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PERSONIFIED TREATMENT AND PREVENTION OF SEXUAL DEVELOPMENTAL DISORDERS IN PUBERTAL AGE GIRLS WITH DIFFUSIVE LIVER DISEASES

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Abstract

Diffuse liver disease can have a pronounced detrimental effect on the developing reproductive system. Hepatoprotection in gynecological practice is not so much in the choice of drugs that protect or restore the liver, as in the appointment of optimal safe therapy for this category of patients, especially in adolescence**. The aim:** to study the effectiveness of therapeutic and prophylactic drugs for disorders of the reproductive system in adolescent girls with diffuse liver disease. **Material and methods.** Under observation for the period 2010-2020 were 486 girls aged 12-17 years, of which 120 - with chronic viral hepatitis (CVH), 120 - with non-alcoholic fatty liver disease (NAFLD), 66 - with autoimmune hepatitis (AIH), 180 - conditionally somatically and gynecologically healthy girls with normal sexual development of the control group. All patients underwent general clinical, hepatological examination, determination of features of neuroendocrine status, sexual development. The author proposed a differentiated method of treatment and prevention measures to restore reproductive health in adolescents with chronic diffuse liver disease, which included the appointment of vitamin D, phytocompositions, vitamin-mineral complexes with myo-inositol, if necessary - hormonal hemostasis. **Results.** Against the background of improved neuroendocrine status in the examined girls there was a decrease in the number of cases of amenorrhea in the group with

CVH from 5.00% to 0.00% (p<0.01), in the group of NAFLD - from 27.50% to 3.33% (OR 11.00 [3.757-32.207]), in the AIH group - from 13.64% to 0.00% (p<0.01); opsomenorrhea - from 24.17% to 2.50% (OR 12.43 [3,670-42,092]), from 67.50% to 7.50% (OR 25.62 [11.750-55.843]) and from 27. 27% to 6.06% (OR 5.81 [1.846-18.304]); oligomenorrhea - from 25.83% to 1.67% (OR 20.55 [4.791-88.152]), from 62.50% to 5.83% (OR 26.91 [11.52-62.83]) and from 27.27% to 4.55% (OR 7.88 [2.192-28.286]); juvenile uterine bleeding - from 18.33% to 1.67% (OR 13.25 [3.039-57.728]), from 10.00% to 0.00% (p<0.01) and from 9.09% to 0.00% (p<0.01); dysmenorrhea - from 38.33% to 12.50% (OR 4.20 [2.181-8.087]), from 14.17% to 5.00% (OR 3.14 [1.191-8.257]) and from 31.82 % to 13.64% (OR 2.96 [1.234-7.078]). **Conclusions.** The applied personalized treatment-and-prophylactic measures taking into account individual disorders of neuroendocrine status and menstrual health in adolescent girls with diffuse liver diseases are effective and allow to recommend this complex as a means of treatment and prevention of reproductive disorders.

Key words: adolescents; chronic diffuse liver disease; chronic viral hepatitis; nonalcoholic fatty liver disease; autoimmune hepatitis; neuroendocrine status; sexual development; menstrual health; therapeutic and prophylactic agents; vitamin D; phytocompositions; vitamin-mineral complexes; mio-inositol; hormonal hemostasis.

The health of women of childbearing age is laid down from the first days of life. In childhood, when the formation of general somatic health, many organic, and even more functional diseases of the female genitals originate, the foundation of sexual behavior is laid, reproductive attitudes are formed. Adolescence, which according to the WHO is from 10 to 19 years [45], is a critical stage in life for the realization of human and reproductive potential. During adolescence, a person acquires physical, cognitive, emotional, social and economic resources, which are the basis of health and well-being in later life [45, 67, 71]. By the end of puberty, even with a regular menstrual cycle, the reproductive system has significant lability and is particularly sensitive to the effects of adverse exogenous and endogenous factors. Diffuse liver disease can have a pronounced detrimental effect on the developing reproductive system. During puberty and older in the first place in the structure of gynecological morbidity in liver disease are menstrual disorders, which often occur due to mild vulnerability, functional imperfections at this age of regulation, mainly the hypothalamic parts of the genital system.

Epidemiological data indicate a steady increase in the prevalence of liver pathology worldwide. Thus, in the European Union, chronic liver disease affects about 29 million people

[8], and worldwide, according to the World Health Organization - more than 2 billion people. Over the last two decades, mortality in the final stages of chronic liver disease, cirrhosis and hepatocellular carcinoma has increased, reaching 50 million deaths per year. Such alarming statistics were the basis for the recognition in 2013 of chronic liver disease by the American Association for the Study of Liver Diseases as a global problem [68]. Not surprisingly, in recent years, doctors of various specialties, including obstetricians and gynecologists, are increasingly encountered in everyday practice with patients who have changed laboratory functional liver markers or have already been diagnosed with liver disease [46, 61]. Determining the causes of the disease, tactics of management and treatment of such patients, of course, the prerogative of gastroenterologists and hepatologists. However, it is obstetricians and gynecologists who have to decide on the appointment of drug therapy for gynecological diseases, which is often difficult due to lack of information on the safety and acceptability of such treatment for adolescents with liver disease. Thus, hepatoprotection in gynecological practice is not so much in the choice of drugs that protect or restore the liver, as in the appointment of optimal safe therapy for this category of patients [68].

The aim of the study was to study the effectiveness of therapeutic and prophylactic drugs for disorders of the reproductive system in adolescent girls with diffuse liver disease.

