Articles

Dysfunctional Uterine Bleeding

BERTHA H. CHEN; MD, *and* LINDA C. GIUDICE, MD, PhD, *Stanford, California*

Abnormal uterine bleeding is a common, debilitating condition. Dysfunctional uterine bleeding (DUB) is the diagnosis given to women with abnormal uterine bleeding in whom no clear etiology can be identified. DUB has been observed in both ovulatory and anovulatory cycles. Medical treatments include nonsteroidal anti-inflammatory drugs, oral contraceptive pills, progestins, danazol (a synthetic androgen), GnRH agonists, and antifibrinolytic drugs. The drawback to medical therapy, in addition to side effects, is that the benefit lasts only while the patient takes the medication. Surgical options have concentrated mainly on endometrial ablation and hysterectomy, and it is unclear whether one is superior to the other in terms of long-term outcome and patient satisfaction. Newer and less invasive ablation techniques, such as thermal balloon ablation, offer more treatment alternatives.

(Chen BH, Giudice LC. Dysfunctional uterine bleeding. West J Med 1998; 169:280–284)

Menorrhagia and intermenstrual bleeding, respectively, account for 31 and 9 per 1000 consultations of women annually (Morbidity Statistics in General Practice, 1981–1982). Although age of menopause has remained the same over this century, the magnitude of menstrual disorders has increased, likely because of shortened breast-feeding intervals, fewer pregnancies per woman, higher frequency of permanent sterilization, and later age of conception. A woman can expect roughly 400 menstrual cycles during her reproductive lifespan, and it is estimated that up to 20% of women will have excessive menstrual blood loss.[1]

Heavy menstrual bleeding or menorrhagia may occur during pregnancy or may be due to organic disease such as myoma, polyps, infection, carcinoma, or systemic illness. The diagnosis of dysfunctional uterine bleeding (DUB) is given to the group of patients in whom there is no definitive underlying lesion. DUB can occur at any time between menarche and menopause in ovulatory or anovulatory cycles. The latter tends to be more common at puberty and after age 40, times at which irregular ovulation is often encountered.

Abnormal Menstrual Loss

According to the strict definition, menorrhagia is menstrual bleeding longer than 7 days or in an amount exceeding 80 ml from normal secretory endometrium after normal ovulation.[2] Only 40% of women with the complaint of excessive menstrual loss have it confirmed by objective methods, however, and the amount of menstrual blood loss is not proportional to the duration of bleeding or the number of sanitary pads or tampons used during menses.[3] Measurements of hemoglobin extracted from sanitary pads using the alkaline hematin method were obtained by Hallberg et al.,[1] who demonstrated that the mean menstrual blood loss between ages 15 and 50 was 35 ml. The upper limit for diagnosis of menorrhagia was set at 80 ml because two-thirds of women (95th percentile) show evidence of iron-deficiency anemia with that degree of bleeding.[4]

The alkaline hematin method gives an accurate and objective measurement of blood loss, but it is time-consuming and impractical for widespread clinical use. A detailed clinical history, with specific questions designed to investigate the use of sanitary protection and degree of social embarrassment, may be more helpful. Most women with an objective diagnosis of menorrhagia use super or maxi pads, often two at a time, or a super pad with a tampon, and change every 0.5 to 2 hours. The passage of blood clots, flooding, or socially embarrassing bleeding are also reliable indicators of menorrhagia. Fraser[5] asked these types of questions of 50 women complaining of menorrhagia and found that physicians' estimates correlated with objective blood loss measurements overall. A third of the women with objective menorrhagia, however, perceived their menses as light or moderate. Currently, the only available clinical objective evidence of excessive bleeding is laboratory diagnosis of iron-deficiency anemia. Abnormal bleeding that presents as prolonged or decreased bleeding at irregular intervals (usually less than every 21 days) can be verified with a bleeding calendar.

