Abnormal Vaginal Bleeding

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Abstract

Abnormal vaginal bleeding is an important cause of morbidity in women, especially during reproductive period. In this first article of our series, will be discusses in detail possible aetiology of abnormal vaginal bleeding. We will focus on uterine bleeding as a response to sexual hormones, abnormal vaginal bleeding complicating pregnancy, abnormal vaginal bleeding of pelvic cause, dysfunctional uterine bleeding and abnormal vaginal bleeding of extra pelvic causes.
Keywords: *abnormal vaginal bleeding*

Introduction

Abnormal vaginal bleeding (AVB) is an important morbidity cause for women, especially during the reproduction period. Approximately 30% of women suffer from menorrhagia, this being one of the fundamental problem for which they consult the gynecologist[1] AVB is responsible for the high number of surgical hysteroscopy procedures (endometrial ablations) and for 2/3 of hysterectomies, thus consuming a lot of money from the health system[2].

In most cases, AVB means abnormal uterine bleeding (AUB), but in rare cases the cause may be related to vaginal, cervical or urethral lesions.

In order to define AUB, it should be mentioned first and foremost the characteristics of the normal menses. The normal menses takes around 28 days (+7), the menstruation takes 4+2 days and the lost blood is 40 ± 20 ml[3,4,5,6]. In the menstruation follicular stage, the estradiol (E2) produced by the dominant follicle induces the proliferation of endometrial glands and stroma. After ovulation, in the luteal stage, the yellow body produces increased quantities of progesterone and less estrogen. In absence of conception and chorionic gonadotropin, the yellow body regression occurs and the blood levels of sexual steroids decreases dramatically. Such decrease leads to normal menstruation, a self-limited periodic process which involves the desquamation of the entire endometrium. This type of physiologic bleeding is called bleeding caused by progesterone withdrawal. The beginning of normal menstruation involves the enzymatic degradation of the endometrial functional layer associated to blood vessel destruction. The hemostasis after this event is ensured by local coagulation, vasoconstriction and re-epithelization. The coagulation mechanisms include formation of platelet thrombus, involving the von Willerbrand (vWF) and production of fibrin (induced by thrombin). Normally, the menstrual blood has no clots because of the activity of endometrial fibrinolytic activity which promotes clots lysis.

Except for withdrawal uterine bleeding at new born babies, any vaginal bleeding before puberty shall be considered abnormal[7].

For women at reproductive age, AVB include any change in frequency, in duration of menstruation and lost blood amount, but also bleeding between menstruations[8].

Find below types of abnormal uterine bleeding[9,10]:

- **Oligomenorrhea** - uterine bleeding occurring at intervals of >35 days.
- **Polymenorrhea** - regular uterine bleeding occurring at intervals of less than 21 days.
- **Menorrhagia** - uterine bleeding occurring at regular intervals but lasts no longer than 7 days or is associated with a lost blond quantity of >80 ml.
- **Menometrorrhagia** is a prolonged (>7 days) and excessive (>80 ml) uterine bleeding, occurring at non-regular intervals.
- **Amenorrhea** is the absence of menses for >6 consecutive months at women at the reproductive age.
- **Metrorrhagia** (inter-menses bleeding) - irregular bleeding occurring between menses.

■ **Spotting at mid-menstruation** - minimum bleeding occurring before the ovulation.

■ **Post-menopause bleeding** - uterine bleeding at >12 months after menstruation stopped, or any unpredictable vaginal bleeding at women in post-menopause undergoing substitution hormone therapy for >12 months.

■ **Acute excessive uterine bleeding** resulting from hypovolemia or shock.

■ **Dysfunctional uterine bleeding** - abnormal uterine bleeding in the absence of genital tract organic lesions or hormone treatment.

Menorrhagia may be subjectively defined as "excessive menstrual bleeding during more consecutive menses"[11]. But between the subjective perception and the blood quantity lost during menstruation there is a weak correlation. Objectively, menorrhagia is defined as an uterine bleeding lasting for more than 7 days and is associated with a quantity of lost blood of >80 ml[5,9,10,12]. This quantity may cause disturbance in the woman's social, professional and sexual life, preoccupation for a serious pathology (cancer) and ferriprive anemia[13].

