DOI: 10.14739/mmt.2024.3.301976 Оригінальні дослідження / Original research
UDC 618.17-008.8:616.36-003.826]-06:616.3]-053.6-02-07

Disorders of menstrual function during puberty and the risk of nonalcoholic fatty liver disease with comorbid diseases of the gastrointestinal tract

V. O. Dynnik*[1,A,C,F], O. O. Dynnik[2,C,D,E], A. Ye. Druzhynina[1,B,D], S. V. Novokhatska[1,B,C,D]

[1]SI "Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine", Kharkiv,
[2]Kharkiv National Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Keywords: menstruation disorders, teenage girls, non-alcoholic fatty liver disease, metabolic disorders.

Ключові слова: розлади менструальної функції, дівчата-підлітки, неалкогольна хвороба печінки, метаболічні порушення.

Надійшла до редакції / Received: 15.04.2024

Після доопрацювання / Revised: 11.07.2024

Схвалено до друку / Accepted: 15.07.2024

Конфлікт інтересів: відсутній.

Conflicts of interest: authors have no conflict of interest to declare.

***E-mail:** viktoriadynnik@gmail.com

The aim of the study was to determine the relationship between disorders of menstrual function in adolescence and the risk of nonalcoholic fatty liver disease (NAFLD) with comorbid gastrointestinal pathology.

Materials and methods. We examined 129 adolescent girls aged 12–17 years with menstrual disorders (61 with abnormal uterine bleeding (AUB) and 68 with oligomenorrhea (OM)) and measured anthropometrics, indices of lipid and carbohydrate metabolism and liver enzymes. Data are presented in the form of mean (M), standard deviation (SD) and median (Me), a factorial model was developed.

Results. The study shows the peculiarities of the clinical course of menstrual function disorders in girls of puberty age. Patients with AUB were characterized by significantly lower average body mass indices, they were younger compared to patients with OM. The nature of metabolic changes that depended on the type of menstrual disorders in teenage girls was clarified. Adolescents with AUB had statistically significantly higher average levels of immunoreactive insulin, HOMA index, triglycerides, very low-density lipoprotein cholesterol, aspartate aminotransferase. This creates conditions for the formation of nonalcoholic fatty liver disease. A model was created regarding the participation of dyslipoproteinemia, changes in the carbohydrate spectrum and levels of liver enzymes in the formation of nonalcoholic fatty liver disease in girls with menstrual cycle disorders.

Conclusions. Disorders of menstrual function are associated with an increased risk of NAFLD formation. Adolescent girls with menstrual disorders need metabolic screening. The atherogenic profile of lipoproteinemia, marked changes in the carbohydrate spectrum and increased serum levels of liver enzymes in girls with menstrual cycle disorders are the basis for the formation of nonalcoholic fatty liver disease.

Modern medical technology. 2024;16(3):197-205

Порушення менструальної функції в періоді пубертату та ризик формування неалкогольної жирової хвороби печінки

В. О. Диннік, О. О. Диннік, А. Є. Дружиніна, С. В. Новохатська

Мета роботи – визначити зв'язок між розладами менструальної функції в підлітковому віці та ризиком виникнення неалкогольної жирової хвороби печінки (НАЖХП) при коморбідній шлунково-кишковій патології.

Матеріали і методи. Обстежили 129 дівчат-підлітків (віком 12–17 років) із розладами менструальної функції: 61 – з аномальними матковими кровотечами (АМК), 68 – з олігоменореєю (ОМ). У пацієнток вивчили показники антропометрії, ліпідного, вуглеводного спектрів, ферментів печінки. Результати наведено як середнє значення (M), стандартне відхилення (SD) та медіану (Me); розроблено факторну модель.

Результати. У дослідженні визначено особливості клінічного перебігу розладів менструальної функції в дівчат пубертатного віку. В пацієнток з АМК визначили достовірно нижчі середні показники індексу маси тіла; крім того, ці дівчата молодші за пацієнток з ОМ. Визначили характер метаболічних змін, що залежали від типу порушень менструацій у дівчат-підлітків. У пацієнток з АМК зафіксували статистично значущо вищі середні рівні імунореактивного інсуліну, індексу HOMA, тригліцеридів, холестерину ліпопротеїдів дуже низької щільності, аспартат амінотрансферази. Це створює умови для формування НАЖХП. Створено модель щодо участі дисліпопротеїдемії, змін вуглеводного спектра та рівнів ферментів печінки у формуванні НАЖХП у дівчат із розладами менструального циклу.

