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OFFICE GYNECOLOGY DILEMMAS

Nonsurgical options for menorrhagia

What the data reveal about common therapies, and why you don't need to "prove" menorrhagia before treating it

LINDSEY'S CASE

Complaints of menorrhagia but normal findings

Lindsey, a 22-year-old gravida 0, complains about periods that interfere with her life. Although she describes her flow as heavy, she says her periods start every 28 to 30 days, last for 5 days, and do not soak tampons or pads. Nonetheless, she finds them difficult and often misses work because of them. She reports no intermenstrual bleeding, medical problems, prior surgery, pregnancy, or smoking. She is sexually active with a single partner using condoms for birth control. Her physical exam is unremarkable, and her hematocrit is 38%.

Should she be treated for menorrhagia?

Although Lindsey appears to be normal, her periods clearly have a negative impact on her life. In the past, her normal findings might have persuaded her physician to forego treatment, but there is good reason to focus on subjective complaints rather than withholding treatment for "unproven" menorrhagia.

Lindsey is an ideal candidate for medical management because her symptoms are subjective and involve quality of life without much medical risk. She can be started on nonsteroidal anti-inflammatory drugs (NSAIDs) and an oral contraceptive (OC). A suggested regimen: ibuprofen 600 to 800 mg every 6 hours, starting at the

beginning of her period, and a progestone-dominant combined OC.

This article surveys the medical treatments most appropriate for menorrhagia:

- NSAIDs,
- progestins,
- OCs,
- antifibrinolytics, and
- the highly effective progestin-releasing intrauterine system (see "How medical therapies stack up," page 49).

Danazol reduces menorrhagia, but severe androgenic side effects limit its use.

The treatments described here are for ovulatory women with a normal uterus, although some may also be effective in women with structural lesions. (Many women reporting menorrhagia have lesions, especially polyps and fibroids. However, in 1 series of hysterectomy for menorrhagia, 50% of patients had no pathology.¹)

Women with anovulatory bleeding (ie, dysfunctional uterine bleeding) are best managed with OCs or progestins.

No formal studies have explored these therapies in combination, but it may be reasonable to use more than 1, such as OCs and NSAIDs at the same time.

If she says it's heavy bleeding, it is

Heavy menstrual bleeding, or menorrhagia, usually is defined:

- subjectively, as heavy menstrual bleeding occurring over several cycles and disturbing to the patient, or

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How medical therapies stack up

THERAPY	TYPICAL REGIMEN	DECREASE IN MEAN MENSTRUAL BLOOD LOSS (%)*	PERCENT OF WOMEN BENEFITING FROM TREATMENT*	ADVANTAGES	DISADVANTAGES	FREQUENT CONTRA-INDICATIONS	RANKING DECISION ANALYSIS†
NSAIDs	Naproxen 500 mg every 12 hours starting at onset of period	29	51	Simple Inexpensive Also relieves dysmenorrhea	Gastrointestinal upset	Gastritis Peptic ulcer disease	2
Progestins	Norethindrone 5 mg 3 times daily on cycle days 5–26	87	86	Inexpensive	Requires frequent pill-taking Side effects	Undiagnosed bleeding	3
	Medroxy-progesterone acetate 10 mg on cycle days 16–25	–4	18	NA	NA	NA	Not recommended
Danazol	100–200 mg daily	50	76	Listed only for completeness	Androgenic side effects; poorly tolerated; need for contraception at this dose	NA	4
Combined oral contraceptives	Ethinyl estradiol 30 µg and desogestrel 15 mg	43	50	Simple Inexpensive Provides contraception	Requires daily pill-taking Poorly tolerated by subgroup of women	Risk factors for thromboembolism, myocardial infarction	3
Anti-fibrinolytics	Tranexamic acid 1 g 4 times daily on cycle days 1–5	47	56	Effective Simple	Not available in United States Nausea Leg cramps Diarrhea	Risk factors for thromboembolism	2
Progestin-releasing intrauterine system	20 µg levonorgestrel per day (released by device)	94	100	Effective Simple Provides contraception	More expensive Some cases of breakthrough bleeding	High risk for sexually transmitted disease	1

* Estimates taken from New Zealand Guidelines Group¹⁰ note 5.

† Decision analysis from New Zealand Guidelines Group¹⁰ note 7.

- objectively, as menstrual blood loss of more than 80 mL.

