

Research Article

Menstrual Disorders and Main Indicators of Hormonal and Metabolic Homeostasis in Teenage Girls Against the Background of Endemic Goiter

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Abstract

Along with the widespread prevalence of goiter endemics, the medical and social significance of this problem is determined by the multifaceted spectrum of pathological abnormalities associated with asymptomatic course or hypothyroxinemia, causing numerous disorders at almost all stages of menstrual and reproductive function development.

The objective of the research was to substantiate and conduct a comprehensive analysis of the prevalence, structure and leading factors of dishormonal disorders of menstrual function in adolescent girls with diffuse endemic goiter, and to develop a diagnostic algorithm based on the risk of the formation of this pathology.

Materials and Methods. Two study groups were formed and a clinical laboratory examination was performed in 210 patients: 120 of them were diagnosed with menstrual dysfunction against the background of thyroid dysfunction (the main group); 60 girls were diagnosed with menstrual dysfunction and healthy thyroid gland (the comparison group); 30 apparently healthy girls made up the control group. Experimental and psychological methods, hormonal investigation of the level of thyroid, gonadotropic and steroid hormones, lipid and carbohydrate metabolism and vitamin D content in blood plasma were used.

Results and Discussion. Hypomenstrual syndrome, secondary amenorrhea, dysmenorrhea, manifestations of premenstrual syndrome and anovulatory conditions are the main menstrual disorders in adolescents suffering from endemic goiter. One third of the girls in the main group had an increase in the proportion of delayed sexual development, while in the control group, physiological rates of sexual development occurred in 96.7% of observations. The presented hormonal studies made it possible to identify differentiated changes taking into account different clinical forms of menstrual disorders in this category of patients. The transition to the "mature" type of reproductive system functioning in girls with endemic goiter is associated with changes in prolactin secretion from low levels to the indicators that exceed the reference values, which is characterized by increased functional hyperprolactinemia. Generalization of the frequencies of the main psycho-emotional characteristics and indicators of the personal profile in the girls of the studied cohort allowed revealing the constant dominance of psycho-emotional manifestations of moderate degree, as well as high levels of psycho-emotional stress and depressive disorders against the background of dishormonal disorders and thyroid gland dysfunction. Obtained deviations of 25-hydroxyvitamin D level were noticed at the initial stages of thyroid disorder, and low 25-hydroxyvitamin D levels contributed to the manifestation of thyroid pathology.

Conclusions. Dissociation of the thyroid system and the hypothalamic-pituitary-ovarian axis initiates menstrual disorders, development of functional cysts and multifollicular structure of the ovarian tissue, and, in case of hypothyroidism, is considered as a factor of metabolic disorders and polycystic ovary syndrome.

Keywords

puberty; thyroid gland; diffuse endemic goiter; menstrual disorders; treatment

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Problem statement and analysis of the latest research

It is the fact that a precondition for growth of intellectual, reproductive and social reserve of society is the health of the young generation, especially adolescents, the dynamics of which in the last decades has been worsening [2, 3, 5, 8]. According to literature sources, a high level of gynecological morbidity is observed among teenage girls, up to 70.0% in sexually active adolescents; hormonal pathology is diagnosed in 78.9% of cases, every fifth patient reports about disorders of the menstrual cycle [2, 3, 5, 8], which is undoubtedly closely linked to the realization of the reproductive function in the future.

In Ukraine, about 47% of the general endocrine pathology is a thyroid disease, and the global medical and social problem is iodine deficiency (ID), first of all diffuse endemic goiter, which keeps the attention of many researchers due to its high prevalence, variety of forms and contradictory moments of pathogenetic influence on reproductive function [3, 4, 6]. Along with the high prevalence of goiter endemic, the medical and social significance of this problem is determined by the multifaceted spectrum of pathological abnormalities associated with asymptomatic course or hypothyroxinemia, which often accompanies diffuse endemic goiter (DEG), causing numerous disorders at almost all stages of menstrual and reproductive function formation. In the structure of puberty disorders, menstrual disorders (MD) are the leading and most dynamic sign of the debut of pathological processes associated with the failure of reproductive function. Considering the incompleteness of the reproductive system development, transient stressor ovarian dysfunction in puberty, which is manifested in MD only, against the disorganized interdependence of the thyroid and gonadal systems, in case of passive or inadequate medicinal tactics, can transform and contribute to the development of polycystic ovary syndrome, hypothalamic puberty syndrome, hyperandrogenic and metabolic syndromes [3, 4, 6]. Psychological stresses accompany the puberty of a girl, increasing the number of

episodes of stressful effects related to social aspects of life, triggering anxiety and depressive tendencies, homeostasis dismetabolism, exchange and vegetative dysregulation, which are possible causes of menstrual and reproductive disorders. In fact, the neuroendocrine system (the first line of protection against stress) is triggered by disadaptation, as the regulation of the menstrual cycle is interrelated with the coordinated activity of hormones, neurotransmitters and biologically active substances synthesized by the girl's endocrine system [4, 8]. The impact of thyroid dysfunction in the functioning of the hypothalamic-pituitary-ovarian axis with the participation of stressors is also controversial and requires detailed clarification.

