Drug Interactions with Contraceptives

20

Milo Gatti and Fabrizio De Ponti

20.1 Drug Interactions: Pharmacological Considerations

Drug interaction is defined as a clinical meaningful alteration in the effect of one drug (*object drug*) as a result of co-administration of another (*precipitant drug*) [1]. Although some drug interactions may be used for therapeutic benefit, usually interactions may increase or inhibit the effects of a drug, leading, respectively, to toxicity or a diminished therapeutic efficacy [1]. The probability of any drug interaction increases on the basis of the number of agents used [2]. Drug interactions may represent a major issue at any age in life, and up to 7% of hospital admission to medical wards and prolonged hospital stays are caused by serious drug interactions [3].

Drug–drug interactions may broadly be categorized as *pharmacokinetic* or *pharmacodynamic* [2]. Pharmacokinetic (PK) interactions occur when the exposure of the object drug is modified by the precipitant agent and may be caused by changes in absorption, distribution, metabolism and elimination. Conversely, pharmacodynamic interactions occur when medications cause additive, synergistic or antagonistic pharmacological effects influencing efficacy or leading to adverse effects [2]. The inhibition or induction of the activity of cytochrome P450 (CYP450) enzymes and the influence on transporters represent generally the most common and important mechanisms of drug interactions [2, 4].

An overview of the main pharmacokinetic mechanisms causing drug interactions is provided in the next section.

M. Gatti · F. De Ponti (✉)
Pharmacology Unit, Department of Medical and Surgical Sciences,
Alma Mater Studiorum, University of Bologna, Bologna, Italy
e-mail: fabrizio.deponti@unibo.it

M. C. Meriggiola, K. Gemzell-Danielsson (eds.),
Female and Male Contraception, Trends in Andrology and Sexual Medicine,
https://doi.org/10.1007/978-3-030-70932-7_20

Absorption
Three distinct mechanisms may be responsible for absorption-related drug interactions: (i) absorption may be affected by chelation with a cation (calcium or iron); (ii) changes in gastric pH may impair the absorption of agents requiring low gastric pH for dissolution; (iii) first-pass intestinal metabolism may be affected by inhibition or induction of CYP450 enzymes (especially the CYP3A4 isoform, representing almost 80% of CYPs expressed in small intestinal mucosa) or the P-glycoprotein (P-gp) efflux transporter in the intestinal epithelium [2]. Drugs affecting first-pass metabolism play an important role in interactions concerning hormonal contraceptives; particularly the induction of intestinal CYP3A4 may lead to reduced hormone levels and consequently impaired efficacy.

Distribution
Distribution of agents to the sites of action is mediated by drug influx and efflux transporters and influenced by protein binding, as only the free fraction is able to penetrate across tissue membranes [2]. Drug interactions may be caused by interference with different transporters or protein binding displacement. Protein binding displacement shows clinical relevance when the two drugs are highly protein bound (as in the case of hormonal contraceptives that have >90% binding protein), competing for the same binding site, and one of them has a low volume of distribution and narrow therapeutic window.

Metabolism
Metabolic interactions are mostly caused by CYP450 isoforms, a superfamily of microsomal enzymes playing a major role during phase I liver reactions [2]. Food, environmental features, other drugs and genetics influence cytochrome activity and consequent drug metabolism [2]. Medications interacting with the CYP450 pathway may be classified as substrates, inhibitors or inducers. Inhibitors may be further subdivided into weak, moderate or potent [2]. A summary of the main inhibitors and inducers for each CYP450 isoform is provided in Table 20.1. Glucuronidation, a phase II metabolic reaction, may be involved in clinically relevant drug interactions caused by inhibition or induction of this process.

Elimination
Inhibition of influx or efflux transporters in renal cells may impair tubular reabsorption or secretion of different medications, leading to enhanced or decreased clearance.

20.1.1 Clinical Relevance of Drug–Drug Interactions

Drug interactions should be considered clinically relevant if they lead to modified efficacy or increased toxicity and adverse effects [2]. A potential drug interaction is an occurrence in which two drugs known to interact are concurrently prescribed, regardless of the onset of adverse events [2].

Table 20.1 Summary of the most important inducers and inhibitors of CYP450 (+ weak; ++ moderate; +++ strong inhibition)

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
Inhibitors				
Ciprofloxacin +++ Levofloxacin + Amiodarone + Fluvoxamine +++	Amiodarone ++ **Fluconazole +++**	Fluoxetine + Omeprazole ++	Fluoxetine +++ Paroxetine +++ Amiodarone + Quinidine +++	**HIV protease inhibitors +++** **Clarithromycin +++** **Azole antifungals +++** Verapamil ++ Amiodarone + Diltiazem +
Inducers				
Tobacco smoke + Omeprazole +	**Rifampicin +++**	–	–	**Carbamazepine +++** **Efavirenz +++** **Nevirapine ++** **Etravirine ++** **Phenobarbital +++** **Phenytoin +++** **Rifampicin +++**

Relevant drug interactions with hormonal contraceptives are highlighted in bold. (Adapted from [8])

Although it was known since the 1970s that drug interactions could lead to serious clinical adverse events, only in 1997 was the first guidance regulatory document to industry on the conduct of premarketing drug metabolism and drug interaction studies drafted [2, 5, 6]. This occurred as a consequence of reports of sudden cardiac death in patients treated concurrently with terfenadine (able to prolong QT interval causing torsade de points) and ketoconazole (a strong inhibitory of CYP450 activity, leading to toxic plasma levels of terfenadine) [7]. Despite a large number of potential drug interactions are detected in vitro or in studies performed in healthy volunteers, predicted interactions lead to discernible toxicity or therapeutic failure only in few cases [2]. Actually, there is no consistent rating system to assess the severity and likelihood of potential drug–drug interactions, leading to a lack of consensus on decision whether to change therapy [2]. Only few drug–drug interactions may be considered clinically relevant, resulting in serious and life-threatening adverse events or in therapeutic failure. The concept of *interaction iceberg* can be put forward to underline the fact that in a real-world setting, clinically relevant drug interactions occur only when several concomitant factors concur in increasing the actual risk bypassing the "filters" encountered at each stage from the bottom (where potential drug interactions are found) to the top (where actual interactions are listed; Fig. 20.1).

The clinical relevance of a potential drug interaction depends on several factors, including the pharmacokinetic/pharmacodynamic relationship, the therapeutic index of the object drug, the proportion of the object drug affected by the specific metabolic, elimination or transport pathway that is inhibited or induced by the precipitant agent and pharmacogenomics issues (poor or extensive metabolizers of the different CYP450 isoforms are common in world population) [2]. Increased or

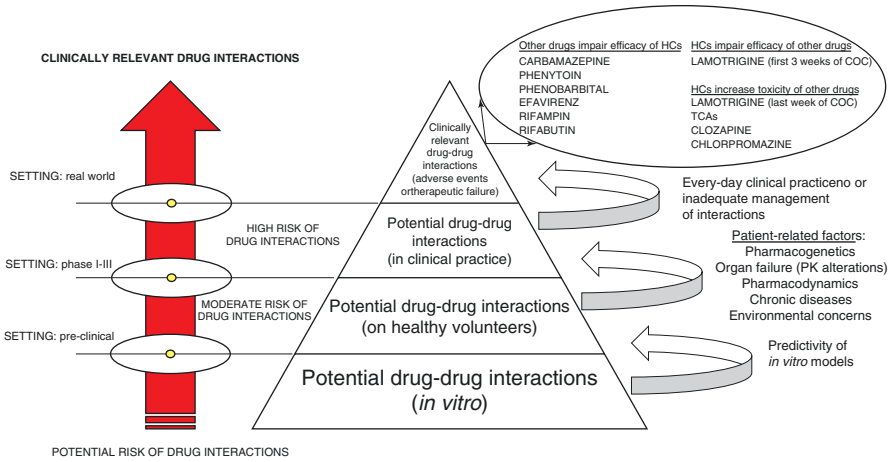

Fig. 20.1 The "interaction iceberg". Only some drug–drug interactions have clinical importance: in a real-world setting, clinically relevant drug interactions occur only when several concomitant factors concur in increasing the actual risk bypassing the "filters" encountered at each stage from the bottom (where potential drug interactions are found) to the top (where actual interactions are listed). Examples of those involving HCs are shown

decreased plasma concentrations of the object drug may be considered clinically relevant for agents characterized by narrow therapeutic window and subjected to rapid metabolism [8].

The clinical relevance of any drug interaction is closely dependent on the duration of treatment with the precipitant agent. For short-term therapies (e.g. antibiotic prophylaxis for dental procedure with once-only amoxicillin or a macrolide), the probability of affecting the bioavailability of the object drug (i.e. hormonal contraceptives – HCs) is very scarce. Conversely, for long-term (e.g. anticoagulants for management of deep vein thrombosis or rifampicin in tuberculosis) and lifelong treatments (e.g. anticonvulsant or antiretroviral agents), the risk of occurrence of clinically relevant drug interactions is higher. These different scenarios must be considered in the management of a woman treated with hormonal contraceptives.

Substitution of drugs with the same therapeutic indications or within the same drug class that are metabolized by different isozymes or separate pathways may be useful strategies to avoid potential interactions. When substitution is not feasible, careful dosing adjustment can minimize drug interactions [2].

20.1.2 Drug–Herbal Interactions

Use of herbal preparations and complementary and alternative medicine therapies is common across the globe, with no substantial difference among countries [9, 10]. In the USA, the use of herbal products is reported in approximately 20% of women of reproductive age [11]. Despite popular belief, herbal preparations and

complementary medicine therapies (food, micronutrients and dietary supplements) are not completely harmless and may affect the pharmacokinetics and pharmacodynamics of co-administered conventional drugs, leading to enhanced toxicity or therapeutic failure [12]. The most important causes of clinically relevant herbal-drug interactions are inhibition or induction of the activity of intestinal and hepatic CYP450 and influence on transporters with consequently potential alterations in absorption, distribution, metabolism and elimination of conventional drugs [12, 13].

It is important to recognize that the most clinically relevant drug–food and drug–herbal interactions are not limited to co-administration of grapefruit juice or the Saint John's wort herbal extract, but several other over-the-counter products may cause severe and life-threatening events [13]. Examples of herbal and dietary supplement capable to produce interactions with conventional drugs are provided in Table 20.2.

