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The Management of Dysfunctional Uterine Bleeding

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1. Introduction

Abnormal uterine bleeding is one of the most common reasons for women to seek for care. Dysfunctional uterine bleeding describes the spectrum of abnormal bleeding patterns in the absence of a medical illness or pelvic pathology. It is responsible for about half of the women with abnormal uterine bleeding in reproductive age (Ewenstein, 1996). It mainly presents as menorrhagia, hence, the term generally refers to heavy, prolonged and frequent bleeding of uterine origin which is not due to any recognisable cause (Farrell, 2004). It is a debilitating disorder both medically and socially. In addition, it is the commonest cause of iron deficiency in the developed world and of chronic illness in the developing world (Royal College of Obstetrics and Gynaecology [RCOG], 1998). The number of menses experienced by women in their lifetimes increased as a result of the reduction of family size leading to shorter periods of childbearing and lactational amenorrhoea. As a consequence, abnormal menstruation is especially a problem of the twentieth century (Farquhar & Brown, 2009). The prevalence of abnormal uterine bleeding in reproductive age group ranges from 9% to 30% (Coulter et al., 1991). One in 20 women aged 30-49 in the UK consult their General Practitioner each year with menorrhagia, and it accounts for 12% of all gynaecology referrals (Vessey et al., 1992).

Dysfunctional uterine bleeding is a diagnosis of exclusion. Menstrual history and physical examination are the mainstay of evaluation of cases. Laboratory tests, imaging studies and histologic examinations may be indicated, as well. Its management is complicated and variable according to the case. Although hysterectomy was the first option in the 1960s, medical treatment and less invasive surgical procedures have evolved recently. The aim of this chapter is to discuss the diagnostic steps and new treatment modalities of dysfunctional uterine bleeding based on a review of the literature.

2. Definition of normal and abnormal uterine bleeding

The usual duration of menstrual flow is 2-7 days with an interval of 21-35 days. The average volume of blood loss is between 30-80 ml. The traditional definitions of abnormal menstrual bleeding are:

- Menorrhagia: Menstrual bleeding with excessive flow or duration. Intervals are regular.
- Metrorrhagia: Irregular menstrual bleeding.

- Menometrorrhagia: Menstrual bleeding with excessive flow or duration. Intervals are irregular.
- Intermenstrual bleeding: Variable amounts of bleeding between normal regular menstrual periods.
- Polymenorrhea: Menstrual bleeding with intervals of less than 21 days.
- Oligomenorrhea: Menstrual bleeding with intervals of greater than 35 days.
- Heavy menstrual bleeding is both menorrhagia and menometrorrhagia, and refers to the menstrual blood loss of higher than 80 ml per month.

3. Measurement of menstrual blood loss

Although heavy menstrual bleeding is defined as menstrual blood loss higher than 80 mL, up to 50% of women complaining of heavy menstrual bleeding have an objective blood loss lower than this level (Gannon et al., 1996). The assessment of menstrual blood loss is a complicated issue. The duration of menses and the number of sanitary pads worn do not correspond to the woman's actual blood loss (Chimbira et al., 1980; Haynes et al., 1977), as the number of tampons worn reflects personal hygiene more than menstrual blood loss (Fraser et al., 1984). For this reason, many techniques have been investigated for a long time, however, none of the objective methods are practical enough for clinical use.

3.1 Direct measurement by using the alkaline hematin test

The alkaline hematin test is an objective way of assessing menstrual blood loss by extracting hemoglobin from used sanitary pads, and converting it to hematin which is then measured spectrophotometrically (Hallberg & Nilsson, 1964; Shaw et al., 1972). In many studies it was shown to be the accurate and simple method of measuring menstrual blood loss (Cheyne & Shepherd, 1970; Van Eijkeren et al., 1986; Vasilenko et al., 1988; Jannsen et al., 1995; Pendergrass et al., 1984). However, this is an impractical method that is rarely used outside of a research setting as it demands collecting the used feminine hygiene products (O'Flynn N & Britten, 2000; Chapple et al., 2001; Wyatt et al., 2001).

3.2 Indirect measurement by using Pictorial Blood Loss Assessment Charts (PBAC)

As the alkaline hematin technique was not appropriate for routine clinical use, a pictorial blood loss assessment chart was developed (Higham et al., 1990). In this method women assess the degree of staining of their used sanitary pads or tampons, and assign a numerical score. When this score was compared with the objective menstrual blood loss measurements, a sensitivity of 86% and a specificity of 89% were achieved with a PBAC score of >100 being positive (Higham et al., 1990). Recently it has been shown that a PBAC score of >150 for diagnosing menstrual blood loss >80 ml provided best precision and accuracy (Zakherah et al., 2011). It is accepted as a simple and accurate method of assessing blood loss that can be used in clinical practice (Zakherah et al., 2011; Barr et al., 1999). However, there are some studies questioning the discriminatory power as a diagnostic test (Deeny & Davis, 1994; Reid et al., 2000). As most of the studies ignored the extraneous blood loss, that is, blood not collected on feminine hygiene products, in one study participants were instructed to mark down the loss each time they changed their napkin or tampon (Wyatt et al., 2001). The authors concluded that some women also lose a significantly large amount of extraneous blood, which cannot be assessed by the alkaline hematin method.

3.3 Self-assessment measures

The symptoms that may signify heavy menstrual bleeding include (Farrell, 2004):

- an unusual increase in blood loss
- more than 7 days of bleeding
- bleeding or flooding not contained within pads or tampons (particularly if wearing the largest size)
- clots larger than 3 cm.

As the first two methods are impractical, measuring menstrual blood loss is not recommended except for research settings. Heavy menstrual bleeding is accepted as excessive menstrual loss which interferes with the woman's physical, emotional and social quality of life. Whether menstrual blood loss is a problem, is advised to be determined not by measuring blood loss but by the woman herself (National Collaborating Centre for Women's and Children's Health, 2007).

