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REVIEW

# Understanding Problematic Bleeding When Using Contraception: Guidance for Clinicians

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**Abstract:** Abnormal uterine bleeding (AUB) is a common side effect of hormonal contraceptive (HC) use and represents a significant cause of treatment discontinuation. Two main types of bleeding are recognized: withdrawal bleeding, which occurs during the hormone-free interval following a sudden drop in hormone levels, and breakthrough bleeding (BTB), defined as unscheduled bleeding during active hormone administration. Combined oral contraceptives (COCs) may induce BTB due to hormonal fluctuations or insufficient endometrial stabilization, while progestin-only contraception (POC) is commonly associated with abnormal bleeding due to endometrial changes induced by continuous progestin exposure. A structured and clinically oriented framework for the management of AUB in the context of HC is presented, highlighting the importance of appropriate counseling. Some strategies to improve adherence have been proposed, recognizing non-compliance as a major contributor to unscheduled bleeding. Contraceptive choice is addressed as an individualized process, involving adjustments to hormone type and dosage based on woman-specific needs. The aim is to provide clinicians with a clear and structured tool to address a highly prevalent yet often overlooked issue, still marked by significant uncertainty and inconsistency in the current literature.

**Keywords:** abnormal uterine bleeding, hormonal contraception, progestin-only contraception, combined oral contraceptives, breakthrough bleeding, withdrawal bleeding

## Introduction

Abnormal uterine bleeding (AUB) is a leading cause of discontinuation of the use of hormonal contraceptive methods.[1] Although this type of bleeding is common during the first few months of hormonal contraceptive use, and often improves over time; frustration can still lead to discontinuation, increasing the risk of unintended pregnancies.

Bleeding patterns vary widely, and can include episodes of spotting, frequent or prolonged bleeding, or no bleeding. This clinical heterogeneity complicates identification of the underlying mechanisms behind the abnormal uterine bleeding, as well as selection of appropriate management strategies.[2] To address this complexity, several systems for the classification of bleeding patterns associated with hormonal contraceptive use have been developed, with the goal of providing a shared language that allows for more accurate data collection and enables a better understanding of the underlying pathophysiological mechanisms. In 2007, Mishell et al[3] proposed introduction a clear distinction between scheduled and unscheduled bleeding, and recommended that bleeding patterns be assessed based on a single contraceptive cycle (eg, 28 days), rather than over a 90-day interval as previously proposed by the WHO classification.[4] More recently, Creinin et al[5] proposed a more refined framework based on three distinct parameters: pattern, flow, and duration. Specific criteria were established for each parameter according to the type of contraceptive used (cyclic/extended vs continuous/long-acting), because the predictability and characteristics of bleeding can differ significantly (Table 1).

Two primary patterns of uterine bleeding are observed with hormonal contraceptive use: withdrawal bleeding and breakthrough bleeding (BTB).[2] Although the terms scheduled and unscheduled bleeding are now predominantly used in



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**Table 1** Recommended Bleeding Outcome Criteria and Descriptor Across Hormonal Contraceptive Regimens

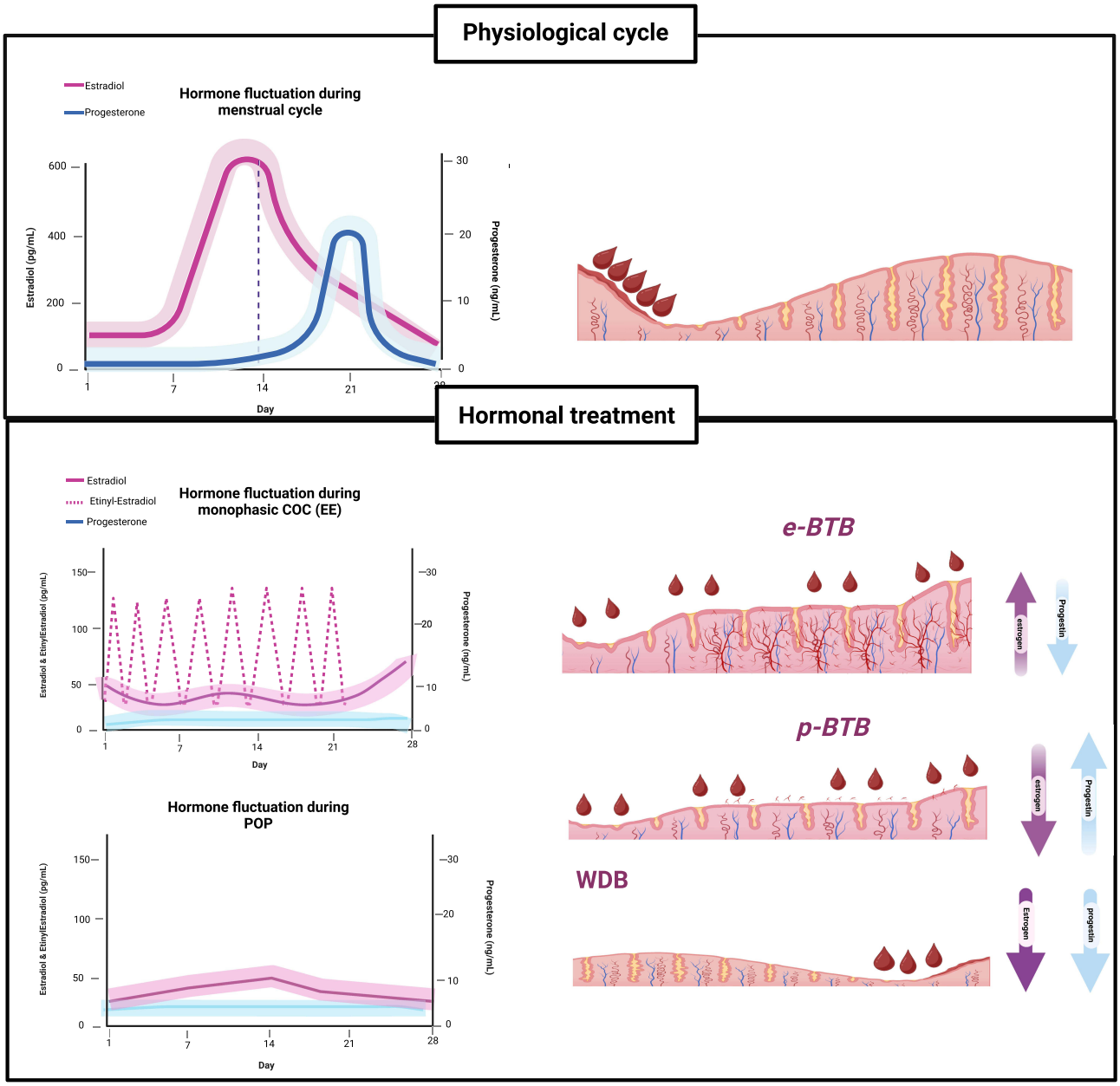
| | | |
|---|---|---|
| **Pattern** | **Cyclic/Extended Regimen (28-Day /84-Day References)** | |
| | ***Descriptors*** | ***Definitions*** |
| | Scheduled bleeding | During expected interval, ≤7 days |
| | Unscleduled bleeding | Not during defined withdrawal period |
| | **Continuous/Long-acting regimen (**90-day reference) | |
| | ***Descriptors*** | ***Definitions*** |
| | Absence of bleeding/spotting | No bleeding/spotting |
| | Infrequent | ≤2 episodes |
| | Normal frequency | 3–4 episodes |
| | Frequent | >4 episodes |
| **Flow** | ***Descriptors*** | ***Definitions*** |
| | None | No bleeding/spotting during the entire cycle |
| | Spotting | Light flow, with no menstrual products |
| | Lighter or Usual or Heavier | Subjective comparison to normal flow with menstrual product use |
| **Duration** | ***Descriptors*** | ***Definitions*** |
| | Prolonged | >7 days |
| | Not prolonged | ≤7 days |

