Management of Unscheduled Bleeding in Combined Oral Contraceptive Users: Postprint

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Abstract

Unscheduled bleeding is a common reason for discontinuation of combined oral contraceptives during use in women. Adequate counseling regarding unscheduled bleeding, together with necessary prevention and treatment, can improve adherence to oral contraceptives. However, the mechanism underlying unscheduled bleeding remains unclear, and there is a lack of effective prevention and treatment methods supported by high-level evidence. For women with new-onset or persistent unscheduled bleeding, it is important to rule out gynecological diseases.

Full Text

Management of Unscheduled Bleeding in Women Using Combined Oral Contraceptives

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Abstract

Unscheduled bleeding is a common reason for discontinuation of combined oral contraceptive (COC) use. Appropriate counseling about the possibility of unscheduled bleeding, along with necessary prevention and treatment, can improve adherence to oral contraceptives. However, the mechanisms underlying this bleeding remain unclear, and there is a lack of high-level evidence supporting

effective prevention and treatment strategies. For women with new-onset or persistent unscheduled bleeding, it is important to exclude gynecological diseases.

Keywords: combined oral contraceptive; unscheduled bleeding; management

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Combined oral contraceptives (COCs) are widely used for contraception in clinical practice due to their high efficacy, convenience, and reversibility. A common reason for discontinuing COCs is dissatisfaction with uterine bleeding patterns, including bleeding amount, duration, and timing. The most troublesome type of uterine bleeding is unscheduled bleeding. For women using oral COCs, preventing or treating unscheduled bleeding can increase contraceptive acceptability and adherence, thereby achieving better contraceptive efficacy. Currently, there is no consensus regarding the possible causes, clinical management, or treatment approaches for unscheduled bleeding during oral COC use. This article reviews the literature on these issues.

1. Introduction to Combined Oral Contraceptives

Combined oral contraceptives are compound preparations containing high-potency progestogens and low-dose estrogen [1]. When used correctly, COCs have a contraceptive efficacy of over 99% [1]. In addition, COCs provide numerous non-contraceptive benefits, such as treating abnormal uterine bleeding, premenstrual syndrome, acne, hirsutism, dysmenorrhea, and endometriosis [2].

Since the introduction of the first COC "Enovid," COCs have undergone more than 50 years of development, with continuous improvements in safety, efficacy, and acceptability [1,3]. These improvements are reflected in three main aspects, which also serve as criteria for classifying different types of COCs: (1) reduction in estrogen dosage from 150 g to 30–35 g, or even 20 g; (2) development and application of new progestogens, including first-generation (norethisterone acetate, ethynodiol diacetate, etc.), second-generation (norethisterone, levonorgestrel), third-generation (desogestrel, gestodene, etc.), and unclassified progestogens (drospirenone, cyproterone acetate); and (3) modification of COC administration regimens, including monophasic, biphasic (two doses of progestogen and one dose of estrogen), and triphasic formulations (three doses of both estrogen and progestogen) to accommodate hormonal fluctuations during the menstrual cycle.

Currently, the standard 28-day cyclic regimen is widely used. In addition, the U.S. Food and Drug Administration has approved 91-day extended-use regimens [4] and 365-day continuous-use regimens [5]. Both traditional cyclic use and extended or continuous use have been proven safe and effective [6].

2. Definition, Causes, and Mechanisms of Unscheduled Bleeding

Scheduled bleeding, or withdrawal bleeding, refers to any bleeding that occurs during the pill-free interval, regardless of the regimen used. Scheduled bleed-

ing may persist until days 1–4 of the subsequent pill cycle [7]. Unscheduled bleeding, also termed "breakthrough bleeding" by some Western scholars, frequently occurs during the first three months of COC use. Currently, there is no unified definition of unscheduled bleeding domestically or internationally. The 2005 Consensus Conference on Hormonal Contraceptive Clinical Trials in Philadelphia recommended the following definition: any bleeding that occurs while actively taking pills, excluding two situations: (1) bleeding from day 1 to day 7 of the first pill cycle, and (2) bleeding that begins during the pill-free interval and continues into days 1–4 of the next pill cycle [7].