There are many studies that compare the clinical parameters with objective menstrual blood volume. While some of them were unable to show a correlation between subjective assessment of menstrual blood loss and actual blood volume (Chimbira et al., 1980), the others revealed some correlation between menstrual blood volume and duration of menses, as well as clot size, ferritin level and frequency of pad change (Snowden & Christian, 1983; Higham & Shaw, 1999; Warner et al., 2004).

4. Pathogenesis of dysfunctional uterine bleeding

4.1 Mechanism of normal menstruation

The seat of normal menstrual bleeding is located in the upper two-thirds of the endometrial mucosa. It is characterized by tissue necrosis, disruption of microvasculature, migratory leukocytes, and platelet/fibrin thrombi in microvessels (Ferenczy, 2003). Menstruation is initiated by the enzymatic degradation of the endometrium as a result of estrogen-progesterone withdrawal. In the first half of the secretory phase of the menstrual cycle, acid phosphatase, and other potent lytic enzymes are confined to lysosomes. The release of these enzymes is inhibited by progesterone which stabilizes the lysosomal membranes. During the second half of the secretory phase, due to the withdrawal of estradiol and progesterone, the enzymes are released into the cytoplasmic substance and intercellular space. In the vascular endothelium lytic-enzyme release leads to platelet deposition, release of prostaglandins, vascular thrombosis, extravasation of red blood cells, and tissue necrosis (Ferenczy, 2003). In addition, the withdrawal of progesterone up-regulates key inflammatory mediators. Among the stimulated agents the α -chemokine CXCL8 (neutrophil chemotactic factor, IL-8) and the β -chemokine CCL-2 (monocyte chemotactic peptide-1, MCP-1), as well as the inducible enzyme, COX-2 are responsible for the synthesis of prostaglandins (Jabbour et al., 2006).

Immediately before and during menstruation, there is the induction of the expression, secretion, and activation of matrix metalloproteinases which have the capacity to degrade all of the components of extracellular matrix (Salamonsen, 2003). Progesterone inhibits endometrial metalloproteinase expression, an action mediated by transforming growth factor- β (Brunnel et al., 1995). As a result of progesterone withdrawal, metalloproteinase secretion and activation are increased, followed by dissolution of the extracellular matrix (Irwin et al., 1996). The enzymatic degradation of endometrium extends to the deepest

extent of functional layer, where the rupture of basal arterioles contribute to bleeding that caused by the dissolution of the surface membrane. A cleavage plane develops at the junction of the loose, vascular, edematous stroma with the basal layer. Desquamation begins in the fundus and gradually extends towards the isthmus (Speroff & Fritz, 2005).

Immediately after separation of the functional layer of the endometrium, endometrial regeneration and vessel growth are initiated by the influence of estradiol. TGF- α , EGF, and platelet derived growth factor (PDGF) are mitogens for epithelial cells that origin from the basal layer (Chan et al., 2004). Vascular endothelial growth factor (VEGF) together with FGF and PDGF are known to stimulate angiogenesis in the endometrium (Weston & Rogers, 2000). Early in menstruation the hemostasis is provided by platelet and fibrin plug formation. However, the cessation of menstrual bleeding depends on vasoconstriction of the denuded spiral arterioles in the basal layer and possibly of the radial arteries of superficial myometrium, an action that is promoted by endothelins and prostaglandins in the menstrual endometrium (Ferenczy, 2003).

In summary, normal menstruation is a process initiated by the release of lysosomal enzymes which leads to the shedding of the functional layer of endometrium, and terminated by the restructuring of the endometrium, and the vasoconstriction of the spiral arterioles and the radial arteries.

4.2 Mechanism of dysfunctional uterine bleeding

There are two types of dysfunctional uterine bleeding; ovulatory (10%) and anovulatory (90%). In ovulatory cycles the menstrual pattern is uniform, regular and heavy but of normal duration. On the contrary, in anovulatory cycles the pattern is variable, irregular and the duration may be longer (Speroff & Fritz, 2005). Ovulatory dysfunctional uterine bleeding is the major pattern in 30s, whereas anovulatory dysfunctional uterine bleeding is more likely to occur at the extremes of reproductive years and in women who have polycystic ovarian syndrome.

In ovulatory dysfunctional uterine bleeding, generally circulating ovarian hormone levels are normal and endometrial histology shows changes identical to women without dysfunctional uterine bleeding. Therefore, the major proposed mechanism of ovulatory dysfunctional uterine bleeding is impaired hemostatic mechanisms. A shift in the ratio of endometrial vasoconstrictor (PGF_{2 α}) to vasodilator (PGE₂), and an increase in total endometrial prostaglandins have been demonstrated in ovulatory dysfunctional uterine bleeding patients (Ferenczy, 2003). Platelet and plug formation are poor due to prolonged vasodilation. In addition, a potent vasodilator parathyroid hormone- related protein and high proteolytic lysosomal enzyme activity are increased in women with ovulatory dysfunctional uterine bleeding (Casey & Mac Donald, 1996). As a result, in ovulatory dysfunctional uterine bleeding, treatment with prostaglandin synthetase inhibitors are more effective than hormonal treatment. However, there are rare hormonal conditions that cause abnormal uterine bleeding in ovulatory cycles. The most common one is midcycle bleeding due to abrupt fall in estrogen levels just before the ovulation which is called as 'estrogen withdrawal bleeding'. Another one is the luteal phase defect which is characterized by spotting before the menstruation because of insufficient progesterone secretion, and known as 'progesterone withdrawal bleeding'.

Anovulatory dysfunctional bleeding occurs as a result of endometrial response to abnormal levels of steroid hormones. As normal menstruation results from estrogen-progesterone withdrawal, hyperestrogenic or hyperprogestogenic states end with anovulatory bleeding.