Material and methods

Under observation for the period 2010-2020 were 486 girls aged 12-17 years, of which 120 patients of group CVH - with chronic viral hepatitis (CVH), 120 patients of group NAFLD - with non-alcoholic fatty liver disease (NAFLD), 66 patients of group AIH - with autoimmune hepatitis (AIH), 180 patients of control group K - conditionally somatically and gynecologically healthy girls with normal sexual development.

The complex included clinical and anamnestic data, anthropometry, clinical blood test, general urinalysis, coprogram, parasitological examination of feces, electrocardiography, lipid profile, glucose, insulin, transferases, total protein, amylase, blood test for hepatitis B markers. C (anti-HAV IgM, HBsAg, anti-HBsIgM, anti-HBsIgG, HBV DNA PCR, anti-HCV IgG and HCV RNA PCR), autoimmunological studies (antinuclear antibodies - ANA, anti-smooth antibodies - SMA, antibodies to liver microsomes and kidneys - LKM 1), ultrasound examination of the hepatobiliary system, echocholecystography according to standard methods, consultation with an endocrinologist, gastroenterologist, hepatologist, according to the indications - cardiologist, pulmonologist, allergist and other specialists. A special set of diagnostic methods included a panel of non-invasive methods for assessing the condition of

the liver - FibroMax test, FibroTest, Geno FibroTest. The diagnosis of diseases of the hepatobiliary system was made by a gastroenterologist or hepatologist.

Peripheral blood serum hormones and sex hormone binding globulin (GHGH) were determined by chemiluminescent detection immunochemically using Roche Diagnostics kits (Switzerland) on a Cobas 6000 analyzer (e 601 module). Levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT_3), free thyroxine (fT_4), estradiol (E_2), progesterone (P_4), free testosterone (fT), a globulin that binds sex hormones (GBSH). Insulin resistance index HOMA-IR (Homeostasis Model Assessment of Insulin Resistance – assessment of homeostasis model for insulin resistance) was calculated by the formula HOMA-IR = fasting insulin (μU / fasting serum glucose (mmol / l) / 22.5.

The level of 25- (OH) D in venous blood was determined by enzyme-linked immunosorbent assay using test systems and analyzer EUROIMMUN (Germany) according to the manufacturer's instructions. The results were evaluated according to the recommendations of the International Society of Endocrinologists [15]: normal vitamin D content - 30-100 ng / ml (76-250 nmol / ml) 25- (OH) D, vitamin D deficiency - 25- (OH) D content 21- 29 ng / ml (51-75 nmol / l), vitamin D deficiency - content of 25- (OH) D less than 20 ng / ml (less than 50 nmol / l).

The degree of sexual development was determined by the conventional method for the totality of the development of secondary sexual characteristics: pubic and axillary hair, the development of the mammary glands and the formation of menstruation by J. M. Tanner (1962) and LG Tumilovich (1975) [60]. For a comprehensive assessment of sexual development used the method of summation of points, which takes into account the degree of development of each of the secondary sexual characteristics. Accordingly, the above characteristics were evaluated taking into account the correction factor. The coefficient for mammary glands was 1.2, for the degree of pubic hair - 0.3, for axillary hair - 0.4, to assess menstrual function - 2.1. The score of the development of each individual trait was calculated as the product of the average quantitative assessment of the secondary sexual trait or menstruation on the degree of development of each trait in a given patient [41]. The sum of the scores of the development of each individual trait was the score of sexual development.

The obtained data were processed statistically using the Excel software package 10. Calculated the mean value (M), standard deviation error (± SE). Student's t-test, Wilcolson-Mann-Whitney U-test, Fisher's φ-test, χ^2-test, odds ratio (OR) with confidence interval ([CI]) were used to identify differences between comparatives.

Results and discussion

Determination of the hormonal status of the examined girls revealed features in different types of diffuse liver disease (Table 1).

Table 1 - Indicators of the functioning of the neuroendocrine system in the examined girls of pubertal age, M ± SE

Indicator	CVH, n=120	NAFLD, n=120	AIH, n=66	K, n=180
LH, μIU / ml	4.35±0.09 ^{k,2,3}	9.89±0.18 ^{k,1,3}	3.77±0.25 ^{k,1,2}	5.13±0.08
FSH, μIU / ml	4.40±0.15 ^{k,2,3}	5.50±0.16 ^{k,1,3}	3.15±0.23 ^{k,1,2}	5.40±0.07
LH / FSH	1.05±0.02 ^{k,2,3}	1.91±0.05 ^{k,1,3}	1.29±0.05 ^{k,1,2}	0.98±0.02
PRL, μIU / ml	215.56±4.76 ^{k,2,3}	327.73±7.15 ^{k,1,3}	198.92±6.96 ^{k,1,2}	282.93±8.36
E_2, pmol / l	468.65±21.32 ^{k,2,3}	121.49±1.24 ^{k,1}	124.15±2.39 ^{k,1,2}	437.45±9.59
P_4, nmol / l	2.09±0.10 ^{k,2,3}	1.47±0.07 ^{k,1}	1.49±0.09 ^{k,1,2}	2.78±0.08
fT, nmol / l	1.98±0.08 ^{k}	1.90±0.07 ^{k}	1.96±0.10 ^{k}	1.16±0.04
TSH, μMO / ml	1.74±0.04 ^{k,2,3}	3.36±0.07 ^{k,1,3}	1.98±0.05 ^{k,1,2}	2.15±0.05
fT_3, pmol / l	9.32±0.09 ^{k,2,3}	4.41±0.12 ^{k,1,3}	3.50±0.06 ^{k,1,2}	5.46±0.07
fT_4, pmol / l	23.35±0.76 ^{k,2,3}	14.61±0.41 ^{k,1,3}	14.78±0.52 ^{k,1}	18.55±0.20
GBSH, nmol / l	72.27±3.29 ^{k,2,3}	34.97±1.73 ^{k,1,3}	51.56±1.87 ^{k,1,2}	64.01±2.56
25-(OH)D, nmol / l	17.25±0.79 ^{k}	17.54±0.79 ^{k}	17.14±1.06 ^{k}	23.27±0.53
HOMA-IR	1.89±0.08 ^{k,2,3}	4.35±0.20 ^{k,1,3}	2.01±0.20 ^{k,1,2}	1.30±0.03
Note. $^{k, 1, 2, 3}$ - statistically significant difference with similar indicators of groups K, CVH, NAFLD, AIH ($p<0,05$).				