Table 20.2 Summary of over-the-counter products causing clinically relevant interactions with conventional drugs

Over-the-counter products	Interaction mechanisms	Clinical consequences
Fruits-vegetables-juices-other beverages		
Grapefruit—grapefruit juice—fruit derived from grapefruit (Seville orange, lime, pomelo) (*Citrus paradise—Citrus sinensis*)	Inhibition of metabolism of drugs by CYP3A4 with increasing in peak plasma concentrations	**Estrogen and progestin plasma levels may be higher and lead to enhanced toxicity** Caution with the use of oral drugs with low bioavailability (<50%) due to an extensive first-pass intestinal metabolism Risk is significant when the interval between the consumption of grapefruit and drug intake is less than 4 h
Cranberry juice (*Vaccinium macrocarpon*)	Inhibition of CYP3A4 and CYP2C9	**Estrogen and progestin plasma levels may be higher and lead to enhanced toxicity** Caution with warfarin (eight cases of bleeding) and midazolam (one case of drowsiness)
Herbal medicines		
Gingko (*Ginkgo biloba*)	Inhibition of CYP2C9 Platelet anti-aggregant activity	**Ethinylestradiol and desogestrel plasma levels may be higher and lead to enhanced toxicity** Increased bleeding risk with warfarin and nonsteroidal anti-inflammatory drugs
Garlic (*Allium sativum)*	Inhibition of intestinal first-pass extraction	**Estrogen and progestin plasma levels may be higher and lead to enhanced toxicity** Caution with warfarin (increased risk of bleeding) and saquinavir (loss of efficacy)

(continued)

Table 20.2 (continued)

Over-the-counter products	Interaction mechanisms	Clinical consequences
Echinacea (*Echinacea purpurea*)	Induction of intestinal and hepatic CYP3A4	**Potential decreased efficacy of HCs** Increased clearance of drugs metabolized by CYP3A4
St. John's wort (*Hypericum perforatum*)	Strong dose-dependent induction of intestinal and hepatic CYP1A2 – 2C9 – 3A4 – 2E1 and P-gp	**Decreased efficacy of HCs** Increased risk of therapeutic failure with drugs metabolized via CYP450
Ginseng (*Panax ginseng*)	Decreased intestinal warfarin absorption	**Use of HCs containing estrogen may enhance the risk of thrombotic events** Impairment of efficacy (warfarin) and increased risk of thrombotic effects
Goldenseal (*Hydrastis canadensis*)	Strong inhibitor of CYP2D6 and CYP3A4	**Ethinylestradiol and progestins plasmatic levels may be higher and lead to enhanced toxicity** Increased risk of toxicity with concomitant drugs metabolized via CYP450
Salvia (*Salvia officinalis*)	Inhibition of CYP2C9	**Ethinylestradiol and desogestrel plasmatic levels may be higher and lead to enhanced toxicity** Increased risk of bleeding with warfarin
Micronutrients and dietary supplements		
Calcium	Hypercalcemia	Avoid combination with digoxin
Calcium, iron, magnesium, zinc, aluminium	Chelation and reduced bioavailability of different drugs	Avoid combination with tetracyclines, fluoroquinolones and bisphosphonates
Tyramine	Enhanced activity in case of inhibition of MAO and increasing risk of life-threatening hypertensive crisis	Avoid combination with linezolid and antidepressants inhibiting MAO
L-Tryptophan	Precursor of serotonin	Increased risk of serotoninergic syndrome in combination with selective serotonin reuptake inhibitors
Vitamin B6	Pharmacodynamic stage impaired	**Decreased efficacy of oral contraceptives**

Relevant interactions with hormonal contraceptives are highlighted in bold. (Data retrieved from [12, 13])

Interactions between over-the-counter products and conventional drugs are probably underreported. Although the use of herbal products is rapidly increasing, there are only few national surveillance systems monitoring and evaluating adverse reactions associated with their use [12]. Pharmacovigilance studies are essential in order to assess safety profile and clinical relevance of interaction with conventional drugs.

20.2 Hormonal Contraceptives: Pharmacological Classification, Pharmacokinetic Issues and Impact on Drug–Drug Interactions

HCs represent one of the most common prescription classes of medications used by women of reproductive age, playing an unequivocal role in improving contraceptive efficacy and minimizing the risk of unintended pregnancies [14]. Despite the high efficacy of HC, almost 0.2–0.3% of women experience an unintended pregnancy within the first year even when usage "follows the book" [15]. Drug–drug interactions involving HCs could partially explain the impaired efficacy reported in real-life setting, so it is important to underline the pharmacokinetic issues of the different types of HC and the relationship with the mechanisms of drug interactions.

Several formulations of HCs are currently available, including either a progestin alone or a combination of estrogen and progestin, and characterized by different PK features depending on the drug used and the route of administration. PK features may explain the different likelihood for an interaction with each HC method. Drug–drug PK interactions may depend on alterations in absorption, distribution, metabolism or elimination causing impaired efficacy or toxicity of hormonal contraceptives, although the role of intestinal and hepatic first-pass metabolism represents the main issue. An overview of the different potential sites of drug interactions involving hormonal contraceptives is provided in Fig. 20.2.

HCs may be responsible for bidirectional drug interactions, which may influence effectiveness and safety of both contraceptives and concomitant drugs. Currently,

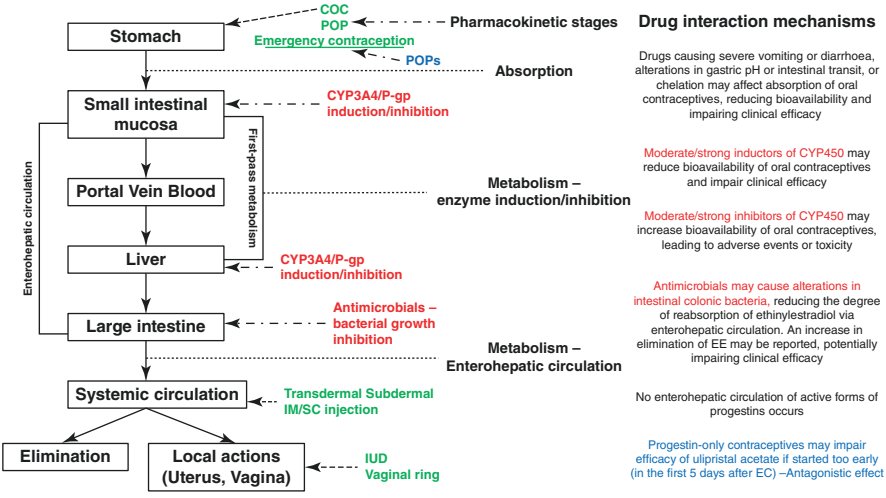

Fig. 20.2 Pharmacokinetic features of different administration routes of hormonal contraceptives and site of potential drug–drug interactions. Green, different routes of administration; red and blue, respectively, mechanisms of PK and PD drug interactions. *COC* combined oral contraceptive, *POP* progestin-only pill, *IM* intramuscular, *SC* subcutaneous, *IUD* intrauterine device; *P-gp* P-glycoprotein, *EE* ethinylestradiol. (Adapted from [71])

HC methods approved by the Food and Drug Administration (FDA) and European Agency of Medicines (EMA) included at least ten categories, of which eight are reversible contraceptive methods and two are emergency contraceptive methods (Table 20.3) [16].

Table 20.3 Classification and pharmacological consideration on different methods of HC approved by the FDA and the EMA. (Adapted from [16])

Hormonal contraceptives	Route of administration	Dosing frequency	Pharmacological consideration
Combined oral contraceptive (COC)	Oral	A pill every day for a complete cycle of 28 days (placebo in the fourth week)	First-pass metabolism with inter- and intra-variability in bioavailability **Higher risk of drug interactions compared to nonoral route**
Progestin-only pills (POPs)	Oral	A pill every day at the same daytime for a complete cycle of 28 days (placebo in the fourth week)	First-pass metabolism with inter- and intra-variability in bioavailability **Higher risk of drug interactions compared to nonoral route. Low-dose progestin in POPs may be responsible for contraceptive failure in concomitant treatment with moderate or strong inducers of CYP450**
Levonorgestrel 1.5 mg – emergency contraception	Oral	Within 3 days after unprotected intercourse	First-pass metabolism with inter- and intra-variability in bioavailability **Relevant drug interactions may occur only in case of ongoing long-term treatments with moderate or strong inducers of CYP450**
Ulipristal acetate – Emergency contraception	Oral	Within 5 days after unprotected intercourse	First-pass metabolism with inter- and intra-variability in bioavailability **Relevant drug interactions may occur only in case of ongoing long-term treatments with moderate or strong inducers of CYP450**
Contraceptive patch – ethinylestradiol/ norelgestromin	Dermal	Put on a new patch each week for 3 weeks (21 total days). No patch during the fourth week	Similar to COC, but gastrointestinal absorption and first-pass metabolism is avoided. Following the first application of the patch, serum hormone levels increase gradually over the first 48–72 h reaching a plateau and then remain constant up to 21-day period **High risk of drug interactions with strong inducers of CYP450**

Table 20.3 (continued)

Hormonal contraceptives	Route of administration	Dosing frequency	Pharmacological consideration
Levonorgestrel-releasing intrauterine devices (LNG-IUDs)	Intrauterine	Up to 3–5 years according to the type	Lack of gastrointestinal absorption and first-pass metabolism. Contraceptive activity mainly at local level **Lower risk of relevant interactions compared to oral route**
Etonogestrel implant	Subdermal	Up to 3 years	Lack of gastrointestinal absorption and first-pass metabolism **Lower risk of relevant interactions compared to oral route, but higher with respect to parenteral HCs or LNG-IUDs**
Depot medroxyprogesterone acetate (DMPA)	Intramuscularly	Every 3 months	Lack of gastrointestinal absorption and first-pass metabolism **Lower risk of relevant interactions compared to oral route**
Vaginal contraceptive ring – ethinylestradiol/ etonogestrel	Vaginal	3 weeks	Similar to COC, avoiding gastrointestinal absorption and first-pass metabolism. Serum hormone levels increase immediately after ring insertion and then decrease slowly over the cycle **High risk of drug interactions with strong inducers of CYP450**

Intestinal and hepatic first-pass metabolism may lead to profound PK variations of oral contraceptives, involving absolute and relative bioavailability, resulting in wide and different levels of steroids that reach systemic circulation and sites of action. After ingestion, steroids enter the stomach and undergo dissolution. The dissolved drugs pass into the intestine where they are subjected to transformation by bacterial enzymes and enzymes in the intestinal mucosa (especially CYP3A4). The mixture of metabolized and unmetabolized drug passes the intestinal mucosa and through the portal vein blood reaches the liver [17]. At this stage, estrogens and progestins undergo additional phase I and II metabolic reactions, mainly via CYP450 and glucuronidation pathways, before reaching systemic circulation. Extensive first-pass metabolism mediated by intestinal and/or hepatic CYP450 is a key stage of metabolic pathway of oral contraceptives, leading to potential occurrence of drug–drug interactions with concomitant agents (conventional drugs, herbal products, dietary supplements) [17]. On the contrary, administration of HCs via nonoral routes effectively bypasses first-pass metabolism, thereby avoiding possible drug interactions occurring at this stage.

