ACADEMICIA
An International Multidisciplinary Research Journal
(Double Blind Refereed & Peer Reviewed Journal)

DOI: 10.5958/2249-7137.2021.02323.5

PATHOGENETIC ASPECTS OF ABNORMAL UTERINE BLEEDING INTEENAGE GIRLS

Rasulova Saodat Xalimovna*; Ashurova Nigora Gafurovna**

[1,2] Bukhara State Medical Institute,
UZBEKISTAN

ABSTRACT

This review presents data revealing the pathogenesis of uterine bleeding during puberty, examines neuro-endocrine and immune mechanisms of regulation of the menstrual cycle in adolescent girls. The authors have formulated a conclusion summarizing modern research devoted to the study of the regulatory mechanisms of the reproductive system.

KEYWORDS: *Uterine Bleeding, Puberty, Adolescent Girls, Reproductive System.*

INTRODUCTION

In modern society, improving the reproductive health of women of all age groups is an important task for the formation of future generations of healthy, capable of full-fledged, social functioning and creative self-expression of people. Gynecological pathology of the puberty period, in particular, uterine bleeding, has a noticeable effect on reproductive health. Women who had uterine bleeding during puberty, subsequently represent a risk group for menstrual cycle disorders and generative function, hormone-related diseases [1,2].

Puberty is a critical period in the formation of the reproductive system. The main difference in the endocrine status in this age period is the immaturity of the hypothalamic-pituitary-ovarian system and inadequate sensitivity of target organs to the effects of gonadotropins. Therefore, it is during this period, under the influence of various both endo- and exogenous influences, various disturbances of the hormonal regulation process are possible, and as a consequence of this, a violation of menstrual function occurs. This is most often manifested by uterine bleeding of the pubertal period (UBPP), the share of which in the structure of gynecological pathology is 20-30% on average [3].

In the pubertal period, abnormal uterine bleeding (AUB) is usually considered to be associated with hormonal dysfunction and changes in the structure of the endometrium. Their frequency in

the structure of gynecological morbidity ranges from 10% to 37.5%. However, in more than 50% of cases, the pathogenesis of the disease remains unclear, which makes it impossible to use a unified treatment regimen. Known mechanisms of uterine bleeding include a violation of contractile activity of the uterus, a decrease in the tone of the uterine arteries due to a violation of the balance of vasoconstrictor and vasodilator prostaglandins, a violation of endometrial regeneration and pathology of thrombosis, especially in the platelet-vascular link, as well as as a result of activation of the fibrinolytic system. Regardless of the mechanisms that initiate abnormal bleeding, the significance of hemostatic reactions that provide thrombosis at the endometrial level is unanimously recognized, since their adequacy prevents the pathological consequences of blood loss and secondary organic changes in the endometrium [4].

One of the most important and clinically manifest forms of menstrual function disorders are UBPP, previously known as juvenile. The more familiar term has been changed recently in accordance with the recommendations of the International Classification of Diseases of the Xth revision. Due to the variety of conditions and causes for the occurrence of uterine bleeding, the term "abnormal uterine bleeding" is more often used in foreign literature to designate them [5].

The first clinical manifestations of UBPP manifest themselves during the formation of the menstrual cycle. The main causes of bleeding caused by changes in blood clotting are associated with impaired platelet function and, most often, Willebrand factor pathology. The functional activity of platelets and the level of the Willebrand factor depend on the general condition of the body, taking medications, physical activity, past illnesses, as well as the patient's blood type. The level of activity of the Willebrand factor in girls can also be influenced by the phase of the menstrual cycle. Hormonal disorders and related changes in prostaglandin levels, endometrial conditions and uterine contractility can also cause hyperpolymenorrhea. After a single study of blood clotting, it is almost never possible to identify the cause of uterine bleeding [6].

AUB in puberty is bleeding from the uterus, excessive in duration (more than 8 days), volume of blood loss (more than 80 ml) and/or frequency (less than 24 days), which has an adverse effect on physical, social and emotional well-being, the ability to verbal learning and memory in adolescent girls aged from menarche to 17 years inclusive. The frequency of AUB is 25-30% of all adolescent girls aged from menarche to 17 years inclusive who have sought medical help. In 33-69%, the disease has a tendency to chronic course and relapses. AUB in the pubertal period, Ovulatory dysfunction ("O") is the most common cause of AUB in adolescent girls aged from menarche to 17 years inclusive. Coagulopathy ("C") is determined in 20% of adolescent girls aged from menarche to 17 years inclusive. Willebrand's disease is found in 36% of teenage girls with regular menstruation. Organic pathology (polyp-P/adenomyosis-A/leiomyoma-L/malignancy and atypical hyperplasia-M) are collectively detected with a frequency of up to 10% in the structure of the causes of AUB in adolescent girls aged from menarche to 17 years inclusive [7].

