Unscheduled vaginal bleeding with progestin-only contraceptive use

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Nearly 20% of women using contraception are using progestin-only contraception, including progestin-only pills, depot-medroxyprogesterone acetate, subdermal etonogestrel implants, and levonorgestrel intrauterine devices. This number will continue to grow with the increased provision of long-acting reversible contraception. Although overall satisfaction among women using progestin-only contraception is high, dissatisfaction and discontinuation may be associated with unscheduled bleeding and spotting. The exact etiology of irregular bleeding associated with progestin-containing contraceptives is not completely understood, yet several mechanisms have been suggested. Several therapies targeting these mechanisms have been evaluated with mixed results. This paper will review the physiology and management of unscheduled bleeding with progestin-containing contraceptives.

Key words: irregular bleeding, long-acting reversible contraception, progestin-only contraception, unscheduled bleeding

Progestin-only methods of contraception include progestin-only pills (POPs), depot-medroxyprogesterone acetate (DMPA), subdermal etonogestrel (ENG) implants, and levonorgestrel intrauterine devices (LNG IUDs). Use of progestin-only methods is increasing, in part because of growing popularity of long-acting reversible contraceptives (LARC) but also because they are safe in women with other medical comorbidities.

The LARC methods, including intrauterine devices (IUDs) and implants are appealing for their ease of use, long-term protection, noncontraceptive benefits, and relatively few contraindications. Despite the benefits, both LARC and shorter acting progestin methods can result in unscheduled bleeding and spotting, which may lead to dissatisfaction and discontinuation.[1]

Unscheduled bleeding and spotting while on active hormones is subjective but has been defined in the literature as any bleeding requiring the use of a sanitary product. Estimating the prevalence is difficult because the literature has not been consistent. A recent study evaluating reasons for early discontinuation (within 6 months of initiation) among LNG IUD and ENG implant users found irregular/frequent bleeding was reported in 9% and 53% of these women, respectively.[2]

The Contraceptive Choice Project evaluated reasons for discontinuation in women who chose the LNG IUD, ENG implant, or DMPA at least once during their study participation. Among discontinuers, 19% of LNG IUD users, 46% of ENG implant users, and 26% of DMPA users listed bleeding changes as their main reason for discontinuation.[3]

Bleeding patterns are not standardized across the different forms of progestin-only contraceptives. Bleeding patterns can range from amenorrhea to unpredictable timing with varying degrees of flow to normal monthly menses. Unscheduled bleeding/spotting has been consistently demonstrated as a side effect for all progestin-only contraceptives.

The etiology of such bleeding is poorly understood: over the past 35 years, 5 different World Health Organization workshops have attempted to investigate the pathogenesis. Part of the difficulty with identifying the predominant etiology is the multiple contributors to the problem. Unscheduled bleeding is likely influenced by type/dose of progestin, how the progestin is delivered, duration of use, and specific effects to the endometrium because of the mechanism of action.

The quantity/duration of bleeding may change between the initiation of a method and continuation of that method. A leading cause of unscheduled bleeding with initiation is thought to be secondary to the rapid endometrial thinning effects of progestins. More practically, if women are going from relatively thick endometrium to relatively thin endometrium, it is biologically plausible that unscheduled bleeding/spotting will result.[4] As women continue their method, sustained exposure can lead to endometrial angiogenesis disruption, resulting in the development of a dense venous network that is fragile and prone to bleeding.[5]

Treatment of unscheduled bleeding/spotting from a progestin-containing contraceptive may increase acceptability, which may increase continuation rates. We will discuss different forms of progestin-containing contraceptives and their mechanisms of action, possible mechanisms for unscheduled bleeding/spotting, and current considerations for management of this bothersome side effect.

Progestin-containing contraceptive methods

Progestin-only pills

Progestin-only pills, or POPs, are available in the United States in 1 formulation: norethindrone 0.35 mg tablets.