**Notes**: Definitions of bleeding during hormonal contraceptive use according to Creinin et al. The table summarizes criteria for pattern, flow, and duration, distinguishing between cyclic/extended (28- or 84-day) and continuous/long-acting (90-day) regimens. The layout has been reorganized for clarity and integration; all content is faithfully derived from the original tables published by the authors. (Adapted from: Creinin MD et al. Contraception. 2022;112:14–22.).

the literature,[4] in this review we have retained the traditional terminology, as it more directly reflects the underlying physiological mechanisms.

- Withdrawal bleeding

Withdrawal bleeding typically occurs during the hormone-free interval of hormonal contraceptive use, due to the abrupt reduction or cessation of exogenous hormones. During the active phase of combined hormonal contraceptive use, the endometrium is maintained in a relatively atrophic and stable state because of the influence of synthetic estrogens and progestins.[6] The progestin component exerts an opposing effect on the proliferative activity of estrogen, resulting in a controlled, less-vascularized and thinner endometrial lining.[2] When exogenous hormone intake is interrupted during hormone-free interval days, the sudden drop in estrogen and progestin causes a constriction and subsequent dilation of the spiral arteries supplying the endometrium, resulting in ischemia and detachment of the superficial endometrial layer. This process is similar to what occurs during physiological menstruation,[7] but with reduced endometrial proliferation due to the effects of synthetic progestins (Figure 1).




Graphical Representation of Hormonal Fluctuations and Endometrial Effects During the Menstrual Cycle and Hormonal Contraceptive Use.

**Notes**: The upper part shows physiological hormone fluctuations and their endometrial effects. The lower part illustrates two contraceptive regimens: a monophasic COCp with EE (upper left), where estrogen peaks may lead to E-BTB; and a POP (lower left), where low endogenous hormones and progestin dominance can cause P-BTB. Withdrawal bleeding (lower right) results from abrupt hormone withdrawal.

**Abbreviations**: E-BTB, Estrogen breakthrough bleeding; P-BTB, Progestin breakthrough bleeding; WDB, Withdrawal bleeding; COCp-EE, Combined Oral Contraceptive Pill with Etinyl-estradiol); POP, Progestin Only Pill.

- Breakthrough bleeding (BTB)

  Breakthrough bleeding (BTB) is defined as unscheduled, abnormal bleeding or spotting that occurs during the active use of hormonal contraceptives.