This chapter will deal with excessive AVB. AVB in minus (oligomenorrhea and amenorrhea) shall be dealt with in another chapter.

Uterine bleeding as a response to sexual steroids

Estrogen withdrawal bleeding - The uterine bleeding occurs after the estrogenic stimulus stop, for instance: after bilateral adnexectomy, ovaries irradiation, or stopping the estrogenic therapy at a castrated woman. Similarly, the bleeding occurring after castration may be stopped after the treatment through the exogenous administration of estrogens. The bleeding re-occurs if the exogenous administration of estrogens is stopped. Thus, the estrogenic withdrawal alone (in absence of progesterone) usually causes endometrial bleeding.

Estrogen breakthrough bleeding - Chronic exposure to estrogens, in absence of progesterone, stimulates the continuous endometrial proliferation, the same with the extragonadal hyperestrogenemia in the polycystic ovarian syndrome. After a certain amount of time, the estrogens quantity produced at the extra-ovarian tissues becomes insufficient to hold the endometrial structural support. This causes unpredictable desquamation events at the endometrial surface. The rather decreased doses of estrogens cause intermittent spotting, which may be prolonged, but moderate. On the other hand, the increased doses of estrogens continued to be administrated cause extended period of amenorrhea, followed by acute episodes of bleeding, which may sometimes be profuse.

Progesterone withdrawal bleeding - Typical bleeding from progesteronic withdrawal occurring after ovulation, in the absence of conceiving a baby. Removal of the yellow body is another example that leads to an endometrial desquamation. A similar result occurs at administrating and then stopping using synthesis progestatives. Bleeding pursuant to progesterone withdrawal occurs only if the endometrium was first stimulated by estrogens (exogenous and endogenous). If the estrogenic therapy continues while the progestative stimulus stops, bleeding occurs again because of progesterone withdrawal. Only if the estrogen level is very high, the bleeding caused by progesterone withdrawal is delayed[14]. Thus, it is foreseen a bleeding caused by progesterone withdrawal only in the presence of a previous stimulus or a current estrogen stimulus.

Progestin breakthrough bleeding is a pharmacological phenomenon which occurs in the presence a high progestatives / estrogens ration. In the absence of a sufficient estrogen stimulus, the continuous therapy with progestatives leads to an intermittent bleeding of variable duration, similar to the bleeding caused by estrogenic breakthrough because of administrating decreased doses of estrogens. This kind of bleeding is associated to the combined oral contraceptives which contain low doses of estrogens and contraceptives with only progestatives with prolonged action (Norplant, Depo-Provera)[15]. The bleeding caused by progestative breakthrough is less predictable and variable.

Etiology

For didactic purposes, the causes of AVB are classified in four categories:[16]

- ✓ Pregnancy complications.
- ✓ Pelvic causes (benign or malign)
- ✓ Dysfunctional uterine bleeding
- ✓ Extra-pelvic causes (coagulopathies, endocrinopathies, iatrogenics).

AVB has different characteristics according to the woman's age. This is why they can be classified as pre-puberty AVB, AVB during the reproductive age and post-menopause AVB.

■ **Pre-puberty AUB causes**

Any vaginal bleeding during prepuberty (<9 years old) shall be considered abnormal (except withdrawal bleeding with new born babies)[7,16]. The possible causes of AVB at this age are infections, neoplasms, trauma, foreign bodies and sexual abuse.

Vulvovaginitis is the most frequent problem in paediatric gynaecology[17]. It is usually about a bacterial or fungi infection or T. Vaginalis in rare cases. It may or may not be associated to an intra-vaginal foreign body. It shows itchiness, erythema, leucorrhoea and sometimes minimum bleeding. Vulvovaginitis is usually caused by a deficient hygiene, but occasionally by an irritation caused by soap, cosmetic products or sand.

