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FREQUENTLY ASKED QUESTIONS ON HORMONAL CONTRACEPTION

-  **The potential for drug interactions with hormonal contraceptives should always be considered**
-  **Combined hormonal contraceptives are contraindicated in patients experiencing migraine with aura**
-  **All forms of hormonal contraception are contraindicated in patients with breast cancer**
-  **Women > 40 years who are sexually active should be offered an effective contraceptive method**

INTRODUCTION

The NMIC receives many queries in relation to contraception and we are pleased to provide information on this topic. As described in the previous bulletin (Hormonal Contraception Vol 16, No 4) there are many hormonal contraceptive methods available for women and the choice of which method to use depends on the individual patient. The UK Medical Eligibility Criteria (UKMEC) is a useful resource, which should be used in association with other sources including the individual Summary of Product Characteristics (SmPCs). This bulletin reviews some of our frequently asked questions.

IS THERE AN INTERACTION BETWEEN ANTIBACTERIAL THERAPY AND HORMONAL CONTRACEPTIVES?

Rifampicin and rifabutin induce cytochrome P450 hepatic enzyme activity, which increases the rate of metabolism of estrogens and progestogens, **thereby affecting contraceptive efficacy** of some hormonal contraceptive methods.¹ **The effectiveness of combined hormonal contraception (CHC) [including combined oral contraception (COC), patch and vaginal ring], progestogen only pills (POP), progestogen only (PO) implant and emergency hormonal contraception can be considerably reduced by these potent enzyme-inducing antibiotics.**²

For **short courses of an enzyme-inducing antibiotic** (e.g. a 2 day course of rifampicin or rifabutin),³ the dose of COC should be adjusted to provide ethinylestradiol (EE) 50 micrograms [unlicensed use] **as well as using additional contraceptive precautions** whilst taking the enzyme-inducing drug and for 4 weeks after stopping it.^{2,4} The pill-free interval should be omitted,^{2,4} and no gap should be left when transferring back from the higher to lower EE dose.³ Additional contraceptive precautions are also required for women using the POP, the PO implant and the contraceptive patch or vaginal ring, whilst taking the enzyme-inducing drug and for 4 weeks after stopping it. If concomitant administration runs beyond the 3 weeks of patch or vaginal ring use, a treatment cycle should be started immediately without a patch-free or vaginal ring-free break.²

Women requiring a **long-term course of these liver enzyme-inducing antibiotics** should **always** use alternative methods of contraception, during treatment and for up to 8 weeks after.² In general, liver enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effects of the **levonorgestrel intrauterine system (LNG-IUS)** and additional precautions are not required.² Similarly, the effectiveness of **depot medroxyprogesterone acetate (DMPA)** is not reduced.^{2,5}

The effectiveness of **levonorgestrel as emergency contraception** may be reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping the enzyme inducing drug); a copper intra-uterine device (Cu-IUD) can be offered instead, or the dose of levonorgestrel may be increased to a total of 3 mg taken as a single dose [unlicensed dose].^{2,6}

Non liver enzyme-inducing antibiotics do not reduce the effectiveness of progestogen-only (PO) contraception.^{2,4} Evidence has suggested that some non liver enzyme-inducing antibiotics may reduce the efficacy of CHC by reducing enterohepatic circulation of EE, although it is difficult to say which antibiotics may or may not be implicated.¹ Although recent guidelines suggest that CHC effectiveness is not affected by co-administration of most broad spectrum antibiotics,⁴ **many sources including individual SmPCs recommend additional contraceptive precautions for women on CHC with certain antibiotics.** Until further guidance becomes available the following is generally recommended.^{2,3,7}

COC users starting a short course of a non liver enzyme-inducing antibiotic should take additional contraceptive precautions whilst taking a short course and for 7 days after stopping. If these 7 days run beyond the end of a packet the next packet should be started immediately without a pill-free break.² Similar advice applies for those using the contraceptive patch or vaginal ring.² **COC users starting a long course of a non liver enzyme-inducing antibiotic** should use additional contraceptive precautions for the first 3 weeks after starting the antibiotic, with elimination of the next pill free interval if the first 2 weeks of antibiotic use extends into the last 7 days of the pack.³ After 3 weeks the bacterial flora develop antibacterial resistance, and additional precautions become unnecessary unless the antibiotic is changed or another antibiotic is started.^{2,3,7} Similar advice applies for those using the contraceptive patch or vaginal ring.