While estrogen is the principal hormone which is effective on the endometrial glands and vasculature, progesterone mainly affects the stroma. In normal menstruation cycle, estrogen and progesterone stimulus is balanced leading to stable endometrial epithelium, stroma, and microvasculature. Random breakdown is avoided, and endometrial shedding occurs uniformly throughout the endometrial cavity. Prolonged hyperestrogenism unopposed by progesterone, leads to proliferative endometrium and hyperplasia with a poor stromal matrix (Ferenczy, 2003). The bleeding caused by focal stromal breakdown is called 'estrogen breakthrough bleeding'. Endometrial shedding is irregular, and not universal. There is constantly changing patchwork of small repairs instead of organized and well structured remodeling. In persistent proliferative endometrium, spiral arterioles are often suppressed and venous capillaries are dilated and increased in number (Ferenczy, 2003). Also, the sensitivity of abnormal vasculature in hyperestrogenic endometrium is suspected to be greater to vasodilation by prostaglandins than to their vasoconstrictor counterparts (Smith et al., 1982). In addition, a potent vasoconstrictor, angiotensin-2 is decreased in endometrial hyperplasia (Li & Ahmed, 1996). Anovulatory dysfunctional uterine bleeding is initiated by an increase in vascular density with abnormal structural abnormalities leading to rupture or degradation of the microvascular system (Ferenczy, 2003). As tissue loss involves the superficial endometrium only focally, vasoconstriction of basal and radial arteries does not occur and this causes abnormalities in hemostasis. This is the mechanism of bleeding in chronic anovulation. The amount and duration of bleeding can vary according to the amount and duration of unopposed estrogen exposure (Speroff & Fritz, 2005). Low level chronic estrogen stimulation typically results in intermittent spotting, whereas sustained high level estrogen exposure commonly results in acute episodes of profuse bleeding. Anovulatory dysfunctional uterine bleeding due to hyperprogestogenism, known as 'progesterone breakthrough bleeding' manifests in continuous progestin or low-dose oral contraceptive users. Endometrial histology is chiefly influenced by progesterone and ranges from severe atrophy with or without stromal decidualization to mixed proliferative/secretory patterns according to the duration and amount of progesterone exposure (Ferenczy, 2003). As the progesterone/estrogen ratio increases, secretory-type atrophy becomes prominent with a gland-stroma ratio largely in favour of the stroma. Histologically there is a decrease in the number and tortuosity of spiral arterioles and many of the subepithelial microvessels are dilated and lined by a very thin endothelial cell layer (Hickey et al., 2000). Since the basement membrane is poorly formed or absent, and there are gaps between endothelial cells, pools of extravasated red blood cells are often seen (Hourihan et al., 1986). These structural alterations and vascular fragility lead to breakdown and bleeding.

5. Differential diagnosis

Dysfunctional uterine bleeding is a diagnosis of exclusion. In half of women with menorrhagia there is no organic cause (Pitkin, 2007). In the first place, the aim is to exclude the structural and histological abnormalities and dysfunctional uterine bleeding is diagnosed when all of the organic causes are ruled out. Table 1 shows the list of etiologic factors leading to abnormal uterine bleeding.

Pregnancy is the most important etiologic factor that should be excluded primarily. Ectopic pregnancy, abortion, placental abnormalities and gestational trophoblastic diseases are the major causes of abnormal uterine bleeding.

Structural abnormalities of uterus such as leiomyoma, polyp or endometrial hyperplasia manifest as heavy menstrual bleeding. In addition, abnormal uterine bleeding is the most frequent symptom of women with cervical and endometrial malignancies. Adenomyosis is characterized with heavy painful bleeding with dyspareunia. Furthermore, women with chronic endometritis and cervicitis can experience irregular bleeding. A woman who has multiple partners, and complains for the symptoms of heavy menstrual bleeding and dysmenorrhea should be evaluated for pelvic inflammatory disease (PID).

Endocrine abnormalities account for an important proportion of abnormal uterine bleeding. Both hypothyroidism and hyperthyroidism are associated with abnormal uterine bleeding. Hyperprolactinemia and diabetes mellitus are associated with anovulation. Polycystic ovary syndrome (PCOS) is the most common cause of anovulation with a prevalence of 5% to 8% (Azziz et al., 2004). The diagnostic criteria for PCOS include at least two of the following (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004):

1. Menstrual irregularity due to oligo- or anovulation.
2. Signs of androgen excess, either on physical examination (eg, hirsutism, acne) or laboratory testing (eg, elevated testosterone)
3. Evidence of polycystic ovaries by ultrasound.

Conditions that should be ruled out include congenital adrenal hyperplasia (manifested by an elevated early morning 17-hydroxyprogesterone), androgen-secreting tumors (manifested by a serum testosterone >200 ng/dl or dehydroepiandrosterone sulfate >800 µg/dl), and hyperprolactinemia (Ely et al., 2006).

Coagulopathies and anticoagulant drug intake should be taken into account during the evaluation of heavy menstrual bleeding. Von Willebrand disease is a common cause of pubertal menorrhagia. Besides, a systemic review of 11 studies from Europe and the USA showed an overall prevalence of 13% in reproductive years (Shankar et al., 2004). Thrombocytopenia and leukemia also may cause abnormal uterine bleeding.

6. Diagnostic evaluation

Detailed menstrual history can provide most of the information needed to differentiate anovulatory bleeding from the other causes of abnormal uterine bleeding. Intermenstrual intervals, volume and duration of bleeding, previous menstrual patterns, associated symptoms and temporal associations, such as postcoital or postpartum, should be asked. Medications, especially exogenous hormones and systemic diseases, such as renal or liver dysfunction, should be considered during the evaluation. Physical examination is necessary to determine the origin of bleeding and to exclude vaginal and cervical pathologies. Vaginal discharge, uterus size and contour, and uterine tenderness should be noted.

