

Contraception: general considerations

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Introduction

Contraception is a fundamental component of reproductive health, yet its use, acceptance, and outcomes vary significantly across global regions. These differences are shaped by a wide range of cultural, socioeconomic, and policy factors that influence both method preferences and access. From regional variations in contraceptive use to the impact of societal norms, healthcare infrastructure, and religious beliefs, understanding these dynamics is key to improving reproductive autonomy and health equity. This text explores how these factors intersect globally and examines the specific role that estrogens, particularly natural estrogens, can play in optimising contraceptive experiences and outcomes.

Variations in contraceptive methods used based on the region

The development of reliable and safe contraceptive methods stands as one of the most significant public health advancements of the 20th century [1]. During the 60 years since the introduction of combined oral contraceptives (COCs), there have been significant innovations in relation to methods of delivery as well as changes in formulations. These advancements have minimised adverse effects and thereby enhanced safety and tolerability, all while maintaining their effectiveness as a highly reliable method of contraception [2].

Contraceptive method use varies significantly by region, reflecting cultural, economic, and healthcare accessibility factors [3]. In Eastern and South-Eastern Asia, intrauterine devices (IUDs) are the most widely used method, with 18.6% of women relying on them, followed closely by male condoms at 17.0% [3]. In Europe and North America, oral contraceptive pills (17.8%) and male condoms (14.6%) are the most common choices, likely due to their accessibility and ease of use. In Latin America and the Caribbean, female sterilisation (16.0%) and the pill (14.9%) are predominant, reflecting both high rates of permanent contraception and hormonal birth control usage. Oceania follows a similar trend, where the pill is the leading contraceptive method (16.9%). In Central and Southern Asia, female sterilisation (21.8%) is the most frequently used method. Northern Africa and Western Asia show a preference for the pill (10.5%) and IUDs (9.5%), possibly influenced by healthcare policies and social norms. Meanwhile, Sub-Saharan Africa stands out as the only region where injectables are the dominant form of contraception, with 9.6% of women using them [3]. This pattern may reflect their convenience and effectiveness in settings with limited healthcare access, as well as the influence of various non-governmental organization programmes.



Cultural, policy, and socioeconomic influences on contraceptive use and unintended pregnancy

Contraception is a cornerstone of reproductive health. In 2022 alone, contraceptive use prevented over 141 million unintended pregnancies, 29 million unsafe abortions, and almost 150,000 maternal deaths [4]. Yet the use of contraceptives, acceptance, and cultural norms and policy frameworks across regions deeply shape implementation. These factors contribute to global disparities in access to and utilisation of contraceptive methods, which directly impact rates of unintended pregnancy. Despite the broad availability of contraceptive options, unintended pregnancies remain a significant public health concern, particularly in settings with limited access, education, or cultural acceptance.

Cultural beliefs and values profoundly shape attitudes towards contraception. In many societies, traditional gender roles and religious teachings influence reproductive decisions. For instance, in parts of sub-Saharan Africa, such as the Busoga region of eastern Uganda, societal expectations favouring large families and persistent misconceptions about contraception restrict its acceptance [5]. Similarly, in some interpretations of Catholicism and Islam, artificial contraceptive methods are discouraged in favour of natural ones [6]. However, religious interpretations are not uniform, and individuals often navigate these teachings alongside personal and family health considerations [6].

Policy is another key determinant of access to contraceptives. In the United States, coverage is shaped by both federal and state regulations. While the Affordable Care Act improved access by mandating contraceptive coverage without cost-sharing [7], recent political developments have introduced new barriers, disproportionately affecting low-income and minority populations [8]. India provides a contrasting example. Despite a long-standing national family planning programme, socio-cultural stigma and provider bias still restrict contraceptive use, particularly among unmarried women and adolescents [9,10]. In Japan, oral contraceptives were not approved until 1999, many years after their introduction in other high-income countries [11]. This delay contributed to a cultural reliance on condoms, which remain the main method of contraception in the country. International policy changes also impact global access to contraception. The reinstatement of the “global gag rule” by the United States administration in 2025, which bans funding to organisations that provide or promote abortion services, has disrupted vital reproductive health services in many low-income countries [12].

Socioeconomic factors further intersect with cultural and policy dynamics [13]. In low- and middle-income countries (LMICs), an estimated 74 million unintended pregnancies occur annually, with 30% attributed to contraceptive failure [14]. It has been estimated that nearly 50% of pregnancies in LMICs occur despite reported contraceptive use, often resulting from discontinuation due to side effects, health concerns, or inadequate counselling [15,16]. In Latin America, shifting gender roles and economic pressures have led to a decline in fertility rates. The emergence of communities like Nunca Madres reflects a broader trend of women delaying or avoiding motherhood due to financial insecurity and limited state support [17].

Unmet contraceptive needs still lead to unintended pregnancies. Women with unmet needs are almost four times more likely to face an unintended pregnancy than those whose needs are satisfied [4]. Around 85% of women who discontinue contraception become pregnant within one year [18]. Even among users, method failure remains a significant factor in unintended pregnancies, especially in regions lacking access to reliable, modern methods [19].

