materials and methods

The current research was conducted on the basis of the Center of urogenital infections of SBEI HPE Irkutsk State Medical University of the Ministry of Health of the Russian Federation in accordance with the World Medical Association Declaration of Helsinki on Biomedical Technologies, reviewed and approved by the Ethics Committee of SBEI HPE Irkutsk State Medical University of the Ministry of Health of the Russian Federation on 24.12.2012. There were obtained voluntary informed consents of patients to the study and treatment.

There were observed 150 women of reproductive age with diagnosed CRVVC with recurrence rate 4 and more per year. The age of women constituted from 16 to 50 years, the main age group were female patients from 20 to 40 years – 114 patients (the average age  $30,5 \pm 3,5$  years).

The study did not include pregnant women, patients with other urogenital infections, HIV-infected, patients receiving immunotherapy, women with severe somatic pathology.

All women were examined at the moment of disease exacerbation.

By the history taking there were considered complaints of patients connected with the urogenital and intestinal systems.

The material for laboratory research was gathered from the posterolateral vaginal fornix, fecal matter was also examined.

The culture of fungi was obtained by means of inoculation of Sabouraud's medium (made in Russia, Obolensk), the species of fungi was identified by means of chromogenic culture media HiMedia (India), the antimycotic sensitivity was determined by disk diffusion test to six drugs – nystatin, clotrimazole, fluconazole, amphotericin, itraconazole, ketoconazole.

The minimal concentration of the drug inhibiting the growth of *Candida* spp. fungi was determined by means of serial dilutions in solid media

according to the methodological recommendations "Determination of microorganism sensitivity to antibacterial preparations" [11]. The current research was performed in reference to two antimycotic-macrolides: natamycin and nystatin extracted from vaginal suppositories by means of successive exhaustive extraction of active substances from water solution by organic solvents. Further, there were used solutions for nystatin and natamycin at a dilution of 1:8 which corresponds to the amount

of active substance of one suppository. The initial concentration of active substances constituted: 125 mg/ml for nystatin, 100 mg/ml for natamycin [12, 13, 14]. Afterwards, there were prepared double serial dilutions of the drug from 1:10000 to 1: 320000, then there were introduced 1 ml of every dilution into the Petri dishes containing 4 ml of Sabouraud. The concentration of active substances in dilutions is presented in Table 1.

Table 1

*Concentration of nystatin and natamycin in serial dilutions (mg/ml)*

Medication	1 dilution	2 dilution	3 dilution	4 dilution	5 dilution	6 dilution
nystatin	125,00	62,50	31,25	15,63	7,81	3,90
natamycin	100,00	50,00	25,00	12,50	6,25	3,13

The procedure was conducted with one loop transmitting the medication from lesser concentration to bigger, dishes were left till the gelation of agar. Then the agar was inoculated by the studied culture and incubated at the temperature of 37°C during 48 hours, after that there was determined the minimal concentration of medication inhibiting the growth of cultures by the lack of growth on dishes.

All patients were divided into two groups:

- first group, main, with combined CRVVC and candidal intestinal dysbiosis (CRVVC + CID), - 50 women with Candida fungi revealed in high titers ( $\geq 10^4$  cfu/ml) from vagina and intestine;
- second group, comparison (CRVVC) – 100 women with Candida fungi revealed in high titers ( $\geq 10^4$  cfu/ml) only from vagina, the titer of Candida fungi in the intestine corresponded to normal values -  $10^4$  cfu/ml and lower.

The results of examination of Candida spp. sensitivity to antimycotics became the basis for the development of rational treatment of CRVVC patients.

To reverse CRVVC exacerbation in patients of both groups there was used the polyene antimycotic – natamycin in the form of vaginal suppositories 100 mg (1 suppository) 1 time a day during 6 days.

The treatment of CID in patients of the 1 group included natamycin in the form of gastroresistant tablets 100 mg 91 pill) 4 times a day per os during 10 days.

Upon the end of treatment for CRVVC exacerbation there was prescribed the course of maintenance therapy continuing for 6 months.

Patients of the 1<sup>st</sup> group and 50 patients of the 2<sup>nd</sup> group (group 2a) received natamycin in the form of vaginal suppositories 100 mg 1 time a day during 3 days before the expected exacerbation monthly.

25 patients of the 2<sup>nd</sup> group (group 2b) received fluconazole 150 mg orally once a week.

25 patients of the 2<sup>nd</sup> group (group 2c) received clotrimazole in the form of vaginal tablet 500 mg once a week.