Висновки. Розлади менструальної функції пов'язані з підвищеним ризиком формування НАЖХП. Дівчата-підлітки з порушеннями менструацій потребують метаболічного скринінгу. Атерогенний профіль ліпопротеїдемії, виражені зміни вуглеводного спектра і підвищення рівнів ферментів печінки у сироватці крові дівчат із порушеннями менструального циклу лежать в основі формування НАЖХП.

Сучасні медичні технології. 2024. Т. 16, № 3(62). С. 197-205

Menstrual health affects a woman's life from puberty to menopause. Today there are clear parameters of a normal menstrual cycle. Duration of menstrual cycle varies from 21 to 45 days (5 perc 21 days, 90 perc 90 days) in adolescence, despite the variability. The duration of uterine bleeding itself is from 2 to 7 days, and the volume of blood loss should not exceed 50 ml [1,2]. This knowledge is necessary for identifying abnormalities and making a clinical assessment of the type of disorder. The most common disorder of menstruation in adolescence is oligomenorrhea (OM). According to ICD-10, it is scanty and/or infrequent menstruation. The most severe pathology of menstrual function is abnormal uterine bleeding (AUB), which is excessive and/or frequent menstruation [3,4,5].

Recently, there has been an increasing number of publications on non-alcoholic fatty liver disease (NAFLD) in various diseases, including menstrual cycle disorders [6,7,8]. NAFLD is becoming an increasingly common liver disease, with a worldwide prevalence of 25–30 %, and it's projected to rise to 56 %, paralleling the rise in obesity and type 2 diabetes [9,10,11]. The prevalence of NAFLD and the stage of the disease increases with age and have phenotypic expression. Postmenopausal women have a much higher rate of progression of this disease than men. There are a number of comorbidities that are associated to varying degrees with disease progression in patients with NAFLD. The most common is the metabolic syndrome [12]. Obesity is very common among patients with NAFLD, with up to 75 % of overweight patients and 90–95 % of morbidly obese patients having NAFLD [13]. NAFLD is also closely related to insulin resistance and disorders of lipid metabolism [14,15].

The diagnosis of NAFLD requires confirmation of liver steatosis (according to visualization or histology), as well as the absence of secondary causes of fat accumulation in the liver, such as heavy alcohol consumption, long-term use of steatogenic drugs, monogenic hereditary diseases, etc. [16,17]. Liver biopsy has a number of disadvantages, not least related to complications and even very rarely mortality. However, the assessment of dynamic changes using ultrasound and computed tomography is not reliable. The greatest unmet need in this field is a specific biomarker that can diagnose and determine the stage of disease to replace the demand for liver biopsy [9].

Although liver function tests are not specific and very sensitive, they are recommended for determining the risk of NAFLD. Reference values of alanine aminotransferase (ALT) have been revised and updated [18].

Disorders of menstrual function in adolescence may serve as risk factors for the future development of cardiometabolic dysfunction, including insulin resistance, cardiovascular diseases, etc. [8,19], however, there are very few studies on the relationship between menstrual disorders and NAFLD, they mainly concern polycystic ovary syndrome [20,21] and are absent in adolescence.

Aim

Based on the above, the aim of study was to determine the relationship between disorders of menstrual function in adolescence and the risk of nonalcoholic fatty liver disease with comorbid gastrointestinal pathology.

Materials and methods

There were 129 girls with menstrual disorders under observation. Examination by a pediatrician and a gastroenterologist revealed changes in the gastrointestinal tract. They revealed: functional disorders of the biliary tract, gastroesophageal reflux disease, gastritis and gastroduodenitis. It should be noted that functional disorders of the biliary tract prevailed, which were registered in 88 % of girls with disorders of menstrual function. There were 68 girls with OM and 61 girls with AUB aged 12–17 years among those examined.

According to the FIGO 2018 classification, AUB is defined as uterine bleeding with an intermenstrual interval up to less than 21 days and/or a duration up to more than 8 days and/or between menstrual bleedings [4]. Blood diseases, thrombocytopenia, blood coagulation insufficiency were excluded in the cohort of girls with AUB that were examined using screening for hemostasis disorders. The diagnosis of oligomenorrhea was defined as spontaneous menstruation with an intermenstrual interval up to more than 45 days with a normal duration [5]. Patients with OM and congenital or postnatal forms of adrenogenital syndrome, gonadal dysgenesis and patients with severe disabling extragenital diseases (diabetes mellitus, idiopathic rheumatoid arthritis, autoimmune thyroiditis and others) were excluded from the study.

