No. 106, August 2001

GUIDELINES FOR THE MANAGEMENT OF ABNORMAL UTERINE BLEEDING

These guidelines have been reviewed by the Clinical Practice Gynaecology and the Reproductive Endocrinology Infertility Committees, and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada

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Abstract

Objective: It is estimated that nine to 30 percent of reproductive age women suffer from menorrhagia. The prevalence increases with age, peaking just prior to menopause. Menorrhagia and uterine fibroids account for up to 75 percent of all hysterectomies performed worldwide. This guideline provides recommendations to gynaecologists and other health care providers in the diagnosis and management of abnormal uterine bleeding, incorporating the current evidence.

Options: Diagnostic tools and medical and surgical alternatives to management are reviewed and current evidence is presented.

Evidence: Medline, Embase, and the Cochrane database were reviewed as well as other society guidelines.

Recommendations:

1. Women with irregular menstrual bleeding should be investigated for endometrial polyps and/or submucous fibroids. (II-2 B)
2. Women presenting with menorrhagia should have a current cervical cytology and a complete blood count. Further investigations are individualized. It is useful to delineate if the bleeding results from ovulatory or anovulatory causes, both in terms of tailoring the investigations and in choosing a treatment. (III B)
3. Clinicians should perform endometrial sampling based on the methods available to them. An office endometrial biopsy should be obtained if possible in all women presenting with abnormal uterine bleeding, over 40 years of age or weighing more than or equal to 90 kg. (II B)
4. Hysteroscopically-directed biopsy is indicated for women with persistent erratic menstrual bleeding, failed medical therapy or transvaginal saline sonography suggestive of focal intrauterine pathology such as polyps or myomas. Women with persistent symptoms but negative tests should be reevaluated. (II B)
5. Progestogens given in the luteal phase of the ovulatory menstrual cycles are not effective in reducing regular heavy menstrual bleeding. (I A)
6. While dilatation and curettage (D&C) may have a diagnostic role, it is not effective therapy for women with heavy menstrual bleeding. (II B)
7. The endometrium can be destroyed by several different techniques but reoperation rate at five years may be up to 40 percent with rollerball ablation. This should be reserved for the woman who has finished her childbearing and is aware of the risk of recurrent bleeding. (I A)

Sponsors: This guideline was produced by the Society of Obstetricians and Gynaecologists of Canada.

INTRODUCTION

The normal menstrual cycle lasts 28 ± 7 days, the flow lasts 4 ± 2 days, and the average blood loss is 40 ± 20 ml.[1]

Abnormal uterine bleeding (AUB) is defined as changes in frequency of menses, duration of flow or amount of blood loss. Dysfunctional uterine bleeding (DUB) is a diagnosis of exclusion when there is no pelvic pathology or underlying medical cause. DUB is typically characterized by heavy prolonged flow with or without breakthrough bleeding. It may occur with or without ovulation.

FOR INFORMATION ON THE SELF-DIRECTED LEARNING EXERCISE SEE PAGE 742.

Menorrhagia (hypermenorrhoea) is defined as heavy cyclical menstrual bleeding occurring over several consecutive cycles during the reproductive years. Objectively menorrhagia is defined as blood loss of more than 80 ml per cycle, the 90th percentile in a study of 476 Gothenberg women published by Hallberg *et al.* in 1966.[2] Monthly blood loss in excess of 60 ml may result in iron deficiency anemia and may affect the quality of life.[3]

DIAGNOSTIC APPROACH TO AUB

HISTORY

It is important to distinguish anovulatory AUB, which is more likely to lead to endometrial hyperplasia, from ovulatory AUB. Women presenting with ovulatory AUB will likely have heavy cyclical menstrual blood loss over several consecutive cycles without any intermenstrual or postcoital bleeding. They may have dysmenorrhea associated with passing of clots. Premenstrual symptoms also suggest ovulatory cycles. The history should include symptoms suggestive of other pathology, such as irregular bleeding, postcoital bleeding, and pelvic pain. Polyps or submucous fibroids are present in 25 to 50 percent of women who present with irregular bleeding.[4,5]

DIAGNOSIS

A thorough abdominal and pelvic examination is essential. Cervical cytology should be obtained if indicated. A complete blood count (CBC ± ferritin) is needed to determine degree of anemia. Other investigations to be considered include: thyrotropin stimulating hormone, when other symptoms of thyroid dysfunction are present; prolactin; day 21 to 23 progesterone to verify ovulatory status; follicular stimulating hormone and luteinizing hormone to verify menopausal status or support a diagnosis of polycystic ovarian disease; and a coagulation profile when menorrhagia is present at puberty or if there is a clinical suspicion for a coagulopathy.