The etiology of UBPP is diverse: infections of various nature, metabolic disorders, psycho emotional state, significant physical exertion occupy an important place. According to the literature, the pathogenesis of UBPP is mainly associated with changes in the central nervous and endocrine regulation of the menstrual cycle in adolescent girls, which is accompanied by a change in the concentration of gonadotropin, leads to a violation of folliculogenesis and

anovulation. Iron deficiency anemia of varying severity due to chronic iron loss is often a complication of UBPP [8].

The functional state of the higher nervous activity controlling the regulatory mechanisms of the reproductive system is unstable during puberty; the development of differentiations in the cerebral cortex and, especially, the hypothalamic-pituitary centers is insufficient. The uterus has not yet completed its final development, its receptors are imperfect, the potential for the uterus to perceive irritations and conduct them into the central nervous system is poorly expressed. At the same time, the pituitary gland receives perverted impulses and the synthesis of gonadotropins is not coordinated in it; follitropin production prevails, and lutropin and prolactin are not produced sufficiently. Various external and internal stimuli acting against this background can easily disrupt the regulatory mechanisms of the reproductive system, preventing the establishment of its stereotype and accompanied by uterine bleeding. The hormonal function of the ovaries during this period in girls is insufficiently expressed due to the imperfection of the receptor apparatus, as a result of which follicular and steroidogenesis is disrupted, and bleeding is most often of a hypoestrogenic nature. Prolonged monotonous exposure to low estrogen levels causes necrobiotic processes in the endometrium, which is accompanied by the appearance of bleeding. Taking into account that the mechanism of bleeding is not associated with a sharp drop in hormones, as it happens during normal menstruation, therefore, the endometrium is not rejected simultaneously, but in separate areas, therefore bleeding is more often not abundant. Since the level of estradiol is not high enough for rapid regeneration of the endometrium, bleeding is prolonged. Along with this, the question of the role of the endometrium itself in the occurrence of bleeding is discussed. It is assumed that endocrine, hemostasiological, as well as immunological mechanisms are important in the development of bleeding at the endometrial level [9].

Relative hyperestrogenism in puberty is due to the insufficiency or absence of the luteal phase of the cycle, which leads to disruption of secretory transformation processes and the development of endometrial hyperplasia [10].

The study of uterine bleeding is impossible without taking into account the peculiarities of the state of the blood coagulation system. Blood clotting is an important protective mechanism, the violation of which can lead to serious conditions, even to death. The maintenance of the liquid state of the blood is provided by the principle of self-regulation with the formation of an appropriate functional system. The main reaction apparatuses of this functional system are the coagulation and anticoagulation systems. In the study of the blood clotting system, the greatest attention is paid to thrombocytopoiesis due to the fact that platelets are the main supplier of thromboplastin, from which the blood clotting process begins [11].

The main modulators of cell growth with pronounced mitogenic properties in the tissues of the uterus and ovaries are insulin-like growth factor (IGF) -1, endothelial growth factor (EGF) and vascular-endothelial growth factor (VEGF). Angiogenesis is considered as a key factor in the development of tumor processes, but normally cyclic changes and the development of new microvessels from existing ones occur monthly in the ovaries and eutopic endometrium – cyclic angiogenesis. In other intact tissues of an adult, angiogenesis is not detected. The main inducers of the angiogenesis process are VEGF, angiogenin and the main fibroblast growth factor (FGF-2). VEGF expression is detected only in well-vascularized tissues: ovarian cysts, "mature"

follicles, yellow bodies in the vascularization phase, in the epithelium of the fallopian tubes, in smooth muscle cells and ovarian gates. Changing the processes of cyclic angiogenesis leads to inadequate vascularization of follicles, which disrupts their growth and can contribute to both atresia and persistence at various stages of maturity, up to cystic formation. VEGF expression is not observed in atretic follicles and degenerating corpus luteum [12-14].

