Review article

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GUIDELINES FOR MONITORING WOMEN WITH COAGULATION DISORDERS

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Irrespective of the progress in the recognition and treatment of women who suffer from bleeding disorders, modern medical science has yet to adjust the diagnosis, therapy and care to their needs. An increasing number of women are being diagnosed with the mentioned disorders. Some who consult a gynaecologist owing to heavy menstrual bleeding actually have a coagulation disorder. Failure to recognise this disorder is widespread. Heavy menstrual bleeding is a condition that women with such disorders experience from the onset of the reproductive period. It affects their quality of life. What is more, they face the problem of accepting the potential risks of transmitting the disease to their child. Timely recognition and registration of these patients are essential. It is important to talk with and consult healthcare professionals, as well as to prescribe adequate therapy that enables physicians to cope with the various needs of women during the reproductive period.

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Introduction

The maturation of the central nervous system (CNS), the hypothalamus and the pituitary gland lead to the synthesis of a more significant amount of gonadotropin, which becomes sufficient for activating ovarian function. The increased and cyclical production of hormones accelerates the growth and development of secondary sexual characteristics. The most important event at the beginning of puberty is the first menstrual bleeding - menarche, and in our climate, it occurs at the age of 12, on average. Normal menstrual bleeding results from a decrease in the concentration of estrogen and progesterone in the blood two days prior to its occurrence, and the cessation of bleeding occurs when the estrogen level increases once more. Bleeding is a result of vasoconstriction, myometrial contraction and local platelet aggregation (1). Menstrual bleeding lasts from 2 to 7 days, with a blood loss of 40 ml per cycle, and happens at 21 to 45 days (2). International Federation of Gynaecology and Obstetrics (FIGO) introduces a new classification system for abdominal bleeding: Abnormal Uterine Bleeding (AUB) (3). The diagnosis of AUB depends on the volume and length of the bleeding, the existence of pain with respect to the first day of the cycle, data on the present infections, physical and emotional stress, weight change, data on the use of drugs (warfarin, heparin, hormones) or herbal preparations (ginkgo, ginseng), history of coagulation diseases with a positive family history, evaluation of being overweight, symptoms of the Polycystic Ovary Syndrome (PCOS) syndrome, insulin resistance, thyroid disease, presence of changes on the vulva, vagina, cervix, presence of possible pregnancy, fibroids, adnexal tumours, adenomyosis and infection. A pregnancy test, blood count, vaginal and urinary analysis, especially for *Chlamydiae trachomatis*, cervical cytology, and thyroid hormone level should be considered. A coagulation status test should be performed in the event of profuse and prolonged bleeding. Furthermore, an ultrasound examination needs to be employed in order to determine the thickness of the endometrium and to observe the possible presence of pregnancy, as well as the changes in the small pelvis. Cervical biopsy and curettage, hysteroscopy and laparoscopy can be additionally used in diagnosis. The treatment of patients depends on the aetiology, physical examination, laboratory and other analyses. In patients with submucosal myomas, infections, thrombophilia and early abortions or pelvic tumours, it is essential to administer therapy for the underlying condition (4). A large number of

patients have ovarian dysfunction (AUB-O), which is treated in the following manner:

- Hormonal therapy: Progestins (medroxyprogesterone acetate – 10 mg per day, or norethindrone acetate – 5 mg per day) for ten days, with the monitoring of bleeding;
- Oral hormonal contraceptives (OHC) may be prescribed to reduce bleeding. At first, these should be administered four times a day for 1−2 days, then two pills a day until the 5th day, and then one a day until the 20th day. The therapy is to be conducted in three successive cycles with one tablet a day;
- Gonadotropin-releasing hormone agonists (GnRH agonists) can be included in treating severe bleeding, in the form of one injection per month during six cycles;
- Conjugated estrogens can be intravenously administered in hospitalized women experiencing heavy bleeding for 4 hours, in 3 to 4 doses, followed by oral therapy with conjugated estrogens, 2.5 mg daily, or ethinyl estradiol, 20 mcg daily, for three weeks, with the addition of progestagen for the last ten days of therapy.

In case of abnormal bleeding after unsuccessful hormone treatment, hysteroscopy should be performed, and organic lesions (polyp, submucosal myoma) or neoplasm (endometrial cancer) should be ruled out.

In the absence of a specific pathology, the therapy for bleeding can be one of the following: endometrial ablation, placement of an intrauterine system with levonorgestrel or hysterectomy (5, 6).

