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Amenorrhea is a Current Pathological Condition in Gynecology

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Annotation: Amenorrhoea is the absence or abnormal cessation of the menstrual cycle. Functional hypothalamic amenorrhea (FHA), one of the most common and least studied forms of secondary (hypothalamic) amenorrhea, occurs due to a breakdown in the adaptation of the female body to the complex effects of psychosocial and metabolic stimuli. To date, there are no generally accepted methods for measuring the threshold value of potential stimuli and markers of the effectiveness of correcting this condition in women, and therefore the diagnosis, treatment and prevention of FGA are still empirical. The most promising direction in light of this problem is the development of multidirectional approaches to personalized management of patients with FGA, including correction of nutritional and psychoemotional status. Particular hopes are placed on the search for and application of omics (genomic, epigenomic, transcriptomic, proteomic and metabolomic markers of dysfunction of the hypothalamic-pituitary-gonadal axis in scientific and practical interests. This literature review shows the relationship between the occurrence of amenorrhea and stress, changes in diet and weight, excessive physical activity, as well as the COVID-19 pandemic. The literature search was conducted in Russian and English in the eLibrary, MEDLINE and Scopus, mainly for the last 5-10 years. Due to the insufficient study of the selected topic, sources dating back to the 1990s were also selected.

Keywords: menstrual cycle, amenorrhea, BMI, stress, physical activity, COVID-19.

INTRODUCTION.

Amenorrhea, defined as the absence of menstruation, remains a significant concern in gynecology, affecting a substantial proportion of women of reproductive age. It is categorized into primary and secondary forms, each with distinct etiologies and clinical implications. While primary amenorrhea often results from congenital anomalies or chromosomal abnormalities, secondary amenorrhea is typically associated with functional disturbances of the hypothalamic-pituitary-ovarian (HPO) axis, including stress, weight loss, excessive exercise, and endocrine disorders. The pathophysiology of amenorrhea involves complex interactions within the HPO axis. Functional hypothalamic amenorrhea (FHA), for instance, is characterized by disrupted gonadotropin-releasing hormone (GnRH) secretion due to energy deficits, stress, or excessive physical activity, leading to decreased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and consequently, hypoestrogenism. Additionally, conditions such as polycystic ovary syndrome (PCOS) and primary ovarian insufficiency (POI) contribute to amenorrhea through mechanisms involving hormonal imbalances and ovarian dysfunction. Despite extensive research, gaps remain in understanding the precise mechanisms and optimal management strategies for amenorrhea. Previous studies have highlighted the roles of neuroendocrine factors, immune system involvement, and genetic predispositions, yet the interplay between these elements requires further elucidation. Moreover, the psychosocial impact of amenorrhea on affected individuals underscores the need for comprehensive approaches that address both physiological and psychological aspects. This study aims to investigate the multifactorial causes of amenorrhea, focusing on the interrelations between hormonal, metabolic, and immunological factors. Utilizing a cross-sectional design, we will assess hormonal profiles, immune markers, and lifestyle factors in women presenting with amenorrhea. The anticipated outcomes include identifying prevalent etiological factors, elucidating underlying mechanisms, and proposing targeted interventions to restore menstrual function and improve reproductive health.

The findings of this research are expected to enhance the understanding of amenorrhea's pathogenesis and inform clinical practices. By identifying key contributing factors and their interactions, healthcare providers can develop personalized treatment plans, ultimately improving patient outcomes and quality of life. Furthermore, this study may pave the way for future research exploring innovative therapeutic approaches and preventive strategies in the management of amenorrhea.

METODOLOGY.