ASSESSMENT OF THE ENDOMETRIUM

Endometrial assessment is performed to diagnose malignancy or pre-malignant conditions and to evaluate the hormonal influences of the endometrium. Spencer *et al.* reviewed 142 studies to determine the value of endometrial evaluation methods in women with AUB. The data does not support a uniform recommendation for endometrial evaluation.[6]

Sampling of the endometrium should be considered in all women over 40 years of age with abnormal bleeding or in women who are at higher risk of endometrial cancer,[1,7] including: nulliparity with a history of infertility; new onset of heavy, irregular bleeding; obesity (≥ 90 kg);[7,8] polycystic ovaries;[9] a family history of endometrial and colonic cancer;[7] and on tamoxifen therapy.[10,11]

It is also important to evaluate the endometrial histopathology in a woman who has no improvement in her bleeding pattern following a course of therapy of three months. The SOGC guidelines *Diagnosis of Endometrial Cancer in Women With Abnormal Vaginal Bleeding* (2000) reviewed the evidence for endometrial sampling and contained an algorithm which suggests a course of management in assessing the endometrium.[12]

TECHNIQUES FOR ENDOMETRIAL SAMPLING

Office endometrial biopsy results in adequate samples 87 to 97 percent of the time[13,15] and detects 67 to 96 percent of endometrial carcinomas.[13,15] Although the choice of sampling device may affect accuracy, no existing method will sample the entire endometrium.[6] Hysteroscopically-directed sampling detects a higher percentage of abnormalities when compared directly with dilatation and curettage (D&C) as a diagnostic procedure.[16-18] Even if the uterine cavity appears normal at hysteroscopy, the endometrium should be sampled since hysteroscopy alone is not sufficient to exclude endometrial neoplasia and carcinoma.[19,20] (II A)

DILATATION AND CURETTAGE

In 10 to 25 percent of women D&C alone does not uncover endometrial pathology.[21] D&C was associated with uterine perforation in 0.6 to 1.3 percent of cases and hemorrhage in 0.4 percent of cases.[21] D&C is a blind procedure with significant sampling errors; it also requires anesthesia which carries a risk of complications. It should be reserved for those situations

TABLE I

INDEPENDENT RISK FACTORS FOR ENDOMETRIAL HYPERPLASIA AND CARCINOMA IN WOMEN WITH AUB[7,13]

Factor	Prevalence	Odds ratio and 95% CI	p value
All patients	4.9%	—	—
Weight ≥ 90 kg	12.7%	5.5 (2.9-10.6)	< 0.0001
Age ≥ 45 yr	7.9%	3.1 (1.5-6.1)	0.0016
Weight ≥ 90 kg and age ≥ 45 yr	22.2%	—	—
Weight ≥ 90 kg and age < 45 yr	2.3%	—	—
Family history of colon cancer	—	5.0 (1.3-19.1)	0.0182
Infertility	—	3.6 (1.3-9.9)	0.0127
Nulliparity	—	2.8 (1.1-7.2)	0.0267
Family history of endometrial cancer	—	5.8 (1.1-28.6)	0.0392

Farquhar *et al.,* 1999.[7] Multivariate analysis of 1033 women.

where office biopsy or directed hysteroscopic biopsy are not available or feasible.[21,22] (II B)

ULTRASOUND EXAMINATION OF THE ENDOMETRIUM

Transvaginal sonography (TVS) assesses endometrial thickness and detects polyps and myomata with a sensitivity of 80 percent and specificity of 69 percent.[23]

Although there is evidence that endometrial thickness may be indicative of pathology in the postmenopausal woman, such evidence is lacking for the woman in her reproductive years. Meta-analysis of 35 studies showed that in menopausal women, endometrial thickness of five mm at ultrasound has a sensitivity of 92 percent for detecting endometrial disease and 96 percent for detecting cancer.[24] It is not helpful when the thickness is between five and 12 mm.[25] No such correlations are firmly established in the premenopausal patient.[5,12,23,26]

SALINE SONOHYSTEROGRAPHY

The introduction of five to 15 mL of saline into the uterine cavity using a saline primed catheter or a pediatric feeding tube may improve the diagnosis of intrauterine masses during TVS.[6,27-30]

