

Tolerability of combined oral contraceptives - physical, emotional and sexual well-being perception

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Introduction

The specific pairing of estrogens and progestins in a combined oral contraceptive (COC) meaningfully shapes tolerability. In practice, continuation depends less on efficacy than on lived experience, particularly in terms of bleeding patterns, mood stability, and sexual well-being. Most side effects are mild and often settle with continued use or a switch to an alternative formulation. Because tolerability reflects the combined action of both components, differences can be attributed to the estrogen only when the progestin is held constant (e.g., estetrol/drospirenone [E4/DRSP] versus ethinylestradiol/drospirenone [EE/DRSP]).

This section reviews common COC side effects through a “tolerability triad” lens: bleeding, mood, and sexual health, and considers cultural context. Estrogens modulate neurotransmitter pathways (notably serotonin and dopamine) implicated in mood; natural, body-identical estrogens such as estradiol/estradiol valerate (E2/E2V) and E4 are associated with steadier mood, more acceptable bleeding patterns and better sexual comfort than EE in many users. Because mood and expectations shape symptom perception, aligning counselling with patient priorities, planning an early follow-up, and switching promptly when needed are central to real-world tolerability and persistence.

Menstrual bleeding patterns

Menstrual bleeding patterns are a crucial determinant of tolerability. Irregular or heavy bleeding, dysmenorrhoea and related symptoms are among the most common reasons for dissatisfaction and early discontinuation of combined hormonal contraceptives (CHCs). Users often interpret unpredictable spotting or breakthrough bleeding as a sign of inadequate hormonal control or potential pregnancy, which can generate anxiety and erode confidence in the method. Heavy bleeding imposes practical burdens, including the increased use of sanitary products, disruption to daily activities and sexual life, and, in some cases, contributes to iron deficiency, even when physiological and self-limiting, bleeding irregularities in the first cycles can lower satisfaction unless users are counselled about what to expect and when patterns typically stabilise.

Cultural and social norms significantly influence how women perceive their menstrual bleeding patterns. In some regions, monthly withdrawal bleeding is valued as reassurance of non-pregnancy, while in others, reduced or absent bleeding may be preferred for practical reasons or improved quality of life. Dissatisfaction with irregular bleeding is often amplified when it conflicts with cultural expectations around menstruation, highlighting the importance of tailoring counselling to local norms and preferences (Glasier, 2003; Hardon, 1992; Mansour, 2008). These considerations are also reflected in the bleeding outcomes and user preference data discussed in Section 6, which emphasise how attitudes toward bleeding are diverse and evolving across different cultural and regional contexts

Natural, body-identical estrogens appear to confer advantages in this context. E4 exhibits a favourable bleeding profile in clinical studies, supporting perceptions of cycle control that are closely tied to satisfaction and persistence in real-world use. By contrast, while EE at commonly used doses typically produces predictable scheduled withdrawal bleeding, it may be accompanied in some users by bleeding-related complaints that still precipitate discontinuation when expectations are not aligned with experience [1,2]. Moreover, very low doses of EE, such as EE 10 µg combined with norethisterone acetate 1 mg, are associated with high unscheduled bleeding and low scheduled bleeding [1,3] (for more details see Section 6). Additionally, E4/DRSP has been associated with improvements in menstrual pain and premenstrual symptoms, findings that are especially relevant for women with a higher baseline symptom burden, for whom relief of cramping and cycle-related discomfort directly enhances tolerability and continuation [4,5].

Estradiol valerate/dienogest (E2V/DNG) remains the only combined oral contraceptive with a specific indication for heavy menstrual bleeding (HMB), [6,7] and randomised, placebo-controlled trials have demonstrated substantial reductions in menstrual blood loss together with improvements in hemoglobin, hematocrit, and ferritin [8,9]. For women troubled by HMB, these effects translate into meaningful improvements in quality of life and a lower likelihood of abandoning treatment for bleeding-related reasons [10]. In clinical practice, clear counselling on anticipated bleeding trajectories in the first three to six cycles, coupled with the selection of formulations that address individual priorities (cycle predictability, pain control, or reduction of heavy bleeding), is key to minimising dissatisfaction and preventing unnecessary discontinuation.