The statistical processing of the obtained results was performed by means of package of computer programs Primer of Biostatistics [15]. Differences of compared parameters were considered significant by  $p < 0,05$ . The evaluation of statistical significance of differences of clinically compared groups was conducted by means of non-parametric Mann-Whitney U test, differences between the parameters were considered significant by  $p < 0,05$ ; Z-criterion, differences between the parameters were considered significant by  $p < 0,05$ . Frequencies (%) for qualitative parameters were determined on the basis of contingency tables.

### Results and discussion

The majority of patients of the 1<sup>st</sup> group were characterized by congestive hyperemia of external genital organs, moderate or expressed infiltration, numerous genital fissures. The inflammation was accompanied by moderate itching and burning. In patients of the 2<sup>nd</sup> group there were more often marked intense edematous hyperemia, excoriation, "crumbly" fur accompanied by intensive itching and burning (Table 2).

Anamnestic data of patients on the state of gastro-intestinal tract are presented in Table 3.

From the clinical point of view, conspicuous is the state of urogenital tract in women with combined CRVVC and CID during the disease recurrence: it was not characterized by expressed acute inflammatory component in contrast to the compared group. In the majority of patients there prevailed infiltration, congestive vaginal mucous membrane hyperemia, fissures, "creamy" secretions, itching and burning were moderately expressed. Moreover, the number and intensity of subjective and objective intestinal symptoms differed significantly from the comparison group:



in 32% of patients – loss of appetite, in 68% - abdominal discomfort and meteorism, in 74% - expressed flatulence. None of the patients of the stated group were characterized by normal stool: in 52% of women it was characterized by the changed consistency and increase of frequency up to 3 times a day, 48% had complaints about regular constipations con-

tinuing from 2 to 5 days. Undoubtedly, gathering of anamnesis in patients with CRVVC in relation to the state of GIT can afford the practicing physician ground for suspecting a particular pathology and targeted planning of examination and further rational treatment.

Table 2

*Objective symptoms in women with CRVVC*

Clinical symptoms n= 50 %		CRVVC+CID		CRVVC		
		n=100	%			
Genital changes	congestive hyperemia + moderate infiltration + fissure + «creamy» fur	22	44	18	18*	
	intense edematous hyperemia + excoriation + “crumbly” fur	5	10	43	43*	
	moderate hyperemia + single excoriations	20	40	32	32	
subjective symptoms	itching	no evidence	4	8	2	2
		moderate	35	70	41	41*
		intense	11	22	57	57
	burning	no evidence	21	42	5	5
		moderate	19	38	57	57*
		intense	10	20	38	38*

\* - value for Mann–Whitney U test (significance of differences by the comparison of groups P<0,05)

Table 3

*Intestinal changes in women with CRVVC*

Changes n=50		CRVVC+CID		CRVVC	
		%	n=100	%	
Appetite	normal	34	68	97	97
	reduced	16	32	3	3*
Flatulence		37	74	51	51*
Abdominal discomfort, meteorism		34	68	47	47*
stool type	formed once a day	-	-	69	69*
	constipations from 2 to 5 days	24	48	28	28*
	loose stool 2-3 times a day	26	52	3	3*

\* - z-criterion (significance of differences by the comparison of groups P≤0,05)

The vaginal culture examination of patients of the 1<sup>st</sup> group showed: *C. albicans* – in 38 patients (in 76%), *C. krusei* – in 10 (in 20%), *C. glabrata* – in 2 (in 10%). The intestinal examination revealed in the 1<sup>st</sup> group revealed: *C. albicans* – in 35 (70%), *C. krusei* – in 11 (22%), *C. glabrata* – in 3 (6%), *C. tropicalis* – in 1 (2%). Moreover, in 43 (86%) women of the 1<sup>st</sup> group the fungi cultures from vagina and intestine were identical: *C. albicans* – in 33 (66%) patients, *C. krusei* – in 8 (16%), *C. glabrata* – in 2 (4%).

In three patients there was determined the combination *C. albicans* (vagina) + *C. krusei* (intestine), in two – *C. krusei* (vagina) + *C. albicans* (intestine), in one – *C. albicans* (vagina) + *C. tropicalis* (intes-

tine), in one – *C. albicans* (vagina) + *C. glabrata* (intestine).

The study of *Candida* spp. sensitivity to antimycotics isolated from the vagina of patients of the 1<sup>st</sup> group showed that 100% of *C. albicans* cultures were sensitive to nystatin, 68,4% - to fluconazole, 65,8% - to clotrimazole and itraconazole, 60,5% - to ketoconazole, 47,4% - to amphotericin B.

