

Polski
Mercuriusz
Lekarski



POLISH MEDICAL JOURNAL

ISSN 1426-9686



VOLUME LII, ISSUE 4, JULY-AUGUST 2024

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Abnormal uterine bleeding and its causes. Literature review

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ABSTRACT

Based on the analysis of information from available sources of scientific literature, the article provides an overview of the problem of abnormal uterine bleeding and its causes. Preservation of women's reproductive health is an urgent problem of the whole world. AUB is a debilitating symptom that affects a large number of women and one of the most common gynecological abnormalities. AUB, as a rule, does not threaten a woman's life, but significantly decreases its quality. Menstrual disorders affect all aspects of a woman's life, even increasing the risk of premature death. Women with AUB are more likely to seek medical care due to social and physical factors, while 50% of female patients have mental health problems due to anxiety and depression. Structural causes of uterine bleeding increase as a woman ages, which can affect reproductive health. Extragenital disorders are considered one of the most frequent causes of AUB. This is explained by the features of the endometrium, the state of which is influenced by general changes in a woman's hormonal status and the functional state of some organs and systems. AUB can be caused by diseases of the thyroid gland, uncorrected diabetes, obesity, blood coagulation disorders (most often von Willebrand's disease), infectious diseases, certain drugs (corticosteroids, antipsychotic or antiepileptic drugs), climate change and diet, psychological stress, etc. Management of patients with abnormal uterine bleeding is a complex problem that should include assessment of gynecological status and consultation of related specialists (endocrinologists, cardiologists, etc.).

KEY WORDS: Abnormal uterine bleeding, extragenital disorders, hormonal background

Pol Merkur Lek, 2024;53(4):457-461. doi: 10.36740/Merkur202404112

INTRODUCTION

Abnormal uterine bleeding (AUB) is a common impairment with menstrual cycle disorders related to the frequency, regularity, duration, and volume of blood lost outside of pregnancy [1-5]. The prevalence of AUB in the general population varies from 5% to 35.6%, depending on age, profession and origin [6], and is considered a reason for consultation in 75% of adolescents [7].

AUBs have a significant impact on the physical, psychological, social, professional and family aspects of a woman's life: prospects of losing a job due to the inability to leave the house due to heavy bleeding, reduced work productivity due to frequent changes of pads and tampons, limitation of social activity due to fear and psychological discomfort as a result of fear of contamination of outer clothing with blood [8].

Not only gynecological, but also extragenital impairment plays an important role in the etiopathogenesis of AUB. On the one hand, this is due to the fact that the endometrium, as a hormone-dependent target organ, always reacts to any changes in the hormonal status of the body as a whole. On the other hand, the functioning of the hemostasis system is closely interconnected with the hormonal status and the functions of other organs and systems in the body in general. AUB is a polyetiological condition, so it is necessary to take into account the influence of various aggravating factors, individual characteristics of the body and the state of other organs and systems, especially in case of comorbidities [9, 10].

AIM

According to literature sources, to analyze the state of the problem of abnormal uterine bleeding and its causes.

MATERIALS AND METHODS

PubMed, Medline, and the Cochrane Library databases were used for the literature review. The study involved assessment of 50 literary sources from 2011 to 2024, which relate to menstrual cycle abnormalities in women of different age groups and their causes.

REVIEW AND DISCUSSION

Any process that disrupts the normal endocrine, paracrine, or homeostatic functions of the endometrium, as well as any interference with the contractility of the myometrium, can cause AUB [11]. According to a number of authors, functional disorders, in particular, ovulatory dysfunction, are the most frequent cause of AUB, which accounts for 50% of cases [12]. Polycystic ovary syndrome, excess body weight, obesity, insulin resistance, thyroid gland and kidney diseases often cause anovulation and menstrual cycle disorders.

