

# Faculty of Sexual & Reproductive Healthcare Clinical Guidance



## Drug Interactions with Hormonal Contraception


Clinical Effectiveness Unit

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## ABBREVIATIONS USED

BNF	<i>British National Formulary</i>
CEU	Clinical Effectiveness Unit
CHC	combined hormonal contraception
COC	combined oral contraceptive
Cu-IUD	copper-bearing intrauterine device
DMPA	depot medroxyprogesterone acetate
EC	emergency contraception
EE	ethinylestradiol
FSRH	Faculty of Sexual and Reproductive Healthcare
HIV	human immunodeficiency virus
LNG	levonorgestrel
LNG-IUS	levonorgestrel-releasing intrauterine system
NET-EN	norethisterone enantate
PEPSE	post-exposure prophylaxis after sexual exposure to HIV
POP	progestogen-only pill
SPC	Summary of Product Characteristics
UKMEC	<i>UK Medical Eligibility for Contraceptive Use</i>
UPA	ulipristal acetate
UPSI	unprotected sexual intercourse
USMEC	<i>U.S. Medical Eligibility Criteria for Contraceptive Use</i>
WHOMEK	<i>World Health Organization Medical Eligibility for Contraceptive Use</i>

## GRADING OF RECOMMENDATIONS

- A** Evidence based on randomised controlled trials
- B** Evidence based on other robust experimental or observational studies
- C** Evidence is limited but the advice relies on expert opinion and has the endorsement of respected authorities
-  Good Practice Point where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group

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## SUMMARY OF CHANGES FROM PREVIOUS FACULTY GUIDANCE

- **Antibiotics (pages 7–9)**

Recommendations on antibiotics have changed since publication of previous Faculty guidance on *Drug Interactions with Hormonal Contraception* (2005)<sup>1</sup> and the *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC) 2009.<sup>2</sup> In line with the World Health Organization (WHO)<sup>3</sup> and *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*<sup>4</sup> the CEU no longer advises that additional precautions are required when using combined hormonal contraception (CHC) with antibiotics that are not enzyme inducers. Minor changes have been made to recommendations on concomitant use of enzyme-inducing rifamycins (such as rifabutin and rifampicin) and CHC.

- **Antiretroviral drugs (Appendices 3 and 5)**

Information on antiretroviral drugs has been updated since the 2005 version of this document.

- **Coumarin anticoagulants (e.g. warfarin)**

Use of estrogens and/or progestogens has been associated with both increased and decreased anticoagulant effect of coumarin anticoagulants. Given the lack of consistent evidence a true interaction is unlikely and is no longer included.

- **Enzyme-inducing drugs (pages 5–7, Appendix 4)**

New contraceptive options are recommended for women on short- or long-term treatment with an enzyme-inducing drug, including extended regimens and a shortened hormone-free interval when using CHC.

- **Griseofulvin**

The classification of griseofulvin as an enzyme-inducing drug originated from studies in rats<sup>5</sup> that have not been confirmed in human studies. Although menstrual disturbance and pregnancies have been reported,<sup>6–8</sup> the apparent lack of interactions of griseofulvin with many other drugs that are substrates of liver enzymes suggests that griseofulvin is not a clinically important enzyme inducer.

- **Lamotrigine (pages 4, 9,10, Appendix 6)**

As a result of new evidence, CHC is not usually recommended in women on lamotrigine monotherapy due to the risk of reduced seizure control whilst on CHC, and the potential for toxicity in the CHC-free week. Preliminary data suggest that levels of some progestogens may be slightly reduced by lamotrigine and that some progestogens may increase levels of lamotrigine, but the clinical significance is unknown and further evidence would be required to alter existing recommendations.

- **Lansoprazole**

There is good evidence that lansoprazole does not induce or inhibit the enzymes involved in the metabolism of contraceptive hormones. Therefore lansoprazole has not been listed as an enzyme-inducing drug as in previous Faculty guidance.<sup>1</sup>

- **Norethisterone enantate (page 4)**

As in previous Faculty guidance on *Drug Interactions with Hormonal Contraception*<sup>1</sup> and on *Progestogen-only Injectable Contraception*<sup>9</sup> the CEU recommends that norethisterone enantate (NET-EN) can be used with enzyme-inducing drugs without additional contraception or alteration of the dosing interval. UKMEC 2009<sup>2</sup> and WHOMEK 2010<sup>3</sup> give more cautious advice based on the product licence.

## SUMMARY OF CHANGES FROM PREVIOUS FACULTY GUIDANCE

- **Tacrolimus (Appendices 5 and 6)**

Previous Faculty guidance on *Drug Interactions with Hormonal Contraception* (2005)<sup>1</sup> contained an error indicating that tacrolimus is an enzyme-inducing drug, whereas it is in fact an enzyme-inhibiting drug (see Appendices 5 and 6).

- **Ulipristal acetate (pages 5–7, Appendices 3–5)**

Guidance is provided on potential interactions with this emergency contraceptive drug, which was introduced to the UK in 2009.

## SUMMARY OF KEY RECOMMENDATIONS

### What should be discussed with women when prescribing drugs to women using hormonal contraception?

- ✓ Health professionals supplying hormonal contraception should ask women about their current and previous drug use including prescription, over the counter, herbal, recreational drugs and dietary supplements.
- ✓ Women using hormonal contraception should be informed about the potential for interactions with other drugs and the need to seek the advice of a health professional before starting any new drugs.

### Advice for women using drugs that may reduce contraceptive efficacy

- C** All women starting enzyme-inducing drugs should be advised to use a reliable contraceptive method unaffected by enzyme inducers [e.g. progestogen-only injectable, copper-bearing intrauterine devices (Cu-IUDs) or the levonorgestrel-containing intrauterine system (LNG-IUS)].
- ✓ Women who do not wish to change from a combined method while on short-term treatment with an enzyme-inducing drug (and for 28 days after stopping treatment) may opt to continue using a combined oral contraceptive (COC) containing at least 30 µg ethinylestradiol (EE), the patch or ring along with additional contraception. An extended or tricycling regimen should be used with a hormone-free interval of 4 days. Additional contraception should be continued for 28 days after stopping the enzyme-inducing drug.
- ✓ With the exception of the very potent enzyme inducers rifampicin and rifabutin, women who are on an enzyme-inducing drug and who do not wish to change from COC may increase the dose of COC to at least 50 µg EE (maximum 70 µg) and use an extended or tricycling regimen with a pill-free interval of 4 days.
- ✓ In women using enzyme-inducing drugs with COC, breakthrough bleeding may indicate low serum EE concentrations. If other causes (e.g. chlamydia) have been excluded, the dose of EE can be increased up to a maximum of 70 µg EE.
- ✓ Women who do not wish to change from the progestogen-only pill (POP) or implant while on short-term treatment with an enzyme-inducing drug or within 28 days of stopping treatment may opt to continue the method together with additional contraceptive precautions (e.g. condoms). Additional precautions should be continued for 28 days after stopping the enzyme-inducing drug.
- ✓ Women using enzyme-inducing drugs who require emergency contraception (EC) should be advised of the potential interactions with oral methods and offered a Cu-IUD.
- C** Women who request oral EC while using enzyme-inducing drugs or within 28 days of stopping them, should be advised to take a total of 3 mg LNG (two 1.5 mg tablets) as a single dose as soon as possible and within 120 hours of unprotected sexual intercourse (UPSI) (use of LNG >72 hours after UPSI and double dose are outside the product licence).
- C** Ulipristal acetate (UPA) is not advised in women using enzyme-inducing drugs or who have taken them within the last 28 days.
- ✓ Women should be advised that UPA has the potential to reduce the efficacy of hormonal contraception. Additional precautions are advised for 14 days after taking UPA (9 days if using or starting the POP, 16 days for Qlaira®) (outside product licence).

### Advice for women using drugs that may reduce contraceptive efficacy

- ✓ Women using drugs that affect gastric pH (e.g. antacids, H2 antagonists and proton pump inhibitors) and who require EC should be offered a Cu-IUD or LNG as the efficacy of UPA may be reduced.

### What advice should be given to women using hormonal contraception and antibacterial drugs that are not enzyme inducers?

