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Comorbid pathology issues in pediatric gynecology

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The problems of diagnosis, therapeutic tactics and medical prognosis in comorbid, polymorbid pathology stand out among the most actual problems of modern health care.

Purpose — to study the frequency and nature of comorbid conditions in patients with pubertal abnormal uterine bleeding (PAUB).

Materials and methods. The study included 342 girls aged 11–17 suffering from PAUB. All patients were examined by a multidisciplinary team of doctors.

Results. It has been shown that menstrual irregularities are combined with other somatic, mental and endocrine pathologies in the vast majority of patients. Only 9.6% of the patients examined had no concomitant pathologies. More than half of girls have a combination of more than three comorbidities. The first three ranks are occupied by endocrine, mental and digestive system disorders. More than a third of patients with endocrine disorders had deviations in terms of body weight — overweight and obesity, which is much more often accompanied by changes in carbohydrate and lipid metabolism. In patients with mental disorders astheno-neurotic syndrome and vegetative-vascular dystonia syndrome prevailed. Functional disorders of the biliary tract were mainly recorded among the disorders of the digestive system, about 18% of girls suffered from gastritis, cholecystitis. The presence of comorbid pathology reduced the effectiveness of non-hormonal therapy by 1.5 times and increased the number of relapses by 3.5–4 times. The effectiveness of non-hormonal therapy was 81.8% on the absence of concomitant pathology; relapses were recorded only in 16.7%.

Conclusions. Comorbid pathologies in patients with PAUB aggravate the severity of the girl's condition, reduces adaptive capabilities, adversely affects the effectiveness of non-hormonal therapy, contributes to the recurrence of the disease and is a risk factor for the development of serious metabolic, endocrine and cardiovascular diseases in the future. The category of patients with concomitant pathology requires a special examination algorithm and the appointment of an adequate therapeutic intervention, taking into account all the identified nosological forms and drug compatibility.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of all participating institutions. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: comorbid pathology, abnormal uterine bleeding, adolescent girls.

Питання коморбідної патології у дитячій гінекології

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Серед найбільш актуальних проблем сучасної охорони здоров'я виділяється проблема діагностики, терапевтичної тактики і медичного прогнозу при коморбідній, поліморбідній патології.

Мета — вивчення частоти і характеру коморбідних станів у хворих з аномальними матковими кровотечами пубертатного періоду (АМК ПП).

Матеріали та методи. Під наглядом перебувало 342 дівчинки у віці 11–17 років з АМК ПП. Усі пацієнтки були оглянуті мультидисциплінарною командою лікарів.

Результати. Показано, що у абсолютної більшості хворих порушення менструального циклу поєднуються з іншою соматичною, психічною та ендокринною патологією. Тільки у 9,6% пацієнток відсутні будь-які екстрагенітальні захворювання. Більш ніж у половини дівчат є поєднання більше трьох супутніх захворювань. Перші три рангові місця займають ендокринні, психічні порушення та розлади з боку травної системи. Серед ендокринних порушень більш ніж у третини відзначалися відхилення з боку маси тіла — надмірна маса тіла та ожиріння, яке значно частіше супроводжується змінами вуглеводного та ліпідного обмінів. Серед психічних розладів переважали астено-невротичний синдром та синдром вегето-судинної дистонії. Серед порушень травної системи в основному реєструвалися функціональні розлади біліарного тракту, близько 18% дівчат страждали на гастрити, холецистити. Наявність коморбідної патології у 1,5 раза знижувала ефективність негормональної терапії та у 3,5–4 раза збільшувала кількість рецидивів. За відсутності супутньої патології ефективність негормональної терапії становила 81,8%, рецидиви реєструвалися лише в 16,7%.

