Review Article

Practical approach for abnormal uterine bleeding

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Abstract: Abnormal uterine bleeding is one of the most common reasons of which patients seek for medical attention. This article reviews the patterns and causes of abnormal uterine bleeding. Laboratory and radiologic studies for evaluation of abnormal uterine bleeding are mentioned. Medical therapy and surgical options are also discussed.

Key words: Uterine, bleeding

Abnormal uterine bleeding (AUB) is a common complaint seen in gynecological practice and only menorrhagia alone accounts for 12% of all gynecological examinations [1]. Although in many cases the symptoms are relatively minor, it must be kept in mind that it will be a sign of underlying pathology [2]. In fact, menstrual abnormalities are one of the commonest problems of women seeking for medical attention from primary care practitioners [3]. To manage these patients with an efficient manner, methodological approach must be applied. Once the underlying cause is clarified, a suitable management plan can be applied.

Terms used to describe abnormal uterine bleeding:

1) Heavy menstrual bleeding (Menorrhagia); AUB is a broad term referring to a wide range of clinical presentations. Menorrhagia classically defined as menstrual blood loss greater than 80 mL per cycle or menstrual blood loss longer than 7 days. This amount of blood loss is important because it is known that this amount of blood loss is associated with iron deficiency and seen in 10% of all reproductive age women [4]. Even though this classical definition is appropriate; Royal Collage of Obstetricians and Gynecologists prefer to use a more subjective definition. They define the situation as heavy clinical bleeding over several consecutive cycles [2]. Women with menorrhagia must be screened for coagulation defects. The most common inherited coagulation defect is von Willabrand Disease. It is followed by factor X deficiency, factor VII, XII and XIII deficiencies [5]. Because of these common causes; patients with menorrhagia should be asked for background history of paternal consanguinity and family history of bleeding diathesis.

2) Polymenorrhoea, oligomenorrhea, amenorrhea; Polymenorrhoea, oligomenorrhea and amenorrhea are the terms used for expressing frequency of periods. Normal menstruation typically occurs every 28 days ± 7 days. Cycles with intervals longer than 35 days and shorter than 21 days are known as oligomerrhoea and polymenorrhoea, respectively. Amenorrhea is diagnosed in a female who has not menstruated by age 13 years without any sign of puberty, or by age 15 years with presence of pubertal signs, or for a length of time equivalent to a total of three previous cycle intervals or 6 months [6].

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3) Postcoital bleeding; Postcoital bleeding (PCB) is a bleeding of genital tract seen after intercourse. In most of the cases it is related with cervical dysplasia, polyps, ectropion and genital tract infections. That's why; patients with this symptom must be referred to gynecologist for smear test, cervical biopsy or colposcopy.

4) Intermenstrual bleeding (Metrorrhagia); Intermenstrual bleeding (IMB) can be defined as bleeding arising from genital tract after cessation of menstrual bleeding.

5) Menometrorrhagia; Menometrorrhagia is a combination of heavy menstrual bleeding and intermenstrual bleeding patterns.

6) Postmenopausal bleeding; Postmenopausal bleeding (PMB) is defined as the situation of experiencing genital bleeding more than 12 months after last menstrual bleeding. For a basic and effective approach AUB can be defined as any deviations from individual's normal menstrual pattern or adverse feelings about her quality of life because of adverse impacts of menstrual changes [7]. Treatment options must be chosen with a correct diagnosis and by regarding the patient's concerns and expectations about her own life like childbearing plans.

Causes of abnormal uterine bleeding:

As initial step, all non-uterine causes of bleeding must be excluded. Non-uterine causes of genital bleeding are atrophic vaginitis, vulval intraepithelial neoplasia, vulval carcinoma, skin conditions, vaginal lesions, trauma and foreign body. Uterine causes of genital bleeding can be classified as pregnancy related, physiological, benign endometrial and cervical pathology, malignant endometrial and cervical pathology, systemic causes, pelvic infections and dysfunctional uterine bleeding.

1) Pregnancy Related Bleeding; Before starting to investigate the uterine bleeding pregnancy must be excluded in any reproductive age women.

2) Physiological Bleeding; Physiological cycle disturbances can be seen in the age group around menarche and near menopause. In reproductive age group; inter menstrual decrease of estrogen levels following follicular phase peak can lead to inter menstrual bleeding.