Apart from few exceptions, the estrogenic component of virtually all currently marketed HCs (combination oral contraceptive, transdermal patch and vaginal ring) consists of ethinylestradiol (EE) [17]. EE is absorbed from the stomach and the upper intestine during the first hour after ingestion, reaching peak concentration after 1–2 h in most women, despite that wide variability is reported [17]. EE is subjected to intestinal and hepatic metabolism (first-pass metabolism), where the 2-hydroxylation catalysed by the hepatic CYP3A4 and CYP2C9 is the most important metabolic pathway. EE is then rapidly conjugated in part to an inactive glucuronide via glucuronosyltransferase isoenzymes (UGT1A1) and is subjected to renal elimination, and in part to sulphate metabolites, which may partially deconjugate during enterohepatic recirculation to EE, adding to the active circulating levels of EE [17]. Bioavailability and elimination half-life show wide intra- and inter-variability between women, ranging from 25% to 65% and from 6 to 27 h, respectively [17]. Intestinal and hepatic first-pass metabolism plays a key role in establishing bioavailability of EE, while enterohepatic recirculation may affect elimination half-life. While oral administration of EE shows a peak-trough fluctuating pattern in serum levels, transdermal and vaginal dosing are not affected by first-pass metabolism, leading to more constant levels [17].

Progestins contained in HCs may be classified into four generations based on chemical structure (related to progesterone or testosterone). They present larger inter- and intra-variability in metabolism, blood levels and pharmacokinetic parameters [17]. Many of the progestins used for oral contraception are prodrugs requiring to be metabolized for activation [17]. They are subjected to intestinal and hepatic first-pass metabolism and are well absorbed, although differences in bioavailability among different progestins are reported. The major metabolic transformation consists in reduction via CYP3A4. Successively, the unreduced and reduced progestins are subjected to hydroxylation and conjugation to form sulphates or glucuronides, which will be eliminated by the kidney [17]. Norethindrone and dienogest have relatively low half-lives, ranging from 8 to 12 h, while cyproterone acetate shows the longest half-life (50–80 h), followed by drospirenone (almost 30 h) [17]. Other progestins show half-life ranging from 12 to 24 h [17, 18]. A summary of pharmacokinetic parameters of EE and progestins, with a focus on the role of CYP450 in their metabolism, is provided in Table 20.4.

Emergency contraception includes levonorgestrel and ulipristal acetate. Levonorgestrel is a synthetic progestin available in a single dose of 1.5 mg for emergency contraception [19]. It does not undergo first-pass metabolism and has 100% bioavailability [19]. Levonorgestrel is highly protein bound (almost 99%), and any displacement to the bound protein could potentially lead to adverse events (drug–drug interactions with other highly bound agents) [19]. It is metabolized by CYP450 and metabolites are excreted in urine and faeces (terminal half-life almost 24 h).

Ulipristal acetate is a selective progesterone receptor modulator, available in a single dose of 30 mg [19]. It is highly bound to plasma proteins (>98%), including albumin, and it is metabolized by hepatic CYP3A4 [19]. Ulipristal acetate has a terminal half-life of almost 30 h. Induction or inhibition of the activity of CYP450 with ulipristal administration is not reported; however it may be a strong inhibitor

Table 20.4 Summary of pharmacokinetic aspects of HCs. (Adapted from [32, 35]; data retrieved from [17])

Hormonal contraceptive	Available delivery routes	Bioavailability	Protein binding	Clearance	CYP substrate	CYP inhibitor	CYP inducer	UGT1A1
Estrogen								
Ethinylestradiol	Oral Transdermal Vaginal ring	25–65% (oral)		Urine Faeces	3A4 2C9 *Minor pathway* 1A2, 2C19, 3A5	2B6 2C19 3A4 (only in vitro)	2A6 (only in vitro)	Substrate Inducer
Estradiol valerate	Oral	3–5% High first-pass metabolism (>95%)	97–98%	Urine (90%)	3A4, 1A2, 2C8, 2C9, 3A5	1A2 (unknown strength)	3A4 (unknown strength)	Substrate
Progestins								
First generation: derived from 17-hydroxyprogesterone or testosterone								
Medroxyprogesterone acetate	IM SC	100%		Faeces	3A4	–	3A4 (almost 25%)	–
Norethisterone	Oral	49–73%	>95%	Urine	3A4	2C9 (weak and only in vitro) 3A4 (modest)	–	Substrate
Second generation: derived from testosterone								
Levonorgestrel	Oral IUD Subdermal	100% (no first-pass metabolism)	98.5%	Urine Faeces	3A4	3A4 2C19 (weak and only in vitro)	-	Substrate (minor)
Norgestrel	Oral	100%	>98%	Urine Faeces	3A4	–	–	–

(continued)

Table 20.4 (continued)

Hormonal contraceptive	Available delivery routes	Bioavailability	Protein binding	Clearance	CYP substrate	CYP inhibitor	CYP inducer	UGT1A1
Third generation: derived from levonorgestrel								
Desogestrel	Oral	70% prodrug converted to etonogestrel	96–99%	Urine Bile Faeces	2C9 (only data in vitro)	–	–	Substrate
Etonogestrel	Vaginal ring Subdermal	70%	96–99%	Urine	3A4	3A4 (weak and only in vitro)	–	Substrate
Gestodene	Oral	99%	98–99%	Urine Bile	3A4	3A4 (potent in vitro – no clinical relevance at usual doses)	–	–
Norgestimate	Oral	95–100% prodrug converted to norelgestromin and norgestrel	>97%	Urine Faeces	3A4	3A4 (weak and only in vitro)	–	–
Norelgestromin	Transdermal	95–100% undergoes hepatic metabolism to norgestrel	>97%	Urine Faeces	3A4	–	–	–
Fourth generation: non-ethylated estranges (antiandrogen and antimineralocorticoid activity)								
Drospirenone	Oral	76–85%	95–97%	Urine Faeces	3A4 (minor)	3A4 2C19 1A1 2C9 (in vitro – not relevant)	–	–

IM intramuscular, *SC* subcutaneous, *IUD* intrauterine device, – available data show no inducing or inhibitory activity on CYP450 or UGT1A1

of P-gp at clinically relevant concentration [19]. Pharmacodynamic interactions between ulipristal acetate and progestin-containing HCs are reported [19]. Quickly starting hormonal contraceptives after ulipristal acetate administration may reduce effectiveness of emergency contraception. Hormonal contraception may not be started until 12 days following ulipristal acetate administration, as reported in the Summary of Product Characteristics (antagonistic pharmacodynamic interactions between progestins and ulipristal) [19].

20.3 Clinically Relevant Drug Interactions Involving HCs

Several classes of drugs may potentially interact with HCs, leading to enhanced toxicity caused by higher estrogen and progestin plasma concentrations or impairment of efficacy and occurrence of unintended pregnancies. Women of reproductive age requiring HCs may face different scenarios with specific concerns to be addressed.

First, it is expected that strong or moderate inducers of CYP3A4, namely, carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin and St. John's wort (see Table 20.1), may lead to clinically relevant interactions and affect efficacy of HCs.

Second, women of reproductive age may require therapeutic management with drugs able to cause teratogenicity (e.g. isotretinoin, carbamazepine, valproate, phenytoin, warfarin). In this case, effective contraceptive strategies must be provided to these patients, in order to avoid the consequences of unintended pregnancies. Clinicians should be aware of potential efficacy-impairing drug interactions between teratogenic agents and HCs. Particularly, different antiepileptic drugs with teratogenic potential (carbamazepine and phenytoin) are also strong inducers of CYP3A4. It is important that clinicians manage potential interactions, prescribing agents having lower teratogenic risk or unable to interact with hormonal contraceptives whenever possible. In case a teratogenic agent with strong or moderate induction activity on CYP3A4 cannot be withdrawn, alternative contraceptive methods must be implemented.

Third, women of reproductive age may be affected by different disease conditions requiring long-term or lifelong treatment. Indeed, several chronic diseases may lead to organ failure and consequently increase the risk of clinically relevant drug interactions. Epileptic disorders, tuberculosis, HIV infection and psychiatric illnesses are common worldwide, with women of reproductive age representing a non-negligible subgroup. Different therapeutic strategies may be implemented in low- and middle-income countries, based on the difference in drug access (see below Sect. 22.3 concerning HIV treatment). Women living in developing countries may have limited access to alternative compounds characterized by reduced teratogenic risk or relevant interactions with HCs. Therefore, long-term or lifelong treatments lead to higher risk of drug–drug interactions, particularly when inducers of CYP450 are chronically utilized.

Finally, drug interactions may be bidirectional, and HCs may impair the efficacy or lead to severe toxicity of concomitant drugs. Poor control of the underlying diseases may be an occurring risk.

It is important to underline that the most important and relevant drug interactions involving HCs are caused by agents raising one or more of the concerns listed above. For example, carbamazepine and phenytoin are strong inducers of CYP3A4 and may lead to teratogenic events, and a long-term treatment is required with these agents. A second example, efavirenz, exhibits the same issues: lifelong treatment, strong induction of CYP3A4 and a non-negligible teratogenicity. Finally, treatment including rifampicin and rifabutin is required for several months, and the agents are strong inducers of CYP3A4. High risk of relevant drug interactions affecting contraceptive efficacy is expected in women of reproductive age treated in these settings.

20.3.1 Antiepileptic Agents

Epilepsy may have major impacts on several important aspects of life. The severity of the diseases ranges from good seizure control up to absence of seizures, to a debilitating disease requiring polytherapy that may lead to severe adverse events and drug interactions [20]. Antiepileptic agents are widely used, not only as standard treatment of epilepsy but also in the management of several non-epileptic disorders, including neuropathic pain, generalized anxiety disorders, fibromyalgia, migraine prophylaxis and bipolar spectrum disorders [21]. In many countries, women of reproductive age constitute the majority of users of anticonvulsants [22].

