Curr Obstet Gynecol Rep (2017) 6:198–206
DOI 10.1007/s13669-017-0219-x

FAMILY PLANNING (A BURKE, SECTION EDITOR)

Bleeding Associated with Hormonal Contraceptives: Understanding and Managing a Common Problem

Stacey Leigh Rubin[1] · **Jennifer A. Robinson**[1]

Published online: 22 July 2017

Abstract
Purpose of Review Changes in menstrual bleeding are common with hormonal contraceptives, and unfavorable bleeding profiles are leading reasons for method dissatisfaction and discontinuation. Studies suggest that acceptance of menstrual disturbance is highly dependent on appropriate counseling. This review presents an overview of the pathophysiology of uterine bleeding related to hormonal contraceptive use, the expected bleeding profiles of the various hormonal contraceptives, and evidence supporting various management strategies for treatment of unscheduled bleeding.
Recent Findings Published trials on treatments for bleeding with hormonal contraceptives are heterogeneous in methodology and outcome measures. Overall, data show mixed results and disappointingly small treatment effects for medications studied to manage unscheduled bleeding. Short courses of NSAIDs and oral estrogen may have modest benefits. Tranexamic acid and mifepristone require larger trials and additional study.
Summary Treatment of bleeding associated with hormonal contraception hinges on understanding the bleeding profiles of the hormonal contraceptives, employing anticipatory counseling, and understanding the spectrum and limitations of treatment options for menstrual disturbance.

This article is part of the Topical Collection on *Family Planning*

✉ Stacey Leigh Rubin
Stacey.OBdoc@gmail.com

[1] Division of Family Planning, Department of Gynecology and Obstetrics, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, A Building, Room 121, Baltimore, MD 21224, USA

Keywords Hormonal contraceptives · Unscheduled bleeding · Treatment of unscheduled bleeding

Introduction

Hormonal contraceptives are widely utilized, and have both contraceptive and non-contraceptive benefits. In addition to permitting women to plan and space pregnancies, hormonal contraceptives are used to treat heavy, painful, or abnormal menstrual bleeding, and to manage other gynecologic conditions. Changes in menstrual bleeding are common with hormonal contraceptives, and unfavorable bleeding profile is a common reason for method dissatisfaction and discontinuation [1]. Discontinuation of hormonal contraception can result in unintended pregnancy or suboptimal management of a gynecologic condition, so considerable efforts have been made to understand and manage bleeding irregularities from hormonal contraceptives.

Counseling women on expected bleeding patterns has been shown to increase hormonal contraceptive method satisfaction and continuation [2, 3]. It is therefore important to understand the expected bleeding profiles of the various hormonal contraceptives, and the potential treatments for bothersome unscheduled bleeding. This review presents an overview of the pathophysiology of uterine bleeding related to hormonal contraceptive use, the expected bleeding profiles associated with each class of hormonal contraceptive, and the evidence supporting various management strategies for unscheduled bleeding.

Physiology and Pathophysiology

During each spontaneous ovulatory menstrual cycle, the endometrium goes through proliferative and secretory phases,

followed by coordinated shedding that results in menstrual bleeding if a pregnancy does not occur. This cycle of events occurs due to ovarian production of estrogen and progesterone. It is primarily the withdrawal of progesterone that triggers changes in the functional layer of the endometrium that lead to menstruation.

Following progesterone withdrawal, there is an influx of cytokines and prostaglandins into the endometrium [4••]. These pro-inflammatory mediators, such as COX-s, NFkB, and IL-8, lead to an increased presence of leukocytes, activation and release of matrix metalloproteinases (MMPs), and eventual destruction of the endometrial extracellular matrix. In addition, pathways of vasoconstriction of spiral arterioles within the endometrium, coagulation, and vascular repair contribute to the overall balance of bleeding and hemostasis occurring during menstruation. Alterations in many of these factors have been linked to heavy menstrual bleeding.