Intra-vaginal foreign bodies are ~4% of gynaecological problems with children[18]. An intra-vaginal foreign body presents a bad smell leucorrhoea and/or minimum or intermittent red vaginal bleeding.

Trauma in the perineum area is another frequent cause of AVB with little girls. Considering the fact that at this age vulva has no subcutaneous fat, it is more fragile. Sexual abuse may cause perineum or vagina cracks. Any suspicion shall be investigated with due care and discretion.

Urethra prolapse is another cause of AVB. Usually it occurs at girls aged 6-9 and it is more frequent at white girls. The predisposing factors

are congenital abnormalities, urethral mucous excess, increase of intra-abdominal pressure and external trauma. The urethral prolapse shall present bleeding, pain and dysuria. Urethra examination shall show a painful tissue mass, colored in dark red outside the external urethral meatus.

Genital neoplasms are very rare in the pre-puberty period.

Benign tumors include cervical and vaginal polypi, vaginal adenosis and vaginal or vulva hemangiomas[19]. The latter bleed a lot especially if they are injured or undergo biopsies.

Malign tumors include botryoid sarcoma, cervical or vaginal adenocarcinoma (especially in cases of exposure in utero to DES) and ovarian tumors[19]. Ovarian tumors with granular-thecal cells, tumors of sexual cords stroma, dysgerminomas may cause uterine bleeding and early incomplete isosexual puberty because of estrogen production.

AVB causes during the reproductive age

AVB at women during the reproductive age may have obstetrical or gynecological causes. The obstetrical causes are beyond the scope of this chapter and shall be dealt with briefly.

AVB caused by pregnancy complications

A woman at reproductive age having AVB has to always be suspected of a pregnancy complication. The potential causes of AVB related to pregnancy include:

- ✓ abortion (miscarriage, incomplete abortion, abortion in course, pregnancy that stopped developing),
- ✓ ectopic pregnancy,
- ✓ molar pregnancy,
- ✓ placenta pathology (placenta praevia, placenta detachment).

This group of pathologies shall not be dealt with in this chapter.

AVB related to pelvic causes

In normal flows, the blood quantity lost during menstruation is controlled by local vascular tonus, local hemostasis and fibrinolytic activity[20]. As mentioned above, menorrhagia may be caused by a pelvic, extrapelvic or iatrogenic pathology. However, for 50% of hysterectomies for an objective menorrhagia, no pathologic cause has been identified[21].

Uterine fibroids are very often found with women with menorrhagia. It is estimated that 20-50% of women at reproductive age have uterine fibroids, but only a part of them become symptomatic[22]. Occasionally, a pediculate endocavitary myoma with a long pedicel may be externalised through the cervical channel. The uterine fibroid which deforms the uterine cavity (in the submucous or intramural area) causes menorrhagia by local inhibition of hemostasis and/or increase, ulceration or injury of endometrial surface[22]. Recent studies have shown alteration of several increase factors in the fibromatous uterus. Because a lot of these factors are involved in angiogenesis or have other effects in vascular structures, it is believed that angiogenesis alteration with the formation of abnormal vessels may be the cause for which women with uterine fibroids have menorrhagia. Angiogenic factors that may be involved in this process are the vascular endothelial growth factor (VGEF) and adrenomedullin[23].

Adenomiosis, defined as the ectopic presence of endometrial glands and of stroma in the uterine myoma, is associated with fibroids in >80% of cases and it is also considered a cause of menorrhagia[24].

Endometrial polypi are more often with women aged 40-50 and very rarely at teenage girls[25]. Their prevalence among women at the reproductive age is 20-25%. They can be unique or multiple, sessile or pedunculate. They are more often at the level of uterine back, especially at the horns level. Endometrial polyposis is a condition under which multiple polypi are to be found n the endometrial cavity. Endometrial polypi are found at more than 25-35% of women undergoing tamoxifen treatment. Endometrial polypi have a certain risk of malign transformation (2 times)[26]. Fortunately, it is about forms of decreased malignity.

Their etiology is not clear yet. The rather frequent association to endometrial hyperplasia and with the endometrial cancer may involve the unbalanced estrogenic stimulation.