From the Department of Gynecology and Obstetrics/Division of Gynecology, Stanford University, Stanford, California.
Reprint requests to Bertha H. Chen, MD, 300 Pasteur Drive, HH333, Stanford, CA 94305-5317.

ABBREVIATIONS USED IN TEXT

DUB = dysfunctional uterine bleeding
GnRH = gonadotropin-releasing hormone
IUD = intrauterine device
NSAID = nonsteroidal anti-inflammatory drug

Differential Diagnosis

Because DUB is a diagnosis of exclusion, one must rule out organic causes for the abnormal bleeding (after excluding pregnancy). Organic causes can be classified into three major categories: pelvic pathology, systemic diseases, and iatrogenic causes (Table 1); most are in the local pelvic pathology category. Benign pelvic lesions, such as myomas, have been shown to contribute to menorrhagia with varying severity, depending on their location in the uterus.[6] Other benign pathologic conditions include adenomyosis, endometriosis, endometrial or cervical polyps, cervicitis, and severe vaginal infection. These conditions should always be ruled out when a woman presents with abnormal ovulatory bleeding.

Malignant causes of menorrhagia include carcinoma of the reproductive tract and premalignant changes of the endometrium such as hyperplasia. The incidence of endometrial carcinoma in older women is sufficiently high to recommend that all women ages 35 years and above with menorrhagia or abnormal uterine bleeding undergo evaluation of the endometrium. Nearly 40% of premenopausal women with endometrial carcinoma will present with menorrhagia as their only complaint.[7]

Systemic diseases are another important group to consider, including coagulation disorders (thrombocytopathies, Von Willebrand's disease, and leukemia), hypothyroidism, systemic lupus erythematosus, and cirrhosis. Only a small proportion of menorrhagia cases are caused by systemic disease, but severe consequences could result if the diagnosis were missed. Adolescents with coagulation disorders often present with recurrent menorrhagia causing anemia and at times requiring hospitalization.

Iatrogenic etiologies include use of hormone therapy, contraceptive injections and devices, and medications including tranquilizers, antidepressants, anticoagulants, and corticosteroids.

When all the above have been excluded, the diagnosis of dysfunctional uterine bleeding can be given. DUB is a diagnosis that does not apply to menorrhagia only, but also includes excessively prolonged and frequent bleeding (menometrorrhagia). DUB occurs more frequently in anovulatory than ovulatory cycles.

Anovulatory DUB is the end result of unopposed estrogen effects on the endometrium, leading to proliferative, disordered proliferative, hyperplastic, or neoplastic changes. Eventually, desquamation of irregular tissues and focal bleeding occur. Little is known about biochemical disturbances in the local endometrial environment that lead to menorrhagia in anovulatory DUB. Smith et al.[8] demonstrated that arachidonic acid availability is reduced and prostaglandin production is impaired in proliferative endometrium. The imbalance in prostaglandin activity may alter vascular tone, endometrial blood flow, and hemostatic functions. Other factors such as endothelins, endothelium-derived relaxing factor (nitric oxide), and other vasoactive substances may play a role.[9]

TABLE 1.—*Differential Diagnosis of Abnormal Uterine Bleeding*

I. Pelvic Pathology
A. Benign
Pregnancy
Myoma
Adenomyosis
Endometriosis
Endometrial/cervical polyp
Pelvic inflammatory disease
Vaginal/cervical infection
B. Malignant
Carcinoma of the reproductive tract
Endometrial hyperplasia
II. Systemic
A. Coagulation disorder
Thrombocytopathy
Von Willebrand's disease
Leukemia
B. Hypothyroidism
C. Systemic lupus erythematosus
D. Cirrhosis
III. Iatrogenic
A. Hormone therapy
B. Contraceptive devices and injections
C. Medications
Tranquilizers
Antidepressants
Anticoagulants
Corticosteroids
IV. Dysfunctional uterine bleeding

Dysfunctional uterine bleeding associated with ovulatory bleeding is also poorly understood. There is evidence that local factors have a significant influence in the breakdown process. Endometrial lysosomal enzyme activity in ovulatory DUB is increased, leading to the hypothesis that hydrolytic enzymes may participate in the process.[9] There is also evidence that endothelins responsible for local vasoconstriction, migratory leukocytes, and defects in the endometrial repair process may all contribute to abnormal bleeding in ovulatory DUB.

