

## FEATURES OF THE FORMATION OF REPRODUCTIVE FUNCTION IN GIRLS WITH CHRONIC DIFFUSE LIVER DISEASES AND CORRECTION OF ITS DISORDERS

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### Abstract

Diffuse liver disease is considered a global problem and is growing steadily around the world. Given that the liver coordinates both adaptive and reproductive processes in the body, and during puberty it is the formation of pituitary-gonadal connections, the impact of liver pathology in this period is undoubtedly negative. **The purpose** of the study was to improve the indicators of the formation of reproductive function in adolescent girls with chronic diffuse liver disease by developing a comprehensive system of diagnostic and therapeutic measures based on the study of their age-related functional development.

**Material and methods.** The study included 139 girls with chronic diffuse liver disease aged 12-17 years, of whom 53 patients with chronic viral hepatitis, 55 - with non-alcoholic fatty liver disease, 31 patients - with autoimmune hepatitis, and 108 healthy adolescent girls aged 12-17 years with adequate sexual development. In order to evaluate the effectiveness of the proposed comprehensive system of diagnostic and treatment-and-prophylactic measures to maintain reproductive health in girls with chronic diffuse liver disease, a main group was formed (54 patients aged 12-14 years with chronic diffuse liver disease observed by specialist in the treatment of the underlying disease and received the proposed system of diagnostic and treatment-and-prophylactic measures) and the comparison group (62 patients aged 12-14 years who received treatment-and-prophylactic measures only from a specialist in the treatment of the underlying disease) and the control group (49 healthy girls at the age of 12-14 years with age-appropriate sexual and physical development). Clinical and anamnestic and anthropometric research methods, assessment of the degree of sexual development, ultrasound examination of the pelvic organs, ultrasonic densitometry, enzyme-linked immunosorbent assay, immunofluorescent, psychometric, statistical methods were used.

**Results.** Peculiarities of sexual and physical development, echostructure of internal genitalia, functional activity of pituitary-ovarian and pituitary-thyroid system, personality profile, autonomic dysfunction and quality of life, structural and functional state of bone tissue, as well as anti-ovarian antibody production are established. The efficiency of the developed complex system of diagnostic and treatment-and-prophylactic measures for preservation of reproductive health at girls with chronic diffuse liver diseases is shown.

**Conclusions.** Adolescent girls with diffuse chronic liver disease should be examined by a pediatric gynecologist for evaluation of sexual development and menstrual function when seeking medical attention after treatment for the underlying disease during complete or incomplete clinical remission. At detection of deviations from formation of reproductive function timely complex correction should be carried out.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

**Keywords:** *girls, puberty, chronic diffuse liver diseases, sexual and physical development, pituitary-ovarian system, pituitary-thyroid system, personality profile, autonomic dysfunction, anxiety, quality of life, vitamin D, anti-ovarian functional antibody, structural tissues, menstrual dysfunction, diagnosis, treatment, prevention.*

## Introduction

The problem of maintaining the reproductive health of adolescents in its importance, scale, prospects, strategic nature is one of the most pressing today [1-4.] influence of adverse exogenous and endogenous factors. At the same time, epidemiological data indicate a steady increase in the prevalence of liver pathology worldwide. Thus, in the EU countries about 29 million people suffer from chronic liver disease [5], and worldwide, according to the WHO - more than 2 billion people. The main forms of chronic diffuse liver disease are chronic viral hepatitis (CVH), non-alcoholic fatty liver disease (NAFLD) and autoimmune hepatitis (AIH).

According to WHO estimates, every third person in the world is infected with the hepatitis B or C virus. In highly endemic regions, more than 90% of children are infected with the hepatitis A virus by the age of 10 [6, 7]. Adolescents are the most vulnerable group in the risk of parenteral viral infections due to physiological and psychological characteristics of this age [8].

NAFLD is currently the most common form of chronic diffuse liver disease, affecting 10-20% of the total pediatric population, including 8% of children who are not obese and 50-80% of those who are obese [9-11].

AIH is a rare immune-mediated chronic disease that, when inadequately treated, leads to progressive liver damage, which in turn leads to cirrhosis, liver failure, or death [12]. AIH is characterized by a sharp increase in recurrence during perimenarche and the peak incidence - after menarche [13, 14]. However, the features of physical and sexual development of girls with AIH at puberty have been little studied.

