Faculty of Sexual & Reproductive Healthcare Clinical Guidance

Combined Hormonal Contraception

Clinical Effectiveness Unit

October 2011
(Updated August 2012)

ABBREVIATIONS USED

BMI	body mass index
BNF	*British National Formulary*
BP	blood pressure
CEU	Clinical Effectiveness Unit
CHC	combined hormonal contraception/combined hormonal contraceptives
CI	confidence interval
COC	combined oral contraception
CTP	combined transdermal patch
CVR	combined vaginal ring
DSP	drospirenone
EC	emergency contraception
EE	ethinylestradiol
FSRH	Faculty of Sexual and Reproductive Healthcare
HPV	human papillomavirus
LNG	levonorgestrel
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
NET-EN	norethisterone enantate
POP	progestogen-only pill
RR	relative risk
SPC	Summary of Product Characteristics
STI	sexually transmitted infection
UKMEC	*UK Medical Eligibility Criteria for Contraceptive Use*
UPSI	unprotected sexual intercourse
VTE	venous thromboembolism
WHOMEC	World Health Organization *Medical Eligibility Criteria for Contraceptive Use*

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

CONTENTS

SUMMARY OF KEY RECOMMENDATIONS

How does combined hormonal contraception (CHC) work?

C Women can be informed that the bleed experienced during the hormone-free interval or placebo week of pill taking is due to withdrawal of hormones rather than a menstrual bleed.

C Health professionals may wish to advise women about the use of extended or continuous regimens of CHC but should be aware that such use is off licence.

CHC efficacy

B Women can be informed that the efficacy of all CHCs is generally similar.

Initial assessments for CHC

✓ Health professionals should take a detailed history from women requesting CHC and should recheck the history at least annually. The history should include medical conditions such as migraine, drug use, family medical history, and lifestyle factors such as smoking.

C A blood pressure recording should be documented for all women prior to first prescription of CHC.

✓ Body mass index (BMI) should be documented for all women prior to first prescription of CHC.

Drug interactions

C Additional contraceptive precautions are not required when antibiotics that do not induce enzymes are used in conjunction with combined hormonal contraceptives (CHCs).

✓ 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 and the hormone-free interval shortened to 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 taking an enzyme-inducing drug and who do not wish to change from COC or use additional precautions may increase the dose of COC to at least 50 µg EE (maximum 70 µg EE) and use an extended or tricycling regimen with a pill-free interval of 4 days.

C Women taking lamotrigine (except in combination with sodium valproate) 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 should be advised that ulipristal acetate (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 progestogen-only pill, 16 days for the estradiol valerate/dienogest pill) (outside product licence).

Risks, non-contraceptive health benefits and side effects

B Health professionals should be aware that compared to non-users, the risk of venous thromboembolism (VTE) with use of CHC is approximately doubled but that the absolute risk is still very low.

B Health professionals prescribing CHCs should be guided by the individual's own personal preference, risk of VTE, any contraindications, possible non-contraceptive benefits and experience with other contraceptive formulations.

Risks, non-contraceptive health benefits and side effects

C A personal history of VTE or a known thrombogenic mutation are conditions that represent an unacceptable health risk if CHC is used.

C For women with a family history of VTE, a negative thrombophilia screen does not necessarily exclude all thrombogenic mutations.

C A thrombophilia screen is not recommended routinely before prescribing CHC.

B Use of CHC in women aged ≥35 years who smoke is not recommended.

B Health professionals should be aware that there may be a very small increase in the absolute risk of ischaemic stroke associated with CHC use.

C The risks of using CHC in women with properly taken blood pressure (BP) which is consistently elevated generally outweigh the advantages. Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg is a condition that represents an unacceptable health risk if CHC is used.

B The risk of using CHC in women with a BMI ≥35kg/m^2 usually outweighs the benefits.

B Migraine with aura is a condition for which the use of CHC presents an unacceptable health risk.

B Health professionals should be aware that any risk of breast cancer associated with CHC use is likely to be small, and will reduce with time after stopping.

B Health professionals should be aware that CHC use may be associated with a small increase in the risk of cervical cancer which is related to duration of use.

✓ Health professionals should check that women coming for CHC are up to date with cervical cytology screening in accordance with screening recommendations.

B Women can be advised that CHC use does not appear to have a negative effect on overall mortality.

B Use of COC is associated with a reduced risk of ovarian and endometrial cancer that continues for several decades after stopping.

A Health professionals should be aware that CHC may help to improve acne.

B Health professionals should be aware that COC use is associated with a reduction in the risk of colorectal cancer and this may also apply to other CHCs.

C Health professionals should be aware that use of CHC may help to reduce menstrual pain and bleeding.

C Women can be advised that CHC may reduce menopausal symptoms.

✓ Before starting CHC women should be advised about expected bleeding patterns both initially and in the longer term.

C Women can be advised that CHC may be associated with mood changes but there is no evidence that it causes depression.

C Women can be advised that the current evidence does not support a causal association between CHC and weight gain.

CHC whilst travelling or at high altitude

✓ Women taking CHC should be advised about reducing periods of immobility during flights over 3 hours.

✓ Women trekking to altitudes of >4500 m for periods of more than 1 week may be advised to consider switching to an alternative method.

Faculty of Sexual and Reproductive Healthcare
Clinical Effectiveness Unit

A unit funded by the FSRH and supported by NHS Greater Glasgow & Clyde
to provide guidance on evidence-based practice

FSRH Guidance (October 2011)
Combined Hormonal Contraception

(Update due by October 2016)

1 Purpose and Scope

This document provides clinical guidance on combined hormonal contraception (CHC). It is intended for any healthcare professional or service providing contraception or contraceptive advice in the UK. This document updates and replaces previous Faculty of Sexual and Reproductive Healthcare (FSRH) guidance on *First Prescription of Combined Oral Contraception*[1] and the new product reviews for the combined transdermal patch (CTP) (Evra®)[2] and the combined vaginal ring (CVR) (Nuvaring®).[3] The main changes from the previous guidance are the inclusion of:

- All combined hormonal methods
- New advice in relation to CHC and antibiotics that do not induce enzymes
- New missed pill advice
- Advice in relation to incorrect use of the patch and ring
- Updated *UK Medical Eligibility Criteria for Contraceptive Use*.

Recommendations within this document are based on available evidence and consensus opinion of experts. They 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. 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 and in the CEU section of the FSRH website.

2 Background

One of the most commonly used contraceptive methods in the UK is the combined oral contraceptive pill (COC).[4] Combined hormonal contraceptives (CHCs) contain estrogen and progestogen and there are currently three methods available in the UK:

- Combined oral contraceptive pill (COC)
- Combined transdermal patch (CTP)
- Combined vaginal ring (CVR).

Currently available CHCs contain synthetic estrogen [ethinylestradiol (EE) or mestranol], except for the COC Qlaira®, which contains estradiol valerate. Recommendations apply to all CHCs unless otherwise stated.

The majority of women can use combined hormonal methods without harm. However, there are some medical conditions and lifestyle factors that are associated with either theoretical or proven health risks if a combined hormonal method is used. Women should be empowered to make informed decisions about choosing and using COC (see Section 5 on assessment, page 4).

3 How Does CHC Work?

CHC works primarily by inhibiting ovulation via action on the hypothalamo-pituitary-ovarian axis to reduce luteinising hormone and follicle-stimulating hormone.[5–7] Alterations to cervical mucus and the endometrium may also contribute to the efficacy of CHC.

3.1 Standard regimen

3.1.1 Combined oral contraception (COC)

The majority of COCs in the UK are monophasic (fixed dose) pills containing between 20 and 35 µg of EE in combination with a progestogen. Variable dose (phasic) COCs are also available. The majority of COCs contain 21 active pills; the first seven pills inhibit ovulation and the remaining 14 pills maintain anovulation. Traditionally women have then either had seven pill-free days or taken seven placebo tablets before starting the next packet of pills. During this time most women will have a withdrawal bleed due to endometrial shedding.