Most research uses the objective definition, while most patient referrals are based on subjective symptoms. Although the objective definition may be more precise, it is difficult to use in clinical practice, as it relies on patient self-perception, pad counts, pictograms, and measures of anemia, with varying degrees of accuracy. Besides, there is ample reason to believe that subjective findings warrant treatment as much as objective ones do.

Typical menstrual blood loss is 30 to 40 mL per cycle, with 90% of women experiencing blood loss of less than 80 mL. Many more women meet the subjective definition of menorrhagia than the objective one: 31% describe their bleeding as “heavy.”²²

The roughly 20% of women who do not meet the objective definition but perceive themselves as having heavy menstrual bleeding usually have real symptoms and experience substantial morbidity.

Objective and subjective groups overlap significantly. Warner et al³ noted compara-

ble increases in mood changes, pain with periods, difficulties in containment, and impact on daily life regardless of whether women lost 50 to 79 mL or 80 to 119 mL of menstrual blood. Differences were noted only between extremes: women whose blood loss was less than 50 mL and women with blood losses of 120 mL or more.

Higham and Shaw⁴ noted that 49% of outpatients who complained of heavy periods had normal blood loss (<80 mL), and 27.7% of women who reported normal periods had blood loss exceeding 80 mL.

Nor does sanitary product use reflect blood loss or its impact. Warner et al⁵ showed that women with 30 to 40 mL of blood loss used anywhere from less than 21 to more than 45 products per cycle.

Quality-of-life impact is enormous

Menorrhagia is thought to occur in 9% to 14% of healthy women.⁶ It is a frequent cause of anemia, but its quality-of-life implications go far beyond that. Women in the United Kingdom with heavy menstrual bleeding reported that it had a substantial negative impact on their sex life, social life, and domestic responsibilities.⁷

In the National Health Interview Survey, US women with self-reported heavy bleeding were 45% more likely to use health services than other women,⁸ and 38% less likely to be working, with an estimated \$1,692 in lost annual wages.⁹

Who to treat

Given the difficulty of achieving an objective diagnosis, and the negative effect on quality of life in patients with subjective symptoms alone, offering treatment to any woman complaining of heavy bleeding makes sense. Unfortunately, all randomized trials to date have involved only women with objectively determined blood loss. Nevertheless, the findings of randomized trials are probably generalizable to women with subjective complaints.

How success is measured is important in any treatment. Most studies rely

on objective measurements of changes in blood loss. However, the impact on quality of life may not be related to measured blood loss. Thus, we have only limited data on the subjective effect of treatment.

This article summarizes evidence of decreasing blood loss and improved quality of life. For more extensive reviews, see the Cochrane database.

In addition, the New Zealand Guidelines Group¹⁰ developed a superb summary that uses decision analysis to balance cost, efficacy, and quality-of-life. The same group authored both the Cochrane reviews and the New Zealand guidelines, so the overlap is substantial.

Although these guidelines are 7 years old, little new data has been published in the intervening years for most regimens. When newer data are available, they are summarized here.

Preliminary evaluation

Imaging studies. In general, women with an enlarged uterus, history of polyps or fibroids, or other history or findings suggestive of structural lesions should be evaluated with ultrasound, sonohysterogram, or hysterosalpingogram. Hysteroscopy can be used when there is reason to suspect submucosal myomas or polyps.

Endometrial biopsy may be indicated in older patients with intermenstrual bleeding or risk factors for endometrial carcinoma such as diabetes, obesity, or hypertension.

Confirm ovulatory status to rule out anovulatory bleeding, which usually is well managed with progestins or OCs.

Consider bleeding disorders in adolescents with severe menorrhagia, for whom the American College of Obstetricians and Gynecologists¹¹ recommends screening for von Willebrand's disease. A recent meta-analysis¹² found no evidence to support routine screening in adult women.

Two studies have demonstrated higher risks of bleeding disorders in women reporting heavy bleeding.^{13,14} However, neither suggest routine measurement of the

FAST TRACK

Subjectivity is everything: 49% of women who complain of heavy periods have flow <80 mL, and 27.7% who report normal flow lose >80 mL of blood

prothrombin or partial thromboplastin times. A CBC is helpful, and can be used to monitor therapy in women with anemia.

A poor response to initial therapy may warrant studies for structural lesions, endometrial sampling, and more extensive hematologic evaluation, if these assessments have not already been done.