3) Benign endometrial and cervical pathology; Fibroids: Fibroids are benign smooth muscle tumors of the myometrium and are present in one out of five women [8]. Although the majority of patients are asymptomatic, the most common symptom attributed to fibroids is menorrhagia [9]. Although there is no consensus about a relation between the location and size of the fibroids and symptoms, it is believed that sub mucous fibroids are prone to cause abnormal bleeding. Polyps: Polyps can be defined as focal overgrowth of endometrial glands and stroma. Polyps are the significant causes of AUB especially menorrhagia, IMB and PMB. And they have 1% malignancy rate especially in the postmenopausal age group. Cervical ectropion: Cervical appearance like erosion due to the eversion of endocervical columnar epithelia to the ectocervix is called cervical ectropion. Cervical ectropion is more common among pubertal girls, pregnant and combined oral contraceptive users [10]. If ectropion is only an incidental gynecological finding, there is no need for a treatment. And also, any cervical destructive methods must be applied after exclusion of cervical dysplasia and infection.

4) Malignant endometrial or cervical pathology; Endometrial Carcinoma and endometrial Hyperplasia: The excessive estrogenic stimulation is the main reason of both endometrial carcinoma and endometrial hyperplasia. Endometrial hyperplasia can be classified as simple, complex and atypical hyperplasia. Although the risk of malignant transformation rate is low for simple and complex hyperplasia, recent reports show 43% transformation rate for atypical hyperplasia [11]. Hyperplasia can be manifested if self by IMB, PCB or menorrhagia. The increased age is the most significant risk factor for endometrial malignancies. Because of this reason, patients with postmenopausal bleeding must be evaluated carefully. Besides this classical knowledge it must be outlined that 20-25% of all endometrial malignancies can occur from premenopausal patients with menorrhagia [12]. In addition to increased age, obesity, nulliparity, polycystic ovarian syndrome and tamoxifen therapy are the other etiological factors associated with unexposed estrogenic stimulation [13].
Cervical cancer and cervical intra-epithelial neoplasia: Cervical cancer remains to be the most common gynecological malignancy. The incidence of cervical cancer is especially higher in the developing countries. The age 35-39 and 60-64 are the two age groups for peak incidence [14]. Although 80-85% of the cases are squamous cell carcinomas, adenocarcinomas began to appear especially in women under 35 years old [15]. It must be kept in mind that most of the premalignant changes seen in cervix are more common than cervical cancer and generally asymptomatic. The most common symptoms are PCB and IMB. Nationwide screening programs are needed for early diagnose and reduction of death rate like achieved in UK [16].

5) Systemic causes;
Exogenous hormones: The usage of any form of hormonal contraceptives can lead to disturbance of menstrual cycle. Progesterone only pill usage can cause irregular bleeding and combined oral contraceptives may cause IMB. Hormone replacement therapy can lead to abnormal bleeding in pre and postmenopausal women.

Medical Conditions: Some endocrine, hematological, auto-immune, hepatic, renal, cardiac and metabolic diseases can cause different AUB patterns. For example hypothyroidism is associated with menorrhagia; hyperthyroidism is associated with oligo and amenorrhea. Although only small proportion of cases is caused by medical conditions, medical conditions of patients must be investigated prior to diagnosis and treatment.

6) Pelvic Infection;
Pelvic infections can lead to AUB. Especially reproductive age patients must be evaluated against pelvic infections. Servisitis can cause IMB and PCB. PID, endometritis and salpingitis can lead to irregular bleeding.

7) Dysfunctional uterine bleeding;
Dysfunctional uterine bleeding can be defined as irregular or excessive uterine bleeding which could not be associated with an organic etiology. It is therefore a diagnosis of exclusion of other causes [17]. This state may be ovulatory or anovulatory bleeding. The majority of cases are menarchial and perimenopausal women in a state of hormonal dysfunction [18].

Evaluation of abnormal uterine bleeding:

1) History; History taking must be focused on frequency, amount and the causes of AUB. Pregnancy must always be excluded before starting an investigation. A special attention must be paid on the risk factors associated with endometrial carcinoma and endometrial hyperplasia. Hormonal therapy and intrauterine device usage must be assessed. History of cervical disease and intervention including cervical smear and colposcopy must be asked. The wishes about fertility must be noticed because it is important in planning treatment options. Urological and gastrointestinal bleeding must be referred to related clinics.

2) Examination; During general examination attention must be paid on anemia, thyroid disease and clotting abnormalities. Grossly enlarged uterus may indicate abnormalities. By inspection of vulva and vagina gross lesions can be noticed. Speculum examination of the cervix is essential for identifying cervical lesions, polyps and macroscopic tumors. Smear must be taken especially in the cases of IMB and PCB. Pelvic tenderness, uterine size and adnexial masses must be noticed during bimanual pelvic examination.