In most cases they are asymptomatic, but sometimes they are associated to AVB, which may look like menorrhagia, spotting or pre-menstrual uterine bleeding. Occasionally, an endometrial polypus with a long pedicel may be externalized through the cervical channel.

Endometrial hyperplasia may also be a cause of AVB. It is very often associated with chronic anovulation, ovarian tumors secreting estrogens and non-balanced estrogenic therapy.

Endmoetrial cancer is the most frequent genital neoplasm. In general, it affects women at perimenopause and postmenopause (average age = 63 years old)[27]. Only 5% of patients with endometrial cancer are <40 years old[28]. Most of the cases develop on an endometrial hyperplasia and are the result of a continuous estrogenic stimulation (exogenous, endogenous) on a sensitive hormonal endometrium. Apart from chronic anovulation, functional ovarian tumors and non-balanced estrogenic therapy, other risk factors are obesity (by transforming the androstenedione in estrone at the level of adipose tissue), a history of infertility, nulliparity, old age, tamoxifen therapy, early menarche and tardy menopause[29,30]. AVB is the most frequent symptom in cases of endometrial cancer (80% of the patients). It may be minimum (spotting) or excessive.

Infectious causes include cervicitis, non-puerperal endometritis and pelvic inflammatory disease. They are mostly encountered with young women.

✓ **Cervicitis** in most cases is asymptomatic. In symptomatic cases, besides leucorrhoea, dyspareunia, the patient may experience spontaneous or post-coital AVB[31]. The most frequent cases are caused by C. Trachomatis. Other involved micro-organisms are N. Gonorrhoeae, viruses (HSV, Parvoviruses), C. albicans, Mycoplasma, T. Vaginalis etc.

✓ **Pelvic inflammatory disease** occurs in 40% of AVB cases, but this symptom does not dominate the clinical chart[32]. Micro-organisms which are most often involved are:

✓ **Endometritis.** It has been shown recently that non-puerperal endometritis may occur alone, not associated to salpingitis. Non-puerperal endome-

tritis may sometimes be accompanied by AVB (menorrhagia, metrorrhagia)[31,33].

Arteriovenous uterine malformations are a rare cause of AVB. These complex malformations are usually congenital. In rare cases, they can be the result of infections, traumatisms (surgeries) or cancer. These abnormalities are characterized by the communication between the artery and the adjacent vein and are discovered through brutal hemorrhage. Usually it involves the uterine body and in rare cases the cervix[34].

Cervical lesions. Almost all cervical lesions may be a cause of AVB.

✓ **Cervical polypi** (endo- or exo-cervical) are the most frequent benign cervical neoplasms. It is observed in 4% of gynaecological patients, especially at multiparous women aged 40-50[35]. Their classic symptom is inter-menstrual bleeding, especially post-coitus or after the vaginal touch.

✓ **Cervical dysplasia** may be a rare cause of AVB, especially post-coitus[36].

✓ **Cervical cancer** is mostly found at women aged 50-60, the average age being 64 years old[37]. Cervical cancer may be asymptomatic or may have AVB (inter-menstrual and post-coitus).

Coagulopathies. Normally the tissue factor (TF) and the plasminogen activator inhibitor (PAI-1) differ in the dynamics at the endometrium level, controlling thus the lost blood flow. Excessive bleeding can be noticed when the fibrinolytic activity grows because of PAI-1 quantity decrease, which leads to plasminogen activator level increase, or when there is a faulty coagulation process[38]. Coagulopathies causes menorrhagia in rare cases. The prevalence of coagulopathies at women with menorrhagia goes as high as 17%, being more frequent at teenage girls[39,40]. The Von Willebrand disease, an autosomal pathologic condition localized in chromosome 12, is the most frequently involved coagulopathy and may elude the menorrhagia differential diagnosis. Approximately 80% of women suffering from Von Willebrand disease have menorrhagia[41]. Other rarer cases of coagulopathies which alter platelets and coagulation factors (idiopathic thrombocytopenic purple, acute and chronic leukemia, lymphomas, deficit of V, VII, X, XI factors) may also cause menorrhagia. Because a lot of coagulopathies have genetic causes, they are suspected especially at teenagers suffering from AVB[42].