Under the influence of exogenous progestins, such as those used in hormonal contraceptives, changes occur in the endometrium that lead to altered bleeding patterns. The bleeding profile of a contraceptive method describes the induced pattern of uterine bleeding, and can range from regular monthly withdrawal bleeding, to amenorrhea or infrequent bleeding, to frequent, prolonged, or irregular bleeding [5].

Several studies have been conducted to characterize the effects of various contraceptive hormones on the intrauterine environment. Human endometrial stromal cells (HESCs) were used to investigate the effects of depot medroxyprogesterone acetate (DMPA) and etonogestrel (ENG), compared to endogenous progesterone, and found that both DMPA and ENG induced altered gene expression patterns related to activation of local glucorticoid receptors [6]. Exogenous progestin seems to result in a focal (rather than global) peri-menstrual distribution of MMP expression in the endometrium. In addition, exogenous progestin appears to promote abnormal angiogenesis and superficial dilated vessels with increased fragility, which may also contribute to unscheduled bleeding [7].

Another study that aimed to evaluate the effects of a combined oral contraceptive pill and doxycycline on endometrial MMP-2 and MMP-9 found an increase in MMP expression after one cycle of the COC, although in subsequent cycles these levels declined [8]. Participant dropout limited the authors' ability to draw conclusions regarding the combined effects of the COC and doxycycline. Other studies have suggested that progestins used in contraceptives lead to endometrial vascular changes [9] and alterations in mediators of thrombin deposition and degradation, which may contribute to irregular uterine bleeding [10].

The Hormonal Contraceptives

Available hormonal contraceptives can be categorized in several ways, but one of the most common is to consider methods which contain both estrogen and progestin (combined hormonal contraceptives, or CHCs) separately from progestin-only contraceptives (POCs).

Combined Hormonal Contraceptives

The combined hormonal contraceptives (CHCs) include three broad categories: combined oral contraceptives (COCs), the transdermal contraceptive patch, and the contraceptive vaginal ring (VR). All three contain an estrogen and progestin. The estrogen in most COCs, the patch, and the ring is ethinyl estradiol (EE), while there is much greater variety in the progestin components. The contraceptive patch that is currently available in the USA contains EE and norelgestromin (NGMN) [11], while the VR contains EE and etonogestrel (ENG) [12].

CHCs are largely intended to be taken in a cyclic manner, with a hormone-free interval (HFI) following 21 to 24 days of active pill, patch, or ring use. It is during the HFI that women experience a scheduled bleeding episode. Since the first COC was approved by the FDA in 1960, several modifications have been introduced, including varying the hormone doses throughout each 28-day cycle (multi-phasic preparations), or taking COCs in an extended or continuous manner, with infrequent or absent HFIs. The patch and ring may also be taken in an extended or continuous manner, although this is considered off-label use.

With standard cyclic use of CHCs, the expected bleeding profile includes a monthly withdrawal bleed that occurs only during the HFI. Multiple Cochrane reviews have found no significant differences among the different phasic preparations in either contraceptive efficacy or bleeding profiles [13–16]. For women who experience bothersome unscheduled bleeding on a cyclic COC, a common treatment option is to increase the dose of estrogen in each pill (for example, changing from 20 to 30 mcg EE), or to switch to a pill containing a different progestin.

Recent studies have investigated the use of different estrogen preparations and whether these novel drugs improve side-effects, including bleeding. Estradiol valerate and estretol are two alternate estrogens. In a study comparing women who switched from an EE-containing COC to a COC with estradiol valerate and dienogest, or a progestin-only pill, the estradiol valerate COC had lower rate of discontinuation and a longer time to discontinuation due to bleeding irregularities [17]. The FIESTA trial assessed the bleeding pattern and cycle control achieved with COCs containing estretol and either levonorgestrel (LNG) or drospirenone (DRSP) (four different combinations) [18]. The experimental COCs were compared to each other, as well as to a reference group who received

a quadriphasic pill containing estradiol valerate and dienogest. The COC with the most favorable bleeding pattern contained 15 mg of estretol and 3 mg DRSP.