- C Additional contraceptive precautions are not required during or after courses of antibiotics that do not induce enzymes.
- ✓ Women should be advised about the importance of correct contraceptive practice during periods of illness.

### Effect of contraceptive hormones on drug metabolism

- C Women on lamotrigine monotherapy should be advised that due to the risk of reduced seizure control whilst on combined hormonal contraception (CHC), and the potential for toxicity in the CHC-free week, the risks of using CHC may outweigh the benefits.
- ✓ Women on drugs which are affected by contraceptive hormones may require monitoring of drug levels or effect when starting, changing or stopping hormonal contraception. The woman's hospital doctor and/or general practitioner should be involved in decisions to change contraception and appropriate follow-up should be arranged.







## Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit

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# FSRH Guidance (January 2011) Drug Interactions with Hormonal Contraception

(Update due by January 2016)

## 1 Purpose and Scope

This document provides guidance for health professionals on interactions between hormonal contraception and other drugs. Changes from previous Faculty guidance are summarised on pages ii and iii. This guidance does not consider the effects of underlying conditions on hormonal contraception. Recommendations are based on the evidence available at the time of writing and consensus opinion of experts. A key to the Grading of Recommendations, based on levels of evidence, is provided on the inside front cover of this document. Details of the methods used by the Clinical Effectiveness Unit (CEU) in developing this guidance are outlined in Appendix 1. The recommendations should 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. As new drugs are introduced and pharmacological knowledge expands, information in this guidance document may become outdated. The CEU strongly recommends using the guidance in conjunction with regularly updated sources of information such as those listed in Appendix 2.

## 2 Background

Serum levels of contraceptive hormones may be increased or decreased by concomitant drug use and hormonal contraceptives may themselves increase or decrease serum levels of concomitant drugs. Therefore drug interactions should be considered when prescribing medication for women who may use hormonal contraception and could be at risk of contraceptive failure or other adverse effects.

For many drugs there is a paucity of good quality, robust evidence on their interaction with hormonal contraception. Most of the available data are from case reports, observational studies, pharmacovigilance reports and studies of new contraceptive products. Pregnancies are reported in women using hormonal contraception with other drugs, but this does not necessarily mean that the concomitant medication was responsible for the contraceptive failure.

## 3 Mechanisms of Drug Interactions with Contraceptive Hormones

### 3.1 Pharmacokinetics and pharmacodynamics

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 increasing or decreasing its serum concentration and its effects.

To have a clinical effect (e.g. inhibition of ovulation or thickening of cervical mucus) there needs to be sufficient amount of hormone available at the site of action. Bioavailability of contraceptive hormones depends primarily on absorption (including secondary absorption

via the enterohepatic circulation) and metabolism (Figure 1). 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, contraceptive steroids might reduce the efficacy of antihypertensives, lipid-lowering drugs and antidiabetics because they can have opposing actions.

3.1.1 Absorption

Orally administered ethinylestradiol (EE) and progestogens are absorbed from the small intestine. Absorption may be affected indirectly by drugs that cause vomiting or severe diarrhoea, chelating drugs and drugs that alter gastric pH or gut transit.

3.1.2 Metabolism

Orally administered EE and progestogens undergo extensive 'first-pass metabolism' in the small intestinal mucosa and liver before reaching the systemic circulation.<sup>10,11</sup> EE is metabolised in the mucosa of the small intestine and in the liver, forming sulphate and glucuronide conjugates (Figure 1).

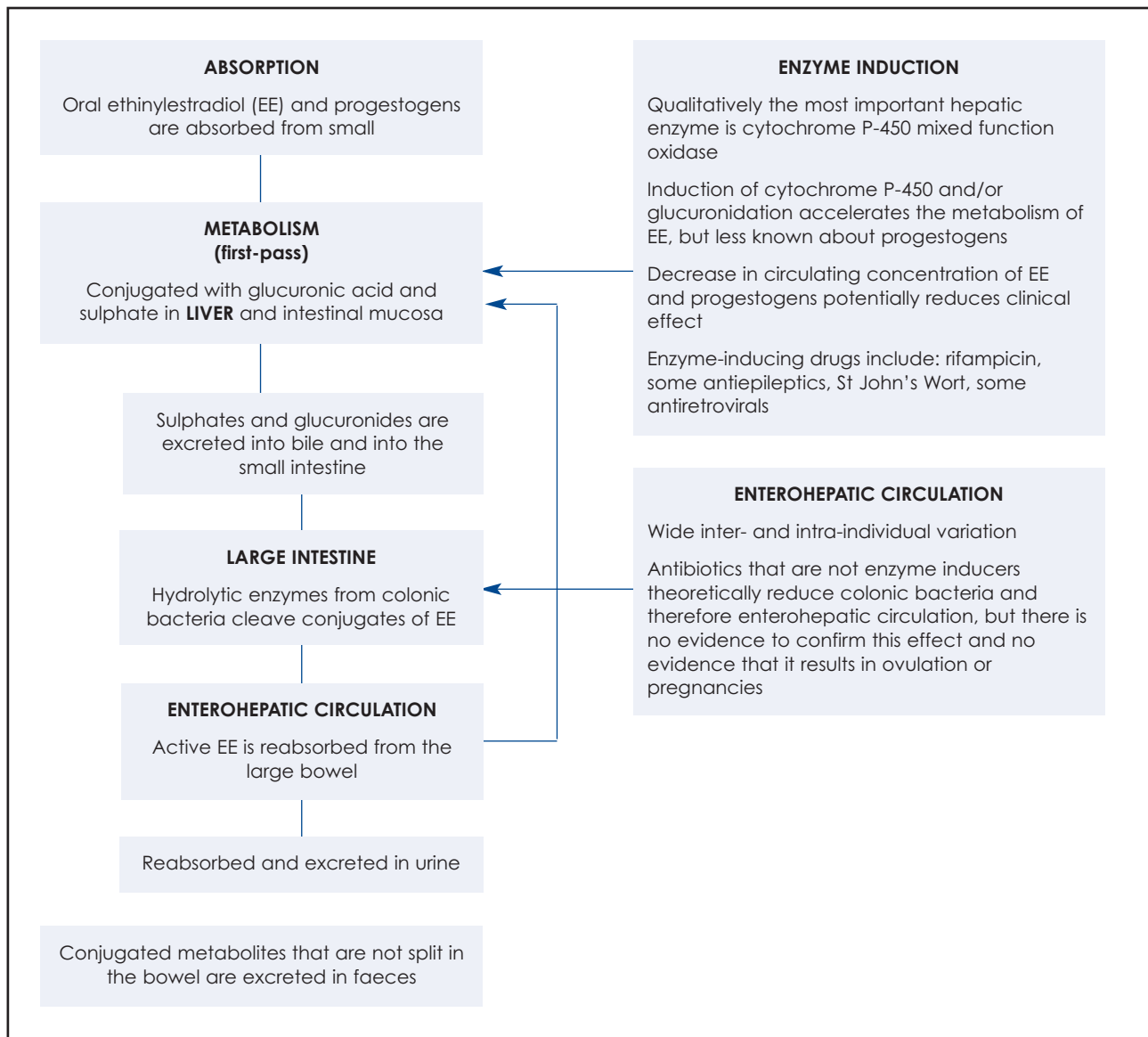


Figure 1 Pharmacokinetics of ethinylestradiol (EE) and progestogens and interaction with enzyme-inducing drugs

As much as 60% of orally administered EE undergoes first-pass metabolism and thus only 40% is bioavailable. The bioavailability of progestogens varies.

Some hormones are ingested in inactive forms (prodrugs) and are only active after metabolism. For example, mestranol is metabolised to EE; desogestrel is metabolised to etonogestrel; norgestimate is partly metabolised to levonorgestrel (LNG); and etynodiol diacetate is metabolised to norethisterone.<sup>12</sup>

Microsomal enzymes involved in the metabolism of contraceptive hormones and other drugs are found in the liver and intestinal mucosal cells. There are two types of microsomal enzymes: Phase I enzymes (mixed-function oxidases), which catalyse oxidation, reduction and hydrolysis; and Phase II enzymes, which catalyse glucuronidation, sulphation and acetylation.<sup>10,11,13</sup> Cytochrome P-450 is the most important family of enzymes in drug metabolism and CYP3A4 is the major subtype found in adult hepatocytes and intestinal mucosal cells. There is marked inter-individual variation in the activity of cytochrome P-450. Drugs that inhibit or induce cytochrome P-450 enzymes or induce glucuronidation may affect concurrent medications. In this document we use the term 'enzyme inducers' to mean inducers of cytochrome P-450 enzymes, since all of the established enzyme inducers are known to induce cytochrome P-450, although some may also induce glucuronidation.

