

Bleeding outcomes and cycle control in combined hormonal contraception

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Introduction

Unpredictable bleeding is a common concern among users of hormonal contraception and a leading cause of early discontinuation. For combined hormonal contraception (CHC) users, the severity and pattern of bleeding changes depend on the type and dose of estrogen and progestogen, with bleeding often improving with duration of use. While the synthetic estrogen ethinylestradiol (EE) has long been the standard estrogen component, newer formulations now include natural, body-identical estrogens such as estradiol (E2), estradiol valerate (E2V), and estetrol (E4), primarily to potentially reduce cardiovascular risks. Since bleeding outcomes influence satisfaction and continuation, proper counselling and personalised contraceptive choices are essential. This section examines how various hormonal combinations affect bleeding outcomes and emphasises the importance of tailoring contraceptive options to individual expectations.

Bleeding patterns and cycle control in combined hormonal contraception

Irregular bleeding, such as absence of scheduled withdrawal bleeding or unscheduled flow, is an infrequent side effect of hormonal contraception but is one of the most common reasons for discontinuation [1,2]. These irregularities typically occur more frequently during the first few cycles of CHC use and usually decrease or resolve in most users adherent to their regimen.

In CHCs, both the progestin and estrogen components inhibit ovulation and impact endometrial stability, thereby affecting bleeding patterns¹. Systemic hormonal contraceptives that contain estrogen have a more regular bleeding pattern [3]. Consequently, changes in type or dose of the estrogen can affect its stabilising role, potentially altering bleeding patterns [3,4].

Most CHCs today contain the synthetic estrogen EE, with doses progressively reduced, from over 50 µg in the 1960s to as low as 10 µg, to reduce the risk of venous thromboembolism (VTE). However, this trend toward lower EE exposure can come at the expense of bleeding control, depending on the progestin and active pill-taking regimen. Among low-dose options, EE 20 µg formulations are the most common, but their bleeding outcomes vary depending on the progestin component. Some, such as EE 20 µg/DRSP, show bleeding control comparable to higher EE doses (e.g. EE 30 µg/DRSP), whereas others are associated with more unscheduled bleeding. For example, in a comparative trial, EE 20 µg/LNG 100 µg provided acceptable cycle control, whereas EE 20 µg/norethisterone (NET) 500 µg was associated with substantially higher rates of intermenstrual bleeding and amenorrhea, both of which performed less favourably than EE 30 µg/LNG 150 µg. These differences likely reflect the balance of estrogen and progestin half-lives, with shorter half-lives and lower estrogen doses leading to less stable endometrial support [3]. In contrast, ultra-low-dose EE (10 µg) in combination with norethisterone acetate (NETA) has been associated with high rates of unscheduled bleeding (ranging from 38.1% to 52.7% across cycles) and a low rate of scheduled bleeding (>22.8% across cycles) [5].

¹DRSP 4 mg is a progestin-only pill (POP) taken in a 24/4-day cycle, unlike traditional continuous POPs. This cycle aims to improve bleeding patterns, often causing POP discontinuation. In phase 3 trials, scheduled bleeding decreased from 81.2% in Cycle 1 to 26.4% in Cycle 12, and unscheduled bleeding from 54.4% to 41.6%. Bleeding-related discontinuation was 4.2% (Archer, D. F., Mansour, D., & Foidart, J. M. (2022). Bleeding Patterns of Oral Contraceptives with a Cyclic Dosing Regimen: An Overview. *J Clin Med*, 11(15). <https://doi.org/10.3390/jcm11154634> . Compared to continuous DSG 75 µg, DRSP 4 mg had fewer bleeding events and lower discontinuation rates (3.3% vs. 6.6%), indicating better cycle control for estrogen-free contraception. (Palacios, S., Colli, E., & Regidor, P. A. (2020). Bleeding profile of women using a drospirenone-only pill 4 mg over nine cycles in comparison with desogestrel 0.075 mg. *PLoS One*, 15(6), e0231856. <https://doi.org/10.1371/journal.pone.0231856>

Bleeding patterns across cyclic CHC formulations

Table 1 details bleeding data and discontinuation rates due to bleeding-related adverse events from 12-month phase 3 trials of products containing natural body-identical estrogens, E4 with drospirenone (DRSP), E2 with norgestrel acetate (NOMAC), and E2 valerate with dienogest (DNG). The table also includes commonly used CHCs with EE, such as EE with levonorgestrel (LNG), EE with DRSP, and an ultra-low dose of EE with NETA. As shown, each type of CHC has a unique bleeding pattern, which is described in more detail in the following paragraphs².