There are limited data regarding direct comparisons of COCs with either the contraceptive patch or VR. One study found that women randomized to either a contraceptive patch containing EE and norelgestromin (NGMN) or a COC (EE and LNG) had a higher incidence of breakthrough bleeding or spotting with the patch, but only during the first 2 months of use; there was no overall difference in breakthrough bleeding between the two methods [19]. A study comparing the VR with a COC containing EE and DRSP found no difference in contraceptive efficacy, but the VR was associated with lower incidence of breakthrough bleeding [20]. Another study comparing the VR with a COC (EE and LNG) for treatment of abnormal uterine bleeding found similar improvements in bleeding, continuation, and satisfaction with the two methods [21].

More recent studies have investigated new contraceptive patch formulations, which combine EE with either gestodene (GSD) or LNG. Bleeding profiles were comparable between the EE/GSD patch and a COC containing EE/LNG, although the COC had more frequent absence of withdrawal bleeding [22]. When compared to the EE/NGMN patch, the EE/GSD patch was associated with shorter length of withdrawal bleeding episodes [23]. There was no difference in unscheduled bleeding when a patch containing EE/LNG was compared to a COC with the same hormone combination [24].

Extended and Continuous Use

A large global study that investigated women's preferred bleeding patterns suggests that approximately 1/3 of women prefer amenorrhea, 1/3 prefer to bleed 2–4 times per year, and 1/3 prefer regular monthly menses [25•]. For this reason, extended or continuous regimens of combined hormonal contraception are increasingly used. A Cochrane review found no significant differences in bleeding patterns among women using extended or continuous CHCs compared to cyclic CHCs [26]. A more recent study of continuous use of either VR or COC showed similar rates of breakthrough bleeding, which decreased in frequency over time [27]. When a bleeding episode lasted longer than 4 days, stopping method use (either VR or COC) for 4 days led to resolution of bleeding in 91% of women who were able to comply with these recommendations. It is notable that only 42% of women in the study successfully adhered to the "menstrually signaled regimen" of method interruption.

Progestin-Only Contraceptives

Overall, women experience fewer total bleeding and spotting days on progestin-only contraceptives (POCs) than with spontaneous menstrual cycles. Expected bleeding patterns vary among POCs, but all methods can produce bothersome unscheduled bleeding. Bleeding profiles on POCs range from amenorrhea, to unpredictable bleeding and spotting, to normal monthly bleeding. Changes in bleeding patterns were listed as the main reason for method discontinuation by 19% of LNG-IUS users, 46% of ENG implant users, and 26% of DMPA users [28].

The Progestin-Only Pill

The primary contraceptive mechanism of action for the progestin-only pill (POP) is cervical mucous thickening that impedes sperm penetration. Endometrial atrophy and ovulation suppression also contribute to contraceptive action. The POP is associated with unscheduled bleeding, experienced by 40% of women using this method, while half of women experience regular monthly cycles, and 10% are amenorrheic [29].

Depot Medroxyprogesterone Acetate

Depot medroxyprogesterone acetate **(**DMPA) is available in both intramuscular and subcutaneous formulations, which are injected every 13 weeks. The primary mechanism of action for DMPA is ovulation inhibition, though endometrial atrophy and cervical mucous thickening also contribute to contraceptive efficacy.

Unscheduled bleeding episodes are common in the first several months of use, with episodes frequently lasting longer than 7 days [30]. Bleeding among women using DMPA declines over time, with amenorrhea rates of around 12% after the first 90-day reference period, and 46% after 1 year [30].