3.1.2 Combined transdermal patch (CTP)

The CTP measures 20 cm² and releases an average of 33.9 µg EE and 203 µg norelgestromin per 24 hours.[8] One patch is applied and worn for 1 week to suppress ovulation. Thereafter the patch is replaced on a weekly basis for two further weeks. The fourth week is patch-free to allow a withdrawal bleed. A new patch is then applied after seven patch-free days.

3.1.3 Combined vaginal ring (CVR)

The CVR releases EE and etonogestrel at daily rates of 15 µg and 120 µg, respectively. A ring is inserted into the vagina and left in continuously for 21 days. After a ring-free interval of 7 days to induce a withdrawal bleed, a new ring should be inserted.

3.2 Tailored regimens

The traditional cyclical pill regimens were designed to induce a bleed each month, mimicking naturally occurring menstrual cycles. However, the bleed experienced during the placebo or pill-free week is due to the withdrawal of hormones rather than physiological menstruation.

There are COCs that are licensed to be used continuously[9] or with pill-free intervals less than 7 days.[10,11] In the UK the only currently available regimen is the COC containing estradiol valerate with dienogest (Qlaira), which consists of 26 active pills and two placebo tablets.[11]

Continuous dosing or extended regimens of CHCs are an alternative approach to CHC administration. A Cochrane review[12] has concluded that continuous dosing/extended regimens are a reasonable approach to CHC use. The review[12] found that the included study findings were similar in terms of contraceptive efficacy (i.e. pregnancy rates), safety profiles and compliance, and that where satisfaction was assessed, women reported high satisfaction with extended regimens.

The potential advantages of such regimens are that they enable women to eliminate or reduce the frequency of their withdrawal bleed and any related symptoms. Within a small prospective study, greater pituitary and ovarian suppression was observed when the hormone-free interval was shortened from 7 to 3–4 days.[13] An observational study[14] looking at the effectiveness of a 24/4 regimen compared with a 21/7 regimen suggests improved efficacy with the 24/4 regimen, although bias and confounding cannot be excluded.

A variety of regimens and preparations have been studied; however, there is currently insufficient data to recommend one approach over another.[12]

The CEU supports the use of tailored regimens such as those detailed in Table 1. The regimens in Table 1 only apply to monophasic CHCs. Women using everyday COCs would need to be advised to omit the placebo pills in a packet or to switch to a monophasic 21-day COC. The CEU does not have separate guidance on missed pills when using such regimens and when emergency contraception (EC) would be required. This would be a matter of clinical judgement based on the missed pill rules for cyclical regimens.

C Women can be informed that the bleed experienced during the hormone-free interval or placebo week of pill taking is due to withdrawal of hormones rather than a menstrual bleed.

C Health professionals may wish to advise women about the use of extended or continuous regimens of CHC but should be aware that such use is off licence.

Table 1 Tailored regimens for use of combined hormonal contraception (CHC)

Type of regimen	Suggested regimen	CHC-free period
Extended use	Tricycling (3 cycles taken continuously back to back, i.e. 3 pill packets or 3 rings, or 9 patches)	7 days taken after finishing the 3rd packet, 3rd ring or 9th patch
Shortened pill-free interval	3 weeks of CHC use	4 days taken after each packet of pills, each ring or 3rd patch
Extended use with shortened pill-free interval	Method used continuously (≥21 days; pill, patch and ring-free weeks omitted) until breakthrough bleeding occurs for 3–4 days	4-day interval
Extended use with regular pill-free interval	Method used continuously (≥21days; pill, patch and ring-free weeks omitted) until breakthrough bleeding occurs for 3–4 days	7-day interval

4 How do Each of the CHC Methods Compare to One Another?

4.1 Efficacy

A Cochrane review comparing the combined patch, ring and pill has concluded that these methods have similar efficacy.[15] With perfect use (following directions for use) the failure rate is 0.3% and with typical use (actual use including inconsistent or incorrect use) is 9%.[16]

Epidemiological studies[17,18] have produced conflicting findings about whether the contraceptive efficacy of different methods varies with the weight of the user. The difficulty with observational studies is separating the influence of weight from other factors such as inconsistent pill taking. Several small pharmacokinetic studies have examined differences in indicators such as ovarian suppression, hypothalamic-pituitary-ovarian activity, and follicular diameters among obese and normal weight women using combined oral contraception.[19,20] A Cochrane review[21] has concluded that the current evidence examining the effects of body mass index (BMI) on COC effectiveness is limited and that COC appears to be effective in all women when the recommended regimen is followed.

The Summary of Product Characteristics (SPC) for the CTP[8] specifies that contraceptive efficacy may be decreased in women weighing ≥90 kg, therefore additional precautions or an alternative method should be advised.

4.2 Cycle control

Unscheduled bleeding is less common with CHC than with progestogen-only methods.[22] The CTP and COC provide similar cycle control, with the CVR providing similar or improved cycle control compared with COCs.[15] Cycle control may be better with COCs containing 30–35 μg EE compared with those containing 20 μg EE.[23]

4.3 Side effects

Data on side effects predominately come from observational studies rather than placebo-controlled trials, therefore causation is difficult to prove. A Cochrane review noted that overall compared to pill users, CTP users experience more breast discomfort, dysmenorrhoea, nausea and vomiting.[15] CVR users report less nausea, acne, irritability and depression than pill users, but studies suggest they experience more vaginal irritation and discharge.[15]

4.4 Adherence

Discontinuation of hormonal contraception is common and occurs frequently within the first 6 months of use.[24] Figures from the USA suggest that approximately 68% of women will have discontinued contraception by the end of 12 months, although oral contraceptives were the least likely method of contraception to be discontinued for method-specific reasons (32%).[24] Discontinuation is likely to be followed by resumption of another method rather than complete abandonment of contraception.[24] In relation to CHC, rates are generally similar for COC and CVR users, whereas in clinical trials CTP users have reported better compliance than COC users.[15]

4.5 Cost

Presently there are insufficient data to make cost-effectiveness comparisons between the combined hormonal methods. The CVR and CTP are generally more expensive than COCs. Costs of the different CHCs are listed in the *British National Formulary* (BNF).[25]

B	Women can be informed that the efficacy of all CHCs is generally similar.

5 What Assessments are Needed Before Prescribing a Woman CHC for the First Time?

In order to assess medical eligibility, it is important that health professionals take a detailed history which should include: medical conditions (past and present); family history of medical conditions (past and present); and drug history (prescription, non-prescription and herbal remedies). Specific attention should be given to enquiring about migraine and cardiovascular risk factors [smoking, obesity, hypertension, thrombophilia, previous venous thromboembolism (VTE) and hyperlipidaemia]. A recording of blood pressure (BP), weight and BMI should be documented for all women before a first prescription of CHC. Routine screening for thrombogenic mutations prior to CHC prescription is not appropriate because of the rarity of the conditions and the high costs of screening.[26]

UK Medical Eligibility Criteria for Contraceptive Use (UKMEC)[26] provides evidence-based recommendations on the use of contraceptive methods in the presence of different medical and social factors. UKMEC should be referred to when assessing a person's eligibility for combined hormonal contraception. Unless specifically stated, UKMEC does not however take account of multiple conditions. Therefore assessing a person's eligibility in the presence of multiple medical and social factors will require clinical judgement and balancing of risks and benefits. Table 2 highlights the definitions for UKMEC categories relevant to CHC.

✓	Health professionals should take a detailed history from women requesting CHC including medical conditions such as migraine, drug use, family medical history, and lifestyle factors such as smoking, and should recheck the history at least annually.
C	A blood pressure recording should be documented for all women prior to first prescription of CHC.
✓	BMI should be documented for all women prior to first prescription of CHC.

