FSRH The Faculty of Sexual & Reproductive Healthcare

Clinical Guidance: Drug Interactions with Hormonal Contraception

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Drug Interactions with Hormonal Contraception

Purpose and scope

This document provides a summary of guidance for healthcare professionals on interactions between hormonal contraception and other drugs. This guidance does not consider the effects of underlying medical conditions on hormonal contraception. The recommendations can be used to guide clinical practice but they are not intended to serve alone as a standard of medical care or to replace clinical judgement in the management of individual cases.

Background

Serum levels of contraceptive hormones may be altered by concomitant use of other drugs and hormonal contraceptives may themselves alter serum levels of concomitant drugs. Therefore drug interactions should always be considered when prescribing hormonal contraception and other drugs to women; there could be a risk of contraceptive failure or other adverse effects.

Contraceptive efficacy may be affected by both changes in **pharmacokinetics** and **pharmacodynamics** of hormonal contraceptives.

- **Pharmacokinetic interactions** occur when one drug alters the absorption, distribution, metabolism or excretion of another, thereby altering its serum concentration and its effects. Therefore, drugs that reduce the absorption, metabolism or excretion of hormones may affect their bioavailability and potentially affect contraceptive efficacy.
- **Pharmacodynamic interactions** occur when one drug directly influences the clinical actions of another by synergy or antagonism. For example, progestogen-only contraception might reduce the efficacy of ulipristal acetate emergency contraception (UPA-EC) because of opposing action on progesterone receptors or vice versa.

Useful sources of information

As new drugs are introduced and pharmacological knowledge expands, information in this guidance document may become outdated. The Clinical Effectiveness Unit (CEU) strongly recommends using the guidance in conjunction with sources of information that are updated regularly including:

- British National Formulary (BNF) (www.bnf.org). The BNF App is available online.
- Stockley's Drug Interactions (www.medicinescomplete.com/mc/index.htm) – this is the most relevant and accurate drug interaction resource for the UK population. Many National Health Service (NHS) healthcare professionals can get free access to Stockley's using an OpenAthens login.
- Electronic Medicine Compendium (www.medicines.org.uk/emc) – for summary of product characteristics for most UK-licensed medicines.
- Online HIV Drug Interaction Checker (www.hiv-druginteractions.org) – highlights potential drug interactions between hormonal contraception and antiretroviral drugs.
- Clinicians should note that when using any third-party resource, the decision to follow the advice is the user's and should be based on their clinical judgement and the woman's individual circumstances.

Please note:

The Medscape Drug Interaction Checker has previously been widely used.

- Caution must be exercised with the Medscape Drug Interaction Checker. It is based primarily on drugs used in the USA and there are some inconsistencies in terms of drug interactions with contraception hormones used in the UK such as desogestrel.
- In 2011 both CEU and BNF advice changed in line with expert opinion to advise that combined hormonal contraception (CHC) users are not required to use additional contraception when taking non-enzyme-inducing antibiotics. Medscape does not reflect this advice.
- The Medscape Drug Interaction Checker may highlight interactions with contraceptive hormones of which the clinical significance is unknown. For example, drugs which inhibit hepatic enzymes may increase serum levels of contraceptive hormones. This does not affect contraceptive effectiveness, and any potential effect on contraceptive side effects or risk profile is unknown.

Drugs affecting the metabolism of hormonal contraception

Stages of metabolism

Absorption

Small intestine

- Oral ethinylestradiol (EE) and progestogens are absorbed.

Metabolism (first pass)

Liver and intestinal mucosa

- Contains Phase I enzymes (mixed-function oxidases) and Phase II enzymes, microsomal enzymes involved in the metabolism of contraceptive hormones and other drugs.
- EE and progestogens are conjugated with glucuronic acid and sulphate to form glucuronides and sulphates.
- Excreted into bile and into the small intestine.

Large intestine

- Hydrolytic enzymes from colonic bacteria cleave conjugates of EE.
- Active EE is reabsorbed from the large bowel via enterohepatic circulation.

Enterohepatic circulation

Excretion

- Active EE is excreted from urine.
- Conjugated metabolites that are not split in the bowel are excreted in faeces.

Drug interactions/effects

Absorption

- May be affected by drugs that cause vomiting or severe diarrhoea, chelating drugs and drugs that alter gastric pH or gut transit.