  It is a common side effect of hormonal contraceptive use, particularly during the initial three to six months. BTB can be further classified into two primary subtypes, based on the dominant hormonal influence: progestin-breakthrough bleeding (p-BTB) and estrogen-breakthrough bleeding (e-BTB) (Figure 2). These terms are introduced in this manuscript as descriptive terminology to delineate the specific circumstances under which unscheduled bleeding may occur.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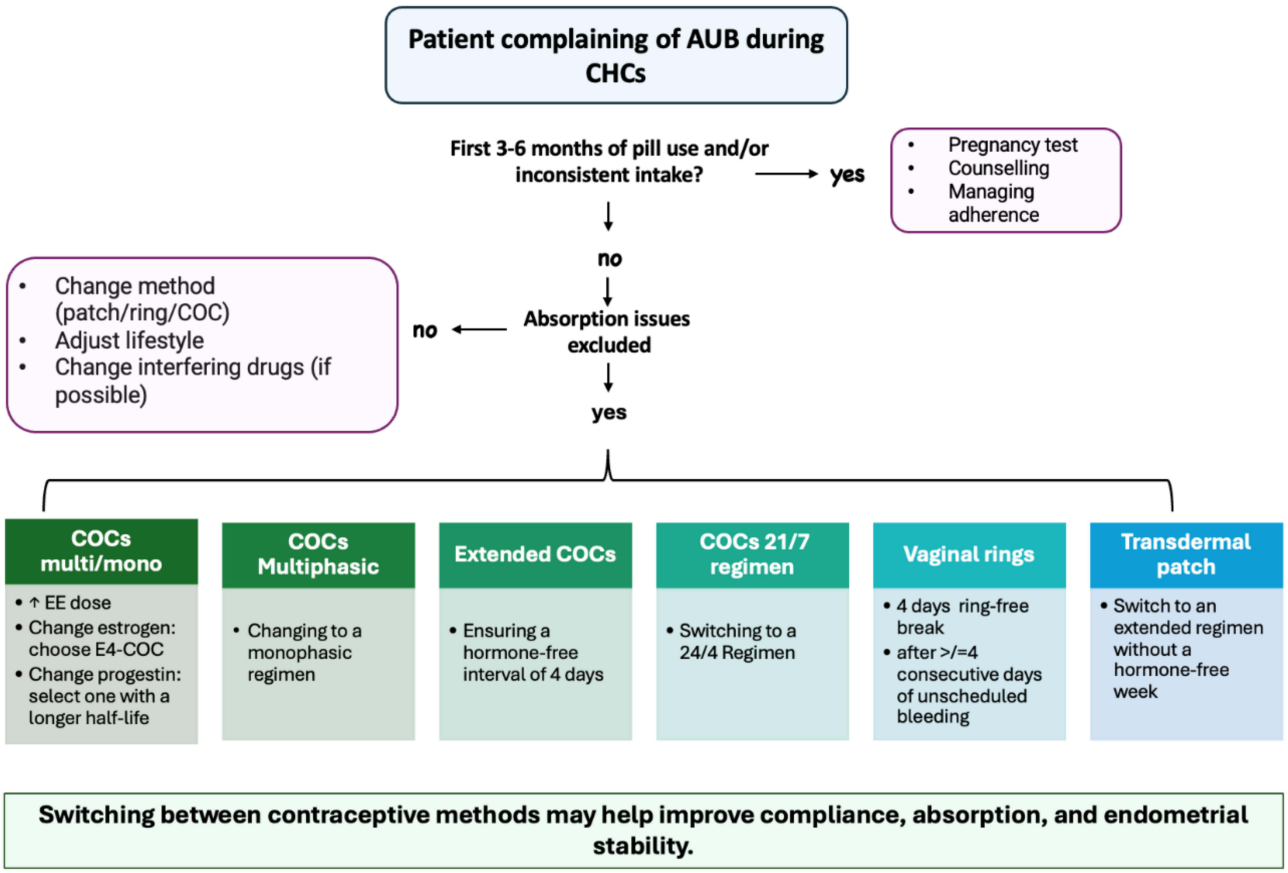


**Figure 2** Management of Abnormal Uterine Bleeding in Users of Combined Hormonal Contraceptives (CHCs).

- Estrogen-breakthrough bleeding (e-BTB): e-BTB occurs when elevated or fluctuating estrogen levels lead to excessive proliferation of endometrial glands and increased stromal angiogenesis.[8] This process results in the formation of a structurally fragile endometrium, because glandular overgrowth exceeds stromal support. Similarly, vascular fragility is also evident, due to the development of immature and unstable capillaries. The combined effects of glandular instability (focal shedding) and capillary rupture (micro-bleeding) results in unscheduled spotting or light bleeding.[9] This phenomenon is most frequently observed during the first 3 to 6 months of the commencement of hormone therapy, or with the use of certain types of combined oral contraceptives (COCs), particularly for those associated with fluctuations in endogenous estrogen levels that are insufficiently controlled, as discussed in the following section.
- Progestin-breakthrough bleeding (p-BTB): p-BTB occurs when sustained exposure to progestins induces excessive thinning and atrophy of the endometrial lining, leading to instability of the endometrial microvasculature. Progestins suppress endometrial proliferation by counteracting the proliferative effects of estrogen. Over time the endometrial lining becomes atrophic, less vascularized, and structurally fragile. This instability is associated with increased endometrial focal shedding, where small areas of the endometrium detach, resulting in spotting or light bleeding.[9] In fact, this focal shedding is a hallmark of both progestin-only methods and regimens that rely on continuous progestin exposure (eg, POP, implants, hormonal IUDs, injectables, or continuous COC use).

Despite the high prevalence of AUB in hormonal contraceptive users, research in this area has been hindered by methodological heterogeneity, where differences in dosage, formulations, and study protocols make it difficult to establish clear and generally accepted guidelines. In addition, inconsistencies in the definition and classification of bleeding types — such as those used to distinguish between spotting, breakthrough bleeding, and withdrawal bleeding —

further complicate the identification of the underlying causes of abnormal uterine bleeding and the development of effective management strategies. In light of these challenges, this review analyses the causes of AUB associated with hormonal contraceptive use, and provides an individual examination of AUB for each class of contraceptive, including: combined oral contraceptives (COCs), progestin-only pills (POPs), intrauterine devices (IUDs), and subdermal implants. Finally, this review gives practical guidance for the clinical management of AUB associated with hormonal contraceptive use.

# Combined Hormonal Contraceptives (CHCs)

Unscheduled bleeding is a relatively common side effect of combined hormonal contraception (CHC), with an incidence of approximately 10–18% per cycle, regardless of the route of administration.[10] For women who use estrogen-progestin contraceptives, abnormal uterine bleeding is a complex multi-factorial problem that, in addition to the resulting delicate imbalance between hormonal components, also depends on pharmacokinetics, administration routes, and patient behavior. This section outlines the main pathophysiological mechanisms underlying abnormal uterine bleeding in CHC users and presents evidence-based strategies to address them in clinical practice.

## Management Strategies (Figure 2)

### Counseling and Patient Education

Timely and thorough counselling is crucial for the management of patient expectations. For example, informing women that breakthrough bleeding is common during the first 3 to 4 months of using CHCs and that this generally decreases over time, can help reduce patient anxiety and prevent CHC discontinuation. Moreover, patients should be reassured that abnormal bleeding does not signify contraceptive failure, and that in most cases, abnormal bleeding patterns stabilize within the first few cycles. Women should be encouraged to persist with their oral contraceptive (OC) and only discontinue it after a thorough discussion with their healthcare provider.[11]

### Managing Adherence

Non-compliance, such as missed doses or inconsistent timing of hormone intake, is one of the most common causes of breakthrough bleeding.