The Levonorgestrel Intrauterine Systems

There are currently four different levonorgestrel intrauterine systems (LNG-IUSs) approved by the FDA. The LNG-IUS prevents pregnancy primarily due to local progestin effects on the female reproductive tract, including cervical mucous thickening and endometrial atrophy. Ovulation suppression is not a primary mechanism of action, and 45–75% of cycles may be ovulatory among LNG-IUS users [31]. Overall the LNG-IUS can reduce menstrual blood loss by up to 90%, and one version of the LNG-IUS is therefore approved for non-contraceptive indications such as heavy menstrual bleeding [31].

The LNG-IUS 52/5 (trade name Mirena®; Bayer, Whippany, NJ) contains 52 mg of LNG and is FDA-approved for 5 years of use, though recent data suggests that it is effective for at least 6 years [32, 33]. Continuation rates for LNG-IUS 52/5 are high, with 87% continuation at 1 year, 77% at 2 years, and 70% at 3 years [34]. Unscheduled

bleeding can be problematic, but frequently improves within the first 3 months of use [35]. Frequent and prolonged bleeding episodes initially occur in 13–22% of women, but only affect 1–3% of women after 1 year [36]. The amenorrhea rate at 1 year of use is 20%, and by 2 years of use 50% of women will be amenorrheic or oligomenorrheic [31]. Of women who discontinued the LNG-IUS 52/5 in the first 6 months of use, 9% reported irregular or frequent bleeding (compared to 53% of women who discontinued the ENG implant) [37].

The LNG-IUS 52/3 (trade name Liletta®; Allergan/Medicines360, Irvine, CA) contains 52 mg of LNG and is FDA-approved for 3 years of use, though there is ongoing data collection with plans to apply for future FDA approval for up to 7 years [38]. Currently, the reported amenorrhea rate for LNG-IUS 52/3 is 19% at 1 year, 26% at 2 years, and 38% at 3 years [39].

The LNG-IUS 19.5/5 (trade name Kyleena®; Bayer, Whippany, NJ) contains 19.5 mg LNG and is FDA-approved for 5 years of use. Rates of amenorrhea with the LNG 19.5/5 are lower than with the 52 mg LNG formulations: 12% at 1 year, and 23% at 5 years of use [40].

The LNG-IUS 13.5/3 (trade name Skyla®; Bayer, Whippany, NJ) contains 13.5 mg LNG and is FDA-approved for 3 years of use. Skyla contains the lowest dose of LNG, and is also associated with the lowest rates of amenorrhea (6% at 1 year, and 12% at 2 years) [41]. Women using LNG-IUS 13.5/3 are more likely to experience regular monthly bleeding than women using LNG-IUS 52/5 [42, 41].

The Etonogestrel Implant

The etonogestrel (ENG) implant Nexplanon® (Merck, Whitehouse Station, NJ) is the only implantable contraceptive currently available in the USA. The ENG implant is a single rod containing 68 mg ENG that is placed in the subcutaneous tissue of the upper inner arm, and provides contraception for up to 3 years. The ENG implant is the most effective form of reversible contraception, with a typical failure rate of 0.05% at 1 year [43]. The primary contraceptive mechanism of action is ovulation suppression, but ENG also contributes to endometrial atrophy and cervical mucous thickening [44].

While there are fewer overall bleeding and spotting days on the ENG implant than in spontaneous menstrual cycles, unscheduled bleeding may persist for the duration of implant use. Seventy-eight percent of women reported unscheduled bleeding in the first 3 months, and only about 50% of women experienced improvement with continued use [45]. Menstrual disturbance is the most common reason for ENG implant discontinuation [46], and 53% of women who discontinued the ENG implant within the first 6 months reported irregular or infrequent bleeding [37]. Despite this, continuation rates of the ENG implant remain high, with 82% continuation at 1 year, 69% continuation at 2 years, and 56% continuation at 3 years [28].

