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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Unscheduled Bleeding on Hormonal Contraceptives: Pathophysiology, Evaluation, and Management Options

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Abstract
Purpose of Review Unscheduled bleeding is a common side effect of hormonal contraception and is a common reason for method discontinuation. This review summarizes the pathophysiology, evaluation, and current evidence-based management recommendations for the unscheduled bleeding that can occur with hormonal contraception use.
Recent Findings Prior to initiation of a hormonal contraceptive method, detailed structured counseling about the likelihood of unscheduled bleeding and its likely improvement with continued use is an important component of method continuation and patient satisfaction. For unscheduled bleeding that is persistent and bothersome, non-steroidal anti-inflammatory drugs (NSAIDs) and estrogen alone or estrogen and progestin in combined oral contraceptive (COC) are commonly used for management. The antibiotic doxycycline is somewhat effective at reducing unscheduled bleeding in users of combined hormonal contraceptive methods and progestin implants. Small randomized controlled trials of mifepristone, an antiprogestin, and tranexamic acid, an antifibrinolytic, demonstrated a decrease in unscheduled bleeding in users of depot medroxyprogesterone acetate (DMPA), progestin implants, and levonorgestrel intrauterine devices (IUDs). Tamoxifen, a selective estrogen receptor modulator (SERM), in progestin implant users reduces unscheduled bleeding. Ulipristal acetate, a selective progesterone receptor modulator (SPRM), is not effective at reducing unscheduled bleeding in levonorgestrel IUD users and may result in an increase in bleeding.
Summary Expectant management is a mainstay of treatment of unscheduled bleeding that occurs as a result of hormonal contraceptive use. NSAIDs and COCs are commonly used for treatment. Small randomized controlled trials of other methods have demonstrated some effectiveness, although evidence is limited.

Keywords Unscheduled bleeding · Irregular bleeding · Hormonal contraception · Bleeding management

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Introduction

Dissatisfaction with bleeding patterns associated with hormonal contraception is a common reason for method discontinuation [1]. Unscheduled bleeding, in particular, is bothersome for many women. Though the unscheduled bleeding that accompanies the initiation of many contraceptive methods improves with continued use, dissatisfaction can lead to discontinuation which can increase the risk of unintended pregnancy. Setting expectations for changes in menstrual bleeding patterns and discussing potential management options for unscheduled bleeding are important for effective method use and continuation.

Evaluation

As a component of routine comprehensive contraceptive counseling, expectations for unscheduled bleeding should be discussed to ensure that women have clear expectations of

bleeding patterns and are equipped to make informed decisions about their contraceptive method. Women who experience unscheduled bleeding while using a contraceptive method may be concerned about decreased contraceptive efficacy. Women should be reassured that unscheduled bleeding is not indicative of decreased contraceptive efficacy.

When a woman reports unscheduled bleeding while using a contraceptive method, clinicians should obtain a detailed history regarding the timing and amount of bleeding as well as any associated symptoms. An understanding of a woman's bleeding patterns prior to method initiation and the changes that have occurred since initiation are important to ascertain whether bleeding patterns are typical of the type of bleeding that can occur with a specific method or indicative of a pathologic process.

Unscheduled bleeding or changes in an established bleeding pattern should trigger the clinician to rule out pregnancy, even in women using highly effective methods such as implants and intrauterine devices (IUDs). Cervicitis may cause the cervix to be friable, which can result in unscheduled bleeding; thus, clinicians should ask about symptoms of infection or risk factors for sexually transmitted infections. Clinicians should also ask about medical conditions or medications, such as bleeding or hypercoagulable disorders, endocrine disorders such as hyper or hypothyroidism, and use of anticoagulants or herbal supplements as these may alter bleeding patterns. In women using combined hormonal contraception, smoking has been associated with more persistent unscheduled bleeding [2]. Cervical cancer screening should be performed in accordance with recommended screening guidelines. In the setting of a longstanding history of unscheduled bleeding, an endometrial biopsy may be indicated based on professional guidelines. A pelvic ultrasound may be performed to evaluate for uterine fibroids or polyps. Women who report unscheduled bleeding with an IUD should be evaluated for correct IUD placement with a physical exam or imaging. IUD malposition within the uterus or perforation into the abdomen may present with both pain and a change in bleeding pattern, though the absence of pain does not rule out these diagnoses.