Thus, girls with CVH and AIH were distinguished by lower levels of gonadotropins and PRL compared with controls and patients with NAFLD. Elevated LH and PRL levels were characteristic of girls with NAFLD. E_2 production in patients with CVH was increased compared with control and NAFLD and AIH groups, while P_4 levels were reduced and fT was increased in all groups with diffuse liver disease compared to that in group K. The most pronounced changes in the thyroid profile were observed in girls. with NAFLD, in which in most cases there was a hidden insufficiency of the thyroid gland.

Among patients with diffuse liver disease, the lowest levels of GBSH were observed in the group with NAFLD, while in girls with CVH they were elevated relative to controls.

The decrease in GBSH expression in the AIH group was less pronounced than in individuals with NAFLD.

Girls with NAFLD and obesity were characterized by insulin resistance and increased levels of leptin expression.

All patients with diffuse liver disease were distinguished by the presence of vitamin D deficiency.

Patients with CVH and AIH had a delay in sexual development compared with the control, which was manifested by a decrease in the score of sexual development in all age groups (Table 2).

Table 2 - The average score of sexual development in the surveyed adolescent girls, M ± SE

Age, years	CVH, n=120	NAFLD, n=120	AIH, n=66	K, n=180
12	3.10±0.28 к,2	9.90±0.57 к,1,3	3.21±0.40 к,2	4.94±0.37
13	3.72±0.72 к,2	8.42±0.47 к,1,3	3.46±1.00 к,2	7.91±0.58
14	6.53±1.02 к,2	10.91±0.34 1,3	7.03±1.44 к,2	11.08±0.25
15	8.49±0.15 к,2	11.55±0.22 1,3	8.56±0.23 к,2	11.25±0.20
16	7.74±0.47 к,2	12.00±0.01 1,3	7.80±0.65 к,2	11.86±0.10
17	10.51±0.58 к,2	12.00±0.01 1,3	10.65±0.79 к,2	11.98±0.02
12-17 years	6.68±0.34 к,2	10.66±0.19 к	6.78±0.46 к,2	9.84±0,23
Note. k, 1, 2, 3 - statistically significant difference with similar indicators of groups K, CVH, NAFLD, AIH (p<0,05).				

For 12- and 13-year-old girls with NAFLD and unhealthy morbid obesity was characterized by an advance in sexual development compared with controls and patients with HCV and AIG, but in 14-, 15-, 16- and 17-year-old patients it did not differ from the same indicator. control, but still was higher than in the groups AIG and HVG (see table. 2).

According to the peculiarities of neuroendocrine status and degree of sexual development, girls with various diffuse liver diseases were characterized by various menstrual health disorders (Table 3).

Table 3 - Spectrum of menstrual health disorders in the examined adolescent girls with diffuse liver disease, M ± SE

Indicator	CVH, n=120	NAFLD, n=120	AIH, n=66	OR $_{1-2}$ [95% CI]	OR $_{1-3}$ [95% CI]	OR $_{2-3}$ [95% CI]
Amenorrhea	6 (5.00)	33 (27.50)	9 (13.64)	0.139 [0.056-0.346]	0.551 [0.113-0.982]	2.402 [1.070-5.396]
primary	4 (3.33)	18 (15.00)	5 (7.58)	0.195 [0.064-0.595]	0.689 [0.109-1.624]	0.531 [0.761—6.093]
secondary	2 (1.67)	15 (12.50)	4 (6.06)	0.119 [0.027-0.531]	0.880 [0.047-1.475]	2.214 [0.703-6.971]
Opsomenorrhea	29 (24.17)	81 (67.50)	18 (27.27)	0.034 [0.015-0.078]	0.190 [0.078-0.468]	5.538 [2.854-10.746]
Oligomenorrhea	31 (25.83)	75 (62.50)	18 (27.27)	0.055 [0.026-0.115]	0.242 [0.104-0.564]	4.444 [2.307-8.563]
Juvenile uterine bleeding	22 (18.33)	12 (10.00)	6 (9.09)	1.304 [0.620-2.473]	4.889 [1.831-13.052]	1.111 [0.397-3.111]
Dysmenorrhea	46 (38.33)	17 (14.17)	21 (31.82)	3.766 [2.003-7.082]	1.273 [0.672-2.410]	0.338 [0.163-0.703]

As can be seen from table. 3, oligomenorrhea (25.83%), opsomenorrhea (24.17%), juvenile uterine bleeding (18.33%) and dysmenorrhea (38.33%) were most common in girls with CVH on the background of delayed sexual development. Among patients with NAFLD and unhealthy morbid obesity, amenorrhea (27.50%), opsomenorrhea (62.50%), oligomenorrhea (62.50%) were most common. Among patients with AIH, dysmenorrhea (31.82%), opsomenorrhea (27.27%) and oligomenorrhea (27.27%) were the most common in the spectrum of menstrual disorders.

