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The relationships of the pituitary-gonadal regulation link of the menstrual cycle and hormones of energy metabolism in adolescents with abnormal uterine bleeding at different times of menstrual disorders debut

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The objective: **to study the relationship between gonadotropic, steroid, metabolic hormones and sex steroid-binding globulin (SSBG) at different times of the debut of abnormal uterine bleeding (AUB) in adolescents relative to menarche based on the development of a mathematical model.**
Materials and methods**. 200 adolescent girls with AUB were examined. They were divided into groups depending on the time of onset of uterine bleeding relative to menarche. The blood serum concentration of gonadotropic, steroid hormones, insulin, leptin, and SSBG was determined. The comparison group consisted of 45 girls of the same age with a normal menstrual cycle. The variance and regression analyses of the obtained data were performed using the application program package Statgraphics Plus for Windows 5.0 and SPSS-17.**
Results**. The formation of uterine bleeding in adolescent girls occurs on the background of increased levels of luteinizing hormone, estradiol, and testosterone, and the highest rates are observed in patients with AUB that occurred after previous disorders of the oligomenorrhea type.**
The sensitivity of the reproductive axis to energy-regulating hormones, which depends on the time of disease debut, has been proven. There is a relationship between gonadotropic hormones, energy metabolism hormones, steroid hormones.
Menstrual dysfunction with menarche or in the first year of the menstrual cycle formation, regardless of the type of disorder (AUB or oligomenorrhea), is accompanied by identical changes in hormonal and metabolic status and is formed on the background of immaturity of the pituitary-gonadal system components. AUB which occurs after 2 or more years of normal menstrual function, is formed on the background of a more mature relationship between estradiol and follicle-stimulating hormone, and insulin, interacting with luteinizing hormone, modulates mainly the production of testosterone, which contributes to the prolongation of the period of anovulatory cycles, which in the future can contribute to the formation of polycystic ovary syndrome.
Conclusions**. The variability of gonadotropic hormone production in AUB during puberty is determined with a high degree of significance ($p < 0.001$) by leptin, insulin, SSBG and steroid hormones. This indicates the sensitivity of the reproductive axis to available energy and demonstrates that the level of energy hormones affects not only the production of gonadotropins, but is also associated with ovarian function. Moreover, the features of the associative relationships of pituitary hormones depend on the time of the debut of menstrual disorders.**
Keywords: *abnormal uterine bleeding, adolescent girls, hormonal and metabolic status, debut of the disease.*

Взаємовідношення гіпофізарно-гонадної ланки регуляції менструального циклу та гормонів енергетичного обміну в підлітків з аномальними матковими кровотечами при різних термінах дебюту захворювання

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Мета дослідження: вивчення взаємозв'язку гонадотропних, стероїдних, метаболічних гормонів та глобулін-зв'язувальних статевих стероїдів (ГЗСС) при різному часі дебюту виникнення аномальних маткових кровотеч (АМК) відносно менархе у підлітків на підставі розробки математичної моделі.
Матеріали та методи. Було обстежено 200 дівчат-підлітків з АМК, розділеними на групи залежно від часу появи маткової кровотечі відносно менархе. Визначали вміст у сироватці крові гонадотропних, стероїдних гормонів, інсуліну, лептину, ГЗСС. Групу порівняння становили 45 дівчат того ж віку з нормальним менструальним циклом. Дисперсійний та регресійний аналіз отриманих даних проводили за допомогою пакета прикладних програм Statgraphics Plus for Windows 5.0 та SPSS-17.
Результати. Формування маткових кровотеч у дівчат-підлітків відбувається на тлі підвищених рівнів лютеїнізуючого гормону, естрадіолу та тестостерону, причому найвищі показники відзначаються у пацієнток з АМК, що виникли після попередніх порушень за типом олігоменореї.
Доведено чутливість репродуктивної осі до енергорегулювальних гормонів, що залежить від часу дебюту захворювання. Існує взаємозв'язок між гонадотропними гормонами, гормонами енергетичного обміну та стероїдними гормонами.
Порушення менструальної функції з менархе або в перший рік становлення циклу незалежно від типу порушень (АМК або олігоменорея) супроводжуються ідентичними змінами з боку гормонально-метаболічного статусу та формуються на

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тлі незрілості компонентів гіпофізарно-гонадної системи. АМК, що виникають після 2 років і більше нормальної менструальної функції, формуються на тлі більш зрілих взаємовідношень естрадіолу й фолікулостимулювального гормону, а інсулін, взаємодіючи з лютеїнізуючим гормоном, модулює переважно продукцію тестостерону, що сприяє подовженню періоду ановуляторних циклів, що надалі може сприяти формуванню синдрому полікістозних яєчників.