Imaging studies may be needed for differential diagnosis. Transvaginal ultrasound is the first-line diagnostic tool for identifying structural abnormalities in dysfunctional uterine bleeding (National Collaborating Centre for Women's and Children's Health, 2007). It is performed for the diagnosis of fibroid, endometrial polyp, intrauterine and ectopic pregnancy. Saline infusion sonography is a noninvasive imaging study which has a high sensitivity in diagnosis of endometrial polyp and submucous myom. Hysteroscopy should be used as a diagnostic tool only when ultrasound results are inconclusive, for example in order to determine the exact location of a fibroid or the exact nature of the abnormality (National Collaborating Centre for Women's and Children's Health, 2007). In addition, CT and MRI can be used for the evaluation of pelvic masses and malignancies.

Pregnancy-related bleeding	Ectopic pregnancy Abortion Gestational trophoblastic diseases Placenta previa Ablatio placenta
Anatomic causes	Fibroids Endometrial and endocervical polyps Endometrial hyperplasia Adenomyosis
Infectious causes	Endometritis Cervicitis
Neoplasia	Endometrial cancer Cervical cancer
Endocrine causes	Hypothyroidism and hyperthyroidism Hyperprolactinemia Adrenal gland dysfunction Hypothalamic and pituitary dysfunction Estrogen producing tumors Polycytic ovary syndrome Diabetes mellitus
Hematologic causes	Coagulopathies: von Willebrand disease Thrombocytopenia Leukemia
Exogenous hormones and the other iatrogenic causes	Contraceptive hormones Intrauterine devices Anticoagulants Corticosteroids Antipsychotics
Systemic illnesses	Chronic renal failure Chronic liver diseases Obesity Anorexia Depression Alcoholism
Dysfunctional uterine bleeding	Ovulatory Anovulatory

Table 1. Causes of abnormal uterine bleeding

Complete blood count should be performed in all cases to determine the level of anemia and to estimate the amount of bleeding. β -hCG is necessary in order to exclude pregnancy. Women with family history or additional bleeding symptoms, adolescents with acute bleeding, and those who have abnormal bleeding since menarche should be investigated for hematologic diseases with platelet count, prothrombin time and partial thromboplastin

time. Also in chronic liver disease and alcoholism coagulation parameters should be considered. Thyroid stimulating hormone (TSH) should be screened early in the evaluation (Ely et al., 2006). Prolactin level is evaluated in the presence of galactorrhea or oligomenorrhea. Follicle stimulating hormone (FSH) and estradiol levels may be assessed in perimenopausal women. FSH, LH, testosterone, 17-OH progesterone and DHEAS are performed if polycystic ovary syndrome is suspected. Liver and renal function tests are not recommended during the first evaluation, but should be assessed according to the medical history of patient.

Pap-smear should be a part of clinical examination. Endometrial sampling is mandatory in the evaluation of women older than 35 years of age (ACOG, 2001). Also, it should be performed to the younger women with the history of chronic anovulation in order to exclude endometrial carcinoma and hyperplasia. In addition, any cervical mass should be investigated with a biopsy. Table 2 summarizes the diagnostic evaluation of abnormal uterine bleeding.

History	Intermenstrual interval Volume of bleeding (number of sanitary pads or tampons per day) Duration of bleeding Associated symptoms (dysmenorrhea, hirsutism, galactorrhea, pelvic pain) Temporal associations (postcoital, postpartum, postpill, weight change) Systemic illnesses Medications
Physical examination	Origin of bleeding Structural abnormalities Malignancies Infections
Imaging studies	Transvaginal ultrasonography Saline infusion sonography Hysteroscopy CT and MRI
Laboratory tests	Complete blood count B-hCG Thyroid function tests Prolactin FSH, LH, estradiol Testosterone, 17-OH- P, DHEAS PT, APTT Renal and liver function tests
Histologic examination	Pap-smear Endometrial sampling Cervical biopsy

Table 2. Summary of diagnostic evaluation of abnormal uterine bleeding.

7. Treatment of dysfunctional uterine bleeding

Hysterectomy was the most commonly performed treatment for menorrhagia in the past. 80% of the women treated for menorrhagia had no uterine abnormality and over a third of the women undergoing hysterectomies for heavy menstrual bleeding had a normal uterus removed (Gath et al., 1982; Clarke et al., 1995). Today, in spite of the high patient satisfaction rate of hysterectomy, medical therapies or less invasive surgical procedures are preferred instead of hysterectomy in order to avoid its serious complications. Need for contraception, contraindications for treatment and patient choices are the factors influencing the selection of therapy. Iron supplements should be prescribed in addition to any kind of therapy. Table 3 shows a list of treatment modalities of dysfunctional uterine bleeding.

1. Medical treatment
I. Hormonal medications
a. Progestogens
b. Estrogen
c. Oral contraceptives
d. Danazol
e. GnRH analogues
II. Non-hormonal medications
a. Nonsteroidal anti-inflammatory drugs (NSAIDs)
b. Tranexamic acid
III. Levonorgestrel-releasing intrauterine system
2. Surgical treatment
I. Hysterectomy
II. Endometrial resection and ablation
a. First generation techniques
b. Second generation techniques

Table 3. Treatment of dysfunctional uterine bleeding

7.1 Medical management

Medical therapy is the first-line therapy in dysfunctional uterine bleeding. Cyclic progestogens are the most common prescribed drugs for dysfunctional uterine bleeding. Combined oral contraceptives and levonorgestrel intrauterine system provide additional contraceptive effect. Nonsteroidal anti-inflammatory drugs and tranexamic acid are medications that offer a simple therapy to be taken only during menses. Although danazol and gonadotropin-releasing hormone analogues are highly effective, they are not used frequently due to their side effects and high costs. They can be used for a short period in women waiting for surgery. Effective use of medical therapies reduces the number of

surgical procedures. A combination of two or more of these agents may be required to successfully control the abnormal uterine bleeding.

