

Safety of estrogens in combined hormonal contraceptives: evidence beyond thrombotic risk

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Introduction

The estrogen and progestin components of combined hormonal contraceptives (CHCs)[†] primarily function to prevent pregnancy by inhibiting ovulation and altering cervical mucus. Menstrual benefits are realised due to the manner in which the hormones limit endometrial development, resulting in reduced menstrual blood loss and alleviation of menstrual pain. CHCs also provide several additional non-contraceptive health benefits, including the improvement of premenstrual symptoms, acne, hirsutism, and hormonal migraine, as well as a reduction in the incidence of colorectal, endometrial, and ovarian cancers.

Although these well-supported benefits are recognised, worries about the long-term safety of CHCs remain, especially concerning breast cancer, cardiovascular, metabolic, and bone health. Nonetheless, extensive prospective, retrospective, and epidemiological studies demonstrate that many of these concerns are largely unfounded.

Historically, most CHCs have contained the synthetic estrogen ethinylestradiol (EE). More recently, natural/body-identical estrogens such as estradiol (E2) and estetrol (E4) have been introduced as alternative estrogens in combined oral contraceptives (COC), designed to maintain contraceptive efficacy while potentially improving safety. Growing evidence suggests that these estrogens may offer advantages in metabolic and vascular health, support a broader range of women's health needs, and enhance quality of life across different life stages [1].

In this section, we review the roles of synthetic and natural/body-identical estrogens in these complex medical conditions and diverse populations, providing a balanced risk–benefit analysis.

Cancer Risk

Breast cancer

The relationship between COC use and breast cancer risk remains under active investigation, with an extensive body of literature available [2]. As such risks are evaluated, it is important to do so with an understanding that risks differ across ethnic groups and are influenced by factors related to genetic risk, socioeconomic status, and healthcare access [3]. For instance, Black women are more likely to develop aggressive breast cancer subtypes, such as triple-negative breast cancer, at younger ages compared to White women, contributing to higher mortality rates despite a lower overall incidence [4,5]. Socioeconomic factors and variations in access to healthcare services may influence these differences in genetic predisposition. Further, the impact of COCs on the individual cancer risk in high-risk populations remains less well characterised [4].

Most large epidemiological studies have evaluated COCs containing EE, in combination with different progestins. Across these studies, findings consistently show a modest increase of about 20–30% from the low baseline (no COC use) 10-year incidence of breast cancer diagnosis (Table 1) [6–9]. In addition, lifetime risks of breast cancer and breast cancer mortality remain unchanged in long-term follow-up [9–11].

[†]Throughout this section, we use the term combined hormonal contraceptives (CHCs) to describe the overall class, which includes oral pills (combined oral contraceptives, COCs), transdermal patches, and vaginal rings. However, most of the available evidence, particularly for long-term outcomes such as cancer, bone accrual, cardiovascular, and metabolic effects, comes from studies of COCs. Data on non-oral CHCs remain scarce. To reflect this, we specify COC when summarising studies restricted to COC use, CHC only when referring to the class more broadly or when evidence includes multiple formulations. Readers should therefore be aware that most safety outcomes presented here are based on pill users, with limited direct evidence available for patches and rings.

The elevated breast cancer incidence appears confined to the period of active or recent use and returns to baseline within approximately five years after discontinuation. These temporal patterns, incompatible with a genotoxic effect, together with the observation that tumours diagnosed in COC users are more often lower-stage and lower-grade, support the hypothesis that COCs may promote the growth of pre-existing, subclinical tumours rather than initiate new cancers [11,12]. Part of this apparent increase may also reflect detection bias, since women using COCs are often under closer medical surveillance, leading to earlier detection [13-15].

Some evidence suggests that the magnitude of risk may be greater when EE is combined with levonorgestrel, although further studies are required to confirm this association. Importantly, no sustained excess risk has been observed beyond the period of recent use.

Tables 2 and 3 summarise the heterogeneity in findings, which partly reflects differences in exposure definitions (current, recent, past, or ever-users), follow-up duration, and formulation type. Most risk estimates in these tables are based on EE-containing formulations; data for E2-containing COCs remain sparse, and no epidemiological data exist for E4-containing COCs.

Table 1. Absolute breast cancer 10-year risk by age and impact of a 30% relative increase due to COC use

Age (years)	Baseline		With a 30% increase*		
	10-year risk (%)†	Cases per 1,000	10-year risk* (%)	Cases per 1,000	Absolute excess per 1,000
20	0.10	1.0	0.13	1.3	0.3
30	0.50	5.0	0.65	6.5	1.5
40	1.60	16.0	2.08	20.8	4.8
50	2.50	25.0	3.25	32.5	7.5
60	3.60	36.0	4.68	46.8	10.8
70	4.20	42.0	5.46	54.6	12.6

COC: combined oral contraceptive

* A 30% relative increase is applied to show the estimated impact of combined oral contraceptive use, based on epidemiological studies [6-9].