Висновки. Варіабельність продукції гонадотропних гормонів при АМК пубертатного періоду з високим ступенем значущості ($p < 0,001$) детермінують лептин, інсулін, ГЗСС та стероїдні гормони. Це свідчить про чутливість репродуктивної осі до доступної енергії та демонструє, що рівень енергетичних гормонів впливає не тільки на вироблення гонадотропінів, а й пов'язаний із функцією яєчників. Причому особливості асоціативних зв'язків гіпофізарних гормонів залежать від часу дебюту порушень менструальної функції.

Ключові слова: *аномальні маткові кровотечі, дівчата-підлітки, гормонально-метаболічний статус, дебют захворювання.*

The modern period is characterized by an increase in the number of adolescent girls with menstrual disorders [1, 2]. However, it is well known that the pathology of the reproductive system in adolescence, especially in conditions of untimely and inadequate care, negatively affects the reproductive health of an adult [3–5]. The wide distribution of diseases of the reproductive system in childhood leaves an urgent problem of finding out their occurrence and treatment.

The menstrual cycle is a physiological process characterized by cyclical changes in all parts of the reproductive system, which are outwardly manifested by regular uterine bleeding. In 2011, International Federation of Gynecologists and Obstetricians (FIGO) published standards and established parameters for normal andabnormal uterine bleeding (AUB) based on data from the 5th to 95th percentiles from available large-scale epidemiological studies [6]. In the following years, the International Federation of Obstetricians and Gynecologists continued to refine and, if necessary, revise previously published standards. According to the updated FIGO recommendations (2018), created using the 75th percentile, changes were made: the duration of menstrual bleeding in adolescence should not exceed 8 days, the volume of blood loss as defined by NICE (National Institute for Health and Clinical Excellence) is evaluated from the standpoint of impact on physical, social, emotional or material quality of life, and the regularity of the menstrual cycle may vary, but the difference from the shortest to the longest should not exceed 9 days, unlike previous recommendations, where this interval could reach 20 days [7]. Conditions in which the cyclicity, duration of menstruation and the volume of blood lost are considered as disorders of menstrual function and AUB is among the most severe in its course. AUB is the most common form of menstrual dysfunction in the structure of gynecological diseases in girls seeking medical help and is the main reason for hospitalization in gynecological departments. According to the studies of various authors, their quantity has a significant range of fluctuations from 20.0 to 50.0% [8–10].

Challenges in medicine that are difficult to solve have been existed for many years. Doctors of various specialties are trying to understand the variety of neurohormonal regulation of the body fundamental life processes. It's included reproductive function, the causes of menstrual disorders (including AUB during puberty), especially taking into account the fact that every year new links of regulation are opened [11, 12].

It is considered that the main cause of AUB in adolescence is the functional "immaturity" of the central nervous system and a violation of the regulation of the ovarian-menstrual cycle at the level of the hypothalamic-pituitary complex, as a result of which changes of steroid hormones production also occurs [13–16]. The immaturity of the pituitarytropic structures of the hypothalamus at puberty, which is reflected in the absence of a formed circhoral rhythm of the releasing hormone, leads to violations of the cyclical formation and release of gonadotropins. It's, in turn, contributes to disorders of folliculogenesis processes in the ovaries and causes anovulation. The activity of the hypothalamic-pituitary system is regulated by steroid hormones of the ovaries, which can have both an inhibitory (negative feedback) and a stimulating (positive feedback) effect on the secretion of gonadotropins [17, 18].