Small number of scientific studies concerning the leading causes of hormonal abnormalities and MD against the background of iodine deficiency, even in case of euthyroidism, contradictory issues of the structure and clinical forms of puberty, the possibility of prediction and preventive measures in the adolescent period, have become a prerequisite for this study.

The objective of the research was to substantiate and conduct a comprehensive analysis of the prevalence, structure and leading factors of dishormonal disorders of menstrual function in adolescent girls with diffuse endemic goiter and to develop a diagnostic algorithm based on the risk of the formation of this pathology.

1. Materials and Methods

Sociological, clinical and anamnestic, anthropometric, instrumental and laboratory methods of research, as well as mathematical and statistical approaches, were used to accomplish the tasks. Two study groups were formed and a clinical laboratory examination was performed in 210 patients: 120 patients were diagnosed with menstrual dysfunction against the background of thyroid dysfunction (the main group); 60 girls were diagnosed with menstrual dysfunction and healthy thyroid gland (the comparison group); 30 apparently healthy girls made up the control group. The inclusion criteria were girls aged 12-18 years with MD and more than

2 years of menarche in case of the consent obtained from the patient and her parents to participate in the study. The criteria for exclusion were severe extragenital pathology, MD of hypothalamic-pituitary, adrenal and ovarian genesis, congenital pathology of the female genital organs, obesity, autoimmune pathology of the thyroid gland, nodular third-degree goiter.

In diagnosis and structuring of endemic goiter, the recommendations of the Consensus on Endemic Goiter and Autoimmune Thyroiditis (Health of Ukraine, 2015), ultrasound, visual and palpatory methods of investigation were used. Psychoemotional status was studied using the following experimental and psychological methods: score assessment of personal anxiety and reactive anxiety of Spielberg test, adapted by Yu. L. Khanin; the Beck depression inventory. The Freiburg Personality Inventory (FPI) was used to diagnose psychopathic conditions and personality traits. Hormonal studies were performed by testing serum levels of thyroid, gonadotropic and steroid hormones using enzyme-linked immunosorbent assay. Lipid and carbohydrate metabolism studies were performed using unified techniques, and the plasma content of vitamin D was determined by the concentration of 25-hydroxyvitamin D (25 (OH) D) using the electrochemiluminescent method. Statistical processing of the results was performed by conventional methods of variational statistics.

2. Results and Discussion

Visual and palpatory study of the thyroid gland in the main group showed the frequency of its enlargement: first-degree thyroid enlargement was diagnosed in 58 (48.3%) patients; second-degree thyroid enlargement was diagnosed in 26 (21.7%) girls; in 36 (30.0%) patients, there were no deviations from the reference limits. According to the results of ultrasound examination, the proportion of girls with diffuse endemic first-degree, second-degree and 0 degree goiter was 56.7%, 25.0%, and 18.3%, respectively; more often the discrepancy between the data of clinical and ultrasound examination was found in girls with first-degree thyroid

enlargement (8.4%), much less often it occurred in girls with second-degree thyroid enlargement (3.3%). The endocrinologist's counseling (taking into account the results of clinical and laboratory and ultrasound studies) proved that euthyroidism (63.3%) and subclinical hypothyroidism (28.3%) were more common; in some cases, manifestations of increased thyroid function (8.4%) were noticed. Evaluation of the results of thyroid echovolumometry showed that among the patients with DEG, the severest changes in the structure and echogenicity of the thyroid gland were found in 27.6% of teenage girls with euthyroidism and 39.3% of female patients with hypothyroidism; heterogeneity was in 15.8% of cases.

The level of sexual development in more than half of patients in the period of puberty corresponded to the calendar limits in both groups; however, in the comparison group, the period of menstrual function up to 16-18 years corresponded to the age norm in two thirds of the observations (73.3%); the advance was detected in 16.7% of cases. On the contrary, one third of the girls in the main group showed an increase in the proportion of delayed sexual development, while in the girls of the control group, physiological rates of sexual development were noted in almost 96.7% of observations.