Because of the long-term nature of epilepsy and non-epileptic disorders requiring antiepileptic agents, the treatment is continued for many years and commonly for a lifetime. Consequently, patients will use several medications for the management of concurrent or intercurrent disorders, leading to higher risk of pharmacokinetic and pharmacodynamic drug interactions [23]. Clinicians should be aware that women in reproductive age taking hormonal contraceptives and requiring antiepileptic agents may experience bidirectional drug interactions, resulting in unintended pregnancy or increased seizure activity [24]. Although drug interactions involving hormonal contraceptives are well-established with the concomitant use of older antiepileptic agents, interactions may occur also with the use of second-generation anticonvulsants [25]. Failure rate with oral contraceptives is higher in women affected by epilepsy in comparison to healthy subjects (3–6% vs. 1%), and lack of efficacy of hormonal contraceptives is the cause of one in four unplanned pregnancies in women taking antiepileptic agents [26, 27]. Contraceptive inefficacy may represent a critical issue for women treated with anticonvulsant drugs, considering their teratogenic potential. Consequently, it is important to prevent the occurrence of clinically relevant drug interactions between hormonal contraceptives and antiepileptic agents. A brief overview of the potential bidirectional drug interactions between hormonal contraceptives and antiepileptics is provided in Table 20.5.

20.3.1.1 Effects of Antiepileptic Agents on HCs

"First-generation" antiepileptic agents including carbamazepine, phenobarbital, phenytoin and primidone are strong enzyme inducers enhancing the metabolism of both ethinylestradiol and progestins. These drugs cause also an increased amount of

Table 20.5 Bidirectional drug interactions (DDIs) between HCs and antiepileptic agents (AEDs) (green, reported no interaction; yellow, some concerns with concomitant use and increased risk of treatment failure; red, avoid concomitant use; grey, no available data; COCs, combined oral contraceptives; POPs, progestin-only pills; LNG-IUD, levonorgestrel-releasing intrauterine device). (Data retrieved from [23–25])

Antiepileptic agents	Reduction in Ethinylestradiol serum levels caused by AED	Reduction in Progestins serum levels caused by AED	Reduction in AED serum levels caused by HC	Route of HCs administration involved in DDIs
First-generation antiepileptic drugs				
Carbamazepine				COCs, POPs, progestin subcutaneous implants, LNG-IUD
Phenobarbital				COCs, POPs, progestin subcutaneous implants, LNG-IUD
Phenytoin				COCs, POPs, progestin subcutaneous implants, LNG-IUD
Valproate				COCs, vaginal ring, dermal patch
Second-generation antiepileptic drugs				
Eslicarbazepine				COCs
Felbamate*				Low-dose COCs
Gabapentin				
Lacosamide				
Lamotrigine				COCs, vaginal ring, dermal patch (for reduction in AED serum levels) COCs and POPs (for reduction in progestins serum levels)
Levetiracetam				
Oxcarbazepine				COCs, POPs
Perampanel				COCs, POPs
Pregabalin				
Retigabine/ezogabine				
Rufinamide				COCs, POPs
Stiripentol				
Tiagabine				
Topiramate				COCs
Vigabatrin				COCs
Zonisamide				

*Orphan drug

sexual hormone binding globulin, leading to decrease in free active proportion of endogenous and exogenous sexual steroid hormones. Increased risk of unplanned pregnancy is reported with the concomitant use of carbamazepine, phenytoin, phenobarbital and primidone and hormonal contraceptives, including combined oral contraceptives (COCs), progestin-only pills (POPs), levonorgestrel and etonogestrel subcutaneous implants and levonorgestrel-releasing intrauterine device (LNG-IUD) [26]. Available data suggest that the metabolism of hormone-releasing contraceptives is not affected by concomitant use of valproate [26].

As regards "second-generation" or newer antiepileptics, oxcarbazepine, eslicarbazepine, felbamate and rufinamide are moderate inducers and may reduce serum concentrations of both ethinylestradiol and progestins, leading to contraceptive failure [23, 24]. Breakthrough bleeding is reported with felbamate in women taking low-dose COCs [27]. Dose-dependent topiramate showed to induce the metabolism of ethinylestradiol, although no clinical relevance was reported with low doses used for migraine prophylaxis [24]. Lamotrigine and high-dose perampanel showed to induce progestins metabolism, leading to the possible occurrence of contraceptive failure, particularly with low-dose POPs [23, 24]. Breakthrough bleeding and increased levels of follicular stimulating hormone (FSH) and luteinizing hormone (LH) were reported in women concomitantly treated with lamotrigine and low-dose COCs [28]. Reduced ethinylestradiol levels were reported in 2 of 13 healthy women taking COCs and vigabatrin, although clinical relevance is unknown [26].

Available data suggest that metabolism of HCs is not significantly affected by the concomitant administration of gabapentin, lacosamide, levetiracetam, retigabine, zonisamide or tiagabine, as reported also in Summary of Product Characteristics.

In order to improve contraceptive efficacy in women treated with antiepileptic agents inducing CYP450 enzymes, it is often recommended the use of COCs containing at least 50 μg of ethinylestradiol. However, there are no published data to prove the efficacy of this therapeutic strategy, and unintended pregnancies occurred also with the use of older COCs containing more than 100 μg of ethinylestradiol (in any case, this dosage is no longer used today) [29]. The use of a COC containing a progestin dose well above the dose required for inhibition of ovulation and the continuous use of oral contraceptives without a pill-free interval (the so-called long cycle) may be useful strategies to reduce contraceptive failure [29]. However, full oral contraceptive efficacy cannot be guaranteed in women treated with strong inducer anticonvulsants. In this setting, also POPs and etonogestrel/levonorgestrel subcutaneous implants may lead to contraceptive failure. High-dose injectable progestin-only formulation (despite the several possible side effects) and LNG-IUD may be practicable alternatives for epileptic women taking strong inducers of CYP450.

20.3.1.2 Effects of HCs on Antiepileptic Agents

Ethinylestradiol may affect the metabolism and serum concentrations of some antiepileptic agents through inhibition of CYP450 isozymes or induction of UGT enzymes. Clinically relevant drug interactions were reported with the concomitant use of lamotrigine. Ethinylestradiol may enhance the metabolism of lamotrigine via

an action on UGT 1A4, leading to lower serum concentrations during the phase of HC intake, causing consequently an increased seizure frequency and seizure recurrence [23]. An increase in lamotrigine dosing of almost 50–75% may be required in women taking HCs containing ethinylestradiol [30]. Significant increasing in serum lamotrigine concentrations during the washout contraceptive week was found, leading to intermittent lamotrigine-related toxicity [23].

The concomitant administration of lamotrigine and valproate may lead to avoidance of the above interaction, because of the potent inhibitory activity of valproate on lamotrigine metabolism [23, 24]. Clinically relevant drug interactions involving lamotrigine are reported with the use of COCs, vaginal ring and transdermal patches containing ethinylestradiol, while metabolism of lamotrigine is not affected by the use of progestin-only contraceptive methods, thereby resulting in the best choice in order to improve seizure control while maintaining contraceptive efficacy.

Ethinylestradiol showed to modestly reduce serum valproate concentrations. However, the clinical relevance of this interaction is unclear [24].

Potential effects of HCs on other antiepileptic agents were studied only in few cases. Metabolism and activity of levetiracetam, zonisamide, lacosamide and retigabine are not affected by the concomitant use of hormonal contraceptives; however no data are available for the remaining anticonvulsants [23].

Overall, a high risk of bidirectional drug interactions is reported with the concomitant use of HCs and antiepileptic agents. However, the large number of alternatives for both anticonvulsants (almost 20 drugs showing different metabolic pathways) and HC strategies (characterized by different PK features) allows to avoid relevant and serious drug interactions in most cases.

Currently, no data are reported concerning potential interactions between emergency contraception, which implies once-only administration, and antiepileptic agents.

20.3.2 Antiretroviral Agents

Currently, more than 17 million women are affected by HIV worldwide, mainly living in low- and middle-income countries [31]. The well-proved efficacy antiretroviral therapy (ART) shifted HIV infection from a disease presenting high lethality to a chronic condition requiring lifelong treatment. The largest proportion of HIV-infected women are of reproductive age, and hormonal contraceptives play a key role in avoiding unintended pregnancy and in decreasing perinatal HIV transmission. The prevention of perinatal HIV transmission is important considering that vertical transmission actually represents a significant infection route worldwide and the teratogenic potential of several antiretroviral agents, particularly efavirenz [32].

Several classes of antiretroviral agents in different combination ART regimes are used: nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), CCR5 inhibitors, fusion inhibitors, integrase strand transfer inhibitors (INSTIs) and pharmacokinetic enhancers (boosters) [31, 32]. In Europe and the USA, the recommended first-line

regimens include an INSTI or PI in association with two NRTIs, while in low- and middle-income countries, efavirenz is recommended as the third drug in first-line ART. Nevirapine and dolutegravir represent alternative options [33].

Based on these guidelines, ART containing efavirenz is the most widely used regimen in HIV-positive women, representing a major issue in management of drug–drug interactions including HCs, given the peculiar pharmacokinetic of efavirenz.

Additionally, HIV infection is associated with high risk of several opportunistic and non-opportunistic infections, including tuberculosis and other non-tuberculous *mycobacteria*, leading to a more complex scenario concerning the occurrence of drug interactions with rifamycins [34].

The impact of different classes of antiretroviral agents on CYP450 causing potentially relevant drug–drug interactions (including co-administration of HCs) is reported in Table 20.6.

Given the relatively large number of women with HIV and the widespread use of HCs in this setting, clinicians should be aware of the significant risk of relevant drug–drug interactions, potentially impairing treatment efficacy (contraceptive failure and antiretroviral ineffectiveness).

20.3.2.1 Effects of Antiretroviral Agents on HCs

Efficacy of HCs does not seem to be affected by the concomitant use of NRTIs, INSTIs and CCR5 inhibitors, while enfurtivide is not expected to impair the pharmacokinetic of contraceptives [35, 36].