Anthropometry included determination of height, body weight, and body mass index (BMI) was calculated. Interpretation of the obtained results was carried out using age centile tables [22,23]. Blood samples were taken from the ulnar vein to measure fasting blood glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) on a general-purpose photometer using Cormay sets, with subsequent calculation of low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C), atherogenic coefficient (AC). Levels of ALT, aspartate aminotransferase (AST) were measured using SpL kits, Ukraine. The concentration of immunoreactive insulin (IRI) was determined by the method of immunoenzymatic analysis (Rayto RT-2100C photometer) using commercial kits of reagents from the company "Best Diagnostics", Kyiv.

Insulin resistance was determined based on the following equation of the homeostatic model of insulin resistance assessment (HOMA-IR): insulin in fasting blood (μU/ml) × glucose in fasting blood (mmol/L) / 22.5. The threshold point for insulin resistance was determined as HOMA-IR 3.45 (75 perc) based on the results of the examination of 59 healthy girls of the same age without disorders of menstrual function.

According to the protocol of the Ministry of Health of Ukraine (September 24, 2022 No. 1732) "On the approval of the standards of medical care "Obesity in children", normal diagnostic values of ALT should not exceed 22 IU/L. The levels of aspartate and alanine aminotransferase may to some extent indicate changes in liver function and the formation of NAFLD.

Statistical processing of the research results was carried out by classical mathematical methods of variational statistics using the statistical package "Statgraphics Plus 5.0". Data are presented as mean (M), standard deviation (SD), and median (Me). The Student's t-test, Wilcoxon–Mann–Whitney, χ^2 was used to compare indicators. The difference in indicators was considered

Table 1. Percentage of girls with AUB and OM and different BMI values, %

BMI	Diseases of the gastrointestinal tract	
	AUB	OM
Normative	65.6	60.7
Body weight deficit	18.0	16.9
Excess body weight	11.5	15.7
Obesity	4.9	6.7

reliable at $p < 0.05$. System analysis was carried out using factor analysis. The structure of factor models is presented in the form of tables containing information on the informativeness of factors and the value of factor loading coefficients (FLC).

The study was approved by the ethics committee at the SI "Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine" and was performed in compliance with the requirements, norms and basic provisions of bioethics, meets the ethical principles of medical research with human participation and the requirements of European and local protocols.

Results

A comparison of the percentage of different BMI values in connection with the type of menstrual dysfunction with comorbid gastrointestinal pathology is shown in *Table 1*.

As shown in *Table 1*, there was no significant difference in BMI between patients with AUB and OM. However, only 61–66 % of patients had normal BMI values. Body weight deficit and its excess occurred with the same frequency.

An excess of androgens can be the factor that provokes NAFLD in the case of a violation of the menstrual cycle [8,24].

Considering that clinically hyperandrogenism can manifest with hirsutism, acne vulgaris, stretch marks, fatty seborrhea [25], analysis of these signs revealed the presence of clinical manifestations of hyperandrogenism in some girls *(Fig. 1)*. Their frequency in patients with OM was slightly higher than in girls with AUB ($p < 0.06$). Moreover, 12.2 % of girls with AUB and 14.6 % with OM had minor manifestations of hirsutism (from 4 to 14 points on the Ferriman–Galway scale), and 19.6 % with AUB and 30.8 % with OM had severe ones (more than 15 points; $p < 0.05$).

Some researchers believe that the development and progress of NAFLD can be influenced by age of menarche [11]. Menarche is the first menstruation and an event that symbolizes reproductive health and the transition from childhood to womanhood as the final chord of sexual maturation *(Fig. 2)*.

It was established that the average age of menarche in adolescents with AUB was significantly lower than in girls with OM ($p < 0.01$).

In most teenage girls, menstruation comes at the age of 12–14 years. It should be noted that among adolescents with OM this happened probably more often – 62.6 % than with AUB 49.2 % ($p < 0.05$).

Early menarche is considered an important medical and social problem because it can lead to increased morbidity and mortality

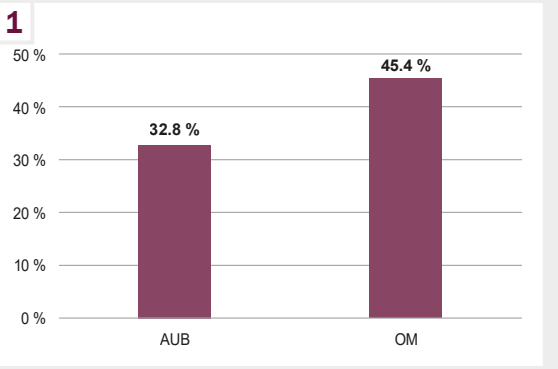

Fig. 1. Percentage of girls with manifestations of hyperandrogenism and comorbid gastrointestinal pathology.