While Table 1 allows for a general comparison of bleeding patterns and discontinuation rates across different CHC formulations, such comparisons should be interpreted with caution due to inconsistent bleeding definitions, data collection methods, and reporting standards across contraceptive trials, which limit the ability to draw firm conclusions about relative bleeding tolerability [4]. The standardised recommendations proposed by Creinin et al. for analysing and reporting bleeding data in hormonal contraceptive studies serve as an important step towards improving consistency and enabling more meaningful future comparisons [7].

Ethinylestradiol

CHCs are most commonly marketed as 28-day cycle regimens, although a few extended regimens (84-day cycles) are available. Products containing EE are available with either 4- or 7-day placebo intervals, with newer formulations more commonly with a 4-day placebo interval, which results in greater ovulation suppression compared to products with 7-day placebo intervals [8]. Typically, withdrawal bleeding occurs within a few days of starting placebo pills [4].

Both the traditional 7-day placebo (21/7) and the newer 4-day placebo (24/4) EE-based CHC regimens offer good cycle control, characterised by consistent scheduled bleeding and relatively low rates of unscheduled bleeding. However, very low doses of EE, such as EE 10 µg/ combined with NETA 1 mg, are associated with high unscheduled bleeding and low scheduled bleeding (Table 1) [5,9]. In clinical trials, the 21/7 regimen with EE 30 µg combined with DRSP resulted in scheduled bleeding in 94.2% to 96.6% of participants during Cycles 2 to 12, with a median bleeding duration of 5 days during the 7-day hormone-free interval (range: 4–6 days) (Table 1). Unscheduled bleeding was relatively infrequent, reported in 13.4% of participants in Cycle 2, decreasing to 8.6% in Cycle 6, and 9.6% in

Cycle 12 [10]. In the 24/4 regimen, EE 20 µg combined with DRSP 3 mg resulted in scheduled bleeding in 87.6% to 92.1% of users over six cycles, with a mean duration of 4.1 days. Unscheduled bleeding rates ranged from 10.2% to 14.9% across seven cycles [11]. These studies were conducted at different times and with varying populations; therefore, the overall rates should be considered comparable.

Estradiol

Combined oral contraceptives containing 17β-estradiol (E2) are available in two distinct formulations. One is a multiphasic 26/2-day regimen (2/22/2/2) that combines estradiol valerate with dienogest (E2V/DNG), with two placebo days in the 28-day cycle. In this regimen, doses of E2V are gradually reduced while dienogest is progressively increased, a dynamic dosing strategy intended to support endometrial stability [12,13]. The other formulation combines E2 with norgestrel acetate (E2/NOMAC) in a monophasic 24/4 regimen, offering a simpler, fixed-dose schedule [14]. These structural differences in regimen design influence hormone exposure and may explain the distinct bleeding profiles observed with these COCs [15].

Estradiol valerate with dienogest

In clinical trials, scheduled bleeding rates with E2-containing CHCs are generally lower than those observed with EE-containing formulations. This difference is related to the relatively short half-life of E2, even when micronised for combined oral contraceptive (COC) use, and may also be partly explained by the rapid hepatic conversion of E2 to estrone (E1), particularly in the presence of a progestin, which can impair endometrial stability [15]. In a 7-month comparative trial, scheduled bleeding was reported by 77.7% to 83.2% of participants using E2V/DNG, compared to 89.5% to 93.8% of those using EE/LNG. Unscheduled bleeding occurred in 10.5% to 18.6% of E2V/DNG users and in 9.9% to 17.0% of EE/LNG users [16].