In addition, many ENG implant users experience favorable bleeding patterns, with rates of infrequent bleeding estimated at 34%, and 1-year amenorrhea rates of up to 30% [45]. A favorable bleeding pattern is the first 3 months frequently persists, but amenorrhea rates actually decline over time, with only 12% of women reporting amenorrhea by the third year of use [47].

Treatment of Unscheduled Bleeding on Progestin-Only Contraceptives

Development of treatment options has been limited by the poorly understood, likely multifactorial, etiology and mechanisms of unscheduled bleeding on POCs. A number of medical treatments have been explored, each targeting a different mechanism that may contribute to unscheduled bleeding. Most research has focused on stopping or shortening current bleeding episodes, though several studies have investigated weekly or monthly dosing to influence ongoing bleeding patterns of POCs. Overall treatment effects have been modest and transient, with unscheduled bleeding reoccurring after treatment has been completed.

Non-Steroidal Anti-Inflammatory Drugs

Some studies suggest that elevated prostaglandin levels may be present in the secretory endometrium of women who experience irregular bleeding [48]. Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase and reduce prostaglandin synthesis, have consequently been studied to treat unscheduled bleeding on POCs.

Two trials comparing the effects of NSAIDs to placebo for treatment of bleeding on DMPA found that fewer women were still bleeding at the end of treatment with mefenamic acid or valdecoxib [RR 0.42; 95% CI 0.25, 0.72] [49]. A study in ENG implant users showed that mefenamic acid 500 mg three times daily for 5 days was more likely to stop bleeding within a week compared to placebo (65.2 vs. 21.7%, $p < 0.05$), and decreased total bleeding or spotting days from 16.8 to 10.5 days ($p < 0.05$) in a 90-day reference period [50]. However, a placebo-controlled trial of mefenamic acid administered after LNG-IUS 52/5 initiation did not appear improve bleeding [51].

A trial of prophylactic naproxen at the time of LNG-IUS 52/5 insertion resulted in 10% fewer bleeding and spotting days than placebo. Naproxen 500 mg was administered twice daily for the first 5 days of each 4-week cycle, for a total of 3 cycles. However, the reduction in unscheduled bleeding did not persist 4 weeks after treatment [52].

Estrogen

Estrogen may stop prolonged bleeding episodes by stabilizing endometrial vasculature, promoting tissue repair and proliferation, and increasing coagulation [53, 54]. For these reasons, oral and transdermal estrogen preparations have been explored as treatments for unscheduled bleeding related to POCs. However, many studies suffered from design and methodological flaws that excluded them from the most recent Cochrane review on management of unscheduled vaginal bleeding due to POCs [49].

A study in DMPA users showed that EE 50 mcg for 14 days stopped bleeding episodes better than placebo (93 vs. 74%, $p < 0.001$) [55]. In another small study, ENG implant users with troublesome bleeding were randomized to a combined oral contraceptive (COC) or placebo for 4 weeks. While 100% of the bleeding episodes stopped with the COC (compared to 74% with placebo), the study was ended early due to recruitment difficulties, so conclusions are limited [56].

In contrast, a more recent study found that use of a weekly transdermal 0.1 mg estradiol patch actually increased total bleeding and spotting days during the first 3 months of LNG-IUS 52/5 use, and decreased overall method satisfaction compared to placebo [52].

Antifibrinolytic Agents

Tranexamic acid is an antifibrinolytic drug that may reduce progestin-induced bleeding by stabilizing and delaying dissolution of clots overlying exposed endometrial vessels [57]. A placebo-controlled randomized trial of tranexamic acid 1000 mg daily for 5 days in DMPA users found that the percentage of women who stopped bleeding during the week after treatment was significantly higher in the tranexamic acid group (88 vs. 8.2%, $p < 0.001$) [58]. In addition, the treatment effect seemed to persist, with fewer total bleeding days in the subsequent 4 weeks among women treated with tranexamic acid.