6 When in the Menstrual Cycle can CHC be Started?

Conception is most likely to occur following unprotected sexual intercourse (UPSI) on the day of ovulation or in the preceding 24 hours.[27] Due to the natural variation in timing of ovulation the timing of the 'fertile period' is highly variable, particularly among women with more irregular cycles[27] and there are few days in the menstrual cycle when women are not theoretically at risk of pregnancy.[27] However, the probability of pregnancy from a single act of intercourse in the first 3 days of the cycle appears to be negligible.[28]

A small prospective study[29] designed to examine the effects of initiating COCs at defined stages of ovarian follicle development found that when a 30 μg EE COC was initiated at a follicle diameter of 10 ± 1 mm (mean Day 7.6 ± 0.5; range Day 1–16) no women ovulated (0/16). However 36% of women (5/14) ovulated when COC was initiated at 14 ± 1 mm (mean Day 11.7 ± 0.7; range Day 5–20) and 93% of women (14/15) ovulated when COC was initiated at 18 ± 1 mm (mean Day 13.6 ± 0.8; range Day 7–20).

On the basis of data from a variety of studies,[5,30,31] CEU guidance is currently that COCs containing EE can be started up to and including Day 5 of the cycle without the need for additional contraceptive protection. This is in line with advice from the World Health Organization (WHO).[32] Beyond Day 5 a woman may start COC at any other time if it is reasonably certain she is not pregnant (Box 1). When starting COCs after Day 5 women should

Table 2 Definition of *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC) categories[26]

Category	Definition
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. Provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since the use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
UKMEC 4	A condition which represents an unacceptable health risk if the contraceptive method is used.

Box 1 Criteria for excluding pregnancy (adapted from *UK Selected Practice Recommendations for Contraceptive Use*)[8]

Health professionals can be 'reasonably certain' that a woman is **not currently pregnant** if any one or more of the following criteria are met and there are no symptoms or signs of pregnancy:
- Has not had intercourse since last normal menses
- Has been correctly and consistently using a reliable method of contraception
- Is within the first 7 days of the onset of a normal menstrual period
- Is within 4 weeks postpartum for non-lactating women
- Is within the first 7 days post-abortion or miscarriage
- Is fully or nearly fully breastfeeding, amenorrhoeic, and less than 6 months postpartum.

A pregnancy test, if available, adds weight to the exclusion of pregnancy but only if ≥3 weeks since the last episode of UPSI.

NB. Health professionals should also consider if a woman is **at risk of becoming pregnant** as a result of UPSI within the last 7 days and undertake pregnancy testing where appropriate (≥3 weeks since last UPSI).

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use additional precautions such as condoms or avoid sex for the next 7 days. The CEU advise that the estradiol valerate/dienogest-containing pill (Qlaira) should be started on Day 1, with additional precautions used for 9 days if starting any time after this.

For the CTP and CVR there is little direct evidence on the safety of starting after Day 1. In a randomised study[33] comparing ovarian suppression between the CVR started on Day 5 and COC started on Day 1 a difference was found in the maximum follicular diameters in the first treatment cycle, with those starting the ring having larger follicular diameters than those starting the COC. However, ovulation was adequately suppressed with no ovulations occurring in either group.[33] In a small, open-label, randomised study ovarian suppression has been demonstrated with 3 days of ring use.[34] No evidence is available for the CTP and therefore the advice is extrapolated from COC evidence.

Table 3 Starting combined hormonal contraception

Circumstance	When to start	Additional contraceptive protection required?
Women having menstrual cycles	Up to and including Day 5 (Day 1 for estradiol valerate/dienogest pill)	No
	At any other time if it is reasonably certain she is not pregnant	Yes (7 days, 9 days for estradiol valerate/dienogest pill)
Women who are amenorrhoeic	At any time if it is reasonably certain she is not pregnant	Yes (7 days, 9 days for estradiol valerate/dienogest pill)
Postpartum (not breastfeeding)	Start on Day 21 postpartum if no additional risk factors for VTE[a]	No
(See UKMEC[26] for guidance on CHC use in breastfeeding women)	After Day 21 postpartum, if menstrual cycles have returned, start CHC as for other women having menstrual cycles[a]	No if starting up to Day 5
		Yes (7 days) if starting after Day 5
		No if starting estradiol valerate/dienogest pill on Day 1
		Yes (9 days) if starting estradiol valerate/dienogest after Day 1
	After Day 21 postpartum if menstrual cycles have not returned start as amenorrhoeic women[a]	Yes (7 days, 9 days estradiol valerate/dienogest pill)
Post first- or second-trimester abortion	Up to and including Day 5[b] post abortion (Day 1 for estradiol valerate/dienogest pill)	No
	At any other time if it is reasonably certain she is not pregnant	Yes (7 days, 9 days for estradiol valerate/ dienogest pill)

[a]It should be noted that in 2010 World Health Organization guidance in relation to postpartum women starting CHC was revised to advise more restrictive use, particularly if women have additional risk factors for venous thromboembolism.
[b]The CEU advises that women ideally start CHC on the day of or day after a first- or second-trimester abortion
CHC, combined hormonal contraception; UKMEC, *UK Medical Eligibility Criteria for Contraceptive Use*.

Table 4 Clinical Effectiveness Unit advice on switching to and between combined hormonal contraception

Switching from	Switching to	When to start	Additional contraceptive protection required?	Notes
CHC	Another CHC	Start on day after last active COC, CTP, CVR	No	If a 7-day interval is taken the need for additional precautions and EC should be assessed on an individual basis, taking account of correct use before the hormone-free period
Traditional POPs and LNG-IUS	CHC	Can be started immediately if the previous method was used consistently and correctly	Yes (7 days, 9 days estradiol valerate/dienogest pill)	The primary mode of action is not inhibition of ovulation and therefore additional precautions are required in case ovulation occurs before contraceptive efficacy of CHC has been established. The cervical mucus effect may be maintained but there is no evidence to prove adequate contraceptive protection
Progestogen-only anovulatory methods (implant, injectable and desogestrel-only pill)	CHC	Can be started any time up to when the repeat injection is due or implant is due for removal or next day after pill	No	The primary mode of action of these methods is inhibition of ovulation. CHC suppresses ovulation by the time the inhibitory effect of the previous method is lost
Non-hormonal method (other than an IUD)	CHC	As per starting advice	No if starting Day 1–5 (Day 1 only for estradiol valerate/dienogest pill) Yes (7 days, 9 days estradiol valerate/dienogest pill) if amenorrhoeic or starting any time after Day 5	As per starting advice
IUD	CHC	Up to Day 5 of menstrual cycle. IUD can be removed at that time (Day 1 only estradiol valerate/dienogest pill)	No	
		At any other time during the menstrual cycle or if amenorrhoeic	Yes (7 days, 9 days for estradiol valerate/dienogest pill)	Additional precautions are required unless CHC was started 7 days prior to IUD removal (9 days estradiol valerate/dienogest pill)

CHC, combined hormonal contraception; COC, combined oral contraceptive pill; CTP, combined transdermal patch; CVR, combined vaginal ring; EC, emergency contraception; IUD, intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; UKMEC, *UK Medical Eligibility Criteria for Contraceptive Use*.

With regard to advice for women with short cycles it should be noted that fewer than 5% of women aged 15–44 years and fewer than 2% of women aged 20–39 years have menstrual cycles less than 20 days.[35] Even smaller numbers (<1%) of women aged 14–42 years have cycle lengths less than 15 days.[36] However, if there is concern about very short or variable cycles, women can be given the option to use condoms when starting after Day 1.

In certain circumstances, the CEU also supports starting CHC where pregnancy cannot be excluded, for example following the administration of EC if it is likely the woman will continue to be at risk of pregnancy or if she has expressed a preference to start contraception without delay.[37] More detailed guidance is available in the CEU's guidance on quick starting contraception,[37] including the need to have a pregnancy test no sooner than 3 weeks after the last episode of UPSI.

Table 3 summarises when combined hormonal methods can be started and the requirements for additional precautions. For advice on starting immediately after EC health professionals should refer to CEU guidance on quick starting contraception[37] or EC.[38] Table 4 summarises the CEU's guidance on switching to and between CHC methods.

7 What Should be Advised Regarding Incorrect Use of CHC?

Women should be advised that the contraceptive efficacy of their method may be compromised if they deviate from the recommended regimen.

7.1 COC (except estradiol valerate/dienogest pill)

7.1.1 Missed pills

A missed pill is a pill that is completely omitted [i.e. more than 24 hours have passed since the pill was due (48 hours since last pill taken)]. When pills are missed, the inhibitory effects on the ovaries may be reduced sufficiently for ovulation to occur[39,40] and women may therefore be at risk of pregnancy.