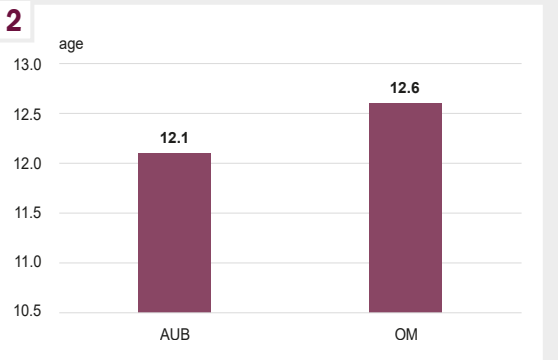

Fig. 2. Average age of menarche in adolescents with various disorders of menstrual function and comorbid gastrointestinal pathology.

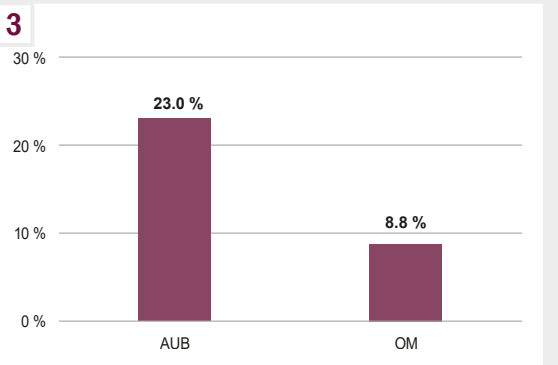

Fig. 3. Percentage of girls with various disorders of menstrual function and comorbid gastrointestinal pathology and early menarche.

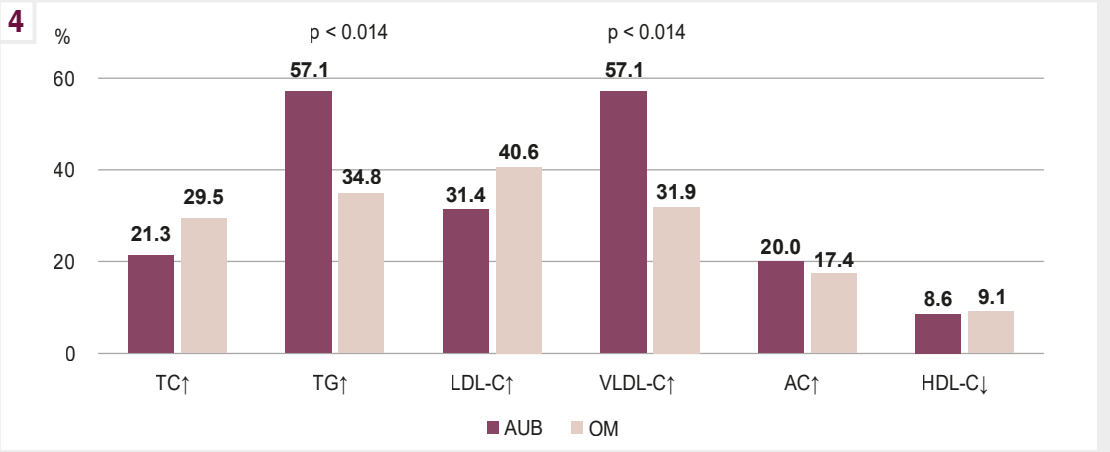

Fig. 4. Percentage of altered levels of the blood lipid spectrum in adolescent girls with menstrual cycle disorders and comorbid gastrointestinal pathology.