As regards NNRTIs, although studies evaluating pregnancy as main outcome are few, evidence showed a slightly higher pregnancy rate in women subjected to co-administration of oral contraceptives and efavirenz as compared to nevirapine. Also surrogate markers of ovulation were found to be higher in patients taking oral contraceptives and efavirenz [35, 36]. PK studies demonstrated that progestin levels decreased by approximately 60% in women treated with efavirenz, while ethinylestradiol concentrations were not significantly altered. Concomitant administration of nevirapine leads to decreased ethinylestradiol concentrations of almost 30–60%, while progestin levels were not affected. Additionally, no changes in hormone levels with co-administration of COCs and etravirine, rilpivirine or fosdevirine were reported [35, 36]. Contraceptive efficacy of intramuscular medroxyprogesterone acetate was not affected by co-administration of efavirenz or nevirapine, while pregnancy rates were higher among women using levonorgestrel subdermal implant concomitantly with efavirenz [36]. Significant reduction in etonogestrel levels (almost 50–70% lower) was found in women using subdermal implant and concomitantly taking efavirenz-containing ART. No difference in pregnancy rate was reported with the use of levonorgestrel implant and nevirapine. Finally, significant reduction in levonorgestrel levels was reported in emergency contraceptive pills users when efavirenz was administered [36].

As regards PIs, in women taking COCs, POPs or combined transdermal patches, no difference in surrogate markers of ovulation was reported with the concomitant administration of different PI regimens (darunavir/ritonavir or

Table 20.6 Activity on CYP450 isoforms of the different antiretroviral agents used in HIV management (–, available data show no inducing or inhibitory activity on CYP450; green, no or low potential risk of relevant drug–drug interactions; yellow, moderate risk; red, elevate risk) (data retrieved from [31, 32, 35, 36])

Antiretroviral agents	CYP450 inducer	CYP450 inhibition	Potential implication in relevant drug-drug interactions
NRTIs			
Zidovudine	-	-	
Abacavir	-	-	
Tenofovir	-	-	
Emtricitabine	-	-	
Didanosine	-	-	
Lamivudine	-	-	
Stavudine	-	-	
NNRTIs			
Efavirenz	3A4 – 2B6	3A4 – 2C9 – 2C19	
Etravirine	3A4 (weak)	2C9 – 2C19	
Nevirapine	3A4 – 2B6	-	
Rilpivirine	3A4 (weak)	-	
Delaviridine	-	3A4 – 2C9 – 2D6 – 2C19	
Fosdevirine	-	3A4 – 2D6 – 2C9 – 2C19	
PIs			
Ritonavir	3A4 – 1A2 – 2C9 – 2C19	3A4 – 2D6	
Atazanaivr	-	3A4	
Darunavir	-	3A4 – 2D6	
Fosamprenavir	3A4	3A4	
Saquinavir	-	-	
Tipranavir	1A2 –2C19 – 3A4	3A4 – 1A2 – 2C9 – 2C19– 2D6	

(continued)

Table 20.6 (continued)

Nelfinanivr	-	3A4	
Indinavir	-	3A4 – 2D6	
CCR5 inhibitors			
Maraviroc	-	2D6 (high dose)	
Vicriviroc	-	-	
Fusion inhibitors			
Enfurtivide	-	-	
INSTIs			
Dolutegravir	-	-	
Elvitegravir	2C9	-	
Raltegravir	-	-	
Pharmacokinetic enhancers			
Cobicistat	-	3A4 – 2D6 (weak)	

NRTIs nucleotide reverse-transcriptase inhibitors, *NNRTIs* nonnucleoside reverse-transcriptase inhibitors, *PIs* protease inhibitors, *INSTIs* integrase strand transfer inhibitors

lopinavir/ritonavir) [35, 36]. PK studies showed lower ethinylestradiol levels, but higher progestin concentrations, in women taking COCs, POPs or combined transdermal patches and treated with different PIs (ritonavir, atazanavir/ritonavir, lopinavir/ritonavir and darunavir/ritonavir) [35, 36]. Concurrent use of COCs or combined transdermal patches with PIs does not impair contraceptive efficacy despite the observed decreasing in estrogen levels, as the progestin component is primarily responsible for contraceptive efficacy [36]. Additionally, the higher progestin levels reported with the concomitant use of COCs, POPs or combined transdermal patches and PIs compared to controls may better preserve from unintended pregnancies.

The efficacy of depot medroxyprogesterone acetate and of etonogestrel subdermal implants are not affected by the co-administration of PIs (lopinavir/ritonavir and nelfinavir) [36]. In these women, levels of progestins administered through intramuscular or subdermal route were higher than in patients not treated with PIs. Despite the high concentrations of progestin in women treated concomitantly with HCs and PIs, enhanced toxicity was not reported [36]. However, clinicians should

carefully monitor women at high risk of increased hormone exposure for excess hormone-related toxicities, including thrombosis and hypertension.

Limited observational data suggest that the contraceptive efficacy of LNG-IUD is not impaired in women taking concomitantly ART, based on localized delivery and action of the progestin released from the device. ART is not expected to significantly affect hormone concentration in the genital tract and may be used with relative safety in well-controlled women affected by HIV infection [35].

A summary of relevant drug–drug interactions between HCs and antiretroviral agents is shown in Table 20.7.

Management of relevant drug–drug interactions reported with the co-administration of HCs and NNRTIs and/or PIs includes the following: (i) the use of combined contraceptives with minimum 30 μg of ethinylestradiol or additional methods or contraception in women taking PIs (excluded indinavir) [31], (ii) the use of intramuscular medroxyprogesterone in women taking efavirenz [31, 35] and (iii) the use of 3 mg levonorgestrel for emergency contraception (off-label use) in women treated with efavirenz [31, 32]. No specific action is required for other antiretroviral agents.

20.3.2.2 Effects of HCs on Antiretroviral Agents

A systematic review reported no effects of HCs, particularly with the use of combined oral contraceptives, levonorgestrel implants or injectable medroxyprogesterone acetate, on the efficacy of NNRTI-containing or PI-containing ART [36]. Outcomes evaluated were death, $CD4^+$ cell count or plasma viral load. Although the use of injectable medroxyprogesterone acetate may lead to immunosuppression based on the high affinity of binding to glucocorticoid receptor, clinical significance of this finding is currently unclear, and available data suggest that medroxyprogesterone acetate does not affect HIV disease progression [35].

Pharmacokinetic studies reported lower concentrations of efavirenz with the concomitant use of COCs (potentially caused by inducing activity of ethinylestradiol on CYP3A4 involved in efavirenz metabolism) and slightly higher nevirapine concentrations in women after the administration of medroxyprogesterone acetate, although clinical relevance is unknown and HIV disease progression was not affected [36].

As regards PIs, co-administration of COCs led to slight increase in atazanavir levels, while combined transdermal patches may decrease concentrations of lopinavir and ritonavir, although clinical significance remains unknown [36]. Concentrations of saquinavir and darunavir were not affected by concomitant use of COCs.

No alterations in pharmacokinetic parameters were found with the concomitant use of NRTIs and maraviroc with COCs or medroxyprogesterone acetate [35, 36].

Overall, the most clinically significant drug–drug interactions with the concomitant use of antiretroviral agents and HCs involved efavirenz-containing ART. This is

Table 20.7 Effects of antiretroviral agents on efficacy of different hormonal contraceptive methods (green, no or low risk of significant drug–drug interactions; yellow, some concerns; red, high risk, avoid association; grey, no available data) (data retrieved from [31, 32, 35, 36])

Antiretroviral agents	COC	POP	IM/SC injection	Progestin implants
NRTIs				
Zidovudine				
Abacavir				
Tenofovir				
Emtricitabine				
Didanosine				
Lamivudine				
Stavudine				
NNRTIs				
Efavirenz				
Etravirine				
Nevirapine				
Rilpivirine				
Delaviridine				
Fosdevirine				
PIs				
Ritonavir				
Atazanaivr				
Darunavir				
Fosamprenavir				
Saquinavir				
Tipranavir				
Nelfinanivr				
Indinavir				

Table 20.7 (continued)

CCR5 inhibitors				
Maraviroc				
Vicriviroc				
Fusion inhibitors				
Enfurtivide				
INSTIs				
Dolutegravir				
Elvitegravir				
Raltegravir				
Pharmacokinetic enhancers				
Cobicistat				

NRTIs, nucleotide reverse-transcriptase inhibitors; NNRTIs, nonnucleoside reverse-transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors; COC, combined oral contraceptive; POP, progestin-only pill; IM, intramuscular; SC, subcutaneous

a major issue in women living in low- and middle-income countries given that efavirenz-containing ART is recommended as first-line therapy for HIV infection. Clinicians should be aware of this significant drug interaction, strictly monitoring women treated with efavirenz and HCs and recommending additional and/or alternative contraceptive strategies.

20.3.3 Antitubercular Agents

Approximately ten million people every year develop new cases of tuberculosis worldwide (especially in low- and middle-income countries), of which about one third are women mostly of reproductive age. Tuberculosis requires long-term treatment with a combination regimen including isoniazid, rifampicin, pyrazinamide and ethambutol, while infections caused by non-tuberculous *mycobacteria* require management with rifampin or other rifamycin antibiotics [34]. It is important to underline that rifamycins are moderate to strong inducers of CYP450, leading to several clinically relevant drug interactions, also involving HCs. Given the relatively large number of women with tuberculosis and the widespread use of HCs in this setting, clinicians should be aware of the significant risk of relevant drug–drug interactions, potentially impairing treatment efficacy (contraceptive failure and antitubercular ineffectiveness).

20.3.3.1 Effects of Antitubercular Agents on HCs

A recent systematic review assessed the risk of significant drug interactions between rifamycins and COCs [37]. No studies evaluated nonoral formulations of HCs. Although no evidence directly assessing the risk of pregnancy are reported, surrogate markers of contraceptive efficacy showed more common events of breakthrough bleeding in women affected by tuberculosis and managed with concomitant COCs and rifampicin [37]. PK studies confirmed these findings, showing reduction in estrogen and progestin levels when COCs were co-administered with rifampicin.

Additionally, rifabutin caused significant reduction in estrogen and progestin exposure. However, rifampicin resulted in larger reduction concentrations for both ethinylestradiol and norethisterone compared to rifabutin [37]. PK parameters of COCs were not affected by co-administration of rifamixin (as expected on the basis of PK features, since rifamixin is only poorly absorbed) and rifalazil, while no studies evaluated potential interactions between rifapentine and HCs. Rifapentine shows intermediate level of CYP3A4 induction with respect to rifampin and rifabutin, so a similar degree of interaction would be expected [38].