The study of *Candida* spp. sensitivity to antimycotics isolated from the intestine of patients of the 1<sup>st</sup> group showed that 100% of *C. albicans* cultures were sensitive to nystatin, 68,6% - to clotrimazole, 65,7% - to itraconazole, 62,9% - to fluconazole, 60% - to ketoconazole, 48,6% - to amphotericin (Figure 1).

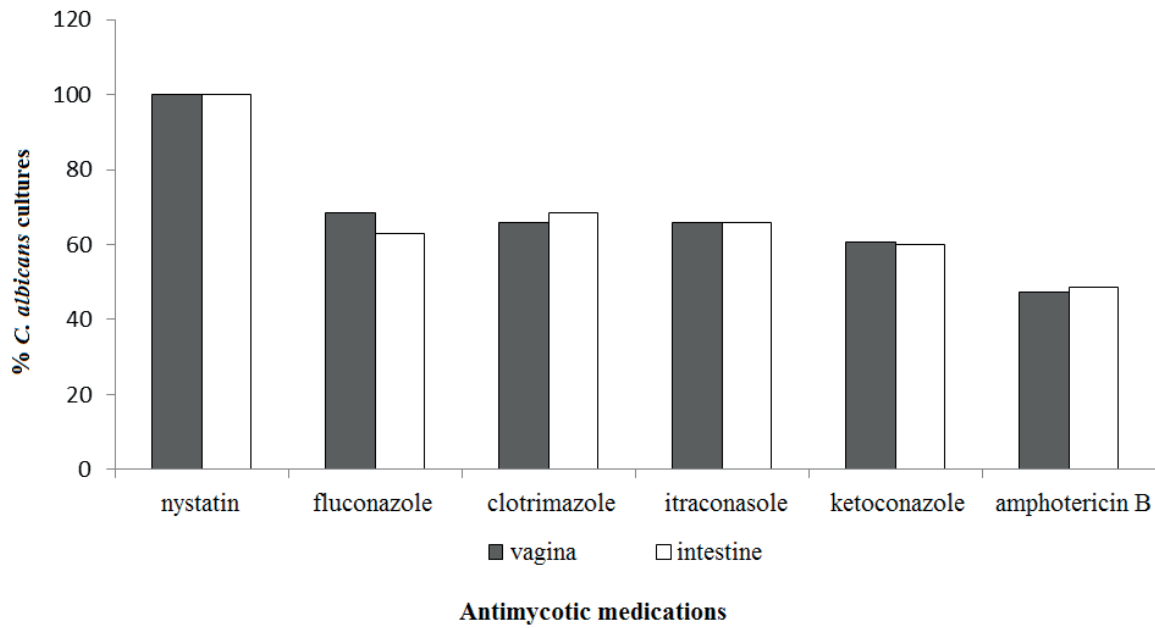


Figure 1. Sensitivity of *C. albicans* cultures isolated from vagina and intestine to antimycotics (disk diffusion test)

All 10 *C.krusei* cultures isolated from the vagina and intestine of patients of the 1<sup>st</sup> group were sensitive to nystatin and resistant to fluconazole. 7 *C.krusei* cultures were sensitive to clotrimazole, 5 – to ketoconazole, 4 – to itraconazole, 2 – to amphotericin B. One *C.glabrata* culture was resistant

to fluconazole, second – to fluconazole, clotrimazole and amphotericin B (Figure 2).

11 *C.krusei* cultures isolated from the intestine of patients of the 1<sup>st</sup> group were sensitive to nystatin and resistant to fluconazole, 6 cultures were sensitive to clotrimazole, 3 – itraconazole, 5 - to ketoconazole (Figure 2).