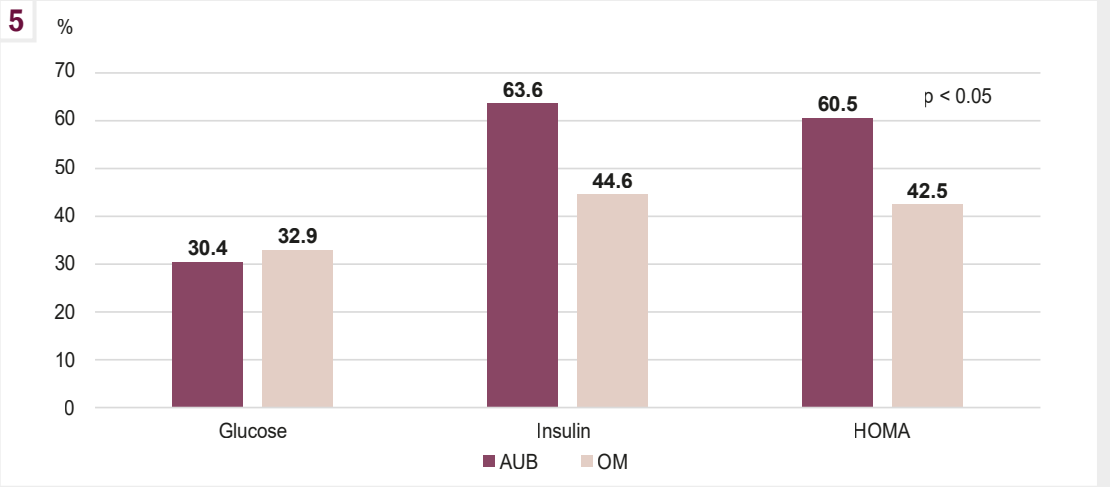

Fig. 5. Percentage of girls with elevated values of glucose, insulin and HOMA index (above 75 percent).

in later life [26,27]. Every fourth girl with AUB and one in 10–11 girls with OM had early menarche (*Fig. 3*; p < 0.007).

The liver is a dynamic organ that plays a crucial role in many physiological processes, including the regulation of systemic glucose and lipid metabolism. Dysfunctional lipid metabolism in the liver is the cause of NAFLD, the most common chronic liver disease worldwide [7].

Girls with AUB are characterized by significantly lower mean BMI, they are younger compared to patients with OM. Adolescents with AUB have statistically significantly higher average levels of IRI, HOMA index, TG, VLDL-C, AST *(Table 2)*.

An individual analysis of lipid spectrum levels revealed that the overall frequency of lipid spectrum disorders was 71.4 % in girls with AUB and comorbid pathology and 60.9 % in adolescents with OM and comorbid pathology *(Fig. 4)*. It should be noted that lipidograms without pathological changes were registered in patients with AUB significantly less frequently than in girls with OM (28.6 % vs. 39.1 %, respectively; p < 0.05).

About one third of girls with disorders of menstrual function and comorbid pathology of the gastrointestinal tract had elevated fasting glucose level *(Fig. 5)*.

63.6 % of patients with AUB and 44.6 % with OM (p < 0.02) had elevated IRI values, and in adolescents with AUB, more than a third (36.4 %) of these figures exceeded 90 percent. In patients with OM, IRI higher than 90 percent was registered much less frequently, in only 7.7 % of girls (p < 0.0001). The HOMA index above 90 percent was found in every fifth girl with OM and much more frequently in adolescents with AUB (20.9 % vs. 39.5 %; p < 0.02).

The average values of ALT were higher than 22 IU/L both in girls with AUB and OM with comorbid pathology of the gastrointestinal tract *(Table 2)*. Individual analysis revealed that the increase in ALT concentration occurred in 54.2 % of girls with AUB and in 42.5 % with OM. Moreover, it did not depend on age, BMI, insulin resistance, age of menarche. That is, more than half of girls with AUB and almost half of teenagers with OM have elevated levels of liver enzymes, which may be a risk factor for the formation of NAFLD.

In almost 100 % of cases, abdominal ultrasound revealed deformations of the gallbladder, most often its folds (100 % in patients with AUB and 96.8 % in girls with OM). In 44.4 % of

Table 2. Average values of clinical and biochemical indicators in girls with menstrual cycle disorders and comorbid gastrointestinal pathology

Parameter, units of measurement	Statistical indicator	AUB	OM	p
Age, years	n	61	68	<0.000001
	M ± SD	13.78 ± 1.88	16.25 ± 1.68	
	Me	13.40	15.00	
BMI, unit	n	61	68	<0.001
	M ± SD	20.00 ± 4.45	21.20 ± 4.35	
	Me	18.99	20.58	
Glucose, mmol/L	n	46	68	>0.05
	M ± SD	4.95 ± 0.61	5.02 ± 0.60	
	Me	4.99	4.94	
IRI, cU/ml	n	44	65	<0.01
	M ± SD	19.26 ± 9.15	15.56 ± 7.29	
	Me	17.95	14.98	
HOMA-IR, unit	n	43	62	<0.02
	M ± SD	4.26 ± 2.02	3.49 ± 1.75	
	Me	3.81	3.23	
TC, mmol/L	n	46	68	>0.05
	M ± SD	4.69 ± 0.83	4.91 ± 0.90	
	Me	4.70	4.80	
HDL-C, mmol/L	n	35	68	>0.05
	M ± SD	1.66 ± 0.41	1.79 ± 0.38	
	Me	1.62	1.70	
TG, mmol/L	n	35	68	<0.002
	M ± SD	1.14 ± 0.42	0.93 ± 0.33	
	Me	1.13	0.83	
LDL-C, mmol/L	n	35	69	>0.05
	M ± SD	2.49 ± 0.85	2.76 ± 0.86	
	Me	2.57	2.66	
VLDL-C, mmol/L	n	35	68	<0.002
	M ± SD	0.52 ± 0.19	0.42 ± 0.15	
	Me	0.51	0.38	
AC, conventional units	n	35	68	>0.05
	M ± SD	1.94 ± 0.67	1.88 ± 0.68	
	Me	1.86	1.72	
AST, IU/ml	n	24	40	<0.008
	M ± SD	26.33 ± 5.28	23.78 ± 6.81	
	Me	25.50	23.78	
ALT, IU/ml	n	24	40	>0.05
	M ± SD	23.58 ± 5.80	22.35 ± 5.98	
	Me	23.50	22.00	