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This pill should be taken daily at the same time because POPs have a short duration of action and short half-life.[6] The primary mechanism of action for the POPs is increased viscosity of cervical mucus, which inhibits sperm penetration. Secondary mechanisms of action include the thinning of the endometrium, decreased action of the tubal cilia, and suppressed ovulation.[7]

Two hours after ingestion, POPs reach a maximum serum level, and therefore maximum effect, within hours. This effect persists for approximately 20−24 hours, when serum levels return to near baseline, making consistently timed daily administration imperative.[7,8]

A previous study suggested that when compared with combined oral contraceptive (COC) users, women using POPs have more frequent and longer episodes of bleeding as well as shorter, less predictable intervals between bleeding.[9] Although unscheduled bleeding is the most common side effect in women using POPs, with approximately 40% of users having irregular cycles, up to 50% of users have regular monthly menses, and approximately 10% report amenorrhea.[4,7,9,10] These differences are likely secondary to large variations of serum levels of progestin among users and daily fluctuations in serum levels.[7]

Previous endometrial biopsy studies have shown a variable/unpredictable endometrial response to POPs. Patterns include irregular secretory endometrium, lack of proliferation, suppressed proliferation, and an increase in the number of veins and number of dilated veins at the endometrial/myometrial junction.[11] The variety of histological findings further supports the difficulty in clearly identifying the etiology and effective treatment approaches.

Depot medroxyprogesterone acetate

Depot medroxyprogesterone acetate, or DMPA, is currently the only form of injectable contraceptive in the United States. Previously, DMPA was administered in only 1 form: 150 mg per 1 mL given intramuscularly every 13 weeks. Now DMPA can also be administered in a subcutaneous formulation (104 mg per 0.65 mL) every 13 weeks. Because of the higher serum levels of progestin, DMPA will suppress ovulation via inhibition of gonadotropin secretion. With decreased ovarian function, a hypoestrogenic state occurs, which will ultimately inhibit endometrial proliferation. Cervical mucous changes as well as decreased tubal motility may also occur with DMPA.[12]

Both formulations of DMPA reach their peak blood concentrations within the first 3 weeks after administration. The subcutaneous formulation persists at 0.2 ng/mL through day 91, and the intramuscular formulation persists at 0.4 ng/mL through day 84. They both become undetectable between days 120 and 200.[13,14]

The majority of women using DMPA experience menstrual changes as a result of the high level of progestin. During the months after the first to second injection, episodes greater than 7 days of unscheduled bleeding/spotting are common.[15] This potentially is due to endometrial instability and subsequent capillary leakage from scant uterine lining.[16] The frequency/duration of these episodes decreases with continued use. Forty-six percent of users will be amenorrheic by 1 year and 70% with longer use.[15] These rates are similar in both intramuscular and subcutaneous formulations.[16]

Endometrial biopsy studies show a predominance of endometrial atrophy and chronic endometritis. The latter most often is due to atrophy rather than an infectious process.[4,17]

Subdermal implant

The implant is currently marketed in the United States as Nexplanon and contains the progestin ENG. This implant is a 40 mm × 2 mm semirigid plastic rod containing 68 mg of ENG and is currently approved by the Food and Drug Administration for 3 years of use. Recent data suggest extended efficacy to at least 5 years.[18,19] As with DMPA, the ENG implant prevents conception by inhibiting gonadotropin secretion to aid in ovulation suppression. Secondary mechanisms include cervical mucus and tubal motility changes.[20]

Once placed, the implant slowly releases etonogestrel. These rates are the highest after placement and then slowly decrease, peaking at 70 μg/d and slowly decreasing to 25−30 μg/d by the end of 3 years of use.[21]

The ENG implant is associated with unpredictable alterations in a woman's bleeding pattern, from amenorrhea to recurrent, unscheduled bleeding.[22] Bleeding patterns with the ENG implant tend to be more unpredictable than with DMPA and the LNG IUD. In a previous study, 78% of women had unscheduled bleeding in a 3 month period.[23] Yet if a woman has a favorable bleeding pattern during her first 3 months after initiation, she will likely continue to have a favorable bleeding pattern.