Висновки. Наявність коморбідної патології у пацієнток з АМК ПП посилює тяжкість стану дівчинки, знижує адаптаційні можливості, несприятливо впливає на ефективність негормональної терапії, сприяє рецидиву захворювання та є фактором ризику розвитку в майбутньому серйозних обмінно-ендокринних, серцево-судинних захворювань. Категорія хворих із супутньою патологією потребує особливого алгоритму обстеження та призначення адекватного терапевтичного втручання з урахуванням усіх виявлених нозологічних форм та поєднання препаратів.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом усіх зазначених у роботі установ. На проведення досліджень отримано інформовану згоду пацієнтів.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: коморбідна патологія, аномальні маткові кровотечі, дівчата-підлітки.

Introduction

Puberty is the transition from childhood to adulthood. During this period, the body reaches puberty and the reproductive system is formed completely. Fertility largely depends on the harmonious functioning of the neuroendocrine system. Any violations may result in disruption and formation of endocrine-dependent gynecological pathologies. It is believed that the menstrual cycle is a biological marker of the general health of an adolescent, and its disorders may indicate a decrease in reproductive potential [2,9,22]. Abnormal uterine bleeding during puberty (PAUB) is a menstrual function disorder. Reproductive potential disorders among girls are of special importance, since they have a significant impact on the formation of chronic diseases in adulthood. Recently, the attention of scientists has been increasingly drawn to issues of comorbidity, i.e. additional distinct clinical findings parallel with the current disease. According to the literature data, about 10% of people aged under 19 already have various comorbid conditions. With age, the possibility of developing comorbid pathologies increases [5,6,11]. Comorbidity is widespread among patients admitted to multidisciplinary hospitals [16,17,19]. Prevention and treatment of chronic diseases are designated by the World Health Organization as a priority project of the second decade of the XXI century, aimed at improving the quality of life of the world's population [4,13,16].

Due to the fact that adolescent girls suffering from menstrual disorders seek medical help from pediatric and adolescent gynecologists, they should be focused on obtaining skills that enable them to suspect and refer the patients to relevant specialists to identify various concomitant disorders and carry out joint treatment. The task of multidisciplinary clinics is to provide consultations with doctors of related specialties in order to form a general diagnostic and treatment concept.

Purpose of the study — to study the frequency and nature of comorbid conditions in patients with PAUB.

Materials and methods of the study

The study included 342 girls aged 12–17 suffering from PAUB, who were treated in the clinic of the SI «Institute for Health Protection of Children and Adolescents of the NAMS of Ukraine». All patients underwent anthropometric measurements to determine height, body weight, and calculate body mass index (BMI). Blood lipid spectrum indices — total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) cholesterol — were determined photometrically on a general-purpose photometer using Cormay Multi kits. Carbohydrate metabolism status was analyzed based on the glycemic level (fasting), immunoreactivity insulin concentration (IRI) in the venous blood using the enzyme-linked immunosorbent assay method. To calculate insulin resistance (IR), a mathematical hemostasis model (Homeostasis Model Assessment — HOMA) was used, and the HOMA — IR index was determined. Ultrasound investigation of the pelvic organs was carried out on the Lodgic-100 apparatus using a sectoral sensor with a frequency of 3.5 MHz. All patients were examined by a multidisciplinary team of doctors. All material obtained was processed statistically using the descriptive variation statistics methods. Differences were considered statistically significant at $p<0.05$ (95% confidence level). The study is approved by the Committee of Bioethics and Deontology at the SI «Institute for Health Protection of Children and Adolescents of the NAMS of Ukraine». The informed consent of the patient was obtained for conducting the studies.

Results and discussion of the study

Considering that «comorbidity» is currently defined as a combination of two / or more chronic diseases in one patient, inter-related pathogenically or coinciding in time, we analyzed the comorbidity in the patients examined. The data demonstrating a high comorbidity of endocrinological, mental, gastrointestinal tract disorders in patients with PAUB are obtained. Only 33 (9.6%) patients that were examined had no concomitant pathologies (Fig. 1).

Overweight and obesity were recorded in almost a third of patients (90 (26.3%) girls). Various abnormalities in the thyroid gland functioning were detected in 215 (62.8%) girls (Fig. 2). Mental health disorders (borderline mental disorders) were observed in 280 (81.7%) adolescents. Moreover, it should be noted that 75 (22%) girls had a combination of both endocrinological and mental disorders.