† Baseline probabilities reflect the chance of being diagnosed with breast cancer in the next 10 years for women with no prior cancer, by current age. For example, at age 30, the baseline 10-year risk is 0.50%. This means that out of 1,000 women aged 30, five will be diagnosed with breast cancer by age 40. With COC use, the relative increase is 1.5, so in total, 6.5 per 1,000 women will be diagnosed with breast cancer by age 40.

Source: American Cancer Society, Breast Cancer Facts & Figures 2024–2025; National Cancer Institute SEER DevCan estimates [16].

Table 2. Publications reporting no increase in breast cancer risk associated with COC use

Study (publication year)	Design	N	Risk analysis results
CSHS (CDC) (1986) [17]	Case–control	4,711	RR: 1.0 (95% CI: 0.9–1.1)*
Nurses' Health Study (1997) [18]	Prospective cohort	1.6 million	>10 years use: RR 1.11 (95% CI: 0.94–1.32)
RCGP[†] (2007) [11]	Prospective cohort	339,000/744,000 person-years (never/ever users)	Ever vs never use: RR 0.98 (95% CI: 0.87–1.1)
Jordan (2015) [19]	Case–control	1,502	One-year (2010) PAF 0.7% [‡]
Marchbanks (2002) [15]	Case–control	4,682	Current use: RR 1.0 (95% CI: 0.8–1.3) [§] Past use: RR 0.9 (95% CI: 0.8–1.0) [§]
Oxford-FPA (2013) [20]	Prospective cohort	17,032	Ever vs never use: RR 1.0 (95% CI: 0.9–1.1)
Michels (2018) [21]	Prospective cohort	100,000	>10 years use: RR 1.04 (95% CI: 0.97–1.11)

CI: confidence interval; CDC: Centers for Disease Control; COC: combined oral contraceptive; CSHS: Cancer and Steroid Hormone Study; Oxford FPA: Oxford Family Planning Association; PAF: population attributable fraction; RCGP: Royal College of General Practitioners; RR: risk ratio.

Most COCs used in these cohorts and case–control studies contained ethinylestradiol (EE) combined with various progestins. Risk estimates, therefore, largely reflect EE exposure. Data specific to estradiol (E2)-containing COCs are limited, and none of these studies included formulations with estetrol (E4).

* The duration of oral contraceptive use and the time since last use did not influence the risk.

[†] RCGP study (started in 1968): ~23,000 oral contraceptive users and ~23,000 never-users were recruited over 14 months; mean age 29 years; mostly married/stable relationships, predominantly White.

[‡] The PAF is the proportion of cancers in a population that could have been avoided if no one had used oral contraceptives (e.g., 0.7 means that of 1,000 cases, seven could have been avoided).

[§] No consistent increase in risk with more prolonged use or higher estrogen dose; results similar in White and Black women. No excess risk with family history or early initiation of oral contraceptives.

Table 3. Publications reporting an increased breast cancer risk associated with COC use

Study (publication year)	Design	N	Never vs ever RR	Current/recent RR	Past RR (≥5 years)
Collaborative Group (1996) [13]	Meta-analysis	153,536 (54 studies)	1.24 (95% CI: 1.15–1.33)	1.16 (95% CI: 1.08–1.23)	5–9 years after stopping: 1.07 (95% CI: 1.02–1.13) ≥10 years after stopping: 1.01 (95% CI: 0.96–1.05)
Hunter (2010) [6]	Prospective cohort	1,246,967 person-years	N/A	1.33 (95% CI: 1.03–1.73)*	1.12 (95% CI: 0.95–1.33)*
RCGP (2017) [22] [†]	Prospective cohort	46,022	1.04 (99% CI: 0.91–1.17)	1.48 (99% CI: 1.10–1.97)	1.12 (95% CI: 0.91–1.39)
Mørch (2017) [7]	Prospective cohort	~1.8 million	N/A	1.19 [‡] (95% CI: 1.13–1.26)	1.05 [‡] (95% CI: 0.98–1.13)
Phillips (2025) [23]	Pooled analysis	3,882 BRCA1/ 1,509 BRCA2 mutation carriers	BRCA1 mutation carriers (HR 1.29) [§]	N/A	N/A

BRCA1/2: Breast Cancer gene 1/2; CI: confidence interval; COC: Combined oral contraceptive; HR: hazard ratio; N/A: not available; NS: not significant; RCGP: Royal College of General Practitioners; RR: risk ratio.

Most COCs used in these cohorts and case–control studies contained ethinylestradiol (EE) combined with various progestins. Risk estimates, therefore, largely reflect EE exposure. Data specific to estradiol (E2)-containing COCs are limited, and none of these studies included formulations with estetrol (E4).