Metabolism – enzyme induction

- Cytochrome P-450 is the most important family of enzymes in drug metabolism.
- If cytochrome P-450 enzymes are ***induced,*** the metabolism of concomitant drugs may be increased, potentially reducing the clinical effect. Once started, these drugs may induce cytochrome P-450 enzymes within 2 days and the effects are generally maximal within 1 week. After cessation, enzymes generally return to their previous level of activity within 4 weeks.
- If cytochrome P-450 enzymes are **inhibited**, the metabolism of concomitant drugs may be decreased, potentially leading to toxicity and increased side effects.

Metabolism – enterohepatic circulation

- The degree of reabsorption of EE via the enterohepatic circulation may vary between individuals.
- There have been theoretical concerns about the effect that this reabsorption of EE may have in terms of contraceptive efficacy but to date it is unproven.
- There is no enterohepatic circulation of progestogens in their active forms and thus contraceptive efficacy is unaffected by changes in gut flora.

Types of drugs

Absorption

- Drugs that increase gastric pH (including **proton pump inhibitors**, **antacids** and **H2-receptor antagonists)** may reduce absorption and efficacy of ulipristal acetate (UPA).
- Drugs that induce diarrhoea or vomiting.

Metabolism

Enzyme inducing drugs that may **decrease** contraceptive efficacy:

- **Antiepileptics** (e.g. ***carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, topiramate***)
- **Antibacterials** (e.g. ***rifabutin, rifampicin***)
- **Antiretrovirals** (e.g. ***efavirenz, nevirapine***). ***Ritonavir*** reduces the bioavailability of estrogen and may reduce the bioavailability of progestogens by inducing glucuronidation.
- **Antidepressants** (e.g. ***St John's wort*** – a herbal preparation)
- **Others** (e.g. ***modafinil, bosentan, aprepitant, lumacaftor***).

Enzyme inhibiting drugs that may **increase** hormone levels:

- **Antibacterials** (e.g. ***erythromycin***)
- **Antifungals** (e.g. ***fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole***)
- **Antiretrovirals** (e.g. ***atazanavir***)
- **Immunosuppressants** (e.g. ***tacrolimus***)
- **Non-sterodial anti-inflammatories** (e.g. ***etoricoxib***)
- **Statins** (e.g. ***atorvastatin, rosuvastatin***)
- **Vasodilators** (e.g. ***sitaxentan sodium***).

Others

- ***Lamotrigine*** (antiepileptic) and ***griseofulvin*** (antifungal) are not thought to be enzyme-inducing drugs; however, contraceptive efficacy may be reduced by concurrent use. The clinical significance of this effect is unknown.

Effects of contraceptive hormones on other drugs

- The plasma concentration of some drugs can be altered by concurrent hormonal contraceptive use.
- Women on drugs that are affected by contraceptive hormones may require monitoring of drug levels or drug effects when starting, changing or stopping hormonal contraception. The woman's specialist and/or general practitioner should be involved in decisions to change her contraception in these situations.

Decreased levels or clinical effect

- **Antiepileptics**: Combined hormonal contraception (CHC) moderately reduce ***lamotrigine*** exposure. This can lead to decreased seizure control in the active hormone phase, and then increased ***lamotrigine*** exposure with a risk of toxicity in the hormone-free week. Desogestrel might increase ***lamotrigine*** levels and adverse effects. EE may modestly reduce ***sodium valproate*** levels.
- **Progestogen receptor modulators**: Recent evidence suggests that quick starting hormonal contraception after ***ulipristal acetate (UPA)*** for emergency contraception (EC) may reduce EC effectiveness. There is also a theoretical risk that ***ulipristal acetate*** (e.g. ***EllaOne***® for EC or ***Esmya***® for treatment of fibroids) may reduce efficacy of hormonal contraception, although this has not been demonstrated to date in clinical studies.

Possible adverse effects and/or consider some monitoring:

- **Antihypertensives:** Estrogens may increase blood pressure and antagonise antihypertensive efficacy.
- **Antidiabetics:** Estrogens may antagonise the hypoglycaemic effect of antidiabetics. The control of diabetes may be affected in some women while taking hormonal contraceptives but it is unusual for it to be seriously disturbed.
- **Anxiolytics and hypnotics:** Estrogens and progestogens may reduce plasma concentration of ***lorazepam***, ***oxazepam*** and ***temazepam***.
- **Thyroid hormones:** Estrogens may increase the requirements for thyroid hormones in hypothyroidism.