The most common symptom is menorrhagia (bleeding that lasts more than seven days, or more than 80 ml) (7). Other symptoms may include haemorrhagic ovarian cysts and endometriosis. ACOG (American College of Obstetricians and Gynaecologists) recommends that all female patients under 18 who experience abnormal bleeding should be tested for coagulation disorders, especially von Willebrand disease. It has a prevalence of 1.3% and is the most common disorder which causes menorrhagia during menarche (8). Screening involves determining partial thromboplastin time (aPTT), prothrombin time (PT), the evaluation of platelet function, and the determination of the von Willebrand factor antigen in the plasma and VWF activity in the plasma. This disorder often remains unrecognized. Heavy menstrual bleeding is a problem faced by girls and women, and it significantly affects their quality of life. Menorrhagia is not the only manifestation of a blood clotting disorder. In most cases, anamnestic data on menstrual bleeding show that a woman has more abundant and prolonged bleeding, which is significant for suspecting the existence of a bleeding disorder. Women face problems owing to the symptoms themselves and other challenges of the reproductive period, primarily concerning planning pregnancy (9). A history of ovarian cysts was detected (52% vs. 22% of controls) in a study of 102 women with vWD, conducted by the United States Centers for Disease Control and Prevention (CDC). In the same study, 30% of the women with vWD suffered from endometriosis, compared to 13% of those in controls (10).

The ten European principles of care for girls and women with congenital bleeding disorders are:

- Equal access and quality of care for all persons, regardless of gender;
- Timely and accurate diagnosis of coagulation disorders in women and girls;
- Awareness of the additional challenges these people face;
- Access to the patient and family, and providing comprehensive care;
- Inclusion of a dedicated gynaecologist and obstetrician in the team;
- Education of women, girls and their families about the menstrual cycle and its regulation;
- Early recognition and control of heavy menstrual bleeding;
- Counselling before conception and access to prenatal diagnostics;
- Providing a comprehensive plan during pregnancy and after birth;
- Inclusion of patients in registries and clinical research.

Coagulation disorders significantly affect the quality of a person's life owing to the way in which they are inherited, the impact of bleeding on the patient's life and the life of the family, the impact on social life, productivity, stress and anxiety. Menstrual bleeding is often not discussed openly in the family circle, so more work should be done to normalize discussions on this topic. Educating the family, healthcare workers and the public about normal and abnormal bleeding patterns can help to create the conditions for an effective diagnosis and therapy of this group of patients (11). A woman experiences approximately 450 menstrual cycles in her lifetime, and the haemostatic challenges of ovulation and menstrual bleeding occur in each instance (12). Education should be adapted to the age and needs of women in different stages of the reproductive period. Adolescent girls are at particular risk of heavy menstrual bleeding due to the immaturity of the ovaries and the high percentage of anovulatory cycles. Women face dilemmas when it comes to family planning. A woman should be introduced to the mechanism of disease inheritance and the risks to the offspring. Pregnancy is a hypercoagulable state. Women with coagulopathies face an increased risk of bleeding complications during pregnancy, childbirth and postpartum. In the case of these women, planning pregnancy should ideally happen before conception (11).

Counselling

This is necessary for the purpose of preparing the patient and her parents for the appearance of the first menstruation. The first signs of puberty appear at the age of 10, on

average. The counselling goals are to explain the risk of bleeding, monitor the volume and length of menstrual bleeding, and the procedure in case of heavy bleeding. As the onset of the first menstruation approaches, insist on the importance of early medical supervision for better efficiency, make a plan of action in case of heavy bleeding, and provide a prescription with therapy and laboratory instruction for haemoglobin determination on the first and third days of menstrual bleeding (13).

Treatment during the First Menstruation and Puberty

1. Take tranexamic acid from the very beginning of the menstruation: 2 tablets of 500 mg 3 times a day,
2. Determine the haemoglobin level on the first and third day of the cycle,
3. Establish contact by phone or e-mail with the selected gynaecologist and haematologist.

The therapy is considered effective and menstrual bleeding is regular:

- if the number of sanitary napkins does not exceed 4/day (+ 1 at night),
- if the haemoglobin level remains > or = 11g/l,
- if menstruation lasts < or = 7 days.

Apply the same protocol during subsequent cycles. If the cycles are irregular, add progestagen therapy from the 16th to the 25th day of the cycle. If the therapy is insufficiently effective: prescribe an estroprogestagen pill of 30 µg, from 2 to 3 pills a day, until the bleeding stops (i.e. over 2 to 3 days) and continue with one pill a day until the end of the pack. Consultation is necessary every six months.

