

Absorption, distribution, metabolism, and excretion of estrogens used in combined oral contraceptives

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Introduction

Understanding the pharmacokinetic and metabolic profiles of estrogens is essential for optimising contraceptive efficacy and safety. The pharmacokinetic behaviour of estrogens in combined hormonal contraceptives is determined by the interrelated processes of absorption, distribution, metabolism, and excretion (ADME). This section provides an overview of the ADME characteristics of the three main estrogens used in combined oral contraceptives (COCs): the synthetic estrogen ethinylestradiol (EE), the natural estrogens 17 β -estradiol (estradiol [E2]), and estetrol (E4). The four pharmacokinetic core processes are described in Table 1. Table 2 summarises the main pharmacokinetic and metabolic profiles of these three estrogens.

Despite structural similarities, the three estrogens exhibit significant differences in bioavailability, half-life, and metabolic pathways, which influence their clinical effects and potential for interaction when used in COCs. Special attention is given to the extensive first-pass hepatic metabolism of E2, the selective metabolism and long half-life of E4, and the vigorous hepatic activity of EE, as well as its interaction with cytochrome P450 (CYP450) enzymes. Additionally, the impact of genetic and ethnic variability in estrogen pharmacokinetics on contraceptive use is also considered.

Table 1. Absorption, Distribution, Metabolism, and Excretion (ADME)

Absorption	Refers to the process by which a drug enters the systemic circulation from the site of administration, and is influenced by formulation, solubility, and physiological conditions such as gastrointestinal pH
Distribution	Describes the reversible transfer of the drug between the blood and various tissues, governed by factors like plasma protein binding, tissue permeability, and blood flow
Metabolism	Involves the biotransformation of the parent compound into metabolites, often via hepatic phase I (e.g., cytochrome P450-mediated oxidation) and phase II (e.g., conjugation via glucuronidation or sulphation) pathways, which may alter activity, toxicity, or clearance
Excretion	The removal of the parent drug and its metabolites from the body via renal (urine) or biliary/faecal routes.



Table 2. ADME profiles of ethinylestradiol (EE), estradiol (E2), and estetrol (E4)

ADME Process	Description (including estrogen-specific details)
Absorption	For orally administered estrogens, this process is influenced by physicochemical properties such as lipophilicity, molecular weight, and pKa, as well as gastrointestinal physiology, including pH, enzymatic activity, and bile salt availability. First-pass intestinal and hepatic metabolism can substantially reduce oral bioavailability, as observed for E2. In contrast, synthetic modifications, such as the ethinyl group in EE, increase metabolic stability and improve systemic exposure. EE is rapidly and completely absorbed with a bioavailability of ~45% (not affected by food); E2 has a relatively poor absorption with 2–10% bioavailability due to extensive first-pass metabolism; E4 has high oral bioavailability, but food can reduce C _{max} by ~50%.
Distribution	EE binds almost exclusively to albumin, E2 binds both to albumin and sex hormone-binding globulin (SHBG), and estetrol (E4) binds only to albumin. This binding pattern affects both free hormone concentrations and pharmacodynamic activity. The elimination half-lives are ~5–30 hours for EE, 13–20 hours for E2, and 19–28 hours for E4.
Metabolism	EE and E2 undergo extensive CYP-mediated metabolism (notably CYP3A4, CYP1A2, and CYP1B1), leading to catechol estrogens and further hydroxylated derivatives. EE metabolism occurs mainly via 2-hydroxylation (CYP3A4) with minor 4-, 6-, and 16β-hydroxylation, followed by glucuronidation and sulphation. E2 undergoes 2-, 4-, and 16α-hydroxylation with extensive conjugation to glucuronides and sulphates. In contrast, E4 metabolism is CYP-independent and primarily dominated by Phase II conjugation, specifically glucuronidation (UGT2B7) and sulphation (SULT1E1), resulting in inactive metabolites.
Excretion	Conjugated metabolites of estrogens are excreted in urine and faeces, with the relative contribution varying among EE, E2, and E4. Enterohepatic recirculation, particularly pronounced for E2 and EE, can prolong systemic exposure by recycling estrogen conjugates that are deconjugated by intestinal flora. EE is eliminated ~62% in faeces and ~38% in urine; E2 is mainly excreted in urine with some biliary excretion; E4 is eliminated ~69% in urine and ~22% in faeces, with minimal enterohepatic recycling.