Similar findings were observed in non-comparative phase 3 trials of E2V/DNG, where scheduled bleeding remained above 68.4% in a North American trial and 78.2% in a European trial. Unscheduled bleeding declined over time, from 28.8% to 11.2% in North America and from 26.4% to 12.1% in Europe [12,13] (Table 1).

²Here, we do not present details on continuous CHC regimens, designed to extend active hormone intake and reduce or eliminate withdrawal bleeding, offering an option for users seeking greater control or fewer periods. These regimens generally show reduced bleeding over time but may be associated with increased spotting in early cycles. [6] Edelman A, Micks E, Gallo MF, et al. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst Rev. 2014;2014(7):CD004695.

Estradiol with norgestrel acetate

In pooled Phase 3 data, scheduled bleeding was reported by 82.4% of participants in Cycle 2, declining to 68.6% in Cycle 12, which is significantly lower than the rates of 96.6% and 94.2% reported with EE/DRSP in the same cycles. Unscheduled bleeding was also more frequent with E2/NOMAC, ranging from 15.4% to 24.1% across various cycles, compared with 10.9% to 17.4% for EE/DRSP (Table 1) [10]. By contrast, lower unscheduled bleeding rates were observed with E2V/DNG (see above); however, this comparison is indirect, as it is based on data from different trials.

Estetrol and drospirenone

E4/DRSP is the newest of the natural estrogen COC products. E4/DRSP is available in a 24/4 regimen. During the E4/DRSP phase 3 trials, the rate of scheduled bleeding remained stable and relatively high over a 12-month treatment period, with over 92% of participants in a Europe/Russia trial and over 83% in a United States/Canada trial experiencing scheduled bleeding [17,18]. The percentage of participants reporting unscheduled bleeding or spotting decreased from 19.2% in Cycle 2 to 13–18% from Cycle 3 onwards in Europe/Russia, and from 21.8% in Cycle 2 to 15–20% from Cycle 5 onwards in the United States (Table 1) [17,18]. A pooled analysis of these two trials, including more than 3,400 participants and >33,000 cycles, confirmed the favourable bleeding profile: 87.2–90.4% of women experienced scheduled bleeding/spotting across Cycles 1–12 (median duration 4–5 days), while unscheduled bleeding declined from 27.1% at Cycle 1 to

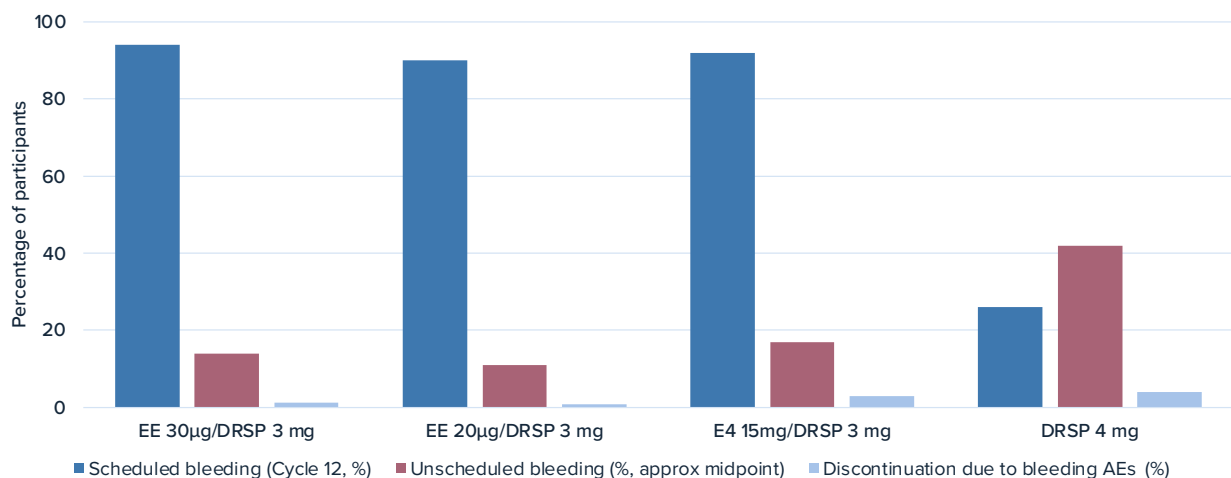
≤17.5% from Cycle 5 onwards. Absence of scheduled bleeding occurred in 10–13% of cycles, and discontinuations due to bleeding-related adverse events were low (3.0%)[19].