Pathophysiology

The etiology of unscheduled bleeding that occurs in the setting of hormonal contraceptive use is not well understood. Immediately following initiation of a hormonal method, unscheduled bleeding is hypothesized to occur secondary to progestin which results in the transition from a relatively thick endometrium to a relatively thin endometrium [3]. As the duration of use increases, progestin promotes the formation of a network of superficial, thin-walled vessels in the endometrium that are structurally fragile and prone to bleeding [4, 5]. Matrix metalloproteinases (MMP) are upregulated in the presence of progestin from hormonal contraceptives and contribute to the degradation of the endometrium [6–8]. Changes in endometrial perfusion, vascular architecture, and hemostasis may also contribute to unscheduled bleeding in this setting [5].

Management options for unscheduled bleeding with hormonal contraception vary depending on the contraceptive method. The US Selected Practice Recommendations for Contraceptive Use (US SPR) 2016 contains recommendations for unscheduled bleeding management. Additional evidence-based recommendations can be found in the primary literature. These recommendations are summarized in Table 1.

Combined Hormonal Contraception

Prior to initiation of an estrogen-progestin combined oral contraceptive (COC), counseling should include expectations for unscheduled bleeding, including the likelihood that unscheduled bleeding will improve over time. Up to 30% of women experience unscheduled bleeding with COC initiation [3, 9]. By 3 months, only 10% report unscheduled bleeding [9].

Selecting a pill with 30 to 35 mcg of ethinyl estradiol (EE) may result in less unscheduled bleeding; COC formulations containing 20 mcg of EE or less have been associated with slightly higher rates of unscheduled bleeding when compared to formulations containing 30 or 35 mcg EE [10–12]. No difference in unscheduled bleeding with monophasic compared to multiphasic COC formulations has been demonstrated [9], although triphasic COC formulations have been associated with fewer days of unscheduled bleeding when compared to monophasic COCs in some studies [13–15].

Traditional COC formulations include hormonal withdrawal bleeding every 4 weeks. Continuous use of COCs refers to the use of hormonally active pills continuously with no scheduled withdrawal bleed. Extended cycle use of COCs refers to the use of hormonally active pills with withdrawal bleeding less frequently than every month, usually three to four times per year. Although women on continuous or extended cycle COCs experience less scheduled bleeding, they experience more unscheduled bleeding, particularly in the first few months following initiation [16, 17]. In randomized controlled trials of continuous COCs, amenorrhea with no unscheduled bleeding was achieved in fewer than 50% of users during the first 3 months of use [16–18]. By 12 months of use, however, 80 to 90% of continuous users reported amenorrhea [16–19].

The amount of unscheduled bleeding reported with the use of contraceptive patches or rings is similar to unscheduled bleeding with COCs [18]. While these methods have not been approved for continuous or extended use, a randomized trial of continuous and extended use of the contraceptive vaginal ring demonstrated an increased number of days of

Table 1 Summary of treatment options for unscheduled bleeding with hormonal contraception

Contraceptive method	US SPR recommendations	Additional available evidence-based recommendations
Combined hormonal contraception (CHC)	Discontinue CHC use for 3–4 days (only following 21 consecutive active hormone days)	• Increase in estrogen dose from 20 mcg EE to 30 mcg EE • Change in progestin type (norethindrone versus levonorgestrel) • Prophylactic subantimicrobial 40 mg doxycycline
Depo medroxyprogesterone acetate (DMPA)	5–7 day course of NSAIDs	None
Progestin-only pills	None	Short course of estrogen supplementation
Progestin implant	• 5–7 day course of NSAIDs • 10–20 day courses of COCs or estrogen supplementation	7-day course of tamoxifen
Levonorgestrel intrauterine device (IUD)	None	None

unscheduled bleeding but decreased scheduled or withdrawal bleeding days when compared to cyclic use [16].

Management

When evaluating unscheduled bleeding in a woman using a combined hormonal contraceptive, it is important to ascertain a woman's adherence to the regimen, particularly with respect to missed pills. Users who do not take pills every day are likely to experience a 60 to 70% increased relative risk of unscheduled bleeding [20]. If pills are frequently missed or the patch or ring is not replaced in a timely manner, switching to another method may be the best course of action.