Due to the peculiarities of the neuroendocrine profile, sexual development and the range of menstrual health disorders, we have proposed a differentiated approach to the treatment and prevention of reproductive health.

- Patients with CVH and AIH received vitamin D at the level of 25 (OH) D 20-30 ng / ml at a dose of 2000 IU / day, at the level of 10-20 ng / ml - 3000 IU / day, at the level of <10 ng / ml - 4,000 IU / day per month; with NAFLD and unhealthy morbid obesity - 4,000 IU / day for 6-8 weeks according to the existing recommendations of 2018 [52].

At normal levels of vitamin D in any diffuse liver disease for prophylactic purposes was prescribed vitamin D at a dose of 1,000 IU / day from late autumn to early spring. The dose of the vitamin was adjusted taking into account its content in the IUDs received by the girls.

In recent years, it has been shown that vitamin D, in addition to participating in the control of morphofunctional features of the skeleton, directly or indirectly regulates up to 1250 genes, performs so-called extraskeletal actions [52]. Many studies suggest that insulin resistance may be closely associated with NAFLD [5, 10, 22, 29, 63, 76]. M. Luger et al. (2016) [35] found that increased serum insulin resistance and vitamin D deficiency are clinically significant predictors of fibrosis. H. Kitade et al. (2017) [29] found that excessive accumulation of lipids in the liver causes the activation of macrophages and Kupffer cells, which leads to increased insulin resistance, as well as inflammation of the liver and fibrogenesis. Currently, research data suggest that vitamin D deficiency contributes to the progression of both insulin resistance and the development of NAFLD [14, 33, 50].

Low concentrations of vitamin D have been reported to be associated with menstrual irregularities [24]. In a study by K. Jagowska (2018) [31], it was found that women with oligomenorrhea and amenorrhea are characterized by significantly lower concentrations of vitamin D than women with regular cycles. In addition, lower plasma levels of 25 (OH) D are associated with an increased risk of menstrual irregularities (oligomenorrhea or amenorrhea). Similar results were obtained in a study by M. Sadhir et al. (2015) [51]. In the work of A. M. Jukic et al. (2015) [24] found that a lower concentration of 25 (OH) D correlates with irregular menstrual cycles, but not with short (<21 days) or long (> 32 days) cycles.

Vitamin D deficiency has been linked to testosterone, dehydroepiandrosterone sulfate and GBSH levels. A positive correlation between the level of GBSH and 25 (OH) D in blood plasma is described, as well as a negative correlation between vitamin D and the bitter number. Decreased levels of vitamin D can be considered in women as a trigger in the formation of hormonal imbalances with hyperandrogenic dominance [21].

Vitamin D deficiency can lead to an increase in parathyroid hormone, accompanied by PCOS, infertility due to lack of ovulation and high testosterone levels. Vitamin D controls estrogen biosynthesis by directly regulating the aromatase gene and maintaining extracellular calcium homeostasis. Vitamin D also significantly affects the action of insulin, which affects the presence of VDR receptors in the β-cells of the pancreas to which calcitriol binds, and stimulates insulin secretion [4, 39]. Vitamin D deficiency together with an additional violation of the regulation of calcium metabolism in the body contributes to the suppression of ovarian follicle maturation in women with PCOS [51, 55].

Girls with CVH, AIH and NAFLD with a normal level of PRL for six months were prescribed a phytocomposition, which includes extracts of *Symplocos racemosa* - 125 mg;

Asparagus racemosus - 100 mg; *Glycyrrhiza glabra* - 50 mg*; Curcuma longa* - 7.5 mg 1-2 capsules per day for 3-6 months.

Symplocos racemosa restores the normal connection of the axis "pituitary - hypothalamus - ovaries" [65]. Against the background of hormonal disorders, it normalizes the content of estrogen, P_4 and has an antiandrogenic effect [1]; helps to restore the level of high-density lipoprotein (HDL) and significantly improves the antiatherogenic index, reduces pathologically elevated cholesterol in the liver, normalizes CoA-reductase activity and reduces excess body weight, characteristic of metabolic syndrome, improves histoarchitecture [16]; has high antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Proteus mirabilis* [17]; has a pronounced hepatoprotective activity, shows significant dose-dependent recovery of marker enzymes of cytolysis (alanine aminotransferase, aspartate aminotransferase) and inflammation (alkaline phosphatase), as well as normalization on the background of toxic acute hepatitis bilirubin [albumin], albumin, albumin,

Asparagus racemosus normalizes hormonal imbalance in women by restoring the balance of FSH-LH in the hypothalamic-pituitary system, affects the synthesis of P_4 in the ovaries and interferes with the biotransformation of estrogen, helping to stimulate the conversion of E_2 to inactive estrone [58]; competes with estrogens for binding to the ligand-binding domain of estrogen receptors [102]; effective in the treatment of stress-mediated reproductive health disorders in women [44]; in patients with PCOS restores the level of FSH, which promotes the growth and development of follicles, improving the quality of oocytes, restoring fertility, possibly by reducing oxidative stress and increasing the activity of the endogenous antioxidant system [27, 43, 44, 62]; inhibits pro-inflammatory cytokines and stimulates the cellular immune response in addition to generating a stable adaptive response without any adverse effects (cytotoxicity, allergic reactions) [9].