* 116,608 nurses (ages 25–42 at enrolment, 1989); lifetime OC use and formulations recorded.

[†] RCGP study (started in 1968): ~23,000 OC users and ~23,000 never-users recruited over 14 months; mean age 29 years; mostly married/stable relationships, predominantly White. Past RR: 5–15 years.

[‡] Follow-up period 10.6 years.

[§] Particularly with more prolonged use (a 3% risk increase per year). No significant risk was found in BRCA2 carriers. Period of ever use: ≥1 year (median cumulative duration of use, 4.8 and 5.7 years, respectively).

For natural estrogens, breast cancer risk appears to vary depending on the specific compound and the clinical context [24]. Evidence supporting E2- and E4-containing COCs remains limited due to their recent introduction. E4, possibly because of its lower biological potency and ability to inhibit the membrane estrogen receptor (ER), which is involved in the enhanced proliferation of breast cancer cells in the presence of estrogens, has shown reduced stimulation of breast cancer cell growth in vitro and a dose-dependent decrease in tumour growth in mouse xenograft models using human breast cancer cell lines [25-27]. In triple-negative breast cancer (TNBC) cells, E4 binds to the G protein-coupled ER and upregulates plasminogen activator inhibitor type 2 (SERPINB2). This activation reduces cell migration and invasion. High SERPINB2 levels are linked with better outcomes in ER-negative patients, suggesting E4's potential even as a therapy for TNBC [28]. Together, these findings suggest that E4 might have a more favourable breast cancer risk profile, although individual risk-benefit assessments remain essential. Long-term studies are necessary to determine whether E2- or E4-based COCs present a different breast cancer risk profile compared to those containing EE.

Colon cancer

Substantial evidence links COCs to a decreased risk of colorectal cancer. The prevalence and mortality rates of colorectal cancer, however, show significant ethnic disparities. For example, the incidence and mortality rates among Black individuals in the United States are higher than those of other ethnic groups [29,30]. These disparities may be attributed to differences in socioeconomic status, access to screening, and lifestyle factors [31]. While COCs offer protective benefits, their impact on colorectal cancer risk across diverse populations requires further investigation to understand these ethnic variations.

Three meta-analyses support the beneficial impact of COCs on colon cancer risk. A 2009 meta-analysis of 23 studies (14 case-control and 9 cohort studies) found that ever-use of COCs was associated with a reduced relative risk (RR) of colorectal cancer (RR = 0.8) compared to never-users. However, the analysis did not account for the duration of use. Notably, recent use appeared even more protective (odds ratio [OR] 0.7) [32]. A 2015 meta-analysis, which included 29 studies and nearly 16,000 cases of colorectal cancer, found a similar reduction in risk among ever-users (RR = 0.8), with longer duration of COC use linked to greater protection, independent of dose [33]. A more recent 2022 meta-analysis of studies published between 2000 and 2022 found a significant protective association between oral contraceptive use and colorectal cancer risk in women, with ever-users showing a pooled risk ratio of 0.53 compared to never-users [34].

Several mechanisms have been proposed to explain this protective effect, including modulation of insu-

lin-like growth factors, reduced levels of proliferative bile acids, and estrogen's tumour-suppressive actions via receptor-mediated pathways in the colon [2]. The protective effect is believed to extend to natural ER β -mediated anti-tumour pathways in the colon, as demonstrated in preclinical studies with ER agonists. Epidemiological evidence for E2 and E4 in women is currently lacking, emphasising the need for further research to confirm this association [35].

Endometrial, ovarian, and cervical cancer

COCs are strongly linked to a reduced risk of endometrial and ovarian cancer, with studies showing approximately a 50% risk reduction and protective effects lasting up to 20 years after discontinuation [36]. This benefit is primarily attributed to the progestin component, which counteracts estrogen-induced endometrial proliferation [36,37]. The incidence of endometrial and ovarian cancers varies among ethnic groups. For instance, Asian and Pacific Islander women tend to have lower rates of ovarian cancer compared to White women [38]. In Black women, mortality rates are higher, with a greater incidence of aggressive histologic subtypes of endometrial cancer [39]. Genetic factors, reproductive histories, and disparities in healthcare access may influence these discrepancies. As such, the protective benefits of COCs on endometrial and ovarian cancer risk should be considered within the context of these ethnic variations.

A systematic review of over 15 case-control studies and at least four large cohort studies confirms the long-term protective benefits of COCs against endometrial cancer [37]. Similarly, the National Cancer Institute reports a 30% or greater lower risk among ever-users, with more pronounced reductions associated with prolonged use and sustained benefits for years after discontinuation [21,29].