Because unscheduled bleeding is common during the first 3–6 months following COC initiation and improves with time, expectant management and an emphasis on regimen adherence is often the most appropriate option. If a woman desires treatment for unscheduled bleeding that is bothersome to her, the US SPR (2016) recommends a 3–4 day discontinuation of COCs [21]. If she experiences unscheduled bleeding but it is tolerable, she does not need to discontinue the COC. Following discontinuation, women will have a hormonal withdrawal bleed and may have an improved bleeding pattern when they resume taking COCs. This recommendation is based on limited evidence from a few randomized controlled trials [22]. To ensure contraceptive efficacy, a hormone-free interval can only be attempted after 21 days of hormonally active pills and may be repeated as long as this requirement has been met. For women using the vaginal contraceptive ring continuously, removal of the ring for a 4-day period after 5 days of unscheduled bleeding resulted in fewer subsequent unscheduled bleeding days [23].

Because estrogen stabilizes the endometrium and promotes coagulation, it has been hypothesized that pills with higher doses of estrogen or estrogen supplementation at any time during the cycle will result in less unscheduled bleeding [10–12]. Women using a COC with 20 mcg EE or less who experience unscheduled bleeding may benefit from switching to a 30 or 35 mcg EE pill. In a randomized controlled trial of EE doses, 35.5% of 30 mcg EE users reported unscheduled bleeding, compared to 47.7% of 20 mcg EE users [24]. A 7-day course of 1.25 mcg conjugated estrogen or 2 mg estradiol at any time during the cycle has been recommended to treat unscheduled bleeding [3] although no studies have been conducted to demonstrate that this is an effective treatment.

Progestin type may also affect unscheduled bleeding days; a randomized controlled trial of continuous COC use demonstrated a significant decrease in bleeding days with the use of a norethindrone-containing COC compared to a levonorgestrel-containing COC [25•].

A study comparing 21- to 24-day hormonally active COC formulations demonstrated fewer unscheduled bleeding days with a 7-day placebo week (4.6 compared to 6.1 days) [26], although another study reported no difference in unscheduled bleeding [27]. While the use of a 21-day formulation may result in an improvement in unscheduled bleeding, it is also associated with more overall bleeding days, scheduled and unscheduled combined, compared to a 24-day formulations [26] as well as a higher contraceptive failure rate [28].

Doxycycline has been studied for the treatment of unscheduled bleeding secondary to its role as a matrix metalloproteinase inhibitor [8]. Though doxycycline was not effective at treating bleeding once it occurred [29], subantimicrobial doses of 40 mg of doxycycline daily administered prophylactically resulted in a decrease in the time it took to achieve amenorrhea with continuous COCs (61.7 days in treatment group compared to 85.2 days in placebo group) [30].

Depot Medroxyprogesterone Acetate

Changes in bleeding patterns should be expected with depot medroxyprogesterone acetate (DMPA) initiation. Though the majority of women who use DMPA will achieve amenorrhea over time, only 12% report amenorrhea within the first 3 months of use [31]. By 12 months, 50% of women report

amenorrhea, and by 5 years, this proportion rises to 80% [32, 33]. One-quarter of women discontinue DMPA within the first year because of bleeding [34]. Unscheduled bleeding with DMPA use is thought to be due to endometrial atrophy and inflammation secondary to chronic progestin exposure [35, 36]. Prior to initiation of DMPA, clinicians should emphasize that unpredictable, prolonged bleeding is common though the likelihood of amenorrhea is high with continued use. For women who prefer monthly bleeding, DMPA is not an optimal contraceptive.

Management

The US SPR (2016) recommends a course of NSAIDs for 5–7 days or a course of COCs for 10–20 days for the treatment of unscheduled bleeding with DMPA. A randomized controlled trial of a 5-day course of mefenamic acid demonstrated efficacy in controlling bleeding during the first week of DMPA administration, but this effect was no better than placebo by the fourth week [37]. Valdecoxib has also demonstrated some efficacy in decreasing unscheduled bleeding; however, this medication has been withdrawn from the market due to cardiovascular risks [38].