Any chronic pathology of infectious or non-infectious nature affects the somatosexual development of the growing organism, including the formation of chronic diffuse liver disease, especially during the period of intensive growth of children, complicating puberty and prepuberty [15]. But the work devoted to the study of the peculiarities of the formation of reproductive function in adolescent girls with chronic diffuse liver disease is rare. Aspects of sexual development disorders in girls with chronic diffuse liver disease

have not been identified, there is no systematic approach to the prevention and treatment of reproductive disorders, especially the formation of menstrual function. All this is the basis for finding new approaches to solving this problem, which clearly justifies the relevance of the chosen field of research.

**The aim of the study:** to improve the indicators of the formation of reproductive function in adolescent girls with chronic diffuse liver disease by developing a comprehensive system of diagnostic and therapeutic measures based on the study of their age-related functional development.

## Materials and methods

139 girls of group A with chronic diffuse liver diseases aged 12-17 years, as well as 108 healthy adolescent girls aged 12-17 years with adequate sexual development (group K). All examined patients with chronic diffuse liver disease entered puberty with the presence of the disease.

The diagnosis of chronic diffuse liver disease was established by a specialist in the treatment of the underlying disease. Examination and treatment by a pediatric gynecologist were performed after the onset of complete or incomplete clinical remission of chronic diffuse liver disease, confirmed by the results of clinical and biochemical studies.

Ultrasound examination of the uterus and ovaries was performed on expert-class devices using convex sensors with a frequency of 3.5-5.0 MHz, determined 3 uterine sizes (length, width, thickness), determined the ratio of body length and cervix, the size of the middle uterine echostructure (M-echo), three ovarian sizes (length, width, thickness), assessed the structure of the ovary (the presence and size of cysts, location, capsule thickness).

Enzyme-linked immunosorbent assays were used to determine serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), total ( $T_3$ ) and free triiodothyronine ( $T_{3f}$ ), total ( $T_4$ ) and free thyroxine ( $T_{4f}$ ), estradiol ( $E_2$ ), progesterone ( $P_4$ ), free testosterone ( $T_f$ ), insulin, sex hormone binding globulin (SHBG), antibodies to thyroid peroxidase (AT-TPO) using kits Roche Diagnostics GmbH (Switzerland) on the Cobas 6000 analyzer (e 601 module).

Patients were tested twice: before and after treatment (6 months).

## Results

At the first stage of the study, a comprehensive examination of group A girls with chronic diffuse liver disease aged 12-17 years, as well as 108 conditionally somatically healthy adolescent girls aged 12-17 years with normal sexual development of group K.

The proportion of girls with chronic diffuse liver disease with the establishment of regular menstruation in the study groups during the year was the highest in patients with CVH - 83.02%. This indicator did not differ statistically significantly from that in the control (95.37%).

In girls of all ages of puberty with chronic diffuse liver disease, there was a decrease in all sizes of the uterus compared to the control, most pronounced in AIH; the length and width of the uterus were the largest in CVH, the smallest - in AIH (Table 1).

In girls with chronic diffuse liver disease, ultrasound parameters characterizing uterine size (length, width, anteroposterior size) and mean ovarian volume had a probable direct correlation with the age of girls ( $r = 0.68$ ,  $p < 0.01$ ;  $r = 0.71$ ,  $p < 0.01$ ;  $r = 0.70$ ,  $p < 0.01$ ;  $r = 0.52$ ,  $p < 0.01$ ) and body length ( $r = 0.68$ ,  $p < 0.01$ ;  $r = 0.73$ ,  $p < 0.01$ ;  $r = 0.69$ ,  $p < 0.01$ ;  $r = 0.55$ ,  $p < 0.01$ ).

Assessment of the functional state of the pituitary-ovarian system of adolescent girls with chronic diffuse liver disease revealed statistically significant deviations in serum concentrations of gonadotropins, PRL, steroid hormones and SHBG relatively similar in control (Fig. 1).

Analysis of the production of gonadotropic hormones depending on the form of chronic diffuse liver disease and age revealed that in CVH and AIH there was a decrease in LH in all age groups, while in NAFLD - an increase in age.

The high proportion of autonomic and psychoemotional disorders in girls with chronic diffuse liver disease led to a decrease in quality of life (according to the SF-36 Health Status Survey) in all groups with chronic diffuse liver disease. Girls with CVH, NAFLD, AIH rated their physical functioning compared to somatically healthy girls statistically significantly lower in 1.14, 1.14 and 1.17

times, role physical functioning - in 1.18, in 1.34 and in 1.21 times, pain intensity - 1.14, 1.17 and 1.13 times, general health - 1.47, 1.43 and 1.49 times, viability - 1.47, 1.43 and 1.49 times, social functioning - 1.18, 1.25 and 1.19 times, role emotional functioning - 1.29, 1.39 and 1.40 times, psychological health - 1.38, 1.43 and 1.37 times. Significant differences in the assessment of quality of life between the studied groups A1, A2 and A3 were not found (Fig. 2).