Adolescent girls with AUB have a defect of negative feedback between ovaries and the hypothalamic-pituitary region of the central nervous system. An increase in the level of estrogens, characteristic of adolescence, does not lead to a decrease in the secretion of gonadotropic hormones: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This, in turn, causes inadequate and acyclic development of the cavity follicle: its atresia or persistence. There are reports that both atresia and persistence of follicles occur with uterine bleeding in adolescence [19–21]. In these conditions, there is a violation of steroidogenesis in the ovaries, estrogen production is relatively monotonous, but long-lasting, progesterone is produced in very small quantities. A state of progesterone deficiency is formed, which is reflected on the endometrium primarily. A long uncoordinated effect of estrogens on the endometrium causes its proliferation (estrogen-mediated proliferation). Due to progesterone deficiency, the endometrium does not undergo secretory transformation, but hyperplasia and glandular-cystic changes develop. The endometrium begins to reject in response to a decrease in the level of estrogens or a violation of blood circulation in the endometrium, and its accompanied by prolonged and profuse bleeding [22, 23]. The bioavailability of steroid hormones depends on the function of sex steroid-binding globulin (SSBG). It is traditionally considered a carrier of sex steroids, controls the concentration of free hormones and regulates their access to target tissues. Until recently, it was believed that the only function of the SSBG is the transport of sex steroids. However, researches of recent years indicate the connection of circulating SSBG with the level of insulin and the presence of metabolic and endocrine disorders [24, 25].

In recent decades, the role of leptin and insulin in the regulation of reproductive function has been increasingly discussed. Energy security is the key condition of life. Maintaining the normal function of the reproductive system is an energy-intensive process. Mechanisms

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controlling energy balance must be closely integrated with mechanisms ensuring reproductive function. An example of such integration is the effects of the classic metabolic hormones leptin and insulin. Central control of reproductive function is impossible without information about energy status.

The objective: to investigate the relationship between gonadotropic, steroid, metabolic hormones and SSBG at different times of onset of AUB in relation to menarche in teenage girls based on the development of a mathematical model.

MATERIALS AND METHODS

Clinical and paraclinical examination of 200 girls with AUB aged 11–17 who were undergoing treatment in the Department of Pediatric Gynecology of the SI "Institute for Children and Adolescents Health Care of NAMS of Ukraine" in the period 2019–2021. The average chronological age was 14.80 ± 0.17 years, the average age of menarche was 12.60 ± 0.13 years. Menstrual history was assessed retrospectively. All patients were divided into three groups according to the nature of menstrual function (established or not) before the disease and the time (relative to menarche) of uterine bleeding. The I gr. included 76 adolescents with the manifestation of AUB from menarche or in the first year of menstrual function. The II gr. consisted of 64 girls, in whom AUB occurred in the second and later years of the existence of the menstrual cycle. The III gr. – 60 patients with an irregular menstrual cycle, uterine bleeding occurred in the second and later years of menstrual function, but this bleeding was preceded by other menstrual disorders (mainly oligomenorrhea). The study of the health status of adolescent girls with AUB at the time of examination allowed to establish the presence of extragenital pathology in the absolute majority of patients (78.4%). However, it should be noted that these diseases did not have a severe course. In the cohort of girls with AUB who were examined, blood diseases, thrombocytopenia, and blood coagulation insufficiency were excluded. The functional state of different levels of the reproductive system was judged by determining the content of LH, FSH, prolactin (PRL), estradiol (E_2), testosterone (T) in the blood serum by the enzyme-linked immunosorbent assay method on the "Rayto RT 2100C" analyzer (Germany) using standard commercial kits "Best Diagnostic", Kyiv. The level of leptin (L), SSGB was estimated by their level in the blood serum by the enzyme-linked immunosorbent assay method using "ELISA" kits (Germany), determination of insulinemia – immunoreactive insulin (IRI) was performed by the enzyme-linked immunosorbent assay method (Rayto RT 2100C photometer) using reagents from the company "DRG Instruments Gmb" Hamburg, Germany. It was not always possible to take a sufficient amount of blood from a vein to determine all indicators in adolescents aged 11–17 years, therefore not all indicators were determined in all study participants.

The comparison group consisted of 45 girls of the same age with a normal menstrual cycle, examined in the early follicular phase. Hormonal and metabolic characteristics were compared between the girls of the 3 groups and the comparison group. Regression models were built to assess the relationship and influence of sex steroids, SSBG, insulin and leptin on the production of gonadotropins and PRL.

Statistical analysis was reduced to variance analysis of basal hormone levels. Results are presented as tables of mean values, standard deviation (M ± SD). Associations of gonadotropic hormones, PRL with metabolic, steroid hormones and SSBG were analyzed using multivariate regression analysis. Dispersion and regression analyzes of the obtained data were performed using the package of application programs Statgraphics Plus for Windows 5.0 and SPSS-17.