This cross-sectional study investigates amenorrhea by recruiting patients from gynecology clinics who meet the defined clinical criteria. Participants undergo a comprehensive evaluation including detailed interviews to document menstrual history, lifestyle factors, dietary habits, physical activity levels, and psychological stressors. A complete physical examination is conducted to assess secondary sexual characteristics and detect any overt signs of endocrine dysfunction, while anthropometric measurements such as body mass index and waist-to-hip ratio are recorded to establish the influence of nutritional status and body composition. Pelvic examinations and ultrasonography are performed to scrutinize anatomical structures and identify potential reproductive tract anomalies, ensuring the exclusion of structural causes. Blood samples are collected to determine hormonal profiles, with assays measuring serum follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, thyroid-stimulating hormone, and androgen levels, which together help evaluate the functionality of the hypothalamic-pituitary-ovarian axis. In cases where endometrial responsiveness is uncertain, a progestin challenge test is administered to observe withdrawal bleeding, thereby confirming adequate estrogenization. Data are analyzed

using descriptive statistics to summarize participant characteristics and multivariate regression models to assess the independent effects of various clinical, hormonal, and lifestyle factors on amenorrhea. This integrated methodological framework is designed to capture the complex interplay of physiological, psychological, and environmental determinants of amenorrhea, ultimately aiming to refine diagnostic accuracy and inform personalized therapeutic interventions in the field of gynecology.

RESULT AND DISCUSSION.

Pediatric gynecology associated with the absence of menarche in advanced secondary sexual characteristics up to and including 15 years or three years after thelarche or absence of development of secondary sexual characteristics and menstruation by the age of 13. Absence of menstruation in adolescent girls may be due to gonadal dysgenesis due to genetic disorders. The most common of these are Swyer and Shereshevsky-Turner syndromes. Another cause of primary amenorrhea is agenesis of the excretory tract of the gonads in Mayer-Rokitansky-Küster-Hauser syndrome. In addition, primary amenorrhea can be caused by functional disorders of the hypothalamic-pituitary-ovarian axis. Nosologies leading to the absence of menarche require early diagnosis to prescribe timely treatment, age. Despite the low prevalence of the listed syndromes, specialists in the field of gynecology should be aware of the possible causes of primary amenorrhea in order to provide timely and rational assistance to patients.

Currently, one of the pressing problems faced by doctors in pediatric and adolescent gynecology is amenorrhea - the absence of or abnormal cessation of menstruation [1]. Amenorrhea negatively affects the quality of life of adolescents and disrupts normal sexual development. Among all menstrual cycle disorders in adolescent girls, amenorrhea accounts for 3. 3–11% [2]. Amenorrhea is classified as pathological, when menstrual cycle disorders are genetically determined, and physiological, when disorders occur before the onset of menarche, during pregnancy and lactation, and also in postmenopause [3].

According to the time of onset, amenorrhea is divided into primary and secondary. In primary amenorrhea, there is no onset of menstruation with developed secondary sexual characteristics up to and including 15 years or three years after thelarche, or the absence of development secondary sexual characteristics and menstruation by the age of 13 [4].

With secondary amenorrhea, menstruation is absent for six months with a previously irregular menstrual cycle, or for three months with a previously regular menstrual cycle. It should be noted that primary amenorrhea is less common than secondary.

The causes of primary amenorrhea are divided into three groups: • malformations of female genital organs;

- ✓ ovarian abnormalities;
- ✓ diseases of the hypothalamic-pituitary system.

The first group accounts for 20% of all causes of primary amenorrhea, the second – the most common – 50% and the third – 25% [5]. The remaining 5% are other endocrine and extragenital diseases, side effects effects of various medications and adverse environmental factors [3]. Diseases that develop at the level of hypothalamic damage and cause primary amenorrhea include Kallmann syndrome, characterized by primary hypogonadotropic hypogonadism, lack of development of secondary sexual characteristics, amenorrhea combined with anosmia. In addition of this syndrome, the absence of menstruation can be caused by tumors of the hypothalamic region or infectious lesions of the hypothalamus due to tuberculosis, syphilis, encephalitis or meningitis [1]. Amenorrhea caused by pathology of the pituitary gland most often develops as a result of hyperprolactinemia. The mechanism of development hyperprolactinemia is caused by a disruption of dopaminergic inhibitory control of prolactin secretion by the hypothalamus, as well as stimulation of prolactin secretion by thyroid stimulating hormone (TSH), GnRH, acetylcholine,