The results of the instrumental studies showed that girls in the main group had a significant tendency to retarded uterine growth as compared to the adolescents of the comparison and control groups ($p < 0.05$), primarily due to the reduction in the anteroposterior size of the uterus. In addition, girls of this category had a significant decrease in endometrial thickness on the 21st-23rd days of the cycle as compared to similar indicators of adolescents in the comparison and control groups ($p < 0.05$). In the patients of the main group, signs of uterine hypoplasia with reduction in length and anteroposterior size, as well as a decrease in endometrial thickness, were found in 56 (46.7%) cases, with a direct correlation between impaired MC formation, resistance to therapy, age of diagnosis of sonographic changes and deviation of uterine body size from reference values. In two thirds of the patients of both groups (72.7%) and half of the observations in

case of coexistence with DEG (59 – 49.2%), both ovaries showed a tendency to decrease in size; the homogeneity of their structure and small-cystic follicular changes by the type of primary atresia were observed. Thirty-four (28.3%) girls of the main group had multifollicular ovarian structure, which is obviously an early sign of polycystic ovary formation in this category of adolescent girls. In fact, reliable indicators of reduction in all uterine body size and endometrial structure in the main group of girls throughout the period of menstrual function formation, show a lack of estrogenic saturation of the organism in puberty, with some adjustment of the indicators to the benchmarks to the end of the puberty period in the comparison group.

In the main group, a proportion of hypomenstrual syndrome (by 1.5 times), algodysmenorrhea (by 1.6 times) and amenorrhea (by 1.4 times), as well as premenstrual syndrome and anovulatory conditions associated with polycystic ovary syndrome was significantly higher, which was 2.0 times higher than in the comparison group ($p < 0.05$).

The use of experimental and psychological methods at this stage of scientific research allowed us to establish that personal profile of girls with MD and DEG differed by 1.8 times ((5.59 ± 0.12) against (3.18 ± 0.10) points) in increased levels of neuroticism, by 1.5 times ((2.44 ± 0.10) against (1.59 ± 0.12) points) in spontaneous aggressiveness, by 1.4 times ((4.46 ± 0.12) against (3.08 ± 0.16) points) in depression, by 1.7 times ((4.56 ± 0.11) against (2.68 ± 0.12) points) in irritability, by 1.4 times ((3.56 ± 0.11) against (2.48 ± 0.10) points) in reactive aggressiveness, by 1.3 times ((5.76 ± 0.09) against (4.58 ± 0.11) points) in shyness, by 1.2 times ((4.96 ± 0.08) against (4.18 ± 0.12) points) in openness, by 1.7 times ((5.98 ± 0.11) against (3.48 ± 0.12) scores) in emotional lability, by 1.2 times ((2.52 ± 0.10) to (2.08 ± 0.02) points) in masculinism according to the questionnaire of girls in the comparison group ($p < 0.05$). However, sociability score of the patients in this group was 1.6 times higher ((4.26 ± 0.18) against (6.98 ± 0.12) points), tranquility score was 1.5 times higher ((3.39 ± 0.12) against (5.18 ± 0.10) points), extraversion score

was 1.3 times higher ((3.26 ± 0.08) against (4.12 ± 0.12) points) as compared to the main group ($p < 0.05$).

Generalization of frequency values of basic psycho-emotional characteristics and indicators of personal profile in the girls of the studied cohort allowed revealing the constant dominance of psycho-emotional manifestations of moderate degree and a small percentage (5.8%) of severe manifestations, against the background of dishormonal disorders and thyroid dysfunction, while the comparison group showed a higher proportion of mild manifestations – 1.6 times higher than in the main group ($p < 0.05$), as well as a high level of psycho-emotional tension and depressive disorders.

The results of the evaluation of hormonal studies allowed us to note significantly higher levels of cortisol and reduced levels of luteinizing hormone, follicle stimulating-hormone as compared to the control and comparison groups of patients. Obviously, these indicators of hormonal imbalance emphasize the predominance of reproductive system disorders in the genesis of MD against the background of DEG. Elevated cortisol levels are evidence of enhanced adaptive responses; in addition, high levels of cortisol stimulate the synthesis of hypothalamic dopaminergic factor, which can lead to a transient increase in prolactin level, the concentration of which in girls at the age of 16-18 years is significantly higher as compared to the data in the comparison and control groups.