Timely onset of puberty is an important factor in ensuring the peak of bone mass. Due to the high percentage of development in diffuse chronic liver disease in girls with disharmonious physical development and delayed sexuality, a study of bone mineral density was performed using ultrasound.

On the basis of the received results, at the second stage the complex system of diagnostic and treatment-and-prophylactic actions for preservation of reproductive health at girls of pubertal age with chronic diffuse liver diseases was estimated.

Therapeutic and prophylactic measures included phytopreparations that normalize the function of the pituitary-ovarian system, levels of PRL,  $E_2$  and  $T_{\beta}$ , have anti-inflammatory, analgesic and sedative properties, vitamin D preparations, vitamin-mineral complexes with calcium, magnesium and inositol, as well as therapeutic nutrition, individual and group psychocorrection, therapeutic physical training, sanatorium treatment.

Assessment of quality of life on the scale of the questionnaire "SF-36 Health Status Survey" in the dynamics of treatment showed statistically significantly higher rates for all indicators in group O compared with group P (table 2).

It should be noted that in 4 patients of comparison group P, one of whom was with NAFLD and obesity, 3 - with AIH, during the treatment of severe abnormal uterine bleeding with hormonal hemostasis, deterioration of clinical and biochemical remission of the underlying disease. There were no such cases in group O.

The treatment helped to improve the menstrual cycle in girls with chronic diffuse liver disease and led to an increase in the number of cases of regular menstrual cycles at 6 months from the start of treatment by 2.08 times (53.70% vs. 25.81% (OR 3.34 [1.53-7.28])) and a year later - 2.30 times (29.63% vs. 12.90% (OR 2.84 [1.11-7.31])). The proportion of regular menstruation cycle only 1-3 years after the

start of treatment decreased by 2.76 times (11.11% vs. 30.65% (OR 0.28 [0.10-0.77])) and the proportion of unspecified regular menstrual cycle after 3 years from the beginning of treatment - 5.52 times (5.56% vs. 30.65% (OR 0.13 [0.04-0.48])) (Fig. 3).

The applied comprehensive diagnostic and treatment-and-prophylactic measures in adolescent girls with chronic diffuse liver disease are effective and allow to recommend this complex for the treatment and prevention of reproductive disorders in this contingent.

### Conclusions

Adolescent girls with chronic diffuse liver disease should be monitored for serum levels of prolactin, thyroid-stimulating hormone, free testosterone, estradiol, 25 (OH)D.

Girls of puberty with diffuse chronic liver disease for therapeutic and prophylactic purposes should be prescribed herbal medicines that normalize the function of the pituitary-ovarian system, levels of prolactin, estradiol, free testosterone.

Patients with chronic viral hepatitis and autoimmune hepatitis should receive vitamin D according to existing guidelines. The dose of the vitamin should be adjusted taking into account its content in the vitamin-mineral complexes used by patients.

Patients of pubertal age with diffuse liver disease should be prescribed vitamin-mineral complexes containing calcium and magnesium in accordance with the instructions.

In the presence of heavy menstruation during puberty for hemostasis, patients should use tranexamic acid at a rate of 15-25 mg / kg body weight 2-3 times a day and herbs or their drugs with hemostatic and uterotonic action.

Girls with chronic liver disease, especially those with autoimmune hepatitis, are at high risk for clinical and biochemical remission with combined oral contraceptives for hemostasis. In case of abnormal uterine bleeding in this group of patients, it is advisable to use non-hormonal hemostasis.

As treatment-and-prophylactic and rehabilitation measures for adolescent girls with diffuse chronic liver diseases, therapeutic nutrition, individual and group psychocorrection, therapeutic physical training, and sanatorium treatment are recommended.

### Conflict of interest

The authors declare that there are no conflicts of interest.