There is evidence to suggest that taking hormonally active pills for 7 consecutive days prevents ovulation.[41] Therefore as long as seven pills have been taken, theoretically up to seven can be missed without any effect on contraceptive efficacy. A systematic review[41] undertaken by the WHO assessed evidence in relation to follicular activity and ovulation during correct and incorrect use of COCs (missed pills and extended pill-free interval). The review found that missing up to four consecutive pills on days other than those next to the pill-free week resulted in minimal follicular activity and low risk of ovulation. It is for these reasons that pills missed in Weeks 2 or 3 are unlikely to result in loss of efficacy. However, follicular activity has been shown to resume during the pill-free week.[42–45] Therefore, extending this interval increases the likelihood of ovulation occurring and the risk of pregnancy is greatest when pills are missed at the beginning or the end of a packet.

The systematic review included studies in which the pill-free interval was extended from between 8 to 14 days.[41] There was wide variability in the amount of follicular activity and incidence of ovulation observed in these studies and although sample sizes were small, it would appear that the effects of missing pills with very low doses of estrogen (≤20 µg) may be greater than with low-dose pills (>20 µg but <50 µg).[41]

On the basis of the evidence reviewed, the WHO developed guidance that was adopted by the FSRH in 2005.[46] The scientific evidence base has not changed significantly since 2005, but anecdotal evidence suggests that women and health professionals found the 2005 rules complicated and difficult to use. The rules were not universally adopted and the pharmaceutical industry continued to give patient information advising the original missed pill rules in patient information leaflets, which suggested reduced efficacy after a pill was 12 hours late.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) identified a need for clearer, more consistent rules and issued new missed pill guidance in 2011, which has been approved by the FSRH (Figure 1).[47]

For advice on missed pill rules for the estradiol valerate/dienogest pill (Qlaira), health professionals should refer to the specific manufacturer's advice.[11]

7.2 CTP

7.2.1 Unscheduled removal of the patch

The SPC for the CTP[8] indicates that if a patch has been partially or fully detached for less than 24 hours contraceptive efficacy is maintained and no additional precautions are required. A study[48] looking at the effect incorrect dosing of the CTP had on ovulation and follicular development found that in women who used the patch for 7 days followed by 3 days of not wearing the patch, follicular size and incidence of ovulation was significantly reduced compared with women using COCs.[48] The CEU would suggest that if the patch has been worn for 7 days a patch can remain off for up to 48 hours before contraceptive efficacy is reduced. After 48 hours of being detached additional contraception would be required (Table 5).

7.2.2 Extended use of the patch

Pharmacokinetic data suggest that there is sufficient release of norelgestromin and EE to maintain serum levels within the reference range for up to 10 days.[49] The SPC indicates that a
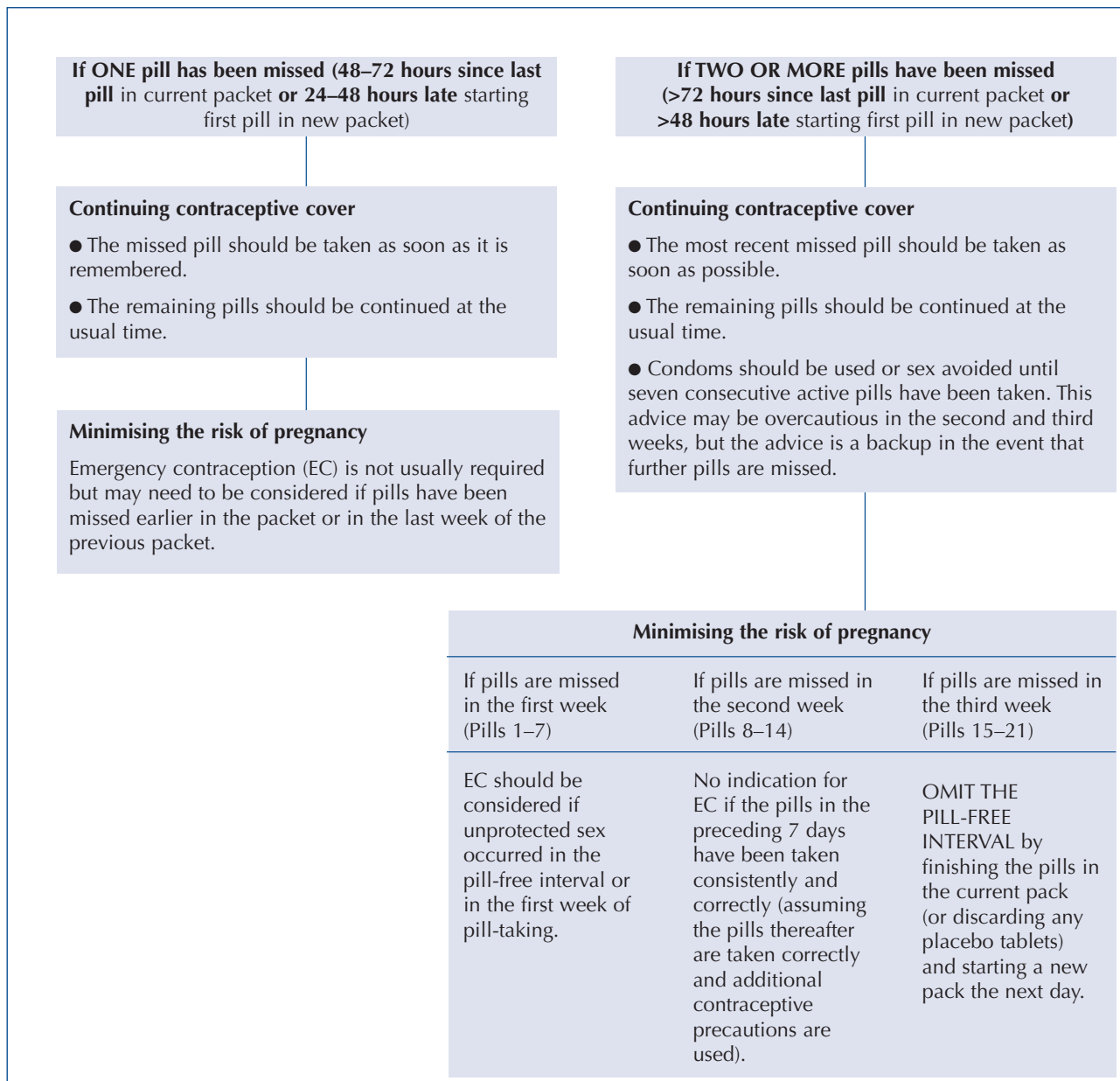
If ONE pill has been missed (48–72 hours since last pill in current packet **or 24–48 hours late** starting first pill in new packet)

Continuing contraceptive cover

● The missed pill should be taken as soon as it is remembered.

● The remaining pills should be continued at the usual time.

Minimising the risk of pregnancy

Emergency contraception (EC) is not usually required but may need to be considered if pills have been missed earlier in the packet or in the last week of the previous packet.

If TWO OR MORE pills have been missed (>72 hours since last pill in current packet **or >48 hours late** starting first pill in new packet)

Continuing contraceptive cover

● The most recent missed pill should be taken as soon as possible.

● The remaining pills should be continued at the usual time.

● Condoms should be used or sex avoided until seven consecutive active pills have been taken. This advice may be overcautious in the second and third weeks, but the advice is a backup in the event that further pills are missed.

Minimising the risk of pregnancy		
If pills are missed in the first week (Pills 1–7)	If pills are missed in the second week (Pills 8–14)	If pills are missed in the third week (Pills 15–21)
EC should be considered if unprotected sex occurred in the pill-free interval or in the first week of pill-taking.	No indication for EC if the pills in the preceding 7 days have been taken consistently and correctly (assuming the pills thereafter are taken correctly and additional contraceptive precautions are used).	OMIT THE PILL-FREE INTERVAL by finishing the pills in the current pack (or discarding any placebo tablets) and starting a new pack the next day.