Medical Treatment

Medical therapy for menorrhagia has been poorly researched because of difficulty with objective assessment of menstrual blood loss. Although relatively inexpensive and low in morbidity, side effects are common and benefits cease when the treatment is terminated (Table 2). Long-term side effects and patient compliance should be factors in the decision to treat.

TABLE 2.—*Efficacy and Side Effects of Pharmacotherapy for Management of Menorrhagia*

Drugs	*Efficacy (Reduction in Flow)*	*Side Effects*
NSAIDs	~20–30%	Gastrointestinal
Oral Contraceptives	~50%	Headaches, nausea, edema, weight gain, mood changes, androgenic/hypoestrogenic effects
Progestins	~15%	Headaches, nausea, edema, weight gain, mood changes, androgenic/hypoestrogenic effects
Danazol	~60%	Androgenic
GnRH agonists	100%	Hypoestrogenic/bone loss
Antifibrinolytic Drugs	~80%	Headache, gastrointestinal, vertigo, possible increased thrombotic activity

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Various authors have described disorders of prostanoid synthesis as underlying factors in DUB. Smith et al.[10] reported altered ratio of prostaglandin E2 to F2, and Makarainen and Ylikorkala[11] reported an increased ratio of prostacyclin to thromboxane (prostacyclin causes vasodilation and inhibits platelet aggregation; thromboxane has the opposite effect). It therefore seems reasonable that NSAIDs would be effective treatment, since they reduce prostaglandin levels by inhibiting the cyclooxygenase enzyme when taken during the time of menstruation, and thus tip the balance toward the thromboxane effects. Objective studies measuring menstrual blood loss have shown that NSAIDs can decrease menstrual blood loss by 20–30% in women with menorrhagia.[12]

Oral Contraceptives

The mechanism of action of treatment using oral contraceptives is probably by induction of endometrial atrophy, since their effect is mainly progestational. Reduction of 53% of menstrual blood loss has been reported with oral contraceptive pills containing 50 μg ethinyl estradiol.[13] No controlled study has looked at low-dose oral contraceptive pills in patients with menorrhagia, although the benefit is assumed to be similar.

Progestins

Progestins are frequently used in patients with anovulatory DUB as luteal phase replacement from cycle day 15 to 26. Their role in the treatment of ovulatory dysfunction was not investigated until recent years. In 1990, Cameron et al.[14] noted a reduction of 15% in menstrual blood loss after treatment with norethisterone from cycle day 19 to 26, findings confirmed by Higham and Shaw in 1993.[15] It appears that medicated intrauterine devices (IUDs) may show promise in the treatment of DUB. Levonorgestrel-releasing IUDs have been shown to reduce menstrual blood loss by up to 86% after 3 months of use in women with menorrhagia.[16] IUDs also have the advantage of fewer side effects, since relatively little progestin is absorbed systemically.

Gonadotropin-Releasing Hormone Analogs

A new approach to treatment of DUB is based on the ability of the gonadotropin-releasing hormone (GnRH) antagonists to deplete the pituitary of bioactive gonadotropins and desensitize the pituitary to further GnRH stimulation. The end result is inhibition of further gonadotropin release, suppression of ovarian activity, and hypogonadotrophic hypogonadism. Amenorrhea usually results by 4–6 weeks after initiation of treatment. Postmenopausal symptoms, high cost, and bone demineralization with long-term use are of concern. Combined hormone replacement therapy and GnRH agonists may be a solution.