Increased levels or adverse effect

- **Immunosuppressants:** EE might increase ***tacrolimus*** concentrations and levels can be monitored by the woman's specialist if required. Theoretically ***tacrolimus*** might also increase hormonal contraceptive exposure. ***Ciclosporin*** levels may be increased by estrogens and progestogens. UPA is predicted to increase ***everolimus*** and ***sirolimus*** concentrations.
- **Dopaminergics:** ***Selegiline*** levels potentially increased by estrogens and progestogens. Increased risk of toxicity. Manufacturers advise concurrent use should be avoided. EE reduces the clearance of ***ropinirole*** by about one-third.
- **Anxiolytics and hypnotics:** Estrogen increases plasma concentrations of ***melatonin***.

Possible adverse effects and/or consider some monitoring:

- **Antifungals:** Estrogens and progestogens may increase levels of ***voriconazole***.
- **Anxiolytics and hypnotics:** Estrogens and progestogens may increase plasma concentrations of ***chlordiazepoxide***, ***diazepam*** and ***nitrazepam***.
- **Bronchodilators:** Estrogens slightly reduce the clearance of ***theophylline*** resulting in increased plasma concentrations. Reducing dosage is recommended if adverse effects occur.
- **Muscle relaxants:** Estrogens and progestogens may increase ***tizanidine*** levels and its adverse effects.
- **Potassium-sparing diuretics and aldosterone antagonists:** Additive hyperkalaemia or hypotension might occur with ***drospirenone*** and ***potassium-sparing diuretics***.
- **Retinoids:** Any adverse effects of oral contraceptives on lipids may be additive with those of ***isotretinoin***. As retinoids are teratogenic, highly effective methods of contraception (intra-uterine contraception and progestogen-only implants) are recommended. If COC together with condoms was being used, lipids could be monitored during retinoid treatment if there was a clinical concern.
- **Triptans:** COCs appear to slightly raise level of ***frovatriptan***, ***naratriptan*** and ***zolmitriptan***, but this is not thought to be clinically significant. Please refer to UKMEC as CHC is contraindicated in some women with a history of migraine.

Clinical assessment and key considerations

General points to remember

- Healthcare professionals advising on and prescribing hormonal contraception should always ask women about their current and previous drug use including prescription, over the counter, herbal, recreational drugs and dietary supplements.
  - Recent reports suggest widespread use of modafinil (an enzyme-inducing drug) as a 'smart drug' to enhance cognitive function during exam periods. Women known to be taking modafinil off-licence should be warned about the potential impact on contraceptive efficacy and be counselled regarding appropriate methods of contraception to use.

- Women using or considering hormonal contraception should be informed about the potential for interactions with other drugs and the need to seek the advice of a healthcare professional before starting any new drugs.
  - **Women can be reassured that the contraceptive efficacy of both intrauterine contraception (Cu-IUD and LNG-IUS) and injectable contraception (DMPA) are not affected by any drug interactions.**
  - Quick starting may be appropriate – consult FSRH guideline on quick starting contraception.

- Women should be advised about the importance of correct contraceptive practice during periods of illness.
  - According to recent evidence, most broad-spectrum antibiotics are non-enzyme-inducing and do not require any special precautions. No additional contraceptive precaution is required unless the antibiotics (and/or illness) cause vomiting or diarrhoea.

For women using enzyme-inducing drugs

- Women starting enzyme-inducing drugs should be advised of potential interaction with hormonal contraception and be offered a reliable method unaffected by enzyme-inducers.
- Women using enzyme-inducing drugs who require EC should be advised of the potential interactions with oral methods and offered a copper intrauterine device (Cu-IUD). If a Cu-IUD is unacceptable or unsuitable, a double dose of levonorgestrel EC (LNG-EC) can be used.
- Short-term use of enzyme-inducing drugs (<2 months) can be managed more flexibly than longer-term use. Continuing the method with consistent and careful use of condoms may be appropriate.

A note on women using teratogenic drugs

- It is essential that women of reproductive age who are taking known teratogenic drugs (e.g. methotrexate, some antiepileptic drugs and retinoids) or drugs with potential teratogenic effects should always be advised to use highly effective contraception (such as Cu-IUD, levonorgestrel intrauterine system (LNG-IUS) and progestogen-only implant) both during treatment and for the recommended timeframe after discontinuation. ***A pregnancy prevention plan should be in place to ensure there is no risk of conception.***
- Detailed information regarding teratogenic drugs is available from the UK Teratology Information Service (UKTIS) website (www.uktis.org).