Iatrogenic cases the most frequently involved in AVB are use of contraception treatments only with progesterone (oral, implantable or injections), use of anticoagulants, antipsychotics, corticosteroids, hormone therapy, tamoxifen and insertion of intra-uterine devices.

Intra-uterine devices (IUD) which contain copper or the inert ones with great surface are also causes of excessive menstrual bleeding. The menorrhagia mechanism would be a combination between the local inflammatory response (misbalance between prostaglandins and tromboxan) and the activation of the fibrinolytic process by the foreign body[43,44]. The endometrium suffers a hyperaemia, congestion and degenerates, causing interstitial hemorrhage and metrorrhagia[45].

Table 1

AVB causes

Dysfunctional uterine bleeding (DUB)	Coagulopathies
Anovulatory DUB	Trombocitopenia
Ovulatory DUB	von Willebrand disease
Pregnancy-related bleeding	**Other platelet pathologies**
Abortion (miscarriage, incomplete)	Deficits of the coagulation factors
Ectopic pregnancy	Anti-coagulant therapy
Molar pregnancy	Severe hepatic failure
Bleeding from the 3rd term / postpartum	Benign anatomic lesions
Miscellaneous	**Endoemtrial hyperplasia**
Lacerations or pelvic trauma	Uterine fibroid
Intra-uterine devices (IUD)	Adenomiosis
Intra-vaginal foreign body	Endo-cervical or endometrial polypi
Hormonal drugs	Vaginal or cervical endometriosis
Hypothyroidism	Vaginal adenosis
Uterine sarcoidosis	Müllerien abnormalities associated to partial obstruction
Neoplasias	**Arteriovenous uterine malformations**
Endometrial adenocarcinoma	Uterine scars
Uterine sarcoma	Inflammatory processes
Cervex or vaginal cancer	Pelvic inflammatory disease
Gestational trophoblastic disease	Atrophic or infectious vagina

Phipps WR. Abnormal vaginal bleeding. In: Leppert PC, Peipert JF, eds. Primary Care for Women, 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2004:136

Herbal substances Duch as gingseng, gingko and soya supplements may be the cause of AVB by altering the estrogen level or the coagulation factor[46].

Substitution hormonal therapy. AVB may be a side effect of the substitution hormonal therapy (SHT), being a cause for stopping the treatment[47]. In the first year of therapy, AVB may occur frequently in cases when SHT is administrated daily as compared to cases when SHT is used cyclically[10,48].

Tamoxifen therapy. Tamoxifen is a selective estrogen receptor modulator (SERM) used as adjuvant in breast cancer treatment (cases with receptors for estrogens). Its effect is a paradox; while it reduces the estrogen action on the mammary tissue, its effect on the endometrium is to stimulate the proliferation induced by estrogens, causing endometrial hyperplasia, endometrial polypi, endometrial cancer or uterine sarcomas, all being causes of AVB[49,50]. This is why women undergoing tamoxifen treatment having AVB have a great at risk to develop endometrial cancer.

Anticoagulants. Even though the significance of anticoagulants in menorrhagia is not clear, the warfain therapy increases menstrual bleeding[51]. However, the thrombolytic therapy (administration of plasminogen tissue activator) at patients at menstruation does not seem to be associated to an increase of menstrual flow, except cases when women already suffer from menorrhagia[52,53].

Systemic diseases are a rare cause of AVB. Hepatic cirrhosis may be a cause of menorrhagia because of the estrogen low metabolism. AVB is also to be found with thyroid diseases: 23,4% of hypothyroidism cases and 21.5% of hyperthyroidism cases[54,55].

Dysfunctional uterine bleeding. Inexplicable menorrhagia referring to cases of excessive menstrual bleeding in absence of an organic pathology is known as dysfunctional uterine bleeding (DUB). Almost 50% of women with AVB have DUB[56]. From all patients with DUB, almost 50% are between 40 and 50 years old, and 25% are teenagers[57].