Estrogen supplementation with estrogen alone or COCs has been studied in DMPA users for the management of unscheduled bleeding. Although the US SPR (2016) recommends the use of 10–20 days of a low-dose COC for the treatment of heavy or prolonged bleeding [21], no studies support this recommendation. A randomized controlled trial demonstrated that a 14-day course of 50 mcg EE was more effective than estrone sulfate or placebo at stopping unscheduled bleeding, although bleeding returned after estrogen was discontinued [39]. In new DMPA users, randomized controlled trials of prophylactic estrogen supplementation have not demonstrated any clear evidence of benefit [40–42].

Other treatments that have been investigated include doxycycline, tranexamic acid, and mifepristone. A randomized controlled trial of a 5-day course of doxycycline beginning at the start of an unscheduled bleeding episode demonstrated no difference in amount or duration of bleeding in DMPA users [43]. Tranexamic acid, an antifibrinolytic that has been used for heavy menstrual bleeding, was investigated in a randomized controlled trial of a 5-day course of tranexamic acid 250 mg orally four times a day versus placebo in DMPA users. Investigators demonstrated a significant reduction in unscheduled bleeding (88 versus 8.2%) in the first week of treatment. This effect persisted over the 4-week follow-up period after treatment [44]. A 50-mg dose of mifepristone every 2 weeks in women initiating DMPA significantly decreased the proportion of women reporting unscheduled bleeding days (15 versus 36% of placebo users) [45]. While this is a promising approach, mifepristone is not available in the US in doses lower than the 200 mg tablet used for medical abortion.

Progestin-Only Pills

Bleeding patterns with progestin-only pills (POPs) are variable; approximately 40% of women have irregular or unscheduled bleeding, while 40 to 50% have regular menstrual cycles, and 10% achieve amenorrhea [3]. Prior to initiation, it is important to counsel women that POPs have a high likelihood of unscheduled bleeding which is likely to continue for the duration of method use.

Management

For women who experience unscheduled bleeding while using POPs, a short course of estrogen has been demonstrated to decrease the duration of bleeding [46]. The anti-progestin ORG 31710, similar to mifepristone, has been demonstrated in a randomized controlled trial to reduce unscheduled bleeding when taken every 28 days, although this effect was less pronounced with increased duration of treatment and this medication is not commercially available [47].

Progestin Implant

The contraceptive implant currently available in the US is a 68 mg etonogestrel implant. A two-rod 150 mg levonorgestrel implant is available in other countries. The six-rod 216 mg levonorgestrel implant has not been available in the US since 2002.

Bleeding patterns with progestin implants range from frequent, unscheduled bleeding to amenorrhea [48]. Most (75 to 80%) implant users report unscheduled bleeding in the first 3 months of use [49, 50]. Though bleeding episodes can last for a long time, they are typically light consisting of spotting or light bleeding. Bleeding patterns in the first 3 months of use are predictive of patterns for the duration of use; favorable bleeding patterns are likely to continue, while unfavorable bleeding patterns have a 50% likelihood of improvement [50]. Unscheduled bleeding is the primary reason cited for implant discontinuation; approximately 6 to 23% of users who discontinue etonogestrel implants do so because of unscheduled bleeding [51]. Prior to insertion, women should have an understanding of the high likelihood of unscheduled bleeding.

Management

Expectant management is a mainstay of treatment for women who are experiencing unscheduled bleeding with a progestin implant. Implant users can also be given reassurance that there is a 50% likelihood that bothersome bleeding patterns noted in the first 3 months of use will improve over time. For women who desire an intervention, a short course of NSAIDs or

estrogen supplementation with estrogen alone or COCs is recommended by the US SPR (2016) [21]. Courses of NSAIDs or use of a COC are both effective at reducing unscheduled bleeding, although bleeding typically recurs following treatment cessation.

Much of the literature pertains to the six-rod levonorgestrel implant, which is no longer in use. While some of these therapies may be used in etonogestrel implant users, the degree to which they are effective is unclear. There are no treatments that have been conclusively demonstrated to offer sustained correction of unscheduled bleeding patterns.

