FACULTY OF FAMILY PLANNING & REPRODUCTIVE HEALTH CARE

ROYAL COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS

Faculty of Family Planning & Reproductive Health Care Clinical Guidance

First Prescription of Combined Oral Contraception

Clinical Effectiveness Unit
July 2006
(Updated January 2007)

IMPORTANT ADVICE NOTICE

Readers should note that the print version of this CEU Guidance Document (which was first published and distributed to Faculty Members in July 2006) contained errors in Table 2 that the Clinical Effectiveness Unit felt ought to be corrected in the website version. In addition, Faculty Members have been sent a replacement copy of Table 2 containing the correct information for insertion in their printed copy of the Guidance Document.

The error concerned the inclusion of inaccurate information pertaining to breast disease in UKMEC Category 2 (Benefits generally outweigh risks), which should instead have been listed under UKMEC Category 3 (Risks generally outweigh benefits). In addition, further details on hyperlipidaemias have been added to Table 2 for clarity.

Note that this website version of the CEU Guidance Document includes the correct version of Table 2.

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Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit

A unit funded by the FFPRHC and supported by the University of Aberdeen to provide guidance on evidence-based practice

FFPRHC Guidance (July 2006)
First prescription of combined oral contraception

(Date for planned revision July 2009)

This Guidance provides information on a *first prescription* of combined oral contraception, and it updates and replaces previous Faculty Guidance. A key to the grades of recommendations, based on levels of evidence, is given at the end of this document. Details of the methods used by the Clinical Effectiveness Unit in developing this Guidance and evidence tables summarising the research basis of the recommendations are at the end of this document. Abbreviations (in alphabetical order) used include: BMI, body mass index; COC, combined oral contraception/combined oral contraceptive; DVT, deep vein thrombosis; EE, ethinylestradiol; MI, myocardial infarction; VTE, venous thromboembolism; UKMEC, UK *Medical Eligibility Criteria*; WHO, World Health Organization; WHOMEC, WHO *Medical Eligibility Criteria*; WHOSPR, WHO *Selected Practice Recommendations*.

Background

This Guidance provides evidence-based recommendations and good practice points for clinicians advising women considering a *first prescription* of combined oral contraception, and it updates and replaces previous Faculty Guidance.[1] Unless otherwise stated, this Guidance refers to combined oral contraception (COC) as monophasic pills containing 20–35 μg (micrograms) of ethinylestradiol (EE) in combination with a progestogen. Readers are referred to other Guidance documents that provide further information about the use of COC in specific circumstances, namely: young women,[2] women aged over 40 years,[3] women who are breastfeeding,[4] women with inflammatory bowel disease,[5] use of contraception outside the terms of the product licence[6] and drug interactions with hormonal contraception.[7]

Combined oral contraceptives (COCs) work primarily by inhibiting ovulation. Ovulation is inhibited by action on the hypothalamo-pituitary-ovarian axis to reduce luteinising hormone and follicle-stimulating hormone.[8] In addition, COC has contraceptive effects on cervical mucus and the endometrium. The first seven pills in a packet inhibit ovulation. The remaining 14 pills maintain anovulation. If used consistently and correctly the COC provides effective contraception. The Pearl index for COC (i.e. the number of failures per 100 woman-years of exposure) is estimated at 0.3 to 4.0. The failure rate with perfect use (*true pill failure*) is 0.1% and with typical use (*user and method failure*) is up to 5%.[9] During the usual seven pill-free days the endometrium sheds and most women will have a withdrawal bleed. Contraceptive protection is maintained during the pill-free interval as long as pills before and after are taken consistently and correctly.[8,10–12]

A holistic approach should be taken when assisting women in making contraceptive choices, and services should be organised to optimise access and choice. COC is the most used hormonal method of contraception.[13] The use of both COC and male condoms is highest among younger women but falls with increasing age. Promoting safer sex is good practice but not essential for the safe use of COC.[14,15]

