

ONLINE EXCLUSIVE

Menstrual disturbances in perimenopausal women: What's best?

Evidence-based answer

It's best to start with nonsteroidal anti-inflammatory drugs (NSAIDs), which effectively reduce heavy menstrual bleeding (strength of recommendation [SOR]: **B**, systematic review of randomized clinical trials [RCTs]).

Perimenopausal women with heavy bleeding not controlled by NSAIDs, or other forms of dysfunctional uterine bleeding, can benefit from continuous, combined hormonal therapy with estrogen and progestin; hormonal therapy with estrogen and a cyclical progestin; or a cyclical progestin alone (SOR: **B**, RCTs and a

systematic review of RCTs). Intrauterine devices (IUDs) containing levonorgestrel also effectively reduce bleeding and may avoid surgical intervention (SOR: **B**, systematic review of RCTs).

If medical management fails, endometrial ablation offers an effective, minimally invasive alternative to hysterectomy (SOR: **B**, systematic review of RCTs and 1 RCT). Hysterectomy should be considered when medical management or endometrial ablation fails (SOR: **B**, systematic review of RCTs and 1 RCT).

Evidence summary

Perimenopause encompasses the period of irregular menstrual cycles and flow that precedes menopause (absence of menstrual bleeding for 1 year). Menopause generally occurs between 45 and 55 years of age; the average is 51 years. A review of 500 perimenopausal women seen sequentially by a gynecology service found that 18% had menorrhagia (heavy bleeding), metrorrhagia (intermenstrual bleeding), or hypermenorrhea (frequent periods).¹

Because few studies have examined the treatment of abnormal menstrual bleeding specifically during perimenopause, therapeutic approaches are based primarily on studies of women before and shortly after this stage. Once malig-

nancy and other causes of abnormal uterine bleeding (pregnancy, bleeding disorders, infection, thyroid disorders, uterine fibroids, or polyps) have been excluded, treatment of perimenopausal dysfunctional uterine bleeding should address the goals of:

- stopping acute bleeding
- avoiding future irregular or heavy bleeding
- considering future family planning needs
- preventing complications (anemia, unnecessary therapeutic procedures).

NSAIDs reduce heavy bleeding

A Cochrane review of 16 small RCTs that examined the use of NSAIDs for menor-

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Medical management with NSAIDs is the first choice for initial treatment of abnormal uterine bleeding.

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rhagia found NSAIDs to be superior to placebo and comparable to other medical treatments such as luteal progestin, oral contraceptive pills, and progestin-releasing intrauterine systems.²

Hormone therapy is also effective

An RCT of 132 perimenopausal women compared 24 weeks of combination hormonal therapy (20 mcg ethinyl estradiol/1 mg norethindrone acetate) with placebo for treating climacteric symptoms, including abnormal uterine bleeding.³ The combination therapy shortened the menstrual cycle (27.7 vs 30.4 days), decreased its variability (17.5-46.7 days vs 22.4-66 days), and lowered bleeding severity scores (6.9 vs 10.2).

Hormonal therapy didn't shorten bleeding episodes, however, and was associated with a higher incidence of intermenstrual bleeding during the first 3 months of treatment.

Continuous, combined estrogen/progestogen therapy

An RCT of 120 perimenopausal women with irregular menstrual cycles compared low-dose (1 mg) continuous estradiol and cyclical progestogens (10 mg dydrogesterone) with cyclical progestogens alone.⁴ In the combined treatment group, the incidence of cyclical menstrual bleeding was 86%, and 76% of all cycles were rated normal in amount and duration of bleeding. In the cyclical progestogen group, the incidence of cyclical menstrual bleeding during treatment was 76%, and 70% of all cycles were rated normal.

A systematic review, comprised primarily of RCTs, examined uterine bleeding patterns in 3000 postmenopausal women taking combined continuous hormones (various regimens of estrogen and progestin).⁵ In 22 of 23 studies that included data past 6 months, 75% or more of participants became amenorrheic while on therapy. Irregular uterine bleeding before 6 months of therapy was common, however, and was presumed to lower patient compliance.

Combined therapy avoids risk of endometrial hyperplasia

A more recent Cochrane review of 30 RCTs examined hormone replacement therapy for irregular bleeding and endometrial hyperplasia in postmenopausal women who had been amenorrheic for at least 6 months (a more liberal criterion for inclusion).⁶ The review concluded that many of the women treated with continuous estrogen and progestin became amenorrheic after 1 year of therapy. It also reiterated that unopposed estrogen increased the risk of endometrial hyperplasia, whereas continuous combined estrogen and progestogen treatment didn't.

Continuous progestogen regimen has blood loss benefit

No randomized trials have compared oral progestogens with placebo. A Cochrane review examined the use of cyclical progestogens (given from 10 to 20 days per cycle) for heavy menstrual bleeding.⁷ Cyclical progestogens appeared comparable in efficacy to NSAIDs for their effect on duration of menstruation; no statistically significant difference in menstrual blood loss was noted. Progestogens given in more continuous regimens offered greater benefit in terms of blood loss.

IUDs help avoid surgery, but can have side effects

A Cochrane review found that progestogen-releasing IUDs significantly reduce heavy menstrual bleeding and are more effective than cyclical norethisterone (21 days). Patients did, however, report greater progestogenic side effects (breast tenderness and intermenstrual bleeding) than cyclical therapy.⁸

One unblinded RCT that randomized women scheduled for hysterectomy for heavy bleeding to the levonorgestrel intrauterine device (LNG-IUD) or their existing medical therapy (not further described) found that women in the LNG-IUD group were more likely to cancel surgery.