Danazol

Danazol is a derivative of 17-α-ethinyltestosterone with mild androgenic properties. It works by direct enzymatic inhibition of sex steroid synthesis and competitive inhibition of the binding of sex steroids to androgen and progesterone receptors. It also alters pulsatile gonadotropin release and thus, at higher doses, inhibits ovulation. The end result is endometrial atrophy. The effect of danazol (200 mg/day) has been compared to mefanamic acid (500 mg/day) in a randomized study by Dockeray et al.,[17] who found a 58.9% reduction in menstrual blood loss in the danazol-treated group compared with 22.2% in the NSAID-treated group. Danazol also proved to be more effective than cyclic norethisterone for control of menstrual blood loss.[15] In spite of its proven efficacy, danazol is not frequently used in the United States for menorrhagia because of its androgenic and long-term lipid profile side effects.

Antifibrinolytic Drugs

Antifibrinolytic drugs target the increased fibrinolytic activity in menstrual blood of patients with menorrhagia. Drugs such as tranexamic acid prevent the activation of plasminogen and have been shown to decrease menstrual blood loss by as much as 84%.[13] Reports of intracranial thrombosis with this drug have limited its clinical use.

Surgical Treatment

For many patients, surgical treatment may ultimately be necessary in spite of the effectiveness of medical therapies. Traditionally, dilatation and curettage (D and C) and hysterectomy have been the main forms of treatment for menorrhagia, the former mainly for stabilization of acute episodes of bleeding. The estimated proportion of hysterectomies for DUB annually ranges from 24,750 (4.5% of all hysterectomies per year in the United States)[18] to 292,000 (40%).[19] As with any surgical procedure, cost and morbidity are of concern.

TABLE 3.—*Summary of Randomized Studies Comparing Endometrial Ablation to Hysterectomy*[32]

Reference	Year	Procedure	Number of Patients	Length of Stay (days)	Complications (%)	Patient Satisfaction (%)	Return to Activity (weeks)	Reoperation (%)	Follow-Up (years)
Gannon et al.[27]	1991	Endometrial ablation	25	1	0	NA	2–3	16	1
		hysterectomy	26	7	46	NA	8	—	—
O'Connor et al.[28]	1997	Endometrial ablation	116	1	13	85	3	22	3
		hysterectomy	56	6	45	96	7	—	—
Dwyer et al.[29] and Sculpher[30] et al.	1993 1996	Endometrial ablation	99	2	4	85	1	23	2
		hysterectomy	97	6	47	94	4	—	—
Pinion et al.[31]	1994	Endometrial ablation	105	3	15	78	2–4	16	1
		hysterectomy	99	7	47	89	8–12	—	—

Laparoscopic hysterectomy was introduced to decrease morbidity and cost associated with abdominal hysterectomy, but recent studies have reported greater overall direct cost with laparoscopic hysterectomy compared with abdominal and vaginal hysterectomy because of longer operating times and the use of expensive disposable instruments. The complication rate for abdominal hysterectomy has been reported to be ~9.1%, for vaginal hysterectomy ~7.8%, and for laparoscopic hysterectomy ~8.8%.[20] The majority of complications are due to febrile morbidity and bleeding. Less common, but severe, complications include damage to the urinary tract and gastrointestinal system.

Endometrial Ablation

Endometrial ablation was introduced in the 1980s as an alternative to hysterectomy for DUB. Since then, various types of energy modalities and methods have been used. The ablation is accomplished by hysteroscope using a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser or electrocautery (rollerball and resectoscope). Electrocautery is more commonly used in the clinical setting because of ease of use and lower cost. Other research procedures include the use of radiofrequency energy and cryotherapy for ablation.

Short-term data indicate that endometrial ablation is at least 90% effective in eliminating or reducing bleeding.[21] Surgical complications include uterine perforation, infection, hemorrhage, and fluid overload with pulmonary and cerebral edema. Ablation does not involve the removal of the uterus and thus decreases the recovery and operative time and complications associated with wound healing. Several reports with longer follow-up time, 4 years, have emerged and are finding that up to 34% of women who had an initially successful ablation treatment experience recurrent symptoms requiring additional treatment.[22,23] Other symptoms such as pain can also evolve.[24] Potential long-term complications also include hematometra and occult development of endometrial hyperplasia/carcinoma.[25] Another area of concern is the potential diagnostic difficulty in the evaluation of an ablated uterine cavity; areas of scarring in the cavity may make visualization of potential lesions via hysteroscopy and endometrial biopsy difficult.