In addition, a 6-cycle dose-finding phase 2 trial showed that the frequencies of unscheduled bleeding and absence of scheduled bleeding at Cycle 6 were lower with E4/DRSP (33.8% and 3.5%, respectively) compared to E2V/DNG (47.8% and 27.1%, respectively) at the end of treatment [20].

Impact of the estrogen component in DRSP-containing regimens

Comparisons of drospirenone-containing regimens (Table 1, Figure 1) demonstrate the role of the estrogen component in regulating the menstrual cycle. Products with EE/DRSP (20 or 30 µg) provide consistent scheduled bleeding (>90% of cycles) and low rates of unscheduled bleeding. E4/DRSP achieves a similarly favourable and predictable profile, with >90% scheduled bleeding in European trials and a decline in unscheduled bleeding over time, despite using a natural estrogen. In contrast, DRSP-only (4 mg) is associated with a progressive loss of scheduled bleeding (falling from >80% at Cycle 1 to <30% at Cycle 12) and persistently high unscheduled bleeding (>40%). Since DRSP is constant across these regimens, these differences clearly reflect the impact of including an estrogen to work with the progestin, stabilising the endometrium and ensuring more predictable bleeding outcomes [4].

Figure 1: Bleeding outcomes in DRSP-containing COC regimens [4]*



*This figure is based on data presented in Table 1. Scheduled bleeding values represent outcomes reported across 12 cycles and are taken directly from phase 3 trial data. In Table 1, unscheduled bleeding is presented as ranges across cycles; for visual clarity, approximate midpoints of these ranges are plotted in the figure (EE 30 µg/DRSP 3 mg: 10.9–16.5%, EE 20 µg/DRSP 3 mg: 8–14%, E4 15 mg/DRSP 3 mg: 14–20%, DRSP 4 mg: 38–52%). Discontinuation rates due to bleeding-related AEs are shown as reported. E4: estetrol, EE: ethinylestradiol; DRSP: drospirenone; AE: adverse event

Table 1. Bleeding data (% participants) from phase 3 trials and pooled analyses with a duration of at least 12 months