A Danish cohort study showed that contemporary COCs offer significant long-term protection against both endometrial and ovarian cancers in women of reproductive age. COC use was associated with a 43% reduction in endometrial cancer risk, particularly for type I carcinomas, with greater protection from prolonged use and benefits persisting for over a decade after discontinuation [14]. Natural estrogens, when combined with appropriate doses of progestin, are expected to confer comparable protection, as the primary mechanism involves progestin-mediated inhibition of endometrial proliferation [36,37]. However, dedicated studies directly evaluating the long-term effects of COCs containing E2 or E4 on endometrial and ovarian cancer risk are still lacking.

The most comprehensive pooled analysis, the Collaborative Group on Epidemiological Studies of Cervical Cancer, which included 24 studies mainly conducted between the 1970s and 1990s, demonstrated that current or recent use of COCs was linked to nearly doubling the risk of cervical cancer [40]. This

risk increased further with extended use but decreased after stopping COCs. Subsequent systematic reviews and meta-analyses have consistently found a modest risk increase of approximately 1.5 times, particularly with long-term use and for adenocarcinoma subtypes [41,42]. Narrative reviews highlight that this elevated risk diminishes after discontinuation, typically returning to baseline within 10 years [2]. The increased risks are thought to be associated with human papillomavirus (HPV) infection; however, more recent analyses controlling for HPV status show no consistent association [42,43]. As with breast cancer, part of this apparent risk

may reflect detection bias, as COC users are more likely to undergo regular screening, increasing the likelihood of detection rather than an actual rise in incidence [42,43].

Overall, the consensus is that although COCs may slightly increase cervical cancer risk during prolonged use, this risk is reversible. Regular screening and vaccination further significantly reduce long-term effects. Importantly, all this data pertains to formulations containing EE, as COCs with E2 and E4 were not available during the studied time frame.

Table 4. Publications reporting cervical cancer risk associated with COC use

Study (publication year)	Design	Risk analysis results
Collaborative Group (2007) [40]	Meta-analysis of 24 studies	Current/recent use: RR ~1.9; risk increases with duration (>10 yrs: RR ~2.2). Risk declines after discontinuation.
Gierisch (2013) [42]	Systematic review	Elevated risk with longer duration, particularly among women with HPV infection.
Asthana (2020) [41]	Systematic review & meta-analysis	OC use is associated with ~1.5-fold increased risk of invasive cervical cancer; higher risk for adenocarcinoma and carcinoma in situ.
Gadducci (2020) [44]	Review of epidemiological data	Reported ~1.5-fold increased cervical cancer risk in pooled case-control and cohort studies.
Anastasiou (2022) [43]	Systematic review controlling for HPV	No consistent increased risk after adjusting for HPV infection status.
Kamani (2022) [2]	Narrative review	Risk increases after more than 5 years of use; it returns to baseline within 10 years of discontinuation.

COC: Combined oral contraceptive; CSHS: Cancer and steroid hormone study; HPV: Human papillomavirus; ICO: International collaboration on cancer reporting; RR: Risk Ratio; WHO: World Health Organization.

Overall balance of cancer risk with combined oral contraceptives

In summary, the overall impact of COCs on cancer risk is complex but increasingly well understood. Some studies have reported a modest increase in the risk of breast and cervical cancers during current or recent use, but this elevation is transient. Typically, it returns to baseline within approximately five to ten years after discontinuation. Importantly, no new cancer risks have been observed to emerge later in life among past users [2,22]. While concerns remain, recent evidence shows that beyond their proven contraceptive efficacy, COCs offer significant and long-lasting protection against endometrial, ovarian, and colorectal cancers, and as shown by the presented data, these protective effects are substantial. Moreover, some of the apparent increases in breast and cervical cancer risk may reflect detection bias, with higher detection from regular screening among COC users rather than an actual rise in incidence.

Large-scale evidence from the UK Biobank demonstrates that, despite a modest, time-limited increase in breast cancer risk during or shortly after oral contraceptive use, lifetime breast cancer risk is not elevated, and the benefits against ovarian and endometrial cancer persist for more than three decades after discontinuation [45]. Taken together, and when lifetime risks are considered, the substantial protection against ovarian and endometrial cancer provided by COCs outweighs any potential breast cancer risk [45].

While most of the available evidence comes from ethinylestradiol-containing COCs, emerging data suggest that natural estrogens, such as E2 and E4, may offer comparable protective benefits with a potentially improved safety profile; however, more research is needed to confirm long-term outcomes across various cancer types.

Cardiovascular, metabolic, bone, and neurological health effects of COCs

Cardiovascular health

Heart

Most women using COCs have a low absolute risk of cardiovascular disease, and within this group, the benefits surpass the associated risks. When reviewing the impact of COCs on cardiovascular health, it is crucial to recognise that ethnic disparities in cardiovascular disease (CVD) prevalence are well-documented and carry significant implications for clinical decision-making. For instance, Black women tend to have higher rates of hypertension and subsequent heart disease compared to White women. At the same

time, South Asian populations are more prone to developing diabetes and related CVD complications. Similarly, Black individuals experience roughly twice the rate of peripheral arterial disease (PAD) compared to non-Hispanic Whites and other ethnic groups. These differences may affect the cardiovascular risks linked to COC use among various ethnicities, and they should be considered when selecting the most suitable COC for each individual, especially in older women or those with additional vascular risk factors.