Figure 1 Advice for women missing combined oral contraceptive pills [except estradiol valerate/dienogest pill (Qlaira®)] updated 2011[46]

patch can be worn for up to 9 days without contraceptive efficacy being affected.[8] After 9 days additional precautions are required and EC may need to be considered (Table 5).

7.2.3 Extended patch-free interval

The CEU did not find any data on extension of the patch-free interval. As efficacy of the CTP, CVR and COC have been shown to be comparable, advice for the CTP is extrapolated from data relating to the ring and COC. The CEU would therefore advise that the patch-free interval can be extended up to 48 hours (9-day patch-free interval) with no effect on contraceptive efficacy, providing the patch was worn consistently and correctly prior to the patch-free interval (Table 5).

7.3 CVR

7.3.1 Extension of the ring-free interval

A small, open-label randomised trial[34] looked at ovarian function in 45 women assigned either to the recommended regimen or an alternative regimen. Group A and B were respectively assigned to either the recommended regimen or to using the ring for just 3 days in their second

cycle and then monitored to establish the median time to ovulation. For Group A this was 19 days and Group B 17 days; however, the earliest ovulation was noted after 13 days in Group A and 12 days in Group B. Although the numbers of women were small, the similarities between the two groups suggests 3 days of using the CVR may be sufficient to suppress ovulation. Group C in this study did not start their second cycle of CVR until a 13 mm follicle was observed. In 50% of women this meant extending the ring-free cycle by four or more days (i.e. Day 11), although in one woman a 13 mm follicle was observed after extending by just 1 day. However, after insertion of the new CVR in women in Group C none of the women ovulated, suggesting insertion of the CVR may arrest development of follicles up to 13 mm diameter. The CEU therefore recommends that if the ring-free interval is extended by 48 hours or more additional contraception is required. EC may be required if sexual intercourse has occurred in the ring-free interval or Week 1. Such use is off licence (Table 5).

7.3.2 *Unscheduled removal of the ring*

The SPC for the CVR indicates that if the ring has been out of the vagina for more than 3 hours, the efficacy may be reduced. The CEU would advise that in Week 1, the advice in relation to extended ring-free interval applies (Table 5). In Weeks 2 and 3 the CEU would advise that providing the CVR has been used consistently and correctly for the previous 7 days it can be left out of the vagina for up to 48 hours without affecting efficacy (outside the terms of the product licence). After 48 hours, additional contraception is required until there have been 7 days of CVR use. In Week 3 a woman may opt to start a new cycle by inserting a new ring immediately and missing her ring-free week or providing the CVR has been in for 7 days previously she can have her withdrawal bleed and insert a new ring no later than 7 days from the time the CVR was expelled/removed (Table 5).

7.3.3 *Extended use of the ring*

A small, randomised, open-label crossover study[6] found that in participants who used the CVR for 2 weeks longer than the recommended 3 weeks of use, inhibition of ovulation was maintained in all the participants (*n* = 16). Although not recommended, the SPC[50] for the CVR indicates that the ring can be worn for up to 4 weeks without efficacy being affected and that a ring-free interval can still be taken. It advises additional precautions from Week 4 onwards.

The CEU would suggest that if a ring-free week can still be taken after 4 weeks of wear that theoretically additional precautions would not be required until the end of the 5th week providing a new ring is inserted immediately and no ring-free week is taken. Such use is off licence and the CEU would not advocate that women wear the ring beyond 3 weeks (Table 5).

8   What Drug Interactions are Important to Consider in Relation to CHC?

Detailed guidance has been produced by the CEU on drug interactions with hormonal contraception.[51] Guidance is also provided in UKMEC.[26]

Table 5 Summary of advice in relation to incorrect use of the combined transdermal patch/combined vaginal ring

Situation	Timeframe	Additional contraceptive protection required?
Extension of patch/ring-free interval	≤48 hours	No
	>48 hours	Yes (7 days). Consider EC if UPSI occurred in patch/ring-free interval
Patch/ring detachment/removal	≤48 hours	No (providing there has been consistent and correct use for 7 days prior to removal/detachment)
	>48 hours	Yes (7 days). Consider EC if patch/ring was detached/removed in Week 1 and UPSI occurred in patch/ring-free interval or Week 1
Extended use of patch	≤9 days	No
	>9 days	Yes for 7 days
Extended use of the ring	≤4 weeks	No (ring-free interval can be taken)
	>4 weeks	Yes. However, if the woman has worn the ring for >4 but ≤5 weeks, efficacy could be maintained by starting a new ring immediately without a ring-free interval

EC, emergency contraception; UPSI, unprotected sexual intercourse.

8.1 Antibiotics (non enzyme-inducing)

CEU advice changed in 2011 and, in conjunction with the BNF, we now advise that additional precautions are not required when using antibiotics (non enzyme-inducing).[51] The only proviso would be that if the antibiotics caused vomiting or diarrhoea then the usual additional precautions relating to these conditions should be observed. The CEU would advise that health professionals remind women about the importance of correct contraceptive practice during periods of illness.[51]

8.2 Enzyme-inducing drugs

Enzyme-inducing drugs increase the metabolism of estrogens and progestogens, which may in turn reduce the contraceptive efficacy of CHC. Women using enzyme-inducing drugs should ideally switch to a method that is unaffected (e.g. intrauterine methods or the progestogen-only injectable). However, if these drugs are to be used short term, women may use additional precautions in addition to their CHC (any COC used must contain at least 30 µg EE) during and for 28 days after stopping the enzyme-inducing drug.[51] For women using the COC in conjunction with enzyme inducers (except rifampicin or rifabutin), health professionals can consider increasing the dose to at least 50 µg EE (maximum 70 µg EE) and advising women to shorten (4 days)/omit their pill-free interval to reduce follicular ovarian activity.[51] Women using rifampacin or rifabutin should use condoms in the short term or switch to a method unaffected by enzyme-inducing drugs.

8.3 Lamotrigine

Serum levels of lamotrigine are reduced by CHC.[52–58] Increased side effects have been reported on cessation of CHC. A case series[55] reported increased frequency of seizures in four women with reduced lamotrigine levels following the initiation of COC. There are also data to show an increase in lamotrigine levels during the pill-free week[53] and following cessation of oral contraceptives.[52] When lamotrigine is combined with sodium valproate, no reduced effect occurs.[59] Due to the risk of drug interactions, the use of lamotrigine (except in combination with sodium valproate) with CHC is a UKMEC Category 3.[26]

8.4 Other drugs

Ulipristal acetate (UPA) blocks the action of progesterone. Therefore in theory UPA could reduce the efficacy of progestogen-containing contraceptives.[60,61] Additional precautions are advised for 14 days after using UPA and CHC concomitantly (16 days estradiol valerate/dienogest pill).[51] Although mifepristone is similarly a progesterone receptor modulator, the SPC for mifepristone does not currently indicate a possible interaction.

Some drugs such as anti-obesity drugs may have the potential to reduce the efficacy of contraceptives indirectly by causing severe diarrhoea or vomiting. 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.

C Additional contraceptive precautions are not required when antibiotics that do not induce enzymes are used in conjunction with CHCs.

✓ 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 along with additional contraception. An extended or tricycling regimen should be used and the hormone-free interval shortened to 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 taking an enzyme-inducing drug and who do not wish to change from COC or use additional precautions may increase the dose of COC to at least 50 µg EE (maximum 70 µg EE) and use an extended or tricycling regimen with a pill-free interval of 4 days.

C Women taking lamotrigine (except in combination with sodium valproate) 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 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 estradiol valerate/dienogest pill) (outside product licence).

9 Risks, Non-contraceptive Health Benefits and Side Effects

Women should be provided with additional information about non-contraceptive health benefits, risks associated with use, and side effects to enable them to make informed choices about their contraception. This information should be tailored to the individual woman and address any specific health concerns she might have. There is little epidemiological evidence in relation to the estradiol valerate/dienogest pill, the patch or ring due to the relative newness of these products. Recommendations are therefore often based on COC data and applied to all three CHC methods.

