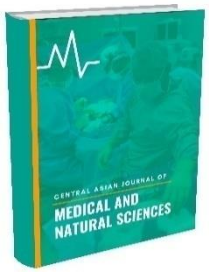
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 04 Issue: 02 | Mar-Apr 2023 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

Menstrual Cycle Disturbances in the Reproductive Period

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Received 11th Feb 2023,
Accepted 10th Mar 2023,
Online 12th Apr 2023

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Abstract: Abnormal uterine bleeding has a significant negative impact on the quality of life of patients, has significant economic consequences for both the patients themselves and the healthcare system as a whole. Examination and management of women of reproductive age with abnormal uterine bleeding is difficult due to the lack of standardized methods for identifying and classifying potential causes. Currently, there are no unified approaches to the examination and treatment of such patients, inadequate therapy can lead to the development of complications, and unreasonable surgical treatment can lead to a complex of somatic problems and an increase in economic costs.

Key words: abnormal uterine bleeding, regulation of the menstrual cycle.

Abnormal uterine bleeding (AMB) is a collective concept of various types of menstrual irregularities characteristic of the pubertal, reproductive and perimenopausal periods of a woman's life. This group of conditions accounts for up to 20% of all visits to the gynecologist's office [1, 2]. AUBs cause a significant number of missed work days and school hours, and have significant economic consequences for the patients themselves. In a woman with heavy menstruation, reduced work capacity results in a loss of approximately $1,692 per year [3–5]. International studies show that only every fifth patient with AUB turns to a doctor for help. Based on this, it is difficult to estimate the total costs associated with the diagnosis and treatment of AUB. It is believed that most women self-administer non-steroidal anti-inflammatory drugs (NSAIDs) and over-the-counter hemostatic drugs [6]. The direct costs of insurance companies associated with AMC are approximately $1 billion per year [7].

A number of authors note a significant negative impact of AUB on the quality of life of a woman, arguing that chronic menstrual disorders are associated with anger, fear, unmotivated anxiety and aggression [8, 9]. In a study by Chapa (2009), 40% of 100 women with symptoms of menorrhagia noted the restriction of daily and social activities, sexual abstinence, and a decrease in interest in participating in recreational activities [10]. Data from other studies show that AUB is correlated with low socioeconomic status, lack of employment, abdominal pain, and psychological stress [11]. In addition to the direct negative impact on the quality of life, AUB can lead to the development of various complications, in particular, menorrhagia is the most common cause of iron deficiency anemia in developed countries [7]. In order to understand the pathogenesis of AUB, it is necessary to briefly dwell on the processes of regulation of the menstrual cycle and folliculogenesis in healthy women of

reproductive age. There are five levels of regulation of the menstrual cycle: 1st - target organs, 2nd - ovaries, 3rd - pituitary gland, 4th - hypothalamus and 5th - highest - areas of the brain that have connections with the hypothalamus and affect its function, including the neocortex.

The role of the extrahypothalamic structures of the brain, including the cerebral cortex, is the synthesis of neurotransmitters and neuromodulators by neurons, such as acetylcholine, catecholamines, serotonin, dopamine and histamine, which have a regulatory effect on the pituitary functions of the hypothalamus. The hypothalamus, due to the synthesis of gonadoliberins (GL) and prolactin-inhibiting factor in the arcuate and paraventricular nuclei, has a direct effect on the pituitary gland. The synthesis of gonadotropin-releasing factors is influenced by:

- neurotransmitters and neurotransmitters of extrahypothalamic structures of the CNS - direct stimulation and suppression;
- autoregulation of GL secretion - ultrashort feedback;
- pituitary tropic hormones - short feedback;
- sex steroid hormones - long feedback.

In the adenohypophysis, various substances are synthesized, including hormones that are directly involved in the regulation of the reproductive system: LH, FSH and prolactin. The level of tonic secretion of tropic hormones is mainly influenced by the circoral release of GL, i.e., the hypothalamus, and cyclic secretion is regulated mainly by the mechanism of negative and positive feedback, therefore, depends on the effect of steroids on the pituitary gland. In the ovaries, the synthesis of steroid hormones occurs, as well as the maturation and release of gametes and the formation of the corpus luteum. The main hormone-synthesizing ovarian tissues include theca and granulosa, which contain a complete set of enzymes that allow the synthesis of all 3 classes of sex steroids: androgens, estrogens and progesterone. As a result of complex embryonic processes of differentiation, migration and cell division, by the time a girl is born, according to various authors, from 300 thousand to 2 million primordial follicles are present in her ovaries. By menarche, the number of follicles decreases to 200-400 thousand, of which about 400 later become a source of egg formation.