Overall, the risk of clinically significant interactions leading to contraceptive failure appears to be different between rifamycins: rifampin > rifabutin > rifapentine > rifalazil ≈ rifamixin [37].

A PK study showed no variation in estrogen and progestin levels in women treated with isoniazid or streptomycin [37].

20.3.3.2 Effects of HCs on Antitubercular Agents

COCs do not appear to affect the clinical course of tuberculosis in women treated concomitantly with rifampin-containing regimes [37]. Additionally, PK parameters of rifampin were unchanged with the concomitant use of COC containing ethinylestradiol and norethindrone [37].

20.3.4 Other Antimicrobials

Antimicrobials are commonly used in reproductive-aged women. Short-term (e.g. prophylaxis for dental procedures or treatment of uncomplicated cystitis) and long-term antimicrobial treatments (e.g. outpatient treatment of community-acquired pneumonia or candidiasis vulvovaginitis) exhibit different risks in terms of potentially relevant drug interactions, since a longer length of therapy exposes to greater chance of interactions with concomitant agents. Theoretical mechanisms leading to contraceptive failure in association with antimicrobial treatment include decreasing in intestinal bacteria (implicated in enterohepatic recirculation of ethinylestradiol) and alterations in HC metabolism via CYP450. However, the contribution of enterohepatic recirculation on active ethinylestradiol circulation is limited, so the reduction in estrogen reabsorption is unlikely to produce significant effect on systemic levels. Additionally, rifampicin is the only antimicrobial known to induce CYP450 enzymes, causing relevant decrease in HC levels and possible unintended pregnancies. However, treatment with rifampicin is mainly used in tuberculosis management (see 22.3.3).

Clinical concerns of drug interactions between antimicrobials and HCs are based primarily on case reports of unintended pregnancies or on surveys limited severely by recall bias [39, 40]. Additionally, most pharmacists recommend alternative and/or additional contraceptive methods with respect to hormonal strategies in women treated with antibiotics [40, 41]. However, these alerts may result in interruption of HCs or poor compliance with antimicrobial regimens, leading to possible treatment failure with either drug. In the event that no relevant drug interaction is present, risks of treatment failure caused by poor adherence are assumed unnecessarily [40]. The existence of drug interactions between HC and non-rifamycin antibiotics is not supported by evidence reported from a recent review [40]; thereby clinicians should be aware that most women may expect no reduction in HC efficacy with the concomitant use of antimicrobials. Currently, evidence evaluated only the potential interactions with COCs, emergency contraceptives and vaginal ring. No data exist on the combination between antimicrobials and other nonoral hormonal formulations [40].

20.3.4.1 Effects of Antimicrobials on HCs

Two studies [42, 43] found no increased risk of pregnancy in oral contraceptive users treated with any type of antibiotics in comparison with women taking oral contraceptives and not treated with antimicrobial agents. Additionally, two studies [44, 45] found no higher odds of antibiotic use at the time of conception in women taking oral contraceptives experienced unintended pregnancies. However, it is important to underline that all these studies were retrospective characterized by case-control or crossover design and showed fair to poor quality and several biases, so the strength of the evidence is questionable.

Surrogate markers of contraceptive efficacy and pharmacokinetic data support the evidence of the absence of relevant effects caused by the most important classes of antimicrobials (penicillins, cephalosporins, macrolides, fluoroquinolones, tetracyclines, metronidazole, azoles) currently used in outpatient treatment on hormonal contraceptives [40, 46, 47]. Breakthrough bleeding in COCs users was reported in two women treated with ampicillin and in two taking trimethoprim/sulfamethoxazole, while a PK study reported a significant decrease in ethinylestradiol levels during co-administration with dirithromycin, a macrolide no longer available in Europe and the USA [40].

Some antimicrobials, including ciprofloxacin, macrolides, metronidazole, trimethoprim and azole antifungals, are known inhibitors of CYP450. Concomitant use of these agents and HCs may lead to increase in ethinylestradiol and progestin levels, theoretically exposing women to toxicity. Increased estrogen concentrations were found with the co-administration of erythromycin, dapsone and voriconazole, while progestin levels augmented with the co-administration of tetracycline or voriconazole (norethindrone) and erythromycin (dienogest and ulipristal acetate) [40, 47]. However, no adverse effects were reported correlating with the increasing in HC levels. In any case, clinicians should be aware of potential risks produced by estrogen or progestin exposure (e.g. thrombotic risk, weight gain, dyslipidemia).

20.3.4.2 Effects of HCs on Antimicrobials

COCs could affect the metabolism of co-administered antimicrobials, potentially leading to alterations in safety or efficacy profile. Increased azithromycin and voriconazole levels were reported with co-administration of ethinylestradiol, which may moderately inhibit several CYP450 enzymes [40, 47]. Although ethinylestradiol is not known to induce CYP450 enzymes, decreased exposure of ampicillin, cephaloridine, trovafloxacin and moxifloxacin was reported [40]. However, the clinical relevance of these potential drug interactions in terms of toxicity or treatment failure is unknown.

Overall, although current evidence is limited and incomplete, no clinically relevant drug interactions between HCs and the most common antimicrobials used in outpatient settings were reported [40]. However, clinicians should carefully monitor HC users requiring long-term antimicrobial regimens or treatment with newer antibiotics.

20.3.5 Antidepressants and Antipsychotics

Depression is a leading cause of global disability and morbidity. Almost 15% of women of reproductive age in developed countries are affected by depression, and half of them is treated with antidepressant agents [48]. Additionally, concurrent or isolated anxiety is the most common mental health disorder, and women are 60% more likely than men to experience an anxiety disorder [49]. Finally, unintended pregnancies in women with a diagnosis of schizophrenia or other psychotic disorders may have a major impact on the health of women and children and on the cost of healthcare [50]. Psychiatric disorders in women of reproductive age are associated with inconsistent or misuse of HCs [51, 52]. Clinicians should be aware of the potential drug–drug interactions involving co-administration of HCs with psychotropic medications.

A recent systematic review reported clinical and pharmacokinetic studies evaluating drug interactions between HCs and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), oral benzodiazepines, bupropion, atypical antipsychotics and chlorpromazine [52]. To the best of our knowledge, no studies reported the assessment of potential drug interactions between HCs and serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, trazodone, buspirone, monoamine oxidase inhibitors (MAOIs) or other traditional antipsychotics. Actually, no published data on the potential drug interactions between psychotropic agents and progestin-only oral contraceptives or nonoral hormonal methods are reported.

20.3.5.1 Effects of Antidepressants and Antipsychotics on HCs

Although some psychotropic agents may inhibit different CYP450 isozymes, only fluvoxamine (a SSRI) is a known inhibitor of CYP3A4 and 2C9, which are involved in hepatic metabolism of ethinylestradiol and several progestins. Additionally,

moderate or strong inhibitory effects on CYP3A4 or 2C9 enzymes were not reported for any psychotropic drugs. Consequently, limited theoretical concern exists for any of the antidepressant or antipsychotic drugs to significantly inhibit the metabolism of HCs, leading to clinically relevant interactions responsible to affect contraception-related safety [52]. A clinical study found slightly increased odds of headache in women taking HCs concomitantly with fluoxetine compared to HCs plus placebo users [52, 53]. Moreover, a greater psychomotor performance impairment was produced with the co-administration of alprazolam, lorazepam or triazolam in hormonal contraceptive users, although a correlation between symptoms and pharmacokinetic changes was not found [52–54]. Dysmenorrhoea was reported in a case of concurrent assumption of lurasidone and association of ethinylestradiol and norgestimate, despite no changes in pharmacokinetic parameters of the two hormones [55].

The potential for antidepressant and antipsychotic agents to induce the CYP450 enzymes, thus theoretically decreasing steroid hormone concentrations leading to impaired efficacy, is currently unknown [52]. Four studies (one clinical and three pharmacokinetic) investigated the potential decrease in contraceptive effectiveness caused by drug interactions [52]. No significant differences were reported in women treated concomitantly with HCs and fluoxetine, vortioxetine, ziprasidone or lurasidone in terms of unintended pregnancies or reduction in pharmacokinetic parameters predictive of hormonal efficacy (namely, AUC or C_{Max}). A study [56] reported breakthrough bleeding with the concomitant use of HCs and benzodiazepines, especially chlordiazepoxide and meprobamate. Breakthrough bleeding may be used as surrogate marker for HC efficacy, suggesting low serum hormone levels and possibly impaired suppression of ovulation.

20.3.5.2 Effects of HCs on Antidepressants and Antipsychotics

Considering possible effects of HCs on psychotropic agents, it is important to underline that ethinylestradiol inhibits CYP3A4, 1A2, 2B6 and 2C19 isozymes and induces the glucuronidation pathway, while several progestins are weak inhibitors of 3A4 and 2C19 isozymes, despite that their inhibitory activity was assessed only in vitro [17].

HCs may potentially increase the exposure of different antidepressants (duloxetine, TCAs, mirtazapine) and antipsychotics (olanzapine, clozapine, ziprasidone) metabolized via hepatic CYP1A2 [52]. Pharmacokinetic studies [57, 58] showed increased exposure and decreased clearance of amitriptyline and imipramine in women taking HCs, although the clinical relevance of these findings is unknown. Despite that TCAs are replaced by SSRIs as first-line therapy of depression, they are used for the management of chronic pain disorders (particularly neuropathic) and chronic migraine, commonly affecting women of reproduction age. Given the narrow therapeutic window and the serious events related to TCAs toxicity, clinicians should be aware of the potential relevance of drug interactions in women taking HCs. Clinically significant adverse events are reported with the use of clozapine or chlorpromazine in association with oral contraceptives, caused by metabolic inhibition of antipsychotics and increased exposure [59, 60].

Although there is no known theoretical concern for HCs to induce CYP450 enzymes and consequently affect the efficacy of psychotropic agents [52], pharmacokinetic studies [61, 62] showed significant decrease of bupropion, lorazepam and temazepam. Ethinylestradiol may inhibit CYP2B6 isozyme, involving in metabolism of bupropion from prodrug compound to active metabolite. Additionally, ethinylestradiol may induce glucuronidation via UGT1A1, increasing the metabolism and clearance of oxazepam-like benzodiazepines (such as lorazepam and temazepam), reducing serum concentrations and potentially clinical efficacy of these agents.