With inadequate vascularization of the corpus luteum, luteal phase insufficiency develops, leading to various obstetric and gynecological pathology associated with progesterone deficiency.

R. Barbieri's studies have confirmed the role of insulin and insulin-like growth factors in the regulation of ovarian function. Both substances have a mitogenic effect, stimulating the proliferation of granulosa cells, which, by potentiating the effect of gonadotropins, leads to increased steroidogenesis in the ovaries. Insulin and IGF-1 stimulate the synthesis of estradiol and progesterone induced by follicle-stimulating hormone (FSH) in granulosa cells and luteinizing hormone (LH)-induced androstenedione synthesis in theca and stroma cells. A direct inducing and activating effect of insulin and IGF-1 on aromatase was noted [15,16].

Reviews have shown that hyperplastic processes in the uterine mucosa occur against the background of neuro-endocrine disorders and a progressive decrease in the ability of cells to apoptosis, which leads to a decrease in the degree of degradation of deoxyribonucleic acid (DNA) and an increase in the number of proliferating cells. Apoptosis is the natural end of the life cycle of any cell, the mechanisms of its regulation are universal, do not have tissue specificity and can act at various levels. The development of tumors, pathology of the cardiovascular system, neurodegenerative diseases, acute and chronic inflammatory processes is associated with a violation of the processes of regulation and implementation of apoptosis in the form of its premature induction or pathological suppression.

Currently, the uniformity of the premorbid background has been established in patients with various combinations of hyperplastic processes in hormone-dependent organs of the reproductive system, which suggests a similarity of the pathogenetic mechanisms of their development. Cytokines, growth factors and other proteins included in the cell microenvironment participate in the regulation of apoptosis. Tumor necrosis factor-α (TNF-α) is a cytokine that exhibits cytotoxicity by activating the corresponding receptors — p55 (TNFRI) and p75 (TNFRII) [17].

According to modern views, UBPP is associated with a violation of the function of the regulatory centers of the brain, namely the hypothalamic-pituitary system, which is a reflection of the age characteristics of the adolescent organism - the physiological immaturity of the regulatory centers and their unsteady connections with the ovaries. The functional state of the higher nervous activity controlling the regulatory mechanisms of the reproductive system is unstable during puberty, the development of differentiations in the cerebral cortex and, especially, in the hypothalamic-pituitary centers is insufficient. The uterus has not yet completed its final development, its receptors are imperfect, the potential for the uterus to perceive irritations and conduct them into the central nervous system is poorly expressed. At the same time, the pituitary gland receives perverted impulses and the synthesis of gonadotropins is not coordinated in it – the production of follitropin prevails, lutropin and prolactin are not produced in sufficient quantities. Various external and internal stimuli acting against this background can easily disrupt

the regulatory mechanisms of the reproductive system, preventing the establishment of its stereotype and accompanied by uterine bleeding [18].

Polymorphism of phenotypic manifestations of hereditary disorders, and often connective tissue dysplasia, is associated today with an increased risk of the formation of vascular intracranial abnormalities. Violation of the development of connective tissue involves not only somatic, but also all parts of the reproductive system. The formation of the function of the latter in adolescence is interrelated with the collagen formation of the reproductive organs and the functioning of vascular-platelet and coagulation hemostasis. The mutual influence of these links determines the preservation of not only the reproductive, but also the general somatic health of a teenage girl [19].

CONCLUSION

1. The pathogenesis of UBPP is caused by a complex of neuroendocrine, metabolic and immune disorders, among which the main place was previously given to the phenomenon of relative or absolute hyperestrogenism.
2. Endocrine, hemostasiological, as well as immunological mechanisms are important in the development of bleeding at the endometrial level.
3. The main modulators of cell growth with pronounced mitogenic properties in the tissues of the uterus and ovaries are insulin-like growth factor (IGF) -1, endothelial growth factor (EGF) and vascular-endothelial growth factor (VEGF).
4. The functional state of the higher nervous activity and its receptors are imperfect, the potential for the uterus to perceive irritations and conduct them into the central nervous system is poorly expressed. At the same time, the pituitary gland receives perverted impulses and the synthesis of gonadotropins is not coordinated in it, preventing the establishment of a normal menstrual cycle and accompanied by uterine bleeding.