A large UK prospective study (161,017 participants) found no increase in CVD events or all-cause mortality with COC use (including progestin-only pills). In fact, COC use was associated with a 9% reduction in CVD events and a 8% decrease in all-cause mortality. The study also reported an 8% to 13% lower risk of coronary heart disease, heart failure, and atrial fibrillation, with larger reductions observed with longer durations of OC use [46].

The effects of EE-containing COCs on blood pressure (BP) are well-documented, with studies showing a modest increase. For example, in the Nurses' Health Study, which included over 68,000 US women aged 25 to 42 years, current oral contraceptive users had slightly higher systolic (+0.7 mmHg) and diastolic BP (+0.4 mmHg) than non-users, even after adjusting for various cardiovascular risk factors. Over four years, the risk of developing hypertension nearly doubled among current users (RR 1.9) and remained modestly higher among past users (RR 1.2). These findings are supported by a meta-analysis of 24 studies involving 270,000 women across multiple continents, reporting a 13% increased risk of hypertension for every five years of OC use, indicating a cumulative effect.

Currently, large cohort or population-based studies comparable to the Nurses' Health Study are not available for E2- or E4-based COCs. The existing evidence is limited to Phase 3 trials and small observational studies, which, by design, include young, generally healthy women with low baseline cardiovascular risk and are not sufficiently powered to detect long-term cardiovascular outcomes.

A pooled analysis of two phase 3 trials with E4 15 mg combined with drospirenone (DRSP) 3 mg found that this combination did not significantly alter BP after 13 cycles, with hypertension attributable to treatment reported in only 0.09% of all users [47]. Importantly, more than 40% of participants had one or more cardiovascular risk factors (smoking, age over 35 years, body mass index of 30 kg/m² or higher, or high-normal BP). However, the incidence remained very low: only three women (0.2% of those with risk factors) discontinued due to hypertension, all of whom had high-normal baseline BP and at least one additional risk factor [47]. Similarly, a prospective study using 24-hour ambulatory BP monitoring evaluated COCs containing E2 valerate (E2v) plus dienogest (DNG) or E2 plus norgestrel acetate over six cycles in healthy, normotensive

women. Both formulations demonstrated a neutral effect, with no significant changes in systolic, diastolic, or mean BP, either during the day or night, and no increase in heart rate [48]. These observations suggest that CHCs containing natural estrogens may have a more neutral effect on BP compared to EE-based formulations. However, larger studies are required to confirm this preliminary evidence.

Vessels

COCs are associated with an increased risk of thrombotic events, including both venous thromboembolism (VTE) and arterial complications such as ischemic stroke and PAD. Current users of COCs have about twice the risk of ischemic stroke compared to non-users (adjusted incidence rate ratio 2.0; 95% CI: 1.9–2.2) [49]. Data from the RATIO study indicate a nearly fourfold increase in the odds of PAD (adjusted OR, 3.8; 95% CI, 2.4–5.8). Despite these associations, hormonal contraceptives do not appear to impair vascular smooth muscle function or affect arterial stiffness or vascular structure [50].

A large Danish registry study showed that the risk of thrombosis with COCs depends on both the dose of EE and the type of progestin. Formulations containing 50 µg of EE presented the highest risks. Lowering the EE dose from 30 µg to 20 µg reduced the risk for COCs with desogestrel (DSG) and gestodene (GSD), but not for DRSP. Among progestins, levonorgestrel-based COCs consistently had the lowest risk of VTE, whereas DSG, GSD, DRSP, and cyproterone were associated with approximately twice the risk compared to levonorgestrel [51]. These results emphasise the importance of considering both estrogen dose and progestin type when evaluating vascular safety.

Notably, COCs containing natural estrogens have been linked to a significantly lower risk of VTE, 33% less than synthetic formulations, suggesting a more favourable vascular safety profile [52]. These data are described in greater detail in Section 8. Interestingly, one of the randomised clinical studies included there also provided proteomic evidence: EE-containing COCs altered more than 120 serum proteins, including those involved in complement and inflammatory pathways, whereas E2V combined with DNG had only minimal effects, and DNG alone had no effect [53,54].