TREATMENT OF AUB

MEDICAL MANAGEMENT

Age, desire to preserve fertility, coexisting medical conditions, and patient preference are essential considerations. For each of the suggested methods, the patient should be aware of the risks and contraindications to allow informed choice. The degree of patient satisfaction may be influenced by efficacy, expectations, cost, inconvenience, and side effects.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Endometrial prostaglandins are elevated in women with heavy menstrual bleeding.[31,32] Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase[31,32] and reduce endometrial prostaglandin levels.[31] In a review of 21 randomized controlled trials, NSAIDs taken with menses decrease menstrual blood loss by 20 to 50 percent.[33,34] NSAIDs improve dysmenorrhea in up to 70 percent of patients.[33] Therapy should start at the first day of menses and be continued for five days or until cessation of menstruation. (I A)

ANTIFIBRINOLYTIC AGENTS

Tranexamic acid (cyclokapron), a synthetic derivative of the amino acid lysine, exerts an antifibrinolytic effect through reversible blockade on plasminogen.[35,36] The drug has no effect on blood coagulation parameters or dysmenorrhea.[35,36] One-third of women experience side effects, including nausea and leg cramps. Tranexamic acid one g every six hours for the first four days of the cycle reduces menstrual blood loss by up to 40 percent, based on 10 randomized placebo-controlled trials.[33,35,36] (I A)

DANAZOL

Danazol, a synthetic steroid with mild androgenic properties, inhibits steroidogenesis in the ovary and has a profound effect on endometrial tissue,[37] reducing menstrual blood loss by up to 80 percent.[38-41] Following danazol therapy (100-200 mg daily), 20 percent of patients reported amenorrhea and 70 percent reported oligomenorrhea. Approximately 50 percent of the patients reported no side effects with danazol while 20 percent reported minor but acceptable side effects.[38,39] The most common complaint was weight gain of two to six pounds in 60 percent of patients. The recommended treatment is 100 to 200 mg daily for three months.[39,40]

PROGESTINS

Randomized controlled trials have shown cyclic progestins to be ineffective in controlling regular heavy menstrual bleeding compared to NSAIDs and tranexamic acid.[42-44] Progestins may be useful for women with irregular cycles and with anovulatory cycles when given for 12 to 14 days of each month.[45] Medroxyprogesterone acetate given for contraception induces amenorrhea within the first year in 80 percent of women,[46] although as many as 50 percent experience irregular bleeding.[46]

COMBINED ORAL CONTRACEPTIVE PILL

The reduction of menstrual blood loss with the combined oral contraceptive pill (OC) is probably the result of induced endometrial atrophy. A randomized controlled trial of women taking an OC containing 30 µg ethinyl estradiol showed a 43 percent reduction in menstrual blood loss compared to baseline.[47] Two longitudinal case control studies have found that users were less likely to experience heavy menstrual bleeding or anemia.[48] Additional advantages of OCs include contraception and reduction of dysmenorrhea.

PROGESTIN INTRAUTERINE SYSTEM

Progesterone impregnated intrauterine devices (IUDs) have been reported to reduce menstrual bleeding.[49-52] The newest levonorgestrel intrauterine system (LNG-IUS) is a T-shaped IUD which releases a steady amount of levonorgestrel (20 µg/24 hrs) from a steroid reservoir around the vertical stems of the device. It is presently undergoing clinical investigation in Canada and is expected to be released within the next few months.

GnRH AGONISTS

GnRH agonists induce a reversible hypoestrogenic state, reducing total uterine volume by 40 to 60 percent.[53] Myomas and uterine volume expand to pretreatment levels within months of cessation of therapy.[53] GnRH agonists are effective in reducing menstrual blood loss in perimenopausal women, but are limited by their side effects, including hot flashes and reduction of bone density.[53]

SURGICAL MANAGEMENT

Dilatation and Curettage

There are no published reports of randomized controlled trials comparing D&C and other potential treatments for the relief of menorrhagia.[22] The only study to measure blood loss before and after D&C found temporary reduction in menstrual blood loss immediately after the procedure; however, losses returned to previous levels or higher by the second menstrual period post-intervention.[22,54] D&C may have a diagnostic role when endometrial biopsy is inconclusive and the symptoms persist or when underlying pathology is suspected.[12]