Another RCT comparing hysterecto-

my with the LNG-IUD found that women with the LNG-IUD reported greater pain. The LNG-IUD was more cost effective at 1 and 5 years, primarily because of reduced surgical expenses. Some patients or physicians may have ethical issues with the device's mechanism of action.

Uterine ablation when preserving fertility doesn't matter

A review article of currently available evidence on endometrial ablation for heavy menstrual bleeding concluded that both resectoscopic endometrial ablation (via hysteroscopy) and nonresectoscopic endometrial ablative technologies (radio-frequency electrosurgical ablation, balloon thermal ablation, free fluid ablation, cryotherapy, microwaves) significantly reduce menstrual blood flow.⁹ These minimally invasive techniques were an option for women who weren't concerned about preserving fertility. However, 20% to 40% of patients who were followed for more than 5 years required repeat treatment or hysterectomy.

Heavy bleeding and transcervical endometrial resection

An RCT of 187 women, average age 42 years, compared immediate transcervical resection of the endometrium to medical management for heavy menstrual bleeding.¹⁰ A 5-year follow-up was completed on 144 patients. The study showed transcervical resection of the endometrium to be superior with regard to menstrual status (less bleeding or no bleeding), patient satisfaction with outcomes, and health-related quality of life as indicated on patient questionnaires.

When other options fail...

Patients who fail medical treatment and minimally invasive uterine ablation may require hysterectomy. An RCT of 63 premenopausal women (30-50 years of age) with abnormal uterine bleeding compared hysterectomy with medical treatment.¹¹ Hysterectomy was superior with regard to symptom resolution and health-

related quality of life after 6 months.

A Cochrane review of 5 RCTs that compared endometrial resection and ablation with hysterectomy for heavy menstrual bleeding reported a significant advantage for hysterectomy in symptom resolution and patient satisfaction.¹² Although the initial cost was higher for the hysterectomy group, the difference narrowed over time because of the need for retreatment in the endometrial destruction group.

Recommendations

The American College of Obstetricians and Gynecologists (ACOG) recommends initial medical management (cyclic progestins, low-dose oral contraceptives, or cyclic hormone replacement therapy) for anovulatory bleeding in women 40 years and older.¹³

The Practice Committee of the American Society for Reproductive Medicine lists low-dose combination hormonal pills, progestin, progestin-containing IUDs, and hormone replacement therapy as medical treatment options.¹⁴

ACOG notes that minimally invasive surgical options such as hysteroscopic endometrial ablation result in less short-term morbidity and cost less than hysterectomy.¹⁵ Results with resectoscopic and nonresectoscopic techniques are similar. Hysterectomy rates following these approaches are at least 24% at 4 years.¹⁵ ■

References

1. Seltzer VL, Benjamin F, Deutsch S. Perimenopausal bleeding patterns and pathologic findings. *J Am Med Womens Assoc.* 1990;45:132-134.
2. Lethaby A, Augood C, Duckitt K. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2007;(4): CD0004000.
3. Casper R, Dodin S, Reid R, et al. The effect of 20 micrograms of ethinyl estradiol/1 mg norethindrone acetate (Minestrin), a low-dose contraceptive, on vaginal bleeding patterns, hot flashes, and quality of life in symptomatic perimenopausal women. *Menopause.* 1997;4:139-147.
4. De Francis P, Cobellis L, Fornaro F, et al. Low-dose hormone therapy in the perimenopause. *Int J Gynaecol Obstet.* 2007;98:138-142.
5. Udoff L, Langenberg P, Adashi EY. Combined con-

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Among patients followed for more than 5 years after endometrial ablation, 20% to 40% required repeat treatment or hysterectomy.

- tinuous hormone replacement therapy: a critical review. *Obstet Gynecol.* 1995;86:306-316.
6. Suckling LA, Barlow D, Farquhar CM, et al. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst Rev.* 2004;(3):CD000402.
 7. Lethaby A, Irvine G, Cameron I. Cyclical progestogens for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2008;(1):CD001016.
 8. Lethaby A, Cooke I, Reese M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2005;(4):CD002126.
 9. Munro MG. Endometrial ablation for heavy menstrual bleeding. *Curr Opin Obstet Gynecol.* 2005;17:381-394.
 10. Cooper KG, Jack SA, Parkin DE, et al. Five-year follow-up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes. *BJOG.* 2001;108:1222-1228.
 11. Kuppermann M, Varner RE, Summitt RL Jr, et al. Effect of hysterectomy vs. medical treatment on health-related quality of life and sexual functioning. The medicine or surgery (Ms) randomized trial. *JAMA.* 2004;291:1447-1455.
 12. Lethaby A, Shepperd S, Cooke I, et al. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 1999;(2):CD000329.
 13. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Management of anovulatory bleeding. *In J Gynaecol Obstet.* 2001;72:263-271.
 14. Practice Committee of the American Society for Reproductive Medicine. Committee opinion: the menopausal transition. *Fertil Steril.* 2006;86(suppl 5):S253-S256.
 15. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Endometrial ablation. *Obstet Gynecol.* 2007;109:1233-1248.

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