Consistent with these proteomic results, targeted biomarker analyses from this and other research groups further highlight EE's pro-inflammatory action [54–58]. In a separate randomised trial, Kangasniemi et al. demonstrated that EE combined with DNG significantly increased circulating high-sensitivity C-reactive protein (CRP) and pentraxin-3, whereas E2V combined with DNG induced only minor changes with no alterations observed for DNG alone [54]. These increases happen independently of adiposity or lifestyle factors and are believed to originate from hepatic first-pass metabolism of EE [55]. Importantly, pentraxin-3 is not a marker of

liver excretion, suggesting that EE promotes low-grade inflammation through extrahepatic target tissues as well [59]. Although subclinical, this inflammatory activation contributes to endothelial dysfunction, procoagulant changes, and an elevated risk of cardiovascular disease [60]. Over time, persistent low-grade inflammation is recognised as a driver of atherosclerosis, insulin resistance, and cardiometabolic disease, raising concerns that prolonged EE exposure may cause cumulative vascular effects [61]. Conversely, preparations containing natural estrogens, such as E2 or E4, show little to no effect on CRP levels, indicating a more favourable inflammatory and vascular profile [25,62].

Metabolic health

Most data on the impact of COCs on lipid metabolism come from formulations containing EE, which has been associated with elevated levels of triglycerides and low-density lipoprotein (LDL), as well as modest increases in high-density lipoprotein (HDL). However, these increases in HDL have not been consistently linked to improvements in HDL functionality. In a large population-based cohort study, adolescent users (815 COC users, 13 users of progestin-only contraceptives) had significantly higher total cholesterol (179.6 vs. 162.4 mg/dL), LDL (106.4 vs. 94.6 mg/dL), and triglycerides (104.0 vs. 67.0 mg/dL) levels compared to non-users, without differences in HDL levels [63]. Data from the Hoveyze cohort confirmed that mean lipid profiles were higher in OC users (considering also progestin-only contraceptives), with a 29% increased odds of abnormal total cholesterol compared to non-users [64].

Unlike EE, natural estrogens are linked to more favourable lipid profiles, generally increasing HDL and decreasing LDL. Importantly, E2 does more than elevate HDL-C levels; it improves HDL functionality by supporting its antioxidant, anti-inflammatory, vasodilatory, and antithrombotic properties, all of which help protect the endothelium [63–66]. In menopausal women, higher E2 levels are associated with improved HDL particle composition and greater cholesterol efflux capacity, both of which are indicators of more functional, protective HDL [64]. Furthermore, clinical data suggest that E2 or E4 may have little effect on triglycerides and carbohydrate metabolism [65].

Overall, natural estrogen-based contraceptives seem to better maintain lipid balance than EE-based contraceptives. This difference could enhance metabolic safety, especially in women with other risk factors for dyslipidaemia or cardiovascular disease, although long-term outcome data are still unavailable.

Bone health

Estrogen is essential for building bone mass and maintaining bone density, particularly during adolescence when peak bone mass is being established. Ethnic differences in bone density and osteoporosis risk, influenced by genetic, lifestyle, and cultural factors, are well-documented [67]. For example, Black women

generally have higher bone density and lower osteoporosis risk compared to White and Asian women [68,69]. These variations highlight the need for personalised contraceptive counselling that considers individual risk factors and ethnic background.

Studies on COCs containing EE suggest that their use in post-menarche adolescents may impair bone accrual compared to non-users [70]. The degree of impact appears to depend on the estrogen dose (with higher effects observed at $\geq 30 \mu\text{g}$ EE), the specific progestin formulation used, and the duration of use, with studies indicating that use beyond two years is consistently linked to reduced bone mass gains. Findings on dose are mixed: some studies observed reduced accrual with lower-dose EE (15–20 μg), while others reported greater effects at 30 μg (Lim et al., 2025) [71]. A two-year clinical trial demonstrated reduced bone mass acquisition and lower bone formation markers, particularly in users of EE 30 μg combined with DRSP 3 mg [72]. Biomarkers of bone formation also decreased, suggesting impaired bone development during a critical growth period. A meta-analysis of nine prospective studies confirmed a modest but statistically significant reduction in spinal bone mineral density (BMD) accrual with EE-containing preparations over 12–24 months (weighted mean difference -0.02 g/cm^2), raising concerns about long-term bone health and underscoring the need for further randomised controlled trials [73].

Based on their more physiological profile, natural estrogens such as E2 may better support normal bone metabolism. A recent meta-analysis evaluating bone turnover markers found that COCs containing E2 resulted in minimal reductions in bone formation markers (mean standardised mean change for PINP of +0.12; 95% CI, -0.10 to 0.33), while EE-containing COCs showed significant decreases (-0.55) [62].

Limited clinical data are available for E4, but existing analyses suggest that E4 combined with DRSP reduces bone turnover markers less markedly than EE-containing COCs, which, in some contexts, could represent a favourable modulation of excessive bone resorption, and preserve bone and lower fracture risk [62]. However, while this pattern suggests neutrality or benefits in adults, interpretation in younger women remains uncertain, as bone turnover markers do not reliably predict long-term BMD and pooling data across age groups, as done by Tassi et al., may obscure critical differences [62,74]. Moreover, preclinical studies in osteoporotic models have demonstrated that E4 can increase BMD, enhance bone strength, and elevate osteocalcin levels compared to untreated controls [75].