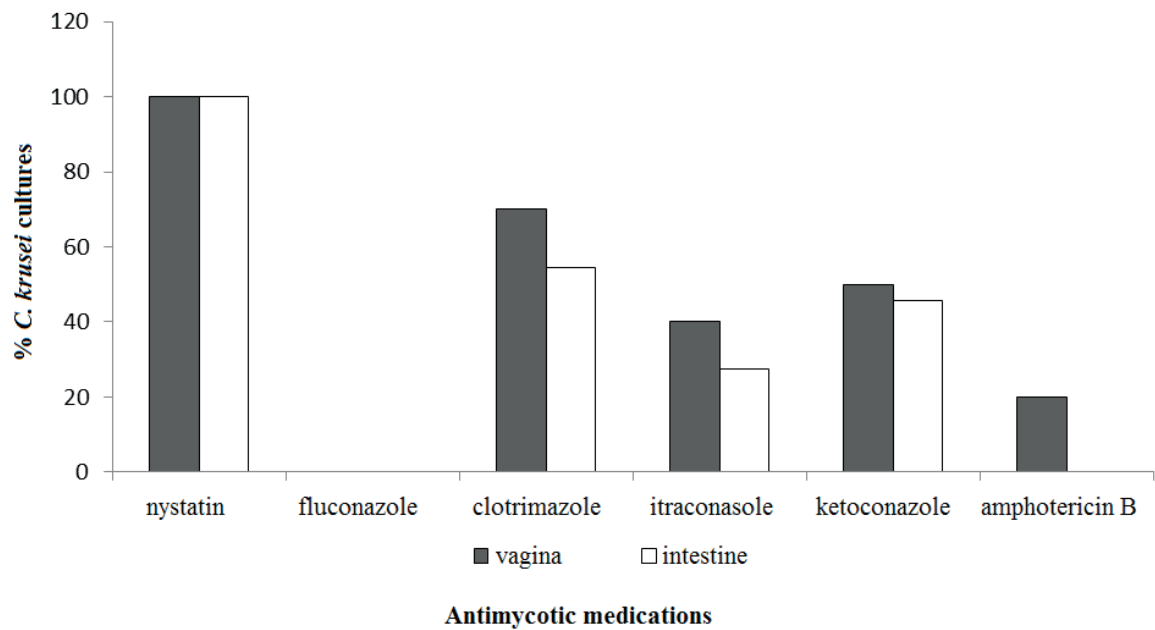


Figure 2. Sensitivity of *C. krusei* cultures isolated from vagina and intestine to antimycotics (disk diffusion test)

*C. tropicalis* culture was sensitive to nystatin, clotrimazole, ketoconazole. One *C. glabrata* culture was resistant to fluconazole and ketoconazole, second – to fluconazole, ketoconazole, clotrimazole, third – to fluconazole, ketoconazole and amphotericin B.

The analysis of data presented in Figures 1 and 2 allows to state that the sensitivity of *Candida* fungi – both *C.albicans* and *C.non-albicans*, isolated from two locuses – vagina and intestine, is practically identical which gives the practicing physician

the opportunity to prescribe one antifungal drug for sanation of both locuses.

The fungi cultures isolated from the vagina of patients of the 2<sup>nd</sup> group were presented

in the following way: *C. albicans* – in 82 (82%) out of 100 patients, *C. krusei* – in 7 (7%), *C. glabrata* – in 11 (11%). Table 4 shows the results of study of *Candida* spp. fungi sensitivity.

Table 4

*Sensitivity Candida spp. fungi isolated from the vagina of women of the 2<sup>nd</sup> group to antimycotics (abs./%)*

Candida spp.	nystatin	fluconazole	clotrimazole	itraconazole	ketoconazole	amphotericin
<i>C. albicans</i>	82/100	54/65,9	63/76,8	51/62,2	49/59,8	47/57,3
<i>C. krusei</i>	7/100	-	6/85,7	2/28,6	2/28,6	6/85,7
<i>C. glabrata</i>	11/100	-	9/81,8	4/36,7	4/36,7	4/36,7

According to the study results, all *Candida* spp. fungi cultures isolated from women with CRVVC of both groups possessed the highest sensitivity to the polyene antimycotic – nystatin.

At the present time, there is available one more polyene drug – natamycin which is, according to the Federal Recommendations of RSDV 2013, recommended for VVC treatment.

The comparative analysis of minimal concentrations of nystatin and natamycin inhibiting the growth of *Candida* fungi (Tables 5, 6, 7) revealed that the majority of *Candida* spp. cultures isolated from vagina (65%) and intestine (80%) are mostly sensitive to the lowest concentrations of natamycin and 94, respectively, to high concentrations of nystatin.