Quick reference for enzyme-inducing drugs and contraception

Drug type	CHC	POP	IMP	DMPA	LNG-IUS	Cu-IUD (EC)	LNG-EC	UPA-EC
Enzyme-inducers (during use and for 4 weeks afterwards)	✗	✗	✗	✓	✓	✓	?	✗

Examples:	
Antiepileptics	carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide topiramate
Antibiotics	rifabutin, rifampicin
Antiretrovirals	***Always use the HIV Drug Interaction Checker (www.hiv-druginteractions.org) to identify potential interactions***
Antidepressants	St John's wort
Others	modafinil, bosentan, aprepitant

✗ **Known clinical interaction:** avoid use & advise alternative method

? **Potential interaction:** caution required

✓ **No clinical interaction**: method suitable

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; EC, emergency contraception; IMP, progestogen-only implant; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill: UPA, ulipristal acetate.

Norethisterone enanthate (NET-EN) is rarely used in UK practice but should be considered as for DMPA.

Quick reference for non-enzyme-inducing drugs and contraception

Drug type	CHC	POP	IMP	DMPA	LNG-IUS	Cu-IUD (EC)	LNG-EC	UPA-EC
Lamotrigine (antiepileptic; non-enzyme-inducer)	?	?	✓	✓	✓	✓	✓	✓
Griseofulvin (antifungal; non-enzyme-inducer)	✗	✗	✗	✓	✓	✓	?	✗
Drugs that alter gastric pH (e.g. antacids, H2 antagonist, proton pump inhibitors)	✓	✓	✓	✓	✓	✓	✓	?
Drugs that cause severe diarrhoea or vomiting (e.g. orlistat)	?	?	✓	✓	✓	✓	?	?
Progestogen receptor modulators (e.g. UPA)	?	?	?	?	?	✓	?	✓

✗ **Known clinical interaction:** avoid use & advise alternative method

? **Potential interaction:** caution required

✓ **No clinical interaction**: method suitable

Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; EC, emergency contraception; IMP, progestogen-only implant; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill: UPA, ulipristal acetate.

Norethisterone enanthate (NET-EN) is rarely used in UK practice but should be considered as for DMPA.

Use of contraceptive methods when woman is using an enzyme-inducer
(and within 28 days of stopping treatment)

Examples:

Antiepileptics	carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide topiramate
Antibiotics	rifabutin, rifampicin
Antiretrovirals	***Always use the HIV Drug Interaction Checker (www.hiv-druginteractions.org) to identify potential interactions***
Antidepressants	St John's wort
Others	modafinil, bosentan, aprepitant

- Women starting enzyme-inducing drugs should be advised of potential interaction with hormonal contraception and be offered a reliable method unaffected by enzyme-inducers.
- Women using enzyme-inducing drugs who require EC should be advised of the potential interactions with oral methods and offered a Cu-IUD. If a Cu-IUD is unacceptable or unsuitable, a double dose of LNG-EC may be used.
- Short-term use of enzyme-inducing drugs (<2 months) can be managed more flexibly than longer-term use. Continuing the method with consistent and careful use of condoms **may** be appropriate.

Method	Clinical recommendation
CHC	• Not advised. • Recommend an alternative method. ▶ Women taking rifampicin and rifabutin should **always** be advised to change to an alternative method. ▶ If a woman wishes choice with other enzyme-inducing drugs, consider use of a minimum 50 µg (30 µg + 20 µg) EE monophasic pill during treatment **and** for a further 28 days with a continuous or tricycling regimen plus pill-free interval of 4 days. ▶ Breakthrough bleeding may indicate low serum EE concentrations. Exclude other causes (e.g. chlamydia) and dose of EE can exceptionally be increased up to a maximum of 70 µg EE after specialist advice. ▶ Use of two patches or two rings is not recommended.
POP	• Not advised. • Recommend an alternative method.
IMP	• Not advised. • Recommend an alternative method.
DMPA **LNG-IUS**	• No interaction. • No need for extra precautions.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
LNG-EC	• Can use **DOUBLE DOSE** i.e. 3 mg (2 x 1.5 mg tablet) as a single dose within <72 hours of unprotected sexual intercourse (UPSI) if Cu-IUD is declined or unsuitable. • The effectiveness of 3 mg LNG is unknown in this situation.
UPA-EC	• Double dose not recommended • There is no evidence to support an interaction between ***ritonavir*** and ***UPA***