If cytochrome P-450 enzymes are **induced** the metabolism of concomitant drugs may be increased, potentially reducing the clinical effect. Drugs known to be enzyme inducers are listed in Appendix 3. 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 return to their previous level of activity generally 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.

### 3.1.3 Excretion and the enterohepatic circulation

After metabolism, conjugates of EE, unaltered EE, and conjugates of estrogen and progestogen metabolites are excreted into bile and subsequently released into the small intestine. Conjugates cannot be absorbed from the small intestine and are excreted in faeces.

In the large intestine, a proportion of the conjugates are split by hydrolytic enzymes released from colonic bacteria (*Clostridia*, *Bacteroides* species, lactose-fermenting coliforms and some *Staphylococci*). Conjugates are split, releasing the free drug or metabolite, which can then be reabsorbed. These are eventually excreted in urine.

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.

## 4 What Should be Discussed When Prescribing Drugs to Women Using Hormonal Contraception?

When prescribing hormonal contraception [including emergency contraception (EC)] and when prescribing other medicines to women using hormonal contraception, the possibility of drug interactions needs to be considered.

Women on hormonal contraception should be advised that some drugs could reduce contraceptive efficacy and that additional precautions may be required. The duration for which a woman has to take a concomitant medicine and the nature of the condition for which it is used may influence contraceptive choice. Although there is currently no strong evidence that recreational drugs or dietary supplements interact with contraception, it is good practice to document all concomitant drug use in case of adverse effects or new evidence of an interaction. Appendix 3 lists drugs that potentially reduce levels of contraceptive hormones or decrease contraceptive efficacy.

- ✓ Health professionals supplying hormonal contraception should ask women about their current and previous drug use including prescription, over the counter, herbal, recreational drugs and dietary supplements.
- ✓ Women using hormonal contraception should be informed about the potential for interactions with other drugs and the need to seek the advice of a health professional before starting any new drugs.

## 5 Drugs that have the Potential to Affect Contraceptive Efficacy

### 5.1 Enzyme-inducing drugs

Enzyme-inducing drugs may increase the metabolism of EE and/or progestogens, decreasing bioavailability of the hormone and potentially reducing contraceptive efficacy. The summary of product characteristics (SPC) for depot medroxyprogesterone acetate (DMPA)<sup>14</sup> states that the clearance of DMPA is approximately equal to the rate of hepatic blood flow. For this reason, it is unlikely that drugs that induce hepatic enzymes will significantly affect the kinetics of DMPA. Pharmacokinetic data from studies of antiretroviral drugs support this theory.<sup>15,16</sup>

The SPC for depot norethisterone enantate (NET-EN) states that enzyme-inducing drugs might reduce its levels and efficacy.<sup>17</sup> However, this is a theoretical interaction extrapolated from data on combined oral contraceptives (COCs). There have not been any published cases of contraceptive failure as a result of this postulated interaction, nor does the manufacturer have any cases on file. Therefore, in line with previously published CEU guidance,<sup>1,9</sup> the CEU would advise that NET-EN can be used with enzyme-inducing drugs without any need for additional contraception or alteration of the dosing interval. More cautious advice is given in *UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) 2009*<sup>2</sup> and the World Health Organization *Medical Eligibility Criteria for Contraceptive Use (WHOMEK) 2010*.<sup>3</sup>

Most of the contraceptive effect of the levonorgestrel-releasing intrauterine system (LNG-IUS) is mediated via the direct release of progestogen into the uterine cavity and is unaffected by metabolism in the liver. A small study investigating use of the LNG-IUS concurrently with antiepileptic and other enzyme-inducing drugs concluded that if there is any increase in pregnancy risk, it is small.<sup>18</sup> As the copper-bearing intrauterine device (Cu-IUD) is non-hormonal it is unaffected by enzyme-inducing drugs.

Whilst no specific interaction studies have been performed with the etonogestrel-only implant,<sup>19</sup> true contraceptive failures have been reported in women using antiepileptic drugs (AEDs)<sup>20,21</sup> and the SPCs for Implanon<sup>®19</sup> and Nexplanon<sup>®22</sup> advise that efficacy may be affected. Therefore with the exception of progestogen-only injectables (DMPA and NET-EN) and the LNG-IUS, the efficacy of hormonal contraception, including progestogen-only EC and ulipristal acetate (UPA), may be reduced by enzyme-inducing drugs.

Commonly used enzyme-inducing drugs include some antiepileptic drugs such as carbamazepine or phenytoin. A detailed statement on antiepileptics and hormonal contraception has been produced by the Faculty of Sexual and Reproductive Healthcare.<sup>23</sup> These drugs may be used for indications other than epilepsy (e.g. migraine, neuropathic pain).

### 5.2 Lamotrigine

Lamotrigine is not thought to be an enzyme-inducing drug, however a small study of women using lamotrigine with a LNG-containing combined pill confirmed that although EE pharmacokinetics were unaffected, there was a slight decrease in levels of LNG, which was associated with an increase in follicle-stimulating hormone (FSH) and luteinising hormone (LH) and an increase in intermenstrual bleeding.<sup>24</sup> The mechanism for this effect is unknown. Despite these findings, contraceptive efficacy was maintained and it is not thought that the contraceptive efficacy of combined hormonal contraceptives is affected by lamotrigine. The significance of this modest decrease in LNG levels for users of progestogen-only contraception and lamotrigine is unknown. Unless new evidence emerges the CEU does not advise any need for additional contraception (see pages 9–10 and Appendix 6 for other lamotrigine interactions).

### 5.3 Progesterone receptor modulators

UPA (ellaOne®) is a selective progesterone receptor modulator (SPRM) licensed for EC up to 120 hours after unprotected sexual intercourse (UPSI) or contraceptive failure.<sup>25,26</sup> Interactions with hormonal contraception have not been studied. However, because UPA blocks the action of progesterone, it could in theory reduce the efficacy of progestogen-containing contraceptives.<sup>25,26</sup>

### 5.4 Drugs that affect absorption

Some drugs potentially affect the absorption of other drugs by altering gastric pH. In theory, drugs that increase gastric pH (e.g. proton pump inhibitors, antacids and H<sub>2</sub>-receptor antagonists) may reduce the absorption and efficacy of UPA<sup>26</sup> but there is no evidence to confirm this interaction.

The anti-obesity drug orlistat (Xenical®), also available over the counter as Alli®, may theoretically affect absorption of oral contraceptives by inducing diarrhoea. The SPC<sup>27</sup> states that orlistat has the potential to reduce contraceptive efficacy and advises additional precautions in those with severe diarrhoea.

Concomitant medication may also induce vomiting. Women who vomit within 2 hours of taking an oral contraceptive should repeat the dose as soon as possible.<sup>28–30</sup> The general advice for women using oral contraceptives who have persistent vomiting or severe diarrhoea for more than 24 hours is to follow the instructions for missed pills.

## 6 Advice for Women Using Drugs that May Reduce Contraceptive Efficacy

### 6.1 Enzyme-inducing drugs

Appendix 4 summarises the advice for women using enzyme-inducing drugs. Women taking enzyme-inducing drugs in either the short or long term should be advised to use a reliable method that is unaffected by enzyme-inducing drugs. Other methods will not provide reliable contraceptive protection and therefore the use of condoms or other alternatives such as increased dosing will be required (see recommendations for each specific method). Enzyme activity returns to normal within 28 days of stopping most enzyme-inducing drugs, thus 28 days is sufficient for recovery of contraceptive efficacy. For some drugs with associated teratogenic effects, the manufacturers recommend barrier protection for longer than 28 days. Health professionals should check the SPC for specific drug recommendations.

