FACULTY OF FAMILY PLANNING AND REPRODUCTIVE HEALTH CARE
OF THE ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

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REVIEW

This review is intended as an educational exercise and reports the personal views of the authors

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Interactions with hormonal contraception

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How to use a FACT

A FACT is an up-to-date review of a subject relevant to the speciality, intended to help you fulfil your CPD requirements in your home or place of work. Whilst FACTs are edited and reviewed at various levels within the Faculty, the actual contents and views expressed are those of the authors and not the Faculty. More specifically, these reviews are not guidelines. The CEC is producing clinical guidelines separately.

FACTs have three sections: a review, a true/false test, and discussion points. To use a FACT to earn CPD credits you should do the following:

1. **Working alone**: Read the review and do the test. The answers are provided on page 122 so you can mark yourself. If there are points you are unsure about, disagree with, or need further clarification on, make a note of these for use at a later date. This should take you no more than 1 hour. Keep a record of having done this in your CPD diary and, unless indicated otherwise on the FACT, this will earn you 1 hour (DFFP), 1 credit (MFFP).
2. **Working as a group**: arrange a meeting of at least 1 hour with colleagues to discuss the discussion points given in the FACT (page 111) and any issues the participants have come up with as a result of reading the FACT. Keep a record of having done this in your CPD diary and, unless indicated otherwise on the FACT, this will earn you 1 hour (DFFP), 1 credit (MFFP).

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.

The synthetic hormones ethinyloestradiol (EE) and progestogens are absorbed (if taken orally), transported to the liver, metabolised, and returned to the large bowel. Progestogen is excreted, whereas oestrogen is reabsorbed (the enterohepatic circulation, EHC).

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.[1] Competition for sulphuration between EE and Vitamin C causes no increased circulating levels of EE, or rebound reduction on stopping the vitamin,[2] 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[3] are bound with high affinity to sex hormone binding globulin (SHBG). The level of SHBG is increased by liver enzyme inducers,[4] 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, vigabactrin, gabapentin and lamotrigine), griseofulvin, barbiturates, and ritonovir (and possibly other protease inhibitors) all increase metabolism of EE and progestogens,[5] during and up to 1 month after stopping treatment.

A COC user needs at least 50 mcg of EE to ensure contraceptive action; efficacy *may* be further increased by tricycling, and/or decreasing the pill-free interval. It is common practice (for which there is no evidence) to consider the absence of break through bleeding as a marker of sufficient contraceptive cover in this situation.

POP users should switch to injectables or another form of contraception. Injectable progestogen methods are often given 2 weeks early; however the data sheet for Depo Provera states that no adjustment is needed, as the drug is cleared at a rate equal to the rate of hepatic blood flow and not changed by enzyme inducers. As there is debate about this, many family planning experts err on the side of caution. Users of progestogen implants require additional barrier methods or abstention from intercourse.[6] At present there is no evidence of interaction with the levonorgestrel IUS; most of its progestogenic effect is directly on the endometrium, with little absorption. The dose of combined hormonal emergency contraception should be increased by 50% to 3+3 pills.[7] There is no evidence about how much increase is required for progestogen-only emergency contraception, but experts suggest that the dose should also be increased by 50%.

Rifampicin and rifabutin are such powerful enzyme inducers that even short courses of 2 days of the former (used as prophylaxis in close contacts of cases of Neisseria meningitis) reduce contraceptive efficacy for a month.[8] Longer courses may have an interactive effect for up to 2 months after stopping. Oral contraceptive methods should not be relied on during this time. The same principles should apply to injectables, implants and IUS as stated above under enzyme inducers.

The following examples of theoretical enzyme induction or inhibition appear to have no clinical significance. The Summary of Product Characteristics for tacrolimus (used to induce immunosuppression in transplant patients) and lansoprazole (an ulcer-healing proton pump inhibitor) suggest non-hormonal contraception should be used due to increased metabolism of the hormones, but no evidence was found for an effect on levels of EE in 24 women on the latter drug.[9] Grapefruit juice (which contains nariginen) may increase bioavailability of EE due to reduction of metabolism.[10] Tretinoin (Vesanoid) is listed as interacting with POP and possibly COC in BNF March 1998; there is no published evidence of contraceptive failure with this drug or other retinoids. Modafinil seems to be at most a weak inducer of liver enzymes in vitro,[11] but again there are no published reported pregnancies linked to its use. In smokers, catabolism of EE was found to be increased in one small study,[12] but no increased failure rate was found in a study of 12 000 women in the Oxford FPA study.[13] A study of 16 509 cycles[14] 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.[15]

Does taking contraceptive hormones have any effect on metabolism of other drugs? There are lists of drugs with changed circulating metabolites.[16] 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,[17] with the recommendation to monitor liver function.

Conjugation in the liver

EE is conjugated to glucuronides and some sulphates, while there is no action on progestogens. Competition for conjugation does not seem to affect reliability of COC.