Recent data suggest that women who initially reported unfavorable bleeding patterns ultimately had an approximately 50% chance of improvement with continued use.[23] Furthermore, 30% of users will be amenorrheic by 1 year of use.[24,25] Bleeding pattern with the implant is thought to be secondary to atrophy as well as disruption in endometrial angiogenesis, creating a fragile venous network.[23,26]

Intrauterine device

The LNG IUD is currently marketed in 4 forms in the United States: Mirena, Liletta, Kyleena, and Skyla. The mechanism for all LNG IUDs is dominated by local effects of thickened cervical mucus, endometrial decidualization, glandular atrophy, and increased glycodelin A production, which inhibits fertilization.[27] Ovulation suppression is not a primary mechanism of action for the LNG IUD.[28]

Mirena, or LNG IUD 52/5 (mg of LNG per years of Food and Drug Administration approval), releases 20 μg/d for 5 years. After 5 years, the release rate decreases slowly to 10−14 μg/d. Recent data suggest extended efficacy to 7 years.[18,29]

Liletta, or LNG IUD 52/3, releases 18.6 μg/d over 3 years. After 3 years, this rate slowly decreases to 13 μg/d. There is ongoing data collection with plans to apply for extended approval of up to 7 years.[30]

Kyleena, or LNG 19.5/5, releases 17.5 μg/d for 5 years. After 5 years, this rate slowly decreases to 7.4 μg/d.[31]

Finally, Skyla, or LNG IUD 13.5/3, releases 14 μg/d for 3 years. After 3 years, this rate slowly decreases to 5 μg/d.[32]

Rates of amenorrhea differ among the formulations. For LNG IUD 52/5 and LNG IUD 52/3, 20% of users experience amenorrhea within 1 year and 50% within 2 years.[33,34] The LNG IUD 19.5/5 has a lower rate of amenorrhea, 12%, at the end of year 1. Data for amenorrhea at 2 years are not available, but rates at 5 years are reported to be 23%.[31] The LNG IUD 13.5/3 behaves differently, likely attributable to a lower dose of LNG released, causing amenorrhea in only 6% and 12% of users within 1 and 2 years, respectively.[32]

Up to 52% of women using any form of LNG IUD have some form of unscheduled bleeding.[32-34] Importantly, unlike the ENG implant, data suggest that bleeding patterns experienced with the LNG IUD tend to improve with continued use and for most within 12 weeks of insertion.[35] This likely is due to strong endometrial suppression provoked by high local LNG concentration within the endometrial cavity, leading to atrophy of the glandular epithelium.[35] Other changes noted are extensive decidualization of endometrial stromal cells and changes in vascular morphology.[36]

Management of unscheduled bleeding

Anticipatory counseling regarding unscheduled bleeding for women initiating progestin-only methods is important. Even with adequate counseling, many women may still express dissatisfaction with their bleeding pattern. It is important to remind women that unscheduled bleeding is not indicative of decreased efficacy of their method. Yet pregnancy should always be ruled out if a woman complains of an abrupt change in her bleeding pattern.

A detailed description of the bleeding pattern should be elicited. It is important to distinguish between unscheduled bleeding that is bothersome to the patient and unscheduled bleeding that is tolerable or insignificant to the patient. Women in the latter category do not necessarily require intervention. For women in whom the bleeding changes are bothersome, the following questions may be helpful in eliciting potential causes:

- What was her bleeding pattern both before and during her current contraceptive use?
- How many bleeding days is she having per month?
- If she is using a non-LARC method, such as POPs or DMPA, is she using it correctly?
  - Is her bleeding heavy or light?
  - Is she having regular/irregular cycles or is the bleeding intermenstrual?
- Is she taking any other medications (ie, antiepileptic drugs, St John's Wort) that could interact with her contraceptive and therefore affect her bleeding?
- Are there any symptoms that are associated with her bleeding (ie, pain, nausea, vomiting, breast tenderness)?
- Does the bleeding occur at specific times (ie, after sex)?

