CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will utilize menstrual manipulation safely to match each patient's needs

CAITLIN W. HICKS, BA
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

ELLEN S. ROME, MD, MPH
Head, Section of Adolescent Medicine, Department of General Pediatrics, Cleveland Clinic Children's Hospital

Menstrual manipulation: Options for suppressing the cycle

ABSTRACT

Menstrual manipulation, ie, adjusting the menstrual cycle by taking hormonal contraceptives, allows women to have their period less often or to avoid bleeding at inconvenient times. The authors review the various options, the benefits, and the disadvantages of this practice.

KEY POINTS

The options for menstrual manipulation are extended or continuous regimens of oral, transdermal, or vaginal hormonal contraceptives; a levonorgestrel-releasing intrauterine device; a progestin implant; and depot medroxyprogesterone injections.

Benefits include fewer menstrual-related syndromes, less absenteeism from work or school, and greater overall satisfaction. Medical indications for it are conditions exacerbated by hormonal changes around the time of menses.

The main disadvantage is a higher rate of breakthrough bleeding.

Myths and misperceptions about menstrual manipulation persist; some physicians believe it is somehow inadvisable.

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If they wish, women can have more control over when and if they menstruate. By using hormonal contraceptives in extended or continuous regimens, they can have their period less often, a practice called *menstrual manipulation* or *menstrual suppression*.

Actually, with the help of their clinicians, women have been doing this for years. But now that several products have been approved by the US Food and Drug Administration (FDA) specifically for use in extended or continuous regimens, the practice has become more widely accepted.

Reasons for suppressing menstrual flow range from avoiding bleeding during a particular event (eg, a wedding, graduation, or sports competition) to finding relief from dysmenorrhea or reducing or eliminating menstruation in the treatment of endometriosis, migraine, and other medical conditions exacerbated by hormonal changes around the time of menses.[1] Alternatively, some women may practice menstrual manipulation for no other reason than to simply avoid menstruation.

MENSTRUAL DISORDERS ARE TROUBLESOME, COMMON

Each year in the United States, menstrual disorders such as dysmenorrhea (painful menstruation), menorrhagia (excessive or frequent menstruation), metrorrhagia (irregular menstruation), menometrorrhagia (excessive and irregular menstruation), and premenstrual syndrome affect nearly 2.5 million women age 18 to 50 years.[2] Menstrual disorders are the leading cause of gynecologic morbidity in the United States, outnumbering adnexal masses

TABLE 1

Current methods of menstrual manipulation

METHOD	TRADE NAME	HORMONAL DOSAGE	DOSING SCHEDULE	ADVANTAGES	DISADVANTAGES
Continuous or extended oral contraceptives	Seasonale Seasonique Lybrel	Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg [a]	Daily	Least invasive	Inconvenience of daily dosing
Intrauterine device	Mirena IUS	Levonorgestrel 20 μg released daily for 5 years	Changed every 5 years	Can be used in women in whom estrogen is contraindicated	75% women continue to have regular cycles
Medroxyprogesterone injections	Depo-Provera	About 1.6 mg/day (150 mg over 90 days)	Intramuscular injection every 90 days	73% women achieve amenorrhea after 1 year	Breakthrough bleeding is common
Transdermal patch	Ortho Evra	Ethinyl estradiol 0.02 mg and norelgestromin 0.15 mg released daily	Weekly	Minimally invasive	Possible increased risk of thromboembolism in some users
Vaginal ring	NuvaRing	Ethinyl estradiol 0.015 mg and etonogestrel 0.12 mg released daily	Every 3 weeks	Produces most uniform serum ethinyl estradiol levels	Increased spotting
Progestin implant	Implanon	Etonogestrel 0.06–0.07 mg/day initially, declining over time (68 mg over 3 years)	Up to every 3 years	Infrequent dosing	78% of women continue to have regular cycles

[a] With Lybrel, ethinyl estradiol 0.02 mg and levonorgestrel 0.09 mg.

(the second most common cause) by a factor of three.[2] In addition, these disorders extend into the workplace, costing US industry about 8% of its total wage bill.[3]

A BRIEF HISTORY OF CONTRACEPTIVE DEVELOPMENT

The idea of using progestins for birth control was first advanced in the 1950s by Dr. Gregory Pincus, who proposed a regimen of 21 days of active drug followed by 7 drug-free days to allow withdrawal bleeding, mimicking the natural cycle.[4] This "21/7" regimen was designed to follow the lunar cycle in the hope it would be, in the words of Dr. John Rock, "a morally permissible variant of the rhythm method,"[5] thereby making it acceptable to women, clinicians, and the Catholic Church.

