



# ABNORMAL UTERINE BLEEDING

Randomized data shed light on AUB associated with fibroids, adenomyosis, and the use of progestins



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As recently defined by the International Federation of Gynecology and Obstetrics (FIGO)—and endorsed by the American College of Obstetricians and Gynecologists—the term “abnormal uterine bleeding” (AUB) now describes any departure from normal menstrual bleeding.<sup>1</sup> To determine the most appropriate intervention for this widespread problem, FIGO proposed that clinicians consider potential contributors to the clinical problem by investigating and categorizing patients according to the following system:

- Polyp
- Adenomyosis
- Leiomyoma
- Malignancy and hyperplasia

- Coagulopathy
- Ovulatory disorders
- Endometrial dysfunction
- Iatrogenic
- Not otherwise classified.

A given individual may be found to have one or more of these features, but not all of the features may contribute to the AUB. To facilitate their use, these nine causes are more commonly identified using the acronym PALM-COEIN.

In this article, I focus on three of these categories, presenting recent data on AUB associated with leiomyomata (AUB-L) or adenomyosis (AUB-A), and AUB of an iatrogenic nature (AUB-I).

## AUB-L: Satisfaction rates are similar 5 years after fibroid treatment by surgery or uterine artery embolization

Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev.* 2012;5:CD005073. doi:10.1002/14651858.CD005073.pub3.

Women who undergo uterine artery embolization (UAE) for the treatment of symptomatic uterine fibroids are just as satisfied with the outcome as women treated with hysterectomy or myomectomy, according to

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this 2012 review from the Cochrane Database.

Gupta and colleagues found similar patient-satisfaction rates at 5 years (odds ratio [OR] 0.9; 95% confidence interval [CI], 0.45–1.8), although women undergoing UAE were more likely to require additional interventions within 2 years (56 additional interventions per 1,000 women for surgery vs 250 per 1,000 women for UAE; OR, 5.64).

### Details and general findings

Gupta and colleagues selected randomized, controlled trials comparing UAE with surgery:

- three trials of UAE versus abdominal hysterectomy (n = 291)
- one trial of UAE versus hysterectomy or myomectomy (the specific surgery was determined by patient preference) (n = 157)
- one trial of UAE versus myomectomy in women desiring future childbearing (n = 121).

In these trials, UAE was bilateral and involved the use of permanent embolic material.

Among the findings:

- **Costs were lower with UAE**, as assessed by measuring the duration of the procedure, length of hospitalization, and time to resumption of normal activities.
- **Ovarian-failure rates were comparable** between women in the UAE and surgery groups. Ovarian function was assessed by measuring follicle-stimulating hormone (FSH), although FSH thresholds varied in some of the studies.

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

This review demonstrates that women are satisfied with outcomes five years after UAE and that ovarian failure is not more common after UAE than after surgery. Although the available evidence demonstrates that pregnancy following UAE is possible, women requiring a surgical procedure for AUB-L who are uncertain about their childbearing plans or who are hoping to conceive should be encouraged to select myomectomy as their intervention of choice.

- **Pregnancy was less likely after UAE than after myomectomy.** In the trial comparing UAE with myomectomy, 26 women later tried to conceive after UAE versus 40 after myomectomy. Significantly fewer women became pregnant after UAE (OR, 0.29; 95% CI, 0.10–0.85).



**Compared with hysterectomy and myomectomy, UAE costs were lower and postprocedure ovarian-failure rates were comparable**

### Bleeding outcomes were not measured

Strengths of this systematic review are its inclusion of high-quality, randomized, controlled trials and its assessment of ovarian-failure rates. However, a major weakness is the fact that its design does not allow for discrete evaluation of bleeding outcomes. Nor can its findings be broken down by the type of leiomyoma being treated.