Taken together, the findings overall support E2 as potentially more favourable for bone health in healthy adolescents compared to EE, while E4 still offers advantages, although further research is needed [63]. More clinical studies with both E2 and E4 formulations are necessary to assess bone gain outcomes.

Importantly, to date, there is no evidence that CHC use increases the risk of bone fractures, suggesting that the observed changes in bone biomarkers and density may not translate into clinically relevant harm [62,72,73,76,77].

Nervous system

Research on the neurological effects of estrogens in the context of contraceptive use remains in its early stages. However, available studies indicate that estrogens may provide neuroprotective benefits, helping to preserve cognitive function [78,79]. Natural estrogens, due to their similarity to endogenous hormones, are believed to support neuronal health and reduce the risk of neurodegenerative diseases. Preclinical studies, for example, suggest that E4 may modulate central neurosteroid pathways by increasing levels of allopregnanolone and β -endorphins, reducing markers of neuronal injury while promoting neurogenesis and angiogenesis [80]. These findings point to potential neurotrophic and neuroprotective roles of E4, but their relevance for human brain health in the context of contraceptive use is still unknown, warranting further research.

Safety in complex medical conditions and the potential role of natural estrogens

Assessing COC safety in the context of complex medical conditions is crucial, particularly given the burden of chronic diseases and notable ethnic disparities that influence both disease course and contraceptive safety. Mental and neurological disorders, autoimmune and inflammatory diseases, chronic kidney disease, and chronic infectious diseases, are not only prevalent and clinically complex but also carry a significant long-term burden on women's health and healthcare systems. Ethnic disparities significantly influence the prevalence, severity, and outcomes of these conditions, with important clinical implications for women's health, particularly concerning the safety and effectiveness of CHCs [81–84]. In this context, the World Health Organization (WHO) [85,86] and the Centers for Disease Control and Prevention (CDC) [87] have developed Medical Eligibility Criteria (MEC) for CHC use across a range of medical conditions and individual health characteristics (Table 5) [88]. These guidelines provide evidence-based recommendations on the safety of contraceptive methods to support safe contraceptive choices tailored to specific clinical scenarios, enabling informed decision-making by both patients and healthcare providers.

COCs containing natural estrogens may offer improved safety for women with complex medical conditions. Unlike EE, natural estrogens have a more selective pharmacological profile and a reduced impact on metabolic, hepatic, and haemostatic parameters [64,65] (See Section 8). This is particularly important for women affected by chronic or high-risk conditions, such as autoimmune disorders, neurological diseases, chronic

kidney disease, or inflammatory states. Although clinical guidelines from the WHO and CDC provide a framework for CHC eligibility in such contexts, they have yet to reflect the emerging evidence supporting natural estrogen formulations fully. Therefore, further clinical research is necessary to validate the long-term benefits of these interventions in these populations.

Current gaps in knowledge

Despite the promising safety profile of natural estrogens in CHCs, several gaps remain:

Long-term safety data: extended studies are needed to assess the long-term effects of natural estrogen use in diverse populations, including adolescents.

Comparative research: direct comparisons between natural and synthetic estrogens across various safety outcomes are limited.

Mechanistic insights: further research is required to elucidate the mechanisms underlying the differential effects of natural versus synthetic estrogens.

Population-specific studies: investigations focusing on specific demographic groups, including different age ranges and ethnicities, are necessary to tailor contraceptive recommendations.

Natural estrogens in the context of complex medical conditions: there is a lack of clinical evidence on the safety and effectiveness of CHCs containing natural estrogens (E2/E4) in women with complex medical conditions, despite their potential for improved tolerability and reduced thrombotic risk.



Table 5. WHO/CDC Medical Eligibility Criteria for CHC use across clinical and autoimmune conditions