In 1977, Loudon et al[6] reported the results of a study in which women took active pills for 84 days instead of 21 days, which reduced the frequency of menstruation to every 3 months. Since then, extending the active pills beyond 21 days to avoid menses and other hormone-withdrawal symptoms has become popular in clinical practice, and many studies have investigated the extended or continuous use of oral and other forms of contraception to delay menses.[7–18]

CURRENT METHODS OF MENSTRUAL MANIPULATION

A variety of available products prevent conception by altering the menstrual cycle:

- Oral estrogen-progestin contraceptive pills
- A drug-releasing intrauterine device

- Depot medroxyprogesterone acetate injections
- A transdermal contraceptive patch
- A contraceptive vaginal ring
- An implantable etonogestrel contraceptive.

Their use in menstrual manipulation is summarized in TABLE 1.

Oral contraceptive pills

The most common way to manipulate the menstrual cycle is to extend the time between hormone-free weeks in an oral contraceptive regimen.

If the patient is young, you can prescribe a monophasic 21/7 oral contraceptive and tell her to take one active pill every day for 21 days and then start a new pack and keep taking active pills for up to 84 consecutive days, skipping the placebo pills until she wants to have her menstrual period. She can choose which week to have it: if the scheduled 12th week of an extended-cycle oral contraceptive regimen is inconvenient, she can plan it for week 10, or week 9, or whichever week is convenient.

The rationale for using an 84-day (12-week) cycle is that it still provides four periods per year, alleviating fears of hypertrophic endometrium.[19]

In this scenario, unscheduled or breakthrough bleeding can be managed by taking a "double-up pill" from a spare pack on any day breakthrough bleeding occurs and until it resolves. Menstrual periods should not be planned for intervals shorter than 21 days, owing to the risk of ovulation. Missed days of pills or use of placebo pills should also not exceed 7 days to prevent escape ovulation.[20]

In some women with endometriosis and other medical reasons, continuous oral contraception with no placebo week can be prescribed.

Unfortunately, the downside to suppressing withdrawal bleeding is unscheduled or "breakthrough" bleeding. The best way to treat this unscheduled bleeding is not known. Patients who are not sexually active can be reassured that the goal of an atrophic endometrium can still be achieved, with resultant pill amenorrhea (particularly useful for those with severe dysmenorrhea or other reasons to want to avoid flow). Patients could also try to manage flow by periodically taking a 3- to 5-day break from hormone-containing pills to allow flow. They can also try switching to another oral contraceptive that has a different progestin that would spiral the arterioles of the endometrium more tightly and thus more aggressively induce atrophy.[13,17,21] For instance, levonorgestrel is 10 to 20 times more potent than norethindrone. Choosing a pill with a higher monophasic dosing of levonorgestrel or a similar progestin may minimize unscheduled bleeding.

Currently, several oral contraceptives are approved for use in an extended regimen.

Seasonale was the first oral contraceptive marketed in the United States with an extended active regimen.[22] It comes in a pack of 84 pills containing ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg, plus 7 placebo pills.

Seasonique is similar to Seasonale, but instead of placebo pills it has seven pills that contain ethinyl estradiol 0.010 mg.

Lybrel is a low-dose combination containing ethinyl estradiol 0.02 mg and levonorgestrel 0.09 mg. Packaged as an entire year's worth of active pills to be taken continuously for 365 days without a placebo phase or pill-free interval,[23] it is the only FDA-approved continuous oral contraceptive available in the United States.

The most common way to manipulate the menstrual cycle is to extend the days of active oral contraceptive pills

An intrauterine device

Intrauterine devices were originally developed as contraceptives. The addition of a progestin to these devices has been shown to reduce heavy menstrual bleeding by up to 90%.[24,25]

Mirena IUS, a levonorgestrel-releasing device, is the only medicated intrauterine device that is currently available in the United States. ("IUS" stands for "intrauterine system.") It was recently approved by the FDA to treat heavy menstrual bleeding in women who use intrauterine contraception as their method of pregnancy prevention.[26] About 50% of women who use this device develop amenorrhea within 6 months of insertion, while 25% report oligomenorrhea.[27]

The Mirena device can be left in the

uterus for up to 5 years. It may be a good choice for inducing amenorrhea in women with hemostatic disorders or in whom estrogen either is contraindicated or causes health concerns.[18] The copper intrauterine device (Paragard; Duramed Pharmaceuticals Inc., Pomona, NY) remains a viable option for those who cannot or do not tolerate hormonal therapy. However, Mirena may provide less unscheduled bleeding than the copper intrauterine device.