When observation may be helpful

Many women have been coping with their menorrhagia for some time prior to seeking care. If the bleeding is not causing anemia, its main impact is on quality of life. Although observation has not been formally studied, many women have—intentionally or not—selected no treatment.

Observation is an option for women who merely want reassurance and are willing to live with heavy periods, provided they have no signs of becoming seriously iron-deficient. Observation can continue as long as they desire, but these patients should be followed with serial measurements of hemoglobin or hematocrit. Iron supplementation should be encouraged.

■ Medical therapies

NSAIDs are cheap and effective

These drugs are inexpensive, well tolerated, and moderately effective. A Cochrane review¹⁵ of 9 randomized trials concluded they were significantly better than placebo at reducing blood loss, but less effective than antifibrinolytics or danazol. No differences were noted in comparison with progestins, the progestin-releasing intrauterine system, or OCs—but these studies were underpowered. The New Zealand Guidelines Group¹⁰ found a 20% to 50% decrease in mean menstrual blood loss with NSAIDs.

No real differences between NSAIDs. The oldest and most frequently studied drug is mefenamic acid, but investigators have also considered newer, more commonly used drugs, such as ibuprofen and naproxen, finding no differences.

The drugs in the COX-2 inhibitor

Why some women with normal flow report menorrhagia

In a study of 226 women between the ages of 35 and 49 who complained of menorrhagia, Hurskainen and colleagues²⁴ found normal menstrual flow (ie, <60 mL) in 29%. When they explored whether other factors might be linked to the perception of heavy menstrual flow in these women, they detected an increased incidence of psychosocial problems.

For example, these women were more likely to be unemployed and to have had more pain than women with more blood loss. In addition, on univariate analysis, they had higher levels of anxiety and were more likely to have a history of nongynecologic surgery and physician appointments for reasons other than menorrhagia.

These women appear to differ from women with objectively measured menorrhagia, but it is unclear if they have different personality types that render them less tolerant of bleeding or if their bleeding exacerbates underlying conditions.

class are far more expensive, have not been studied for this use, and were recently linked to an increased risk of cardiovascular complications. Thus, their routine use for menorrhagia should be avoided.

The few trials of NSAIDs that showed no effect involved lower doses, suggesting that maximal doses are important. These drugs usually are initiated at prescription strength at the onset of menses and continued past the usual time of heavy bleeding. **Gastrointestinal side effects** limit use of NSAIDs, which should not be given to women with peptic ulcer disease or gastritis. Because these drugs are used episodically, some women who cannot use them chronically can tolerate their use for menorrhagia. **Effect extends to dysmenorrhea.** NSAIDs are ideally suited to relieve pain in patients with severe dysmenorrhea.

Women tend to perceive NSAIDs as being less effective than other methods.¹⁵

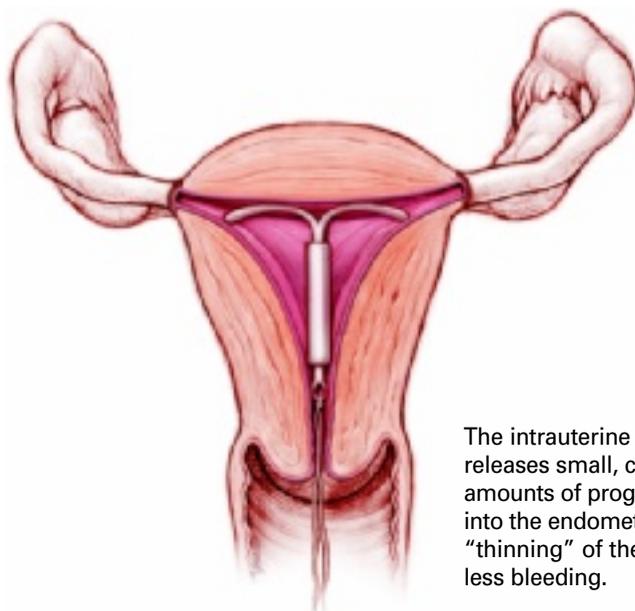
Progestins are effective—but not as they are usually prescribed

Menorrhagia can be managed with a progestin, but not in the way these agents are all too frequently administered: in the luteal phase as medroxyprogesterone (10

FAST TRACK

Start NSAIDs at prescription strength at the onset of menses and continue past the time of heavy bleeding

It's an IUD, but it's hormonal



The intrauterine system releases small, constant amounts of progestin directly into the endometrium, causing “thinning” of the lining and less bleeding.

