Introduction

All methods of contraception have failure rates. Additional failures may occur when interacting drugs are used, and knowledge of these mechanisms should help minimise such problems. This article will look at interactions with hormonal methods of contraception, only some of which, at the present state of knowledge, have clinical significance.

Absorption of oral preparations

The hormones are absorbed from the upper small intestine, either unaltered or conjugated to sulphates and some glucuronides. Peak plasma levels are reached within 2 hours, with wide variation between women. Vomiting within 2 hours of ingestion reduces the amount of hormones absorbed, and missed pill instructions should be followed during the attack and for the next 7 days. In the case of combined oral contraception, the pill-free interval should be omitted if less than seven pills remain in the packet. Diarrhoea (unless severe) is unlikely to affect drug levels; there are no studies showing any pharmacological basis for failure.

Substances that adsorb other chemicals in vitro (e.g. activated charcoal, and antacids such as magnesium trisilicate and aluminium hydroxide) do not affect absorption to any significant degree.

Competition for sulphuration between EE and Vitamin C causes no increased circulating levels of EE, or rebound reduction on stopping the vitamin, refuting earlier concerns.

Transport in the circulation to the liver

EE and progestogens are transported either free (and so bioavailable) or bound to albumin. Progestogens bind with high affinity to sex hormone binding globulin (SHBG). The level of SHBG is increased by liver enzyme inducers, resulting in decreased free circulating...
progestogens, with the potential for lowered efficacy of both POP and COC (see below).

**Metabolism in the liver**

Microenzymes act on EE and progestogens, reducing the amount of active hormone reaching the bile. Prodrugs (such as mestranol, desogestrel, norgestimate and ethynodiol diacetate) have to be metabolised to their active constituents (EE, 3-keto desogestrel, levonorgestrel and norethisterone, respectively), with some loss of bioavailability. Some drugs may induce or inhibit these liver enzymes.

Anticonvulsants (with the exception of sodium valproate, clobazam, vigabatrin, gabapentin and lamotrigine), griseofulvin, barbiturates, and ritonovir (and possibly other protease inhibitors) all increase metabolism of EE and progestogens, with the potential for lowered efficacy of POP and COC (see below). Microenzymes act on EE and progestogens, reducing the both POP and COC (see below).

Some drugs may induce or inhibit these liver enzymes.

**Conjugation in the liver**

Conjugated, metabolised and unaltered EE is excreted into the bile. Once in the colon, clostridia and other bacteria hydrolyse the compounds, making them less hydrophilic and so able to be reabsorbed into the circulation. In some women, a second peak plasma level of EE is observed, but this is variable and probably contributes little to overall levels.

The only drugs that affect these bacteria are broad-spectrum antibiotics (mainly ampicillin and tetracycline). In many studies, small numbers of pregnancies have been linked with different antibiotics, even where the circulating level of EE is raised by it (e.g. erythromycin and cotrimoxazole). It is possible that the illness for which the antibiotic is being taken may itself effect utilisation of EE, or that use of contraceptive pills during an illness is inconsistent. Because of the marked between-women differences in circulating free hormone levels, the contribution made by an antibiotic to COC failure is hard to evaluate. Back sums up the difficulty of predicting which women risk pill failure with antibiotics; factors are:

- The level of bioavailable EE (which varies with the amount of conjugation and liver metabolism, and is partly genetically determined)
- An EHC affecting significantly the overall plasma levels
- A colony of colonic bacteria that are especially sensitive to the antibiotic.

The plasma half-life elimination of EE (5-8 hours) again varies between women, and depends on the reliance on the EHC. Ileostomy patients (who have no EHC) do not have significant changes to this half-life, giving further indirect evidence of the very small part the EHC makes to COC efficiency.

The international consensus statement specifies that women taking tetracyclines and penicillins require other contraception in addition to COC, even though no study has consistently shown an effect on circulating EE levels. A literature review highlights the lack of good evidence for antibiotics, except rifampicin, being responsible for COC failure, and lack of consistency in advice given to patients for using extra contraceptive precautions in data sheets. There is also variation across continents. It is accepted UK practice that COC used alone is unreliable while taking short courses of penicillins and tetracyclines, and for 7 days after stopping. The pill-free interval should be omitted if less than seven pills remain in the pack. When the drug is continued beyond 2 weeks, the study of 12 000 women in the Oxford FPA study. A study of 16 509 cycles showed increased break through bleeding in smokers, which was dose related, but does not seem to be linked to reduced contraceptive efficacy. Three reports of break through bleeding in COC users taking St John’s Wort (Hypericum perforatum) for depression have not been linked to pregnancies. Does taking contraceptive hormones have any effect on metabolism of other drugs? There are lists of drugs with changed circulating metabolites. There are few interactions that have clinical significance for the therapeutic or toxic effects of other concurrent medication, but there have been case studies of liver toxicity when taking cyclosporin, with the recommendation to monitor liver function.

**Transport of EE to the colon and reabsorption (EHC)**

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tetracycline or its derivatives. Barrier methods are required for the first 2 weeks. However, tetracyclines are started in someone already on COC, extra barrier methods are required for the first 2 weeks. However, some pregnancies have been reported in long term users of tetracycline or its derivatives.

The dose of combined hormonal emergency contraception does not need to be altered if taking antibiotics, as sufficient hormone is assumed to be initially absorbed from the small bowel.

Progestogen does not undergo an EHC. Thus the effectiveness of the POP, progestogen-only emergency contraception, injectables, implants and IUS are not affected by broad spectrum antibiotics.

Conclusion
Awareness of drugs that may affect the reliability of hormonal contraception is important for the patient and the clinician, and pill-taking rules should be checked at return visits. The only drugs known to have a clinically significant impact on contraceptive efficacy are rifampicin and rifamycin, griseofulvin, some anticonvulsants (topiramate, barbiturates, carbamazepine, and primidone), tetracyclin and, in some women, short courses of tetracyclines and ampicillin. For the other drugs discussed, there is very little direct evidence at the moment for any practical implications, and further research is needed.

References

Discussion points
1. What type of contraception would you prescribe for a patient on liver enzyme inducers?
2. How can prescribers determine if their patients have understood the pill taking rules?
3. How can awareness of the reporting of suspected drug interactions to the Committee on Safety of Medicines be raised?

FACT Review
A CPD Self-Assessment Test

QUESTION SHEET

Interactions with hormonal contraception

Indicate your answer by ticking the appropriate box for each question

1. The use of ampicillin reduces the contraceptive reliability of POP.
2. The enterohpatic circulation plays a large part in the effectiveness of the COC
3. Lamotrigine for the treatment of epilepsy requires extra contraceptive measures in COC users
4. The dose of combined emergency contraception should be changed when taking tetracycline
5. A patient taking griseofulvin should double the dose of Yuzpe emergency contraception (PC4)
6. Doxycycline use affects COC reliability
7. Break through bleeding while taking a liver enzyme inducer may indicate too low a dose of COC
8. Vitamin C in grapefruit juice raises the level of circulating EE
9. Enzyme inducers reduce the level of SHBG
10. A patient on long-term tetracyclines needs to use barrier protection for 7 days when starting the COC on Day 1 of the cycle

Turn to page 122 for answers
Interactions with hormonal contraception

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