**C** All women starting enzyme-inducing drugs should be advised to use a reliable contraceptive method unaffected by enzyme inducers (e.g. progestogen-only injectable, Cu-IUD or LNG-IUS).

#### 6.1.1 Combined hormonal contraception

If a woman using a combined method does not wish to change to a method unaffected by enzyme inducers, she may choose one of the following options. Women on short-term treatment (arbitrarily defined by the CEU as  $\leq 2$  months) may continue using the combined patch, ring or standard strength combined pill but they should be advised to use additional contraceptive precautions (e.g. condoms) while taking the enzyme-inducing drug and for 28 days after stopping treatment. To minimise the risk of contraceptive failure the CEU recommends an extended regimen (taking CHC continuously for  $\geq 3$  weeks until breakthrough bleeding occurs for 3–4 days) or tricycling (taking three pill packets continuously without a break) and a shortened pill-/patch- or ring-free interval of 4 days. Reducing the number of hormone-free intervals and shortening the duration of the interval means that there is less opportunity for follicular development and ovulation due to falling hormone levels.<sup>31,32</sup> Only monophasic 21-day pill packs are suitable for extended use or tricycling, and the CEU recommends a minimum COC strength of 30  $\mu\text{g}$  EE.

Women who do not wish to use additional contraception or women on long-term treatment ( $> 2$  months) with an enzyme-inducing drug who do not wish to change to another method may be offered an increased dose of COC containing at least 50  $\mu\text{g}$  EE (e.g. a 30  $\mu\text{g}$  COC plus a 20  $\mu\text{g}$  or two 30  $\mu\text{g}$  COCs) during treatment and for 28 days after. An extended or tricycling regimen and pill-free interval of 4 days are recommended but additional contraception is not essential.

As rifampicin and rifabutin are particularly potent enzyme inducers women using these drugs long term should be advised to switch to a method that is unaffected by enzyme-inducing drugs.

The use of two COCs, extended/tricycling regimens and shortening the pill-free interval are outside the product licence for COCs and there is no evidence that such practice is effective in women using enzyme-inducing drugs.

Breakthrough bleeding in women using combined hormonal methods has been suggested as an indicator of low serum hormone concentrations, which could indicate a possible risk of ovulation. If breakthrough bleeding occurs in women using enzyme-inducing drugs, and other causes are excluded, (see FSRH guidance on the *Management of Unscheduled Bleeding in Women Using Hormonal Contraception*)<sup>33</sup> it may be prudent to increase the dose of EE in 10 µg increments up to maximum of 2 x 35 µg COCs), use additional precautions, or switch to a method unaffected by enzyme-inducing drugs.

- ✓ Women who do not wish to change from a combined method while on short-term treatment with an enzyme-inducing drug (and for 28 days after stopping treatment) may opt to continue using a COC containing at least 30 µg EE, the patch or ring together with additional contraception. An extended or tricycling regimen should be used with a hormone-free interval of 4 days. Additional contraception should be continued for 28 days after stopping the enzyme-inducing drug.
- ✓ With the exception of the very potent enzyme inducers rifampicin and rifabutin, women who are on an enzyme-inducing drug and who do not wish to change from COC may increase the dose of COC to at least 50 µg EE (maximum 70 µg) and use an extended or tricycling regimen with a pill-free interval of 4 days.
- ✓ In women using enzyme-inducing drugs with COC, breakthrough bleeding may indicate low serum EE concentrations. If other causes (e.g. chlamydia) have been excluded, the dose of EE can be increased up to a maximum of 70 µg EE.

#### 6.1.2 Progestogen-only contraception

For those women using the progestogen-only injectables (DMPA or NET-EN)<sup>9</sup> or the LNG-IUS,<sup>2</sup> concomitant use of enzyme-inducing drugs does not necessitate additional precautions, dose adjustment or alteration to the dosing/replacement interval (12 weeks, 8 weeks and 5 years, respectively).

Women using the progestogen-only pill (POP) or implant should be advised that the efficacy of these methods may be reduced by enzyme-inducing drugs and that they should use an alternative method. Women using the POP or implant with a short-term course of enzyme-inducing drug (≤2 months) could be offered a one-off injection of DMPA.

Women using enzyme-inducing drugs in the short term who do not wish to change their contraceptive method should be advised that they must take additional contraceptive precautions whilst using the enzyme-inducing drug and for 28 days after stopping treatment.

- ✓ Women who do not wish to change from the progestogen-only pill or implant while on short-term treatment with an enzyme-inducing drug or within 28 days of stopping treatment may opt to continue the method together with additional contraceptive precautions (e.g. condoms). Additional precautions should be continued for 28 days after stopping the enzyme-inducing drug.

#### 6.1.3 Emergency contraception

The efficacy of both levonorgestrel (LNG) EC and the progesterone receptor modulator, UPA, may be affected by enzyme-inducing drugs.<sup>26,34–36</sup> Women who require EC while using an enzyme-inducing drug or within 28 days of stopping enzyme-inducing drugs should be advised that the Cu-IUD is the most effective method of EC and that it can be used for ongoing contraception.

Women using enzyme-inducing drugs (or who have taken enzyme-inducing drugs within 28 days) who decline or who are not eligible to have a Cu-IUD for EC should be offered a total of 3 mg LNG (two Levonelle<sup>®</sup> One Step or Levonelle 1500<sup>®</sup> tablets) as a single dose, as soon

as possible and within 120 hours of UPSI. Using LNG between 72 and 120 hours after UPSI, and doubling the standard dose, are outside the product licence and there is limited evidence in relation to the efficacy.

The SPC for UPA states that it is not advisable to use UPA with enzyme-inducing drugs.<sup>26</sup> In the absence of data the CEU does not currently advise doubling the dose of UPA, and advises that UPA should not be used by women using enzyme-inducing drugs or who have stopped them within the last 28 days.

In certain circumstances HIV post-exposure prophylaxis for sexual exposure (PEPSE) and EC may be required simultaneously. Although it can take several days for enzyme-inducing drugs to take effect, the exact mechanisms of action of LNG are unknown and there have been no interaction studies on LNG and HIV PEPSE. Therefore, the CEU recommends the same advice as for other enzyme inducers [i.e. 3 mg LNG (two 1.5 mg tablets) taken as a single dose].

- ✓ Women using enzyme-inducing drugs who require EC should be advised of the potential interactions with oral methods and should be offered a Cu-IUD.
- C Women who request oral EC while using enzyme-inducing drugs or within 28 days of stopping them should be advised to take a total of 3 mg LNG (two 1.5 mg tablets) as a single dose as soon as possible and within 120 hours of UPSI (use of LNG >72 hours after UPSI and double dose are outside the product licence).
- C Ulipristal acetate is not advised in women using enzyme-inducing drugs or who have stopped them within the last 28 days.

## 6.2 Progesterone receptor modulators

Interactions with hormonal contraception have not been studied but UPA could in theory reduce the efficacy of progestogen-containing contraceptives.<sup>25</sup> The SPC<sup>26</sup> advises that women continuing hormonal contraception after use of UPA, should use condoms or avoid sexual intercourse until the next menstrual period. No contraceptive advice is given for women who are amenorrhoeic. In the absence of evidence, the CEU has taken a pragmatic approach in developing its recommendations, which may be amended if new evidence becomes available. If starting or continuing with a method following use of UPA, the CEU advises use of additional contraceptive precautions for 1 week plus the time required for contraceptive efficacy to be established [i.e. 7 days (14 days in total) for most methods, 2 days (9 days in total) for POP or 9 days (16 days in total) for Qlaira].<sup>37</sup>

There is also a theoretical concern that progestogen-containing contraceptives could antagonise the action of UPA if taken concurrently or started soon after UPA administration. Although there have been no studies investigating this interaction, UPA has been approved for use following contraceptive failure. The SPC for ellaOne<sup>®26</sup> warns of a possible interaction if continuing hormonal contraception but it does not mention any contraindication to use following failure of hormonal contraception

- ✓ Women should be advised that UPA has the potential to reduce the efficacy of hormonal contraception. Additional precautions are advised for 14 days after taking UPA (9 days if using or starting the POP, 16 days for Qlaira<sup>®</sup>) (outside product licence).