7.1.1 Hormonal medications

7.1.1.1 Progestogens

Progestogens are the mainstay of the treatment of anovulatory bleeding. Progestogens account for 55% of the total prescribed drugs for menorrhagia and norethisterone is the most commonly prescribed progestogen in the UK (Coulter et al., 1995). In anovulatory women with menorrhagia, progestin treatment control the bleeding coordinating regular uterine shedding. Progestogens have an anti-mitotic effect on the endometrium, because they stimulate 17β -hydroxysteroid dehydrogenase and sulfotransferase activity, the enzymes that convert estradiol to estrone sulfate (Gurpide et al., 1976). They also inhibit estrogen's induction of its own receptor and suppress estrogen-mediated transcription of oncogens (Kirkland et al., 1992). As a consequence of these effects, continuous progestogens induce endometrial atrophy, and prevent estrogen-stimulated endometrial proliferation (Hickey et al., 2007).

Progestogens are administered in luteal phase from day 15 or 19 to day 26 in anovulatory cycles. In a comparison of 5 mg norethisteron three times daily with 10 mg medroxyprogesterone acetate three times daily for 14 days, no obvious difference was observed between these two progestogens (Fraser et al., 1990). Recently an increase in the duration and dosage has been investigated in patients with ovulatory dysfunctional uterine bleeding, and administration of oral progestogens from day 5 to day 26 of the cycle produced a significant reduction in bleeding (Lethaby et al., 2008). The studies which compared luteal progestogens with the other medical therapies have revealed that oral progestogens were less effective in reducing menstrual blood loss when compared with tranexamic acid, danazol and progesterone-releasing intrauterine system, whereas there was no significant difference when compared with nonsteroidal anti-inflammatory drugs (Lethaby et al., 2008). In addition, it is shown that progestogens were less effective than levonorgestrel-releasing intrauterine system, but had a lower incidence of intermenstrual bleeding and breast tenderness (Irvine et al., 1998).

For emergency suppression of heavy menstrual bleeding norethisteron at least 15 mg per day, or medroxyprogesterone acetate at least 30 mg per day is prescribed until bleeding ceases and a maintenance dose should be continued until the woman has 3-4 weeks free of bleeding (Farrell, 2004).

Fatigue, mood changes, weight gain, nausea, bloating, edema, headache, depression, loss of libido, irregular bleeding and atherogenic changes in the lipid profile can be associated with the prolonged use of high-dose progestogens (Lethaby et al., 2008).

7.1.1.2 Estrogen

Estrogen is mostly administered in acute and heavy bleeding when the endometrium is grossly denuded. Intravenous administration of 25 mg conjugated equine estrogens every 4 hours until bleeding subsides or for 24 hours is very effective in reducing heavy bleeding (DeVore et al, 1982). In less severe cases high dose oral estrogen (1.25 mg conjugated estrogens or 2.0 mg micronized estradiol every 4-6 hours for 24 hours) can control bleeding (Speroff & Fritz, 2005). After the bleeding lightens the dose should be tapered to once a day for another 7-10 days. If the bleeding is lighter single daily dose of 1.25 mg conjugated

estrogen or 2 mg micronized estradiol for 7-10 days is enough to control bleeding (Speroff & Fritz, 2005). After the initial estrogen therapy a progestogen should be added and continued until the 21st day of therapy in order to generate a withdrawal bleeding.

Due to chronic low level estrogen stimulation, the endometrium becomes very thin and denuded resulting in intermittent spotting and staining. In these cases, progestin therapy cannot be used because progesterone affect only the endometrium stimulated by estrogen previously. Thus, estrogen therapy is preferred in women with a thin endometrium assessed by transvaginal ultrasound. Similarly, in progesterone breakthrough bleeding owing to depot forms of progestin therapy or low dose estrogen-progestin contraceptives, 1.25 mg oral conjugated estrogen or 2 mg oral micronized estradiol is added to therapy for 7-10 days.

7.1.1.3 Oral contraceptives

Oral contraceptives reduce the amount of bleeding by 40% in dysfunctional uterine bleeding (Fraser & McCarron, 1991). When taken in a cyclical fashion it induces regular shedding of a thinner endometrium and inhibits ovulation. Good cycle control together with the provision of contraception makes it more acceptable long term therapy for menorrhagia (Farquer & Brown, 2009). It is also a good option in cases of heavy bleeding when the endometrium thickness is uniformly increased. Although it contains both estrogen and progestin, the main action is performed by the progestin (Speroff & Fritz, 2005). One common oral contraceptive regimen for severe acute bleeding is one pill four times daily for four days followed by three times daily for three days, followed by twice daily for two days, followed by once daily for three weeks. Then after a break of one week, oral contraceptive is taken on a regular basis using three weeks on and one week off, for at least three months (Ely et al., 2006).

In anovulatory cycles in order to prevent the recurrence of heavy bleeding, it should be administered daily throughout following cycles as a maintenance therapy. If there is any contraindication for oral contraceptive use, cyclic progestogens are chosen instead, however, they do not avoid pregnancy. The contraindications of oral contraceptives are; previous thromboembolic event or stroke, history of estrogen-dependent tumor, active liver disease, pregnancy, hypertriglyceridemia and smoking > 15 cigarettes per day of women older than 35 years (Ely et al., 2006). In addition, long-term use of oral contraceptives are not preferred by many women as a therapy of menorrhagia.