Statistical data show that the most common cause of unscheduled bleeding during COC use is missed pills [8]. Other possible causes include organic diseases of the reproductive tract, sexually transmitted infections, and unintended pregnancy.

The exact mechanism of unscheduled bleeding remains unclear. Under conditions of correct pill use and after excluding pregnancy and other organic lesions, current research suggests possible mechanisms include: (1) upregulation of matrix metalloproteinases (MMPs) expression. MMPs are a group of zinc-dependent proteases concentrated in stromal cells and adjacent extracellular matrix that degrade extracellular matrix glycoproteins. During normal menstruation, they degrade endometrial tissue. Studies have shown upregulated MMPs expression in endometrial tissue of women experiencing unscheduled bleeding [9,10]; (2) changes in fragility of superficial endometrial vessels, local endometrial alterations, and changes in structural integrity and tissue perfusion [11]; (3) higher estrogen concentrations and larger follicles. One study found that women with unscheduled bleeding had higher estrogen concentrations and relatively larger follicular structures compared to those without unscheduled bleeding [12]; and (4) additional factors such as smoking and use of medications like rifampicin may increase the likelihood of unscheduled bleeding [13,14].

3. Classification of Unscheduled Bleeding

Different studies have employed various classification methods for unscheduled bleeding during oral COC use, and no unified classification standard currently exists. The 2009 guidance "Management of Unscheduled Bleeding in Women Using Hormonal Contraception," developed by the Royal College of Obstetricians and Gynaecologists in collaboration with the Faculty of Sexual and Reproductive Healthcare (FSRH), proposed the following classification with a 90-day reference cycle [15]: (1) frequent bleeding: more than 5 bleeding episodes; (2) prolonged bleeding: one or more bleeding episodes lasting 14 days; (3) irregular bleeding: 3–5 bleeding episodes with fewer than 3 bleeding-free intervals of 14 days; and (4) spotting: minimal bleeding that may not require sanitary protection.

4. Management of Women with Unscheduled Bleeding

There are no domestic or international guidelines for the diagnosis and treatment of unscheduled bleeding. Foreign publications are limited to guidance documents, such as the "Management of Unscheduled Bleeding in Women Using Hormonal Contraception" developed by the Royal College of Obstetricians and Gynaecologists and FSRH [15]. Almost all guidance documents recommend individualized management for women experiencing unscheduled bleeding during COC use, with further investigation, diagnosis, and treatment decisions based on comprehensive clinical assessment. Excluding gynecological diseases as the cause of bleeding is crucial during clinical management.

4.1 Clinical Assessment

Clinical assessment includes: (a) history taking: bleeding patterns before COC use (any irregular vaginal or intermenstrual bleeding?), correct pill use and any missed pills, whether the 28-day regimen (21 days of use plus 7 days off) or extended-cycle use is being followed, concomitant medications that may interact and affect bleeding patterns, other conditions affecting COC absorption, duration, amount, and frequency of unscheduled bleeding and its timing within the pill cycle (early, middle, or late phase), associated symptoms (pain, dyspareunia, abnormal vaginal discharge, heavy bleeding, contact bleeding), and the woman's specific concerns and their severity; (b) exclusion of sexually transmitted infections: for women under 25 years, those with recent new sexual partners, or those with abnormal vaginal discharge, sexually transmitted infections should be suspected, particularly chlamydia infection [8]. Chlamydia trachomatis is the most common bacterial sexually transmitted infection in both the United States and China, and most infections are asymptomatic, presenting as irregular vaginal bleeding [16,17]. Therefore, women at high risk should undergo vaginal discharge testing to exclude chlamydia infection; (c) verification of cervical screening: check whether the woman has recent cervical screening results. If she has been screened regularly with recent results, repeat screening may be deferred [8]. However, if the cervix appears abnormal or shows contact bleeding during examination, repeat screening may be warranted even with previous results; and (d) necessity of pregnancy testing: inquire about last menstrual period, incorrect pill use, concomitant medications affecting absorption, and conditions affecting COC absorption. Pregnancy testing may be necessary to assess the possibility of unintended pregnancy [8]. Currently, there is no evidence that unintended pregnancy rates increase in women with correct COC use who experience unscheduled bleeding.