ADME: absorption–distribution–metabolism–excretion; C_{max}: maximum plasma concentration; CYP: cytochrome P450; CYP3A4, CYP1A2, CYP1B1: specific cytochrome P450 isoenzymes; E2: estradiol; E4: estetrol; EE: ethinylestradiol; pKa: acid dissociation constant; SHBG: sex hormone-binding globulin; SULT1E1: sulfotransferase family 1E member 1; UGT2B7: UDP-glucuronosyltransferase 2B7.

Estradiol

Absorption

It is well known that orally administered crystalline E2 is poorly absorbed, and that reducing the particle size of E2 (micronisation) increases its surface area for absorption, thereby improving its rate and extent of absorption. Even then, orally administered E2 has a very low bioavailability (2–10%) due to its extensive metabolism in the gut and liver (hepatic first-pass metabolism) [1].

The rate and extent of estrogen absorption can be improved by esterification of the molecule. E2 valerate (E2V) is rapidly hydrolysed into E2 by esterases in the intestines. For this reason, oral E2 and E2V have very similar pharmacokinetics. Due to the presence of valeric acid ester in E2V and the difference in molecular weight between E2V and E2, 1 mg of E2V is equivalent to 0.76 mg of E2. The absolute bioavailability of E2 administered in a COC containing 1.5 mg E2 (as a hemihydrate) and 2.5 mg norgestrel acetate (NOMAC) was shown to be only about 1% [2]. The average plasma E2 concentration achieved with that dose of E2 at steady state was around 50 pg/mL.

After a single oral dose of the E2/NOMAC formulation, the median C_{max} was 253 pg/mL, observed at a median T_{max} of 48 hours (range, 1.0–145 hours) [3]. Corresponding values for E1 were 298 pg/mL and 6.0 hours (4.0–145 hours), respectively. Although E1 is less potent than E2, it may contribute to estrogenic effects. A clinically relevant effect of food has been observed on the bioaccumulation of E2 [2].

Distribution

Compared to a single oral dose, after multiple dosing (24 days) with E2/NOMAC, the median C_{max} and T_{max} values for E2 were significantly lower and delayed: C_{max} 36 pg/mL at 6.0 hours (0.5–144 hours), versus 253 pg/mL at 48 hours (1.0–145 hours) after a single dose [3]. Based on the area under the curve ($AUC_{0-24 h}$), E2 concentrations were approximately 55% lower at steady state compared to the concentrations after single dosing.

Because of the large pool of estrogens formed and their enterohepatic recirculation, the terminal half-life of E2 is a composite parameter, ranging from 13 to 20 hours [4].

The distribution of endogenous and exogenous E2 is similar in the circulation. In premenopausal women, approximately 37% of E2 is bound with high affinity to sex hormone-binding globulin (SHBG), and approximately 61% is loosely bound to albumin; about 2% remains unbound (free) [5]. Free E2 can enter target cells and exert biological activity. Oral administration of estrogens can cause a clinically significant increase

in SHBG-bound E2 and reduce free E2; this is not the case with typical clinical doses of parenteral estrogens.

Metabolism

Theoretically, E2 can be metabolised to a total of more than 100 unconjugated sulphated and glucuronidated compounds, a substantial number of which have been identified. Exogenous E2 is metabolised in the same manner as endogenous E2, except that the metabolites are present in much higher concentrations. Concentrations of E2 and its metabolites measured in women using E2-based COCs are always a composite of endogenous and exogenous E2 and their metabolites [4,6].

The primary circulating metabolites of orally administered E2 are E1, E1S, and E1G. These metabolites are formed from E2 in high amounts through the actions of highly active 17β -hydroxysteroid dehydrogenase type 2 (17β HSD2), sulfuryl transferase, and/or glucuronyl transferases during hepatic first-pass metabolism. As a result, E1, E1S, and E1G are markedly elevated in a highly non-physiological manner. Whereas circulating E2 concentrations are higher than those of E1 during the menstrual cycle, oral E2 produces an E1/E2 ratio of about 5:1 and can be 10 times higher in some women.

It has been shown that during the hepatic first pass, approximately 95% of the oral E2 dose is transformed by bacterial enzymes and enzymes in the intestinal mucosa and liver; 15% is absorbed as estrone (E1); 25% as E1 sulphate (E1S), 25% as E1 glucuronide (E1G), and 25% as E2G [6]. The hepatic first-pass effect is responsible for the large variability observed in circulating estrogen concentrations, both between individuals and within the same person over the course of treatment [7-9].