IMAGE: SCOTT BODELL

FAST TRACK

Oral contraceptives reduced mean menstrual blood loss from 60.2 mL to 36.5 mL after 3 months

mg) for 10 days immediately preceding the expected menses. Although we lack placebo-controlled trials,¹⁶ 4 trials have compared blood loss during this regimen with blood loss during cycles prior to its use in the same patient, showing no improvement.¹⁰ One of these trials showed a 20% *increase* over baseline with this progestin regimen. In addition, the New Zealand Guidelines Group noted a 4% increase in estimated menstrual blood loss.

Prescribing progestins effectively. To be effective, cyclic progestin requires higher doses given throughout the menstrual cycle. The most frequently studied regimen is norethindrone 5 mg, 3 times daily, taken on cycle days 5 through 26. The New Zealand Guidelines Group¹⁰ noted a single randomized trial¹⁷ showing an 87% decrease from baseline with this regimen. Unfortunately, only 44% of women said they liked the treatment “well” or “very well”—probably because of the frequency of administration and the side effects.

Suggested regimen. Despite the limited data, a cyclic progestin can be effective for women who are not candidates for OC use and who hope to avoid surgery. I start patients with the 3-times-daily regi-

men, although some women have been able to take the drug twice or once daily without sacrificing relief.

Alternate strategy: Eliminating menses. Another strategy frequently used but not formally studied is using a progestin—usually depot medroxyprogesterone acetate—to suppress menses entirely.

OCs: Widely used and effective

Evidence is abundant that OCs decrease the length and amount of flow in women with normal menses using them for birth control. A study by Larsson et al¹⁸ showed a reduction from 60.2 mL mean menstrual blood loss to 36.5 mL after 3 months.

Although OCs are frequently used to manage heavy menstrual bleeding, only a single randomized controlled trial was identified by a Cochrane review.¹⁹ The trial²⁰ found OC effects similar to those of naproxen, mefenamic acid, and danazol, with a 43% reduction from baseline. OCs have not been compared with placebo.

OCs also can be given continuously to render the patient amenorrheic.

The vaginal ring and patch have not been studied separately, but probably have similar effects.

Antifibrinolytics: Effective agent is unavailable in United States

This class of drugs decreases fibrinolysis by inhibiting plasminogen activator, and is widely used around the world. It is first-line therapy in many countries, particularly the United Kingdom. However, the most widely used drug, tranexamic acid, is not available in the United States, and this class of drugs is rarely, if ever, used for this indication in this country, although aminocaproic acid, another drug in this class, is FDA-approved for other indications

Usual regimen. Tranexamic acid usually is administered in 1-g units 4 times daily on cycle days 1 through 5.

Efficacy data. The New Zealand Guidelines Group¹⁰ noted a 47% reduction in mean menstrual blood loss and, in its decision analysis, placed tranexamic acid in the second tier of choices, along with NSAIDs,

immediately behind the progestin-releasing intrauterine system, and ahead of OCs.

Side effects include nausea and leg cramps, reported in as many as 33% of users. The main concern is the risk of thrombosis; while this risk is poorly quantified, it is unlikely to exceed the same risk with OCs.

Progestin-releasing intrauterine system: Tops in efficacy

This system is highly effective at reducing menstrual blood loss (see illustration, *left*). It is approved for 5 years of use.

A recent systematic review²¹ noted a 74% to 97% reduction in menstrual blood loss 6 to 12 months after insertion.

The New Zealand Guidelines Group¹⁰ rated this method superior to the other medical options, with a 94% reduction in mean blood loss. This method also fares very well in comparison with surgical alternatives, with only slightly less reduction in blood loss than endometrial resection and equivalent continuation rates at 3 years.²²

In a 5-year follow-up of a randomized trial²³ comparing the intrauterine system with hysterectomy, 58% of women continued use of the device with similar satisfaction with treatment and substantially lower direct and indirect costs.

Disadvantages include its greater expense. In addition, some women experience breakthrough bleeding.

Contraindications include a high risk for sexually transmitted disease. ■

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Dr. Chelmow reports that he has received research support from TAP Pharmaceuticals.

FAST TRACK

Menstrual blood loss decreased 74% to 97% 6 to 12 months after insertion of the progestin-releasing intrauterine system