■ **Anuvolatory DUB** - Most cases of DUB (80-90%) have anovulatory cases because of the hypothalamus-hypophysis-ovary axe dysfunction[58].

Anovulatory DUB involves the rather extended exposure of endometrium to estrogens in the non-balanced progesterone manner. Under this stimulus, it is induced the proliferation of the endometrium, which become thick, high and instable. Sometimes, extended estrogenic stimulation causes proliferation until the occurrence of endometrial hyperplasia[58]. DUB in this endometrium may occur in two different situations. It can be caused by:

✓ **Estrogenic withdrawal.** This mechanism also explains the spotting right before the ovulation, when there is an estrogen level decrease.

✓ The so-called **estrogen breakthrough**. The endometrial test is delicate and causes spontaneous bleeding because of the high number of irregular, dilated and fragile venous capillaries. The process is neither regulated nor self-limited in time, and involves different endometrial areas at different times. Besides, the blood flow in DUB may have clots because of distressing the fibrinolytic activity.

At adult women, DUB may occur after a history of irregular menstruations started in the teenage period, or they may occur suddenly, after a long period of normal periods. Chronic anovulation started in the teenage period generally hides the polycystic ovarian syndrome (hyperandrogenic chronic anovulation)[59]. If it occurs at later times, anovulation usually is caused by other pathologies or endocrinopathies. This is where to include anovulation given by hyperprolactinaemia, physical effort, hyperthyroidism etc[60].

■ **Ovulatory DUB** differ from anovulatory DUB because the ovulation occurs regularly (periodically), and this is why anovulatory DUB is regulated (periodic) in time. The excessive flow of ovulatory DUB is caused by the abnormal metabolism of arachidonic acid in the endometrial function with excessive production of vasodilating prostaglandins as compared to the vasoconstrictive ones. The discrepancy between the vasoconstrictive effects of prostaglandin F2 (PGF2α) and the thromboxane A2 and the vasodilating effects of prostaglandin E2 (PGE2) and prostacyclin (PGI2) in the myometrial and endometrial circulation could be the cause of vascular imbalance which leads to excessive menstrual bleeding[61]. At women with menorrhagia, release of PGE2, PGF2 and PGI2 is increased in endometrium and myometrium; increased concentrations with these cytokines are noticed in the menstrual flow of such women as compared to women with normal menstruations[62]. Besides, increased concentrations of receptors for PGE2 and PGI2 are noticed in the myometrium of women with excessive menstrual bleeding[63].

The increase of vasodilating factors and their receptors may augment even more the menstrual bleeding and the vascular dysfunction by stimulating the prostaglandins synthesis (positive feedback) and by local promotion of VGEF[64].

The nitric oxide (NO) is another vasodilator and may cause excessive menstrual bleeding. The menorrhagic endometrium increases the expression of the enzyme endothelial nitric oxide synthase (eNOS) and contains higher quantities of NO as compared to normal endometrium[65].

Moreover, a significant increase of fibrinolysis in endometrium, caused by the pre-menstrual increase of tissue plasminogen activator antigen with the delayed increase of plasminogen inhibitor type 1 would be another mechanism involved in menorrhagia[66].

There are studies suggesting that an imbalance between the matrix metalproteinases (MMPs), a family of proteinases which degrade the matrix, and their physiologic inhibitors (tissue inhibitors of metalloproteinases, TIMPs) may have an important role in abnormal menstrual bleeding[67,68].

Latest studies have identified a few new local modulators involved in excessive menstrual bleeding. LEFTY-A, a new member in the transforming growth factor-β family, known at the beginning as endometrial bleeding-associated factor (EBAF), has been identified as a candidate for this local control. New data have shown that LEFTY-A may ensure an important signal in the endometrial desquamation and menstrual bleeding by MMPs expression[69].

Conclusion

Abnormal uterine bleeding is a common cause of presentation to the doctor and, with a variety of etiologic factors, often there is necessary further investigation to establish etiology if initial therapy is ineffective or if other causes are suspected. ■

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