Recently, a new method of endometrial ablation has been made available. This technique uses thermal energy for ablation of uterine tissue. A balloon catheter is placed in the uterus through the cervical canal and inflated with 5% dextrose in water. The medium is heated to 87°C while circulating through the balloon during the ablation. The procedure can be done under local anesthesia in the office, and hysteroscopy is not required for insertion. A success rate of 86% after 1 year of treatment has been reported.[26]

Four randomized studies, all from the United Kingdom, have compared hysterectomy to endometrial ablation (Table 3). Overall, ablation was associated with shorter hospital stays, fewer postoperative complications, lower cost, and earlier resumption of activities compared with hysterectomy.[27–31] Because of the relatively small sample size and short follow-up periods, however, it is not clear whether these short-term benefits are sufficient to counteract the disadvantages. A multicenter, randomized study by the Gynecologic Studies Group funded by the Agency of Health Care Policy and Research is investigating these issues further.

Conclusions

Dysfunctional uterine bleeding is a common problem in women of reproductive age, and up to 20% of women affected will seek consultation. Anovulatory DUB, commonly seen at both ends of the reproductive years because of hypothalamic immaturity and changes associated with menopause, is usually treated effectively by replacing the missing component, progesterone, in the luteal phase. The mechanism for ovulatory DUB is less well understood. Medical treatments such as NSAIDs, oral contraceptive pills, progestins, danazol, GnRH agonists, and antifibrinolytic drugs all reduce menstrual flow; however, the benefits are limited to the duration of therapy. Objective measurements of menstrual blood loss continue to be a problem with clinical studies.

Surgical options, other than hysterectomy, have been developed over the past 10 years for treatment of menorrhagia, mainly in the endometrial ablation category. A new form of ablation using thermal energy via an intrauterine balloon appears promising and less

invasive. The main disadvantage of these ablation procedures is potential recurrence of symptoms and missing an occult malignancy, in addition to losing future ability to fully assess the uterine cavity due to scarring. Ongoing studies will help clarify the long-term benefits. Ultimately, good patient selection and long-term follow-up are still the most important factors in success and safety of treatment.

REFERENCES

1. Hallberg L, Hogdahl AM, Nilsson L, Rybo G. Menstrual blood loss: a population study. Acta Obstet Gynecol Scand 1966; 45:320–351

2. American College of Obstetrics and Gynecology. Dysfunctional uterine bleeding. Tech Bull 1982; 66:5

3. Chimbira TH, Anderson ABM, Turnbull AC. Relation between measured menstrual blood loss and patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area. Br J Obstet Gynaecol 1980; 87:603–609

4. Cohen BJB, Gibor Y. Anemia and menstrual blood loss. Obstet Gynecol Survey 1980; 35:597–618

5. Fraser IS. Treatment of menorrhagia. In: Dysfunctional Uterine Bleeding and Menorrhagia. Bailliere's Clin Obstet Gynecol London, Bailliere Tindall, 1989; 3:391–402

6. Fraser IS. Hysteroscopy and laparoscopy in women with menorrhagia. Am J Obstet Gynecol 1990; 162:1264–1269

7. Quinn M, Neale BJ, Fortune DW. Endometrial carcinoma in premenopausal women: a clinicopathological study. Gynecol Oncol 1985; 20:298–306

8. Smith SK, Abel MH, Kelley RW, Baird DT. The synthesis of prostaglandins from persistent proliferative endometrium. J Clin Endocrinol Metab 1982; 55:284–289

9. Fraser IS, Hickey M, Song JY. A comparison of mechanisms underlying disturbances of bleeding caused by spontaneous dysfunctional uterine bleeding or hormonal contraception. Human Reprod 1996; 11(suppl 2):165–178

10. Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. Br J Obstet Gynaecol 1981; 88:434–442

11. Makarainen L, Ylikorkala O. Primary and myoma-associated menorrhagia: role of prostaglandins and effects of ibuprofen. Br J Obstet Gynaecol 1986; 93:974–978

12. Fraser, IS, Pearse C, Shearman RP, Elliott PM, McIlveer J, Markham R. Efficacy of mefenamic acid in patients with a complaint of menorrhagia. Obstet Gynecol 1981; 58:543–551

13. Nilsson L, Rybo G. Treatment of menorrhagia. Am J Obstet Gynecol 1971; 110:713–720

14. Cameron IT, Haining RH, Lumsden MA, Thomas VR, Smith SK. The effects of mefenamic acid and norethisterone on measured menstrual blood loss. Obstet Gynecol 1990; 76:85–88

15. Higham JM, Shaw RW. A placebo controlled study to compare danazol (200 mg), a regimen of decreasing doses of danazol, and norethindrone in the treatment of objectively proven menorrhagia. Am J Obstet Gynecol 1993; 169:1134–1139

16. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990; 97:690–694

17. Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. Br J Obstet Gynaecol 1989; 96:840–844

18. Wilcox LS, Koonin LM, Pokras R, Strauss LT, Xia Z, Peterson HB. Hysterectomy in the United States, 1988–1990. Obstet Gynecol 1994; 83:549–555

19. Brooks PG, Clouse J, Morris LS. Hysterectomy vs. resectoscopic endometrial ablation for the control of abnormal uterine bleeding. A cost-comparative study. J Reprod Med 1994; 39:755–760

20. Weber AM, Lee JC. Use of alternative techniques of hysterectomy in Ohio, 1988–1994. N Engl J Med 1996; 335:483–489

21. Brill AI. What is the role of hysteroscopy in the management of abnormal uterine bleeding? Clin Obstet Gynecol 1995; 38:319–345

22. Unger JB, Meeks GR. Hysterectomy after endometrial ablation. Am J Obstet Gynecol 1996; 175:1432–1436

23. Chullapram T, Song JY, Fraser IS. Medium-term follow-up of women with menorrhagia treated by rollerball endometrial ablation. Obstet Gynecol 1996; 88:71–76

24. Magos AL, Baumann R, Lockwood GM, Turnbull AC. Experience with the first 250 endometrial resections for menorrhagia. Lancet 1991; 337:1074–1078

25. Margolis MT, Thoen LD, Boike GM, Mercer U, Keith LG. Asymptomatic endometrial carcinoma after endometrial ablation. Inst J Gynaecol Obstet 1995; 51:255–258

26. Vilos GA, Fortin CA, Sanders B, Pendley L, Stabinsky SA. Clinical trial of the uterine thermal balloon for treatment of menorrhagia. J Am Assoc Gynecol Laparosc 1997; 4:559–565

27. Gannon MJ, Holt EM, Fairbank J, Mitzgerald M, Milne MA, Crystal MA, Greenhalf JO. A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. BMJ 1991; 303:1362–1364

28. O'Connor H, Broadbert JAM, Magos AL, McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia. Lancet 1997; 349:897–901

29. Dwyer N, Hutton J, Stirrat GM. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for surgical treatment of menorrhagia. Br J Obstet Gynaecol 1993; 100:237–243

30. Sculpher MJ, Dwyer N, Byford S, Stirrat GM. Randomized trial comparing hysterectomy and transcervical endometrial resection: effect on health related quality of life and costs two years after surgery. Br J Obstet Gynaecol 1996; 103:142–149

31. Pinion SB, Parkin DE, Abramovich DR, Naji A, Alexander DA, Russell IT, Kitchener HC. Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. BMJ 1994; 309:979–983

32. STOP-DUB Coordinator Center. Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding. 1997; pp 1–5