Table 5

*Minimal concentrations of nystatin and natamycin inhibiting the growth of Candida spp. isolated from the vagina of women of the 1<sup>st</sup> group*

Candida spp. (number of cultures)	medication dilution (mg/ml)											
	1 dil.		2 dil.		3 dil.		4 dil.		5 dil.		6 dil.	
	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.
<i>C. albicans</i> (38)	22	-	13	-	1	6	2	16	1	14	-	2
<i>C. krusei</i> (10)	10	-	-	-	-	5	-	3	-	1	-	1
<i>C. glabrata</i> (2)	1	-	1	-	-	1	-	1	-	-	-	-

Table 6

*Minimal concentrations of nystatin and natamycin inhibiting the growth of Candida spp. isolated from the intestine of women of the 1<sup>st</sup> group*

Candida spp. (number of cultures)	medication dilution (mg/ml)											
	1 dil.		2 dil.		3 dil.		4 dil.		5 dil.		6 dil.	
	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.
<i>C. albicans</i> (35)	23	-	9	-	1	8	2	18	-	8	-	1
<i>C. krusei</i> (11)	9	-	2	-	-	6	-	5	-	-	-	-
<i>C. glabrata</i> (3)	1	-	2	-	-	1	-	2	-	-	-	-
<i>C. tropicalis</i> (1)	-	-	1	-	-	-	-	-	-	1	-	-

Table 7

*Minimal concentrations of nystatin and natamycin inhibiting the growth of Candida spp. isolated from the vagina of women of the 2nd group*

Candi- da spp. (number of cultures)	medication dilution (mg/ml)											
	1 dil.		2 dil.		3 dil.		4 dil.		5 dil.		6 dil.	
	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.	nys.	nat.
C. albicans (82)	37	-	40	-	5	4	-	41	-	22	-	15
C. krusei (7)	6	-	1	-	-	2	-	3	-	2	-	-
C. glabrata (11)	8	-	3	-	-	1	-	8	-	2	-	-

The results of our microbiological study allowed us to choose natamycin as an etiologic medication both for the treatment of CRVVC recurrence and long-term maintenance therapy.

After the course of CRVVC recurrence therapy the clinical recovery was observed in all (100%) patients of both groups. The culture study was performed in 10 days after the termination of therapy. According to its results, in 86% of patients the growth of fungi in the vagina was not registered, in 24% of women the titer of Candida fungi constituted less than  $10^3$  cfu/ml. According to the culture study of the intestinal material of 1<sup>st</sup> group patients receiving oral gastroresistant tablets in addition to vaginal suppositories of natamycin,

the growth of fungi was not observed in 100% of patients.

After the course of maintenance therapy with natamycin, the CRVVC recurrence developed in 1 woman of the 1<sup>st</sup> group and 1 woman of the 2a group, which was determined by the noncompliance of drug therapy. The effectiveness of maintenance therapy with natamycin constituted 98%.

After the course of maintenance therapy, in 6 patients receiving fluconazole orally and 5 patients receiving clotrimazole intravaginally there developed the clinical picture of CRVVC recurrence, while the titer of fungi in the vagina was  $\geq 10^4$  cfu/ml. The natamycin treatment, in comparison to fluconazole ( $p = 0,008$ ) and clotrimazole ( $p = 0,024$ ) treatment, turned out to be more effective (Table 8).

Table 8

*The effectiveness of maintenance therapy by CRVVC in women*

Medications	1 <sup>st</sup> group natamycin (n=50)	2a group natamycin n=50	2b group fluconazole n=25	2c group clotrimazole n=25	Criterion P 1, 2a – 2b	Criterion P 1, 2a – 2c
Rate of recovery	0,98	0,98	0,76	0,8	0,008	0,024

### Conclusion

Consequently, by combined candida disease of vagina and intestine in women with CRVVC, the microbiota of both locuses is prevailed by C. albicans fungi, respectively: 76% - in the vagina, 70% - in the intestine; C. non-albicans fungi – 24% - in the vagina, 30% - in the intestine. In 86% of patients Candida fungi cultures isolated from vagina and intestine were identical.

In our opinion, by history taking, the practicing physician should specificate possible changes in patients with CRVVC connected with intestine. The obtained data can considerably simplify the pathogenic diagnosis, and, thus, to improve the approach to CRVVC recurrence treatment.

Our microbiological researches showed the highest sensitivity of Candida fungi (albicans and non-albicans) to natamycin which became the ground for prescribing the given drug to patients with CRVVC recurrence with not only dam-

aged urogenital tract (intravaginally), but also to patients with combined vaginal candidiasis with candidal intestinal dysbiosis (intravaginally and orally), and also for maintenance 6-month therapy of CRVVC (intravaginally).

The effectiveness of the suggested approach to treatment of women with combined CRVVC and CID constituted: after the main therapy course – 100%, after the maintenance therapy course – 98%. the suggested approach treatment of women with combined CRVVC and CID can be recommended for use by dermatovenerologists and obstetrician-gynaecologists.