## AUB-A: For adenomyosis-associated AUB, consider the LNG-IUS as an alternative to hysterectomy

*Ozdegirmenci O, Kayikcioglu F, Akgul MA, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. Fertil Steril. 2011;95(2):497–502.*

In a small randomized, controlled trial of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena) versus hysterectomy for adenomyosis-associated AUB, women allocated to the LNG-IUS experienced a

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# UPDATE

## abnormal uterine bleeding

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### WHAT THIS EVIDENCE MEANS FOR PRACTICE

The relationship of adenomyosis to gynecologic symptoms, including heavy menstrual bleeding and dysmenorrhea, needs further study. However, this trial confirmed that transvaginal ultrasound is helpful in the nonsurgical diagnosis of adenomyosis and suggests that the LNG-IUS may be as effective at 1 year as hysterectomy for the treatment of adenomyosis-associated heavy menstrual bleeding (AUB-A).

Clinicians who perform office-based ultrasound to assess AUB should familiarize themselves with the criteria for ultrasonic diagnosis of adenomyosis. These criteria include the presence of heterogeneous myometrial echogenicity, a loss of clarity of the endomyometrial interface, typically radially oriented linear striations, the appearance of myometrial cysts, and an overall globular enlarged uterus characterized by asymmetric thickening of the myometrium.<sup>2</sup>

In patients with heavy menstrual bleeding who have these findings, particularly if there is coexistent dysmenorrhea and uterine tenderness, it behooves the clinician to consider the LNG-IUS as first-line therapy, especially for women who wish to preserve fertility, but also for women for whom fertility is not an issue.

There is some evidence that the therapeutic effect of the LNG-IUS containing 20 µg of levonorgestrel may start to fade at 2 or 3 years, a possibility that should be shared with patients.<sup>3</sup> Other features, such as cavity size, thickness of the myometrium, and the coexistence of clinically relevant leiomyomas, have not been evaluated but may have an impact on the clinical response.


reduction in bleeding and comparable gains in hemoglobin values during the first year of use. Both the LNG-IUS and hysterectomy improved health-related quality of life, but the LNG-IUS was associated with superior improvements in measures of psychological and social functioning.

### Details and general findings of the trial


Eighty-six women were enrolled in the trial after exclusion of endometrial pathology as a cause of their heavy menstrual bleeding and after transvaginal ultrasound and magnetic resonance imaging findings were consistent with the diagnosis of adenomyosis. Participants then were randomly assigned to undergo hysterectomy or insertion of an LNG-IUS (43 women in each group). At baseline, the mean (SD) age was 44.28 (4.36) years among women in the LNG-IUS group versus 46.38 (3.76) years among women undergoing hysterectomy ( $P = .032$ ), a statistical difference that I suspect is not clinically significant.

Menstrual bleeding, hemoglobin levels, and quality of life were assessed prior

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\*From *Obstetrics and Gynecology Specialists, Fairview Health Services, Minneapolis, Minnesota*

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to insertion or surgery, and again at 6- and 12-month follow-up. Eleven women in the hysterectomy group were lost to follow-up.

General findings of the trial include:

- **Women in the LNG-IUS group** had a mean reduction in the volume of menstrual bleeding—as measured by the number of pads used—from two pads to one pad at 6 months, remaining at that level until 12 months. Serum hemoglobin levels increased from a median of just over 11 g/dL at the time of insertion to 13 g/dL at 6 months and slightly higher at 12 months. In the five self-reported quality-of-life domains assessed (physical, psychological, social, environmental, and a national environmental domain), women using the LNG-IUS demonstrated improvement in all five.
- **Women in the hysterectomy group** were treated using an abdominal surgical approach, with one patient experiencing postoperative wound infection that required secondary suture. Postoperative pathologic analysis found that 21 of these women (65.6%) had adeno-

myosis, six women (18.8%) had myomas, three women (9.4%) had both adenomyosis and a myoma, and two women (6.2%) had a normal uterus. Serum hemoglobin levels increased from a median of roughly 10.5 g/dL at the time of treatment to 13 g/dL at 6 months and slightly higher at 12 months. (There were no statistically significant differences in hemoglobin values between the LNG-IUS and hysterectomy groups at any point in the study.) Quality of life improved in three of the five domains assessed (physical and both environmental domains).