3) Investigations; During investigations clinical approach and consideration must be directed to local pelvic pathologies and systemic diseases. In fact, majority of the cases will be diagnosed as DUB [19]. Therefore exclusion of the organic pathologies related with AUB is the key point of diagnosis. In guideline of National Collaborating Centre of Women's and Children's Health it is stated that there is no need for further investigations and physical examinations if the history of patient does not suggest an organic pathology [20]. But in the existence of symptoms such as pelvic pain, pelvic pressure, IMB and PCB, the patient must be evaluated in the aim of finding an organic pathology [20].

a. Blood Tests: By evaluation of an easy full blood count test iron deficiency, anemia and thrombocytopenia can be identified. Iron supplementation should be ordered without a further need for investigation with ferritin levels [2]. If physical examination and history obtained from the patient does not suggestive for a systemic disease there is no need for a further investigation.
During evaluation of patients considerations about systemic diseases must especially be focused on thyroid disease and coagulation disorders. In women with menorrhagia since menarche; tests for coagulation disorders especially for von Willabrand disease should be ordered [20].

b. Assessment of Uterine Cavity: In women with a history or pelvic examination suggestive for pelvic pathology or at high risk for endometrial carcinoma must be assessed for structural and histological pathologies related with uterine cavity. In order to making an investigation ultrasound, endometrial biopsy, dilatation and curettage, hysteroscopy and magnetic resonance imaging can be used separately or in combinations of modalities.

Ultrasonography: Ultrasound must be considered as a first line diagnostic tool during investigations of structural pelvic pathologies [20]. By using ultrasound the presence, location and size of fibroids can be identified. Endometrial thickness and appearance can be obtained. In transvaginal ultrasonography endometrial thickness above 5mm in postmenopausal women and 10-12 mm in premenopausal women may be suggestive for an endometrial pathology [21]. The values above the cut off points may direct the physician to investigate endometrial pathology by an endometrial sampling method. And also the method of instillation of saline during transvaginal ultrasound may be used for obtaining a better endometrial imaging before endometrial sampling [21].

Endometrial Sampling: Endometrial sampling is indicated for all women with persistent menorrhagia and for all pathologies identified by ultrasonography. Using Pipelle endometrial sampler in outpatient practice can be recommended because of satisfied accuracy rates for detecting endometrial serious pathologies such as endometrial cancer and hyperplasia [2,19, 21].

Dilatation and curettage: In modern practice dilatation and curettage is not accepted as a diagnostic or a therapeutic option in evaluation of AUB [19].

Hysteroscopy: Hysteroscopy is a powerful option for patients with AUB because it allows both diagnosis and treatment at the same setting. And also, hysteroscopy can be performed by modern hysteroscopes in an outpatient fashion with an acceptable tolerance of patients. But it is recommended to be preferred as a diagnostic tool when ultrasound examination gives inconclusive results [20]. The exact nature of abnormality can be identified by hysteroscopy because it allows direct visualization of endometrial cavity and directed endometrial sampling for endometrial pathologies. And also hysteroscopy is a better diagnostic tool than ultrasonography in detection of endometrial polyps [20].

Magnetic resonance imaging (MRI): MRI is not a first line investigation tool, it can only be used in selected cases where ultrasound gives inconclusive results [20].

Current treatment options for abnormal uterine bleeding

1) Medical Therapy: Available medical treatments include treatment with anifibrinolitics, cyclo-oxygenase inhibitors, non-steroid anti-inflammatory drugs (NSAIDs), combined estrogen-progesterone pill, progestins, danazol, gonadotropin-releasing hormone analogues and levonorgestrel intrauterine system (LNG-IUS). Good quality evidence shows that all of these medical therapy methods are effective in reducing menstrual blood flow and in delaying the need for surgical management. Hormonal therapy methods can be a treatment option for cases of DUB rather than organic and iatrogenic causes of AUB. The discrimination of DUB as ovulatory and anovulatory can be helpful in choosing appropriate medical treatment option. The absence of a rise of serum progesterone in luteal phase, absence of dominant follicle on serial ultrasound follow up, or deficiency of secretory changes on an endometrial biopsy are the key points for a diagnosis of anovulatory cycle.

Even though there are some several effective medical treatment options for DUB the symptoms usually return once the therapy stopped. So, long duration applicable medical therapies offering infrequent and minimal side effects must be preferred as a medical treatment option. In modern practice local LNG-IUS can be recommended as a good treatment option when it's effectiveness, side-effects, length of treatment and acceptability are taken into consideration [22].
I. Gun et al.: Abnormal uterine bleeding

Progestins: Progestins halt endometrial growth and allow for an organized sloughing of endometrium. The common progestin side effects are breast tenderness, weight gain and headaches. Oral and local administrations by an intrauterine device are the two administration methods for progestins.