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UDC 616.72-002:616.517-056.52

## PECULIARITIES OF CLINICAL PICTURE IN PATIENTS WITH PSORIATIC ARTHRITIS WITH LIPID STORAGE DISEASE

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*The clinical features of joint and skin syndromes in 120 patients with psoriatic arthritis with lipid storage disease were studied. The clinical forms of psoriasis were prevalent in patients with vulgar (50%) and exudative psoriasis (33.3%). The clinical forms of PA were dominated by the distal form and oligoarthritis, respectively, 38.3% and 39.3% of patients. Patients with a prescription of psoriasis for (more than 10 years (53.3%)), with a prescription of articular syndrome from 1 to 5 years (36.7%) prevailed. There were established specific features of the clinical picture and course of psoriatic arthritis against a background of lipid storage disease characterized by the predominance of the distal and oligoarthritis variants of the joint syndrome, with the duration of arthritis from 5 to 10 years, with a minimum and average degree of activity.*

**Key words:** psoriasis, psoriatic arthritis, articular syndrome, skin syndrome, dyslipidemia.

The etiology and pathogenesis of psoriasis and psoriatic arthritis (PA) has been the focus of numerous clinic-epidemiological studies over the whole period of dermatology development and, in recent years, of molecular genetic researches [3, 6, 8, 9, 10]. The majority of patients with psoriatic arthritis are characterized by the association of dyslipidemia with high inflammatory activity of arthritis, which causes subclinical manifestations of atherosclerosis [2]. Considering that in patients with psoriatic arthritis there is observed high frequency of metabolic disorders, consequently, there grows the risk of cardio-vascular complications, the search of means of increasing the efficiency of pathogenetically reasonable methods of psoriatic arthritis treatment with due account for metabolic disorders is quite topical. In this regard, the study of clinical peculiarities of articular and dermal syn-

dromes in patients with psoriatic arthritis with lipid storage disease presents scientific interest.

**Research objective:** the study of clinical peculiarities of articular and dermal syndromes in patients with psoriatic arthritis with lipid storage disease.

### Materials and methods

The studied sample included 120 patients with psoriatic arthritis at the age from 21 to 66 years, 66 men and 54 women. The average age of patients constituted 48 years. 41,7% - patients at the age from 41 to 50, 27,5% - patients at the age from 51 to 60, 15% - patients at the age from 31 to 40, 10% - patients at the age over 60 and 5,8% - patients at the age from 21 to 30. The distribution of patients according to age and sex is presented in Table 1.

Table 1

*Distribution of patients with psoriatic arthritis according to age and sex (n=120)*

Age group	N (number)		%
	Men	Women	
21-30 years	4	3	5,8
31-40 years	10	8	15,0
41-50 years	28	22	41,7
51-60 years	16	17	27,5
Over 60 years	8	4	10,0
Total	66	54	100

PA was diagnosed by rheumatologist on the basis of complaints, clinical examination, clinic-anatomical variant of articular syndrome, degree of activity of articular process, x-ray examination of joints and spine considering international criteria of diagnosis according to CASPAR, 2006 [4, 12]. The dermal syndrome was estimated by means of PASI index (Psoriasis Area and Severity Index) [5]. The intensity

of symptoms (erythema, infiltration, peeling) was evaluated in points from 0 (lack of symptom) to 4 (highly expressed) and summed; the damage area of every body part (head, body, upper and lower limbs) was multiplied by the corresponding index. The minimal index value constituted 0 points, maximum – 72 points.

All patients underwent complex examination (general blood analysis, common urine analysis, biochemical blood analysis, chest X-ray examination, joint and spine X-ray examination, consultation of rheumatologist and therapist). The lipid exchange was measured after 12-hour starvation by determining total cholesterol in blood serum and plasma, triglycerids, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol calculated by computational method according to Friedewald formula.

Dyslipidemia criteria were assessed with due account for Russia recommendations elaborated by the committee of expert of the Russian Society of Cardiology in 2009 [1].

The statistical data processing of clinical and laboratory research implied standard methods of descriptive and variation statistics using

simple and multiple linear analysis determining an arithmetic mean (M), average error mean (m), validity coefficient (P) by means of Student test (t) for parametric values. The results were presented in the form of  $M \pm \sigma$ , where M - sample mean,  $\sigma$  - sample standard deviation. The statistical processing was conducted on the basis of analysis of random variable distribution characterizing the state of patients and distribution parameters. Differences were considered significant by  $P < 0,05$ .

### Results and discussion

The duration of articular syndrome in patients with psoriatic arthritis constituted from 1 to 25 years. In 22,5% of patients articular syndrome had been observed for more than 6 years, in 20,8% of patients - for more than 10 years (Table 2).