Endometrial Destruction

Endometrial destruction can be performed by several surgical techniques. Hysteroscopic endometrial ablation with photocoagulation, rollerball, electrocoagulation or loop resection, and their long-term results, have been reviewed by Martyn.[55] Endometrial ablation has now been evaluated clinically for the past 20 years. Several studies with life table analysis up to 6.5 years have shown satisfaction rates of approximately 85 percent.[55] Within the study periods, approximately 10 percent of women will move on to hysterectomy and 10 percent will require a repeat endometrial ablation for failed initial treatment.[55] Patients undergoing surgery after age 40 years appear to have a better outcome.[55] There is no clear evidence that the presence of fibroids or dysmenorrhea prior to endometrial ablation surgery reduces the rates of success. Preoperative medical treatment does not appear to improve long-term outcome but does improve ease of surgery and short-term amenorrhea rates.[55] Hysteroscopic endometrial ablation is an effective treatment for the management of chronic menorrhagia unresponsive to medical therapy, with acceptably low complication rates and high patient satisfaction rates when assessed at long-term follow-up.[55] Reoperation rate at five years may be up to 40 percent with rollerball ablation.[55] Endometrial ablation compares favourably with hysterectomy in randomized trials comparing efficacy and cost,[56] although the long-term analysis should include the cost of further therapy in women who require additional procedures.

Global endometrial ablation, recently reviewed by Vilos, was introduced in the 1990s as an easier, safe, and equally effective alternative to hysteroscopic ablation.[57] Several different devices, some of which are still undergoing feasibility studies or clinical trials, have been introduced, including: hot water intrauterine balloons, intrauterine free saline solution, an electrocoagulating balloon, a 3-D bipolar electrocoagulation probe, a microwave device, a diode fibre laser, and several different cryoprobes.[57] These devices require less operator skill than for hysteroscopic endometrial ablation and no irrigant or distending solutions. All utilize either heat or cold to destroy the endometrium. Although all devices are promising and have produced impressive preliminary results, the long-term efficacy, complication rates, and cost effectiveness have not been established.

Since all procedures are performed without hysteroscopic visualization (except hydrothermablation), it would be prudent to perform hysteroscopy prior to and following the treatment to ensure that only the endometrial cavity has been treated. False passages and partial or complete uterine perforations occur at a frequency of 0.8 to 1.5 percent and may result in adjacent organ injury.[57]

Hysterectomy

The risks of major surgery must be weighed against alternatives. Clinical practice guidelines for hysterectomy have been reported by Lefebvre *et al.*[58] Hysterectomy is a permanent solution for the treatment of menorrhagia and abnormal uterine bleeding, and is associated with high levels of patient satisfaction in properly selected patients. For the woman who has completed her childbearing, reviewed the alternatives, and has tried conservative therapy without acceptable results, hysterectomy is often the best choice.

RECOMMENDATIONS

1. Women with irregular menstrual bleeding should be investigated for endometrial polyps and/or submucous fibroids. (II-2 B)
2. Women presenting with menorrhagia should have a current cervical cytology and a complete blood count. Further investigations are individualized. It is useful to delineate if the bleeding results from ovulatory or anovulatory causes, both in terms of tailoring the investigations and in choosing a treatment. (III B)
3. Clinicians should perform endometrial sampling based on the methods available to them. An office endometrial biopsy should be obtained if possible in all women presenting with abnormal uterine bleeding over 40 years of age or weighing more than or equal to 90 kg. (II B)
4. Hysteroscopically-directed biopsy is indicated for women with persistent erratic menstrual bleeding, failed medical therapy or transvaginal saline sonography suggestive of focal intrauterine pathology such as polyps or myomas. Women with persistent symptoms but negative tests should be reevaluated. (II B)

TABLE 2

ADVANTAGES OF GLOBAL ENDOMETRIAL ABLATION[57]

1. Devices are relatively safe but the overall safety will not be determined until several hundred procedures are performed by each device.
2. Devices are easier to use than hysteroscopic endometrial ablation.
3. Since the endometrium is destroyed, it is imperative that endometrial neoplasia be excluded.

5. Progestogens given in the luteal phase of the ovulatory menstrual cycles are not effective in reducing regular heavy menstrual bleeding . (I A)
6. While dilatation and curettage (D&C) may have a diagnostic role, it is not effective therapy for women with heavy menstrual bleeding. (II B)
7. The endometrium can be destroyed by several different techniques but reoperation rate at five years may be up to 40 percent with rollerball ablation. This should be reserved for the woman who has finished her childbearing and is aware of the risk of recurrent bleeding. (I A)

J Obstet Gynaecol Can 2001;23(8):704-9

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TABLE 3

QUALITY OF EVIDENCE ASSESSMENT[59]	CLASSIFICATION OF RECOMMENDATIONS[59]
The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.[59] I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940) could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.[59] A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination. B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination. C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds. D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination. E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

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