Table 3. The structure of the factorial model of the relationship between liver enzymes, lipids, and carbohydrates in disorders of menstrual function comorbid with gastrointestinal diseases

Factors	Percent of variance	Variable names	Factor loadings
F1	33.4	VLDL-C	0.96
		TG	0.96
		HDL-C	-0.57
F2	23.3	IRI	0.98
		HOMA	0.99
F3	17.5	LDL-C	0.93
		TC	0.98
F4	13.8	AST	0.86
		ALT	0.83

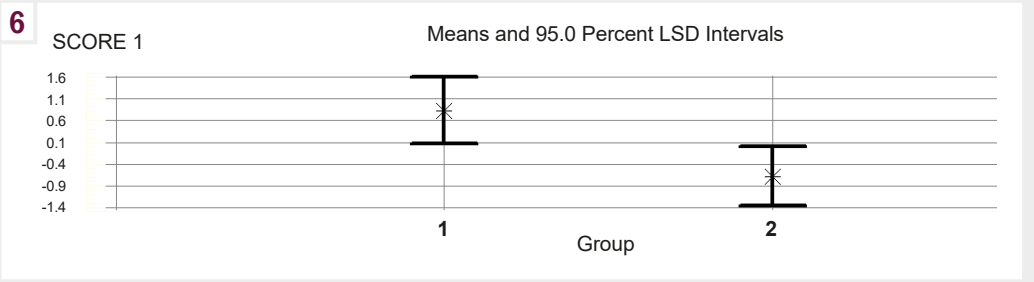

Fig. 6. Distribution of average eigenvalues of Factor 1 in patients with AUB and OM with comorbid gastrointestinal pathology.

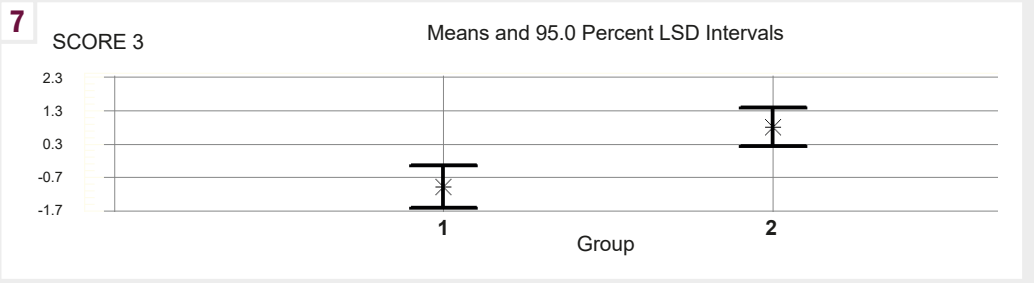

Fig. 7. Distribution of average eigenvalues of Factor 3 in patients with AUB and OM with comorbid gastrointestinal pathology.

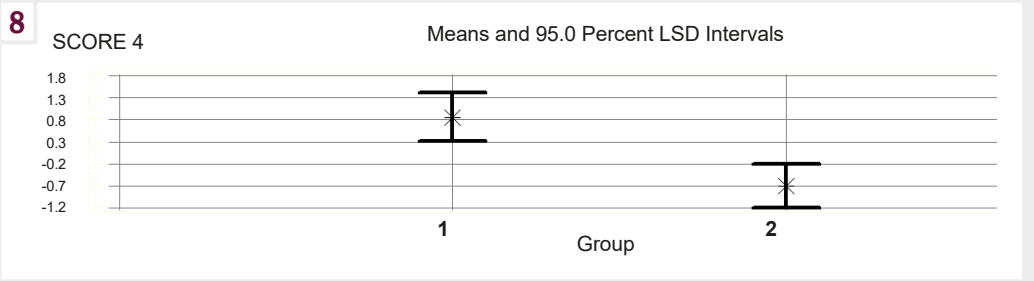

Fig. 8. Distribution of average eigenvalues of Factor 4 in patients with AUB and OM with comorbid gastrointestinal pathology.