REFERENCES

1. Sibirskiy V.K., Stepanov V.G. Knowledge management and human capital in the era of innovation: Monograph. - Moscow: CHOUVO "MU named after S.Yu. Witte", 2014. - P. 272
2. Adamyan Leyla Vladimirovna, Sibirskaya Elena Viktorovna, &Bogdanova Elena Aleksandrovna (2014). Therapy of uterine bleeding during puberty from the point of view of evidence-based medicine. Reproductive health of children and adolescents, (5 (58)), 17-21.
3. Khuraseva Anna Borisovna (2015). Uterine bleeding of puberty - problems and solutions. Reproductive health of children and adolescents, (2 (61)), 84-88.
4. Valeeva, F. V., Zubairova, L. D., &Tagirova, A. A. (2019). Clinical and diagnostic significance of microvesiculation of blood cells in abnormal uterine bleeding. Prakticheskayameditsina, (34), 109-112.
5. Goodman, A. Abnormal genital tract bleeding / A. Goodman // Clin.Comerstone. – 2000. – Vol.3, No. 1. – P. 25-35. 36. Guint, E. H. The conservative management of abnormal bleeding in teenagers with development disabilities / Guint E. H. // J. Pediatric Adolescent Gynecology-2003. – Vol.16, No. 1. – P. 54 - 56.

6. Dmitriev, V. V., Mozheyko, L. F., &Guzey, I. A. (2014). Blood clotting disorders as a cause of juvenile uterine bleeding in adolescent girls aged 12-18 years. Oncohematology, (1), 47-51.

7. Elena VitalievnaUvarova (2021). Clinical Recommendations (Draft). Abnormal Uterine Bleeding During Puberty. Reproductive health of children and adolescents, 17 (3), 5-30.

8. Sashkina A.E., Sibirskaya E.V., &Ordin G.V. (2017). Some aspects of pathogenesis and pathogenetic treatment of uterine bleeding during puberty. Medical business, (2), 63-65.

9. Kalashnikova, I. V., Orlova, V. S., &Adjey, O. K. (2011). Pathogenetically significant factors of abnormal uterine bleeding in puberty. Actual problems of medicine, 16 (22 (117)), 5-12.

10. Andreeva, V. O., Mashtalova, A. A., & Linde, V. A. (2019). The role of growth factors in the pathogenesis of uterine bleeding during puberty. News of higher educational institutions. The North Caucasus region. Natural Sciences, (3), 81-85.

11. Melon V.A. (2015). Violations of dynamic equilibrium in the blood coagulation system in abnormal uterine bleeding of the puberty period. Actual problems of medicine, 32 (22 (219)), 73-80.

12. Regulation of Vascular Endothelial Growth Factor (VEGF) Splicing from Pro-angiogenic to Anti-angiogenic Isoforms / D. Nowak [et al.] // J. of Biological Chemistry. 2019. Vol. 285, No. 8. P. 5532-5540.

13. Cyclic angiogenesis of the eutopic endometrium / Burlev V.A. [et al.] // Problems of reproduction. 2016. No. 6. pp. 22-30.

14. Burlev V.A. Autoparacrine disorders of angiogenesis regulation in proliferative forms of diseases of the female reproductive system // Obstetrics and gynecology. 2016. No. 3. pp. 34-40.

15. Manukhin I.B., Gevorkyan M.A., Chagai N.B. Anovulation and insulin resistance. M., 2016. 416 p. 9. Smirnov A.N. Elements of endocrine regulation. M., 2018. 352 p.

16. Andreeva, V. O., Mashtalova, A. A., & Linde, V. A. (2019). The role of growth factors in the pathogenesis of uterine bleeding during puberty. News of higher educational institutions. The North Caucasus region. Natural Sciences, (3), 81-85.

17. Andreeva, V. O., &Mashtalova, A. A. (2017). The role of apoptosis factors in the pathogenesis of oligomenorrhea and uterine bleeding during puberty. Bulletin of St. Petersburg University. Medicine, (4), 69-80.

18. Orlova, V. S., &Kalashnikova, I. V. (2017). Bioelectric activity of the brain on the background of uterine bleeding in adolescence. Actual problems of medicine, 16 (22 (117)), 44-49.

19. Kudinova Evgeniya Gennadievna, Uvarova Elena Vitalievna, &MaximovaPolinaEvgenievna (2017). Manifestations of vascular syndrome in adolescent girls with menstrual disorders. Reproductive health of children and adolescents, (4-5 (75-76)), 32-39. doi: 10.24411/1816-2134-2017-00030