Glycyrrhiza glabra exhibits significant hypolipidemic effect, effective in the treatment of metabolic syndrome and obesity [7]; has a powerful immunomodulatory ability [19, 74] and due to the fact that it is a synergist of glucocorticoid receptors, can be used in the treatment of immune-mediated diseases; affects the level of estrogen in a woman's body and has a high affinity for estrogen receptors, is a potent E_2 antagonist [59]; has a dose-dependent antitumor effect, which is due to significant inhibition of iNOS and regulation of extracellular signal kinase (JAK2 / STAT3) [23].

Curcuma longa Extract normalizes fatty acid metabolism, the pathway of hexosamine biosynthesis [64]; reduces LDL and increases HDL [13]; has a significant anti-inflammatory effect [36]; has a neuroprotective effect [56]; reduces edema, improves blood circulation,

stimulates the formation of erythrocytes, reduces platelet aggregation, regulates metabolism, correcting both excess and deficiency of metabolic processes, and promotes the assimilation of protein [3].

Girls with NAFLD with elevated PRL levels were prescribed a phytocomposition for six months, which included extracts of *Vitex agnus castus* - 100 mg; *Zingiber offi cinale* - 25 mg; *Trigonella foetumgraecum* - 50 mg; *Malus sylvestre* - 7.5 mg – 1-2 capsules per day for 3-6 months.

Vitex Agnus castus Extract contains bicyclic deterpenes that have dopaminergic, prolactmeinhibitory activity [11, 57, 66]. Casticin, one of the main flavonoids in Vitex extracts, demonstrated the hepatoprotective potential of estrogen-modulating properties of Vitex extracts due to flavonoids (apigenin, orientin and aucubin), which are part of it and carried out by their ER interaction with the receptor). Moreover, the estrogenic activity of flavonoids is quite high. They induced a significant increase in uterine weight in rats with ovaries removed, due to the effect on progesterone receptors in the second phase of the cycle stimulated an increase in P_4 levels. At the same time, due to the effect on estrogen receptors in the first phase of the cycle stimulated an increase in plasma estrogen levels in their absence [21]. In a randomized study conducted by M. D. van Die et al. (2013), showed that the effectiveness of vitex extracts is significantly higher than placebo. Its use normalizes the excessive secretion of PRL, the duration of the shortened luteal phase of the menstrual cycle, raises the levels of P_4 and 17β-estradiol in the middle of the luteal phase, ie increases the reproductive potential [69]. In this regard, the extract of Vitex ordinary is recommended by an independent expert commission on herbal medicines, the Federal Institute of Medicines and Medical Devices of Germany as an effective drug to restore reproductive function in women. A number of components of Vitex ordinary extracts (Vitexin, Casticin, Isoorientin, Kaempferol) exhibit analgesic and antidepressant properties, affecting mainly m- and d-opioid receptors. An additional advantage of standardized extracts of vitex is antitumor effects [34].

Liver fibrosis is a common consequence of chronic diffuse liver disease and is characterized by a multicellular response with stellate cell activation as a critical component [53]. Casticin inhibits liver fibrosis in vitro and in vivo, as evidenced by a decrease in fibrosis-related damage, accompanied by a decrease in collagen deposition and the number of α-SMA-positive cells, as well as a decrease in the expression of profibrogenic markers. Casticin inhibits stellate cell activation and induces apoptosis in already activated stellate cells by blocking the TGF-β / Smad signaling pathway [75].

Zingiber officinale Extract has anti-inflammatory and analgesic effects due to selective inhibition of cyclooxygenase-2 and 5-lipoxygenase enzymes, therefore, reduces the formation of prostaglandins, prostacyclin, thromboxane and leukotrienes [70]. The analgesic activity of Zingiber officinale Extract was demonstrated in a study by R. Mohammadbeigi et al. (2011) and G. Ozgoli et al. (2009) in patients with primary dysmenorrhea. Its effectiveness in a daily dose of 1 g was comparable to the effectiveness of ibuprofen and mefenamic acid [40, 77]. In vitro experiments have shown the ability of Zingiber officinale Extract to activate estrogen receptors with the same strength as sweet Ural [12].

Trigonella foetum graecum Extract has anticancer activity, inhibits cell proliferation along with the induction of apoptosis [48, 49]. In S. Goyal et al. (2016) proved that fenugreek diosgenin on the background of a pronounced inflammatory reaction significantly inhibits tumor necrosis factor-α (TNFα) and anti-inflammatory cytokines IL1 and IL6 [18], also found that fenugreek diosgenin is a precursor of P_4 and is able to stop progesterone-deficient conditions which is especially important in the treatment of pathologies accompanied by a pronounced hormonal imbalance. Polyphenols of *Trigonella foetum graecum Extract*, affecting the β-cells of the pancreas, reduce blood glucose levels, normalize the morphological state of the acinus and cytosol in the islets of Langerhans [65].

Pyrus mafus Extract exhibits sedative activity, which leads to the rupture of the pathological circle "stress - hyperprolactinemia", and also has a beneficial effect on the etiopathogenesis of mastalgia and mastodynia; has anti-inflammatory and antioxidant effects [54]. The presence in the apple extract of forest ascorbic acid, magnesium salts and pectins can lower blood cholesterol. Pectins interfere with the absorption of many toxic substances; organic acids, vitamins and mineral salts regulate the acid-base state of the body, which is relevant in insulin resistance, elevated uric acid levels; improves digestion; normalizes hematopoiesis.

- Patients in all groups of patients with diffuse liver disease for six months received vitamin-mineral complexes (VMC) with the presence of myo-inositol.