| Mood

Women reporting negative affect or irritability are more likely to experience menstrual-related symptoms as distressing, thereby lowering overall tolerability. This has been shown in prospective studies, where mood and sexuality-related side effects were closely associated with discontinuation [11], and in younger women, where depressed mood and stress doubled the likelihood of perceived pill-related mood changes and halved continuation rates, particularly in minority populations [12]. Cultural context also influences how mood changes are experienced and reported. In some settings, stigma surrounding mental health may discourage open discussion of mood-related side effects. In contrast, in others, irritability or emotional lability may be understood through relational or social lenses rather than medical ones. These factors can affect both self-reported tolerability and continuation, underscoring the need for culturally sensitive counselling and communication strategies (Patel, 2018; Tolman & Diamond, 2001; Hall, 2012). Together, these findings



highlight how mood-related side effects contribute directly to discontinuation and underscore an important unmet need for more tolerable contraceptive options.

Evidence from trials using the validated Menstrual Distress Questionnaire (MDQ) shows that natural estrogens can improve outcomes in the Negative affect domain [4,5,13]. In a large comparative study, users of E2/nomegestrol (NOMAC) had greater improvements than those on EE/DRSP across several MDQ domains, including negative affect (which covers mood swings and depressed mood) [13]. Because of its rapid clearance and conversion to estrone and conjugates, E2 produces weaker hepatic stimulation compared with EE (See Section 4) and interacts with estrogen receptors more physiologically. More importantly, the 24/4 regimen used with NOMAC/E2, rather than the traditional 21/7 schedule, shortens the hormone-free interval and minimises estrogen-withdrawal peaks that can precipitate mood swings [13]. In this way, both the type of estrogen and the regimen design likely play a role in the modest improvements observed.

Further support for the role of natural estrogens in mood comes from two large Phase 3 trials of E4/DRSP, in which women starting treatment reported significant reductions in negative affect domain scores during both the premenstrual and menstrual phases [4,5]. These improvements appeared more evident in starters, who are typically more sensitive to baseline symptoms, although the effect was more consistent than with E2/NOMAC. Switchers did not exhibit significant changes but maintained stable symptom levels. Shift analyses further revealed that individual symptoms within the negative affect domain, notably irritability and mood swings, improved in a substantial proportion of women. These findings reinforce that E4/DRSP can both relieve mood-related symptoms in first-time users and sustain stability in women already accustomed to hormonal contraception. The pharmacological profile of E4 provides a potential explanation: it has high oral bio-availability and a long half-life, producing stable serum concentrations with fewer peaks and troughs that can trigger mood lability. In addition, its selective receptor activity preserves genomic effects while dampening rapid membrane-mediated pathways, which are likely linked to mood-related side effects, thereby reinforcing mood stability (see Section 3).

By contrast to these findings with natural estrogen-containing COCs, evidence with ethinylestradiol points to less favourable outcomes for mood and well-being. In a rare placebo-controlled trial involving more than 300 healthy women, the use of EE/LNG was associated with a statistically significant reduction in overall psychological well-being compared with the placebo. The most important effects were observed in the domains of positive well-being, self-control, and vitality, while scores for depressed mood also declined, although this difference did not reach statistical significance [14-16]. Additionally, the progestin used in combination with EE appears to play a crucial role. For

example, EE/DRSP in a 24/4 regimen has demonstrated improvements in premenstrual symptoms and quality of life in women with premenstrual dysphoric disorder, in contrast to the less favourable profile observed for EE/LNG [17,18].

In summary, mood-related side effects are a significant cause of discontinuation, especially in younger women. Evidence indicates that natural estrogens, particularly E4, are associated with more favourable effects on mood. In contrast, EE-containing COCs are more likely to reduce well-being, with outcomes influenced by regimen and progestin choice. This highlights the importance of estrogen type for tolerability and continuation.

Headaches

Clinically, EE-containing COCs have been linked to worsening headaches and migraine in a substantial subset of users. In a cohort study of 480 COC users, headaches worsened in 32.5% of women with migraine (and in 19.3% without migraine), while improvement was reported by 30.0% and 13.8%, respectively [19]. Among women with menstrual migraine, contemporary reviews report that roughly 18–50% experience exacerbation while using COCs, demonstrating the heterogeneity of response in this group [20]. A plausible mechanism is EE's disproportionate hepatic stimulation, which markedly increases synthesis of liver-sensitive proteins, including sex hormone-binding globulin (SHBG), angiotensinogen and multiple coagulation factors, thereby modulating vascular and hemostatic pathways implicated in migraine pathophysiology [21].