The mechanism of the follicle exit from the primordial stage has not yet been deciphered, it occurs throughout the entire prepubertal, pubertal, reproductive and premenopausal periods, this process depends on the hormonal status of the body. It is not interrupted during pregnancy and lactation, during anovulation, when taking hormonal contraceptives, etc. Once it starts growing and goes through the hormone-independent, hormone-sensitive and hormone-dependent stages of growth, the follicle either reaches ovulation or undergoes atresia. The hormone-independent phase lasts about 3 months. until the development of approximately 8 layers of granulosa cells in the primordial follicle and occurs in the absence of nutrition from the vessels. The processes occurring in the follicles do not depend on circulating hormones, the regulation is carried out due to local factors. In the hormone-sensitive growth phase, which lasts about 70 days, as the granulosa layer thickens, the preantral follicle becomes moderately sensitive to FSH. During this period, a significant change in the morphology and functioning of the oocyte occurs: the zona pellucida appears, and the theca sensitive to LH is rapidly formed from the surrounding stroma. After the antral follicle reaches 2 mm in diameter, it is able to grow only under the influence of a high concentration of FSH - the hormone-dependent phase begins. In each menstrual cycle, more than one follicle enters the hormone-dependent phase, but the so-called. the cohort from which the dominant follicle is selected, the rest undergo atresia. In the granulosis of the dominant follicle, receptors for FSH appear, under the influence of which the production of estradiol constantly increases with the formation of a preovulatory peak. At the end of the follicular

phase of the menstrual cycle, luteinization of granulosa cells occurs, receptors for LH are synthesized. The main events of the follicular phase of the menstrual cycle are the growth of a cohort of follicles, including one dominant follicle (rarely two), and atresia of all follicles in the cohort, except for the dominant one. The successive change of peaks in the concentration of estradiol and LH with FSH leads to ovulation - the rupture of the follicle and the release of the egg from the ovipositor hillock.

In the second phase of the menstrual cycle, an increase in the mass of the corpus luteum occurs with an increase in vascularization under the influence of tonic secretion of LH, more progesterone and estradiol are synthesized. In the absence of fertilization of the egg, inevitable luteolysis occurs, leading to the elimination of the FSH and LH block and the onset of a new menstrual cycle. In the endometrium during a normal menstrual cycle, 3 phases are distinguished:

- the phase of desquamation, when, under the influence of a decrease in the concentration of steroid hormones in the absence of fertilization, ischemic changes occur and rejection of the functional layer of the endometrium by 2/3 due to a decrease in the lumen and twisting of the spiral arteries;
- proliferative phase, which begins in the first days of the menstrual cycle, layering on the desquamation phase. There is a restoration of the lost functional layer of the endometrium due to an increase in cells, the uterine glands are formed;
- the secretory phase, which begins after ovulation under the influence of progesterone, the mitotic activity of the endometrium decreases, the uterine glands branch out, and begin to produce a secret.

The harmony of the processes occurring in the menstrual cycle is carried out due to the usefulness of gonadotropic stimulation, adequate functioning of the ovaries, synchronous interaction of the peripheral and central links of regulation - reverse afferentation. The main causes of dysregulation of the reproductive system are: stress, a sharp and / or significant decrease in body weight, increased physical activity, taking drugs that affect the synthesis, metabolism, reception and reuptake of neurotransmitters and neuromodulators, functional hyperprolactinemia, increased synthesis of inhibin by ovarian tissue , as well as impaired metabolism of growth factors and prostaglandins by ovarian tissue. Stress-induced changes in the function of the hypothalamic-pituitary-ovarian system persist for a long time after the end of exposure to the stress factor. In short-stressed primates, menstrual cycles remained ovulatory, but there was a decrease in peak LH and progesterone levels by 51.6% when stress began in the follicular phase and by 30.9% when the luteal phase began. .

Menstrual irregularities persisted for 3–4 cycles after the end of stress, which coincided with the persistence of elevated cortisol levels. Obviously, the existence and adequate functioning of the corpus luteum is the most vulnerable phase of the menstrual cycle. It has been proven that the same menstrual irregularity can be caused by various causes, and the same cause can lead to the formation of various syndromes of menstrual irregularity. With a long-term existence of a pathological process, all links of regulation are gradually involved in it, up to a change in the dominant factor of pathogenesis, and the clinical picture may change [12]. Examination and management of women of reproductive age with abnormal uterine bleeding is difficult due to the lack of standardized methods for identifying and classifying potential causes of AUB and the confusion of the applied nomenclature. Therefore, in 2009 a new classification of pathological uterine bleeding in the reproductive period was introduced [13]. AUB was divided into acute and chronic (bleeding from the uterine cavity, different in volume, duration and frequency from menstruation and present for 6 months, usually not requiring immediate medical intervention).