According to present knowledge, it has been proven that overweight and obesity are often associated not only with reproductive health disorders, but also with the formation of oncological diseases [7,10,14]. We analyzed the ultrasound data of the pelvic organs in our patients and found that endometrial hyperplasia was recorded in 52 (57.7%) patients with overweight and obese, and 19 (36.7%)

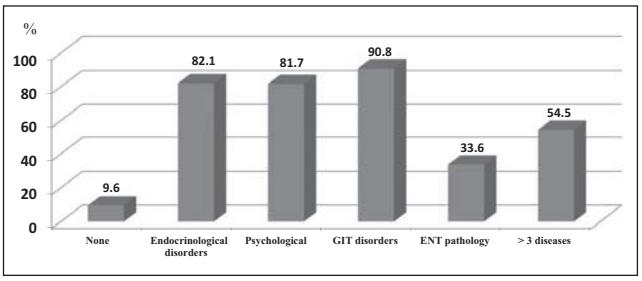

Fig. 1. Incidence and nature of somatic pathologies in patients with pubertal abnormal uterine bleeding

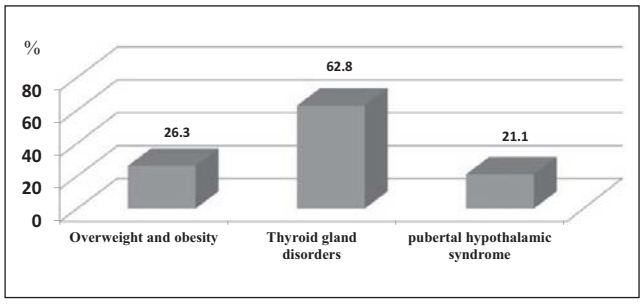

Fig. 2. Incidence and the structure of endocrinological pathologies

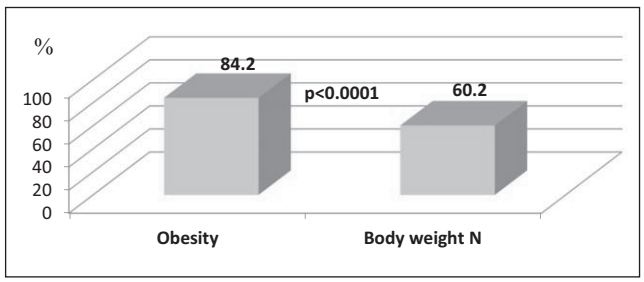

Fig. 3. Incidence of deviations in the lipid spectrum in patients with pubertal abnormal uterine bleeding and varying body weights

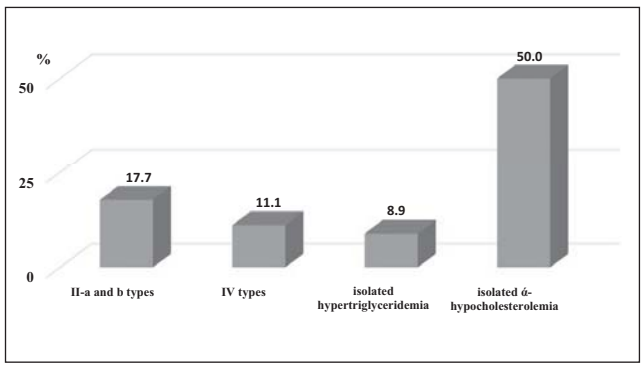

Fig. 4. Incidence of various types of dyslipidemias in patients with pubertal abnormal uterine bleeding and obesity