Overall, the limited evidence on drug interactions between psychotropic agents and HCs suggests low concern for clinically relevant interactions, although a case-by-case risk assessment should be performed, especially with the use of TCAs and clozapine.

20.3.6 Anticoagulants

The co-administration of anticoagulants (warfarin or direct oral anticoagulants – DOACs) and HCs is relatively uncommon, as several conditions requiring anticoagulant treatment occur following reproductive age [63]. However, venous thromboembolism, including drug vein thrombosis and pulmonary embolism, may affect also women of reproductive age, thereby needing limited or chronic management with anticoagulants [64]. In these women, the teratogenic effects of warfarin impose the implementation of contraceptive strategies in order to avoid the consequences of unintended pregnancies. Finally, it is important to underline that estrogen component of combined HCs may increase the thrombotic risk, possibly leading to impaired efficacy of anticoagulant treatment.

20.3.6.1 Effects of Anticoagulants on HCs

Both warfarin and DOACs are not known to show inducer or inhibitory activity on any enzymes of CYP450 system; consequently these agents are not expected to cause clinically relevant drug interactions causing impaired efficacy or toxicity of HCs [64].

Currently, there are no studies reporting negative effects of anticoagulants on HCs [64].

20.3.6.2 Effects of HCs on Anticoagulants

Warfarin is metabolized by CYP450 (mainly 2C9 isozymes), and several DOACs (namely, rivaroxaban and apixaban) are metabolized mainly via 3A4 isoform. Ethinylestradiol inhibits in vitro CYP2C9 and other microsomal isoforms, so theoretically concern exists on potential relevant drug interactions leading to enhanced anticoagulant effect and increased risk of bleeding [64]. Two case reports [63, 65] showed significantly increased international normalized ratio (INR) without concomitant bleeding in women requiring anticoagulant therapy and taking COCs or emergency contraception containing high-dose levonorgestrel. In a case series of 13 women on chronic anticoagulation for prosthetic heart valves and concomitantly

treated with injectable medroxyprogesterone acetate, sporadic increase of INR in 3 of them was reported [66]. Finally, a PK study in ten healthy women found no relevant interaction concerning CYP2C9 activity between a triphasic COC and warfarin, although plasma clearance of warfarin was reduced [67]. However, the clinical relevance of this finding is unclear.

Currently, there are no known PK drug interactions involving heparin, low molecular weight heparin (LMWH) or DOACs and HCs [64]. Treatment with heparin and LMWHs is usually limited to the first week after diagnosis of venous thromboembolism, so it is unlikely that clinically relevant interactions with HCs occur [64]. A potential PD interaction may occur with the use of HCs containing ethinylestradiol and anticoagulant agents, considering the increased thrombotic risk caused by estrogen. In this setting, ethinylestradiol may potentially affect the efficacy of anticoagulants, although no cases are reported and clinical relevance is unknown.

Overall, despite limited data, there is little evidence showing the occurrence of significant drug interactions with the concomitant use of HCs and anticoagulants, including warfarin.

20.3.7 Interactions with Herbal Products and Dietary Supplements

Use of herbal preparations and complementary/alternative medicines is common in women of reproductive age concomitantly taking HCs [11]. Several products may affect HC efficacy and safety. Additionally, for most herbal preparations or dietary supplements, the effects on HCs and the impact on contraceptive failure are still unknown [12, 13].

Unfortunately, St. John's wort (*Hypericum perforatum*) is considered worldwide a remedy for the treatment of depression, and it can induce cytochrome 3A4 isozymes, leading to relevant drug interactions when co-administered with CYP450 substrates, including hormonal contraceptives [13, 68]. Evidence showed increased risk of ovulation and breakthrough bleedings caused by decreased contraceptive efficacy in association with *Hypericum* [68]. Of the 55 drug–food interactions reported to the Netherlands Pharmacovigilance Centre Lareb, 13 reports showed the concomitant use of *Hypericum* with oral contraceptives, leading to their reduced effectiveness [13, 69].

Estrogen-containing oral contraceptives may reduce the serum levels of vitamin B6, folic acid and magnesium [13]. Decreased absorption and increased metabolism and clearance due to estrogen activity may cause drug–food interactions.

Several drug–herbal and drug–food interactions involving HCs may be predicted on the basis of pharmacokinetic and pharmacodynamic of different products used in complementary medicines, leading to impaired efficacy and unintended pregnancies [12, 13]. Clinicians should be aware that not only conventional drugs but also herbal preparations and dietary supplements may be responsible for relevant drug interactions and adverse effects. Additionally, clinicians should carefully check all ingredients contained in each herbal product or dietary supplement, considering that

some may be undeclared, and the dosage in order to assess the risk of relevant interactions and the safety profile.

20.4 Sources of Information on Drug–Drug Interactions

As new drugs and new indications for marketed medications are introduced and pharmacological knowledge expands, the recognition of occurrence of drug–drug interactions and their clinical relevance has become more difficult for clinicians. Additionally, the high number of drug interactions makes it impossible to be aware of all potential interactions. To fill this gap, several sources of information on drug–drug interactions have been developed and updated regularly as clinical decision support tools, as reported in Table 20.8 [70].

In the field of drug–drug interactions, regulatory alerts including FDA boxed warning (in the USA; https://www.levinlaw.com/fda-black-box-warning), reports of EMA concerning safety signals discussed each month in Pharmacovigilance Risk Assessment Committee (PRAC) meeting (in Europe; https://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac) and Italian Medicines Agency (AIFA; http://www.agenziafarmaco.gov.it/content/note-aifa) remarks may provide useful and updated information. Tertiary sources may provide established information in terms of drug interactions [70, 71]. They include the *Stockley's Drug Interaction* (the most relevant and accurate drug interaction resource; www.medicinescomplete.com/mc/index.htm), the *Meyler's Side Effects of Drugs* (international textbook discussing adverse drug reactions and drug–drug interactions; https://www.elsevier.com/books/meylers-side-effects-of-drugs/aronson), *Hansten and Horn Drug Interactions* (producing different textbooks on the most common drug interactions and how to manage them; www.hanstenandhorn.com/index.html) and *Facts and Comparison* (presenting detailed monographies of drug interactions; www.factsandcomparison.com). *Up-to-date* (www.uptodate.com/crlsqul/interact) is the most important electronic sources evaluating clinical relevance and management of drug–drug interactions, characterized by close updating. *Medscape* (reference.medscape.com/druginteractionchecker), *Micromedex* (www.micromedex.com) and *Drugs* (www.drugs.com/drug_interactions.html) may provide useful information on drug interactions. Despite that *Medscape Drug Interaction Checker* is widely used, caution must be exercised because it is based primarily on drugs used in the USA and it may highlight interactions with contraceptive hormones of which the clinical relevance is unknown, leading to possible wrong decisions. Finally, specific electronic sources including *Online HIV Drug Interaction Checker* (www.hiv-druginteractions.org) highlight potential drug interactions between antiretroviral drugs and other agents, including HCs.

Clinicians should remember that when using any third-party resources, the decision to follow the advice rests on individual clinical judgement about the specific risk-benefit ratio in each woman requiring treatment with HCs [71].

Table 20.8 Advantages and disadvantages of the different sources of information on drug–drug interactions

Source of information on drug–drug interactions	Advantages	Disadvantages
Regulatory alerts (FDA boxed warning, EMA reports, AIFA remarks)	– Adverse drug reactions or relevant drug interactions based on large number of cases – "Real-life" data	– It is difficult to maintain an updated overview – Scant information concerning management when both drugs are needed for compelling clinical reasons
Stockley's drug interaction	– Management of several drug interactions is proposed – Drug interactions with herbal products and dietary supplements are reported	– Resource available only upon paid subscription
Meyler's side effects of drug	– Most important drug interactions and adverse drug reactions are reported	– Textbook: may not be updated as compared to electronic sources (last edition 2016) – Resource available only upon paid subscription
Hansten and Horn drug interaction	– Monographies of relevant drug interactions – Management of common drug interactions is covered	– Textbook: may not be updated as compared to electronic sources (last edition 2019) – Resource available only upon paid subscription
Facts and comparison	– Data concerning drug interactions of several classes are reported	– Resource available only upon paid subscription
Up-to-date	– Frequent update – Assessment of clinical relevance of drug interactions – Management of drug interactions is covered	– Resource available only upon paid subscription
Micromedex	– Support to clinical decision is proposed	– Subscription resource
Drugs.com	– Free of charge – User-friendly interface – Data concerning adverse drug reactions and drug interactions of the most important classes are reported – Assessment of relevance of interaction	– Based on drugs used in the USA and may highlight drug interactions with medications not labelled in EU or characterized by unknown clinical relevance
Medscape drug interaction checker	– Free of charge – Used-friendly interface	– Based on drugs used in the USA and may highlight drug interactions with medications not labelled in EU or characterized by unknown clinical relevance
Online HIV drug interaction checker	– Free of charge – Used-friendly interface	– Only drug interactions involving antiretroviral agents