7.1.1.4 Danazol

Danazol is a drug chemically derived from testosterone. It reduces the menstrual blood loss because it inhibits ovulation, reduces estrogen level and causes endometrial atrophy (Beaumont et al., 2007). The standard dose is 200 mg/day, although the studies did not show any difference in effectiveness or frequency of adverse effects when compared with a lower dose of 100 mg/day (Chimbira et al., 1980) and a reducing dose regimen (Higham & Shaw, 1993). Danazol is found to be more effective than progestogens, nonsteroidal anti-inflammatory drugs and oral contraceptive pills, although it caused more severe side effects in comparison to progestogens and nonsteroidal anti-inflammatory drugs (Beaumont et al., 2007). When the treatment is discontinued, the effects of danazol persist for two to three cycles before blood loss returns to pre-treatment levels (Chimbira et al., 1979).

As it is derived from testosterone, it has androgenic effects which may result in acne, seborrhoea, hirsutism, and hoarseness. Also, it may cause weight gain, nausea, tiredness, irritability, musculoskeletal pains, hot flushes, breast atrophy and benign hepatic adenomas

in case of its prolonged administration (Beaumont et al., 2007). Moreover, an additional contraceptive is required because of its teratogenic effect.

7.1.1.5 GnRH analogues

They have a limited role in the treatment of dysfunctional uterine bleeding, but can be used as pretreatment before endometrial ablation. The success of hysteroscopic procedure depends on complete endometrial destruction. The radius of a standard electrosurgical loop used for endometrial resection is about four mm and the dept of tissue destruction with Nd:YAG laser or a roller ball electrode is four to six mm (Goldrath, 1990; Duffy, 1992). The success rate increases if surgery is undertaken in the immediate post-menstrual phase or following the administration of hormonal agents which induce endometrial thinning or atrophy (Sowter, 2002). GnRH analogues are the most common evaluated drugs in the studies. Danazol is also used for this purpose, but less frequently. The use of goserelin acetate (GnRH analogue) before hysteroscope shortens operating time, and reduces intra-operative distension medium absorption (Donnez, 1997). Also it provides an ease of surgery and a higher rate of post-operative amenorrhea after 12 months of surgery (Vilos, 1996; Sowter, 2002). However, in MISTLETOE study in over 10000 endometrial resections, the use of endometrial thinning agents was not associated with any reductions in complication rates (Overton, 1997). Also patient satisfaction is highly irrespective of the use of GnRH-analogues (Sowter, 2002).

7.1.2 Non-hormonal medications

7.1.2.1 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The endometrium of women with menorrhagia has been found to have higher levels of PGE₂ and F_{2a} when compared with normal menses (Willman et al., 1976). Also, the ratio of prostaglandin E₂ to F₂, and the ratio of prostaglandin I₂ to thromboxane are elevated resulting in deranged hemostasis (Smith et al., 1981; Makarainen & Ylikorkala, 1986). Nonsteroidal anti-inflammatory drugs inhibiting prostaglandin synthesis by the enzyme cyclo-oxygenase, reduce the menstrual blood loss approximately 20-40% and to a greater extent in those with excessive bleeding (Hall et al., 1987; Shaw et al, 1994).

Mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin and acetylsalicylic acid are used for the treatment of heavy menstrual bleeding. There are no differences in clinical efficiency between individual prostaglandin inhibitors. However, there are some women who seem to respond well to one agent but less well to another (Lethaby et al, 2007). As a group, Nonsteroidal anti-inflammatory drugs are less effective than tranexamic acid, danazol and levonorgestrel releasing intrauterine system, whereas there was no significant difference in efficacy in comparison with oral luteal progestogen, ethamsylate, and oral contraceptive pill (Lethaby et al, 2007).

The advantage of this treatment is the low incidence of side effects as the drug is used only during the bleeding period. Also, it provides relief from dysmenorrhea which is often related to heavy menstrual bleeding. Side effects of nonsteroidal anti-inflammatory drugs include headache and gastrointestinal symptoms such as nausea, vomiting, diarrhea and dyspepsia. Contraindications are gastrointestinal disorders such as ulcers, intolerance to nonsteroidal anti-inflammatory drugs, or asthma (Farrell, 2004).

7.1.2.2 Tranexamic acid

Tranexamic acid is an anti-fibrinolytic. Plasminogen activators, the enzymes that cause fibrinolysis, are found in higher levels in the endometrium of women with heavy menstrual

bleeding than those with normal menstrual bleeding (Gleeson, 1994). Thus, anti-fibrinolytic drugs are used in the treatment of menorrhagia. Tranexamic acid is more effective than either nonsteroidal anti-inflammatory drugs and oral luteal phase progestogens (Lethaby et al., 2000). Also the studies comparing tranexamic acid with oral progestogens for changes in quality of life showed that the former is more effective in improving flooding and leakage problems and sex life (Lethaby et al., 2000). It is prescribed on only the heavy days of the menses, with a dose of 1 g 3-4 times daily (Farrell, 2004). However, in a study a dose of 2 g/day is shown to be more effective than 10 mg twice-daily medroxyprogesterone acetate (Kriplani et al., 2006). Tranexamic acid may be considered as a first-line treatment for ovulatory dysfunctional uterine bleeding, especially for patients in whom hormonal treatment is either not recommended or not wanted (National Health Committee New Zealand, 1998; Wellington & Wagstaff, 2003).

Although it is known to reduce the menstrual blood loss by 50% (Higham & Shaw, 1991), tranexamic acid has not been used widely because of its possible side effects. Since it is an anti-fibrinolytic drug, it is suggested to be associated with thrombogenic disease. However, the studies were unable to show increased rates of thrombogenic disease with tranexamic acid administration in comparison to placebo (Rybo, 1991). The recent studies proved that tranexamic acid is an effective and safe form of medical therapy in women with menorrhagia without any serious adverse effects (Kriplani et al., 2006; Srinil & Jaisamrarn, 2005; Lukes et al., 2010).