A woman already on a long-term (> 3 weeks) non liver enzyme-inducing antibiotic course who starts a COC does not require additional contraceptive precautions,^{2,3,7} unless the antibiotic is changed.⁷

WHAT CONTRACEPTIVE METHODS ARE SUITABLE FOR PATIENTS ON ANTI EPILEPTIC DRUGS?

Many women with epilepsy, which affects up to 1% of the population, require contraception. The choice of which contraceptive method to use is influenced by many factors including the type of antiepileptic drug (AED) that the woman is taking.⁸ Some AEDs induce cytochrome P450 hepatic enzyme activity resulting in an increase in metabolism of estrogens and progestogens and a **lowering of blood levels of the hormones by $\geq 50\%$ thereby affecting contraceptive efficacy.**⁸ Enzyme inducing AEDs (EIAEDs) include phenobarbitone, primidone, phenytoin, carbamazepine, oxcarbazepine and topiramate (dose dependent).^{6,8} Lamotrigine does not affect EE levels however it does appear to reduce levonorgestrel levels, the clinical significance of which is unknown.⁶ Of note, **EE reduces blood levels of lamotrigine**, therefore commencing CHC in a patient on lamotrigine monotherapy **may result in poorer control of epilepsy.**^{6,8} Conversely an increase in lamotrigine levels has been observed during the pill-free week and on discontinuation of COC.⁶ Due to the risk of drug interactions, lamotrigine is considered a UKMEC 3 (the risks generally outweigh the benefits).⁶ AEDs that do not affect hormonal contraception include: sodium valproate, levetiracetam, gabapentin, tiagabine, vigabatrin, benzodiazepines, pregabalin and zonisamide.^{6,8} In view of the risk of contraceptive failure and teratogenicity, it is recommended that **women on long-term EIAEDS should use a contraceptive method which is not affected by EIAEDs.**

Contraceptive methods which are affected by EIAEDs The following contraceptive methods are affected by EIAEDs and an alternative form of contraception should be offered to those on long-term EIAEDs. All of the **COCs** in Ireland contain ≤ 35 micrograms EE and are likely to be ineffective in women taking EIAEDs.^{6,8} Similarly other forms of CHC i.e. patch and vaginal ring are also not considered suitable for women on long-term EIAEDs.⁶ For women who are unable to use alternative forms of AEDs some sources recommend that COCs may be given at a minimum dose of 50 micrograms EE and that the COC is given in a tricycling regimen (in addition to using barrier methods), however this is an unlicensed indication and only suitable for monophasic pills.^{2,3,6,8,9} The contraceptive efficacy of **POPs** is also affected by EIAEDs.^{2,6,8,10-12} Unintended pregnancies have been reported in women on long-term EIAEDs with the **PO implant**,^{6,8} and an alternative method of contraception is recommended.^{2,13,14} The efficacy of **hormonal emergency contraception levonorgestrel**, is also affected by EIAEDs.^{6,8} A Cu-IUD may be offered instead or the dose of levonorgestrel may be increased to a total of 3mg as a single dose (unlicensed indication).^{2,6}

Contraceptive methods which are not affected by EIAEDs The efficacy of **DMPA** is not reduced by EIAEDs;^{2,5,6,8} there is no requirement to alter the dose or interval between injections.^{6,8} It is a useful option for women on EIAEDs, however patients should be informed about the effects on bone mineral density (see previous bulletin). The **LNG-IUS** is highly effective and not affected by EIAEDs which makes it a suitable option for women with epilepsy particularly those who are parous (it may also be suitable for nulliparous women with good counselling and expertise at insertion).⁸ A Cu-IUD is another contraceptive option for women on long-term EIAEDs.⁶

WHAT CONTRACEPTIVE IS SUITABLE FOR USE IN A WOMAN WITH MIGRAINE?