References

1. Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. Am J Geriatr Pharmacother. 2011;9(6):364–77.
2. Tannenbaum C, Sheehan NL. Understanding and preventing drug-drug and drug-gene interactions. Expert Rev Clin Pharmacol. 2014;7(4):533–44.
3. Thomsen LA, Winterstein AG, Søndergaard B, Haugbølle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007;41(9):1411–26.
4. Shapiro LE, Shear NH. Drug interactions: proteins, pumps, and P-450 s. J Am Acad Dermatol. 2002;47(4):467–84. quiz 485-8
5. US FDA. Guidance for Industry: drug metabolism/drug interactions in the drug development process: studies in vitro, 1997. Available from: www.fda.gov/cder/guidance/clin3.pdf
6. US FDA. Guidance for Industry: in vivo metabolism/drug interactions: study design, data analysis and recommendation for dosing and labelling, 1999. Available from: www.fda.gov/cder/guidance/2635fnl.pdf
7. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Torsades de pointes occurring in association with terfenadine use. JAMA. 1990;264(21):2788–90.
8. Cascorbi I. Drug interactions--principles, examples and clinical consequences. Dtsch Arztebl Int. 2012;109(33–34):546–55. quiz 556
9. Mahady GB. Global harmonization of herbal health claims. J Nutr. 2001;131(3 s):1120S–3S.
10. Tuffs A. Three out of four Germans have used complementary or natural remedies. BMJ. 2002;325(7371):990.
11. Wu CH, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the U.S. adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. Clin Ther. 2011;33(11):1749–58.
12. Oga EF, Sekine S, Shitara Y, Horie T. Pharmacokinetic herb–drug interactions: insight into mechanisms and consequences. Eur J Drug Metab Pharmacokinet. 2016;41(2):93–108.
13. Mouly S, Lloret-Linares C, Sellier PO, Sene D, Bergmann JF. Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort? Pharmacol Res. 2017;118:82–92.
14. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health. 2006;38(2):90–6.
15. Trussell J. Contraceptive failure in the United States. Contraception. 2011;83(5):397–404.
16. Casado-Espada NM, de Alarcón R, de la Iglesia-Larrad JI, Bote-Bonaechea B, Montejo ÁL. Hormonal contraceptives, female sexual dysfunction, and managing strategies: a review. J Clin Med. 2019;25(8):6.
17. Edelman AB, Cherala G, Stanczyk FZ. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. Contraception. 2010;82(4):314–23.
18. Palovaara S, Tybring G, Laine K. The effect of ethinyloestradiol and levonorgestrel on the CYP2C19-mediated metabolism of omeprazole in healthy female subjects. Br J Clin Pharmacol. 2003;56(2):232–7.
19. Matyanga CMJ, Dzingirai B. Clinical pharmacology of hormonal emergency contraceptive pills. Int J Reprod Med. 2018;2018:2785839.
20. Kaneko S. Pregnancy and quality of life in women with epilepsy. Clin Ther. 1998;20(Suppl A):A30–47. discussion A58–60
21. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs. 2008;22(1):27–47.
22. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Gulliford MC. Trends in antiepileptic drug utilisation in UK primary care 1993–2008: cohort study using the general practice research database. Seizure. 2012;21(6):466–70.
23. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)--Part 2: Pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. Clin Pharmacokinet. 2013;52(12):1045–61.

24. Reimers A, Brodtkorb E, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. Seizure. 2015;28:66–70.
25. Reimers A. New antiepileptic drugs and women. Seizure. 2014;23(8):585–91.
26. Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. Contraception. 2011;83(1):16–29.
27. Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, Burn J, Lynch SA. Population based, prospective study of the care of women with epilepsy in pregnancy. BMJ. 2000;321(7262):674–5.
28. Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. Br J Clin Pharmacol. 2006;61(2):191–9.
29. Schwenkhagen AM, Stodieck SR. Which contraception for women with epilepsy? Seizure. 2008;17(2):145–50.
30. Sabers A. Algorithm for lamotrigine dose adjustment before, during, and after pregnancy. Acta Neurol Scand. 2012;26:e1–4.
31. Tseng A, Hills-Nieminen C. Drug interactions between antiretrovirals and hormonal contraceptives. Expert Opin Drug Metab Toxicol. 2013;9(5):559–72.
32. Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. Clin Pharmacokinet. 2015;54(1):23–34.
33. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016.
34. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM, Ho CS, Hopewell PC, Keshavjee SA, Lienhardt C, Menzies R, Merrifield C, Narita M, O'Brien R, Peloquin CA, Raftery A, Saukkonen J, Schaaf HS, Sotgiu G, Starke JR, Migliori GB, Vernon A. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147–95.
35. Scarsi KK, Darin KM, Chappell CA, Nitz SM, Drug-Drug Interactions LM. Effectiveness, and safety of hormonal contraceptives in women living with hIV. Drug Saf. 2016;39(11):1053–72.
36. Nanda K, Stuart GS, Robinson J, Gray AL, Tepper NK, Gaffield ME. Drug interactions between hormonal contraceptives and antiretrovirals. AIDS. 2017;31(7):917–52.
37. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review. BJOG. 2018;125(7):804–11.
38. Aristoff PA, Garcia GA, Kirchhoff PD, Showalter HD. Rifamycins--obstacles and opportunities. Tuberculosis (Edinb). 2010;90(2):94–118.
39. Dickinson BD, Altman RD, Nielsen NH, Sterling ML, Council on Scientific Affairs, American Medical Association. Drug interactions between oral contraceptives and antibiotics. Obstet Gynecol. 2001;98(5 Pt 1):853–60.
40. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between non-rifamycin antibiotics and hormonal contraception: a systematic review. Am J Obstet Gynecol. 2018;218(1):88–97. e14
41. Masters KP, Carr BM. Survey of pharmacists and physicians on drug interactions between combined oral contraceptives and broad-spectrum antibiotics. Pharm Pract (Granada). 2009;7(3):139–44.
42. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. J Am Acad Dermatol. 1997;36(5 Pt 1):705–10.
43. Jick SS, Hagberg KW, Kaye JA, Jick H. The risk of unintended pregnancies in users of the contraceptive patch compared to users of oral contraceptives in the UK General Practice Research Database. Contraception. 2009;80(2):142–51.
44. Toh S, Mitchell AA, Anderka M, de Jong-van den Berg LT, Hernández-Díaz S, National Birth Defects Prevention Study. Antibiotics and oral contraceptive failure—a case-crossover study. Contraception. 2011;83(5):418–25.

45. Koopmans PC, Bos JH, de Jong van den Berg LT. Are antibiotics related to oral combination contraceptive failures in the Netherlands? A case-crossover study. Pharmacoepidemiol Drug Saf. 2012;21(8):865–71.
46. Devenport MH, Crook D, Wynn V, Lees LJ. Metabolic effects of low-dose fluconazole in healthy female users and non-users of oral contraceptives. Br J Clin Pharmacol. 1989;27(6):851–9.
47. Andrews E, Damle BD, Fang A, Foster G, Crownover P, LaBadie R, Glue P. Pharmacokinetics and tolerability of voriconazole and a combination oral contraceptive co-administered in healthy female subjects. Br J Clin Pharmacol. 2008;65(4):531–9.
48. Farr SL, Bitsko RH, Hayes DK, Dietz PM. Mental health and access to services among US women of reproductive age. Am J Obstet Gynecol. 2010;203(6):542. e1–9
49. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.
50. Seeman MV. Women who suffer from schizophrenia: critical issues. World J Psychiatry. 2018;8(5):125–36.
51. Hall KS, Moreau C, Trussell J, Barber J. Role of young women's depression and stress symptoms in their weekly use and nonuse of contraceptive methods. J Adolesc Health. 2013;53(2):241–8.
52. Berry-Bibee EN, Kim MJ, Simmons KB, Tepper NK, Riley HE, Pagano HP, Curtis KM. Drug interactions between hormonal contraceptives and psychotropic drugs: a systematic review. Contraception. 2016;94(6):650–67.
53. Koke SC, Brown EB, Miner CM. Safety and efficacy of fluoxetine in patients who receive oral contraceptive therapy. Am J Obstet Gynecol. 2002;187(3):551–5.
54. Kroboth PD, Smith RB, Stoehr GP, Juhl RP. Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. Clin Pharmacol Ther. 1985;38(5):525–32.
55. Chiu YY, Ereshefsky L, Preskorn SH, Poola N, Loebel A. Lurasidone drug–drug interaction studies: a comprehensive review. Drug Metabol Drug Interact. 2014;29(3):191–202.
56. Somos P. Interaction between certain psychopharmaca and low-dose oral contraceptives. Ther Hung. 1990;38(1):37–40.
57. Edelbroek PM, Zitman FG, Knoppert-van der Klein EA, van Putten PM, de Wolff FA. Therapeutic drug monitoring of amitriptyline: impact of age, smoking and contraceptives on drug and metabolite levels in bulimic women. Clin Chim Acta. 1987;165(2–3):177–87.
58. Abernethy DR, Greenblatt DJ, Shader RI. Imipramine disposition in users of oral contraceptive steroids. Clin Pharmacol Ther. 1984;35(6):792–7.
59. Gabbay V, O'Dowd MA, Mamamtavrishvili M, Asnis GM. Clozapine and oral contraceptives: a possible drug interaction. J Clin Psychopharmacol. 2002;22(6):621–2.
60. Chetty M, Miller R. Oral contraceptives increase the plasma concentrations of chlorpromazine. Ther Drug Monit. 2001;23(5):556–8.
61. Palovaara S, Pelkonen O, Uusitalo J, Lundgren S, Laine K. Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. Clin Pharmacol Ther. 2003;74(4):326–33.
62. Stoehr GP, Kroboth PD, Juhl RP, Wender DB, Phillips JP, Smith RB. Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. Clin Pharmacol Ther. 1984;36(5):683–90.
63. Zingone MM, Guirguis AB, Airee A, Cobb D. Probable drug interaction between warfarin and hormonal contraceptives. Ann Pharmacother. 2009;43(12):2096–102.
64. Culwell KR, Curtis KM. Use of contraceptive methods by women with current venous thrombosis on anticoagulant therapy: a systematic review. Contraception. 2009;80(4):337–45.
65. Ellison J, Thomson AJ, Greer IA, Walker ID. Drug points: apparent interaction between warfarin and levonorgestrel used for emergency contraception. BMJ. 2000;321(7273):1382.
66. Sönmezer M, Atabekoğlu C, Cengiz B, Dökmeci F, Cengiz SD. Depot-medroxyprogesterone acetate in anticoagulated patients with previous hemorrhagic corpus luteum. Eur J Contracept Reprod Health Care. 2005;10(1):9–14.

67. Shelepova T, Nafziger AN, Victory J, Kashuba AD, Rowland E, Zhang Y, Sellers E, Kearns G, Leeder JS, Gaedigk A, Bertino JS Jr. Effect of a triphasic oral contraceptive on drug-metabolizing enzyme activity as measured by the validated Cooperstown 5 + 1 cocktail. J Clin Pharmacol. 2005;45(12):1413–21.
68. Berry-Bibee EN, Kim MJ, Tepper NK, Riley HE, Curtis KM. Co-administration of St. John's wort and hormonal contraceptives: a systematic review. Contraception. 2016;94(6):668–77.
69. de Boer A, van Hunsel F, Bast A. Adverse food-drug interactions. Regul Toxicol Pharmacol. 2015;73(3):859–65.
70. De Ponti F, Raschi E. Interazione tra farmaci. In: Govoni S, editor. Farmacologia. Casa Editrice Ambrosiana; 2014. p. 28–38.
71. Faculty of Sexual & Reproductive Healthcare. Drug interactions with hormonal contraception. Royal College Obstetr Gynecol. 2012:1–26.