- Combined Oral Contraceptives: Since COCs require daily administration, even a single missed dose can lead to fluctuations in hormone levels, which in turn can compromise endometrial stability and increase the likelihood of unscheduled bleeding. This risk is particularly significant with low-dose formulations that rely on consistent hormone levels to maintain endometrial integrity.[12]
- Vaginal ring: The risk of AUB with vaginal ring use is closely linked to adherence to insertion and replacement schedules. Failure to reinsert the ring after the designated interval, or its continuous use, may result in hormonal fluctuations and consequent bleeding.[13] An endometrium exposed to stable but not fully suppressive hormone levels may develop vascular fragility and focal breakdown, leading to unscheduled bleeding. This may occur during the ring-change interval, when hormone levels have not yet peaked,[13] or if the ring remains outside the vagina for more than three hours, in which case hormone levels may fall and, in this situation, contraceptive efficacy may also be reduced.[14]
- Transdermal contraceptive patch: The effectiveness of the transdermal contraceptive patch relies on proper adhesion and timely replacement to ensure consistent hormone delivery. Failure to replace the patch within the recommended interval can lead to a sudden decline in estrogen levels, similar to missing an oral contraceptive dose, and this, in our view, may increase the likelihood of unscheduled bleeding episodes.[15]

Encouraging effective strategies, such as setting reminders, associating contraceptive use with a daily habit, or utilizing digital tracking tools, may improve patient adherence[16.] Nevertheless, comprehensive pre-counselling that fosters a trusting relationship with users and provides clear, method-specific instructions on how to manage missed doses or delayed applications remains essential to prevent unnecessary disruptions in contraceptive efficacy and cycle stability.[17]

## Adjusting the Dosage and Formulation

For combined hormonal contraceptives, maintaining a balance between estrogen and progestin is essential for endometrial stability and bleeding control. In cases of unscheduled bleeding, assessment of the estrogen dose, type of estrogen, and characteristics of the progestin used can help identify potential hormonal imbalances that may affect cycle regulation, and provide guidance for appropriate management.

- Increasing Estrogen Dose: Low doses of estrogen, such as those found in some newer OCs (eg, ≤ 20 µg of ethinylestradiol, EE) may induce greater fluctuations in endogenous estrogen levels, resulting in insufficient endometrial support and an increased risk for breakthrough bleeding. Increasing the estrogen dose to 30 µg or 35 µg may improve cycle control and reduce breakthrough bleeding.[18,19]
- Changing Estrogen Type: Due to their short half-lives (approximately 3 hours) and rapid hepatic metabolism, use of 17β-estradiol (E2) and estradiol valerate (E2V) in COCs is associated with greater hormonal fluctuations, which can lead to irregular endometrial shedding and unscheduled bleeding. In addition, these estrogen types display limited suppression of gonadotropins, and may allow residual ovarian activity, further contributing to unpredictable bleeding patterns. In contrast, estetrol (E4), which is characterized by a longer half-life (~24 hours) and stable metabolism, provides more consistent estrogen levels; resulting in improved endometrial stability, reduced hormonal variability, and better cycle control.[20]
- Switching Progestins: Progestins with a shorter half-life (t½), such as norethindrone acetate (t½ ~ 5–14 hours), are less effective at maintaining stable hormone levels throughout the cycle, leading to an increased risk of unscheduled bleeding. In contrast, progestins with a longer half-life, such as drospirenone (t½ ~ 30 hours), nomegestrol acetate (t½ ~ 46 hours) and levonorgestrel (t½ ~ 17–37 hours), provide better hormonal stability and reduce abnormal bleeding episodes by ensuring more consistent endometrial support. Progestins with weak antiproliferative effects may fail to counteract estrogen-induced endometrial growth, resulting in more fragile endometrial tissue and a higher susceptibility to AUB.[21–24] Conversely, progestins with strong antiproliferative and anti-angiogenic properties are associated with excellent bleeding profiles. Dienogest, for instance, when combined with estradiol valerate (E2V), has been shown to promote significant endometrial stability. According to Ahrendt et al, E2V/DNG, compared with EE/LNG, is associated with shorter and lighter scheduled bleeding without any increase in unscheduled bleeding.[25]

## Regimens and Formulations

- Switching between Phasic Regimens: In cases of breakthrough bleeding associated with the use of a multiphasic pill, switching to a monophasic formulation may be considered, as it provides a constant hormone dose and is generally associated with more stable bleeding patterns.[26] Conversely, when unscheduled bleeding occurs with a low-dose monophasic regimen, a multiphasic formulation may help by increasing estrogen or progestin levels during specific phases of the cycle. However, the available evidence remains inconclusive, as many studies have compared formulations with substantial heterogeneity in hormone dosages and progestin types, making it difficult to determine the actual impact of multiphasic versus monophasic dosing on bleeding control.[27]
- Ensuring implementation of a Hormone-Free Interval in Extended-Cycle and Continuous-Use of Hormonal contraceptive: Extended-cycle and continuous-use contraceptive regimens are often associated with a higher incidence of breakthrough bleeding during the initial cycles. However, this tends to decrease over time as the endometrium stabilizes, potentially making these regimens a favorable long-term option. In cases of unscheduled bleeding during continuous use, introduction of a 4-day hormone-free interval may be effective for promoting an endometrial reset and improving bleeding control.[28] A practical example of the application of this strategy is represented by the flexible regimen known as "Yaz-Flex", described by Klipping et al[29] which involves the daily intake of ethinylestradiol 20 µg/drospirenone 3 mg for a minimum of 24 and up to 120 consecutive days. If breakthrough bleeding or spotting persists for three consecutive days after Day 24, a 4-day hormone-free interval is introduced to facilitate endometrial shedding and restore cycle control. Results from this randomized, controlled, multicenter clinical trial

confirmed that this individualized approach improves bleeding pattern stability, and is associated with good long-term tolerability and safety. Similarly, for users of the contraceptive vaginal ring, a 4-day vaginal ring-free interval after five or more consecutive days of unscheduled bleeding has been shown to improve cycle stability.[13]