E1S is the principal circulating metabolite of E2. About 15% of orally administered E2 is converted to E1, and about 65% to E1S [10]. E1S appears to form a pool from which E2 can be regenerated, first by the transformation of E1S to E1 through the action of sulphatase, and then by the conversion of E1 to E2 via 17β HSD1.

Both E2 and E1 undergo extensive hydroxylation through the action of hepatic microsomal CYP450 enzymes, predominantly in rings A and D of the steroid nucleus. The major transformations result in the formation of 2- and 16α -hydroxylated metabolites, with CYP1A2 and CYP3A4 playing a major role in hepatic 2-hydroxylation of E1 and E2; CYP3A4 is a major catalyst for 16α -hydroxylation.

Another important hydroxylation of E2 and E1 occurs at carbon 4, yielding 4-hydroxy-E1 and 4-hydroxy-E2; 2- and 4-hydroxylated E1 and E2 are referred to as catechol estrogens.

The catechol estrogens have the potential to auto-oxidise into semi-quinones and quinones, posing a risk of

DNA damage and suggesting a possible carcinogenic effect. However, 2-hydroxy-E1 and 2-hydroxy-E2 can be rapidly converted to 2-methoxy-E1 and 2-methoxy-E2 by O-methyltransferase, which has been shown to have an inhibiting effect on breast cell proliferation [11]. Although the oncogenic potential of the 4-hydroxylated estrogens has been reported in male Syrian hamsters, where high renal 4-hydroxylase activity, androgen-dependent renal tissue, and local accumulation of catechol estrogens lead to kidney tumour formation, this effect is considered species-specific and has not been demonstrated in humans [12,13]. In human kidney tissue, catechol estrogen formation is low, and epidemiological studies have not identified kidney cancer as an estrogen-related malignancy [14].

16 α -hydroxy-E1 is another metabolite that has been implicated as being potentially carcinogenic. It has been proposed that this molecule can form large, stable covalent adducts with macromolecules, such as proteins and DNA. Since 16 α -hydroxy-E1 is considered a potent estrogen and 2-hydroxy-E1 is relatively inactive, a hypothesis has been proposed for approximately 30 years stating that the ratio of urinary 2-hydroxy-E1 to 16 α -hydroxy-E1 is inversely correlated with breast cancer risk and serves as a predictor of this risk [15,16]. However, there is insufficient evidence to support this hypothesis [17].

E2 and its metabolites undergo extensive conjugation, yielding sulphated and glucuronidated metabolites via the action of sulfuryl transferase and uridine diphosphate glucuronyl transferase (UGT), respectively. The conjugated metabolites also undergo deconjugation via the sulphatase and β -glucuronidase enzymes. These conjugating and deconjugating enzymes play a key role in the excretion of E2 and E1.

Excretion

E2 is cleared predominantly via urinary excretion of glucuronide and sulphate conjugates. Biliary elimination is also significant; however, most conjugated estrogens secreted into bile are reabsorbed during enterohepatic cycling. Consequently, faecal excretion reflects only the fraction of biliary metabolites that bypass reabsorption. The metabolic clearance rates (MCR) of E2 and E1 are 1,350 and 2,210 L/day, respectively [18]. The lower MCR of E2 is due to its binding to SHBG. A variety of conjugated forms of E1 and E2 are found in urine, predominantly in the form of glucuronides and to a lesser extent as sulphates.

Studies of injected radiolabelled E1, E2, and estriol (E3) in humans show that approximately 48% and 65% of injected E1 and E2, respectively, are excreted in bile [19]. Quantitatively, the most important estrogen in bile is the double conjugate, E3-3S-16G, followed by E3-16G. Both E1 and E2 are present in lower concentrations, mainly as glucuronides. These biliary estrogens undergo enterohepatic circulation, a process that involves their temporary storage in the gallbladder,

passage into the duodenum, absorption in the small intestine, and subsequent return to the liver. A small proportion of the estrogen metabolites in bile that reach the intestine are not reabsorbed but are excreted in faeces.