Product Regimen	Countries Trial Registration No.	Scheduled Bleeding	Unscheduled Bleeding/Spotting	Discontinuations due to Bleeding-Related AEs (%)
E4 15 mg/DRSP 3 mg 24/4	Phase 3 EU/Russia [17] NCT02817828	> 91.9% across 12 cycles	Cycle 2: 19.2% Range Cycle 3 onwards: 12.8%–17.7%	3.4%
	Phase 3 US/Canada [16] NCT02817841	> 82.0% across 12 cycles	Cycle 2: 21.8% Range Cycle 3 onwards: 15.5%–22.1%	2.7%
	Pooled Analysis [18,25] NCT02817828/NCT02817841	> 87.2% across 12 cycles	Cycle 2: 20.6% Range Cycle 3 onwards: 14.0%–19.8%	2.8%
E2 1.5 mg /NOMAC 2.5 mg 24/4	Phase 3 EU/Asia/AUS [13,26] NCT00511199	> 69.4% across 12 cycles	Cycle 2: 21.6% Range Cycle 3 onwards: 14.5%–24.1%	4.0%
	Phase 3 US/LA/Canada [27,28] NCT00413062	> 65.8% across 12 cycles	Cycle 2: 25.6% Range Cycle 3 onwards: 16.4%–24.1%	3.8%
	Pooled Analysis [9,26] NCT00511199/NCT00413062	> 68.4% across 12 cycles	Cycle 2: 23.2% Range Cycle 3 onwards: 15.4%–24.1%	3.9%
E2V 2 mg /DNG 3 mg 2/22/2/2*	Phase 3 EU [12,29] NCT00185289	> 78.2% across 12 cycles	Cycle 2: 26.4% Range Cycle 3 onwards: 12.1%–22.7%	2.5%
	Phase 3 US/Canada [11,29] NCT00206583	> 68.4% across 12 cycles	Cycle 2: 28.8% Range Cycle 3 onwards: 11.2%–25.6%	5.1%
EE 20 µg /LNG 100 µg 21/7	Phase 3 EU [30] NCT00248963	NR	Cycle 2: 19.3% Range Cycle 3 onwards: 10.5%–17.8%	0.6% (vaginal bleeding), 2.8% (metrorrhagia)
EE 30 µg/DRSP 3 mg 21/7	Pooled Analysis [9] NCT00511199/ NCT00413062	> 94.2% across 12 cycles	Cycle 2: 17.4% Range Cycle 3 onwards: 10.9%–16.5%	1.3%
EE 20 µg/DRSP 3 mg 24/4	Phase 3 EU/ US/LA [31,32] Protocol 303740	> 89.6% across 12 cycles	Cycle 2: 14.0% Range Cycle 3 onwards: 8.0%–14.0%	0.7%
EE 10 µg/NETA 1 mg	Phase 3 US [5,33] NCT00391807	> 22.8% across 12 cycles	Cycle 2: 52.7% Range Cycle 3 onwards: 38.1%–52.1%	3.8%

AE: adverse event; AUS: Australia; DRSP: drospirenone; DNG: dienogest; E4: estetrol; EE: ethinylestradiol; EU: European Union; E2: 17-estradiol; E2V: E2 valerate; LA: Latin America; NETA: norethindrone acetate; NOMAC: nomegestrol acetate; NR: not reported; US: United States.

* E2V 3 mg (days 1–2), 2 mg/2 mg (days 3–7), 2 mg/3 mg (days 8–24), E2V 1 mg (days 25–26), placebo (days 27–28).

In summary, bleeding outcomes with CHC use vary by estrogen type and regimen. EE-based CHCs, especially at higher doses, provide predictable scheduled bleeding and minimal unscheduled bleeding with 21/7 and 24/4 regimens. E2-containing CHCs show lower scheduled bleeding, higher unscheduled bleeding, likely due to faster hepatic metabolism and decreased endometrial stability. E4/DRSP offers a more consistent bleeding profile, with unscheduled bleeding decreasing over time. The estrogen half-life affects cycle control; EE and E4, with long half-lives, generally ensure predictable bleeding with a progestin [21].

Bleeding outcomes, user preferences, and counselling

Bleeding outcomes remain a central factor in contraceptive satisfaction, continuation, and overall quality of life. However, attitudes toward bleeding are diverse and evolving. While some CHC users continue to view monthly bleeding as a natural and necessary process, others prefer reduced-frequency or no bleeding, especially when it alleviates menstruation-related symptoms such as dysmenorrhea or menorrhagia. These preferences are shaped not only by individual experiences but also by cultural, social, and regional influences [1,22]. For example, in certain cultures, the absence of bleeding may be viewed with suspicion or concern, while in others, it may be embraced as a sign of modern, body-positive contraceptive use.

Among younger users and those new to hormonal contraception, regular, predictable bleeding often serves as an important reassurance of non-pregnancy, reinforcing trust and confidence in the method [1]. When expectations around bleeding are unmet, particularly in the absence of anticipatory counselling, unpredictable or absent bleeding may cause confusion or concern, potentially leading to early discontinuation and increased risk of unintended pregnancy.

Moreover, while clinical trials consistently demonstrate that most CHCs offer acceptable cycle control, with most users experiencing scheduled bleeding and relatively low rates of unscheduled bleeding, these findings may not fully reflect real-world experiences. For instance, discontinuation rates due to irregular bleeding are generally below 5% in clinical trials (Table 1), yet observational studies have shown that up to 50% of users stop using their method within the first year, often citing menstrual disturbances as the primary reason [1,2,23].