## 6.3 Drugs that affect gastric pH

UPA should not be used and an alternative form of EC will be needed.

- ✓ Women using drugs that affect gastric pH (e.g. antacids, histamine H2 antagonists and proton pump inhibitors) and who require EC, should be offered a Cu-IUD or LNG as the efficacy of UPA may be reduced.

## 6.4 Antibacterial drugs that are not enzyme inducers

Rifampicin-like drugs (e.g. rifampicin, rifabutin) are the only antibiotics that are enzyme inducers and that have consistently been shown to reduce serum levels of ethinylestradiol.<sup>38-45</sup> Pregnancies have also been reported following concomitant use of COC and a wide range of antimicrobial agents, including penicillins, tetracyclines, macrolides, fluoroquinolones and imidazole antifungal drugs, which are not enzyme inducers.<sup>46-56</sup> The main hypothesis that has been used to explain contraceptive failures in antibiotic users is that broad-spectrum

antibiotics temporarily reduce colonic bacteria, which may in turn reduce the enterohepatic recycling of EE (see Figure 1). There is, however, no evidence to prove such an interaction.

Previous CEU guidance has acknowledged the lack of evidence supporting a causal relationship between antibiotics that are not enzyme inducers and reduced COC efficacy.<sup>1</sup> Despite the limited evidence, a cautious approach has generally been taken in the UK. Traditional practice has been to advise use of additional precautions with courses of antibiotics taken for 3 weeks or less, after which time it was believed that gut flora would be sufficiently recovered and contraceptive efficacy would no longer be affected.

In 2009/2010, the World Health Organization produced updated *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC)<sup>3</sup> which included evidence-based guidance on contraceptive use and drug interactions. WHOMEC states that there is intermediate level evidence that the contraceptive effectiveness of COCs is not affected by co-administration of most broad-spectrum antibiotics, and advises no restriction on use (WHOMEC Category 1) of CHC with antibiotics. The *U.S. Medical Eligibility Criteria for Contraceptive Use* (USMEC)<sup>4</sup> 2010 has also adopted these recommendations. For the following reasons the CEU supports this statement and now advises that additional precautions are not required even for short courses of antibiotics that are not enzyme inducers.

### 6.4.1 Direct evidence

- 1 Several studies looking at combined hormonal methods have not demonstrated a decrease in levels of EE with antibiotic use.<sup>57–59</sup>
- 2 Several small non-randomised trials have found no effect on the pharmacokinetics of EE or progestogens when combined contraceptives have been administered in conjunction with tetracycline,<sup>57,58</sup> amoxicillin<sup>60</sup> or doxycycline.<sup>59,60</sup>
- 3 Small, prospective, non-randomised studies<sup>61–63</sup> have failed to show that ampicillin has any effect on gonadotrophin concentration or progesterone in women using a COC with  $\geq 30$   $\mu\text{g}$  EE.
- 4 Three small randomised trials<sup>64–66</sup> suggest that ciprofloxacin and ofloxacin may not affect COC. One study noted no differences in serum concentrations of gonadotrophins or estradiol with concomitant use of ciprofloxacin 500 mg daily.<sup>64</sup> No evidence of ovulation was found in the two other studies when looking at interactions between hormonal contraception and ciprofloxacin<sup>65</sup> and also ofloxacin.<sup>66</sup>

### 6.4.2 Indirect/supporting evidence

- 1 Women who have had a colectomy and ileostomy have no enterohepatic circulation of EE yet the efficacy of COCs does not appear to be reduced in this situation.<sup>67</sup>
- 2 Some of the pregnancies that have been reported with antibiotic use have been in women using COCs containing high doses of EE ( $>30$   $\mu\text{g}$  EE).<sup>56</sup> Given that 20  $\mu\text{g}$  EE COCs are deemed to provide effective contraception, it seems unlikely that the cause of the 'failure' is due to the small reduction in EE circulation that may theoretically result from reduced enterohepatic recycling of EE.
- 3 Pregnancies have been reported in COC users taking both short- and long-term antibiotics.<sup>55,68,69</sup> This is not consistent with the theory that it is short-term use of antibiotics that presents a risk and that after 3 weeks there is no risk. With regard to any potential risk of COC failure in long-term antibiotic users, a retrospective cohort study<sup>68</sup> of women attending dermatology clinics did not support any reduction in COC efficacy compared to COC users not on antibiotics. The study of 356 dermatology patients with a history of antibiotic and COC use found that there were five pregnancies (three women used minocycline and two used cephalosporin for  $>3$  months) in 311.2 women years of COC and antibiotic use (Pearl index 1.6) and 12 pregnancies in the 162 controls (Pearl index 0.96) which, even after accounting for age, was not statistically different.
- 4 Anecdotal reports of pregnancy have been reported with use of fluconazole<sup>70</sup> and erythromycin,<sup>56,71</sup> However, these drugs actually increase rather than decrease levels of EE.



- 5 Studies investigating contraception failure in women presenting for abortion<sup>46,54,72–74</sup> have been cited in support of an interaction with antibiotics. However these studies are often compromised by a lack of controls, recall bias and potential confounders such as missed pills and thus an association cannot be reliably confirmed.
- 6 A cross-sectional study<sup>75</sup> comparing risk factors for COC failure amongst pregnant and non-pregnant women found that although antibiotic use was reported by a proportion of pregnant women, a larger percentage of non-pregnant women also reported antibiotic use.
- 7 Other hypotheses may explain contraceptive failure although none are proven; for example, failure to take COC or reduced absorption due to antibiotic-induced diarrhoea or vomiting<sup>76</sup> or simply failure to take COC because of illness.<sup>76,77</sup>

## 7 What Advice Should be Given to Women Using Hormonal Contraception and Antibacterials that are Not Enzyme Inducers?

Overall the evidence does not generally support reduced COC efficacy with non-enzyme-inducing antibiotics. UKMEC 2009<sup>2</sup> advises additional precautions with antibiotics that do not induce enzymes. This was an interim measure until evidence could be reviewed in detail by the CEU and other UK organisations. Having reviewed the available evidence, the CEU no longer advises that additional precautions are required to maintain contraceptive efficacy when using antibiotics that are not enzyme inducers with combined hormonal methods for durations of 3 weeks or less. The only proviso would be that if the antibiotics (and/or the illness) caused vomiting or diarrhoea, then the usual additional precautions relating to these conditions should be observed.<sup>28–30</sup> The CEU would advise that health professionals remind women about the importance of correct contraceptive practice during periods of illness.

**C** Additional contraceptive precautions are not required during or after courses of antibiotics that do not induce liver enzymes.

**✓** Women should be advised about the importance of correct contraceptive practice during periods of illness.

## 8 Drugs that Increase Contraceptive Hormone Levels

Drugs that can increase the serum levels of contraceptive hormones are listed in Appendix 5. The clinical effect of increased EE and progestogens is unclear. In theory, side effects and other adverse effects may be increased, but there should be no risk of reduced efficacy. Women experiencing side effects may wish to try a lower dose preparation or an alternative contraceptive method.

## 9 Effect of Contraceptive Hormones on Drug Metabolism

The plasma concentrations of some drugs can be increased or decreased by concomitant hormonal contraceptive use (Appendix 6). Dosing adjustments may be required depending on the nature of the interaction and clinical effect.

Serum levels of lamotrigine, for example, are reduced by CHC.<sup>78–82</sup> Lamotrigine's major route of elimination involves conjugation with glucuronic acid (glucuronidation) and EE is thought to induce lamotrigine glucuronidation.<sup>78</sup> The SPC for lamotrigine<sup>79</sup> suggests a two-fold increased clearance of lamotrigine in users of an EE/LNG (30 µg/150 µg) pill and there are data showing increased frequency of seizures in women with reduced lamotrigine levels following the initiation of COC, and an increase in lamotrigine levels during the pill-free week<sup>80</sup> and following cessation of oral contraceptives.<sup>78</sup> Lamotrigine side effects have been reported on discontinuation of COC, suggesting that the rise in lamotrigine levels may be clinically significant.<sup>81</sup> A small study of 26 women stable on lamotrigine therapy showed reductions in lamotrigine levels when administered with the combined vaginal ring, although to a lesser extent than those observed in women receiving COC (15–50% vs 25–70%).<sup>82</sup>

The interaction only applies to lamotrigine monotherapy and when combined with sodium valproate, no reduced effect occurs.<sup>83</sup>

Due to the risk of drug interactions, the use of lamotrigine monotherapy with CHC is a UKMEC Category 3 (risks generally outweigh the benefits). The CEU has produced a detailed

statement on *Antiepileptic Drugs and Contraception*<sup>23</sup> and the SPC for lamotrigine<sup>79</sup> provides more detailed information on dose adjustment when starting or stopping COC.