Examination and/or further testing should be considered based on the individual clinical situation. For example, if she complains of symptoms including pain, vaginal discharge, and postcoital bleeding, a workup for cervicitis or endometritis may be indicated. If unscheduled bleeding is believed to be secondary to progestin-only contraception, further workup is often not necessary; however, a pelvic examination or ultrasound may be helpful in IUD users to confirm that the device has not been expelled.

If pathology is not suspected, or has been ruled out, and the bleeding pattern is bothersome to the patient, intervention may be considered. Because the etiology of unscheduled bleeding with progestin-only contraception is not fully understood and potentially multifactorial, investigated therapies have shown mixed results. Previous studies have been performed in populations of women using progestin contraceptives not used in the United States; therefore, some therapies are extrapolated from those used in similar contraceptive methods.

We will review the available data for all investigated potential treatments. This will include larger and more robust studies as well as those that are smaller and exploratory in nature.

Medical therapy: nonsteroidal antiinflammatory

Nonsteroidal antiinflammatory (NSAID) medications primarily act by inhibiting cyclooxygenase, which is a prostaglandin synthase. Given that some women with irregular bleeding have been shown to have elevated levels of prostaglandin (PGE_2 and PGF_{2a} increase during the secretory phase), short courses of NSAIDs could plausibly have an impact on this particular mechanism (Table 1).[37,38]

Studies using mefenamic acid have shown that it decreases bleeding days in DMPA in the short term as well as both the short and long term in both ENG and LNG implant users.[38,40,43] When tested in women using the ENG implant in a randomized controlled trial (RCT), mefenamic acid users (n = 25) had fewer bleeding episodes over 4 weeks as compared with the placebo group (n = 25) (10.5 days vs 16.8 days, $P < .05$).[40] This study did not include subjective assessment of patient satisfaction of resultant bleeding patterns; therefore, it is difficult to understand the clinical significance of 10.5 vs 16.8 bleeding days. Regardless, this study did suggest that NSAIDs may demonstrate improvement in an LNG method user and thus led to the investigation of naproxen in LNG IUD users.

In an RCT of LNG IUD users, naproxen users (n = 42) demonstrated a 10% decrease in bleeding/spotting days when compared with the placebo group (n = 43) (adjusted relative risk 0.90, 95% confidence interval [CI], 0.84−0.97) during the active treatment period.[46] However, these results were not sustained beyond the 4 weeks following treatment.

These studies suggest a short course of NSAIDs may be helpful in some women, although interruption in bleeding may not be sustained. Although mefenamic

TABLE 1
Previous studies of nonsteroidal antiinflammatory medications

Contraceptive	Medical therapy
DMPA	Mefenamic acid 500 mg 2 times per day × 5 days[38]
	Valdecoxib 40 mg daily × 5 days[39]
ENG implant (Implanon)	Mefenamic acid 500 mg 3 times per day × 5 days[40]
LNG implants (Norplant[a]; Jadelle[b])	Ibuprofen 800 mg 3 times per day × 5 days[41]
	Ibuprofen 800 mg 2 times per day × 5 days[42]
	Mefenamic acid 500 mg 2 times per day × 5 days[43]
	Aspirin 80 mg daily × 10 days[44]
	Celecoxib 200 mg daily × 5 days[45]
LNG IUD	Naproxen 500 mg 2 times per day × 5 days[46]

DMPA, depot-medroxyprogesterone acetate; *ENG*, etonogestrel; *LNG*, levonorgestrel; *LNG IUD*, levonorgestrel intrauterine device.

[a] No longer available in the United States; [b] Available internationally but not in the United States.

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acid was tested only in DMPA and implant users and naproxen in LNG IUD users, it is reasonable to try these therapies in other progestin-only methods. For many patients, naproxen is likely more accessible because it is less expensive and available over the counter. Use of any NSAIDs may be contraindicated in women with some medical conditions such as a history of gastrointestinal bleeding, renal impairment, or allergy.

Medical therapy: estrogen

Estrogen, whether given by itself or as a COC, may be an option for some women. Exogenous estrogen may aid in tissue repair and stabilization of the endometrial lining (Table 2).