An increasingly common disease that disrupts the normal hormonal balance in the endometrium is obesity [13, 14]. The Apple Women's Health Study found prevalence rates of AUB in women with varying degrees of obesity. Thus, in patients with stage 1, this indicator was 1.31, with stage 2 – 1.25, with stage 3 – 1.51 [15]. The conversion of

androstenedione secreted by the adrenal glands into estrone by aromatase in adipose tissue provides an important source of additional estrogen for the endometrium [16]. This leads to excessive growth of the endometrium, caused by estrogens, and often causes AUB associated with the rejection of the hyperplastic functional layer [17].

The researchers used a mouse model to assess the role of increased body weight in endometrial repair and duration of menstrual bleeding. They found that mice fed a high-fat diet, which led to weight gain, had significantly slower endometrial repair compared to mice fed a normal diet. Mice in the high-fat diet group also had higher levels of local inflammatory mediators in uterine tissue after progesterone withdrawal. Therefore, due to an increase in body weight, the function of the endometrium changes, which increases menstrual blood loss [18]. K. Itriyeva [19] assumed the common mechanisms of endometrial hyperplasia and excessive menstrual bleeding: an increase in estrogen levels due to increased aromatization of androgens to estrogens in adipose tissue and production of adipokines by adipose tissue, which promotes a pro-inflammatory state.

Research by J. J. Reavey et al. [20] regarding the relationship between body mass index and menstrual blood loss revealed a weak positive relationship between them. At the same time, an experiment on mice to identify the role of increased body weight on the restoration of the endometrium and the duration of menstrual bleeding revealed a significant slowdown in the restoration of the endometrium in animals fed a high-fat diet. A decrease in the proliferation of epithelial cells of the lumen and an increase in local inflammatory mediators were noted. These results show that increased body weight affects endometrial function during menstruation, leading to increased menstrual blood loss.

I. Querevalú-Pancorbo et al. [21] found a higher frequency of AUB in women at high risk of eating disorder compared to women at low risk: 72.7% and 64.9%, respectively. Low-risk dietary behaviors, which include consumption of whole grains, fruits, vegetables, seafood, and nuts, are associated with a lower incidence of menstrual disorders [22].

Polycystic ovary syndrome (PCOS) is a complex disorder with diverse phenotypes involving metabolic, reproductive and endocrine abnormalities and is one of the most common such disorders in premenopausal women [23]. At the same time, PCOS is associated with AUB. Insulin resistance (IR) is common in women with PCOS and is observed in 70% of cases [24].

Research by Y. X. Wang et al. [25] found a relationship between irregular and rare menstrual cycles and hyperinsulinemia. Ovarian dysfunction due to abnormal hormone levels can cause abnormal menstrual conditions such as anovulation and amenorrhea [26].

X. Li et al. [27] established that menstrual dysfunction, consisting in the interval of vaginal bleeding, correlates with the severity of IR. In women with PCOS, the severity of IR, the LH/FSH ratio, and the level of androgens increased with a higher degree of menstrual cycle disorder.

A cross-sectional study of PCOS cases revealed a correlation between IR and the degree of oligomenorrhea [28].

Since menstruation is influenced by the secretion of sex hormones, IR interacts with the level of estrogen. Elevated estrogen can increase the secretion of luteinizing hormone (LH) and decrease the secretion of follicle-stimulating hormone (FSH), which in turn leads to hyperplasia of follicular membrane cells and granulosa cells. In cases of PCOS, insulin makes the adrenal cortex more sensitive to the activation of adrenocorticotropic hormones, further increasing androgen secretion and disrupting menstruation [29].

U. Ezeh et al. [30] found that women with PCOS and amenorrhea, and to some extent women with oligomenorrhea or anovulatory eumenorrhea, had a higher degree of hyperinsulinemia than women with ovulatory eumenorrhea, despite no significant differences in hyperandrogenism. Therefore, ovulation status and the severity of the menstrual cycle are more closely related to the degree of hyperinsulinemia than hyperandrogenism. These findings are confirmed by the study of E. P. Thong et al. [31], according to which chronic hyperinsulinemia impairs ovarian follicular development, as well as a report of an increased prevalence in women with type 1 diabetes of PCOS associated with ovarian exposure to supraphysiological doses of exogenous insulin [32].