Acute AUB is an episode of severe bleeding that requires immediate medical intervention to prevent further blood loss, which may develop in the presence of existing chronic AUB or without a history

[13]. According to the recommendations of the FIGO expert group, patients with acute AUB should undergo a general laboratory examination (general blood count, blood type and Rh factor, pregnancy test), assessment of the hemostasis system (total thromboplastin time, prothrombin time, APTT, fibrinogen), as well as determination of the von Willebrand factor. It can be assumed that 13% of women with AUB have systemic disorders of hemostasis, most often von Willebrand disease [14]. It is not yet clear how often these disorders cause or contribute to the onset of AUB and how often they are asymptomatic or with minimal biochemical abnormalities, but it is clear that they are often missed by doctors in the examination plan to identify the causes of AUB [15]. Careful history taking with 90% sensitivity makes it possible to identify systemic disorders of hemostasis (Table 2) [16] . Removal of the endometrium during curettage of the walls of the uterine cavity is not required by all patients of the reproductive period with AUB. It is advisable in patients with several factors predisposing to the development of atypical endometrial hyperplasia and carcinoma (obesity or overweight, hypertension, metabolic syndrome, etc.). When determining the indications for separate diagnostic curettage, one should take into account a combination of personal and genetic risk factors, an assessment of M-echo on TV ultrasound. It is believed that curettage of the walls of the uterine cavity is indicated for all patients of the late reproductive period (over 45 years).

A woman with a family history of colorectal cancer has a lifetime risk of endometrial cancer of up to 60%, with a median age at diagnosis of 48–50 years [17, 18]. Screening for endometrial cancer is currently part of the approach to managing patients with AUB [19, 20]. First of all, this applies to women of late reproductive and perimenopausal periods. Various techniques can be used to remove the endometrium, the main thing is that an adequate tissue sample is obtained, which will make it possible to conclude that there are no signs of malignant growth. Given the high likelihood of AUB in chlamydial infection, it is advisable to exclude chlamydial endometritis (PCR endometrial biopsy). In patients with AUB, the incidence of endometrial hyperplasia is 2–10% and can reach up to 15% in women with recurrent menorrhagia during the menopausal transition [28]. Progression from hyperplasia to endometrial cancer occurs in 3–23% of cases within 13 years, with a frequency of 5% for endometrial hyperplasia and carcinoma [27]. 90 kg, age□Separate risk factors are: weight 45 years, history of infertility, history of no childbirth□ and family history of colon cancer. The listed diagnostic measures will allow us to suggest the cause of AUB, assess the severity of the patient's condition, and determine the sequence and direction of therapeutic effects. The total cost of treating AUB in women requiring surgery is about $40,000. The additional cost of treatment equates to $2,291 per patient per year (95% CI, $1,847–$2,752) [8]. The database (NHS Hospital Episode Statistics) UK (2010-2011) includes 36,129 episodes of AUB, for which specialist consultations were held. Hospitalized patients spent 21,148 bed days in hospitals, an annual cost to the NHS of £5.3-7.4 million. Art., based on the range of the cost of a bed-day from 250 to 350 f. Art. respectively. Most experts believe that in countries with effective national guidelines, savings in the treatment of patients with AUB can be achieved primarily by reducing the number of hysterectomies [25]. A global approach to the treatment of women of reproductive age with chronic AUB is to prevent possible complications [26, 27].

Based on this, the need for anti-relapse treatment of AUB is obvious, the main task of which is the regulation of the menstrual cycle to minimize blood loss and prevent excessive stimulation of the endometrium by estrogen [29]. In the reproductive period, it is possible to use three main methods of treating acute AUB [21–24]:

- non-hormonal treatment using antifibrinolytics (tranexamic acid) or NSAIDs;

- hormonal hemostasis - use combined hormonal contraceptives (oral and parenteral, mainly containing analogues of natural estrogens), progestogens, including as part of the Mirena intrauterine releasing system, gonadotropin releasing hormone agonists;
- surgical hemostasis - removal of altered tissue with or without visual control, followed by morphological examination of endometrial fragments. Surgical methods to stop acute AUB are resorted to in cases of patient instability, the presence of a contraindication, or the ineffectiveness of conservative methods. One of the combined oral contraceptives used to treat abnormal uterine bleeding is Qlaira. This is the first product with natural estradiol, identical to natural, including the combination of estradiol valerate with dienogest. Dienogest, which is part of the drug, has pronounced antiproliferative pharmacological properties. The high therapeutic efficacy of Qlaira against AUB has been confirmed in international randomized placebo-controlled trials [30-33]. Analysis of data from three multicenter clinical trials conducted in Europe and North America, which involved 2,266 women, showed that the use of Qlaira is accompanied by a significant reduction in menstrual blood loss and a shortening of the duration of withdrawal bleeding [30, 32]. The drug is 15.5 times superior to placebo in the number of women who are completely cured of AUB (42.0 vs. .5%, $p < 0.0001$) [30]. Its effectiveness is 76.2%, while the therapeutic effect in women with heavy and / or prolonged menstrual bleeding is achieved in the first months of treatment and continues throughout the application, regardless of the initial volume of blood loss [30, 32, 33].

  Thus, the relevance of studying the etiology and pathogenesis of AUB in women of reproductive age is obvious. Currently, there are no unified approaches to the examination and treatment of such patients, inadequate therapy can lead to the development of complications, and unreasonable surgical treatment can lead to a complex of somatic problems and an increase in economic costs.

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