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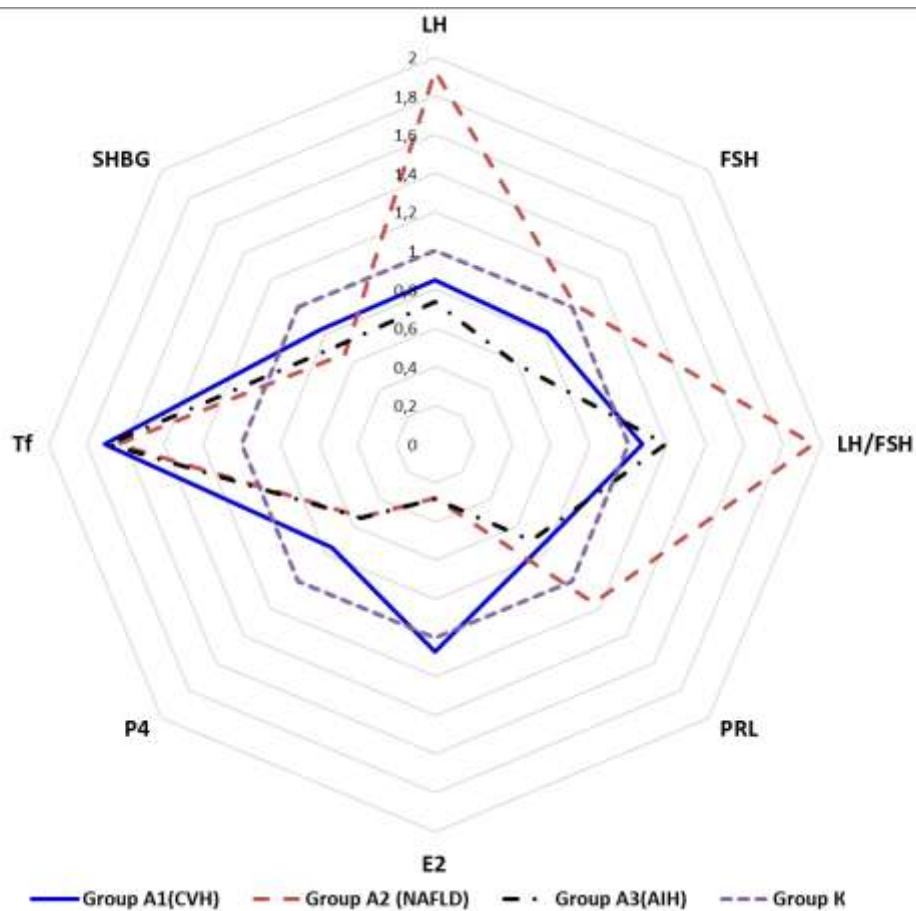
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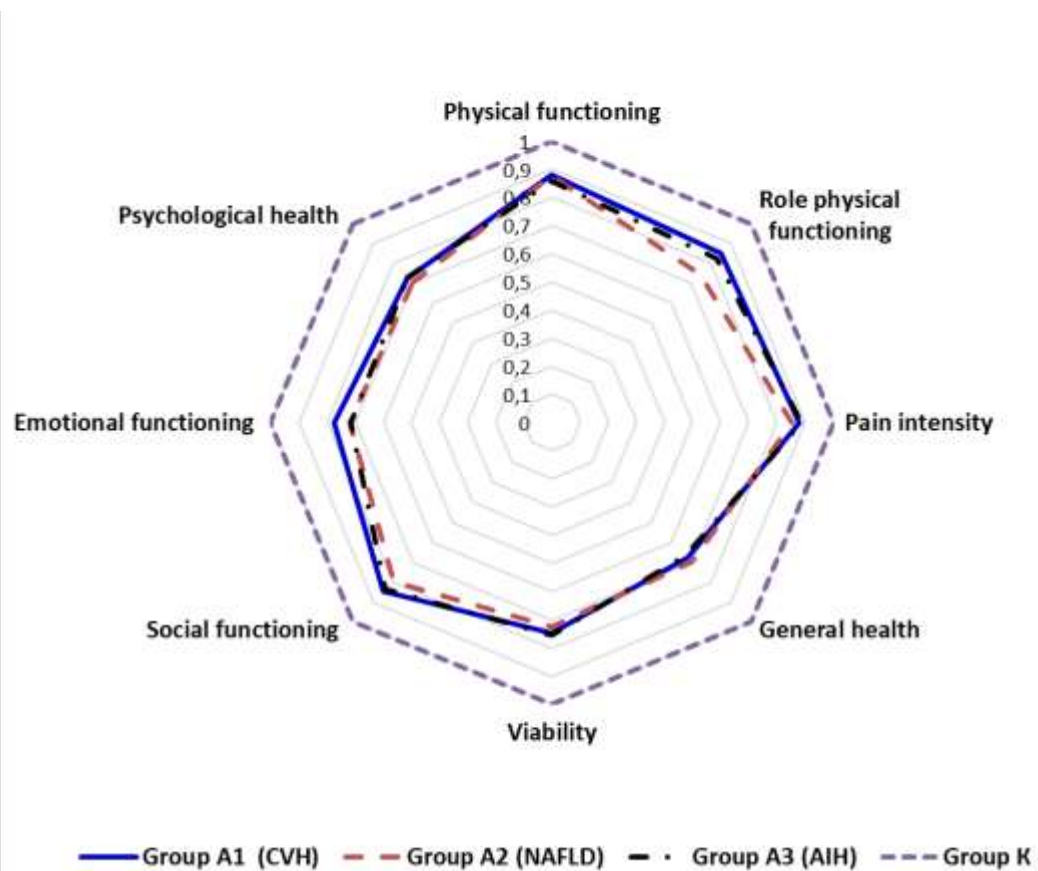
**Table 1.** Echometry data of the uterus in girls of the study groups, M ± SE