Dysfunction of the thyroid gland affects all events of a woman's reproductive health: from menarche to menopause. The specified condition is considered the cause of AUB, but this cause is not always on the surface [33]. The effect of thyroid hormone on the reproductive system was studied. Hypothyroidism has been found to cause heavy and irregular menstrual bleeding, and hyperthyroidism is usually associated with hypo-, oligo-, and amenorrhea [34]. Thyroid-stimulating hormone (TSH) is similar to gonadotropins FSH and LH. Thyroid hormones, through thyroid hormone receptors in the ovaries, affect the menstrual cycle either directly or through effects on sex hormone-binding globulin (SHBG), prolactin, and gonadotropin-releasing hormone (GnRH) [35]. B. R. Joshi et al. [36] found a significant number (15.79%) of patients with AUB who suffered from thyroid dysfunction.

In a study by P. Kattel [37], thyroid dysfunction occurred in 20% of AUB cases, of which the most common type of AUB was menorrhagia, 19% had hypothyroidism, and 1% had hyperthyroidism. R. Komathi et al. [38] note that almost 30% of women with AUB had thyroid dysfunction, in particular, 27% had hypothyroidism and 3% had hyperthyroidism.

In chronic kidney diseases, disruption of the hypothalamus-pituitary-ovary system leads to an abnormal profile of reproductive hormones, where the degree of disruption increases with the progression of the specified impairment. Thus, it is believed that people with renal failure have the most serious hormonal disturbances [39]. With renal failure, the pulsatile secretion of gonadotropin-releasing hormone is disturbed, which leads to the absence of cyclic FSH and LH. Consequently, estradiol levels remain relatively low, preventing LH release and ovulation. Elevated prolactin levels due to reduced clearance and increased production

also contribute to anovulation [40]. A possible mechanism of hormonal abnormalities in renal failure is that high prolactin levels negatively feed back on the hypothalamus-pituitary-ovary axis and inhibit gonadotropin-releasing hormone secretion, thus preventing gonadotropin release and leading to abnormal uterine bleeding [41].

Vitamin D is known to affect reproductive physiology through vitamin D receptors located in the female reproductive tract, for example, in the ovaries (especially in the granulosa cells), uterus, and placenta [42]. Vitamin D likely controls ovarian function and thus the menstrual cycle through anti-Müllerian hormone receptors, which also share a domain with the vitamin D response element [43]. High-dose vitamin D supplementation can correct the metabolic disorders associated with PCOS [44]. Studies have shown that vitamin D may play a role in ovarian reserve and dysmenorrhea [45]. Vitamin D and calcium supplementation in PCOS patients has also been shown to affect follicular maturation and menstruation [46]. Some researchers question the role of vitamin D (in combination with calcium) in any menstrual problems in women [47]. Altered calcium homeostasis and parathyroid hormone

levels due to vitamin D deficiency may also be responsible for dysregulated follicular development leading to menstrual dysfunction in women with PCOS [48].

V. Singh et al. [49] conducted a study on the relationship between vitamin D deficiency and menstrual irregularities and found higher vitamin D levels in women with regular cycles. Lower vitamin D levels were associated with a 13.3-fold increased chance of having an irregular cycle.

In a study conducted by R. Blahoveshchenskyi [50], it was determined that 87% of women with AUB and extragenital disorders had vitamin D deficiency in blood serum, i.e., its level was lower than 20 ng/ml, and 13% had vitamin D deficiency vitamin (20-29 ng/ml). In addition, a statistically significant negative correlation was found between the level of estradiol and vitamin D in this category of patients ($r = -0.61$, $p < 0.05$).

CONCLUSIONS

Abnormal uterine bleeding is one of the most common disorders of the menstrual cycle. AUB is a polyetiological impairment that occurs against the background of changes in the functions of internal organs and systems of the body and is accompanied by an abnormal level of hormones.

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The article was written as part of the research work: Optimization of clinical, diagnostic and therapeutic approaches to the management of gynecological patients taking into account age and the presence of extragenital disorders.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

RECEIVED: 18.03.2024

ACCEPTED: 03.07.2024