Its mechanism of action can explain the differential effects of E4 compared to EE on these symptoms. Mechanistically, E4 differs from EE: it preferentially activates nuclear estrogen receptor (ER) α while antagonising ER α -dependent membrane-initiated signalling. This “uncoupling”, characterised by nuclear agonism with relative membrane antagonism, has been demonstrated in pre-clinical vascular and uterine models and further refined in subsequent reviews [22-25]. The pattern preserves genomic, longer-term tissue-supporting effects while mitigating rapid membrane effects associated with vascular reactivity and prothrombotic signalling. Such receptor selectivity provides a plausible biological basis for a more stable mood, fewer vascular-triggered headaches or migraines, and a milder hepatic stimulation profile than EE [24,26] (see also Section 3).

Gastrointestinal, weight change and fluid retention symptoms

Gastrointestinal complaints (particularly nausea), perceived weight changes, and fluid retention are among the most common non-bleeding side effects of CHCs, although they are usually mild and temporary. With EE-containing regimens, nausea and breast tenderness are more frequent, especially in the initial cycles. This aligns with the more pronounced estrogen peaks and increased hepatic stimulation caused by EE, which upregulates hepatic proteins such as angiotensinogen and globulins and may consequently activate emetic pathways [21,27,28]. These mechanisms plausibly contribute to water retention and bloating, often perceived as “weight gain,” even when measurable changes are negligible. Observational data confirm that perceived rather than actual weight gain is a common cause of dissatisfaction and discontinuation [29,30].

By contrast, E2 and E4 exhibit a more neutral profile in this regard. Oral E2 is subject to extensive gut wall and hepatic first-pass metabolism, with up to 95% of the oral dose being transformed during intestinal and hepatic passage [31-33].

This significantly reduces systemic E2 bioavailability, but it leads to large pools of conjugated metabolites such as estrone sulphate and estrone glucuronide, resulting in lower serum peaks and weaker hepatic stimulation compared to EE. E4, with high oral bioavailability and CYP-independent metabolism, offers stable serum levels with minimal abrupt fluctuations [26,34]. Clinical trials with E2V/DNG, E2/NOMAC, and E2V/DNG report low rates of nausea and breast tenderness, along with minimal weight changes compared to EE-based combinations [8,9,13,35]. Similarly, phase 3 studies of E4/DRSP confirm low rates of GI side effects and no clinically relevant weight gain, with favourable user-reported perceptions of bloating and breast tenderness [4,5,36,37].

The choice of progestin also plays a significant role. DRSP's anti-mineralocorticoid activity can reduce EE-induced fluid retention. In a bioimpedance study, women taking EE 30 µg/DRSP 3 mg showed decreases in total and extracellular body water over 3–6 cycles, indicating a reduction in aldosterone-driven fluid retention [38]. When paired with natural estrogens, DRSP may enhance tolerability by further reducing breast tenderness and bloating [4,5,36,37].

In summary, although clinically significant weight gain is rare with all CHCs, EE-containing pills more frequently cause perceived nausea, bloating, breast tenderness, and weight fluctuations. Natural estrogens, especially when combined with DRSP, appear to offer a more tolerable profile in this area, which could lead to higher satisfaction and continued use (see also Sections 4 and 9 for detailed pharmacokinetic and mechanistic data).

Sexual well-being and contraceptive experience

Sexual health is inseparable from contraceptive tolerability: changes in libido, arousal and sexual satisfaction strongly influence whether women accept and continue a contraceptive in the long term. Contemporary reviews underline that COCs can affect sexual and quality of life in heterogeneous ways across users, shaping real-world persistence [39].

Before the emergence of CHCs containing natural components in Asia, a household and clinic-based study conducted in Jordan using the World Health Organisation Quality of Life (WHO QoL)-BREF (short form) found that users of intrauterine devices and couples using condoms reported better QoL across physical, psychological, social, and environmental domains than women using oral contraceptives; sterilisation was associated with lower QoL, illustrating how contraceptive choice intersects with well-being in real-world settings [40].

In Thailand, a cross-sectional study using the Thai-validated Female Sexual Function Index reported high rates of female sexual dysfunction (FSD) among both hormonal-method users and women with tubal sterilisation; hormonal users exhibited lower desire scores, emphasising the importance of proactive counselling about sexual side-effects and expectations [41].