Few studies have evaluated the use of transdermal estrogen. The first randomized users of the LNG IUD to a 0.1 mg estradiol patch (n = 44) and placebo (n = 43) for the first 12 weeks of IUD use. Surprisingly, the study demonstrated an increase in bleeding/spotting days in women randomized to estrogen therapy (adjusted relative risk 1.25, $P < .05$).[46]

A second study with transdermal estrogen randomized users of the LNG implant to the 0.1 mg estradiol patch (n = 33) and placebo (n = 31) and measured clinical improvement, or bleeding less than 8 days or an interval of bleeding-free days greater than 20 days. Twenty-three of the patch users (69.7%) and 13 of the placebo users (41.9%) had clinical improvement, which was not statistically significant (statistical analysis not shown).[50]

Several studies have evaluated oral estrogen, and most have shown a benefit.[47-49] When compared with placebo, 93% (84 of 90) of DMPA participants randomized to 50 μg ethinyl estradiol for 14 days reported bleeding cessation vs 74% (72 of 97) receiving placebo ($P < .001$).[47]

One study, with a relatively small sample size (n=26), aimed to evaluate COCs in ENG implant users. Participants were randomized to 1 month of COC (n = 13) or placebo (n = 13). Although all women randomized to COCs reported bleeding/spotting resolution as opposed to 75% of placebo users, the study was stopped early secondary to difficulty with recruitment and did not meet its predetermined sample size.[48]

Finally, in a 3 arm study that randomized LNG implant users to ethinyl estradiol (n = 33), COC (n = 45), and placebo (n = 46), 91%, 67%, and 15%, respectively, saw bleeding cessation within 3 days of use. In this study, COC and ethinyl estradiol were significantly different from placebo ($P < .01$) and COCs showed greater improvement than ethinyl estradiol ($P < .01$).[49]

Summation of these studies evaluating estrogen-containing interventions suggest that an oral method may be of benefit. Suggested regimens include oral conjugated estrogen 1.25 mg or estradiol 2 mg (because ethinyl estradiol is not available as a monotherapy in the United States) daily for 1−2 weeks or COCs for 1−3 cycles. More data are needed to know whether extended continuous regimens improve outcomes. Unfortunately, estrogen is contraindicated in many medical comorbidities (ie, migraine with aura, history of venous thromboembolism, or tobacco use over the age of 35 years), eliminating this option for many women.

TABLE 2
Previous studies of estrogen

Contraceptive	Medical therapy
DMPA	EE 50 μg daily × 14 days[47]
ENG implant	LNG 150 μg/EE 30 μg daily × 4 weeks[48]
	LNG 150 μg/EE 30 μg daily × 14 days[26]
LNG implant (Norplant)	EE 50 μg daily × 20 days[41,49]
	EE 20 μg daily × 10 days[42]
	LNG 250 μg/EE 50 μg daily × 20 days[49]
	Estradiol patch 0.1 mg/d × 6 weeks[50]
LNG IUD	Estradiol patch 0.1 mg weekly × 12 weeks[46]

DMPA, depot-medroxyprogesterone acetate; *EE*, ethinyl estradiol; *ENG*, etonogestrel; *LNG*, levonorgestrel; *LNG IUD*, levonorgestrel intrauterine device.

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Medical therapy: doxycycline

At subantimicrobial doses, doxycycline inhibits matrix-metalloproteinase (MMP) activity. MMPs play an important role in tissue remodeling, and it is thought that increased MMP activity within the endometrium is a cause for unscheduled bleeding (Table 3).

An RCT in women using DMPA assigned women to 100 mg of doxycycline daily for 5 days (n = 34) or placebo (n = 34) and demonstrated no benefit of doxycycline when evaluating bleeding cessation by day 10 (relative risk, 0.88, 95% CI, 0.64−1.21).[51] Furthermore, there was no significant difference in the number of bleeding/spotting days in the 3 months following treatment (doxycycline group with 7.28 days of bleeding and 3.77 days of spotting vs placebo group with 7.38 days of bleeding and 3.66 days of spotting, both with $P >$ .05).[51] An RCT in women using the ENG implant comparing doxycycline (n = 45) with placebo (n = 45) did, however, show a statistical difference, with doxycycline being superior.