9.1 Health risks

9.1.1 VTE (including deep vein thrombosis and pulmonary embolism)

The risk of VTE in women of reproductive age is approximately 4–5/10 000 woman-years in those who do not use oral contraceptives.[61] This is higher than figures quoted in previous Faculty guidance.[1] The reasons for the apparent increase in the background prevalence of VTE over time are referred to in a recent consensus statement on COC and VTE.[63] It is postulated that the increase may be due to a true increase in incidence (perhaps due to changing demographic trends such as obesity rates), increased clinician awareness and better diagnostic precision, or a combination of these factors.

The risk of VTE amongst COC users is approximately twice that of non-users [9–10/10 000 woman-years (average across all brands studied)].[64] The risk is greatest in the first few months of starting, after which the risk falls although is still higher than among non-users until COC is stopped.[64–67] The risk returns to that of non-users within weeks of discontinuation.[68] An increased risk in VTE has been observed in women restarting the pill after breaks of 4 weeks or more, but providing there is less than a 4-week break, switching COC preparations does not appear to be associated with an initial excess risk compared to long-term use.[69] Whilst CHC does increase a woman's risk, the consensus statement[63] on oral contraceptives and VTE highlights that the risks of VTE associated with pregnancy and the immediate postpartum period are higher still (29/10 000 woman-years and 300–400/10 000 woman-years, respectively). These figures may help women to understand the risks.

9.1.2 VTE and individual products

Studies have reported differing risks associated with individual COCs.[64,65,70–78] There is continuing debate about the effect that the type of progestogen in a COC has on VTE risk. Observational studies have reported that COCs containing desogestrel, gestodene and cyproterone are associated with a higher risk of VTE than those containing levonorgestrel (LNG), norethisterone and norgestimate.[73–76,79,80] There is conflicting evidence in relation to COCs containing drospirenone (DSP).[64,70,75–78] Recent studies have again suggested a higher risk than with LNG.[70,78] The MHRA[81] has issued a statement to say the risk of VTE associated with DSP-containing COCs is higher than with LNG-containing COCs and may be similar to the risk associated with desogestrel- or gestodene-containing COCs. Much of the debate has focused on whether or not the findings are the result of bias and confounding.[72,82–85] In terms of the CTP, some studies suggest the risk is higher whilst others suggest there is no increased risk.[86–89] The relative risk of VTE associated with the CVR and also the estradiol valerate/dienogest-containing pill are unknown.

The MHRA[81] indicates that LNG-containing pills may be the 'safest' pill choice for women starting or switching contraception. A review[90] of the epidemiology of the contraceptive pill and VTE has also suggested that given none of the newer generation pills have been shown to be associated with a lower risk of VTE, all other considerations being equal, women should probably be offered an older, low-dose formulation in the first instance. The review[90] acknowledges, however, that all of the currently available pills are safe.

When counselling women it is important to emphasise that while some progestogens within COCs may be associated with a higher risk of VTE than others, the risk of a venous thrombosis

in women who use CHC is very small and smaller than that associated with pregnancy. When prescribed appropriately the benefits of using CHC far outweigh the risks of VTE. Health professionals' prescribing of CHCs should be guided by the individual's own personal preference, risk of VTE, any contraindications, possible non-contraceptive benefits and experience with other contraceptive formulations.

9.1.3 *VTE and family history*

A family history of VTE is a poor indicator of risk for those with underlying coagulation problems.[91] The cause of VTE in a family member may not be hereditary (e.g. it may have occurred during pregnancy or a period of immobilisation) and many women with a family history of VTE never develop a VTE. The UKMEC[26] classifies having a first-degree relative with a history of VTE under the age of 45 years as a UKMEC 3.

9.1.4 *VTE and thrombogenic mutations*

Women with reduced levels of naturally occurring anticoagulants (anti-thrombin III, Protein C or Protein S) or factor V Leiden or prothrombin gene mutations (G20210A) are predisposed to VTE.[92] Indeed women with factor V Leiden mutations can have up to a 35-fold increased risk of thrombosis with COC use.[93,94] Having a known thrombogenic mutation represents an unacceptable risk if CHC is used (UKMEC 4).[26] The general use of thrombophilia screening prior to CHC use is not recommended. A negative screen may not exclude all types of thrombophilia.

B Health professionals should be aware that compared to non-users, the risk of VTE with use of CHC is approximately doubled but that the absolute risk is still very low.

C Health professionals prescribing CHCs should be guided by the individual's own personal preference, risk of VTE, any contraindications, possible non-contraceptive benefits and experience with other contraceptive formulations.

C A personal history of VTE or a known thrombogenic mutation are conditions that represent an unacceptable health risk if CHC is used.

C For women with a family history of VTE, a negative thrombophilia screen does not necessarily exclude all thrombogenic mutations.

C A thrombophilia screen is not recommended routinely before prescribing CHC.

9.1.5 *Cardiovascular disease and stroke*

Many studies have investigated associations between COC use and arterial vascular disease. Key papers are referenced in UKMEC.[26] While some authors have not found an association with myocardial infarction (MI),[95] other papers,[96,97] including two meta-analyses,[98,99] have shown an increased risk of MI in COC users, particularly smokers.[96,97] For women over the age of 35 years who smoke <15 cigarettes per day, use of CHC is UKMEC 3 (Table 2); for those who smoke ≥15 cigarettes per day, use is UKMEC 4.[26] As the risk declines with time after stopping smoking, use of CHC in former smokers aged ≥35 years changes to UKMEC 2 a year or more after stopping.[26]

With regard to cerebrovascular disease, although a meta-analysis reported a two-fold increase in risk of ischaemic stroke with use of low dose COCs,[98] other studies have not found that COC use results in a statistically significant increased risk of ischaemic[100,101] or haemorrhagic stroke.[101,102]

The risk of stroke is increased in COC users with migraine compared to COC users without migraine.[102–107] A recent meta-analysis[108] has indicated that the risk of stroke associated with migraine appears only to affect those individuals experiencing migraine with aura, and that oral contraceptive use further increases the risk of ischaemic stroke. Use of CHC in the presence of migraine with aura is UKMEC 4.[26]

Risk of vascular disease may be influenced by other independent risk factors such as hypertension and obesity. Hypertensive COC users have been found to be at higher risk of stroke and MI, but not VTE, than hypertensive non-COC users.[109] Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg is UKMEC 4. Although there are no data, CHC users whose BP is adequately controlled by treatment may be at lower risk (UKMEC 3).

As obesity is associated with an increased risk of cardiovascular, cerebrovascular and venous thromboembolic disease use of CHC needs careful consideration in obese women. There was published criticism[110] of the 2005 UKMEC categories attributed to the use of CHC in obese women suggesting they were overly restrictive in comparison to other UKMEC categories. When UKMEC was revised in 2009[26] the UKMEC 4 category (which previously applied to BMI ≥40 kg/m^2) was removed and UKMEC 3 applied to BMI ≥35 kg/m^2 with no absolute restriction on CHC use based on weight alone.[26] The presence of multiple risk factors for cardiovascular disease is UKMEC 3/4.[26]

B Use of CHC in women aged ≥35 years who smoke is not recommended.

B Health professionals should be aware that there may be a very small increase in the absolute risk of ischaemic stroke associated with CHC use.

C Migraine with aura is a condition for which the use of CHC presents an unacceptable health risk (UKMEC 4).

B The risks of using CHC in women with properly taken blood pressure (BP) which is consistently elevated generally outweigh the advantages. Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg is a condition that represents an unacceptable health risk if CHC is used (UKMEC 4).

B The risk of using CHC in women with a BMI ≥35 kg/m^2 usually outweighs the benefits (UKMEC 3).