4.2 Timing of Symptom Onset

Up to 30% of women experience unscheduled bleeding during the first three months of COC use, which decreases to approximately 10% by the third month [18].

For unscheduled bleeding occurring within the first three months of use: this is

common. FSRH guidance suggests that bleeding within the first three months can be managed with observation and follow-up without extensive investigations or interventions, as it usually resolves spontaneously. Immediate switching to a different COC type is not recommended [15].

For unscheduled bleeding occurring after three months of use: if bleeding persists beyond three months, is irregular, shows changed patterns, occurs in women without prior cervical screening, or is accompanied by other symptoms such as abdominal pain or dyspareunia, malignant tumors such as cervical or endometrial cancer should be suspected and further investigations may be required. After excluding organic gynecological diseases as the cause of persistent bleeding, some scholars suggest changing the regimen or switching to a new type of COC [19].

4.3 Further Investigations

Based on the above assessment and following individualized principles, further investigations may include: (a) cervical screening if the woman has no history of regular screening and the cervix appears friable with contact bleeding; (b) vaginal discharge testing if the woman is at high risk for infection and has abnormal discharge; (c) complete blood count to check for anemia if bleeding is prolonged or heavy, with imaging studies such as gynecological ultrasound or pelvic MRI if a pelvic mass is palpated; and (d) hysteroscopy and endometrial biopsy for unexplained prolonged bleeding or changed bleeding patterns, particularly in women aged 45 years or those <45 years with risk factors for endometrial cancer, to exclude endometrial lesions such as polyps, atypical hyperplasia, or endometrial cancer [8].

5. Prevention and Intervention Measures for Unscheduled Bleeding

Prevention and treatment of unscheduled bleeding during oral COC use is challenging. The most important preventive measure is improving patient adherence and avoiding missed pills. For missed pills used for contraception, specific management strategies apply depending on timing [20]. Additionally, the timing of COC initiation is important; starting on days 1–5 of menstruation is recommended for reliable contraceptive efficacy.

Treatment options for unscheduled bleeding are limited and lack high-quality evidence support, consisting mainly of guidance-based recommendations with varying degrees of controversy. Increasing estrogen dose may achieve better cycle control and reduce unscheduled bleeding. A brief treatment pause may be effective for women using extended or continuous COC regimens. The effectiveness of low-dose doxycycline, changing progestogen type or dose, remains controversial. Changing COC phasic type or regimen does not improve unscheduled bleeding [3,8,15,20].

5.1 Management of Missed Pills

According to the 2013 U.S. Selected Practice Recommendations for Contracep-

tive Use regarding missed COC pills [20]: (a) if one pill is missed (<48 hours): take one pill as soon as remembered and continue the remaining pills on schedule (even if two pills are taken on the same day), with no additional contraceptive protection needed. Emergency contraception is not required but may be considered if the missed pill occurs in the first week or last week of the pack; and (b) if two or more pills are missed (48 hours): take one pill immediately. If seven or more pills remain in the pack, continue regular use while using condoms or other barrier methods for at least 7 days, or use emergency contraception. If fewer than seven pills remain, start the next pack immediately after finishing the current one.

5.2 Increasing Estrogen Content

Both FSRH guidance [15] and the 2013 U.S. Selected Practice Recommendations [20] suggest that increasing estrogen dose (e.g., to 35 g daily) can reduce the duration and incidence of unscheduled bleeding. Most studies support this conclusion, though a minority do not. Kaunitz et al. [21] conducted a multicenter study comparing COCs containing 20, 25, and 30 g of ethinyl estradiol, finding that higher estrogen content was associated with lower unscheduled bleeding rates. A systematic review [22] found that COCs with >20 g estrogen had lower unscheduled bleeding rates compared to those with 20 g. However, Edelman et al. [23] found no significant difference in unscheduled bleeding rates between 30 g and 20 g estrogen groups in an RCT of continuous COC users.