Eythamsylate is a drug used rarely in heavy menstrual bleeding. Even though it is not a true anti-fibrinolytic, it affects in a similar mechanism. It reduces capillary bleeding by correcting abnormal platelet function (Lethaby et al., 2000).

7.1.3 Levonorgestrel-releasing intrauterine system

Levonorgestrel-releasing intrauterine system has been developed primarily as a contraceptive device which does not suppress ovulation. It consists of a T-shaped intrauterine device sheathed with a reservoir of levonorgestrel that is released at the rate of 20 µg daily. This low level of hormone minimizes the systemic progestogenic effects, and patients are more likely to continue with this therapy than with cyclical progestogen therapy (Irvine et al., 1998). It prevents the endometrial proliferation and reduces both the duration and amount of bleeding (Silverberg et al., 1986). It is accepted as an alternative to surgery with a reduction in menstrual blood loss up to 90% (Milsom, 2007; Andersson et al., 1994). It is more effective than the other medical therapies (Lethaby et al., 2005). A study comparing the efficacy of levonorgestrel-releasing intrauterine system to oral contraceptives, showed a more pronounced clinical benefit with levonorgestrel-releasing intrauterine system therapy in terms of decreasing menstrual blood loss score after 6 months of treatment (Endricat et al., 2009). This is a more acceptable treatment than norethisterone taken for 21 days of the cycle for the women, and they are more satisfied with this therapy (Irvine et al., 1998). Levonorgestrel-releasing intrauterine system treatment has been compared to either transcervical resection of the endometrium or balloon ablation (Lethaby et al., 2005). Although there was a higher rate of successful treatment in those undergoing transcervical resection or balloon ablation in four trials, rates of satisfaction and change in quality of life were similar, but women with levonorgestrel-releasing intrauterine system had a greater incidence of progestogenic side effects within a year. In two studies, 82% and 64% of women on a waiting list of hysterectomy cancelled their surgery after using levonorgestrel-releasing intrauterine system (Barrington & Bowen-Simpkins, 1997;

Lähteenmaki et al., 1998). Another study comparing levonorgestrel-releasing intrauterine system with hysterectomy, revealed that there was no significant difference in quality of life scores, but the former treatment had lower costs than the latter (Hurskainen et al., 2001).

Side effects are ectopic pregnancy, expulsion of device and progestogenic effects such as bloating, weight gain and breast tenderness (Lethaby et al., 2005). Irregular bleeding and spotting are temporary and generally seen in the first three months. However, after 12 months of therapy, there is a major reduction in blood loss up to 97%, thus, most of the women have a light bleeding and 20% of them have amenorrhea. As amenorrhea and altered bleeding patterns may be undesirable to some women (Chi, 1993), counselling before insertion is very important. Relief from dysmenorrhea and reduced incidence of pelvic inflammatory disease due to the thickening of the utero-cervical mucus are additional advantages of levonorgestrel-releasing intrauterine system (Andersson et al., 1994). An increased incidence of transient ovarian cysts has been reported with levonorgestrel-releasing intrauterine system use (Brache et al., 2002).

Due to its high efficacy in reducing menstrual blood loss without disturbing fertility, this method offers a first-line therapy for dysfunctional uterine bleeding in women of any reproductive age who wish a contraceptive method and accept hormonal drug use.

7.2 Surgical treatment

Surgical procedures are performed when medical therapy fails or there is an associated symptom such as pain. Also, some of the patients prefer surgery instead of long-term use of medications. These techniques should not be performed to women who wish to have further pregnancies. These procedures include hysterectomy, endometrial resection and ablation. Dilatation and curettage is no longer accepted as a therapeutic treatment (National Collaborating Centre for Women's and Children's Health, 2007).

All of the surgical procedures are much more successful than oral medications (Cooper et al., 1997, Kupperman et al., 2004). In addition, the rate of satisfaction and overall quality of life were higher in women who had surgery (Marjoribanks et al., 2006). Also, when conservative surgery (endometrial resection and ablation) was compared with levonoregretrel-releasing intrauterine system, conservative surgery was more effective in controlling bleeding at one year, however, patients satisfaction rates and quality of life were not different between these two groups (Marjoribanks et al., 2006).

7.2.1 Hysterectomy

Hysterectomy has been traditionally regarded as the definitive surgical treatment for menorrhagia and menstrual disorders have been the leading indication of hysterectomy (Farquhar & Steiner, 2002). There are three types of hysterectomy; laparoscopically assisted, vaginal and abdominal. The laparoscopically assisted hysterectomy by a competent and experienced operator is the most appropriate technique with less morbidity (Farrell, 2004). Hysterectomy is associated with 100% success in treating heavy menstrual bleeding and a high patient satisfaction up to 95% (Marjoribanks et al., 2006), but have complications and rarely operative mortality. For this reason, hysterectomy should not be as a fist-line treatment (National Callobarating Centre for Women's and Children's Health, 2007). It should be only considered when other treatment options have failed or there is a wish for amenorrhea, as well as when the woman has no longer wishes to retain her uterus and fertility.

7.2.2 Endometrial resection and ablation

These procedures involve the destruction of the full thickness of endometrium together with the superficial myometrium including the deep basal glands (Lethaby et al., 2009). First generation techniques utilize hysteroscope, and require general or regional anesthesia, surgical skill and hospital admission (Marjoribanks et al., 2006). By contrast, second generation techniques do not use hysteroscope, do not require surgical skill and can be done as one day or outpatient surgery with a local anaesthetic (Jack et al., 2005). Compared to hysterectomy, endometrial destruction techniques have a shorter operation time and hospital stay, quicker recovery, and fewer postoperative complications (Marjoribanks et al., 2006). On the other hand, hysterectomy is more successful in improvement in heavy menstrual bleeding and higher satisfaction rates compared to endometrial ablation (Lethaby et al., 1999). Repeat surgery due to the failure of the initial treatment, was more likely after endometrial ablation than hysterectomy (3 to 18% versus 1%) (Lethaby et al., 1999). The initial cost of endometrial destruction is significantly lower than hysterectomy, but, since re-treatment is often necessary, the cost difference narrows over time (Lethaby et al., 1999). Although hysterectomy is much more successful than these procedures, there is now evidence that it is used less frequently in clinical practice (Reid, 2007).