One small study suggested that sodium valproate levels may also be affected by EE<sup>83,84</sup> but the SPC<sup>85</sup> for the product does not at present make any reference to this potential effect and therefore the clinical significance of this interaction is therefore currently unknown.

There is evidence to suggest that lamotrigine levels are not reduced by progestogens,<sup>86</sup> although a small study of 10 women found that in 7/10 women taking the desogestrel-only pill in conjunction with lamotrigine, lamotrigine levels actually increased by 20–100%.<sup>87</sup> Until larger studies are reported the CEU would advise health professionals to be aware of the possible effect and monitor patients for lamotrigine side effects upon starting the POP.

The effects of other groups of drugs (e.g. antihypertensives, antidiabetics, diuretics, anticoagulants, thyroid hormones, bronchodilators and immunosuppressants) may be affected by contraceptive hormones and additional monitoring may be required (Appendix 6).

**C** Women on lamotrigine monotherapy should be advised that due to the risk of reduced seizure control whilst on CHC, and the potential for toxicity in the CHC-free week, the risks of using CHC may outweigh the benefits.

**✓** Women on drugs that are affected by contraceptive hormones may require monitoring of drug levels or effect when starting, changing or stopping hormonal contraception. The woman's hospital doctor and/or general practitioner should be involved in decisions to change contraception and appropriate follow-up should be arranged.

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## APPENDIX 1: DEVELOPMENT OF CEU GUIDANCE

### GUIDELINE DEVELOPMENT GROUP

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No conflicts of interest were declared by any members of the multidisciplinary group.

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CEU guidance is developed in collaboration with the Clinical Effectiveness Committee of the FSRH. The CEU guidance development process employs standard methodology and makes use of systematic literature review and a multidisciplinary group of professionals. The multidisciplinary group is identified by the CEU for their expertise in the topic area and typically includes health professionals working in family planning, sexual and reproductive health care, general practice, other allied specialities, and user representation. In addition, the aim is to include a representative from the FSRH Clinical Effectiveness Committee, the FSRH Education Committee and FSRH Council in the multidisciplinary group.

Evidence is identified using a systematic literature review and electronic searches are performed for: MEDLINE (CD Ovid version) (1996–2010); EMBASE (1996–2010); PubMed (1996–2010); The Cochrane Library (to 2010) and the US National Guideline Clearing House. The searches are performed using relevant medical subject headings (MeSH), terms and text words. The Cochrane Library is searched for relevant systematic reviews, meta-analyses and controlled trials relevant to drug interactions with hormonal contraception. Previously existing guidelines from the FSRH (formerly the Faculty of Family Planning and Reproductive Health Care), the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization (WHO) and the British Association for Sexual Health and HIV (BASHH), and reference lists of identified publications, are also searched. Similar search strategies have been used in the development of other national guidelines. Selected key publications are appraised using standard methodological checklists similar to those used by the National Institute for Health and Clinical Excellence (NICE). All papers are graded according to the Grades of Recommendations Assessment, Development and Evaluation (GRADE) system. Recommendations are graded as in the table on the inside front cover of this document using a scheme similar to that adopted by the RCOG and other guideline development organisations. The clinical recommendations within this guidance are based on evidence whenever possible. Summary evidence tables are available on request from the CEU. An outline of the guideline development process is given in the table on the inside back cover of this guidance document.

## APPENDIX 2: USEFUL SOURCES OF INFORMATION ABOUT DRUG INTERACTIONS

Source	Information contained	Website
<i>British National Formulary</i>	Joint publication of the British Medical Association and Royal Pharmaceutical Society containing information on medicines available in the UK. Drug interactions are listed in the appendices	www.bnf.org  Printed copies produced biannually; available from Pharmaceutical Press
electronic Medicines Compendium	Contains the summary of product characteristics for most UK licensed medicines	www.medicines.org.uk/emc/
HIV-Drug Interactions	Site developed and maintained by the Liverpool HIV Pharmacology Group. Designed to provide up-to-date, evidence-based information for professionals on drug interactions	www.hiv-druginteractions.org/
<i>Stockley's Drug Interactions</i>	Comprehensive, evidence-based reference book on drug interactions	www.medicinescomplete.com/mc/index.htm  Available in print from Pharmaceutical Press



### APPENDIX 3: DRUGS THAT REDUCE CONTRACEPTIVE HORMONE LEVELS OR DECREASE CONTRACEPTIVE EFFICACY

Drug category	Drug	Type of interaction	Clinical significance
Antiepileptic	Carbamazepine Eslicarbazepine Oxcarbazepine Phenobarbital Phenytoin Primidone Rifinamide	Enzyme inducer	Modest to marked reduction in EE and progestogens. <sup>88–90</sup> Possible reduced contraceptive efficacy (see Appendix 4)
	Topiramate	Enzyme inducer	Weak enzyme inducer, therefore contraceptive efficacy may be unaffected at lower end of topiramate dose range. <sup>91,92</sup> (follow advice in Appendix 4 when using doses $\geq 200$ mg daily)
	Lamotrigine	Not thought to induce liver enzymes	Some evidence of a minor decrease in LNG when given as a COC <sup>24</sup> but evidence suggests efficacy of combined hormonal methods is unaffected (see also Appendix 6). No data on the effect on progestogen-only methods
Antibiotic	Rifabutin Rifampicin	Enzyme inducer (includes induction of glucuronidation)	Rifabutin associated with a modest reduction in EE or estradiol and progestogen. Rifampicin has a marked effect <sup>93–96</sup> (see Appendix 4)
Antiretroviral (ARV)	<b>Protease inhibitors</b>		
	Ritonavir	Ritonavir has mixed enzyme-inducing and inhibiting effects on different cytochrome P-450 enzymes and is an inducer of glucuronidation	Marked reduction in EE. EE reduced by 40%. <sup>97</sup> Additional and/or alternative contraceptive methods advised
	Ritonavir-boosted atazanavir (for unboosted see Appendix 5)	On its own atazanavir inhibits CYP3A4. When co-administered with ritonavir, the glucuronidation-inducing effects of ritonavir may predominate	Net effect is a minor reduction in EE and a marked increase in norgestimate and NET-EN. <sup>98</sup> As no other evidence for progestogen-containing contraceptives follow advice in Appendix 4
	Ritonavir-boosted tipranavir	Tipranavir is a substrate, an inducer and an inhibitor of cytochrome P-450 CYP3A4. Ritonavir effect may predominate	Net effect is marked reduction in EE. <sup>99</sup> As no other evidence for progestogen-containing contraceptives follow advice in Appendix 4
	Ritonavir-boosted saquinavir	Ritonavir effect may predominate	EE may be decreased. <sup>100</sup> As no evidence for progestogen-containing contraceptives follow advice in Appendix 4