Cyclic oral progestin for anovulatory DUB: Traditionally administration of oral progestin, cyclically 10 days a month in luteal phase, is being used as a treatment option for anovulatory DUB. This treatment modality offers approximately 50% improved cycle control [23, 24]. But there are a few objective data obtained from RCTs about effective treatment of anovulatory DUB by progestins. And also there is no consensus on the type of progestin and dosage.

Progestin for ovulatory DUB: Treating ovulatory menorrhagia with progestin was reported as the least effective treatment method because ovulatory menorrhagia is caused by predominantly due to the imbalances in prostaglandin release rather than deficiency of progestin [25]. Continuous dosing oral progestin may be effective and useful in treating ovulatory menorrhagia by inducing endometrial atrophy but there is no current studies evaluating this approach [26].

Intrauterine Progestin: Mirena is the only available intrauterine progestin in the markets. It contains 52mg of levonorgestrel, which is released at a daily dose of 20 micrograms over 5 years. It causes atrophy of endometrial glands and desquamation of endometrial stroma [27]. Side effects are headache, nausea, mastalgia, acne, functional ovarian cysts, depression, weight gain and lower abdominal pain. But generally most of the side effects are resolved rapidly and the device is well accepted among users [28]. A recent analysis showed that it ranks higher than all other medical treatments when effectiveness, side effects, length of treatment and acceptability are considered [22]. It has been shown to increase hemoglobin [29], decrease menstrual blood loss by approximately 90% [30], reduce bleeding caused by fibroids [31] and adenomyosis [32] and also an acceptable alternative for surgery [33]. Furthermore it may also be a treatment option for stage 1A grade 1 endometrioid carcinoma [34].

Estrogens: High dose estrogen therapy is a useful option for controlling acute heavy bleeding episodes. The predominant action of high dose estrogen is induction of endometrial growth to cover denuded endometrial surfaces. 25 mg IV conjugated equine estrogen (Premarin) every 4 hours is the only estrogen form used for high dose estrogen therapy but it is no longer available in the market.

Medical therapy for atrophic vaginitis: Atrophic vaginitis can be treated with topical estrogen cream.

Combined estrogen and progesterone (Combination oral contraceptives (COC)): Combined estrogen and progesterone can be used both for anovulatory and ovulatory heavy menstrual bleeding. According to expert opinions and medical experience this therapy is effective in treatment of DUB but well designed controlled studies are lacking to support the efficacy of COCs. While effectiveness, contraceptive effect and reduced withdrawal bleeding episodes are major advantages of this type of therapy, strict daily usage and systemic side effects are the disadvantages. Age, tobacco usage, history of thromboembolic disease and specific medical conditions of patients must be evaluated carefully in an individual basis for each case.

Androgenic steroids (Danazol): Danazol suppresses ovulation, reduces ovarian estrogen production, causes endometrial atrophy and reduces menstrual blood flow [35,36]. In a Cochrane systematic review danazol appears to be more effective than placebo, progestin, NSAIDs and COCs in reducing menstrual blood loss [37]. But it has more adverse effects like weight gain, oily skin and acne than other types of treatments. For a conclusion it can be said that danazol could be an effective treatment option for short term therapy plans and infrequent use only.

Gonadotropin-releasing hormone agonists: GnRH agonists reversibly suppress secretion of gonadotropins and create hypo estrogenic state like menopause. There is no RCT study on usage of GnRH agonists in treatment of DUB. In an observational study menstrual blood flow and duration of menstruation decreased by GnRH agonist add-back treatment combined with cyclical hormone replacement therapy [38]. GnRH agonist treatment is usually limited to 6 months because it induces rapid bone demineralization.
And also GnRH agonist treatment has intolerable side effects associated with hypo estrogenic state like hot flashes and other menopausal symptoms. Because of these reasons GnRH agonists must not be considered as a first line therapy for DUB. Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs inhibit prostaglandin synthesis and decrease menstrual blood loss when compared with placebo [39]. Approximately 20% to 40% blood loss reduction can be achieved with NSAIDs in most of the cases [40]. Using in the time frames of premenstrual and menstrual periods is a preferred treatment option for minimizing the side effects of NSAIDs [41]. They can be considered first-line treatment in ovulatory women with DUB. There is no difference among individual NSAIDs in reducing menorrhagia [39,41].