9.1.6 Breast cancer

A large meta-analysis of case-control studies from 25 countries showed an increased risk of breast cancer whilst using COC [relative risk (RR) 1.24, 95% confidence interval (CI) 1.15–1.33],[111] which is approximately an increase of 24% above the background risk. This study suggested that any excess risk of breast cancer associated with COC use increases quickly after starting, does not increase with duration of use, and disappears within 10 years of stopping COC use.[111] Whilst some studies have similarly reported a statistically significant increased risk,[112,113] others have reported findings of borderline or no statistical significance.[114–120]

It is unclear whether any identified associations are due to study artifacts such as confounding or a biological effect of COCs. Women can, however, be informed that use has not been associated with a long-term effect, with studies finding no statistically significant difference in risk between ever-users and never-users.[115,116] Use of COCs have not been found to be associated with increased mortality from breast cancer.[114,121,122]

9.1.7 Breast cancer and family history

For women with a family history of breast cancer, there is an increased risk of breast cancer compared to women with no family history.[123] Although the background risk is increased, current evidence shows that risk of breast cancer amongst women with a family history is not increased further by using COCs.[124] A family history of breast cancer therefore does not restrict use of CHC (UKMEC 1).[26]

9.1.8 Breast cancer and genetic mutations

Evidence is conflicting on whether women who are carriers of BRCA1 or BRCA2 mutations are at further increased risk of breast cancer with COC use.[125–131] Carriers have a higher baseline risk when compared to the general population and therefore any potential small risk may be significant. Current guidance states that having a genetic mutation associated with breast cancer is UKMEC 3.[26] It is not known where the balance of risk lies with regard to protection from ovarian cancer and risk of breast cancer in BRCA mutation carriers.

9.1.9 Current breast cancer

Current breast cancer is a condition which represents an unacceptable risk if CHC is used (UKMEC 4),[26] past and no evidence of current disease for 5 years is UKMEC 3. There is currently a lack of data on which to make separate recommendations with regard to women who have estrogen and/or progesterone receptor-negative disease. UKMEC does not differentiate between types of breast cancer and therefore the CEU advises that the category applies to women with all types. The CEU recommends consulting with a woman's oncologist if there is clinical uncertainty.

B Health professionals should be aware that any risk of breast cancer associated with CHC use is likely to be small, and will reduce with time after stopping.

9.1.10 Cervical cancer

The risk of cervical cancer appears to increase with duration of COC use.[115,116,132–135] A meta-analysis showed that after controlling for a number of factors, the risk is increased with long-term use (>5 years).[133] However, long-term users can be reassured that the benefits of use generally outweigh the risks. Furthermore, after COC use ends the risk of invasive cancer declines, returning to that of never-users 10 or more years after stopping.[133] Women should be informed about the link between human papillomavirus (HPV) and cervical cancer, and advised that the risk of cervical cancer can be reduced through condom use, stopping smoking, regular cervical screening and, where appropriate, vaccination against HPV.

B Health professionals should be aware that CHC use may be associated with a small increase in the risk of cervical cancer which is related to duration of use.

✓ Health professionals should check that women coming for CHC are up to date with cervical cytology screening in accordance with screening recommendations.

9.2 Non-contraceptive health benefits

9.2.1 Mortality

Data from a large cohort study demonstrated that ever-use of oral contraceptives was associated with a 12% reduction in all-cause mortality and no overall increased risk of cancer.[121] Other studies have similarly shown no increased risk on mortality with use of oral contraceptives.[114,136] While these findings may again be subject to confounding and bias due to the observational nature of the studies, women can be reassured that COC use is unlikely to affect overall long-term mortality.

B Women can be advised that CHC use does not appear to have a negative effect on overall mortality.

9.2.2 Ovarian and endometrial cancer

The risk of developing or dying from ovarian and endometrial cancer is reduced with use of COC.[114–116,137–148] A collaborative reanalysis[145] of 45 epidemiological studies demonstrated that with every 5 years of use there is approximately a 20% reduction in the risk of ovarian cancer. A woman's risk after 15 years of use was around half of those who had never used COC.[145] Risk reductions of at least 50% have also been noted for endometrial cancer.[146–149] The protective effect increases with increasing duration of use and whilst it decreases over time after stopping, it has been shown to last up to several decades after use.[116,143,148,150,151] Amongst BRCA mutation carriers, COC use has been shown to provide a protective effect against ovarian cancer.[125,152–155]

Data also suggest a reduction in the incidence of ovarian cysts[156–158] and benign ovarian tumours[156–159] amongst women using COCs.

COC use is not associated with an increased risk of mortality from endometrial or ovarian cancer.[114,121]

B Use of COC is associated with a reduced risk of ovarian and endometrial cancer that continues for several decades after stopping.

9.2.3 Acne

A Cochrane review[160] found that the four COCs studied within included trials were effective in reducing inflammatory and non-inflammatory facial acne lesions. Overall few important differences between the COCs were identified in terms of their effectiveness in treating acne.[160]

Co-cyprindiol (COCs containing EE and cyproterone acetate), which is licensed for the treatment of acne that has not responded to oral antibiotics, can be used for contraception but should not be used solely for contraceptive purposes. Because co-cyprindiol is associated with a higher VTE risk than other COCs (see page 11), it should ideally be withdrawn 3–4 months after the condition has resolved. Women with known hyperandrogenism where

symptoms are likely to reoccur may warrant longer use of co-cyprindiol. In all women, co-cyprindiol can be restarted at any time if acne or hirsutism recurs on stopping treatment. Within small observational studies, some women have reported improvements in their acne with use of the CTP.[161,162] CVR users have reported acne less than COC users.[15]

> **A** Health professionals should be aware that CHC may help to improve acne.

9.2.4 Bone health

A Cochrane review[163] concluded that the influence of steroidal contraception on fracture risk cannot be determined from existing information; however, CHC does not appear to affect bone health. Authors of a cohort study have concluded that amongst their study population ever-use of oral contraception was not associated with fracture.[164]

9.2.5 Colorectal cancer

Studies on the risk of colorectal cancer with COC use are reassuring, with epidemiological data consistently indicating a decreased risk with use of COCs.[165–171] The protective effect appears to be associated with current or recent use and there is currently no evidence of a relationship with duration of use.[115,167]

> **B** Health professionals should be aware that COC use is associated with a reduction in the risk of colorectal cancer and this may also apply to other CHCs.

9.2.6 Dysmenorrhoea and heavy menstrual bleeding

Cochrane reviews have stated there is limited evidence from randomised controlled trials to suggest that COC use can improve pain associated with primary dysmenorrhoea or reduce menstrual blood loss compared with other treatments.[172,173] Data from observational studies suggest that women report improvement with use of different combined methods,[174–178] although dysmenorrhoea has been more commonly reported in patch users than COC users.[179] A placebo-controlled, double-blind, randomised trial has also suggested that low-dose COC could possibly be used to treat pain associated with endometriosis.[180] The National Institute for Health and Clinical Excellence indicates that COC can be used for the treatment of heavy menstrual bleeding.[181]

> **C** Health professionals should be aware that use of CHC may help to reduce menstrual pain and bleeding.

9.2.7 Menopausal symptoms

There is a small amount of data that suggest CHC may help to improve some of the symptoms associated with menopause.[182,183] There may be some theoretical benefit from an extended regimen (Table 1), although such use is outside the product licence.

> **C** Women can be advised that CHC may reduce menopausal symptoms.

9.3 Side effects

A number of side effects are noted with use of CHC. However, proving that CHC is responsible for these effects is often difficult due to the difficulties in controlling for other potential influencing factors. While women should be informed thoroughly about potential side effects when starting contraception, discussions should also cover non-contraceptive benefits and seek to address common myths.

9.3.1 Unscheduled bleeding

Up to 20% of COC users have irregular bleeding.[184] Bleeding usually settles with time and therefore it is generally recommended women experiencing unscheduled bleeding continue their combined hormonal methods for 3 months before considering changing.[184]

Clinicians should be aware of likely causes of unscheduled bleeding such as missed pills, sexually transmitted infections (STIs), pregnancy and malabsorption (vomiting within 2 hours of pill taking or severe diarrhoea). No link has been found between serum steroid concentrations, unscheduled bleeding and loss of contraceptive efficacy.[185,186]

Guidance on the management of unscheduled bleeding in women using hormonal contraception has been produced and should be referred to for detailed advice.[184]

✓ Before starting CHC women should be advised about expected bleeding patterns both initially and in the longer term.