adolescents with AUB and in 64.5 % of girls with OM, a flaky suspension from a small amount to 20–30–50 % was visualized in the gallbladder cavity. A moderate increase in the size of the liver was found in 55.6 % of patients with AUB and significantly less often in patients with OM and comorbid gastrointestinal pathology in 32.3 % ($p = 0.05$). It should be noted that in single cases, small inclusions were noted in the liver parenchyma of the patients with AUB. Dilation of the bile ducts also occurred significantly more often in patients with AUB (27.8 % vs. 16.1 % in patients with OM; $p < 0.0001$). In isolated cases, dilation of the portal vein was

detected. All these changes were more often associated with an increase in liver enzymes levels. That is, almost half of adolescent girls with menstrual cycle disorders and comorbid gastrointestinal diseases are at risk of NAFLD formation.

Currently, the relevance and expediency of applying mathematical methods in medical and biological research is beyond doubt. At the same time, the methods of multivariate statistical analysis become especially relevant, with the help of which it is possible not only to systematize data, but also to reveal the nature and structure of complex relationships between various components of the studied characteristics.

The first main factor (F1), which describes 33.4 % of the variability of the initial data, included TG indicators with a FLC of 0.96, VLDL-C with a factor of 0.96 and HDL-C with a negative FLC of -0.57 *(Table 3)*. The association of variables that are part of this factor indicates that in girls with menstrual disorders, an increased level of TG is associated with a reduced content of HDL-C, which creates preconditions for the development of atherogenic dyslipidemias. The variance analysis of the eigenvalues of the first factor in relation to the observation groups (AUB and OM) indicates that girls with AUB have a probably higher average level of F1 compared to adolescents with OM ($p < 0.003$; *Fig. 6*).

The F2 structure describes 23.3 % of the variance of the analyzed system of features. It is represented by indicators of the carbohydrate spectrum: IRI with FLC 0.98 and HOMA index with FLC 0.99. It characterizes the fact of a positive relationship between the level of insulin and the HOMA index. Probable differences depending on the observation groups were not found.

The third factor determines 17.5 % of the variance of the variability of the variables and indicates a close relationship between TC (FLC – 0.98) and LDL-C (FLC – 0.93), which may indicate the genetic basis of dyslipidemia. The analysis of variance of eigenvalues revealed that its average level in girls with AUB is significantly lower than in teenagers with OM ($p < 0.007$; *Fig. 7*).

The decisive factor for F4 is the pronounced relationship between liver transferases, which gives an approximate estimate of its functional state. The dispersion of the eigenvalues of this factor indicates its significant increase in patients with AUB in comparison to girls with OM ($p < 0.01$; *Fig. 8*).

Thereby, the main factors were established, the combined effect of which explains 87.7 % of the variability of carbohydrate, lipid spectra and liver enzyme indicators in adolescents with menstrual cycle disorders and comorbid pathology of the gastrointestinal tract. The structure of interrelationships of the studied parameters is pathogenetically justified and explains the influence of metabolic disorders on the formation of NAFLD. A difference in the influence of 3 factors was found between patients with OM and AUB. Disturbances of the lipid spectrum of the blood and high levels of liver enzymes, which contribute to the occurrence of NAFLD, had a greater impact on the course of AUB compared to OM.

Discussion

The results, that were obtained in the study indicate a fairly high risk of NAFLD formation among teenage girls with menstrual disorders and comorbid pathology of the gastrointestinal tract. Diagnosis of NAFLD currently requires the exclusion of a number of problems associated with the accumulation of excess macrovesicular fat. This indicates that there is still a lack of a specific biological marker that could accurately characterize this condition, distinguishing it from similar pathologies [28]. However, factors contributing to the occurrence of this pathology are discussed in the literature sources. An excess of androgens can be the factor that provokes NAFLD in menstrual cycle disorders [8,24]. Our study shows that clinical manifestations of hyperandrogenism – hirsutism, hypertrichosis, acne vulgaris, stretch marks, seborrhea – were registered in a fairly large group of girls – more than a third of patients with AUB (32.8 %) and 45 % of patients with OM. Moreover, these manifestations were significant in almost every fourth girl with AUB and in a third with OM. This must be taken into account during the clinical examination of girls with menstrual disorders.