Endometrial resection and ablation should be offered to the women who do not wish further childbearing. However, unlike hysterectomy, pregnancy after endometrial ablation is possible although it is not often (Kdous et al., 2008). Premenopausal women should have a post-operative contraception method, because serious complications such as spontaneous abortion, prematurity, uterine rupture, and placenta adhesion complications in the pregnancies after endometrial ablation have been reported (Laberge, 2008; Kuzel et al., 2010; Yin, 2010).

7.2.2.1 First generation techniques

The first effective ablation of the endometrium under hysteroscopic vision for the treatment of dysfunctional uterine bleeding was performed using laser photovapourisation (Goldrath et al., 1981). A few years later rollerball ablation with electrosurgical equipment (Lin et al., 1988; Vaincaillie, 1989) and transcervical resection of the endometrium (TCRE) with resectoscope (DeCherney et al., 1983, 1987) began to be performed. These procedures have the advantage of diagnosis polyps as they directly visualize the endometrial cavity. Overall complication rate has been reported as 4.4% and ablation either by laser or rollerball were safer than endometrial resection (Overton et al., 1997). The risk of immediate hemorrhage was three times greater and the risk of uterine perforation was four times greater with resection than ablation. In a multicentre study, of the 1866 women followed up for at least one year after laser endometrial ablation, 56% developed complete amenorrhea, 38% reported continuing but satisfactorily reduced menstruation, and 7% patients failed to improve with the first treatment. Overall, 93% had a satisfactory response to laser ablation and only 1.8% required subsequent hysterectomy (Erian, 1994). It is reported that amenorrhea is best attained when complete preoperative atrophy is achieved, by either depot goserelin (GnRH analogue) or danazol, although goserelin appears to be more effective and better tolerated than danazol (Alford & Hopkins, 1996; Garry et al., 1996; Fraser et al., 1996).

7.2.2.2 Second generation techniques

Second generation procedures except hydrothermal ablation and endometrial laser intrauterine thermal therapy are performed without direct visualization through a

hysteroscope (Lethaby et al., 2009). These procedures include cryoablation (Pitroff et al., 1993), hot saline solution irrigation (Baggish et al., 1995), diode laser hyperthermy (heating) (Donnez et al., 1996), microwave ablation (Sharp et al., 1995), a heated balloon system (Singer et al., 1994) and photodynamic therapy (intrauterine light delivery) (Fehr et al., 1995). A meta-analysis of 21 studies with 3395 premenopausal women showed that when these procedures were compared with first generation techniques, there were no significant difference in reducing menstrual blood loss and the rate of re-intervention and satisfaction (Lethaby et al., 2009). Second generation techniques were easier to perform with shorter surgery times using local anaesthesia. While intra and postoperative complications such as fluid overload, perforation, cervical lacerations and hematometra, were more common with first generation, other types of complications, nausea, vomiting, and uterine cramping and pain, were more common with second generation techniques (Lethaby et al., 2009). These methods are complex which have the potential of mechanical breakdown. Considerable experience in intrauterine cavity assessment and manipulation is required for safely use of these devices.

8. Conclusion

Dysfunctional uterine bleeding is a common, debilitating condition. There is no practical method of measuring the amount of bleeding, and the assessment of menstrual blood loss is based on the complains of woman. While anovulatory dysfunctional uterine bleeding is commonly seen at both ends of the reproductive years because of hypothalamic immaturity and perimenopausal changes, ovulatory type is majorly seen in the 30s and its mechanism is less well understood. Physical examination and diagnostic tests are performed with the aim of exclusion of pregnancy and organic diseases. There are many different types of therapy, and the selection is mainly depends on the wishes and conditions of the patient. The treatment of anovulatory dysfunctional uterine bleeding is simple as it is usually treated effectively by replacing the missing component, progesterone, in the luteal phase. However, the treatment of ovulatory dysfunctional uterine bleeding is more complex. Nonsteroidal anti-inflammatory drugs or tranexamic acid is the current first-line treatment for those that wish to conceive or do not accept hormonal treatment. Also, they are preferred while investigations and definite treatment are being organized. Combined oral contraceptives, progestogens from days 5 to 26 of the menstrual cycle, or levonorgestrel-releasing intrauterine system are acceptable for the other women, although the latter seems to be best option when long term use is anticipated. On the other hand, danazol and GnRH analogues are not used routinely. Surgical treatment is considered when bleeding is a severe impact on a woman's quality of life and there is no wish of further conception. Although hysterectomy was the most commonly performed procedure in the past, the recently evolved conservative surgeries are preferred today. Second generation endometrial ablation procedures are going to become more prevalent in the future. However, more studies with longer duration of follow-up are needed to clarify the long-term benefits.

9. References

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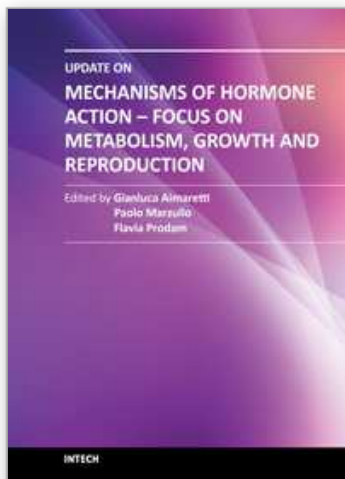
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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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