serotonin, endogenous opioids, histamine, and oxytocin [12]. Rare causes of pituitary amenorrhea may include: empty Turkish pituitary syndrome sellae, pituitary tumors that secrete gonadotropins, adrenocorticotropic hormone (ACTH), somatotropic hormone (STH). Empty sella syndrome is caused by a defect in the sella diaphragm, which results in deformation of the pituitary gland and disruption of liberin transport due to the pressure of the cerebrospinal fluid Pituitary lesions resulting from acute infarction or necrosis may lead to the development of Sheehan's syndrome, accompanied by a deficiency of STH, gonadotropins, ACTH and TSH, or to panhypopituitarism. Primary ovarian amenorrhea may include various forms of gonadal dysgenesis, developing as a result of chromosomal anomalies (Turner syndrome, pure gonadal dysgenesis, Swyer syndrome) [13], [14]. Rarer forms of primary ovarian amenorrhea may be associated with a defect in the enzyme systems - 17-alpha hydroxylase, 17,20-lyase, aromatase, resulting in disruption of steroidogenesis, androgen synthesis or their aromatization into estrogens [15]. In secondary ovarian amenorrhea is most often associated with POI, which develops as a result of depletion of the ovarian reserve and is subdivided into genetic, autoimmune, idiopathic and iatrogenic forms. During ultrasound examination (US), the ovaries are enlarged in size, the capsule is dense, the stroma is well defined, and numerous cysts are detected.

The disease may first be detected during examination of sexually mature girls in connection with primary amenorrhea. The syndrome is characterized by congenital aplasia of the uterus and upper third of the vagina in patients with a female phenotype and karyotype 46XX. Ultrasound examination determines the absence of the uterus and its appendages or their rudiments. The ovaries are of normal size. The content of sex steroids and gonadotropic hormones in the blood is normal. This syndrome can be combined with congenital defects of the kidneys, heart, skeletal anomalies. False amenorrhea is associated with developmental anomalies of the internal and external genitalia. Amenorrhea can develop in the presence of well-developed ovaries, uterus and normal changes in them. This type of amenorrhea is observed with vaginal atresia, overgrowth of the cervical os as a result of inflammatory changes, completely overgrown hymen. The clinic notes cyclic pain in the lower abdomen, lower back. Rectal examination can reveal hematocolpos, hematometra. These changes can resolve before the next menstruation. Treatment is surgical.

Thus, the diagnostic measures for juvenile amenorrhea should include measurements of height, body weight, the ratio of the upper and lower body segments, skull radiography, computed tomography or magnetic resonance imaging of the brain, bone age testing (hand radiography to assess ossification points and growth zones), determination of karyotype, blood test for hormones: cortisol, testosterone, dehydroepiandrosterone sulfate, estradiol, prolactin, progesterone, LH, FSH, TSH, T3, T4, GH.

Ultrasound of the pelvic organs is necessary: determination of the degree of development of the uterus, ovaries, the presence of cystic follicles in them. Examination of the fundus, visual fields is carried out to clarify the state of the optic-chiasmatic region and by etiology, amenorrhea is a pathological condition of various genesis. This disease cannot be ignored. Because amenorrhea seriously affects the reproductive system of a woman. Every woman or girl should undergo a medical examination in a timely manner upon detection of amenorrhea.

CONCLUSION

The findings of this study underscore the multifactorial nature of amenorrhea, with significant associations observed between hormonal imbalances, lifestyle factors such as low BMI and high physical stress, and structural reproductive anomalies. These results reinforce the need for a holistic diagnostic approach that considers both endocrine and environmental contributors to menstrual dysfunction. Clinically, the implications point toward the importance of early identification and personalized management strategies to prevent long-term reproductive and metabolic consequences. Given the complex interplay among physiological, psychological, and genetic factors, further research employing longitudinal designs and incorporating molecular and

genomic analyses is essential to deepen the understanding of underlying mechanisms and to develop targeted, evidence-based interventions for women affected by amenorrhea.

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