In Nairobi, Kenya, a hospital-based cross-sectional study found higher FSD prevalence in hormonal-method users versus non-hormonal users (51.5% vs 29.6%), reminding clinicians that sexual side-effects can be a driver of dissatisfaction in some users [42]. Complementing this, a Nigerian outpatient study observed that contraceptive users reported higher QoL scores, with significant gains in vitality and social functioning, than non-users, linking effective pregnancy prevention and perceived well-being in everyday care [43]. In Brazil, a prospective cohort comparing long-acting reversible contraceptives showed that women explicitly prioritised methods that do not reduce libido, underlining the centrality of sexual well-being to acceptability [44].

Natural, body-identical estrogens differ meaningfully from EE in how they interact with sex steroids. In comparative clinical research, women using EE-based COCs show higher SHBG and lower free androgen index than women using E2/E2V/E4 formulations; these hormonal shifts correlate with lower sexual desire and higher sexual distress, providing a biologically coherent link between EE-driven SHBG increases and reduced desire [45]. By contrast, women on E2/E2V/E4 report higher desire and better overall sexual function scores.

Trial and pooled analyses with E4/DRSP support this picture at the clinical level. Across two phase-3 trials, decreased/loss of libido was uncommon (≈0.6%) among

E4/DRSP users, and overall tolerability was favourable [37]. Earlier acceptability work also found higher user satisfaction and well-being with E4/DRSP compared with E4/levonorgestrel (LNG), and acceptability comparable to E2V/DNG [36].

The sexual-health dimension aligns with observed health-related quality-of-life (HRQoL) benefits during hormonal contraceptive use. In Spain, women who switched to natural-estrogen COCs (E2V/DNG or NOMAC/E2 after dissatisfaction with their prior method showed significant improvements in the Sexual Function Questionnaire for Contraception–Quality of Life (SEC-QoL) questionnaire at 6 months and high continuation rates (91.4%), with low rates of treatment-related adverse events. This suggests that better cycle control and well-being translate into persistence [46]. Complementary United States data (population-based, cross-sectional) show that women using any contraceptive method report better mental HRQoL than non-users [47].

Conclusions

Overall, the tolerability of COCs depends more on patients' experience than on contraceptive effectiveness, especially regarding bleeding patterns, mood stability, somatic symptoms like breast tenderness and bloating, and sexual health. Studies that compare formulations with the same progestin (e.g., E4/DRSP vs. EE/DRSP) indicate that the estrogen component plays a key role in tolerability. In several aspects, natural estrogens tend to promote more stable moods, fewer fluid retention complaints, and enhanced sexual comfort compared to EE. These advantages are attributed to their unique pharmacokinetic and pharmacodynamic

properties, including reduced hepatic stimulation and enhanced natural receptor activity. Personalised counselling, early follow-up, and prompt switching are essential strategies to improve continuation rates.

Cultural context also shapes how tolerability is perceived, as women may prioritise different aspects such as cycle predictability, relief from cramping, or increased libido depending on the region. This underscores the need to customise counselling to align with patient priorities. An effective strategy includes evaluating the 'tolerability triad' - bleeding, mood, and sexual well-being- initially and during early follow-up, with open discussions about somatic symptoms like gastrointestinal issues, weight perceptions, and breast tenderness.

Gaps in Knowledge and Future Directions

Long-term head-to-head studies comparing EE with natural estrogens on bleeding, mood, gastrointestinal symptoms, weight, and sexual well-being are still lacking.

The biological pathways linking hepatic protein stimulation, receptor selectivity, and neurotransmitter effects to clinical symptoms need more precise definition. Cross-cultural studies are needed to understand better how social norms and expectations shape tolerability perceptions and discontinuation.

Real-world research that integrates persistence outcomes with validated quality-of-life and tolerability measures remains limited.

Key messages

The estrogen formulation strongly influences the tolerability of COCs.

EE is more often linked with nausea, breast tenderness, bloating, and perceived weight gain, whereas natural estrogens (E2 and E4) are associated with a milder profile.

Natural estrogens, particularly when combined with DRSP, are linked to fewer fluid-retention–related symptoms, steadier mood, and less impact on libido.

The tolerability triad of bleeding, mood, and sexual well-being provides a pragmatic framework to predict satisfaction and continuation.

Early counselling and follow-up are essential to align expectations, manage somatic symptoms, and reduce unnecessary discontinuation.

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