The US SPR (2016) recommends an initial 5–7 day trial of NSAIDs [21]. Ibuprofen and naproxen are commonly available, low-cost NSAIDs that can be used, although these have not been studied specifically in progestin implant users. Celecoxib and mefenamic acid have both been studied in progestin implant users. Celecoxib 200 mg daily for 5 days was more effective than placebo at reducing unscheduled bleeding associated with levonorgestrel implant use [52]. A 7-day course of mefenamic acid 500 mg three times daily was demonstrated to be more effective than placebo at reducing unscheduled bleeding in etonogestrel implant users [53].

Estrogen supplementation has been demonstrated to decrease the duration of unscheduled bleeding episodes and lengthen the duration of time between bleeding episodes in levonorgestrel implant users. Short courses (20–21 days) of estrogen alone or COCs [54–56] are effective at reducing unscheduled bleeding, while transdermal estrogen patches do not improve bleeding patterns [57]. A randomized controlled trial of a 14-day course of COCs in etonogestrel implant users demonstrated a higher likelihood of bleeding cessation (87.5 compared to 37.5% of placebo users) during treatment, although 85.7% of COC-treated women whose bleeding ceased had a recurrence of bleeding within 10 days of treatment cessation [58•].

Modest evidence supports the use of tranexamic acid, tamoxifen, doxycycline, and combination therapies such as mifepristone and doxycycline, or mifepristone and estradiol in the treatment of unscheduled bleeding with contraceptive implants. A single randomized controlled trial of tranexamic acid 500 mg twice daily for 5 days in users of the six-rod levonorgestrel implant demonstrated a significant reduction in bleeding during the first week of treatment with no difference in unscheduled bleeding between the tranexamic acid group and the placebo group following the treatment course [59]. The use of a 7-day course of tamoxifen, a selective estrogen receptor modulator (SERM), resulted in five fewer bleeding days and 15.2 more continuous days without bleeding compared to placebo in etonogestrel implant users [60]. A pilot study of doxycycline in etonogestrel implant users reported a shorter time to cessation of unscheduled bleeding when compared to placebo; however, this effect did not persist following the treatment course [61]. Mifepristone has been studied in doses of 50 or 100 mg and has demonstrated a reduction in bleeding in users of both the six-rod levonorgestrel implant and the single-rod etonogestrel implant [48, 61–63]. Because it is an antiprogestin, mifepristone could theoretically decrease the efficacy of a progestin implant and is not available in the US in doses of 50 or 100 mg.

Combinations of the abovementioned therapies have been studied. A randomized controlled trial compared mifepristone alone to mifepristone and estradiol in combination in women who reported prolonged or frequent bleeding while using an etonogestrel implant. Mifepristone alone was similar to placebo, but the combination of mifepristone and estradiol demonstrated a decrease in time to bleeding cessation, 4.2 days versus 7.5 days with placebo [61]. A larger trial demonstrated similar results and included the combination of mifepristone and doxycycline, which was superior to placebo in decreasing unscheduled bleeding [64]. While combination therapies are promising, the effect on unscheduled bleeding was only demonstrated during the course of treatment and did not affect subsequent unscheduled bleeding [61, 64].

Levonorgestrel Intrauterine Device

The overall effect of levonorgestrel IUDs is decreased bleeding, with many users experiencing amenorrhea. Counseling about expected bleeding patterns and the high likelihood of amenorrhea with increased duration of use should be emphasized during pre-insertion counseling. In a study of the Mirena IUD (LNG-20), 44% of women reported amenorrhea after 6 months of use. This proportion increased to 50% by 12–24 months of use [65]. Frequent or prolonged bleeding occurs in 35% of women in the first 3 months following hormonal IUD insertion, but this decreases to 4% by 12 months of use [66]. Approximately 6 % of LNG-20 users will have the device removed because of bothersome bleeding patterns [67].

Four levonorgestrel-containing IUDs are currently available in the US. Mirena and Liletta (LNG-20 IUD) both contain 52 mg of levonorgestrel and release 20 and 18.6 mcg of levonorgestrel per day, respectively, [68, 69]. Skyla (LNG-14) contains 13.5 mg of levonorgestrel and releases 14 mcg per day, and Kyleena (LNG-18) contains 19.5 mg of levonorgestrel and releases 17.5 mcg per day [70, 71]. While the use of all levonorgestrel-containing IUDs can result in decreased overall bleeding and increase the likelihood of amenorrhea, IUDs with lower doses of levonorgestrel, such as LNG-14 or LNG-18, have lower rates of amenorrhea. Only 6% of LNG-14 users report amenorrhea at the end of 1 year, while 12% of LNG-18 users report amenorrhea at the end of 1 year [70, 71]. The difference in amenorrhea and unscheduled bleeding rates with different doses of levonorgestrel should also be addressed to facilitate informed decision-making and a higher likelihood of user satisfaction.