- ✓ Patients with diffuse liver disease without overweight and obesity received IUD, which included myo-inositol 2,000 mg; folic acid - 400 mcg; selenium - 55 mg; magnesium - 400 mg; zinc - 10 mg; vitamin D3 -1,000 IU; vitamin B1 (thiamine hydrochloride) - 1.1 mg; vitamin B2 (riboflavin) - 1.4 mg; vitamin B3 (nicotinamide) - 16 mg; vitamin B5 (pantothenic acid) - 6 mg; vitamin B6 (pyridoxine hydrochloride) - 1.4 mg; vitamin B 12 (cyanocobalamin) - 25 mcg.

✓ *Myo-inositol* is involved in intracellular signaling and the functioning of insulin receptors, reproductive hormones, growth factors, catecholamines [21]. Myo-inositol enhances the action of folate, magnesium, vitamins B5 and PP. Increasing the concentration of myo-inositol in the follicular fluid in the preovulatory and ovulatory periods is necessary for the maturation of follicles. Myo-inositol in ovarian tissues normalizes insulin sensitivity. *Folic acid* improves lipid metabolism in the liver by increasing the level of peroxisome proliferator-activated receptors (PPARб) and restores hepatic monocarbon metabolism and intestinal microbiota diversity, thereby reducing the course of diet-induced steatohepatitis [73]. Higher serum concentrations of folic acid protect against anovulation and are associated with higher levels of progesterone in the luteal phase [38]. *Selenium* is involved in many biochemical reactions and primarily in maintaining the redox balance and metabolism of thyroid hormones. Selenium has a pronounced antioxidant effect. *Magnesium* is involved in the regulation of insulin synthesis, maintaining normal blood sugar levels, reduces the progression of insulin resistance. *Zinc* is a necessary element in the metabolism of insulin and sex hormones. *Cholecalciferol* is involved in the regulation of the metabolism of hormones such as antimullerian hormone, FSH, E_2 and P_4. *Thiamine hydrochloride*, as a coenzyme, is involved in carbohydrate metabolism, critical metabolic reactions associated with energy metabolism, in the functioning of the nervous system and in reducing cellular oxidative stress. Vitamin B1 deficiency is associated with lack of ovulation. It is used to improve insulin sensitivity in insulin resistance [21]. *Riboflavin* is an important catalyst for cellular respiration, necessary for lipid metabolism, for the activation of pyridoxine and the conversion of tryptophan to niacin. *Nicotinamide* is involved in the synthesis of cortisone, thyroxine and insulin, as well as estrogen, P_4 and testosterone, improves insulin resistance in insulin resistance. *Pantothenic acid*, as a component of coenzyme A, is necessary for the synthesis of vitamin D, steroid hormones, cholesterol, erythrocytes, porphyrins, neurotransmitters. *Pyridoxine hydrochloride*, as a coenzyme, is involved in protein metabolism and synthesis of neurotransmitters; necessary for the synthesis of female sex hormones. *Cyanocobalamin* is involved in nucleotide synthesis; is an important factor in the normal growth, hematopoiesis and development of epithelial cells; required for folic acid metabolism and myelin synthesis. Participates in the absorption of iron and maturation of oocytes [21].

✓ Patients with diffuse liver disease and overweight and obesity received VMC, which included myo-inositol 2000 mg; vitamin D - 1000 IU; methyl folate - 400 mcg; chromium - 40 mcg; banaba extract - 48 mg.

Myo-inositol restores menstrual cycle in patients with oligo- / amenorrhea on the background of hyperandrogenism and insulin resistance and improves hormonal parameters [47]. *Vitamin D* significantly reduces total testosterone [6], reduces intermenstrual intervals, hirsutism and triglycerides [20]. The role of folic acid is described above. *Chromium (III)* normalizes the permeability of cell membranes to glucose, the processes of its use by cells and deposition, ie acts as a cofactor or secondary insulin transporter, improves insulin sensitivity and promotes glucose utilization by target tissues of insulin [42]. Chromium (III) is involved in the synthesis of fatty acids and cholesterol [32]. The components of *banaba extract* leaves effectively reduce acute inflammation; the content of glucose in human blood; directly activate the insulin receptor; inhibit lipogenesis, slow down the proliferation of adipocytes by 62-64%; inhibit adipocyte differentiation [2, 26, 28, 30].

For the purpose of hemostasis, the following conservative therapy was performed in patients with juvenile uterine bleeding:

1. Tranexamic acid at the rate of 15-25 mg / kg of body weight 2-3 times a day.
2. The use of medicinal plants (nettle, buckthorn, water pepper tincture).
3. Sedative therapy: valerian preparations, motherwort tincture.

At ineffective symptomatic conservative therapy, plentiful bleeding hormonal hemostasis was applied.

Indications for the appointment of hormonal hemostasis in juvenile uterine bleeding were:

1. Profuse uterine bleeding that threatens the patient's life.
2. Severe anemia with ongoing profuse uterine bleeding.
3. No effect of non-hormonal treatment.
4. Recurrent course of the disease.
5. Absence of organic pathology of the endometrium.

Girls with juvenile uterine bleeding to stop bleeding received hormonal hemostasis with a combined oral contraceptive, 1 tablet of which contains ethinyl estradiol 30 mcg and neutral progestogen desogestrel 150 mcg according to the scheme: on the first day - 1 tablet 3 times a day - once a day 2 times a day, from the third day - 1 tablet 1 time a day for 19 days. After seven days, the course was repeated to prevent recurrence of bleeding: 1 tablet 1 time per day for 21 days. Subsequently, patients received phytocompositions and VMC in accordance with the approaches described above.