### APPENDIX 3: DRUGS THAT REDUCE CONTRACEPTIVE HORMONE LEVELS OR DECREASE CONTRACEPTIVE EFFICACY (continued)

Drug category	Drug	Type of interaction	Clinical significance
Antiretroviral (ARV)	<b>Protease inhibitors</b> All other ritonavir-boosted protease inhibitors (darunavir, nelfinavir, fosamprenavir, lopinavir)	Ritonavir effect may predominate	Reduction in EE and progestogen <sup>101,102</sup> (see Appendix 4)
	<b>Non-nucleoside reverse transcriptase inhibitors</b> Efavirenz	Enzyme inducer	No reduction in EE but marked reduction in norgestimate metabolites (norelgestromin and LNG). <sup>96,103</sup> Some pregnancies noted <sup>104</sup> (see Appendix 4). No reduction in DMPA levels
	Nevirapine	Enzyme inducer	Modest reduction in EE and minor reduction in NET-EN <sup>105</sup> (see Appendix 4)
Emergency contraceptive	Ulipristal acetate	Progesterone receptor antagonist	Theoretical reduction in the efficacy of progestogen-containing contraceptives. <sup>25</sup> Additional precautions required for 14 days (9 days if using or starting POP, 16 days for Qlaira®) <sup>37</sup>
Gastrointestinal	Proton pump inhibitors Antacids H2-receptor antagonists	Drugs that increase gastric pH Enzyme inducer Enzyme inducer	Theoretical reduction in plasma concentrations of UPA and may result in decreased efficacy. Concomitant use not recommended <sup>26</sup>
Herbal	St Johns Wort ( <i>Hypericum perforatum</i> )	Enzyme inducer	Is a weak enzyme inducer and has the potential to reduce efficacy. Follow advice in Appendix 4
Other	Bosentan	Enzyme inducer	Modest reduction in EE and progestogen <sup>93,96,106</sup> (see Appendix 4)
	Modafinil	Enzyme inducer	Minor reduction in EE <sup>107,108</sup> (see Appendix 4)
	Aprepitant	Enzyme inducer	Modest reduction in EE and progestogens <sup>93,109</sup> (see Appendix 4)
	Sugammadex	Hormone-binding resin	Hypothetical interaction predicted to modestly reduce progestogen levels from oral contraceptives. Administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral contraceptive steroids (either combined or progestogen-only). Follow missed pill guidance. For other methods use additional precautions for 7 days <sup>110</sup>

Arbitrary definition: marked reduction  $\geq 40\%$ ; modest reduction 20–40% reduction (roughly equivalent to changing from a 30  $\mu\text{g}$  to a 20  $\mu\text{g}$  COC); minor reduction  $\leq 20\%$ .

COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; EE, ethinylestradiol; LNG, levonorgestrel; NET-EN, norethisterone enantate; POP, progestogen-only pill; UPA, ulipristal acetate.

## APPENDIX 4: CONTRACEPTIVE ADVICE FOR WOMEN USING ENZYME-INDUCING DRUGS

Contraceptive method	Short-term use of enzyme-inducing drugs ( $\leq 2$ months)	Long-term use of enzyme-inducing drugs ( $> 2$ months) or difficulty using additional contraceptive precautions
<b>Combined hormonal contraception (CHC)</b> Combined oral contraception (COC) Combined transdermal patch Combined vaginal ring	<b>Recommended option</b>  Change to an alternative method unaffected by enzyme-inducing drugs. This could include temporarily stopping COC and having a one-off DMPA injection to cover the short-term treatment and 28 days after	Change to an alternative method unaffected by enzyme-inducing drugs
	<b>Alternative options</b> Use one COC pill daily (at least 30 $\mu\text{g}$ EE), one patch weekly or one ring 3-weekly and use an extended or tricycling regimen with a hormone-free interval of 4 days  <b>Plus</b> Additional contraceptive precautions (e.g. condoms) while taking and for 28 days after stopping the enzyme-inducing drug  <b>Or</b> Use two COC pills as per long-term treatment (see opposite)	Use two COC pills containing at least 50 $\mu\text{g}$ EE (e.g. 20 and 30 $\mu\text{g}$ COCs). Use an extended or tricycling regimen with a pill-free interval of 4 days  <b>Note</b> Not recommended if using the potent enzyme-inducers rifampicin or rifabutin  Use of two patches or two rings not recommended
<b>Progestogen-only contraception</b> Progestogen-only pills (POPs) and progestogen-only implant	<b>Recommended option</b>  Change to an alternative method unaffected by enzyme-inducing drugs (including one-off dose of progestogen-only injectable to cover period of risk)	Change to an alternative method unaffected by enzyme-inducing drugs
	<b>Alternative option</b> Continue use of POP or implant  <b>Plus</b> Additional contraceptive precautions (e.g. condoms) while taking and for 28 days after stopping the enzyme-inducing drug	No alternative-change advised
<b>Progestogen-only injectable</b> Levonorgestrel-releasing intrauterine system (LNG-IUS)	<b>No change required</b> Efficacy of DMPA, NET-EN and LNG-IUS unaffected by enzyme-inducing drugs and women can continue with the usual dose and dosing/replacement interval of 12 weeks, 8 weeks or 5 years, respectively	
<b>Non-hormonal methods</b> Copper-bearing intrauterine device (Cu-IUD), barrier methods	<b>No change required</b> Efficacy unaffected	
<b>Emergency contraception</b> Copper-bearing intrauterine device (Cu-IUD)	Efficacy unaffected. Unless Cu-IUD is contraindicated, offer to all women (between 0–120 hours of UPSI or within 5 days of expected ovulation) taking or within 28 days of stopping enzyme-inducing drugs	

**APPENDIX 4: CONTRACEPTIVE ADVICE FOR WOMEN USING ENZYME-INDUCING DRUGS (continued)**

Contraceptive method	Short-term use of enzyme-inducing drugs ( $\leq 2$ months)	Long-term use of enzyme-inducing drugs (>2 months) or difficulty using additional contraceptive precautions
<b>Emergency contraception</b> Progestogen-only emergency contraception (POEC)  Progestogen-receptor modulator	Take a total of 3 mg (2 x 1.5 mg tablets) LNG as a single dose as soon as possible and within 120 hours of UPSI (outside product licence)  Do not use with enzyme-inducing drugs	

CHC, combined hormonal contraception; COC, combined oral contraception; Cu-IUD, copper-bearing intrauterine device; DMPA, depot medroxyprogesterone acetate; EE, ethinylestradiol; LNG, levonorgestrel; LNG-IUS, levonorgestrel-releasing intrauterine system; NET-EN, norethisterone enantate; POEC, progestogen-only emergency contraception; POP, progestogen-only pill; UPSI, unprotected sexual intercourse.

**GOOD PRACTICE POINTS**

- Women may need to continue to use condoms for sexually transmitted infection (STI) prevention.
- Consistent use of condoms is advised for women with HIV to reduce transmission and re-infection with a different strain of virus.
- Women advised to use additional contraception should be aware that their usual method may be ineffective and that contraceptive protection is provided only by the condom.
- Women should be reminded that they can use emergency contraception if additional contraception fails or is not used.

## APPENDIX 5: DRUGS THAT INCREASE CONTRACEPTIVE HORMONE LEVELS<sup>93,96,111</sup>

Drug type	Drug	Interaction	Clinical significance
Antibacterial	Erythromycin	Enzyme inhibitor	Modest to marked increases in estradiol and dienogest levels. The clinical significance is not known but increased adverse events might be anticipated
Antifungal	Fluconazole Itraconazole Ketoconazole Voriconazole	Enzyme inhibitor	Modest increases in EE and progestogen. Breakthrough bleeding noted in studies. <sup>112-114</sup> Evidence in relation to fluconazole has been broadly reassuring in relation to contraceptive efficacy <sup>115-117</sup>
Antiretroviral	Atazanavir (unboosted)	Enzyme inhibitor	Modest to marked increases in EE and NET-EN when atazanavir is used unboosted. Concomitant use of combined methods not advised. For the reduced levels of EE with ritonavir-boosted atazanavir see Appendix 3
Immunosuppressant	Tacrolimus	Enzyme inhibitor	Theoretically inhibits the metabolism of estrogens and progestogens leading to increased levels. <sup>93</sup> The clinical significance is not known but the increase is likely to be small (see also Appendix 6)
Non-steroidal anti-inflammatory	Etoricoxib	Enzyme inhibitor	Doses of etoricoxib $\geq 60$ mg raise EE levels by approximately 40% or more. <sup>118</sup> Potential risk of estrogen-related adverse events <sup>119</sup>
Statins	Atorvastatin Rosuvastatin	Enzyme inhibitor	Minor to modest increase in EE and progestogens leading to increased levels. <sup>93</sup> The clinical significance is not known but likely to be small
Vasodilator	Sitaxentan sodium	Enzyme inhibitor	Modest to marked increase in EE and NET-EN levels. <sup>93</sup> The clinical significance is not known but increased adverse events might be anticipated

EE, ethinylestradiol; NET-EN, norethisterone enantate.