Estetrol

Absorption

E4 is rapidly absorbed after ingestion. Following a single oral administration of E4 at a dose of 5, 15, or 45 mg, a mean C_{max} of 6.71, 20.12, and 56.59 ng/mL was attained within 20–30 minutes [20]. The pharmacokinetic properties of E4 after oral administration of 15 mg E4 and 3 mg drospirenone (DRSP) in women show that a mean C_{max} of 17.9 ng/mL is attained at a median T_{max} of 0.5 hours [21]. When E4/DRSP is taken with a high-fat meal, relative to fasting, the geometric mean of the ratio for the C_{max} of E4 is 0.51 [21]. The pharmacokinetics of E4 in E4/DRSP are dose-proportional between 15 and 75 mg of E4 [21].

Distribution

Women who received continuous E4 treatment for 14 days at a daily dose of 15 mg reached a steady state within 6–8 days, with a mean plasma concentration of 3.2 ng/mL [20]. There was no increase in peak E4 systemic exposure. Based on AUC data, there was an approximate 2-fold increase in the extent of E4 exposure with multiple dosing compared to single administration of E4. With multiple administrations of E4/DRSP, steady state is reached after 4 days of E4 [22]. The circulating E4 concentrations are affected by enterohepatic recirculation [21].

E4 is equally distributed between red blood cells and plasma. E4 is bound moderately to albumin; it does not bind to SHBG [23,24]. Administration of three different single doses (5, 15, and 45 mg) of E4 to women showed that the terminal half-life values were 28.2, 19.2, and 26.6 hours, respectively.

Metabolism

In contrast to E2 and EE, which undergo extensive hydroxylation through the action of hepatic CYP450 enzymes, these enzymes play an insignificant role in the metabolism of E4. Instead, E4 undergoes extensive phase II metabolism in the liver to form predominantly glucuronide and, to a lesser extent, sulphate conjugates. In vitro studies show UGT2B7 and SULT1E1 are the key enzymes that catalyse glucuronidation and sulphation of E4, respectively [25]. Following oral administration of E4 to women, the primary metabolites identified in plasma were E4-16-glucuronide (62%), E4-3-glucuronide (17%), and a mixed E4 conjugate (sulphoglucuronide, 9%); no hydroxylated metabolites were found in plasma [25]. E4 was not converted back to one of the principal estrogens, E3, E2, or E1 [25].

Excretion

Following administration of a single oral dose of 15 mg of 14C-labelled E4 to postmenopausal women, 69% of the total radioactivity was recovered in urine and 22% in faeces [25]. Two primary metabolites were identified in urine during the first 6 hours after administration of 14C-E4: E4-16-glucuronide and E4-3-glucuronide (16.5%) [25]. In faeces, E4 metabolites were not identified, but some unconjugated E4 was found.

Ethinylestradiol

Absorption

Following oral administration, EE is rapidly and completely absorbed [26]. After administering 30 µg of EE to women, peak plasma EE levels of 90–130 pg/mL were found within 1–2 hours after ingestion [26]. A second EE peak appeared approximately 10–14 hours after oral EE administration, primarily due to enterohepatic recirculation. Dose-response proportionality in circulating EE levels was observed with doses ranging from 20 to 100 µg [26]. In a study of 23 premenopausal women given a COC containing EE (20 µg) and DRSP (3 mg), the EE C_{max} reached 38 pg/mL on day 1 and 70 pg/mL on day 21 of the cycle, with a T_{max} of 1.5 hours on both days [27].

The oral bioavailability of EE is approximately 45%, with considerable variability both between and within subjects, ranging from 20 to 65% [28]. Because of the large variability in EE bioavailability, the circulating EE levels produced by a specific EE dose in one woman may be indistinguishable from those generated by a higher EE dose in another woman [29]. Concomitant intake of a high-fat meal with EE (10 µg) combined with norethindrone (1 mg) in postmenopausal women showed no effect on the bioavailability of EE [30].

Distribution

Unlike E2, which binds with high affinity to SHBG, EE does not bind to this protein and is bound almost exclusively to albumin. Following oral administration of EE, the time course of plasma EE concentrations can be described by a two-compartment model in most cases, in which a rapid distribution phase is followed by a terminal disposition phase that is characterised by a half-life in the range of 5–30 hours [28]. The large range in the terminal half-life can be partly attributed to intersubject variability and to inaccurate measurement of EE.

Metabolism

In contrast to E2 metabolism, in which 2-hydroxylation and 16α-hydroxylation are quantitatively the most important pathways, 16α-hydroxylation of EE has not been reported. This is presumably due to blockage (steric hindrance) by the ethinyl group at carbon 17.