Although 11 women were lost to follow-up, this trial appeared to have an adequate sample size to examine the selected outcomes, and the population was well defined.

Two weaknesses were the limited follow-up (only 12 months) and the use of quality-of-life measures designed for a Turkish population (the trial was conducted in Turkey), which may or may not be fully applicable to a US population.

## AUB-I: Low-dose doxycycline reduces the time to amenorrhea in users of continuous oral contraceptives

*Kaneshiro B, Edelman A, Carlson NE, Nichols M, Forbes MM, Jensen J. A randomized controlled trial of subantimicrobial-dose doxycycline to prevent unscheduled bleeding with continuous oral contraceptive pill use. Contraception. 2012;85(4):351-358.*

Unscheduled bleeding is the most common complaint among women who use continuous combination oral contraceptives (OCs). Because unscheduled bleeding has been correlated with the upreg-

ulation of matrix metalloproteinases (MMPs), Kaneshiro and colleagues conducted a randomized, controlled trial of doxycycline (an MMP inhibitor) versus placebo among users of continuous OCs. The addition of doxycycline to the OC regimen did not significantly reduce unscheduled bleeding during the first 84 days of use, but it did shorten the time required to achieve amenorrhea (mean of 61.7 days for doxycycline vs 85.2 days for placebo; standard error [SE], 7.7 vs 6.7, respectively;  $P = .03$ ).



**In women with adenomyosis-related AUB, there were no significant differences in hemoglobin values between those treated with hysterectomy and those given an LNG-IUS**



### WHAT THIS EVIDENCE MEANS FOR PRACTICE

This trial increases our insight into AUB associated with the use of progestins and suggests that concomitant doxycycline may reduce unscheduled bleeding and spotting in women using continuous combination OCs. The trial was of adequate sample size for the primary outcomes, lending credence to its findings, although longer-term data would be helpful.

I have included this trial for two reasons:

- It offers useful information regarding the mechanisms and potential prevention or reduction of AUB-I in users of continuous combined estrogen-progestin contraception.
- Doxycycline is one of the agents covered in a Cochrane review of high-quality research into AUB-I in women using progestin-only products, including injectables, implantables, intrauterine systems, and oral agents.<sup>4</sup> Estrogens have been shown to have some value in reducing breakthrough bleeding associated with depot medroxyprogesterone acetate, and individual use of tranexamic acid or doxycycline has shown value in terminating an episode of breakthrough bleeding in women using progestin-only contraceptives.

### Details and general findings of the trial

Participants (n = 65) were healthy women aged 18 to 45 years who had no contraindications to continuous use of combination OCs. Prior to enrollment, they all had used cyclic combination contraception (pill, patch, or ring) without unscheduled bleeding, thereby avoiding the “transition bleeding” that often occurs when continuous OCs are initiated.

All women in the trial were started on continuous OCs (20 µg ethinyl estradiol with 100 µg levonorgestrel; Aviane) and then

randomly assigned to receive one of the following for 84 days in addition to the OC:

- doxycycline 40 mg daily (controlled-release Oracea), a subantimicrobial dose
- placebo.

After 84 days, doxycycline was discontinued, and participants were observed for an additional 28 days on the OC regimen alone for the documentation of bleeding patterns.

General findings:

- The number of bleeding and spotting days decreased in both groups over the course of the study.
- During the first 84 days of the trial, bleeding and spotting occurred among a median of 11 and 17 women in the doxycycline and placebo groups, respectively, and bleeding alone (without spotting) occurred in a median 3 and 4 women in the doxycycline and placebo groups, respectively.
- During the 28-day observation period, bleeding and spotting occurred among a median of 0 and 6 women in the doxycycline and placebo groups, respectively. Bleeding alone (without spotting) was absent in both groups.
- Women in the doxycycline group were significantly less likely to report side effects such as headache, depressed mood, and abdominal cramping. However, they were more likely to prefer continuous OCs *without* doxycycline, compared with women receiving placebo (16.1% vs 10.7%).

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