- Switching from a 21/7 regimen: Regimens with only a 4-day hormone-free interval, particularly for those containing estetrol (E4) and drospirenone, offer superior cycle control and more predictable bleeding patterns. This may be a particularly effective option for women experiencing persistent breakthrough bleeding while on a traditional 21/7 regimen, probably because such a long hormone-free interval can trigger a rise in endogenous estrogen levels and new follicular recruitment, leading to hormonal fluctuations.[30,31] For the vaginal ring, a similar effect can be achieved by either reducing the ring-free interval to four days, or using the ring continuously.[13] The transdermal patch may also provide improved cycle control when used in an extended regimen without a hormone-free week,[32] however, these findings should be interpreted with caution, as the current evidence is limited to a single study and further research is needed to confirm both its efficacy and safety.

## Considering Alternative Hormone Delivery Methods

Switching between oral contraceptives, a vaginal ring, or transdermal patch may help optimize patient compliance, hormone absorption, and endometrial stability, ensuring better cycle control and reducing breakthrough bleeding. Selecting the most suitable method should take into account gastrointestinal tolerability, metabolic factors, ease of adherence and patient preferences, in order to maximize contraceptive effectiveness and patient satisfaction.

- Combined oral contraceptives (COCs), after being absorbed in the gastrointestinal tract, undergo first-pass hepatic metabolism, a process that can reduce their systemic availability. Systemic availability can also be easily affected by common issues such as vomiting, diarrhea, or irregular dose intake, all of which may lower circulating hormone levels and lead to inadequate endometrial support, one of the main causes of breakthrough bleeding.[33] Beyond individual patient compliance, several external factors can affect the systemic availability of COCs by modulating their metabolism. Medications, such as anticonvulsants (eg, carbamazepine, phenytoin), certain antibiotics (eg, rifampin), and herbal products like St. John's wort, are known to induce the cytochrome P450 enzyme system, thereby accelerating hormone degradation and diminishing contraceptive effectiveness. Furthermore, cytochrome P450 induction may contribute to unscheduled bleeding episodes.[34] Lifestyle factors also play a role: for example, smoking can alter estrogen metabolism, increasing the likelihood of cycle irregularity and unscheduled bleeding because of diminished endometrial stability.[35] More recently, gut microbiota have been proposed to be a potential modulator of contraceptive efficacy. Dysbiosis, an imbalance in gut microbial composition, may impair estrogen recycling by altering microbial enzyme activity, particularly β-glucuronidase, thereby influencing hormone levels and possibly reducing COC effectiveness.[36]
- Vaginal rings Vaginal rings deliver hormones directly through the vaginal mucosa, thereby bypassing the gastrointestinal tract and hepatic first-pass metabolism, which results in relatively stable systemic hormone levels and reduces fluctuations related to oral absorption.[14] Vaginal rings containing EE/etonogestrel have also demonstrated a favorable bleeding profile and, in a multicenter randomized controlled trial, were associated with superior cycle control compared to the contraceptive patch.[37] Nevertheless, abnormal bleeding may still occur during the first cycles, particularly with extended regimens, while the endometrium is still adapting to continuous hormone exposure. This, however, is a transient condition that tends to decrease over time.[14]
- Transdermal patches provide continuous hormone release through the skin, ensuring relatively stable serum hormone levels. Unlike oral formulations, hormones released via transdermal patches bypass first-pass hepatic metabolism, potentially reducing variability in hormone concentrations. Clinical evidence suggests that patch adhesion remains robust even under high humidity conditions and during sweating and physical activity, minimizing the risk of detachment and subsequent hormone level fluctuations. However, individual factors such as skin conditions, improper patch application, or the use of lotions and oils at the application site, may still influence patch adhesion and therefore hormone absorption.[15] In addition, it is important to consider that the efficacy of the patch is reduced in women with a weight ≥90 kg, and therefore its use in this group is not recommended.[38]

### Diagnostic Testing

Diagnostic testing is warranted for women who experience prolonged or severe breakthrough bleeding. Patient examinations may include a pregnancy test, pelvic ultrasound, Pap smear, endometrial biopsy, and vaginal and cervical swabs to rule out organic or infectious causes of bleeding.[39]

## Progestin Only Contraceptive (POC)

Abnormal uterine bleeding is a common adverse side effect of progestin-only contraceptives (POCs), and remains a primary cause of POC discontinuation. Thus, it is essential to address this issue in order to ensure sustained contraceptive adherence, and thereby optimize efficacy while minimizing associated risks. However, management of progestin-induced bleeding irregularities poses a significant clinical challenge, because they can be influenced by multiple factors, including progestin type, dose, and administration route (Figure 3).

The timing of AUB onset can provide insight into its underlying cause:[40]

- Bleeding that occurs during the first six months of POC therapy is mainly related to the transition from an estrogen-stimulated proliferative endometrium to a thinner, atrophic lining, due to the antiproliferative effects of progestins. This mechanism is similar to that which we previously described for estrogen-BTB; where the number of endometrial glands is increased due to incompletely suppressed estrogen stimulation, and these interact with stroma that have undergone progesterone-dependent decidualization (Figure 1).
- Bleeding persisting beyond six months is more often associated with chronic progestin exposure, which induces structural changes such as stromal pseudo-decidualization and vascular fragility. These structural changes are important contributing factors behind progestin-BTB, as we discussed in the introduction (see Figure 1).