## APPENDIX 6: DRUGS THAT ARE AFFECTED BY CONTRACEPTIVE HORMONES<sup>93,96,111</sup>

Drug type	Clinical effect
	<b>Decreased levels or clinical effect</b>
Antiepileptics	EE reduces plasma concentrations of lamotrigine. <sup>24,78,81,84,120,121</sup> Possible increased risk of seizures. Consider increasing dose of lamotrigine monotherapy. To avoid toxicity in pill-free week, consider extended regimen. EE may also modestly reduce valproate levels <sup>83,84</sup>
Antihypertensives	Hypotensive effect may be antagonised by combined hormonal contraception. Monitor effect
Antidiabetics	Estrogens and progestogens antagonise the hypoglycaemic effect of antidiabetics. Monitor effect
Diuretics	Estrogens may antagonise diuretic effect of diuretics
Thyroid hormones	Estrogens may increase the requirements for thyroid hormones in hypothyroidism. Monitor thyroid function
	<b>Increased levels or adverse effect</b>
Antifungals	Oral contraceptives modestly increase levels of voriconazole. <sup>122</sup> Clinical significance unknown
Anxiolytics and hypnotics	Estrogens increase plasma concentrations of melatonin <sup>93</sup>
Bronchodilators	Estrogens reduce the excretion of theophylline resulting in increased plasma concentrations. A reduction of the theophylline dosage is recommended <sup>93,123</sup>
Dopaminergics	Estrogens increase plasma concentrations of ropinirole. <sup>93</sup> Defined by BNF as non-hazardous (i.e. does not usually have serious complications)
	Estrogens and progestogens increase plasma concentrations of selegiline. <sup>93</sup> Increased risk of toxicity. Concomitant use should be avoided <sup>124</sup>
Immunosuppressant	Plasma levels of tacrolimus possibly increased by EE, NET-EN and gestodene. <sup>125</sup> Monitor tacrolimus levels
Muscle relaxants	Estrogens and progestogens possibly increase plasma concentration of tizanidine <sup>93</sup> potentially leading to toxicity <sup>126</sup>
Potassium-sparing diuretics and aldosterone antagonists	Theoretical risk of hyperkalaemia when administered with drospirenone but COCs containing drospirenone not usually used in hypertensive patients
Retinoids	The adverse effects of oral contraceptives on lipids may be additive with those of isotretinoin. As retinoids are teratogenic, the benefits of COC use may outweigh risk and lipids should be monitored routinely during retinoid treatment
Triptans	COCs appear to modestly raise level of frovatriptan, naratriptan, zolmitriptan and slightly increase levels of sumatriptan. <sup>96</sup> Before prescribing triptans in CHC users with migraine, health professionals should refer to UKMEC <sup>2</sup> as CHC may be contraindicated in some women with a history of migraine

BNF, *British National Formulary*; CHC, combined hormonal contraception; COC, combined oral contraceptive; EE, ethinylestradiol; NET-EN, norethisterone enantate; UKMEC, *UK Medical Eligibility for Contraceptive Use*.

## Discussion Point for Drug Interactions with Hormonal Contraception

The following discussion point has been developed by the FSRH Education Committee.

### Discussion Point

- 1 Consider how you would talk to a young woman about drug interactions when her mother accompanies her into the consulting room and you are unsure whether she is aware that her daughter is taking the combined contraceptive pill.

## Questions for Drug Interactions with Hormonal Contraception

The following questions and answers have been developed by the FSRH Education Committee.

Indicate your answer by ticking the appropriate box for each question

	True	False
1 Additional precautions are not required for short courses of antibiotics (<3 weeks) that do not induce liver enzymes.	<input type="checkbox"/>	<input type="checkbox"/>
2 Liver enzyme inducers have their maximum effect by 7 days.	<input type="checkbox"/>	<input type="checkbox"/>
3 Conjugates of ethinylestradiol (EE) are absorbed from the small intestine.	<input type="checkbox"/>	<input type="checkbox"/>
4 Unlike depot medroxyprogesterone acetate (DMPA), norethisterone enantate (NET-EN) is affected by liver enzyme inducers and extra precautions should be used.	<input type="checkbox"/>	<input type="checkbox"/>
5 There is evidence that using two combined oral contraceptives (COCs), tricycling and shortening the pill-free interval will ensure contraceptive efficacy in women using enzyme-inducing drugs.	<input type="checkbox"/>	<input type="checkbox"/>
6 Women using the combined patch or vaginal ring should be advised to use two at the same time to give adequate contraception when using an enzyme-inducing drug.	<input type="checkbox"/>	<input type="checkbox"/>
7 Both oral drugs (i.e. levonorgestrel and ulipristal acetate) used for emergency contraception are affected by liver enzymes.	<input type="checkbox"/>	<input type="checkbox"/>
8 DMPA is cleared from the liver at a rate equivalent to the rate of hepatic blood flow.	<input type="checkbox"/>	<input type="checkbox"/>
9 Lamotrigine increases levels of the desogestrel-only pill.	<input type="checkbox"/>	<input type="checkbox"/>
10 There is an interaction between triptans and COCs. Women taking triptans should never be prescribed COCs.	<input type="checkbox"/>	<input type="checkbox"/>

Answers

10 False	9 False	8 True	7 True	6 False
5 False	4 False	3 False	2 True	1 True









## STEPS INVOLVED IN THE DEVELOPMENT OF THIS GUIDANCE DOCUMENT

STEP	TIME TAKEN
<p>Formulation of <b>key clinical questions</b> by the Clinical Effectiveness Unit (CEU).</p> <p><b>Systematic literature review</b> involving searching electronic, bibliographic databases by CEU researcher.</p> <p><b>Obtaining and reviewing</b> copies of the full papers of all relevant publications identified through the searches.</p> <p><b>Formal, critical appraisal</b> of key papers and development of short evidence tables.</p>	<p>This process must be completed in a maximum of 8 weeks.</p>
<p><b>Draft one guidance document</b> is written providing recommendations and good practice points based on the literature review.</p>	<p>The CEU has overall responsibility for writing the guidance document. The multidisciplinary group and other peer reviewers should highlight inconsistencies, errors, omissions or lack of clarity.</p>
<p><b>Peer review by multidisciplinary group</b> comprising stakeholders, the FSRH Clinical Effectiveness Committee (CEC); representation from the FSRH Education Committee and Clinical Standards Committee; and where possible service user representation and representation from FSRH Council. Two independent peer reviewers also review the document.</p>	<p>At this stage the CEU convenes a one-day meeting of the multidisciplinary group.</p>
<p><b>Preparation of draft two guidance document</b> based on written comments of the multidisciplinary group.</p>	
<p><b>Peer review of draft two guidance document</b> by the multidisciplinary group, the FSRH CEC and two independent peer reviewers.</p>	
<p><b>Preparation of draft three guidance document</b> based on written comments from the peer reviewers.</p>	
<p><b>Draft document posted on Faculty website</b> for 1 month for public consultation.</p>	
<p>All <b>written feedback comments on draft three guidance document</b> reviewed by the CEU, multidisciplinary group, independent peer reviewers and FSRH CEC.</p>	
<p>CEU's response to consultation comments posted on FSRH website. Final draft prepared.</p>	<p>Proofreading of the guidance document is then performed by three members of the CEU team independently and comments collated and sent back by the Unit Director.</p>
<p>The <b>final guidance document</b> is published by the FSRH.</p>	<p>A pdf version of the guidance is available on the FSRH website.</p>

## COMMENTS AND FEEDBACK ON PUBLISHED GUIDANCE

All comments on published guidance can be sent directly to the Clinical Effectiveness Unit (CEU) at [ceu.members@ggc.scot.nhs.uk](mailto:ceu.members@ggc.scot.nhs.uk).

You will receive an automated acknowledgment on receipt of your comments. If you do not receive this automated response please contact the CEU by telephone [+44 (0) 141 232 8459/8460] or e-mail ([ceu.members@ggc.scot.nhs.uk](mailto:ceu.members@ggc.scot.nhs.uk)).

The CEU is unable to respond individually to all feedback. However, the CEU and FSRH Clinical Effectiveness Committee will review all comments and make any necessary amendments.