5.3 Brief Treatment Pause

For women using extended or continuous COC regimens (continuous use beyond 21 or 24 days), a brief 3–4 day pause can effectively reduce unscheduled bleeding days. Sulak et al. [24] divided women with unscheduled bleeding during extended COC use into two groups, comparing continued use versus a 3-day pause, and found significantly fewer unscheduled bleeding days in the pause group.

5.4 Low-Dose Doxycycline

Doxycycline is an MMP inhibitor that theoretically could prevent or reduce unscheduled bleeding days. However, since MMP expression requires endometrial biopsy and it is difficult to accurately sample endometrial tissue at the time and location of bleeding [10], relevant research is limited and clinical application is rare, with controversial effectiveness [8,20]. Kaneshiro et al. [25,26] conducted RCTs in continuous COC users and found that continuous antimicrobial-dose doxycycline (100 mg twice daily) had no significant effect on preventing or reducing unscheduled bleeding days, while continuous low-dose doxycycline (20 mg twice daily) reduced unscheduled bleeding incidence compared to placebo.

5.5 Changing Progestogen Type and Content

Overall, whether changing progestogen type or content improves unscheduled bleeding remains controversial, with most evidence suggesting it does not [8,15].

A multicenter RCT [27] comparing COCs containing drospirenone versus levonorgestrel found lower unscheduled bleeding rates with drospirenone. A systematic review found preliminary evidence of lower unscheduled bleeding rates with third-generation versus second-generation progestogens (RR 0.79, 95% CI 0.60–0.98), but when only randomized, double-blind studies were included, no significant difference was found (RR 0.79, 95% CI 0.50–1.26), requiring further evidence [28]. Other studies suggest that changing progestogen dose does not improve unscheduled bleeding. A small-sample RCT comparing continuous use of COCs containing 90 g versus 100 g levonorgestrel found no significant difference in unscheduled bleeding days [26], possibly due to the small dose difference.

5.6 Triphasic Oral Contraceptives

Few studies have compared unscheduled bleeding rates among monophasic, biphasic, and triphasic COCs, with limited evidence [15]. Two systematic reviews [29,30] found no significant differences in unscheduled bleeding rates between monophasic versus biphasic or biphasic versus triphasic COCs.

5.7 Changing Administration Regimens

Almost all studies indicate that extended COC regimens reduce total bleeding days within a fixed period compared to traditional cyclic regimens but do not significantly reduce unscheduled bleeding days [15]. A multicenter RCT found no reduction in unscheduled bleeding incidence with extended versus traditional cyclic regimens [31]. Another multicenter RCT found that extended regimens did not reduce unscheduled bleeding duration and may even increase it [32]. Therefore, when unscheduled bleeding occurs during extended regimens, a brief treatment pause is recommended first.

5.8 Other Management Options for Prolonged Unscheduled Bleeding

If unscheduled bleeding persists after 3–4 months of regular COC use, pathological or physiological causes must be excluded. After excluding pathological causes, women may be advised to switch to a different COC type if bleeding continues [19]. Prolonged antibiotic use is not recommended for women with persistent bleeding, as retrospective studies suggest that concurrent antibiotic use with COCs may reduce contraceptive efficacy and increase failure rates [13]. Additionally, smoking cessation and avoiding unnecessary concomitant medications may reduce unscheduled bleeding in long-term COC users [14].

Conclusion

Unscheduled bleeding is a common problem in women using combined oral contraceptives. There is no unified standard for definition and classification of unscheduled bleeding domestically or internationally, and treatment options are limited and controversial. For women considering COC use, clinicians should provide adequate counseling about correct usage and the possibility of unscheduled bleeding to improve satisfaction and adherence, thereby reducing the risk of

unintended pregnancy. For women who develop unscheduled bleeding, individualized management based on clinical assessment is essential to avoid unnecessary interventions.

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Note: Figure translations are in progress. See original paper for figures.