Age, in years	Group			
	A1 (CVH), n=53	A2 (NAFLD), n=55	A3 (AIH), n=31	K, n=108
Length, cm				
12-13	3.12±0.09 <sup>2,3,4</sup>	2,52±0,08 <sup>1,4</sup>	2.44±0.15 <sup>1,4</sup>	3.83±0.09
14-15	3.22±0.09 <sup>2,3,4</sup>	2.69±0.03 <sup>1,3,4</sup>	2.48±0.11 <sup>1,2,4</sup>	4.23±0.02
16-17	4.20±0.08 <sup>2,3,4</sup>	3.25±0.03 <sup>1,3,4</sup>	3.06±0.11 <sup>1,2,4</sup>	4.57±0.03
Width, sm				
12-13	2.34±0.03 <sup>2,3,4</sup>	1.86±0.04 <sup>1,4</sup>	1.82±0.03 <sup>1,4</sup>	3.13±0.05
14-15	2.49±0.04 <sup>2,3,4</sup>	1.96±0.02 <sup>1,4</sup>	1.87±0.03 <sup>1,4</sup>	3.85±0.03
16-17	2.68±0.04 <sup>2,3,4</sup>	2.10±0.02 <sup>1,4</sup>	2.15±0.03 <sup>1,4</sup>	4.22±0.02
Anterior-posterior size, sm				
12-13	1.59±0.10 <sup>4</sup>	1.65±0.06 <sup>4</sup>	1.53±0.12 <sup>4</sup>	2.19±0.06
14-15	1.66±0.07 <sup>4</sup>	1.68±0.04 <sup>4</sup>	1.62±0.04 <sup>4</sup>	2.79±0.08
16-17	1.71±0.08 <sup>4</sup>	1.72±0.03 <sup>4</sup>	1.70±0.02 <sup>4</sup>	3.25±0.02
M-echo, mm				
12-13	2.94±0.24	2.66±0.32	2.67±0.35	2.77±0.27
14-15	3.64±0.21	4.50±0.23	3.82±0.24	4.41±0.14
16-17	4.77±0.28	5.19±0.25	5.00±0.51	5.14±0.16
Note. <sup>1</sup> – statistically significant difference with the group A1 indicator, <sup>2</sup> – with the group A2 indicator, <sup>3</sup> – with the group A3 indicator, <sup>4</sup> – with the group K indicator (p<0.05).				



**Figure 1.** Indicators of hormone content, reflecting the functional state of the pituitary-ovarian system in adolescent girls with chronic diffuse liver disease relative to the control group K, taken as a unit.