This discrepancy stems from multiple factors. Clinical trial participants are typically better informed, receive structured counselling, and are encouraged to continue treatment unless adverse effects are significant. In routine practice, however, many users may not receive

the same level of anticipatory guidance. As a result, even predictable changes, such as lighter or irregular bleeding during the initial cycles, may be interpreted as problematic or alarming. Moreover, bleeding complaints may serve as a proxy for broader dissatisfaction, encompassing issues like mood changes, sexual discomfort, partner dynamics, or lifestyle considerations [24]. Importantly, participants in contraceptive clinical trials have normal, cyclic bleeding patterns at baseline, and very few CHCs are tested in patients with abnormal uterine bleeding. As such, bleeding outcomes in contraceptive trials do not reflect what happens in practice when users without regular, cyclic bleeding start the method.

Studies have further shown that perceptions of bleeding are tightly linked to users' sense of well-being. A survey by Higgins et al. [25] revealed that heavier or unpredictable bleeding was associated with negative sexual experiences, while lighter and more predictable bleeding enhanced sexual satisfaction and confidence. These findings highlight that bleeding patterns do more than affect physical health; they also shape contraceptive acceptability and quality of life.

These considerations highlight the critical role of personalised counselling. When healthcare providers proactively explain expected bleeding patterns and normalise variability across different hormonal regimens, they empower users to make informed choices. This approach sets realistic expectations and ultimately supports better compliance and satisfaction. In today's context, when a broad range of CHC formulations is available, including those with natural estrogens or extended-cycle regimens, tailoring contraceptive options to individual bleeding preferences is both feasible and advisable [1,22].

Conclusion

Bleeding outcomes are a central factor in contraceptive satisfaction and continuation. These outcomes are influenced by the type and dose of estrogen and progestin used. Ethinylestradiol (EE), particularly at commonly used doses, provides predictable scheduled bleeding, while estradiol (E2) and estradiol valerate (E2V) tend to result in less stable patterns and more unscheduled bleeding. Estetrol (E4), a newer native estrogen, has demonstrated a favourable bleeding profile. All CHC products are tested in contraceptive trials on users with baseline predictable cycles. Hence, the impact of most of these formulations on outcomes in patients with abnormal bleeding is not well studied.

Attitudes toward bleeding are diverse and evolving, influenced by cultural, social, and personal factors. While some women value monthly bleeding as a sign of normalcy and non-pregnancy, others prefer reduced or absent bleeding, especially when it alleviates menstrual symptoms or improves quality of life. These

considerations are particularly relevant for younger users or those new to hormonal contraception, who may rely on predictable bleeding for reassurance and confidence in the method. Without adequate counselling, unexpected changes in bleeding can trigger anxiety and lead to early discontinuation.

In today's landscape, with multiple estrogen types and regimens available, personalising contraceptive counselling around bleeding expectations, whether the goal is regular withdrawal bleeding, no bleeding, or reduced variability, can significantly improve satisfaction, adherence, and long-term use.

Key messages

Bleeding irregularities are common with CHCs, making them a leading reason for discontinuation.

Both the estrogen and progestin components play an important role in cycle control. When considering the estrogen component:

- EE at 30 µg offers reliable scheduled bleeding and low unscheduled bleeding rates.
- Lower doses of EE (e.g., 10 µg) are linked to poorer bleeding control and higher discontinuation rates.
- E2 and E2V are associated with more variable bleeding due to rapid metabolism and less stable endometrial support.
- E4 demonstrates a favourable and predictable bleeding profile among natural estrogens, though individual responses vary.

Discontinuation rates due to bleeding are low in trials but higher in real-world settings, often due to limited counselling or unspoken concerns.

Bleeding preferences vary by individual and are shaped by cultural, social, and personal factors. Regular bleeding can provide reassurance, especially for younger users, while others value reduced bleeding or amenorrhea.

Personalised counselling that sets realistic expectations and addresses bleeding variability improves user satisfaction and supports continuation.



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