Headaches are relatively common in women of reproductive age. Epidemiological studies of migraine have shown that up to **one-third of women will experience migraine during their fertile years.**¹⁵ As such, clinicians are often questioned about the use of hormonal contraceptives in women with coexisting headaches. The occurrence of a migraine headache is an important consideration when prescribing a contraceptive. Migraines are often categorised by the presence or absence of fully reversible, focal neurological deficits known as aura, with approximately 10% of people with migraine having auras.¹⁶ Aura occurs before the onset of headache and symptoms include: homonymous hemianopia, unilateral paraesthesia and/or numbness; unilateral weakness, aphasia or unclassifiable speech disorder and visual symptoms.⁴ There is evidence that **migraine with aura is a risk factor for stroke.** In addition, smoking and age > 35 years can further increase this risk.¹⁶ Studies have also shown an increased risk of ischaemia in COC users; however the absolute risk remains low. Taking all these factors into consideration, concern about using the COC in women with migraine is warranted.^{3,16} It is therefore crucial to identify those women with aura. However, it is also important to identify those women with migraine without aura to ensure that such patients are not excluded unnecessarily from a useful contraceptive.³ Counselling for women without aura should include a warning to report any increase in headache frequency or onset of focal symptoms (discontinue immediately, seek medical help (also to ensure adequate contraceptive cover) and refer to a neurological expert if focal neurological symptoms not typical of aura persist for more than one hour).²

In the presence of multiple risk factors for stroke, non-estrogen containing alternatives can be utilised. Although studies are limited regarding the use of progestogen-only contraceptives (POCs) in women with migraine, there is no evidence to suggest an increased risk of stroke: **POCs are generally considered to be safe in women with migraine.**^{15,16} The UKMEC for contraceptive use rates POCs in this setting as category 2 (apart from initiation in migraine without aura rating=1) i.e. the advantages of using this method generally outweigh the risks (Table 1).⁴ Vomiting associated with migraine may also interfere with the efficacy of oral contraceptives and the use of long-acting methods should be considered in such women.¹⁶

Table 1: Contraceptive choice in women with headache^{4,17}

Headaches	CHC		POP		DMPA	IMP	Cu-IUD	LNG-IUS
	I	C	I	C				
Non-migrainous (mild or severe)	1*	2	1	1	1	1	1	1
Migraine without aura, at any age	2	3	1	2	2	2	1	2
Migraine with aura, at any age	4	4	2	2	2	2	1	2
Past history (≥ 5 yrs ago) of migraine with aura, any age	3	3	2	2	2	2	1	2

* UKMEC 1 - A condition for which there is no restriction for the use of the contraceptive method
 UKMEC 2 - A condition where the advantages of using the method generally outweigh the theoretical or proven risks
 UKMEC 3 - A condition where the theoretical or proven risks usually outweigh the advantages of using the method
 UKMEC 4 - A condition which represents an unacceptable health risk if the contraceptive method is used.

CHC=combined hormonal contraceptive, POP=Progestogen only pill, DMPA=Depot medroxyprogesterone acetate IMP=PO implant, Cu-IUD=Copper intrauterine device, LNG-IUS=Levonorgestrel intrauterine system

I=Initiation - Starting a method of contraception by a woman with a specific medical condition.

C=Continuation - Continuing with the method already being used by a women who develops a new medical condition

IS THERE A LINK BETWEEN USE OF ORAL CONTRACEPTIVES (OC) AND THE DEVELOPMENT OF BREAST CANCER?

Several epidemiological studies have evaluated a possible role of OC use in the development of breast cancer. A meta-analysis from the 1990s suggested that there was a slightly increased risk of breast cancer in current users and in those who had used CHC in the previous 10 years but that the risk diminished steadily after use and had disappeared by 10 years after use.¹⁸ However, this analysis was criticised because it included studies that were very different and it dealt with outmoded CHC preparations.¹⁹ A population-based case control study (n=5,000 cases of breast cancer and 5,000 matched controls) concluded that current or former use of OCs among women aged 35-64 years did not significantly increase the risk of breast cancer.²⁰ These data provided strong evidence that former OC use did not increase the risk later in life when the incidence of breast cancer is higher. The UK Royal College of General Practitioners' OC cohort study has been following up women (recruited as either healthy current OC users or healthy non-users (n=23,000 per group, mean age 29 years) since 1968. It recently reported on the risk of developing, and dying from, cancer in the cohort.²¹ Based on a dataset of over 744,000 woman years (ever users of OC) and 339,000 woman years (never users), results showed no difference in either the risk of developing breast cancer²¹ or in mortality from breast cancer²² between the groups. At the time of this review, virtually all of the cohort were post-menopausal, which reflects a time when the rate of breast cancer is increasing, therefore the results provide reassuring evidence on the safety of OC.

WHAT TYPE OF CONTRACEPTIVE SHOULD I RECOMMEND FOR MY PATIENTS WHO HAVE, OR HAVE HAD, BREAST CANCER OR WHO HAVE A FAMILY HISTORY OF BREAST CANCER?