Progesterone secretion was 4.9 times lower than that in adolescent girls of the control group ($p < 0.05$), indicating that there was no ovulation and luteal phase, irrespective of the presence of thyroid dysfunction in both groups. Thirty-seven (30.8%) girls of the main group had increased serum levels of testosterone being 1.75 times higher than in healthy girls, which led to an increase in the proportion of hyperandrogenic states in 48 (40.0%) and is evidence of steroidogenesis dysfunction in the ovaries.

Taking into account the role of stress factors in the development of MD, dysregulation and divergence of steroid hormonopoiesis, changes in prolactin concentration at different ages of puberty,

tonic inhibitory dopaminergic control of prolactin secretion, the indicators of sympathoadrenal regulation were assessed by the levels of adrenaline and noradrenaline in the blood serum and different nature of its functioning was determined. Over the course of puberty, there was an increase in the level of norepinephrine as a hormone of homeostasis and normalization of adrenaline concentration to reference values ($p < 0.05$), which should be associated with increased disadaptation on the background of thyroid dysfunction and chronic stress, that correlated with increased levels of cortisol in such patients.

Special attention should be paid to transient increase in prolactin levels in girls of the main group, especially against the background of chronic stress of the psychological component, as well as significantly elevated cortisol levels and glucocorticoid dysfunction, indicating enhanced adaptive mechanisms in such patients.

Analytical processing and additional studies of the level of metabolic disorder predictors allowed establishing laboratory criteria for dyslipidemia in every fourth patient of the main group, impaired carbohydrate metabolism in 15.8% of cases, namely impaired fasting glucose and glucose tolerance with a predominance of dysglycemia in patients suffering from hypothyroidism and overweight.

According to recent scientific reports, thyroid dysfunction is closely related to vitamin D deficiency, especially reduced thyroid function (in subclinical and overt hypothyroidism) [1, 7]. The study results showed a statistically significant decrease in serum level of 25 (OH) D in the patients of the main group (to 19.8 ± 1.1 nmol/l) as compared to the patients of the control group (28.2 ± 1.2 nmol/l) ($p < 0.05$), which correlated with the presence of antithyroid antibodies and decreased thyroid function by thyroid-stimulating hormone and free thyroxine levels.

It should be noted that the deviations obtained were observed already at the initial stages of developing thyroid dysfunction, and low 25 (OH) D levels contribute to thyroid pathology manifestation; therefore, vitamin D deficiency is a risk factor for this pathology.

3. Conclusions

The presented hormonal studies allowed to identify different changes taking into account various clinical forms of MD in this category of adolescents, as well as supplemented the existing scientific evidence of functional immaturity of the reproductive system in adolescent girls and the preconditions for developing chronic anovulation as a basis for disorders of the peripheral reproductive organs, primarily due to glucocorticoid dysregulation and failure of the central mechanisms in the regulation of hypothalamic-pituitary-ovarian axis functioning.

There is a clear correlation between the physiological processes of maturation of the whole body and reproductive organs (especially the length of the uterus and its anteroposterior size) and estrogenic saturation of the body. The results obtained at this stage of research confirmed hormonal imbalance to be more pronounced in case of association with thyroid dysfunction.

The transition to the "mature" type of reproductive system functioning in girls with thyroid dysfunction is associated with changes in prolactin secretion from sufficiently low levels to the indicators exceeding the reference values for this age group, which is characterized by increased pituitary prolactin-synthesizing function and functional hyperprolactinemia.

The deviations of 25 (OH) D level obtained were observed already at the initial stages of developing thyroid dysfunction, and low 25 (OH) D levels contribute to thyroid pathology manifestation; therefore, vitamin D deficiency is a risk factor for this pathology.

Generalization of the frequencies of the main psycho-emotional characteristics and indicators of the personal profile in the girls of the studied cohort allowed revealing the constant dominance of psycho-emotional manifestations of moderate degree, as well as high levels of psycho-emotional stress and depressive disorders against the background of dishormonal disorders and thyroid gland dysfunction.

The results obtained are a convincing substantiation of expediency of developing the differenti-

ated program of psychocorrection and psychological practices in this category of patients.

Thus, impaired relationship between the thyroid system and the hypothalamic-pituitary-ovarian axis determines MD, development of functional cysts and multifollicular structure of ovarian tissue and, in case of hypothyroidism, can be considered as factors of metabolic disorders and polycystic ovary syndrome. On the other hand, functional disorders of the reproductive system and changes in steroidogenesis can initiate increased thyroid dysfunction. All of the above retains the feasibility of studying the mechanisms of menstrual function dysregulation against the background of diffuse endemic goiter, which are quite complex and require further clarification.

Conflict of Interest

The authors stated no conflict of interest.

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