Depot medroxyprogesterone acetate injections

Depo-Provera (depot medroxyprogesterone acetate) injections are given at 90-day intervals.[28] This contraceptive method inhibits ovulation and decidualizes the endometrium, thereby reducing or eliminating uterine bleeding.[29]

While new users may initially experience excessive prolonged bleeding (10 or more days) while shedding their existing lining, the rate of amenorrhea has been shown to increase over time as the lining atrophies.[30] Thus, prolonged use of this agent reduces the frequency of menstruation as well as menstruation-related symptoms.

Breakthrough bleeding can be managed by taking a 'double-up pill' from a spare pack

Depot medroxyprogesterone acetate is ideal for patients whose menstrual periods pose a significant hygiene problem (eg, developmentally challenged girls). In our experience, the injections can be given at shorter intervals to induce atrophy of the endometrium quickly. In this scenario, the clinician might give an injection every 4 to 6 weeks for two or three doses to induce amenorrhea and then return to every-12-week dosing.

The main risk when using medroxyprogesterone injections to induce amenorrhea is the potential for bone loss. Users of this method have been shown to have lower mean bone mineral density[31–33] and significantly higher levels of biomarkers of bone formation and resorption[32,34] than nonusers. However, these changes are similar to those seen in breastfeeding women,[35] are reversible with cessation,[36] and are not associated with increased fracture risk.[37] In adolescent girls, pregnancy poses similar risks to the bones, with longer-term consequences.

Medroxyprogesterone can also stimulate appetite, causing 10 to 20 kg of weight gain in adolescents and women who are already obese and have trouble with appetite regulation.[38] Slender users tend not to gain weight, however.

Given this information, depot medroxyprogesterone acetate appears to be a cost-effective contraceptive option that should be considered in the context of the clinical situation and preference of each patient.

Transdermal contraceptive patch

Ortho Evra, a transdermal patch, is designed to deliver ethinyl estradiol 0.02 mg and norelgestromin 0.150 mg daily.[39] It is usually applied weekly for 3 weeks, followed by a patch-free week to induce regular monthly withdrawal bleeding.

Extended use of the patch to manipulate menstruation is an off-label use. In the only trial evaluating extended use of the patch, amenorrhea occurred in 12% of users, but unscheduled bleeding and spotting were common.[16]

Although there is some evidence that the long-term use of the patch may increase the risk of venous thromboembolism,[40,41] the risk in women who use the patch has been found to be similar to that in women using an oral contraceptive.[42] However, serum ethinyl estradiol levels have been found to be higher with the use of the weekly patch than with oral contraceptives or the contraceptive vaginal ring[39]; as a result, many physicians are hesitant to recommend its continuous use.

Pending further data about the safety profile of this contraceptive, the World Health Organization Medical Eligibility Criteria for Contraceptive Use suggest that the same guidelines for the prescription of combination oral contraceptives should also apply to the patch.[43]

Contraceptive vaginal ring

NuvaRing, a contraceptive vaginal ring, releases a daily dose of ethinyl estradiol 0.015 mg and etonogestrel 0.12 mg.[10] It is inserted, left in for 21 days, and then removed and left out for 7 days, during which withdrawal bleeding occurs.[10]

Vaginal administration has been shown to

allow low, continuous dosing, which results in more stable serum concentrations than with the patch or oral contraceptives.[39] In the only trial comparing an extended vaginal ring regimen and the traditional 28-day regimen, extended use resulted in fewer overall days of bleeding than monthly use, but with more unscheduled spotting.[15]

The most common side effects include headache, vaginitis, and leukorrhea,[44] but there is no evidence of bacteriologic or cytologic changes in the cervicovaginal epithelium, even with extended use.[45,46]

Etonogestrel implantable contraceptive

Implanon, a single-rod progestin implant, is available in the United States and elsewhere. It is placed subdermally in the inner upper arm and provides contraception for as long as 3 years.