Among women using the LNG-IUS 52/5, tranexamic acid 500 mg three times daily until cessation of bleeding reduced the number of bleeding and spotting days in a 90-day reference period. However, after adjustment, the reduction in bleeding days was not statistically significant compared to placebo [51].

Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) are proteolytic substances that play a role in tissue remodeling. Since MMP elevations precede normal endometrial bleeding and menstruation, it is possible that inhibitors of MMP, such as doxycycline, might stabilize the endometrium and reduce unscheduled bleeding caused by POCs [59•].

In a small pilot study of women using the ENG implant, doxycycline abbreviated bleeding episodes compared to placebo (4.8 vs. 7.5 days to bleeding cessation, $p = 0.001$), but the effects were transient and subsequent bleeding pattern was unchanged [60]. In addition, efforts to replicate these results in a larger study by the same investigators were unsuccessful, though they were only able to recruit approximately half of the desired sample size [61]. A retrospective chart review noted a lower ENG implant discontinuation rate in patients prescribed doxycycline for bleeding dissatisfaction (45.5 vs. 75.5%, $p = 0.005$) [62].

A randomized placebo-controlled trial of doxycycline 100 mg daily for 5 days showed no significant abbreviation of bleeding episodes caused by DMPA (RR 0.88, 95% CI 0.64, 1.21) [63]. In addition, the total number of bleeding or spotting days in the subsequent 3 months was not affected by a 5-day course of doxycycline [63].

Anti-Progestins

Mifepristone inhibits progesterone, leading to upregulation of endometrial estrogen receptors and mimicking the effects of exogenous estrogen exposure [64]. One trial randomized 20 new DMPA users to mifepristone 50 mg or placebo once every 2 weeks for 6 months, and found that mifepristone significantly decreased the total number of bleeding days and number of prolonged bleeding episodes [64]. None of the 20 participants ovulated during the study period. Compared to placebo, mifepristone 100 mg once monthly for 3 months in LNG-IUS 52/5 users decreased both the number of bleeding and spotting episodes (3 vs. 2.5, $p = 0.05$) and duration of episodes (12.5 vs. 6 days, $p = 0.01$), and increased user satisfaction with the LNG-IUS 52/5 (44 vs. 75%, $p = 0.004$) [65].

In contrast, mifepristone 25 mg once daily did not reduce unscheduled bleeding in women using the ENG implant. Mifepristone 25 mg twice daily, when followed by estrogen for 4 days, or doxycycline for 5 days, shortened the current bleeding episode in ENG implant users, but failed to alter subsequent unscheduled bleeding patterns [60, 61].

Selective Estrogen Receptor Modulators

Tamoxifen, a selective estrogen receptor modulator (SERM), may improve bleeding patterns by antagonizing the angiogenic effects of estrogen in the uterus [66]. A small trial of women using the LNG implant, a POC that is no longer available in the USA, found that tamoxifen 10 mg twice daily for 10 days stopped bleeding episodes more often than placebo (88 vs. 68%, $p = 0.016$) [67]. However, benefits were transient, and by the third month following treatment there was no difference in bleeding pattern or satisfaction between the two groups.

Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs) bind to progesterone receptors with high affinity and selectively antagonize progestin effects [59•]. A trial of ulipristal 50 mg daily for 3 days, administered every 4-week cycle, found that after a transient decrease in bleeding, total bleeding days on the LNG-IUS 52/5 ultimately increased [68]. By the third cycle, ulipristal increased total bleeding by 6 days compared to placebo.

Summary and Recommendations

Bleeding associated with hormonal contraceptives is a common problem. Understanding expected bleeding profiles and treatment options for unscheduled bleeding are important for increasing satisfaction and continuation of hormonal contraceptives.