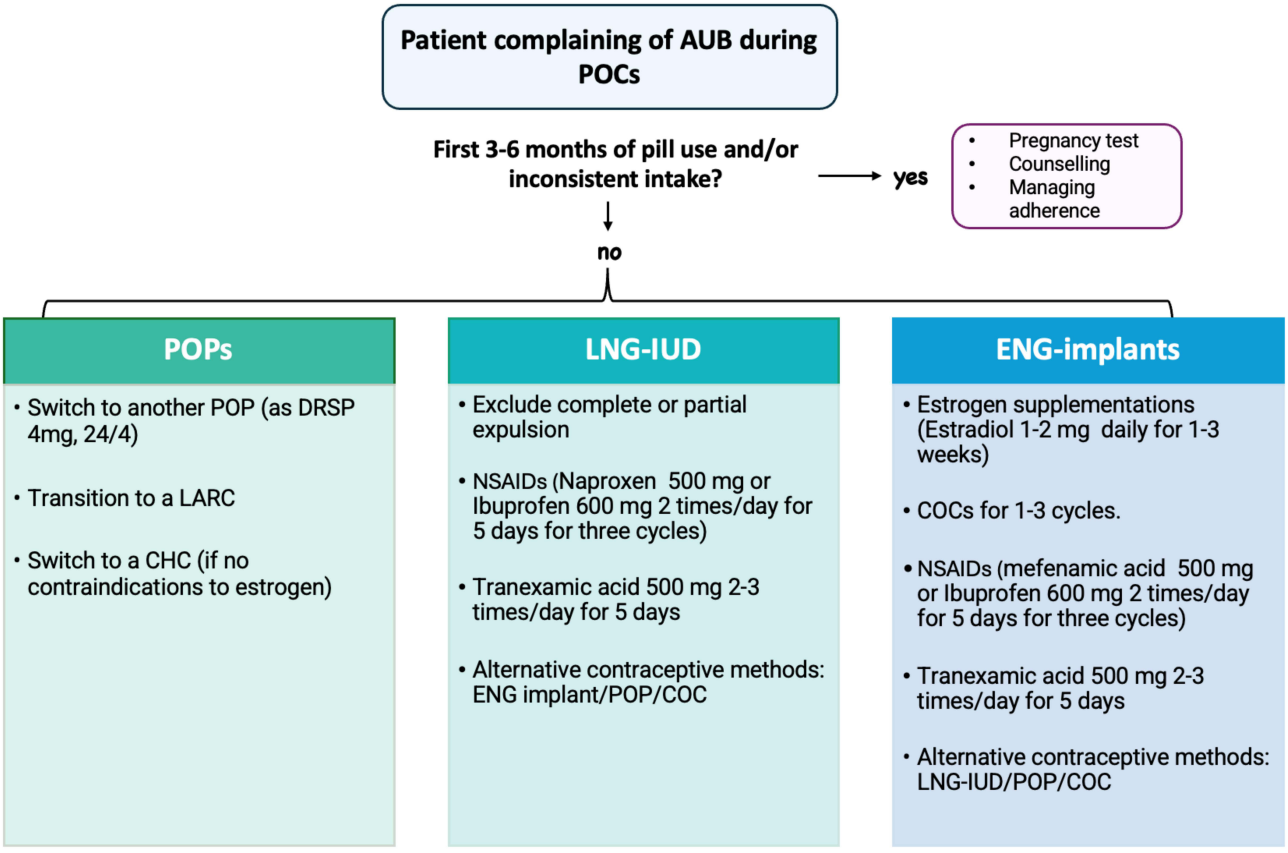


**Figure 3** Management of Abnormal Uterine Bleeding in Users of Progestin-Only Contraceptives (POCs).

This section will explore the different progestin-based contraceptives, their mechanisms of action, the pathophysiological basis of unscheduled bleeding, and evidence-based strategies for its clinical management to enhance contraceptive adherence and patient satisfaction.

## Progestin Only Pills (POPs)

Unscheduled bleeding is the most commonly reported side effect among women using POPs, where approximately 40% of users reported experiencing irregular cycles, and 10% reported amenorrhea.[41–43] These abnormal bleeding patterns are likely secondary to significant differences in serum progestin levels between users and daily fluctuations in serum progestin levels.[41]

## Management Strategies (Figure 2)

### Monitoring and Counselling

Abnormal bleeding is a well-documented effect of progestin-only contraceptives (POCs), particularly within the first 3–6 months of use. Patients should be informed that this abnormal bleeding typically decreases over time, as the endometrium undergoes adaptive changes. Emphasis of strict adherence to dosing schedules is crucial, for some formulations, because delays or inconsistencies in POC administration can exacerbate endometrial instability, increasing the likelihood of breakthrough bleeding.[17]

### Pharmacological Strategies

If bleeding is poorly tolerated, pharmacological treatment may be considered even within the first three months of use[44] with nonsteroidal anti-inflammatory drugs (NSAIDs) representing a therapeutic option, as they can reduce prostaglandin release and thereby modulate endometrial inflammation.[45] While no studies have specifically evaluated the efficacy of NSAIDs in managing AUB in progestin-only pill (POP) users, available evidence suggests a temporary but measurable benefit in LARC (long-acting reversible contraceptive) users.[46] Thus, although further research is required to confirm their role in this setting, it is possible that NSAIDs may have a similar effect in POP users.

### Alternative Contraceptive Methods

If abnormal bleeding persists beyond the first 3–6 months, despite strict adherence to the prescribed regimen, and is perceived by the patient as bothersome or significantly impacts daily life, alternative contraceptive options should be considered.