Use of contraceptive methods when woman is using lamotrigine

Method	Clinical recommendation
CHC	Potential risk of reduced seizure control whilst taking CHC, and potential for toxicity in the CHC-free week. The risks of using CHC may outweigh the benefits and alternative methods should be considered.
POP	• May increase lamotrigine levels. Monitor for side effects. • No need for extra precaution.
IMP DMPA LNG-IUS	• No interaction. • No need for extra precautions.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
LNG-EC UPA-EC	• No interaction. • No need for extra precautions.

Use of contraceptive methods when woman is using griseofulvin (and within 28 days of stopping treatment)

Method	Clinical recommendation
CHC	• Not advised. • Recommend an alternative method. ▶ If a woman wishes choice with griseofulvin, consider use of a minimum 50 µg (30 µg + 20 µg) EE monophasic pill during treatment **and** for a further 28 days with a continuous or tricycling regimen plus pill-free interval of 4 days. ▶ Breakthrough bleeding may indicate low serum EE concentrations. Exclude other causes (e.g. chlamydia) and dose of EE can exceptionally be increased up to a maximum of 70 µg EE after specialist advice. ▶ Use of two patches or two rings is not recommended ▶ As there is a theoretical risk of teratogenic effects with griseofulvin, use of condoms during treatment and for 28 days after is also recommended.
POP	• Not advised. • Recommend an alternative method.
IMP	• Not advised. • Recommend an alternative method.
DMPA LNG-IUS	• No interaction. • No need for extra precautions.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
LNG-EC	• Can use **DOUBLE DOSE** i.e. 3 mg (2 x 1.5 mg tablet) as a single dose within <72 hours of UPSI if Cu-IUD is declined or unsuitable.
UPA-EC	• Double dose not recommended

Use of contraceptive methods when woman is using drugs that affect gastrointestinal function

Drugs altering gastric pH

Examples: regular use of antacids, H2 antagonists and proton pump Inhibitors

The effectiveness of UPA-EC in women using medicines that increase gastric pH has not been studied and so any clinical significance of a theoretical interaction is unknown.

Method	Clinical recommendation
CHC POP IMP DMPA LNG-IUS	• No interaction. • No need for extra precautions.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
LNG-EC	• No interaction. • No need for extra precautions.
UPA-EC	• The effect of drugs that increase gastric pH is unknown. • LNG-EC or Cu-IUD (EC) should be considered.

Drugs that cause severe diarrhoea or vomiting

Examples: orlistat

Severe drug-induced diarrhoea or vomiting is predicted to reduce the bioavailability of contraceptive steroids.

Method	Clinical recommendation
CHC POP	• Follow missed pill rules if vomiting occurs within <3 hours of taking pill or severe diarrhoea occurs for >24 hours. • If persistent diarrhoea or vomiting, consider non-oral method. • Consistent use of condoms is recommended.
IMP DMPA LNG-IUS	• No interaction. • No need for extra precautions.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
EC-LNG EC-UPA	• If vomiting occurs within <3 hours of taking pill or severe diarrhoea occurs for >24 hours, a repeat dose should be given. • If persistent diarrhoea or vomiting, consider Cu-IUD (EC). • Consistent use of condoms is recommended.

Use of contraceptive methods when woman is taking progesterone receptor modulators

Ulipristal acetate

Quick starting hormonal contraception after UPA for emergency contraception may reduce EC effectiveness.

There is also a theoretical risk that UPA (e.g. ***EllaOne***® for EC or ***Esmya***® for treatment of fibroids) may reduce efficacy of hormonal contraception, although this has not been demonstrated to date in clinical studies.

Method	Clinical recommendation
CHC POP IMP DMPA LNG-IUS	• Hormonal contraception should not be quick started until 5 days following UPA administration. • Consistent use of condoms is recommended.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
LNG-EC	• LNG-EC should not be used until 5 days after UPA administration.
UPA-EC	• UPA-EC can be used more than once in the same cycle if further UPSI takes place.

The CEU is grateful to the working group that developed this resource:

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