2-Hydroxylation is quantitatively the primary pathway of EE metabolism, which is catalysed by CYP3A4 [4]. Additionally, 4-, 6-, and 16β-hydroxylation appear to contribute to EE metabolism to a lesser extent [4,31].

EE and its hydroxylated metabolites undergo excessive conjugation, predominantly in the liver. EE is rapidly conjugated to EE-3G and EE-17G; these metabolites undergo rapid renal clearance. In addition, EE-3S and EE-17S circulate at concentrations approximately 10 times higher than those of EE itself [32].

Excretion

Compared to orally administered E2, more EE is eliminated in faeces than in urine. It has been shown that approximately 62% of the total radioactive EE and its metabolites were eliminated in faeces, and approximately 38% in urine, after oral administration of EE in women [33]. Conjugated forms of EE in faeces are poorly characterised. As for unconjugated EE, its faecal excretion is about 9% [4]. In urine, approximately 80% of the EE metabolites are present as glucuronides, including EE-3G, EE-17G, and EE-3G,17G [4]. Only about 8 to 10% of the EE metabolites are present in a sulphated form, and about 6% of the orally administered EE dose is found in an unconjugated form.

Drug interactions

It is well recognised that certain types of drugs can affect hormonal contraception. Drug interactions happen when the bioavailability of one drug changes that of another by altering its pharmacokinetics. CYP450 enzymes are essential in metabolising EE and E2, components of COCs, especially EE, which is the primary component of COCs. Various drugs can influence the CYP450 enzymatic pathway, acting as inducers, inhibitors, or substrates for specific CYP450 pathways. Drugs that induce this pathway may lead to subtherapeutic levels of estrogen and progestin or even contraceptive failure. Conversely, drugs that inhibit the pathway may increase estrogen and progestin levels, potentially causing toxicity. Additionally, it is important to recognise that COCs can also affect the safety and effectiveness of other medications a person is taking.

Drugs that induce hepatic CYP450 enzymes, increasing the breakdown of contraceptive hormones, are involved in most pharmacokinetic interactions affecting hormonal contraception. However, other significant interactions include those that induce vomiting or severe diarrhoea, which alter gut transit and gastric pH.

Common drugs that interfere with hormonal contraception include anti-seizure medications, anti-HIV (antiretroviral) drugs, and herbal supplements. Anti-seizure drugs such as carbamazepine, phenytoin, and topiramate are frequently used to manage epilepsy. These are enzyme inducers and can reduce the

effectiveness of hormonal contraceptives. Conversely, the opposite effect can occur with lamotrigine, another anti-seizure medication; EE in COCs induces glucuronidation of lamotrigine, significantly lowering circulating levels of lamotrigine and potentially impairing seizure control [34]. Likewise, some antiretroviral drugs, such as efavirenz, are metabolised via the enzyme system and may reduce COC effectiveness or have an opposite effect [35]. Some herbal supplements are thought to have healing properties. St. John's Wort, often used to treat depression, has been shown to significantly induce CYP3A4 activity, suggesting it could reduce the clinical effectiveness or necessitate increased doses of substrates such as EE and E2, components of COCs [36].

Previously, there were concerns that broad-spectrum antibiotics could decrease COC effectiveness by interfering with the enterohepatic circulation of EE. However, current guidance supported by available evidence indicates that antibiotics do not compromise the contraceptive efficacy of COCs [34].

For many drugs, there is no direct evidence on how they affect the efficacy of COCs. Often, we must rely on extrapolating data from studies of other drug interactions to predict potential effects on COCs.

Genetic and ethnic variability in estrogen pharmacokinetics and implications for contraceptive use

The pharmacokinetics of estrogens, including absorption, distribution, metabolism, and excretion, as previously described, show considerable variability influenced by both genetic and ethnic factors. Estrogens (except E4) are mainly metabolised in the liver through pathways involving cytochrome P450 enzymes, particularly CYP1A1, CYP1B1, and CYP3A4, which catalyse hydroxylation reactions. Follow-up conjugation by enzymes such as catechol-O-methyltransferase (COMT), sulfotransferases (SULTs), and UGTs helps in the excretion of estrogen metabolites. Polymorphisms in the genes encoding these enzymes can result in differences in enzyme activity between individuals, affecting their estrogen metabolism rates [37,38]. For instance, polymorphisms in the CYP1B1 gene can alter the hydroxylation pattern of estrogens, potentially modifying their biological activity and influencing disease risk [39,40]. Similarly, variations in the COMT gene influence the methylation of catechol estrogens, compounds involved in carcinogenesis [14,41]. These genetic differences may contribute to variations in individual susceptibility to hormone-related cancers and influence the effectiveness and safety of estrogen-based therapies.