- Switch POP: Switching to a progestin-only pill (POP) with a more regular bleeding pattern can be advantageous. Drospirenone 4 mg, which follows a 24/4 regimen, stands out compared with other progestin-only pills currently available because it improves cycle control and reduces unpredictable bleeding.[47] This formulation has demonstrated superior bleeding control compared to desogestrel 0.075 mg, likely due to the combination of its long half-life (~30 hours) and strong pharmacodynamic activity on the endometrium.[48,49] According to a recent study by Grandi et al[50,] the Transformation Index (TI), defined as the ratio between the daily administered dose of a progestin and the minimal clinically effective dose and the minimal clinically effective dose required to induce progestogenic changes in the endometrium, offers a useful measure of this effect. A higher TI reflects a greater ability to promote endometrial stability and reduce unscheduled bleeding. In addition, drospirenone-only pills represent an evolution of POPs by providing a wider missed pill window (up to 24 hours), which improves flexibility and may enhance adherence. Therefore, in patients experiencing breakthrough bleeding with other POPs, switching to a progestin with a high TI, such as drospirenone, may lead to more consistent bleeding patterns, better cycle control, and improved user compliance.[47]
- Switch POC: If patients are dissatisfied with their current contraceptive method, a change in the route of administration may be considered. Careful counseling is essential to present all available alternatives, highlighting their main characteristics and potential implications for use. Alternatives to POPs include long-acting reversible

contraceptives (LARCs), such as the levonorgestrel-releasing intrauterine device and the etonogestrel implant, as well as depot medroxyprogesterone acetate (DMPA).[51,52]

- Switch to CHC: If no contraindications are present, transitioning to a CHC regimen can enhance cycle control by stabilizing estrogen levels and reducing unscheduled bleeding.[53]

## Etonogestrel (ENG) Subdermal Implants

ENG implants are subdermal contraceptives that continuously release progestin, leading to significant changes in endometrial physiology. AUB associated with ENG implants is primarily due to ovulation suppression and hypoestrogenism, which results in persistently low estradiol levels. This hormonal environment limits endometrial proliferation, leading to thinning, vascular fragility, and irregular shedding, which contributes to unpredictable bleeding patterns. In addition, chronic exposure to ENG disrupts endometrial vascular integrity, resulting in fragile and irregularly developed capillaries, which further increases the likelihood of spotting and prolonged bleeding episodes.[2,54]

### Expectant Management

In many users, AUB associated with ENG implants resolves spontaneously over time. Patients should be counselled that early bleeding patterns often predict long-term trends. Bleeding patterns within the first 3 months following ENG implantation are predictive of patterns for the duration of ENG use: favorable bleeding patterns are likely to continue, while unfavorable bleeding patterns have a 50% chance of improvement.[54]

Moreover, recent evidence indicates that the unpredictable bleeding observed during the first months of ENG implant use is associated with markedly elevated serum ENG concentrations.[55] Since these levels are mainly observed immediately after insertion, it is important to counsel patients that any abnormal bleeding occurring at this stage is usually transient.[55,56] Over time, serum ENG levels decline and the endometrium overcomes the transitional phase, adapting to lower and stable concentrations of the hormone. As a result, focal shedding decreases and abnormal bleeding episodes become progressively less frequent.[2,54]

### Pharmacological Interventions

#### Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Prostaglandins play a key role in promoting endometrial vascular fragility and inflammation: two major contributors to abnormal bleeding patterns associated with progestin-only contraceptive methods. NSAIDs inhibit cyclooxygenase (COX) enzymes and thereby reduce prostaglandin synthesis, and thus may help stabilize the endometrium and improve bleeding control in ENG subdermal implant users. They may be particularly useful in the early phase of treatment, when unscheduled bleeding tends to be more pronounced and distressing, although generally self-limiting over time.[52]

Mefenamic Acid In a randomized controlled trial, mefenamic acid, administered at a dose of 500 mg, two to three times daily for 5–7 days, demonstrated greater efficacy than placebo in reducing unscheduled bleeding episodes among ENG implant users.[46]

Ibuprofen, administered at a dose of 600 mg, two to three times daily for 5–7 days, is a widely available NSAID commonly used in clinical practice for bleeding control. However, no specific studies have assessed its efficacy for bleeding associated with ENG implant use.

#### Hormonal Supplementation

Because persistent hypoestrogenism is associated with ovulation suppression and contributes to endometrial instability; estrogen supplementation may be a potential strategy for improving bleeding patterns. Although support for estrogen supplementation is currently only based on anecdotal evidence, addition of low doses of E2 (1–3 mg per day), administered either transdermally or orally for approximately 1–3 weeks, could be considered for the management of bleeding, and can be repeated for three consecutive cycles.[57,58]

Alternatively, COC use has been evaluated as an effective option for controlling bleeding in ENG implant users. A randomized, controlled trial demonstrated that a 14-day course of COCs in ENG implant users resulted in a higher likelihood of bleeding cessation (87.5% vs 37.5% in the placebo group) during treatment. Therefore, addition of a COC (21 plus 7 days), administered for three cycles, may improve the control of abnormal uterine bleeding. Nevertheless, it

should be noted that bleeding control is often transient, with 85.7% of women experiencing recurrence of abnormal bleeding within 10 days following cessation of COC therapy.[59,60]

In patients with contraindications to estrogen use, the addition of a POP with high uterotrophic activity—such as norethisterone acetate (2.5–10 mg/day), dienogest (2 mg/day), nomegestrol acetate (2.5–5 mg/day), or drospirenone (4 mg/day)—administered for three consecutive cycles, may contribute to improved bleeding control.[61] However, it is important to note that many of these management strategies are based on historical clinical practices and are not supported by robust scientific evidence. Well-designed clinical trials are necessary to validate their efficacy in this specific setting.[58]

### Anti-Fibrinolytic Agents

Tranexamic acid administered at 500 mg two to three times daily for five days, demonstrated a temporary reduction in bleeding episodes during the first week of treatment. However, no sustained improvement in long-term bleeding patterns was observed. These findings suggest that while tranexamic acid may offer short-term relief from excessive bleeding, its impact on overall bleeding control remains limited.[62]

### Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen, which acts as an agonist of endometrial estrogen receptors, has been evaluated as a therapeutic option for the management of unscheduled bleeding. When administered at a dose of 10 mg, twice daily, tamoxifen demonstrated superior efficacy compared to placebo in reducing the occurrence of bleeding episodes following three consecutive days of spotting. Tamoxifen promotes endometrial stabilization and improving bleeding patterns via a mechanism similar to that of estradiol (E2) and ethinylestradiol (EE).[63]