It should be recognized that in modern clinical practice, the presence of patients with any chronic liver pathology in the vast majority of cases is regarded by gynecologists as a

contraindication to the appointment of therapy with female sex hormones [25]. In this regard, women are often unreasonably deprived of the possibility of hormone therapy, resulting in more invasive and less effective treatments. However, the presence of many liver diseases is not a restriction on the use of female sex hormones [68]. Numerous studies suggest that the use of combined oral contraceptives does not affect the activity of fibrotic processes in the liver, does not increase the risk of hepatocellular carcinoma and liver dysfunction in carriers of hepatitis viruses [37]. In WHO guidelines (2015) governing the acceptability and safety of various methods of contraception, mild cirrhosis in the compensatory stage, inactive HCV or hepatitis virus carriers are not contraindications to the use of hormonal contraceptives [37]. Of course, against the background of the use of hormone therapy in this category of patients requires dynamic monitoring of liver function. Meanwhile, the use of hormonal contraceptives is contraindicated in acute hepatitis or exacerbation of chronic hepatitis. Short-term use of combined oral contraceptives for hormonal hemostasis in adolescents with juvenile uterine bleeding due to diffuse liver disease is a situation where the benefits outweigh the harms, especially in cases of severe anemia.

After the proposed therapy, the neuroendocrine status of girls with chronic diffuse liver disease was assessed (Fig. 1). In the analysis of pituitary function, it was found that in the groups with CVH and AIH statistically significantly decreased levels of LH and PRL, and FSH - increased, in the group of NAFLD probably decreased levels of LH and PRL. A common result in all groups was a decrease in serum fT content against the background of increased P_4 production. Elevated pre-treatment E_2 levels decreased in the CVH group, and initially decreased E_2 levels increased in the NAFLD and AIH groups. In all studied groups, the level of GBSH increased statistically significantly and vitamin D supply was normalized. The HOMA index in all groups decreased, while in the NAFLD group it became within the reference range (Fig. 1).

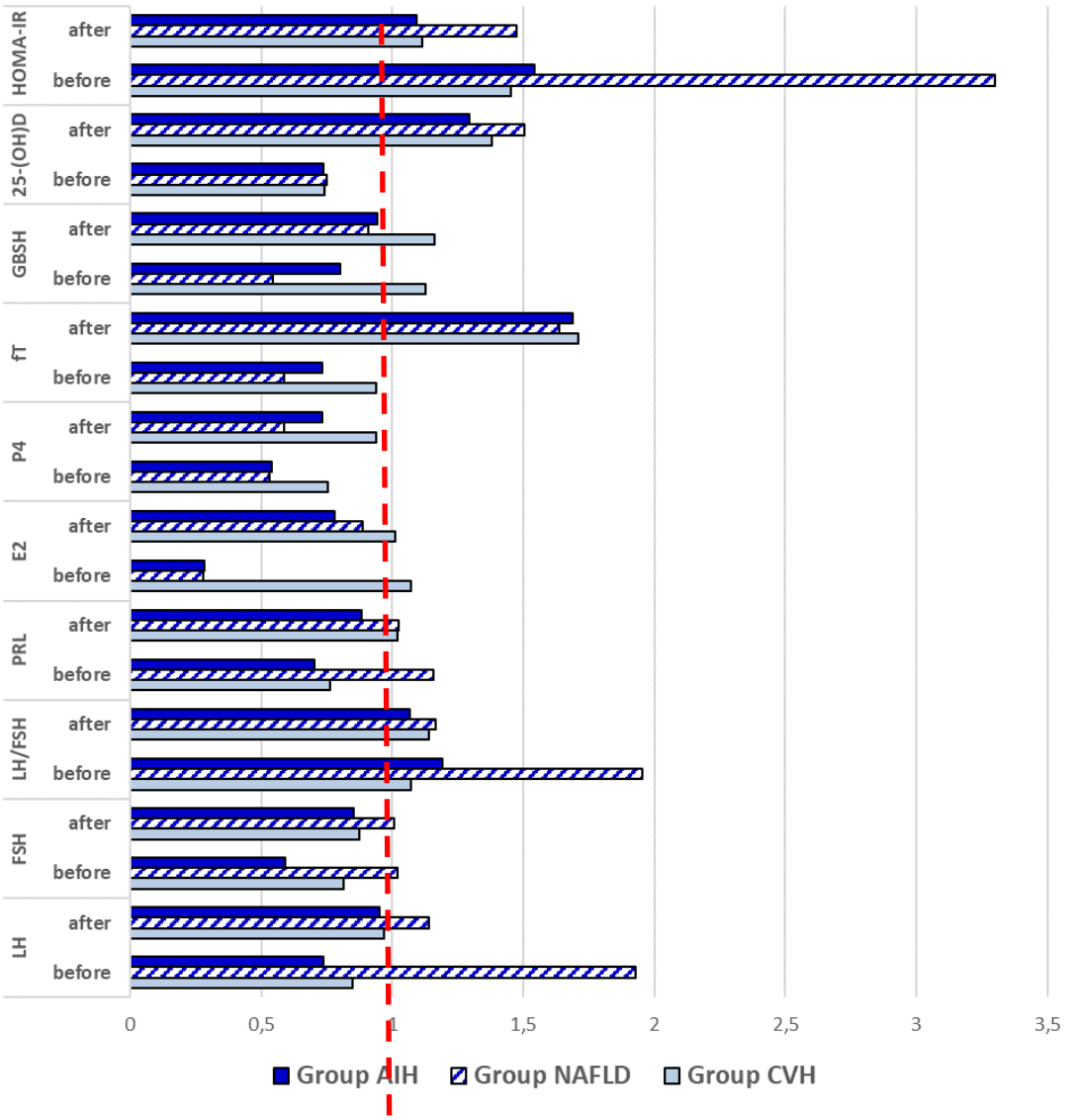

Figure 1 - Displacement of indicators of neuroendocrine status of the examined girls before and after treatment relative to control indicators.