Tranexamic acid: Tranexamic acid can be used for menorrhagia. It acts as an antifibrinolytic agent. It is an oral medication commonly used in Europe. It seems to work better than NSAIDs, but large doses are required and side effects are common [42]. There has been a reluctance to prescribe due to potential increased risk of thrombosis among practitioners and gynecologists. A recent Cochrane Review showed that there are no data available within randomised controlled trials which record the frequency of thromboembolic events during treatment with tranexamic acid [42].

2) Surgical treatment of AUB:

Hysterectomy: Hysterectomy is a 100% successful treatment option of AUB. There are some well-known complications of hysterectomy like other major surgical procedures but it is known that approximately 95% of patients are satisfied after hysterectomy. Hemorrhage, wound healing problems, infection and ovarian failure are some complications that must be counseled with patients before hysterectomy.

Myomectomy (abdominal, laparoscopic, hysteroscopic): Uterine leiomyomas are common. Leiomyomas are benign smooth muscle tumour that is not premalignant. They are found in nearly half of women over age 40. The treatment of choice for leiomyoma is usually surgical. Endometrial resection / ablation: There are various hysteroscopic and nonhysteroscopic full thickness endometrial destruction methods. Various forms of energy like heat, cold and microwave to destroy endometrium can be applicable by these methods. Nowadays less complication rates are achieved by using easy, cost effective newer methods. Endometrial destruction methods require shorter operation time, quicker recovery and fewer complications than hysterectomy [43]. But significant proportion of the cases needs an additional surgical treatment include hysterectomy.

Hysteroscopy: Although clinical evidence is limited, polyps seem to play a causative role in menometrorrhagia [44]. The incidence of polyps in women with AUB has been reported 13% to 50% [45]. Previously they were mostly identified by histological examination of curettage but nowadays they are often diagnosed by transvaginal ultrasound or hysteroscopy. Hysteroscopic resection is the gold standard of treatment for endometrial polyps [46,47]. Nearly 6% to 12% of patients presents recurrent abnormal bleeding or not satisfied after hysteroscopic resection of polyps [47,48].

Approximately 30% of women with fibroids have been reported to have AUB [49]. The presence of submucous fibroids is associated with additional three-fold increase in the risk of having AUB [50]. In majority of patients removal of submucous fibroids results in normalization of menstruation [51]. While planning hysteroscopic resection age, childbearing plans, localization, size and number of fibroids must be considered. Hysteroscopic resection can be an appropriate option for appropriate patient.

Uterine fibroid embolization: Uterine fibroid embolization (UFE) is an outpatient treatment option. UFE is an alternative to hysterectomy in women with symptomatic uterine fibroids. It offers more than 90% elimination of AUB [52]. Transient or permanent amenorrhea has been reported associated with ovarian compromise [52, 53]. Because of possibility of ovarian failure it is not recommended for young and women who have childbearing plans.

Conclusions:

Abnormal uterine bleeding is one of the most common reasons patients seek for medical attention. The need for treatment is often unrecog-
nized by general practitioners. At best, oral medication reduces menstrual blood loss by only 50%. So, significant number of patients will not benefit from medication. Levonorgestrel containing IUD is more effective than other medical treatment options. The ultimate treatment of AUB is hysterectomy. Hysteroscopic surgery is a treatment option for patients who wants to preserve their fertility.

Practice points

* For a basic and effective approach AUB can be defined as any deviations from individual's normal menstrual pattern or adverse feelings about her quality of life because of adverse impacts of menstrual changes
* AUB usually presents as heavy menstrual bleeding (menorrhagia).
* Menorrhagia is clinically defined as a total menstrual blood loss of more than 80ml per menstruation.
* Dysfunctional uterine bleeding (DUB) is defined as abnormal uterine bleeding in the absence of organic disease.
* DUB is more common around the menarche and perimenopause.
* Every woman presenting with heavy menstrual bleeding should have a full blood count taken.
* Serum ferritin, female hormone testing and thyroid testing are not routinely recommended.
* Referral to secondary care for further gynaecological assessment and examination should be made in the following situations:
  - Women over 45 yrs with heavy menstrual bleeding.
  - If there is persistent intermenstrual bleeding.
  - If an abnormality is suspected on physical examination
  - If there is suspicion from the history of increased risk of pathology such as carcinoma
  - If there is treatment failure.
* Pelvic ultrasound is the first-line diagnostic tool for identifying structural abnormalities.
* Oral progestins and COCs are the most common preferred agents for treatment of AUB among gynecologists.
* Levonorgestrel-releasing intrauterine system is a preferred medical treatment option.
* NSAIDs can be considered as first-line treatment option in ovulatory women with DUB
* Hysterectomy is a 100% successful treatment option of AUB.
* Hysteroscopic resection is the gold standard of treatment for endometrial polyps.

References

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