All patients and their parents signed an informed assent form to participate in the clinical study. The study was conducted in compliance with the principles of the Declaration of Helsinki of the World Medical Association "Ethical principles of medical research with human participation as an object of research"; the UN Committee on the Rights of the Child General Comment N 5 (2003) on General measures of implementation of the Convention on the Rights of the Child; European Convention on the Adoption of Children (revised) (CETS N 202; 2008/2011); Law of Ukraine dated April 26, 2001 N 2402-III "On Child Protection" (as amended in 2002-2016); the Order of the Ministry of Health of Ukraine "On Approval of the Procedure for Conducting Clinical Trials of Medicines and Expertise of Materials of Clinical Trials and Model Regulations on Ethics Commissions" N 690 of 23.09.2009 (as amended in 2012–2015), about which there is an extract from the minutes of the meeting of the Committee on Bioethics and Deontology at the SI "Institute for Children and Adolescents Health Care of NAMS of Ukraine".

RESULTS AND DISCUSSION

The study of the hormonal background revealed its heterogeneity. The mean values of FSH and PRL in all three groups and the comparison group had no significant differences. The average level of LH in patients with AUB was significantly higher than in the control group. The highest numbers were observed in adolescents with the debut of bleeding in the second and later years of normal menstrual function. The average concentrations of E_2 in patients of all three groups with AUB were significantly higher than in the comparison group. The highest values of its were observed in adolescents with menstrual cycle disorders of the mixed type. The highest level of T was also observed in patients with AUB and previous disorders such as oligomenorrhea. There were no significant differences between the groups and the comparison group in the average content of SSBG and leptin. The average insulin level was significantly higher in girls with the onset of the disease from AUB (I and II gr.) than in III gr. and the comparison group (Table 1).

Thus, the formation of uterine bleeding in teenage girls occurs against the background of increased levels of LH, E_2 and T, and the highest indicators are noted in patients with AUB that occurred after previous violations by the type of oligomenorrhea.

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Table 1

Average indicators of the levels of gonadotropins, prolactin, sex hormones, hormones of energy metabolism and SSGB in girls with AUB, taking into account the time of manifestation of the disease

Hormones	Statistical indicators	Groups			
		I	II	III	Comparison
FSH, mIU/ml	n, M ± SD	75, 6.46 ± 3.59	64, 6.90 ± 3.48	60, 6.24 ± 2.48	45, 6.12 ± 2.35
LH, mIU/ml	n, M ± SD	75, 6.24 ± 4.83*#	64, 7.74 ± 5.63*#	60, 6.85 ± 4.07*	45, 4.35 ± 3.22
PRL, ng/ml	n, M ± SD	75, 10.53 ± 7.66	64, 10.32 ± 4.70	57, 10.80 ± 5.60	45, 10.39 ± 4.71
E_2, nmol/l	n, M ± SD	75, 0.47 ± 0.29*#	62, 0.53 ± 0.45*	60, 0.55 ± 0.27*#	45, 0.34 ± 0.21
T, nmol/l	n, M ± SD	70, 2.56 ± 1.65	63, 2.78 ± 1.67	57, 3.00±1.44	45, 2.84 ± 1.20
SSBG, nmol/l	n, M ± SD	55, 58.34 ± 23.77	49, 59.89 ± 24.85	45, 62.40 ± 28.74	45, 63.11 ± 22.05
IRI, mIU/ml	n, M ± SD	54, 16.67 ± 8.75*#	42, 16.44 ± 8.40*#	48, 14.73 ± 8.29	45, 14.72 ± 8.17
Leptin, ng/ml	n, M ± SD	38, 18.44 ± 20.33	28, 23.27 ± 21.49	20, 17.08 ± 11.55	45, 16.81 ± 9.93

Notes: * – level of statistical significance p < 0.01–0.001 in relation to the comparison group; # – p < 0.01 at comparing groups with each other.