Table 2

*Distribution of patients with psoriatic arthritis according to the prescription of articular syndrome (n=120)*

Prescription of articular syndrome	N (number)	%
up to 1 year	24	20,0
from 1 to 5 years	44	36,7
from 6 to 10 years	27	22,5
over 10 years	25	20,8
Total	120	100

The duration of dermal syndrome varied within the broad range from 1 to 30 years. In 53,3% of pa-

tients the disease prescription constituted over 10 years (Table 3).

Table 3

*Distribution of patients with psoriatic arthritis according to the prescription of psoriasis (n=120)*

Prescription of psoriasis	N (number)	%
up to 1 year	4	3,3
from 1 to 5 years	20	16,7
from 6 to 10 years	32	26,7
over 10 years	64	53,3
Total	120	100

It was stated that the formation of articular syndrome in 70% of patients occurred on the background of existing dermal manifestations of psoriasis, in 30% of cases it was the cause of such manifestations. the articular process in the majority of patients (78%) was represented by the distal

form of arthritis and oligoarthritis. respectively, 46 (38,3%) patients and 47 (39,3%) patients, polyarthritis - 7 (5,8%) patients, spondylarthritis - 10 patients (8,3%), combination was registered in 10 patients (8,3%) (Table 4).

Table 4

*Distribution of patients with psoriatic arthritis according to the clinical form of arthritis (n=120)*

Clinical form of PA	N (number)	%
distal form	46	38,3
oligoarthritis	47	39,3
polyarthritis	7	5,8
spondylarthritis	10	8,3
combination	10	8,3
Total	120	100

95,1% of patients were characterized by seronegative arthritis, average and low degrees of activity were registered more often, respectively, 55,6% and 30,3%, high degree of PA activity was diagnosed in 14,1% of patients. In 60 (50%) patients the damage of joints started from pains and inflammatory changes in minor joints of hands and feet, including distal interphalangeal joints. Clinical manifestations of the inflammatory process in damaged joints in 70% of patients were characterized by edema, hyperemia. In 65% of patients inflammatory joint changes were asymmetric. In 35% of patients they localized only in the area of great toes. The change of joint configuration was revealed in 80% of patients. Dactylitis was observed in 20% of patients. According to the type of articular syndrome development, 75% of patients were characterized by low progressive PA course.

In such patients, the disease for a long time proceeded without expressed pains and morning stiffness, without joint deformity and expressed muscle hypotrophy and restraint of movement. High progressive course of the disease was registered in 25% of patients. This group of patients was characterized by the appearance of steady inflammatory changes of joints in 1-2 years after the disease onset. The aggravation of articular process was registered 1-2 times a year and correlated with dermal syndrome exacerbation.

Clinical manifestations of psoriasis were characterized by a considerable abundance of eruption. The average PASI index (n=120) constituted 36,5. The distribution of PA patients depending on the clinical form of psoriasis is presented in Table 5.

Table 5

*Distribution of patients depending on the clinical form of psoriasis (n=120)*

Clinical form of psoriasis	Absolute number	%
Vulgar	60	50,0
Exudative	40	33,3
Pustulous	12	10,0
Erythroderma	8	6,7
Total	120	100

According to the present data, 60 (50%) patients were diagnosed with psoriasis vulgaris. 8 patients (6,7%) had the form of psoriatic erythroderma. In 40 patients (33,3%) there was diagnosed psoriasis exudative. The pathological process in such patients was characterized by papules and plaques cover with grew-yellow scaly-barks, and the disease, as a rule, had an extensive nature. In 91 patients (75,8%) the psoriatic process was progressive.

The study of anamnesis showed that psoriasis was seasonal, 81 patients (67,5%) had autumn-winter type of disease, 23 patients (19,2%) – spring-summer type, 16 patients (13,3%) – undifferentiated type, by which the patients could not associate the aggravation of the disease with particular type of the year.

The progressive stage was diagnosed in 91 patients (75,8%), stationary stage – in 29 patients (24,2%). According to the duration of recurrence there were observed 2 variants: in 75 patients (62,5%) the disease recurrence was registered up to 2 months, in 45 patients (37,5%) – from 2 to 6 months.

The predisposing factors of the disease onset were the following: intensive psychoemotional loads and stress situations in 50 (41,7%) patients, cold-related diseases (ARVI, influenza) and hypo-

thermia in 40 patients (33,3%), systemic alcohol consumption was observed in 18 patients (15%), solar insolation effect – in 5 (4,2%), administration of different medications – in 5 patients (4,2%). In 4 patients (3,3%) the occurrence of first symptoms of the disease and its exacerbation were not connected with trigger factors.