Ethnic differences further influence variability in estrogen pharmacokinetics. These variations may stem from differences in allele frequencies of genes encoding metabolic enzymes and transporters across populations. For example, studies have shown that African American women have higher circulating estrogen levels compared to Caucasian women, which could be due to genetic differences affecting hormone metabolism [42,43].

Additionally, pharmacokinetic studies have shown differences in how contraceptive steroids are metabolised among various ethnic groups. For example, research comparing Japanese and Caucasian women revealed notable differences in the pharmacokinetics of a combined oral contraceptive, indicating that ethnic background can impact drug metabolism efficacy [44,45].

The interaction between genetic and ethnic factors in estrogen metabolism has important clinical implications, especially regarding hormonal contraceptives. Variations in enzyme activity caused by genetic polymorphisms can influence how contraceptive steroids are metabolised, potentially changing their effectiveness and the likelihood of side effects. For instance, polymorphisms in the UGT2B7 gene have been linked to differences in the metabolism of EE, a common ingredient in oral contraceptives, which may impact the risk of venous thrombosis in users [46].

Ethnic variations in hormone levels and metabolism also impact the effectiveness and safety of contraceptives. African American women, who generally have higher endogenous estrogen levels, may experience different contraceptive results compared to Caucasian women. Recognising these differences is crucial for healthcare providers to offer personalised contraceptive advice and choose the most suitable formulations based on an individual's genetic and ethnic background. Understanding this variability is vital for optimising estrogen-based treatments to achieve maximum efficacy and reduce adverse effects across diverse populations.

Conclusion

There are significant differences in the pharmacokinetics of the estrogens used in COCs, as summarised in Tables 1 and 2. Whereas the bioavailability of E4 is high, E2 has very low oral bioavailability, and it is moderate for EE. Following oral dosing with E2, the time to reach maximum concentration is considerably longer than with E4 or EE, although the half-life of the three estrogens is broadly similar. In contrast to E4, which undergoes limited metabolism, both E2 and EE are extensively metabolised, particularly by hepatic CYP3A4 enzymes. Drugs that induce CYP3A4 account for most clinically relevant pharmacokinetic interactions with hormonal contraception. Understanding these

ADME characteristics is critical for optimising efficacy and safety. EE, while potent and metabolically stable, carries a higher risk of drug interactions, whereas E2 and especially E4 follow more physiological pathways, with E4 offering advantages due to its high oral bioavailability, CYP-independent metabolism, and lower interaction potential. These distinctions are directly relevant to clinical practice: for example, St. John's wort, a strong CYP3A4 inducer, accelerates the metabolism of EE- and E2-containing contraceptives, reducing plasma levels and potentially affecting efficacy, while E4 is not expected to be affected. Finally, estrogen pharmacokinetics show significant variability by genetic and ethnic background, further supporting individualised contraceptive choices.

Current knowledge gaps

Limited long-term, head-to-head comparative data on the clinical implications of different estrogen ADME profiles in diverse populations.

Insufficient real-world pharmacogenetic studies linking specific polymorphisms to contraceptive efficacy or adverse outcomes.

Lack of robust pharmacokinetics/pharmacodynamics modelling to predict contraceptive performance across ethnic groups and in special populations (e.g., obesity, hepatic impairment).

Key messages

ADME processes shape the pharmacokinetic profiles of estrogens, influencing clinical performance.

A comprehensive understanding of the ADME characteristics of each estrogen is essential for predicting systemic exposure, drug–drug interaction potential, and variability in contraceptive efficacy and safety across populations.

EE undergoes CYP3A4-mediated metabolism, increasing interaction risk; E2 is extensively metabolized during first-pass hepatic processing; E4 avoids CYP metabolism entirely.

Pharmacokinetic properties of E4 suggest a lower potential for drug–drug interactions and possibly improved safety margins.

Genetic polymorphisms (e.g., CYP1B1, COMT, UGT2B7) and ethnic variations influence estrogen handling and may affect efficacy and safety outcomes.

Personalised contraceptive strategies incorporating pharmacogenetics and ethnic background can enhance therapeutic outcomes.

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