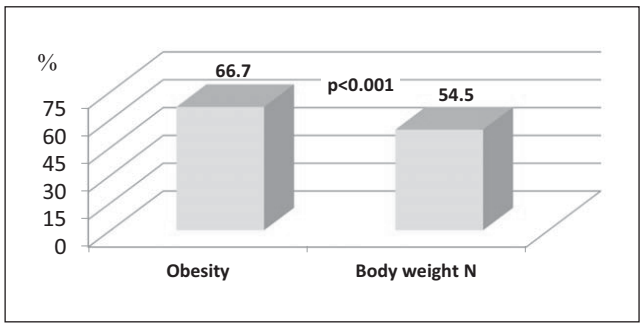

Fig. 5. Incidence of carbohydrate metabolism disorders in patients with pubertal abnormal uterine bleeding and obesity

cases were against the background of hyperestrogenemia, which may serve as a risk factor for the oncopathology in the future. Overweight and/or obese patients are characterized by various dyslipidemias (DLP), which are predictors of a number of cardiovascular diseases (hypertension, atherosclerosis, etc.). In 76 (84.2%) patients with PAUB and obesity examined, various abnormalities in the blood lipid profile were recorded, which is much more frequent than in patients with the normative BMI parameters (119 (60.2%) from 197 girls; $p<0.0001$, Fig. 3).

16 (17.7%) adolescents demonstrated changes characteristic of II-a, and b types of dyslipidemia, 10 (11.1%) — of IV type, 8 (8.9%) had isolated hypertriglyceridemia and 45 (50%) had isolated ά-hypocholesterolemia (Fig. 4).

In overweight and obese patients, carbohydrate metabolism is also impaired, which serious disorders may lead to the formation of type II diabetes mellitus, insulin resistance, metabolic syndrome, sclerocystic ovary syndrome (Fig. 5).

As a result of the standard glucose tolerance test, 60 (66.7%) girls with PAUB and obesity showed deviations from the sugar curves, which incidence is statistically more frequent than in patients with PAUB and normal body weight (107 (54.5%) from 197 girls; $p<0.001$). In general, a flat sugar curve was observed in 72 (80%) girls, and impaired fasting glucose in 18 (20%). An increased HOMA index was determined in 48 (53.3%) patients, corresponding to the 90th percentile and above in 52 (72.2%) girls. These indicators are also statistically significantly higher than those of the patients with normative BMI (82 (41.7%) girls; $p<0.001$).

Confirmation of anemia as an underlying disease contributing to the unfavorable course of the underlying medical condition revealed that it was significantly more frequent in girls with PAUB and obesity than in girls with normal body weight (47 (52.2%) girls vs. 80 (40.6%); $p<0.01$). At present, iron deficiency states with obesity are considered as comorbidity by a number of authors and a special «iron deficiency phenotype» of obesity is proposed [21].

Changes in the thyroid gland function are often combined and associated with menstrual cycle disorders [8,12]. Over the years, the issue of cause-and-effect relationships in the combination of these disorders have been discussed in the literature. Healthy development of the reproductive system and menstrual function is impossible if the thyroid gland does function normally.

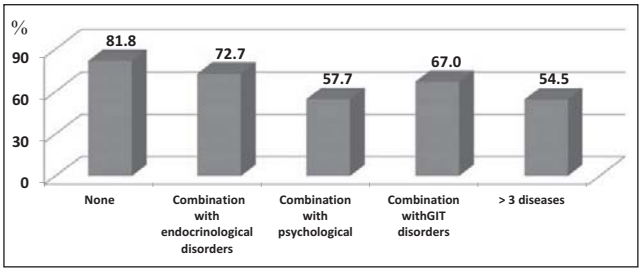

Fig. 6. Effectiveness of non-hormonal treatment with a concomitant pathology

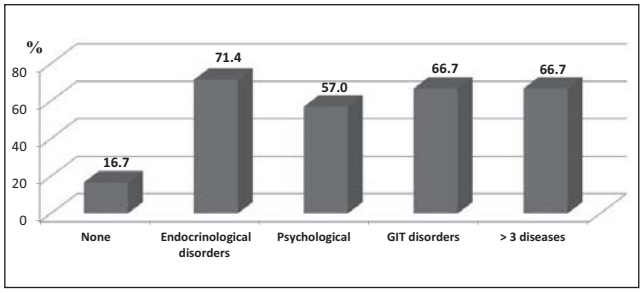

Fig. 7. Recurrence rate in the presence of somatic pathologies

To maintain a sufficiently high activity of the gonads, an appropriate level of metabolism is required, which can only be achieved with a certain concentration of thyroid hormones in the body. In thyroid gland disorders, the hypothalamic-pituitary-gonadal system interrelationship is disrupted. Both hyper- and hypothyroidism cause changes in the production of sex steroid binding globulin (SHBG), LH and sex steroids specifically. In hypothyroidism, secretion of prolactin and estradiol may be stimulated. Changes in SHBG levels disrupt estrogen metabolism, the process of converting androgens into estrogens [1,3,15]. Peripheral estrogen metabolism disorders lead to changes in the secretion of gonadotropins and anovulation [20].