Factors affecting the formation of NAFLD include excess body weight, insulin resistance, and the age of menarche [11,13]. Among the examined girls, about 12–16 % had excess body weight, almost a quarter of teenagers with AUB and every 11 with OM had an early menarche. 64 % of patients with AUB and 45 % with OM had increased IRI and HOMA index. However, in contrast to literature data, the increase in the concentration of liver enzymes was not dependent on age, BMI, insulin resistance, and the age of menarche. It can be assumed that these factors act separately in the case of menstrual disorders in adolescence.

The results of our research and literature data [7] confirm that the leading role in the development and progression of NAFLD due to comorbid pathology of the gastrointestinal tract is played by an increase in the level of triglycerides in the blood. Moreover, such an increase is much more common in AUB than in OM. Lipidograms with atherogenic trend were found in 71.4 % of girls with AUB and in 30.9 % of teenagers with OM.

As follows, in teenage girls with menstrual disorders and comorbid gastrointestinal pathology, atherogenic dyslipidemia and carbohydrate metabolism disorders were registered in more than half of cases, which is a prerequisite for the formation of NAFLD. This confirms the need for metabolic screening in girls with disorders of menstrual function.

Factor analysis showed that there is a close relationship between liver enzymes, lipids, and carbohydrates in the case of disorders of menstrual function in patients comorbid with gastrointestinal diseases, which can be considered as predictors of NAFLD development. A difference in the influence of studied factors was found between patients with OM and AUB. Disturbances of the lipid spectrum of the blood and high levels of liver enzymes, which contribute to the occurrence of NAFLD, had a greater impact on the course of AUB compared to OM. This suggests that AUBs are much more susceptible to hormonal and metabolic shifts than OMs, which create conditions for the formation of complications such as NAFLD.

Conclusions

1. Disorders of menstrual function are associated with an increased risk of NAFLD formation.

2. The atherogenic profile of lipoproteins, changes in the carbohydrate spectrum and increased serum levels of liver transaminases in girls with menstrual cycle disorders are associated with the occurrence of NAFLD. Only in 28.6 % of patients with AUB and 39.1 % with OM had lipidograms that were within normal limits. 63.6 % of patients with AUB and 44.6 % with OM ($p < 0.02$) had elevated IRI values, and 54.2 % of girls with AUB and 42.5 % with OM showed an increase in ALT concentration.

3. A model of the interrelationships of lipids, carbohydrates, and liver enzymes involved in the pathogenesis of menstrual function disorders and associated with the formation of NAFLD was created, consisting of four factors that together describe 88 % of the variance.

4. Early diagnosis of NAFLD in teenage girls with menstrual cycle disorders and risk factors is very important to prevent severe and irreversible complications from the hepatobiliary system.

Prospects for further research in this area – the study of the relationship between menstrual function disorders and various comorbid pathologies and the risk of NAFLD formation, taking into account not only metabolic abnormalities, but also the influence of hormonal background.

Information about the authors:
Dynnik V. O., MD, PhD, DSc, Deputy Director (Scientific Director), SI "Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine", Kharkiv.
ORCID ID: 0000-0002-7692-1856
Dynnik O. O., PhD, Assistant Professor of the Department of Obstetrics and Gynecology No. 1, Kharkiv National Medical University, Ukraine.
ORCID ID: 0000-0002-2410-2760
Druzhynina A. Ye., PhD, Junior Researcher of the Department of Children Gynecology and Preservation of Reproductive Potential of Girls, SI "Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine", Kharkiv.
ORCID ID: 0000-0002-6699-7865
Novokhatska S. V., Postgraduate Student of the Department of Children Gynecology and Preservation of Reproductive Potential of Girls, SI "Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine", Kharkiv.
ORCID ID: 0000-0003-1623-973X

Відомості про авторів:
Диннік В. О., д-р мед. наук, заступник директора з наукової роботи, ДУ «Інститут охорони здоров'я дітей та підлітків НАМН України», м. Харків.
Диннік О. О., канд. мед. наук, доцент, каф. акушерства та гінекології № 1, Харківський національний медичний університет, Україна.
Дружиніна А. Є., канд. мед. наук, молодший науковий співробітник відділення дитячої гінекології та збереження репродуктивного потенціалу дівчат, ДУ «Інститут охорони здоров'я дітей та підлітків НАМН України», м. Харків.
Новохатська С. В., аспірантка відділення дитячої гінекології та збереження репродуктивного потенціалу дівчат, ДУ «Інститут охорони здоров'я дітей та підлітків НАМН України», м. Харків.

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