Procedure in Women during Sexual Maturity

If contraception is desired, a combined estroprogestagen pill or an intrauterine device with levonorgestrel should be used. If menstruation is excessive and contraception is not desired, tranexamic acid, 1 g per os, every 6 to 8 hours, is used during the first five days of menstruation, and/or intranasal desmopressin, one dose of spray in both nostrils during the first 2 to 3 days of menstruation, with or without tranexamic acid.

Planning Pregnancy

It is necessary to follow the married couple. Assess the partner's risk and whether he is a carrier of a haemorrhagic disease. In severe forms of the disorder, prevention strategies include genetic counselling. In the case of in vitro fertilization, pre-implantation genetic diagnostics should be performed, if available. After consulting the haematologist, gynaecologist and obstetric team, the married couple must be informed about the risks during pregnancy, especially for the mother and the fetus. If a woman suffering from haemophilia, vWD or a platelet function disorder suspects pregnancy, she should visit her gynaecologist as soon as possible. They will ensure the provision of the best possible care during pregnancy and delivery. Consultation with a haematologist is imperative. If the woman is already pregnant, recommend prenatal diagnostics (biopsy of the chorionic villi, amniocentesis, determining the sex of the child by ultrasound). It is best to make a plan about monitoring the pregnancy and childbirth with the parents. Pregnancy care and pregnancy monitoring are performed in a specialized centre. This also involves the control of haemostasis during childbirth, as well as after childbirth. The birth must take place in a tertiary institution. Tranexamic acid reduces the risk of early and late postpartum bleeding and does not affect breastfeeding. It can also be used for a more extended period after delivery if there is a higher risk of bleeding. The newborns, who may inherit the disorder, are at risk of bleeding during the delivery, especially in instrumental deliveries (11).

Procedure for Women who no Longer Wish to Give Birth

Tranexamic acid and/or intranasal desmopressin can be administered in women during puberty, which is a short-term therapy. An intrauterine device with levonorgestrel is recommended as long-term therapy, and in more severe cases, it is required to resort to endometrial ablation or hysterectomy (14, 15).

The effectiveness of the therapy is not always the same. Caution is needed with prolonged bleeding owing to the risk of functional haemorrhagic ovarian cysts. Progesterone or the birth control pill should be re-prescribed. Monitor dysmenorrhea and prohibit the use of nonsteroidal anti-inflammatory drugs. Recognize neglecting to take the pill and genital infection as the cause of metrorrhagia. Teach the patient to double the pill dose in case of profuse bleeding.

Conclusion

Identification and registration of these patients are essential. Counselling, monitoring and therapy must be instituted from the onset of puberty if a haemostasis disease is known. Otherwise, menarche (first menstrual bleeding) will reveal a latent haemostasis disease. In severe coagulation disorders, bleeding can be very profuse and prolonged and may lead to the need for hospitalization and/or a blood transfusion. Quality of life may be impaired. With well-conducted hormonal therapy and close cooperation between haematologists and gynaecologists, blood transfusions and infusions of platelet factors that carry the risk of alloimmunization can be avoided. Throughout life, it is necessary to monitor and harmonize therapy with the needs of women during the reproductive period.

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SMERNICE ZA PRAĆENJE ŽENA SA POREMEĆAJIMA KOAGULACIJE

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Uprkos napretku u prepoznavanju i lečenju žena sa poremećajima krvarenja, savremena medicinska nauka još nije uskladila dijagnostiku, terapiju i negu sa njihovim potrebama. Sve većem broju žena dijagnostikuju se ovi poremećaji. Pojedine žene koje se jave ginekologu zbog obilnog menstrualnog krvarenja imaju poremećaj koagulacije. Neprepoznavanje ovog poremećaja veoma je uobičajena pojava. Obilno menstrualno krvarenje predstavlja stanje sa kojim se žene sa pomenutim poremećajima sreću od početka reproduktivnog perioda i utiče na kvalitet njihovog života. Takođe, one se suočavaju sa problemom prihvatanja potencijalnih rizika od prenošenja bolesti na dete. Neophodno je pravovremeno prepoznavanje, kao i registracija ovih bolesnica. Važni su i razgovor i savetovanje sa zdravstvenim radnicima, te primena adekvatne terapije koja omogućava suočavanje sa različitim potrebama žene u reproduktivnom periodu.

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***Ključne reči**: menarha, koagulopatije, abnormalna krvarenja iz materice*