Breast cancer is a hormonally-sensitive cancer, therefore it is important to ensure that the benefits of use of a particular hormonal contraceptive are not outweighed by the risk of developing or worsening breast cancer. Table 2 outlines the current recommendations (as per the UKMEC criteria) for use of the various contraceptive preparations in subjects with risk (potential) factors for breast cancer.^{3,4}

Table 2: Recommended contraceptive methods according to breast cancer risk^{3,4}

Existing Condition	CHC	POP	DMPA	IMP	LNG-IUS	Cu-IUD
Family history of breast cancer	1*	1	1	1	1	1
Current breast cancer	4	4	4	4	4	1
Previous breast cancer but no evidence of disease for 5 years	3	3	3	3	3	1
Carriers of "breast cancer" gene mutations (e.g. BRCA1)	3	2	2	2	2	1

* UKMEC 1 – 4 classification used

Studies have reported no apparent increased breast cancer risk with use of OC among women with a positive family history of breast cancer; therefore any of the contraceptive methods can be recommended for this group.^{3,4,23} Carriers of known gene mutations such as BRCA1 and BRCA2 are reported to have an incidence of breast cancer of approximately 2 per 100/year.²⁴ Most research into the effect of OC in this group has focused on CHC usage and much of the data are derived from retrospective studies.²⁵ The results are conflicting regarding increased risk with use of OC and may be confounded by the higher levels of oestrogen in earlier CHC formulations. The current advice is that the benefits of CHC in this population are outweighed by potential risk and therefore alternative methods such as progesterone only preparations should be used.^{3,4} All forms of hormonal contraception are contraindicated in patients with current breast cancer (UKMEC=4). In those with previous breast cancer, CHC has a negative benefit/risk ratio in patients but the progesterone only formulations are deemed acceptable and may be used (Table 2). As outlined in Table 2, there is no specific restriction or contraindication to use of the Cu-IUD in relation to the presence or risk of breast cancer.

WHAT CONTRACEPTIVE IS SUITABLE TO USE IN WOMEN OVER 40 YEARS OF AGE?

There is a natural decline in fertility from the mid 30s onwards; however effective contraception is required for sexually active women to prevent an unintended pregnancy. The **risks of miscarriage, pregnancy complications, chromosomal complications and maternal morbidity and mortality increase for a woman > 40 years.**^{3,26} There is no such thing as a single best contraceptive method for women > 40 years and no contraceptive method is contraindicated by age alone.²⁶ Age however may become a significant risk factor for developing medical conditions that could impact on the contraceptive method.²⁹ UKMEC is a useful resource for prescribers, however, clinical judgement is also required particularly for patients with multiple medical and social factors. Contraceptive methods that can be used **without restriction** by perimenopausal women include: the LNG-IUS, POP, PO implant, Cu-IUDs, barrier methods, and sterilisation.^{3,26}

Combined hormonal contraception is not contraindicated by age alone in perimenopausal women. However this applies to women who are **entirely healthy and completely free of arterial and venous risk factors,**^{3,26} including being migraine free, a non-smoker and normotensive.²⁶ CHC use may be associated with a very small increased risk of ischaemic stroke, which is increased by hypertension. Prescribers may consider a COC with < 30 micrograms EE as an appropriate choice for such women.^{3,26}

Progestogen only contraceptives (POCs) do not appear to increase the risk of stroke or MI, there is little or no increase in venous thromboembolism risk and no evidence of a link between POC and breast cancer.²⁶ **There is no restriction on the use of POPs, PO implant and the LNG-IUS in women > 40 years.**²⁶ **DMPA** is associated with a reversible reduction in BMD and an alternative method of contraception should be used in women with risk factors for osteoporosis (see bulletin Vol 16, No.4). The risk/benefit of DMPA should be evaluated every 2 years and it should not be used after the age of 50 years.²⁶ As DMPA has a greater effect on lipid metabolism than other POCs, caution is required when prescribing DMPA to women with cardiovascular risk factors.²⁶

Emergency contraception: There are no restrictions on the use of emergency contraception based on age alone.

AT WHAT AGE CAN A WOMAN STOP CONTRACEPTION?