Role of estrogens in contraception

COCs contain both a progestin and an estrogen component, administered through oral, transdermal, vaginal ring, intrauterine, or other invasive methods. Variations in the type of progestin and estrogen used in each COC result in differences in efficacy, mechanisms of action, and duration of use, emphasising the importance of understanding their pharmacological and physiological effects for effective selection. Such knowledge is also crucial for customising COCs to meet users' specific needs, thereby improving adherence and reproductive health outcomes. An overview of the key features of different estrogens used in COCs is provided in Table 1.

In COCs, the progestin suppresses ovulation, while the estrogen component enhances the contraceptive efficacy of progestin by strengthening its suppression of gonadotropin release and exerting additional reduction of fertility within the reproductive system [20,21]. Moreover, the estrogen component in COCs helps maintain endometrial stability, reducing the chance of irregular shedding and breakthrough bleeding, and thus encouraging a more predictable bleeding pattern [22–25].

Achieving a stable bleeding pattern depends on maintaining an appropriate balance between estrogen and progestin. In the case of ethinylestradiol (EE) containing COCs, if the EE dose is too low, as seen in formulations containing EE 10 µg/norethindrone acetate 1 mg, cycle stability may be compromised. Similarly, replacing EE with 17β-oestradiol (E2) or E2 valerate can

cause greater variability in bleeding patterns, likely due to the shorter half-life of E2 relative to progestin [26]. In contrast, the combination of estetrol (E4) 15 mg with drospirenone (DRSP) 3 mg has been shown to provide more regular and predictable bleeding patterns, particularly after the third cycle of use [22].

Eliminating the estrogen, as in progestin-only pills (POPs) such as DRSP 4 mg in a 24/4 regimen, is associated with lower rates of scheduled bleeding and variable rates of unscheduled bleeding compared with COCs [22]. From a practical perspective, one of

the most significant non-contraceptive advantages of COCs over POPs is their ability to provide a consistent and predictable bleeding pattern, which can enhance user satisfaction and adherence [27]. The inclusion of an estrogen in contraceptive formulations is, therefore, primarily aimed at optimising cycle control, enhancing acceptability, and supporting long-term continuation of use [28-31]. However, comparing findings across clinical trials remains complex due to inconsistencies in the definitions used for assessing bleeding patterns and cycle control [32].

Table 1. Key characteristics of estrogens in combined oral contraceptives

Characteristic	Estrogen		
	EE	E2	E4
Type	Synthetic estrogen [44]	Natural estrogen [45,46]	Native, human-specific estrogen [47-49]
Estrogen Receptor (ER) Activity	ERα selective agonist [50]	ERα and ERβ agonist with slightly higher affinity for ERβ [46,50]	Activates nuclear ERα but is a mixed agonist/antagonist at membrane ERα [47]
Mechanism of Action	Decreases luteinizing hormone (LH) to reduce endometrial vascularisation; inhibits gonadotrophic hormone to prevent ovulation [44]	Like EE: inhibits LH and gonadotrophic hormone [46]	NEST: distinctive vascular and metabolic effects [47,48]
Oral Bioavailability	38%–48% [44,51]	2%–10%; improved with micronisation/esterification [45,51,52]	High (70%) [47,53,54]
Plasma Protein Binding	98.3%–98.5% [55]	>95% [45]	<50%; minimal SHBG binding[48]
Metabolic Effects	More substantial effect than E2 on hepatic metabolism and liver protein synthesis [56]	Regulates blood pressure, endothelial healing, angiogenesis, and prevents coronary vasospasm [47,57]	Limited impact on liver, haemostasis, coagulation, angiotensinogen, lipids, and metabolic markers [47,48,58,59]
Half-life (Oral)	≈ 24 h (range: 5–30 h) [46,60]	12–20 h [45,46]	≈ 28 h [46,48]
Environmental Impact	More persistent than natural estrogen; potential environmental concern [61]	Short half-life, rapidly biodegraded [61]	Minimal predicted impact on aquatic ecosystems [54]
Thromboembolic Risk	High due to metabolism resistance [62-64]	Lower than EE [62,65-67]	Lower risk compared to EE due to limited hepatic effects [48,66]

EE: ethinylestradiol; E2: estradiol; E4: estetrol; ER: estrogen receptor; NEST: native estrogen with selective activity in tissues; SHBG: sex hormone-binding globulin

Mechanism of action

The physiological effects of estrogen in COCs depend on their interaction with estrogen receptors ER α and ER β , with receptor affinity having a greater influence on clinical outcomes than concentration [33]. EE selectively activates ER α and has strong effects on the liver, as well as environmental persistence. E2 activates both receptors, which supports cardiovascular health, but has low bioavailability. E4, a fetal-derived estrogen, provides high bioavailability, selective activity, minimal hepatic impact, and low environmental risk, making it more suitable for use in COCs [34] (Table 1). A detailed description of the pharmacokinetics and pharmacodynamics of estrogens used in COCs is provided in Sections 3 and 4.