Table 2

Association of leptin, insulin, steroid hormones and SSBG with gonadotropins according to multiple regression analysis

Determinants	Statistical indicators	Hormonal determinants set		
		I	II	III
Y = FSH X_{i1} = Leptin X_{i2} = IRI X_{i3} = SSBG $X_{i4} = E_2$ X_{i5} = T	$\sum X_i$ R^2 P_{models}	L ± IRI – E_2 + SSBG 98.9 0.001	IRI – L+ E_2 + SSBG 97.5 0.001	L ± IRI – E_2 + T + SSBG 99.2 0.001
Y = LH X_{i1} = Leptin X_{i2} = IRI X_{i3} = SSBG $X^{i4} = E_2$ X_{i5} = T	$\sum X_i$ R^2 P_{models}	L ± IRI – E_2 + T + SSBG 99.3 0.001	IRI – L – T – SSBG 97.6 0.001	L ± IRI – E_2 + T+ SSBG 98.7 0.001
Y = PRL X_{i1} = Leptin X_{i2} = IRI X_{i3} = SSBG $X_{i4} = E_2$ X_{i5} = T	$\sum X_i$ R^2 P_{models}	– IRI + L + SSBG 91.3 0.001	– IRI + L + SSBG 98.3 0.001	– IRI + L + E_2 + T + SSBG 97.5 0.001

Note: the table shows only independent variables that have a statistically significant effect (p < 0.001) on the dependent variable.

The second stage of research was aimed at building a mathematical model. The regression analysis was carried out, and made it possible to evaluate the value and relationships of individual hormones (gonadotropins, hormones of energy metabolism, sex steroids, and SSBG) in the formation of AUB bleeding depending on time the debut of the disease. The analysis of the association of hormones was carried out by the method of multiple regression analysis. The results are presented in the form of tables of a set of dependent (Yj) and independent (Xi) variables (determinants), as well as the coefficient of determination (R2). After applying the stepwise selection procedure, those independent variables whose contribution to the variance has a significance level of $p < 0.05$ are indicated as determinants of the dependent variable. The coefficient of determination R2 shows that regression, that was constructed is highly significant and explains more than 97% of the spread of possible values.

Elucidation of the associative relationships of pituitary hormones revealed the selectivity of the influence of metabolic and sex steroids on the production of gonadotropic hormones depending on the clinical variant of the course of AUB associated with the onset of the disease (Table 2).

Variability of FSH production in patients with the manifestation of menstrual disorders with menarche or in the first year of menstruation with a high degree of significance ($p < 0.001$) is determined by leptin, insulin, SSBG and steroid hormones ($R^2_I = 98.9\%$, $R^2_{II} = 99.2\%$ respectively). Moreover, E_2 maintains a negative feedback loop. When disorders occur in the second and later years of a normal menstrual cycle, a positive relationship between FSH and E_2 is formed. The acquisition of positive feedback is considered the final stage of maturation of the reproductive axis, but it can be assumed that in girls the reactivity of the pituitary gland is not fully formed due to the immaturity of the mechanism of positive feedback induced by estrogens, which leads to the occurrence of menstrual disorders. A negative relationship appears in leptin. Most likely, this is due to the fact that it was in this group of patients that the highest specific weight of overweight and obese patients was noted.

Thus, the variability of FSH secretion depends on energy-regulating hormones (leptin, insulin), which enhance the stimulating effect of FSH on the production of steroids by the ovary.

LH secretion was significantly influenced by a pattern of hormones similar to FSH. However, there are features related to both the time of manifestation of the pathology of menstrual function and the type of its disorders. LH production was associated with the content of insulin, leptin, steroid hormones and SSBG in the cases when menstrual disorders have started from menarche or in the first year, regardless of the type of menstrual disorders (AUB or oligomenorrhea). In case of occurrence of menstrual cycle pathology after 2 or more years of normal menstrual function, the effect of E_2 decreased. It can be assumed that in this cohort of patients, insulin interacting with LH mainly modulates the production of testosterone, which contributes to the prolongation of the period of anovulatory cycles and the occurrence of uterine bleeding, and in the future, perhaps, the formation of PCOS.

The PRL production is related to metabolic homeostasis. It is believed that PRL modulates energy balance. In our study, we can see that the level of insulin, leptin and SSBG in the blood serum affected the content of PRL in the manifestation of the disease with AUB. When uterine bleeding was preceded by oligomenorrhea-type disorders, the production of PRL depended on the content of steroid hormones.

The growth of menstrual disorders is a fundamental problem of women's reproductive health. Appearing in adolescence, they lead to significant problems later, especially in the reproductive age [26]. In order to proper functioning of a girl's body, the coordinated work and interaction of all its systems is necessary. Many components are involved in the life support process. Destabilization of one of them threatens the development of serious ailments, including the occurrence of menstrual disorders.