Management

The most important component of management of unscheduled bleeding in levonorgestrel IUDs is structured counseling about expectations for improvement in bleeding patterns in the months following insertion. A modest amount of evidence supports the use of NSAIDs. Small trials of mifepristone and tranexamic acid have also demonstrated some benefit in reducing the duration of unscheduled bleeding.

Expectant management and reassurance, especially in the first 3–6 months following insertion, are important components of managing unscheduled bleeding. For women who are dissatisfied with their bleeding patterns and desire a management option, a number of medical options have been studied in LNG-20 IUD users. No studies have addressed unscheduled bleeding in users of the lower dose hormonal IUDs.

Naproxen and mefenamic acid have both been studied in women with unscheduled bleeding using the LNG-20 IUD. Monthly naproxen courses of 500 mg twice per day for 5 days for three cycles resulted in a modest (10%) decrease in the number of days of bleeding [72]. This effect did not persist, however, and no difference was noted between the naproxen and placebo group 4 weeks following treatment [72]. Mefenamic acid 500 mg three times daily initiated at the start of a bleeding episode was compared to placebo, and no difference in the reduction of unscheduled bleeding days was noted [73].

Tranexamic acid initiated on the second day of a bleeding episode in doses of 500 mg three times per day was studied in a randomized controlled trial in LNG-20 IUD users and resulted in six fewer bleeding days over a 90-day study period when compared to placebo [73]. No significant difference in the relative risk of unscheduled bleeding with tranexamic acid compared to placebo was reported [73].

Estrogen supplementation is theorized to decrease unscheduled bleeding by stabilizing the endometrium and underlying vasculature. A 0.1-mg transdermal estradiol patch placed 1 day after IUD insertion and reapplied weekly for 12 weeks resulted in an increase in unscheduled bleeding [72]. However, 4 weeks after the treatment, no difference was noted in unscheduled bleeding days. Estradiol users reported higher rates of dissatisfaction with bleeding patterns in the first 4 weeks of treatment; 39.5% compared to 11.6% of placebo users reported dissatisfaction [72].

A randomized controlled trial of mifepristone 100 mg on the day of insertion and every 30 days for 3 additional doses resulted in a decrease in the median duration of unscheduled bleeding and number of bleeding episodes [74•]. After 3 months, the mifepristone group continued to report less intermenstrual bleeding than the placebo group (6 versus 15 days) [74•]. Mifepristone users reported a 75% satisfaction rate compared to 44% of the placebo group [74•].

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) that antagonizes the progesterone receptor [75]. UPA binds the progesterone receptor more selectively than progesterone or mifepristone. Episodic use of UPA 50 mg daily for a 3-day course beginning 3 weeks following IUD placement and repeated every 28 days resulted in 3 fewer days of unscheduled bleeding after the first cycle of treatment. However, this effect is gone by the second cycle and by the third cycle, UPA user had more bleeding than the placebo group [76].

Conclusion

Unscheduled bleeding is common with the use of hormonal contraception and may be bothersome enough to lead to method discontinuation. Bleeding patterns typically improve with continued use. Detailed counseling about expectations for bleeding and improvement with continued use is an important part of contraceptive counseling. Short courses of NSAIDs or COCs are commonly used in the management of unscheduled bleeding with various forms of hormonal contraception. While small, randomized controlled trials suggest that options like antifibrinolytics, antiprogestins, doxycycline, or SERMs may be beneficial with some hormonal contraceptives, additional research is needed to determine the true effectiveness of these medications in the treatment of unscheduled bleeding with hormonal contraception.

Compliance with Ethical Standards

Conflict of Interest Shandhini Raidoo declares no conflicts of interest. Bliss Kaneshiro declares research support to her institution from Merck, ContraMed, and Estetra, and royalties from Up to Date.

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