The added value of “natural” estrogen in COCs across diverse global contexts

Across the globe, contraceptive choices are influenced by a complex mix of cultural norms, policy environments, healthcare access, and socioeconomic factors. These regional differences affect not only which methods are used but also how they are accepted and followed [35]. COCs remain a widely used and versatile option in many settings, with the estrogen component playing a critical role in both contraceptive efficacy and bleeding control [36,37]. Within this landscape, natural estrogens like E2 and E4 provide distinctive benefits that could improve the overall contraceptive experience for users globally.

Natural estrogens in COCs differ from synthetic EE in terms of receptor selectivity, metabolism, and safety. EE's strong hepatic effects and environmental persistence raise concerns about the risk of venous thromboembolism (VTE) and sustainability, particularly in women with metabolic risk factors. By contrast, E2 and E4 exhibit biological activity closely resembling endogenous hormones and can be regarded as natural and “body-identical” [33,38,39]. E2 supports cardiovascular health, whereas E4, with its high bioavailability and minimal hepatic impact, is particularly suitable for women who are sensitive to hormonal side effects [33].

In culturally and politically diverse regions, where contraceptive adherence may be hindered by side effects, stigma, or misinformation, these characteristics become especially important. Predictable bleeding patterns, improved safety—particularly regarding arterial and venous deep thrombosis—and better tolerability with natural estrogens may provide more suitable options for COC users, increasing satisfaction and continuation compared with formulations containing EE [22,40]. Furthermore, E4's limited interaction

with hepatic enzymes and reduced influence on liver proteins may benefit women with comorbidities or those using medications affected by cytochrome P450 (CYP) enzyme metabolism [41-43].

Natural estrogens in combined oral contraceptives (COCs) are also a valuable treatment option during perimenopause, when fluctuations in endogenous oestradiol levels cause symptoms linked to hypoeestrogenism, as well as abnormal uterine bleeding due to anovulatory dysfunction, heavy menstrual periods, or dysmenorrhoea [37].

As global efforts continue to reduce unintended pregnancies and enhance reproductive autonomy, the role of natural estrogens in COCs deserves greater attention. Their physiological effects, improved tolerability, and favourable risk profiles make them a compelling option in both high- and low-resource settings. Integrating natural estrogens into contraceptive strategies may promote more personalised, acceptable, and sustainable contraceptive care, better reflecting users' health needs, values, and lived experiences.

Conclusions

Contraceptive choice is influenced not only by pharmacology but also by women's lived experiences worldwide. Recognising these intersecting factors highlights the importance of offering contraceptive options that are adaptable, tolerable, and tailored to individual preferences. Natural estrogens in combined hormonal contraceptives exemplify a move towards formulations that consider both biological compatibility and broader health concerns. By continuing to refine contraceptive options in this way, healthcare providers and policymakers can better deliver solutions that are not only clinically effective but also personally meaningful and sustainable.

Current gaps and future directions

Future research should generate robust long-term safety data on natural estrogens, with particular focus on cardiovascular and metabolic outcomes.

Clinical studies should expand to include adolescents, women in the perimenopause, and women with comorbidities to reflect the diversity of contraceptive users better.

Develop implementation strategies to ensure affordability, regulatory approval, and a reliable supply of natural estrogen-containing contraceptives worldwide.

Key messages

Global contraceptive use varies significantly across regions because of cultural norms, healthcare access, and socioeconomic factors.

Cultural and religious beliefs shape contraceptive acceptance, with traditional roles and religious doctrines influencing uptake and method preference.

Unintended pregnancies remain a significant concern, especially in low-resource settings, often due to contraceptive failure or discontinuation.

Policy frameworks greatly affect access: countries like the US have expanded coverage via the ACA, but political shifts have reintroduced barriers. India and Japan illustrate how stigma and policy delays can impact contraceptive uptake.

Socioeconomic pressures and gender dynamics further influence fertility choices, with trends like delayed motherhood or voluntary childlessness emerging in some regions.

COCs provide key benefits, combining progestin and estrogen to suppress ovulation and regulate bleeding. Estrogens enhance cycle control and user adherence.

Bleeding control is essential for user satisfaction. E4 combinations have shown excellent bleeding profiles.

Natural estrogens (E2 and E4) offer advantages over synthetic EE, including improved tolerability, reduced hepatic impact, and favourable risk profiles, supporting better adherence, especially in women sensitive to hormonal side effects. Both are good options for oral contraception in women in the perimenopause.

E4's unique mechanism and bioavailability make it suitable for diverse populations, including women in perimenopause or those with comorbidities or CYP-interacting medications. However, it is crucial to consider that, when combined with a progestin, interactions may still occur.

Incorporating natural estrogens into COCs may support more personalised, acceptable, and sustainable contraceptive care globally.

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