Implanon contains 68 mg of the progestin etonogestrel, which it slowly releases over time, initially at 0.06 to 0.07 mg/day, decreasing to 0.035 to 0.045 mg/day at the end of the first year, to 0.03 to 0.04 mg/day at the end of the second year, and then to 0.025 to 0.03 mg/day at the end of the third year.[47]

The amount of vaginal bleeding associated with the use of the implant is generally modest, but the pattern tends to be unpredictable.[48] In addition, because amenorrhea is reported as a side effect in only 22% of women during the first 2 years of its use,[48] the progestin implant is a less satisfactory means of menstrual suppression than the other methods discussed above.

BENEFITS OF MENSTRUAL MANIPULATION

Menstrual manipulation has a number of benefits in terms of both overall health and lifestyle.

For most women, using a long-acting hormonal contraceptive carries low risks and substantial health benefits. Women who take oral contraceptives are less likely to develop osteoporosis, ovarian or endometrial cancer, benign breast changes, or pelvic inflammatory disease.[49] Long-term use of an oral contraceptive can also preserve fertility by reducing and delaying the incidence of endometriosis,[50] and is effective at treating acne vulgaris, which tends to be common among patients with polycystic ovary syndrome.[51,52] In addition, this practice can be used to reduce overall blood loss, an application that is particularly important in women with a bleeding diathesis such as von Willebrand disease, who frequently suffer from menorrhagia.[53]

Reduced menstruation may also prove more convenient during particular occasions, such as vacations and athletic activities. Specifically, it may be useful to women serving in the military. In a study by Schneider et al,[54] a cohort of 83 female cadets reported a significant perceived impact of premenstrual and menstrual-related symptoms on academic, physical, and military activities, as well as difficulties in obtaining, changing, and disposing of menstrual materials in a military setting. Likewise, reduced menstrual frequency or amenorrhea may play an important role in female athletes, who reportedly use oral contraceptives to control premenstrual symptoms, to protect bone health, and to manipulate the menstrual cycle in order to maximize performance.[55]

Adolescent girls are another group who may benefit from reduced or absent menses, once they have reached near-final height. By practicing menstrual suppression, girls can avoid dysmenorrhea and the inconvenience of menstruation during the school day, when their access to painkillers, sanitary pads or tampons, and a change of clothes may be limited.[56] Clinicians who discuss with teenage patients the benefits of innovative hormonal contraceptive schedules that reduce menstrual frequency may be able to improve the quality of life for these young women.

Extended use of the contraceptive patch to manipulate menstruation is an off-label use

In a very short girl just after menarche, care must be taken not to start a hormonal method too early so as not to prematurely close epiphyses and stunt final height; after menarche, most girls still have 1 to 4 inches of potential growth. For a young lady 4 feet 11 inches tall, that extra inch may be important.

Finally, menstrual manipulation may also find a niche among the developmentally challenged. Women with cognitive impairment and physical disabilities may have difficulty with hygienic practice around menses. For a number of years, contraceptives have been used to manage menstrual hygiene in patients with catamenial (ie, menstrual) epilepsy, and

to address caregiver concerns in women with severe mental retardation, with improved behavior noted in some patients.[57–59] In this setting, an agent that suppresses menses and also provides contraception, especially for those girls and women at risk of abuse, may offer substantial benefits.

DISADVANTAGES OF MENSTRUAL MANIPULATION

Rates of adverse events and of discontinuation of extended and continuous oral contraceptive regimens are comparable with those reported for cyclic regimens, except for higher rates of breakthrough bleeding.

In a trial of continuous oral contraceptive use in more than 2,000 patients, 396 (18.5%) withdrew from the study as a result of bothersome uterine bleeding.[60] However, while breakthrough bleeding often occurs during the first few months of extended oral contraceptive use, it usually decreases with each successive cycle of therapy and is comparable to that reported by patients on the conventional oral contraceptive regimen by the fourth extended cycle.[12]

Mirena was recently approved to treat heavy menstrual bleeding

CONTRACEPTIVE EFFICACY

The efficacy of extended and continuous oral contraceptive regimens is comparable with that of cyclic regimens.[12,60,61] One reason for this may be better adherence to continuous regimens: women using this regimen have been shown to miss fewer pills than those on a cyclic regimen, especially during the critical first week of the pill pack.[21]

Several studies have shown that some women ovulate during the standard 21/7 oral contraceptive regimen even if they do not miss any pills or take pills off-schedule, putting them at greater risk of pregnancy.[62] Large studies evaluating the efficacy of an extended-cycle regimen have shown a pregnancy rate during the 1-year study period that was either comparable with[61] or lower than[12,60] rates with standard regimens.