Disorders of the menstrual cycle are one of the most frequent problems of adolescent gynecology. Therefore, the menstrual cycle at this age is considered as a vital sign. Irregular menstrual cycles are very common in adolescence and can cause significant stress for both patients and their parents [27]. The leading position among all gynecological pathology of the puberty period is occupied by the irregularity of the menstrual cycle, such as AUB.

Despite the sufficient number of studies, the pathogenetic features of the development of menstrual disorders in adolescence continue to be clarified. However, we have not come across any reports discussing the specifics of hormonal relationships in accordance with the debut of AUB in adolescence. The emergence of new data allows a new look at the mechanisms of AUB formation during puberty, which can influence the development of new approaches to the treatment of this threatening disease and allow doctors to make timely decisions.

The data obtained in the study confirm the heterogeneity of hormonal changes in AUB. AUBs during puberty are usually formed against the background of anovulation. Anovulatory cycles are triggered by an increase in the basal level of LH, which is found in our patients. Hormonal imbalance is expressed in increased estrogen content. It can be assumed that the concentrations of LH and FSH are able to trigger the synthesis of estrogens and the growth of follicles, but this is not enough for the process of ovulation. At the same time, estradiol stimulates the proliferation of the endometrium, which has the blood flow disrupte and its significant destruction and rejection occurs [28].

The study revealed that the formation of AUB during the pubertal period most often occurs against the background of increased levels of LH, estradiol and testosterone, and the highest indicators are noted in patients with AUB that arose after previous violations of the type of oligomenorrhea.

The construction of a mathematical model based on regression analysis revealed the relationships of individual hormones (gonadotropins, hormones of energy metabolism, sex steroids and SSBG) in the formation of AUB bleeding during puberty, depending on the time of onset of the disease.

The pattern of hormones that determine the secretion of FSH and LH in girls with the manifestation of any disorders of the menstrual function from menarche or in the first year of its formation is practically identical. In adolescents with the debut of AUB after 2 or more years of a normal menstrual cycle, there is a change in the negative relationship between E_2 and FSH to a positive one, which indicates the maturation of the reproductive axis, but it can be assumed that the reactivity of the pituitary gland is not fully formed and remains immature. Apart from energy-regulating hormones, only T affects LH production.

Similarity of pathogenetic features of AUB I gr. and III gr., in our opinion, are associated with the same time of onset of menstrual function disorders (from menarche or in the first year of function formation). There is information in the literature that disorders of menstrual function, regardless of the form of the disorder, are associated with certain changes in the hormonal and metabolic status. This is what we observe in our research. Disorders of menstrual function occurring after 2 or more years of a normal menstrual cycle have distinct specific hormonal and metabolic relationships.

CONCLUSIONS

1. Peculiarities of the relationship between hormones regulating energy metabolism (leptin, insulin), sex steroids, SSBG and the content of tropic hormones (FSH, LH, PRL) that depend on the time of the debut of AUB have been determined. In case of disorders in the

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first year of menstrual function (regardless of the type of disorder), positive relationships of gonadotropins with energy supply hormones (leptin, insulin), SSBG, and some indicators of steroid hormones were observed. Estradiol has a negative relationship with FSH. In uterine bleeding in adolescence, which occurred in the second or more years of the normal cycle, the relationship with leptin and gonadotropins becomes negative, and between FSH and estradiol changes to positive. The content of PRL with a high degree of significance is determined by energy hormones, and leptin has a positive relationship, but insulin has a negative relationship. In girls with the debut of disorders by oligomenorrhea type, the level of PRL is also influenced by steroid hormones.

2. Levels of leptin, insulin, SSBG, steroid hormones affect the activity of the pituitary system and determine the variability of LH, FSH, PRL in patients with AUB during puberty. This indicates the sensitivity of the reproductive axis to available energy and demonstrates that the level of energy hormones affects not only the production of gonadotropins, but is also related to ovarian function. Moreover, the features of associative relationships of pituitary hormones depend on the time of onset of menstrual disorders.

Conflict of interest. The authors declare that there is a conflict of interest.

Authors' contributions. V. O. Dynnik – idea and design of the study, formulation of research objectives; O. O. Dynnik – data collection, analysis and statistical processing of research results; N. V. Bagatska – selection of literary sources, correction of the work performed.

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