Transport of EE to the colon and reabsorption (EHC)

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,[18] 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[16] 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.[19] The International Consensus Statement[20] 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[21] 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

gut flora appear to become resistant, allowing a return to reabsorption of EE. The evidence for this is deduced from a small study,[22] and little work has been done to look at the effect in more detail. Patients already taking tetracyclines long term for acne are generally considered at no higher risk of pregnancy than normal when starting a COC. If long term 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.[23] 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), ritonovir 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

1 Joshi JM, Sankholi GM, Shar RS, Joshi UM. Antacid does not reduce the bioavailability of oral contraceptive steroids in women. *Internat J Clin Pharmacol Ther Toxicol* 1986; **24**: 192–195.
2 Zamah N, Humpel M, Kuhnz W, et al. Absence of an effect of high vitamin C dosage on the systemic availability of ethinyloestradiol in women using a combination oral contraceptive. *Contraception* 1993; **48**: 377–391.
3 Akpoviroro J, Mangalam M, Jenkins N, Fotherby K. Binding of the contraceptive steroids medroxyprogesterone acetate and ethynloestradiol in blood of various species. *J of Steroid Biochem* 1981; **14**: 493–498.
4 Back DJ, Breckenridge AM, Crawford FE, et al. The effect of oral contraceptive steroids and enzyme inducing drugs on sex hormone binding globulin capacity in women. *Brit J Clin Pharmacology, reprinted from proceedings of the B.P.S. 12-14th September 1979*. 1980; **9(i)**: 115P.
5 McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. *Contraception* 1994; **50 (Suppl 1)**: S105–198.
6 Odlind V, Olsson S-E. Enhanced metabolism of levonorgestrel during phenytoin treatment in a woman with Norplant implants. *Contraception* 1986; **33(3)**: 257–261.
7 Kubba A, Wilkinson C. Recommendations for clinical practice: Emergency Contraception. *Faculty of Family Planning and Reproductive Healthcare*. 1998; 1–8.
8 Orme M, Back DJ. Oral contraceptive steroids - pharmacological issues of interest to the prescribing physician. *Advances in Contraception* 1991; **7**: 325–331.
9 Fuchs W, Sennewald R, Klotz U. Lansoprazole does not affect the bioavailability of oral contraceptives. *Br J Clin Pharmac* 1994; **38**: 376–380.
10 Weber A, Jager R, Borner G, et al. Can grapefruit juice influence ethinylestradiol bioavailability? *Contraception* 1996; **53**: 41–47.
11 Chesne C, Kanmacher I, Benel,,L S L, G M **[Author - please check authors in this ref - initials?]**. Effects of modafinil on cytochrome-P450-dependent enzyme activities in cultured human hepatocytes. *14th Eur Workshop Drug Metab (July 3-9, Paris)* 1994: Abstract B23.
12 Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *New Eng J Med* 1986; **317 (21)**: 1305–1309.
13 Vessey MP, Villard-Mackintosh L, HS. J. Antiestrogenic effect of cigarette smoking. *New Eng J Med* 1986; **317 (12)**:769.
14 Rosenberg MJ, Waugh MS, Stevens CM. Smoking and cycle control among oral contraceptive users. *Am J Obstet Gynecol* 1996; **174 (2)**: 628–632.
15 Bon S, Harmann K, Kuhn M. Johanniskraut: Ein Enzyminduktor? *Schweitzer Apothekerzeitung* 1999; **16**: 535–536.
16 Back DJ, Orme ML'E. Drug interactions. In: Goldzieher J, Fotherby K, editors. *Pharmacology of the contraceptive steroids*. New York: Raven Press Ltd, 1994: 407–425.
17 Deray G, Le Hoang P, Cacoub P,et al. Oral contraceptive interaction with cyclosporin. *Lancet* 1987; **1**: 158–159.
18 Kovacs GT, Riddoch G, Duncombe P, et al. Inadvertant pregnancies in oral contraceptive users. *Med J Aust* 1989; **150**: 549–551.
19 Grimmer SFM, Back DJ, Orme ML'E, Cowie A, Gilmore I, Tjia J. The bioavailability of ethinyloestradiol and levonorgestrel in patients with an ileostomy. *Contraception* 1986; **33**: 51–59.
20 Hannaford P, Webb AMC. Evidence-guided prescribing of combined oral contraceptive: consensus statement. *Contraception* 1996; **54**: 125–129.
21 Weaver K, Glasier A. Interaction between broad-spectrum antibiotics and the combined oral contraceptive pill. A literature review. *Contraception* 1999; **59**: 71–78.
22 Leigh DA, Reeves DS, Simmons K, Thomas AL, Wilkinson PJ. Talampicillin: a new derivative of ampicillin. *British Medical Journal* 1976; **1**: 1378–1380.
23 London BM, Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives. *Arch Dermatol* 1994; **130**: 392–393.

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

		True	*False*
1.	The use of ampicillin reduces the contraceptive reliability of POP.	☐	☐
2.	The enterohepatic 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