Note. - - - – the level of control indicators taken as a unit.

The treatment improved the menstrual health of girls with chronic diffuse liver disease and led to a decrease in the number of cases of amenorrhea in the group with CVH from 5.00% (6) to 0.00% (0) ($p<0.01$), in in the NAFLD group - from 27.50% (33) to 3.33% (4) (OR 11.00 [3,757-32,207]), in the AIH group - from 13.64% (9) to 0.00% (0) ($p<0.01$); opsomenorrhea - from 24.17% (29) to 2.50% (3) (OR 12.43 [3,670-42,092]), from 67.50% (81) to 7.50% (9) (OR 25.62 ([11,750-55,843]), from 27.27% (18) to 6.06% (4) (OR 5.81 [1,846-18,304]); oligomenorrhea - from 25.83% (31) to 1.67% (2) (OR 20.55 [4,791-88,152]), from 62.50% (75) to 5.83% (7) (OR 26, 91 [(11.52-62.83]), from 27.27% (18) to 4.55% (3) (OR 7.88 [2,192-28,286]); juvenile uterine bleeding - from 18.33% (22) to 1.67%

(2) (OR 13.25 [3,039-57,728]), from 10.00% (12) to 0.00% (0) (p<0.01), from 9.09% (6) to 0.00% (0) (p <0.01); dysmenorrhea - from 38.33% (46) to 12.50% (15) (OR 4.20 [2,181-8,087]), from 14.17% (17) to 5.00% (6) (OR 3,14 ([1,191-8,257]), from 31.82% (21) to 13.64% (9) (OR 2.96 [1,234-7,078]) (Fig. 2).

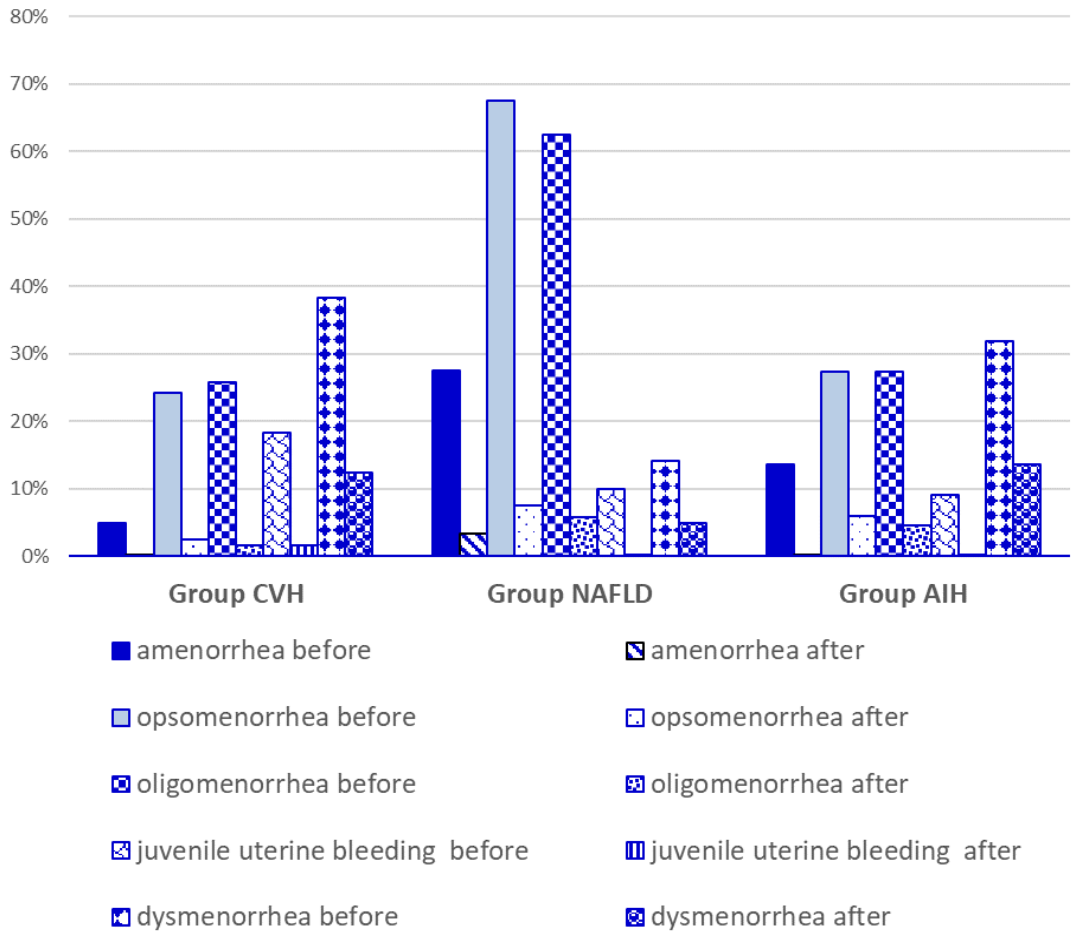

Figure 2 - Dynamics of menstrual disorders in girls with chronic diffuse liver disease after treatment.

In no case was observed refusal of the prescribed treatment and complications from the therapy.

Conclusions

The applied personalized treatment-and-prophylactic measures taking into account individual disorders of neuroendocrine status and menstrual health in adolescent girls with diffuse liver diseases are effective and allow to recommend this complex as a means of treatment and prevention of reproductive disorders.

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