Anticipatory Counseling

Several studies suggest that acceptance of menstrual disturbance is highly dependent on appropriate counseling. In a subgroup of women who received intensive counseling about the effects of DMPA, discontinuation rates at 1 year were significantly reduced (11% in counseled women vs. 42% in uncounseled women) [2]. In addition, structured pretreatment counseling about hormonal side-effects of DMPA, compared to standard counseling about efficacy and frequency of administration only, resulted in fewer women listing menstrual changes as the reason for DMPA discontinuation (8.3 vs. 32%, $p < 0.05$) [69]. Similarly, it was found that women counseled on the expected bleeding pattern with the LNG-IUS 52/5 were more satisfied than less informed women [3].

Reassurance

In addition to counseling women about what to expect with respect to method-specific bleeding profile, it may be necessary to reassure women that unscheduled bleeding can be a normal side-effect of hormonal contraceptives. While menstrual disturbances are common and often benign, it is also important to consider potentially pathological etiologies of bleeding, including an unintended pregnancy. A thorough history and physical exam will guide evaluation and management.

In the absence of pregnancy or pathology, amenorrhea and unscheduled bleeding due to hormonal contraception are not dangerous, and do not necessarily require treatment. For some women, unscheduled bleeding is tolerable as long as they are reassured that it is not dangerous, and the contraceptive method is effective. For other women, unscheduled bleeding can be quite bothersome, and it may be necessary to consider treatment or method discontinuation. It is important to validate each woman's concerns about bleeding on hormonal contraception, and avoid coercing women to continue a form of contraception that is unsatisfactory, even if it is highly effective at pregnancy prevention.

Treatment Recommendations

For women who wish to consider medical management of bleeding associated with hormonal contraceptives, there are several options.

Combined Hormonal Contraceptives

Dose adjustment is a common strategy for women experiencing unacceptable bleeding on COCs, and may include changing the dose of estrogen, the dose of progestin, or choosing a different progestin entirely. With only one contraceptive patch and VR currently marketed in the USA, dose adjustment is less feasible with these methods. Alternatively, a woman may choose to use a cyclic CHC in an extended or continuous manner, which has the potential to decrease overall bleeding [26]. A brief hormone-free interval of 3 to 4 days has also been shown to decrease intermenstrual bleeding in women using continuous CHC [27].

Progestin-Only Contraceptives

While only a few specific combinations of treatments and POCs have been studied systematically, it is reasonable to extrapolate data regarding each intervention to other POCs since it is likely that most exogenous progestins cause unscheduled bleeding via similar mechanisms. Overall, treatment effects are generally modest and transient. Treatment may stop an ongoing bleeding episode, but it is unlikely to alter the POC's long-term bleeding profile.

Short courses of NSAIDs for 5–7 days may abbreviate bleeding episodes due to POCs. Mefenamic acid 500 mg three times daily, or naproxen 500 mg twice daily, may be considered. Estrogen supplementation (either alone for 14 days, or in COCs for up to 3 months) may also shorten ongoing bleeding episodes and decrease unscheduled bleeding. However, estrogen is contraindicated for many medical conditions, and may cause other side-effects. Mifepristone is expensive, highly regulated, and unavailable in the USA in the low-dose formulations that have been studied in this context. These barriers limit the utility of mifepristone for treatment of unscheduled bleeding. Early data on tranexamic acid is promising, but

larger trials are necessary before tranexamic acid can be routinely recommended.

Conclusion

Overall, treatment options for unscheduled bleeding related to hormonal contraceptives are limited, and it may become necessary to alter or discontinue the contraceptive method if bleeding side-effects are intolerable. An effort should be made to avoid coercing women to continue methods with unsatisfactory side-effects merely because they are highly effective at preventing pregnancy. Ultimately, understanding the bleeding profiles of hormonal contraceptives, employing anticipatory counseling, and understanding the spectrum and limitations of treatment options for menstrual disturbances are important strategies to increase the satisfaction and continuation of hormonal contraceptives.

Compliance with Ethical Standards

Conflict of Interest Stacey Leigh Rubin and Jennifer A. Robinson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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