The primary outcome in this study was time to bleeding cessation, and subjects randomized to doxycycline achieved bleeding cessation more quickly, 4.8 days as compared with 7.5 days.[52] The authors set out to replicate the study with a planned enrollment of 490 subjects. Despite not being able to duplicate their findings, they were able to enroll only 42% (n = 204) of their planned sample.[52,53]

Despite inconsistent results, if endometritis is believed to be a potential contributor to the etiology of an individual's disrupted bleeding, doxycycline 100 mg 2 times per day for 10−14 days may be worthwhile. This medication has few contraindications, but we must acknowledge possible side effects including gastrointestinal symptoms and potential for antibiotic resistance.

TABLE 3
Previous studies of doxycycline

Contraceptive	Medical therapy
DMPA	Doxycycline 100 mg 2 times per day × 5 days[51]
ENG implant	Doxycycline 100 mg 2 times per day × 5 days[52,53]

DMPA, depot-medroxyprogesterone acetate; *ENG*, etonogestrel.

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Medical therapy: tranexamic acid

Tranexamic acid (TXA) is an antifibrinolytic medication that has been previously used for heavy menstrual bleeding. It aids in decreasing clot breakdown, thus decreasing bleeding (Table 4).

In an RCT, Senthong et al demonstrated using 250 mg of TXA 4 times a day (n = 50) compared with placebo (n = 49) showed a positive effect with unscheduled bleeding, both in the acute phase and at 4 weeks for DMPA users.[54] Specifically, bleeding cessation was seen in 88% of TXA users as compared with 8.2% of placebo users ($P < .001$). At 4 weeks, this difference persisted, with 68% of TXA users continuing to have no bleeding as compared with 0% of placebo users ($P < .001$).[54]

Yet TXA was effective only during this studied treatment phase and not long term when studied in the LNG implant.[55] In this study, during the first week, 65% of TXA users experienced bleeding cessation as compared with 35% of placebo users, which was statistically significant ($P = .015$), but there was no statistical difference at 4 weeks after treatment when measuring bleeding-free intervals of greater than 20 days (59% TXA vs 77% placebo, $P = .12$).[55]

Finally, when a trial randomized women with LNG IUDs to TXA (n = 63) or placebo (n = 61), they saw a decrease of bleeding and spotting days by a median of 6 days over a period of 90 days ($P = .049$). This significance was not seen after adjusting for multiplicity.[56]

In summary, TXA showed benefit in the DMPA trial and acutely for the LNG implant but not for the LNG IUD. In the United States, TXA is available in 650 mg tablets. A common regimen used for abnormal uterine bleeding can be extrapolated: 1300 mg 3 times a day for 5 days. Because of the mechanism by which it works, TXA must be avoided in women with a personal history of or increased risk of venous thromboembolism.

Medical therapy: mifepristone

Mifepristone is an antiprogestin that may lead to the up-regulation of estrogen receptors within the endometrium, thus stabilizing the endometrium (Table 5).[20]

Mifepristone has been shown to decrease bleeding days in users of DMPA, LNG implant, and LNG IUD when used prophylactically.[57-59] In an RCT of DMPA users in their first 3 months of use, women who also took mifepristone (n = 20) experienced a median percentage days of breakthrough bleeding of 15 as compared with 36 in women taking placebo (n = 20) ($P = .05$). At 6 months, though, results were no longer significant (7 vs 18, respectively, $P = .52$).[57]

TABLE 4
Previous studies of tranexamic acid

Contraceptive	Medical therapy
DMPA	TXA 250 mg 4 times per day × 5 days[54]
LNG implant	TXA 500 mg 2 times per day × 5 days[55]
LNG IUD	TXA 500 mg 3 times per day from bleeding onset until day after bleeding cessation[56]

DMPA, depot-medroxyprogesterone acetate; *LNG*, levonorgestrel; *LNG IUD*, levonorgestrel intrauterine device; *TXA*, tranexamic acid.