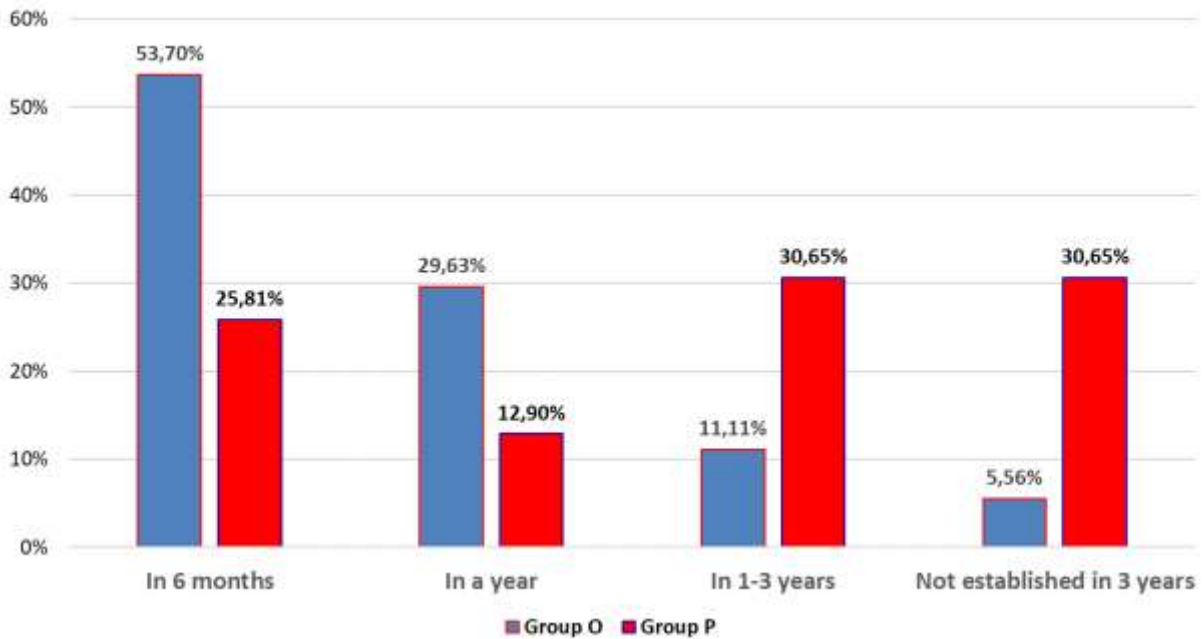


**Figure 2.** Quality of life of surveyed girls with chronic diffuse liver disease and somatically healthy patients of the control group on the scale of the questionnaire "SF-36 Health Status Survey".

**Table 2.** Assessment of the quality of life of the surveyed girls on the scale of the questionnaire "SF-36 Health Status Survey" in the dynamics of treatment, in points

Indicator	Group O, n = 54		Group P, n = 62		Group K1, n = 49
	Before treatment	After treatment	Before treatment	After treatment	
Physical functioning	86,61±2,22 <sup>k</sup>	87,41±1,88 <sup>k,p</sup>	83,87±2,01 <sup>k</sup>	84,46±1,98 <sup>k,o</sup>	94,29±0,81
Role physical functioning	71,30±4,40 <sup>k</sup>	76,31±3,88 <sup>k,p,d</sup>	70,56±4,17 <sup>k</sup>	73,39±3,58 <sup>k,o,d</sup>	88,78±2,53
Intensity of pain	72,72±3,72 <sup>k</sup>	77,31±3,12 <sup>k,p,d</sup>	73,95±3,30 <sup>k</sup>	74,12±3,35 <sup>k,o</sup>	89,43±1,77
General health	58,91±2,09 <sup>k</sup>	65,17±2,43 <sup>k,p,d</sup>	58,15±2,02 <sup>k</sup>	60,84±2,35 <sup>k,o</sup>	88,73±0,92
Viability	53,70±2,66 <sup>k</sup>	58,78±2,59 <sup>k,p,d</sup>	53,87±2,41 <sup>k</sup>	55,76±2,77 <sup>k,o</sup>	75,51±1,94
Social functioning	71,76±2,67 <sup>k</sup>	78,47±2,23 <sup>k,p,d</sup>	71,17±2,52 <sup>k</sup>	73,12±2,23 <sup>k,o</sup>	88,16±2,19
Role emotional functioning	69,14±4,81 <sup>k</sup>	75,32±4,56 <sup>k,p,d</sup>	66,13±4,57 <sup>k</sup>	70,73±4,25 <sup>k,o,d</sup>	89,21±2,44
Psychological health	55,59±2,31 <sup>k</sup>	62,78±2,47 <sup>k,p,d</sup>	55,74±2,15 <sup>k</sup>	56,33±3,14 <sup>k,o</sup>	81,71±0,82

Notes. 1. <sup>k</sup> - statistically significant difference with the group KI indicator, <sup>o</sup> - with the group O indicator, <sup>p</sup> - with the group P indicator (p<0,05); 2. <sup>d</sup> - statistically significant difference with the pre-treatment indicator (p<0,05).

**Figure 3.** Duration of the establishment of a regular menstrual cycle in the examined patients with chronic diffuse liver disease.