The study of influence of hereditary factors showed that the presence of psoriasis was revealed in close relatives of 34 PA patients (28,3%), 20 men and 14 women.

Genetic predisposition to psoriasis (GP) was observed in three lines and two levels of relation: maternally, paternally and both lines of relation, there were also determined the first and the second levels of relation.

Maternally inherited predisposition to psoriasis was registered in 14 people (41,2% of PA patients with GP), paternally inherited – in 13 people (38,2%), both lines – 7 (20,6%).

GP to psoriasis was most frequently observed in men on mother's side of the first level of relation.

There were stated peculiarities of clinical picture and PA course on the background of lipid storage disease characterized by prevalence of distal and oligo-arthritic variants of articular syndrome with arthritic prescription from 5 to 10 years and minimal and average activity.



PA on the background of lipid storage disease is characterized by the following peculiarities: by atherogenic dyslipidemia of 2b type the number of patients with polyarthritic and spondyloarthritic variants of articular syndrome with disease prescription over 10 years with severe forms of psoriasis (exudative, pustulous and erythroderma) of average and high intensity increased; by the 4<sup>th</sup> type of dyslipidemia and hypercholesterolemia there were more often observed distal and oligo-arthritic variants of articular syndrome with arthritic prescription from 5 to 10 years with psoriasis vulgaris and minimal intensity. The analysis of dyslipidemia incidence depending on the age of patients revealed the correlation with the age of patients – increase of incidence in the age group over 51 years.

Thus, in the studied sample, the correlation of men and women constituted – 1,2:1, the average age of PA patients – 48 years. The major part (62,5%) of patients were at the age from 21 to 50 years.

The articular process in the majority of patients (77,6%) was presented by distal from and oligoarthritis, according to the literature, such variants are registered in 75% [11].

According to the literature data, rheumatic factor is observed in 12% of patients, in the current study – in 5% [1].

Average and low degrees of intensity were registered more often, 55,6% and 30,3% respectively, while the high degree of PA activity was diagnosed in 14,1% of patients. According to the character of articular syndrome development, 75% of patients were characterized by low progressive PA course, when the disease for a long time proceeded without expressed pains and morning stiffness, without joint deformity and expressed muscle hypotrophy and restraint of movement which corresponds to the data of literature [12]. High progressive course of the disease was registered in 25% of patients, was characterized by the development of steady inflammatory changes of joints in 1-2 years after the disease onset. The aggravation of articular process was registered 1-2 times a year and correlated with dermal syndrome exacerbation. In 22,5% the prescription of articular syndrome constituted over 6 years, in 20,8% - over 10 years.

Clinical forms of psoriasis were prevailed by vulgar (50%) and exudative psoriasis (33,3%). Among clinical anatomic variants of articular process there prevailed distal and oligoarthritis variants, 38,3% and 39,3% of patients, respectively. The average PASI index = 36,5. The onset of psoriasis is more often observed at the age of 21-30 years (58,3%). There prevailed patients with psoriasis prescription over 10 years (53,3%), articular syndrome prescription from 1 to 5 years (36,7%). 81 patients (67,5%) were characterized by autumn-winter type of the disease. Among possible causes of psoriasis

aggravation the majority of patients (41,7%) stated psychoemotional stress and cold-related diseases (33,3%). The evaluation of clinical course in terms of psoriasis aggravation frequency showed that in the majority of patients psoriasis exacerbation happened in 76 (63,3%) twice a year. The progressive stage was diagnosed in the overwhelming majority of patients – 91 (75,8%), stationary stage – in 29 (24,2%). The recurrence of dermal syndrome lasted up to 2 months in 75 patients (62,5%).

The highest rate among concomitant diseases accounted for cardio-vascular diseases – 42 (35%).

Psoriatic arthritis on the background of lipid storage disease is characterized by the following peculiarities: by atherogenic dyslipidemia of 2b type the number of patients with polyarthritic and spondyloarthritic variants of articular syndrome with disease prescription over 10 years with severe forms of psoriasis (exudative, pustulous and erythroderma) of average and high intensity increased; by the 4<sup>th</sup> type of dyslipidemia and hypercholesterolemia there were more often observed distal and oligo-arthritic variants of articular syndrome with arthritic prescription from 5 to 10 years with psoriasis vulgaris and minimal intensity. The analysis of dyslipidemia incidence depending on the age of patients revealed the correlation with the age of patients – increase of incidence in the age group over 51 years.

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