### Anti-Progestins

Mifepristone, administered at a dose of 100 mg at baseline and repeated every 30 days for three additional doses, has demonstrated efficacy in reducing the median duration and frequency of unscheduled bleeding episodes. Studies conducted in Norplant and ENG implant users indicate that mifepristone significantly decreases the number of bleeding days, especially when used in combination with estradiol or doxycycline.[64,65] However, because of its mechanism as a progesterone receptor antagonist, there is concern that it might reduce the contraceptive effectiveness of the implant, which has limited its use in clinical practice.[66]

## LNG-IUS (Levonorgestrel-Releasing Intrauterine System)

LNG-IUDs are intrauterine devices that provide contraception through the localized release of levonorgestrel, which induces significant endometrial remodeling. The primary mechanism of AUB in LNG-IUD users is due to the direct effects of progestin on the endometrium, which leads to decidualization and subsequent atrophy. These changes result in abnormal bleeding and spotting (breakthrough bleeding), particularly during the initial months following insertion.[67] Unlike ENG implants, LNG-IUDs do not systemically suppress ovulation, meaning that estradiol levels remain within normal ranges. However, despite adequate estrogen levels, localized progestin effects alters the endometrial architecture, resulting in fragile superficial blood vessels that are prone to spotting and abnormal bleeding episodes. Over time, the endometrium gradually stabilizes, and many LNG-IUD users experience a reduction in bleeding frequency or amenorrhea.

## Expectant Management

AUB is particularly common within the first six months following LNG-IUD insertion, with 35% of users reporting frequent or prolonged bleeding episodes. However, these symptoms typically improve over time, and only 4% of users continue to experience excessive bleeding beyond 12 months after LNG-IUD insertion. In fact, 44% of women report amenorrhea by 6 months after insertion, while 50% experience amenorrhea after 12–24 months of LNG-IUD use.[68–70] Expectant management is appropriate if the patient is not particularly significantly impacted by bleeding; however, in women who experience bothersome symptoms, medical therapy can be considered during the initial months after LNG-IUD insertion.[52]

In cases where abnormal bleeding persists beyond six months, an examination for complete or partial device expulsion should be conducted.[63]

### Pharmacological Interventions

#### Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Endometrial vascular instability and local inflammation play a key role in the abnormal bleeding often seen within the first months following LNG-IUS placement. As stated above, NSAIDs have shown effectiveness in limiting bleeding through inhibition of prostaglandin synthesis. They can be offered from the early months after insertion if bleeding is particularly bothersome, providing temporary relief until symptoms improve spontaneously.[52]

Naproxen at a dose of 500 mg twice daily for 5 days, repeated for three consecutive cycles, significantly reduced the number of bleeding days during the first 12 weeks of use.[71]

Ibuprofen at 600 mg two to three times daily for 5–7 days may be considered a more affordable option, although specific efficacy data with respect to LNG-IUS users is currently limited.

#### Hormonal Supplementation

In contrast to what is observed in progestin implant users, serum estradiol levels in women using LNG-IUS remain within physiological ranges. For this reason, estrogen supplementation has generally proven ineffective in reducing bleeding during the early post-insertion phase. In a randomized trial, the use of transdermal estradiol patches resulted in worse abnormal bleeding patterns during the first 12 weeks of use.[72] However, in a small observational study, oral estradiol (2 mg/day for 20–21 days) was associated with a significant reduction in the number of bleeding days (from 21 to 5 days) in patients with persistent abnormal bleeding more than 6 months after insertion.[73] Thus, estrogen therapy should be considered only in cases of long-term bleeding irregularities, which are likely due to endometrial atrophy.

#### Anti-Fibrinolytics

Tranexamic acid reduces endometrial fibrinolysis and can be a useful option for treating episodes of heavy bleeding. In a randomized trial, a dosage of 500 mg three times daily for 5 days reduced the total number of bleeding days by approximately 6 days over a 90-day observation period. However, no significant effects were observed on the overall risk for abnormal bleeding.[74] Tranexamic acid is therefore indicated for the episodic management of particularly heavy bleeding.

#### Anti-Progestins

Mifepristone, a progesterone receptor antagonist, has shown potential in modulating bleeding patterns associated with LNG-IUS use. In a prospective, non-randomized study,[75] monthly administration of low-dose mifepristone after LNG-IUS insertion reduced the number and duration of bleeding and spotting episodes. A randomized, controlled trial by Papaikonomou et al investigated short-term mifepristone treatment prior to insertion and reported similar benefits during the early post-insertion phase.[76] These effects are likely due to partial inhibition of endometrial sensitivity to progestins, promoting faster reorganization. However, the observed improvement was only temporary in both studies, and the available evidence remains limited. Further, high-quality research is needed before mifepristone can be considered for standard clinical use in this setting.

## Conclusion

AUB is one of the leading causes of hormonal contraceptive discontinuation, and is due to multi-factorial mechanisms such as hormonal fluctuations and endometrial instability. Analysis of different contraceptive classes reveals specific bleeding patterns: COC may cause abnormal bleeding due to inadequate suppression of endogenous estrogen or insufficient endometrial stabilization, whereas POP are more often associated with unpredictable bleeding due to continuous progestin exposure. Effective management requires appropriate patient education, strategies to support patient adherence, and personalized adjustments to the contraceptive regimen. In this review, we have provided, for the first time, a practical guide to the management of abnormal uterine bleeding during contraceptive use. In addition, a detailed

interpretation of the underlying mechanisms has been given, clarifying the rationale for therapeutic choices. However, although several treatment strategies are available, the lack of standardized guidelines and the variability of individual responses highlight the need for further research. A better understanding of the mechanisms and bleeding patterns involved could improve clinical management and patient satisfaction.

## Disclosure

Prof. Dr. Giovanni Grandi reports personal fees from Bayer Italfarmaco Exeltis Gedeon Richter Theramex Opocrin, during the conduct of the study. The authors report no other conflicts of interest in this work.

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