Clinical context/Disease type	CHC use considerations	WHO/CDC MEC criteria for CHC*
Following abortion and ectopic pregnancy	CHCs can be initiated immediately post-abortion (spontaneous or induced) without increased adverse events. For women with a history of ectopic pregnancy, CHCs are safe and effective in reducing the likelihood of any pregnancy, including ectopic gestations.	Category 1
Smoking status	Women under 35 who smoke may use CHCs with caution. For women ≥ 35 , especially smoking ≥ 15 cigarettes/day, CHCs are generally not recommended due to increased cardiovascular risks.	Age <35 years: category 2 Age ≥ 35 years i) < 15 cigarettes/day: category 3; ii) ≥ 15 cigarettes/day: category 4
Obesity	Most women with obesity can use CHCs, but additional thrombotic risk factors require caution.	Category 2
After bariatric surgery	CHCs are valid after restrictive procedures. Oral CHCs are not recommended after malabsorptive surgeries; a patch or ring may be a preferable alternative.	Restrictive procedures: category 1 Malabsorptive procedures: category 3
Chronic kidney disease	CHCs are contraindicated in advanced CKD due to an elevated risk of thrombosis.	Category 4
Systemic lupus erythematosus	Avoid in the presence of antiphospholipid antibodies. May be used in patients with stable disease who do not have antiphospholipid antibodies and/or additional risks.	Positive or unknown antiphospholipid antibodies: category 4 No antiphospholipid antibodies: category 2 Immunosuppressive therapy: category 2
Antiphospholipid syndrome	Contraindicated due to high thrombotic risk. Use non-hormonal or progestin-only options.	Category 4
Rheumatoid arthritis	Generally safe, even with immunosuppressive therapy. No increased RA risk shown in recent studies.	Category 2
Autoimmune thyroid disease	No negative effect on thyroid function. CHCs may even be protective.	Category 1
Multiple sclerosis	Safe in ambulatory women. Avoid prolonged immobility due to an increased risk of VTE.	Ambulatory: category 1 Immobility: category 3
Inflammatory bowel disease	Possible increased risk of Crohn's disease with long-term use. Use with caution. Individualised assessment.	Mild disease: category 2 Increased risk of VTE: category 3
Neurologic conditions	CHCs are acceptable in migraines without aura, but should be avoided with aura. Safe in MS unless with significant immobility.	Migraine with aura: category 4 Migraine without aura (includes menstrual migraine): category 2
Epilepsy	CHCs can be used, but interactions with anticonvulsants need consideration.	Category 1 Certain anticonvulsants: category 3
Depressive disorders	CHCs do not worsen depressive symptoms and are considered safe.	Category 1
HIV infection and ART Use	CHCs are appropriate for women with or at risk for HIV, including those on ART. Monitor for drug interactions.	Category 1
Superficial Venous Disorders	CHCs are safe in women with varicose veins (no restriction) and generally acceptable in superficial venous thrombosis.	Category 3

*WHO/CDC MEC 1 = A condition for which there is no restriction on the use of the contraceptive method
 WHO/CDC MEC 2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
 WHO/CDC MEC 3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
 WHO/CDC MEC 4 = A condition that represents an unacceptable health risk if the contraceptive method is used

ART: antiretroviral therapy; CDC: Centers for Disease Control and Prevention; CHC: combined hormonal contraceptive; CKD: chronic kidney disease; MEC: Medical Eligibility Criteria; RA: rheumatoid arthritis; VTE: venous thromboembolism; WHO: World Health Organization

Key messages

General benefits and safety

Pregnancy prevention plus improvement of menstrual and premenstrual symptoms, acne, and hirsutism.
Reduction of colorectal, endometrial, and ovarian cancer risk.
Long-term safety is supported by robust evidence.
Natural estrogens (E2, E4) demonstrate more favourable metabolic and vascular profiles than EE.

Cancer

- **Breast:** Slight, transient risk increase during current/recent use; E4 may offer a safer profile.
- **Colorectal:** Consistent risk reduction (RR ~0.5–0.8); effect may differ by ethnicity.
- **Endometrial & ovarian:** Risk reduced by 30–50%, with benefits persisting for decades.
- **Cervical:** Risk may rise modestly with long-term use, largely HPV-related, but is reversible after discontinuation and mitigated by screening and vaccination.
- **Overall:** When lifetime risks are considered, the protective effects against multiple cancers outweigh the minimal, temporary breast risk.

The apparent increases in breast and cervical cancer risk may reflect detection bias, with higher detection from regular screening among COC users rather than a true rise in incidence.

Cardiovascular health

Most users have low CVD risk; some data show mortality reduction.
EE-containing CHC induces low-grade inflammation, raising long-term cardiometabolic risk; E2/E4 remain neutral.
EE increases VTE, stroke, PAD; E2/E4 lower VTE risk by ~33%.
Natural estrogens have minimal impact on BP.
Ethnic disparities require personalised risk assessment.

Metabolic health

EE raises LDL, triglycerides, and can impair glucose control.
E2/E4 improve HDL function and insulin sensitivity.

Bone health

EE may impair bone accrual in adolescents.
E2 and E4 are bone-neutral or favourable in adults; adolescent effects need further study.
Ethnic differences influence fracture risk and should guide counselling.

Nervous system health

E2 and E4 may support brain health; E4 shows neuroprotective effects in preclinical models.
The clinical significance of E4's brain effects remains under study.

Complex medical conditions

CHCs are generally safe with stable autoimmune or chronic conditions.
Contraindicated in high-risk cases (e.g. antiphospholipid syndrome, advanced chronic kidney disease).
E2 and E4-based CHCs may be safer in selected cases but require more clinical data.

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