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TABLE 5
Previous studies of mifepristone

Contraceptive	Medical therapy
DMPA	Mifepristone 50 mg × 1 every 14 days[57]
ENG implant	Mifepristone 25 mg 2 times daily × 1 day[53]
LNG implant	Mifepristone 100 mg daily × 2 days[58]

DMPA, depot-medroxyprogesterone acetate; *ENG*, etonogestrel; *LNG*, levonorgestrel.

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Although the total number of bleeding/spotting days during a 6 month treatment phase showed a 35% decrease when the mifepristone group (n = 58) was compared with the placebo group (n = 57), in women with LNG implants ($P < .001$), this was not observed at the individual level.[58]

Although this is a promising medication in the acute phase, most studies use a dose that is not available in the United States (available dose is 200 mg). Also, as an abortifacient, this medication is highly regulated, not available for pharmacy distribution, and requires physicians to be registered with the manufacturer. Finally, there have been concerns that an antiprogestin may alter the contraceptive efficacy of progestin-only contraception, although these concerns have not been well studied.[57,58] Allergy is the main contraindication to this medication.

Medical therapy: tamoxifen

Tamoxifen, a selective estrogen receptor modulator, may work by antagonizing the angiogenic effect of estrogen (Table 6).[22]

Although there are not many studies, tamoxifen has been noted to have a beneficial effect in unscheduled bleeding in the acute period. In a recent RCT comparing tamoxifen (n = 28) and placebo (n = 28) in ENG implant users, the investigators found that women using tamoxifen had 5 fewer bleeding/spotting days than those using placebo within a 30 day period (95% CI, −9.9 to −0.05). They also experienced 15 more continuous bleeding free days (95% CI, 2.8−27.5).[59] Benefit was also demonstrated in an RCT of tamoxifen (n = 50) and placebo (n = 50) in LNG implant users. This study demonstrated bleeding cessation was seen in 88% of the tamoxifen group as compared with 68% in the placebo group ($P = .016$) at 3 months.[60] Further research with larger trials is needed before routine use of tamoxifen is undertaken.

Conclusion

Unscheduled bleeding and spotting with progestin-only contraceptive use is of utmost importance because it is a contributing cause for discontinuation, which can leave women vulnerable to unintended pregnancy. Prior to initiation of progestin-only contraception, it is important to discuss the likelihood of unscheduled bleeding/spotting. Setting this expectation may decrease a woman's dissatisfaction. Women should also be counseled, prior to initiation, that up to 3 months may be required to establish their new bleeding pattern and that for many methods, problematic bleeding improves over time.

When a woman presents with irregular bleeding, she should first be reassured. If appropriate, further workup such as ruling out infection or other pathology should be performed. In women with an IUD, correct placement should be confirmed. If bleeding persists and the woman desires treatment, a course of NSAIDs or estrogen (alone or as COC) may be of use. If these medications are contraindicated or unsuccessful, other available options include doxycycline, TXA, mifepristone, and tamoxifen, although not all may be accessible/appropriate for all patients. Doxycycline may be helpful if the patient is believed to have endometritis, either acute or chronic.

TXA has shown some benefit in a DMPA trial and may be of clinical benefit with the IUD. Mifepristone, although promising for acute bleeding, is not available in the United States in the studied dose and is otherwise difficult to obtain.

Finally, tamoxifen has been studied with implant use and may provide an increase in continuous bleeding-free days. Further research is needed on all of these medications because many studies show mixed reviews. Thus, these medications may be helpful in a subset of woman but not helpful in another, and treatment, as in most cases, should be tailored to the individual woman. ■

TABLE 6
Previous studies of tamoxifen

Contraceptive	Medical therapy
ENG implant	Tamoxifen 10 mg 2 times per day × 7 days[59]
LNG implant	Tamoxifen 10 mg 2 times per day × 10 days[60]

ENG, etonogestrel; *LNG*, levonorgestrel.

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