Women using **non-hormonal** methods of contraception can stop contraception after 1 year of amenorrhoea if aged > 50 years and after 2 years if aged < 50 years.^{3,26} In general, **hormonal contraception may be stopped at the age of 55 years**; however, this advice needs to be tailored to the individual woman. Ideally women on DMPA and CHC > 50 years should be advised to switch to an alternative method such as the POP, PO implant, LNG-IUS or barrier method until the age of 55 years or until the menopause can be confirmed. Amenorrhoea is not a reliable indicator of ovarian failure for women using **exogenous hormones**. Follicle-stimulating hormone (FSH) is not a reliable indicator of ovarian failure in women using CHC, even if measured during the hormone-free interval.^{3,26} In women using POC, FSH levels may be used to help diagnose the menopause, but should be restricted to women > 50 years.²⁶ Women > 50 years who are amenorrhoeic and wish to stop POC should have their FSH levels checked on 2 occasions; if the level is ≥ 30 IU/L the FSH should be repeated after 6 weeks and if the second FSH level is ≥ 30 IU/L, POC can be stopped after 1 year.

It is important that sexually active women on **hormone replacement therapy (HRT)**, who may be fertile, be advised to use a contraceptive method.^{3,26} The LNG-IUS is an effective method which can be used with HRT and some sources recommend that POPs can be used in combination with standard HRT.^{3,26} Women using oestrogen replacement therapy may use the LNG-IUS as the progestogen to provide endometrial protection. (While the current marketing authorisation states that LNG-IUS should be removed after 5 years,²⁷ some experts recommend that it should be removed after 4 years when used as the progestogenic component of HRT^{3,28}).

WHAT IS THE CONTRACEPTIVE OF CHOICE FOR AN OBESE WOMAN?

Evidence suggests that obese women are significantly less likely to use contraception as compared to women with normal body mass index (BMI), even though they are at similar risk of pregnancy as those who are not obese.²⁹ Obese women are more at risk of pregnancy complications than those who are not.^{29,30} The efficacy of hormonal contraception in obese women has not been well studied; the results have been inconsistent and there are limitations to many of the studies.²⁹ The UKMEC advice is listed in table 3 and additional information is described below.

Table 3: UK Medical Eligibility Criteria for obesity⁴

Condition	CHC	POP	DMPA	IMP	LNG-IUS	Cu-IUD
Obesity						
≥ 30 - 34 kg/m ²	2	1	1	1	1	1
≥ 35 kg/m ²	3	1	1	1	1	1
Multiple risk factors for cardiovascular disease Such as older age, smoking, diabetes, hypertension and obesity	3/4	2	3	2	2	1

Combined hormonal contraception (CHC): There is conflicting evidence as to whether obesity may be associated with an increased risk of CHC failure.^{29,31-33} The contraceptive patch appears to be associated with reduced contraceptive efficacy in women > 90kg.^{29,32} **CHC use is associated with an increased risk of venous thromboembolism (VTE) (see bulletin Vol. 16, No.4) and morbid obesity is an independent risk factor for VTE.**²⁹ In view of the additional increased risk of VTE associated with COC, their use is usually not recommended in women with a BMI ≥ 35 kg/m².^{3,17,31}

Progestogen only contraception: There is no current evidence that the efficacy of the POP is reduced in obesity, even though this has been suggested in the past.^{3,10,17} Some sources recommend the **desogestrel-only pill for women >70kg.**^{3,17} **DMPA** users should be advised that there is an association between DMPA use and weight gain.^{3,34} Current evidence does not suggest reduced efficacy of DMPA in obesity,³² however it is not recommended in women with multiple risk factors for CVD.⁴ There have been concerns that the efficacy of **PO implant** may be reduced in women with a BMI of > 30 kg/m².¹³ The contraceptive efficacy of the etonogestrel implant is related to the plasma levels of etonogestrel which are inversely related to body weight and decrease with time after insertion.¹⁴ This may result in reduced contraceptive efficacy during the third year of use and clinicians may consider replacement of the implant in these circumstances.^{14,17} There are no restrictions on the use of **LNG-IUS** or **Cu-IUD** in women with obesity.

USEFUL RESOURCES PROVIDING INFORMATION ON CONTRACEPTION

www.medicines.ie / www.imb.ie Access to SmPCs for authorised medicines

www.bnf.org - British National Formulary

Contact the National Medicines Information Centre – nmic@stjames.ie and 01 4730589

Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists -

<http://www.ffprhc.org.uk>

Contraception: Your Questions Answered, John Guillebaud, 5th Edition (2009), Churchill Livingstone Elsevier

NHS Clinical Knowledge Summaries (CKS)- <http://www.cks.nhs.uk/home>

World Health Organisation - <http://www.who.int/topics/contraception/en/>

List of references available on request. Date of preparation: Dec 2010

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug

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