Heterosexual couples need to be advised to use condoms to further reduce the already low failure rate and to prevent sexually transmitted diseases.

ACCEPTABILITY OF MENSTRUAL MANIPULATION

Ever since the earliest trial of an extended oral contraceptive regimen, participants have expressed a favorable response to the resulting decrease in menstrual frequency; in the 1977 study by Loudon et al,[6] patients on the extended regimen cited infrequent periods (82%), fewer menstrual problems (20%), and easier pill-taking (19%) as favorable features.

In 1999, den Tonkelaar and Oddens[63] surveyed 1,300 Dutch women about their preferred frequency of menstruation and found that about 70% between the ages of 15 and 49 preferred a frequency of between every 3 months and never. A similar survey in the United States indicated that 58% preferred a bleeding frequency of either every 3 months or never to more frequent periods.[64]

While patients find menstrual manipulation generally acceptable, clinician approval has been more varied. Loudon et al reported that "the doctors and nurses on the clinic staff were less enthusiastic about this regimen than the volunteers themselves."[6] In a survey of 222 clinicians,[65] 90% of responders reported ever having prescribed extended or continuous dosing regimens to adolescents, and 33% reported that extended cycles made up more than 10% of their total oral contraceptive prescriptions.

Myths and misperceptions about menstrual manipulation abound. Many clinicians believe that routine use of an extended or continuous oral contraceptive regimen is inadvisable, despite the lack of evidence to support this notion.[66] Therefore, many care providers need more education about the practice and benefits of menstrual manipulation.

THE RIGHT METHOD FOR THE RIGHT PATIENT

Manipulation and suppression of menstruation through continuous or extended use of oral contraceptives or by other means may have a number of advantages to women, including fewer menstrual-related syndromes, reduced absenteeism from work or school, and greater overall satisfaction.

For women whose goal is to reduce but not necessarily to eliminate monthly bleeding, the cyclic use of estrogen-progestin contraception (rather than progestins alone or continuous use of combined hormonal preparations) is suggested.

For women whose goal is amenorrhea, depot medroxyprogesterone acetate injections, continuous oral contraceptives, and the levonorgestrel intrauterine device are all effective.[67] Although randomized trials comparing these methods have not been done, depot medroxyprogesterone appears to have the highest rate of amenorrhea, while the levonorgestrel intrauterine device is the most convenient and appears to be associated with fewer bothersome side effects than progestin injection.[68] Patients using depot medroxyprogesterone should have their bone density followed to detect and prevent bone loss, while users of estrogen-progestin pills, the transdermal patch, or the vaginal ring should not have any contraindications to the use of contraceptive doses of estrogen (TABLE 2).[69]

Clinicians should not overestimate the risks of oral contraceptives and other hormonal methods, but rather educate themselves so that they can utilize menstrual manipulation safely to match the individual patient's needs.

TABLE 2

Contraindications to combined estrogen-progestin oral contraceptive use

Breast cancer or other hormone-sensitive cancer, now or in the past
Liver tumors, now or in the past, or liver disease
Any condition predisposing to thrombotic diseases
Thrombophlebitis or pulmonary embolism, now or in the past
Cerebrovascular disease
Coronary artery disease
Thrombogenic valvular or thrombogenic rhythm diseases of the heart
Congenital hypercoagulopathies
Diabetes with vascular disease
Uncontrolled hypertension
Migraines with focal neurologic symptoms
Smoking and age greater than 35 years
Pregnancy

ADAPTED FROM US FOOD AND DRUG ADMINISTRATION. GUIDANCE FOR INDUSTRY LABELING FOR COMBINED ORAL CONTRACEPTIVES, 2004. WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGULATORYINFORMATION/GUIDANCES/UCM075075.PDF.

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***ADDRESS**: Ellen S. Rome, MD, MPH, Department of General Pediatrics, A120, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail romee@ccf.org.*