A decrease in the specific weight of menstrual function disorders in women with thyroid diseases is notedin the publications of the beginning of the 21st century (21.5–23.4% against 50–60% at the end of the last century). Most likely, this is due to the fact that currently disorders of the functioning of the thyroid gland are diagnosed much earlier, when the clinical picture is still erased, has few symptoms and is not accompanied by menstrual function disorders [21].

Among the patients examined, more than half (62.8% — 215 girls) had a combination of menstrual dysfunction and various thyropathies. Diffuse non-toxic goiter (DNTG) of varying severity was predominant.

When assessing the level of mental health in patients with PAUB, data obtained indicated a high comorbidity of mental disorders. The absolute majority of patients (81.7% — 279 girls), had mental disorders of the borderline spectrum. Moreover, the dominant symptoms in their structure were the neurotic register (26.9% — 75 girls) and vegetative dystonia (41.6% — 116 girls) symptoms, i.e., the patients with PAUB develop a clearly expressed vegetative dystonia syndrome. The functional state of the digestive system is regulated by a complex system of nervous and humoral mechanisms, including neurotransmitters and regulatory peptides. An imbalance in the interactions between these systems may lead to the formation of gastrointestinal tract pathologies. These changes formed in the gastrointestinal tract support impaired estrogen metabolism in patients with PAUB.

Gastrointestinal tract changes were detected in 313 (91.5%) patients with PAUB. These mainly manifested in functional biliary tract disorders (80.8% — 253 girls). About 18% (56 girls) suffered from gastritis, cholecystitis or pancreatitis. A comorbid pathology reduces the effectiveness of the non-hormonal PAUB therapy, the most physiological at this age, increases the number of disease recurrences (Fig. 6, 7).

Thus, effectivaeness of non-hormonal therapy is 81.8% (27 cases) in the absence of concomitant pathologies. If PAUB is combined with endocrine pathologies only, the effectiveness decreases to 204 (72.7%) cases ($p<0.01$), up to 124 (57.7%) cases ($p<0.0001$) with non-psychotic mental disorders, up to 209 (67%) cases ($p<0.0001$) with gastrointestinal disorders. In the presence of more than 3 comorbidities, the effectiveness of non-hormonal treatment was only 54.5% (101 cases), ($p<0.0001$). A similar situation is observed in relation to the number of disease recurrences.

Their number increases significantly with combined pathologies. If in girls without concomitant pathologies, recurrence rate was 16.7% (6 cases), it increased to 71.4% (200 cases), ($p<0.0001$) combined with various other disorders. A comprehensive, timely and adequate treatment of functional disorders of various organs and systems in children is an important factor for the prevention of the development of more serious future pathological conditions, which support and aggravate the course of PAUB.

Conclusions

Comorbid pathologies in patients with PAUB aggravate the severity of the girls' condition, reduces adaptive capabilities, adversely affects the recovery of reproductive potential and is a risk factor for the development of serious metabolic, en-

docrine and cardiovascular diseases in the future. Considering the fact that specialty physicians, including gynecologists, rarely pay attention to the concomitant diseases, this category of patients requires a special examination algorithm and adequate therapeutic intervention, taking into account all the nosological forms identified and drug compatibility. The state of the reproductive potential of the country's youth can be ensured only on an interdisciplinary basis with the participation of doctors of various specialties.

Prospects for further research. Study of genetic characteristics of girls with abnormal uterine bleeding and comorbid pathology.

No conflict of interests was declared by the authors.

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