9.3.2 *Mood changes*

As studies examining the effect of CHC on mood are observational, involve different preparations, and largely depend on women's own perceptions, it is difficult to prove a causal relationship between CHC and mood changes. Two studies looking at the relationship between COC use and depressive symptoms in young women have generally found no difference between COC users and non-users.[187,188] A study looking at the effect of COC on premenstrual mood found it largely to be unchanged, although in some women it would improve and in others deteriorate.[189] The authors of this study felt deterioration may in part be influenced by a prior history of depression.[189]

C Women can be advised that CHC may be associated with mood changes but there is no evidence that it causes depression.

9.3.3 *Weight gain*

A Cochrane review has concluded that there is currently insufficient evidence to determine the effect of combination contraceptives on weight gain but that no large effect is evident.[190]

B Women can be advised that the current evidence does not support a causal association between CHC and weight gain.

10 What Follow-up Arrangements are Appropriate?

A follow-up visit 3 months after the first prescription of a combined hormonal method is advised to allow BP to be rechecked, and assessment of any problems. Women may be offered up to a 12 months' supply of COC or CTP at the follow-up appointment. A yearly routine follow-up visit, plus advice to return at any time if there are problems, is recommended. Follow-ups should involve checking BP, BMI and enquiring about any health changes.

After dispensing, rings should be stored at room temperature and used within 4 months. Therefore no more than three rings can be provided.

11 How Long Should Women Use CHC?

Although use of combined methods has been shown to decrease with age,[4] CHC can be used up until the age of 50 years, providing there are no risk factors that would restrict use. After the age of 50 years, women are advised to consider an alternative method.[26,191] No limit is given as to the number of years a woman can use a combined hormonal method. Guidance on stopping hormonal contraception at the menopause is available within the FSRH guidance entitled *Contraception for Women Over 40 Years*.[191]

12 CHC Whilst Travelling or at High Altitude

Various definitions of long-haul travel exist.[192–194] Long duration travel is a moderate risk factor for the development of VTE.[192,193] Women who use CHC have an increased risk of thrombosis, which may be further increased by travel.[193] Guidelines produced by the British Society for Haematology[192] advise that maintaining mobility in all travellers is a reasonable precaution for flights over 3 hours. They state that global use of compression stockings and anticoagulants is not indicated and that risk should be assessed on an individual basis. CHC users who are taking flights over 3 hours should be advised to reduce periods of immobility. Where there are additional risk factors (e.g. obesity), health professionals should refer to the British Society for Haematology guidelines[192] or seek advice from a haematologist. Women travelling through different time zones should be reminded of the importance of taking their pill approximately 24 hours after their most recent pill (i.e. using time of day in the time zone in which the last pill was taken as a reference point rather than local time). A pill is missed when it has been more than 48 hours since the last pill was taken. Two pills have been missed when it has been more than 72 hours since the last pill was taken.

The CEU has found limited evidence or guidance on the use of the COC in women whilst trekking to high altitudes. A consensus statement[195] produced by the International Mountaineering and Climbing Federation (UIAA) Medical Commission on *Contraception and*

Period Control at Altitude (Intended for Physicians and Other Non-medical Interested Persons) indicates that although reported cases are rare, due to theoretical concerns about estrogen-induced thrombosis during long stays at high altitude women should consider avoiding the COC if they are to spend more than a week above 4500 m. Below 4500 m it is almost certainly safe in a healthy, active, non-smoking woman with no personal or family history of venous thrombosis of thrombophilia.

✓ Women taking CHC should be advised about reducing periods of immobility during flights over 3 hours.

✓ Women trekking to altitudes of >4500 m for periods of more than 1 week may be advised to consider switching to an alternative method.

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APPENDIX 1: DEVELOPMENT OF CEU GUIDANCE

GUIDELINE DEVELOPMENT GROUP

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Patient/User Consultation

Sixty-eight women completed a questionnaire on the proposed guidance content prior to its development.

Clinical Effectiveness Unit (CEU) guidance is developed in collaboration with the Clinical Effectiveness Committee (CEC) of the Faculty of Sexual and Reproductive Healthcare (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 clinicians working in family planning, sexual and reproductive health care, general practice, other allied specialties, and user representation. In addition, the aim is to include a representative from the FSRH CEC, 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) (1996–2011); EMBASE (1996–2011); PubMed (1996–2011); The Cochrane Library (to 2011) 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 combined 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 included 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.

Discussion Points for Combined Hormonal Contraception

The following discussion points have been developed by the FSRH Meetings Committee.

Discussion Points

1 A woman using the combined vaginal ring presents at clinic reporting having forgotten to replace her ring at the end of her third week. She is now approaching the end of her fourth week of ring wearing and has had intercourse 2 days ago. Discuss how you would advise her.

2 How would you counsel a woman with a family history of breast cancer requesting combined hormonal contraception?

3 Discuss any potential pros and cons of tailored pill regimens over traditional pill-taking.

Questions for Combined Hormonal Contraception

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

Indicate your answer by ticking the appropriate box for each question   **True   False**

1 The bleed experienced during the pill-free week is a natural menstrual bleed. ☐ ☐

2 Contraceptive efficacy of the combined transdermal patch (CTP) may be decreased in women weighing >90 kg. ☐ ☐

3 Combined hormonal contraception (CHC) can be started at any time in the cycle if the clinician is reasonably certain the woman is not pregnant. ☐ ☐

4 If switching from the progestogen-only pill (POP) to CHC, additional contraceptive protection is not required. ☐ ☐

5 The CTP can be detached for 48 hours before contraceptive efficacy is decreased. ☐ ☐

6 Lamotrigine affects contraceptive efficacy of CHC. ☐ ☐

7 The risk of venous thromboembolism (VTE) when using CHC is highest in the first few months of use. ☐ ☐

8 *UK Medical Eligibility Criteria for Contraceptive Use* states that having a first-degree relative with a history of VTE under the age of 45 years is UKMEC 3. ☐ ☐

9 CHC can be used if there is a family history of breast cancer without genetic mutation. ☐ ☐

10 CHC is not thought to cause weight gain. ☐ ☐

Answers

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

Auditable Outcomes from Combined Hormonal Contraception Guidance

The following auditable outcomes have been developed by the FSRH Clinical Standards Committee.

Auditable Outcomes

1   What proportion of women attending your service have a body mass index and blood pressure measurement documented prior to first prescription/issuing of combined hormonal contraception (CHC)? [Target 100%]

2   What proportion of women attending your service have a documented record showing assessment for cardiovascular risk factors including migraine before first prescription/issuing of CHC? [Target 100%]

3   What proportion of staff prescribing/issuing CHC within your service are aware of current FSRH missed pill guidance? [Target 100%] How are staff informed of new guidance (e.g. via e-mail, newsletter, etc.)?

NOTES

STEPS INVOLVED IN THE DEVELOPMENT OF THIS GUIDANCE DOCUMENT

Appointment of a multidisciplinary group by invitation to main stakeholders.
Revision of key questions by the Clinical Effectiveness Unit (CEU) and multidisciplinary group.
Systematic literature review, critical appraisal and development of evidence tables by the CEU researcher.
Draft one guidance document is written by the CEU.
Peer review by multidisciplinary group (written feedback and one-day meeting).
Preparation of draft two guidance document by the multidisciplinary group, the Faculty of Sexual and Reproductive Healthcare (FSRH) Clinical Effectiveness Committee (CEC) and two independent peer reviewers.
Preparation of draft three guidance document based on written feedback.
The multidisciplinary group are asked to take consensus process.
Preparation of draft four guidance document.
Draft document is published on the Faculty website for up to 1 month for public consultation. Stakeholders are informed of this consultation process.
All feedback comments are reviewed by the CEU and FSRH CEC.
The final draft is prepared and the CEU's response to consultation comments is posted on the FSRH website.
The final document is published by the FSRH.
Printed copies are mailed to FSRH members and an electronic version is made available on the FSRH website.
Post-publication feedback is reviewed by the CEC and the web version is amended as and when necessary.

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.** 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**).

The CEU is unable to respond individually to all feedback. However, the CEU will review all comments and provide an anonymised summary of comments and responses, which are reviewed by the Clinical Effectiveness Committee and any necessary amendments made.