The majority of women can use COC without harm.[16–18] The World Health Organization *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC)[19] provides evidence-based recommendations to ensure women can select the most appropriate method of contraception without imposing unnecessary restrictions. The UK *Medical Eligibility Criteria* (UKMEC) was developed from the WHO document in 2005 and is available on the Faculty website (www.ffprhc.org.uk).[20] The UKMEC categories used in this Guidance (Tables 1 and 2) are for women using COC for contraception and not for use as treatment of other conditions where the risk-benefit profile may be different. For example, the use of COC in a woman with a condition given a UKMEC Category 3 requires expert clinical judgement and/or specialist referral since use of the method is not usually recommended unless other methods are not available or not acceptable (strong contraindication).[20]

Women should be empowered to make informed decisions about choosing and using COC.[21–23] There are important potential harms which need to be discussed with all women when given a *first prescription* of COC. Additional information can be given at the time of first prescription of COC about non-contraceptive benefits, nuisance side effects and specific health concerns. This information should be tailored to individual women. For example, a woman with a family history of breast cancer may require more detailed discussion about breast cancer risk with COC than a woman with no relevant family history; a woman with concerns about weight gain may need more detailed discussion about this scenario.

Table 1 *UK Medical Eligibility Criteria (UKMEC) categories*[20]

Category	Definition
UKMEC 1	A condition for which there is *no restriction* for the use of the contraceptive method
UKMEC 2	A condition for which 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*[a]
UKMEC 4	A condition which represents an *unacceptable health risk* if the contraceptive method is used

[a]The provision of a method to a woman with a condition given a UKMEC Category 3 requires expert clinical judgement and/or referral to a specialist contraceptive provider since use of the method is not usually recommended unless other methods are not available or not acceptable.

Table 2 *UK Medical Eligibility Criteria (UKMEC) for combined oral contraceptive use*[20]

UKMEC Category 1 – Unrestricted use	UKMEC Category 2 – Benefits generally outweigh risks
Age – *menarche to <40 years* **Parity** – *nulliparous and parous* **Breastfeeding** – *>6 months postpartum* **Postpartum** – *>21 days if not breastfeeding* **Post-abortion** – *immediately first and second trimester, and post-septic* **Past ectopic pregnancy** **History of pelvic surgery** **Minor surgery without immobilisation** **Varicose veins** **Non-migrainous headaches** – *mild or severe* **Epilepsy** – *and not using liver enzyme-inducers* **Depressive disorders** **Vaginal bleeding** – *unsuspicious irregular, heavy or prolonged* **Endometriosis** **Benign ovarian tumour** **Severe dysmenorrhoea** **Gestational trophoblastic neoplasia** – *when hCG is normal* **Cervical ectropion** **Breast disease** – *benign breast disease or a family history of breast cancer* **Endometrial or ovarian cancer** **Uterine fibroids** – *with or without distortion of the uterine cavity* **PID** – *current; or past history of, with or without subsequent pregnancy* **STI** – *current, vaginitis or increased risk of STI* **HIV/AIDS** – *risk of HIV/AIDS, current HIV not using antiretroviral therapy* **Schistosomiasis, pelvic and non-pelvic tuberculosis, malaria** **Diabetes** – *history of gestational disease* **Thyroid disorders** **Viral hepatitis** – *carrier* **Anaemias** – *thalassaemia, iron deficiency* **Raynaud's disease** – *primary without lupus anticoagulant*	**Age** – *≥40 years*[a] **Breastfeeding** – *between 6 weeks and 6 months postpartum and partially breastfeeding (medium to low)* **Smoking** – *aged <35 years, or aged ≥35 years and stopped smoking ≥1 year ago* **Obesity** – *BMI ≥30–34 kg/m²* **History of high blood pressure during pregnancy** **Family history of VTE in a first-degree relative aged ≥45 years** **Major surgery without prolonged immobilisation** **Superficial thrombophlebitis** **Known hyperlipidaemias** – *e.g. common hypercholesterolaemia or familial combined hyperlipidaemia* **Valvular and congenital heart disease** – *uncomplicated* **Migraine headaches** – *without aura in women aged <35 years* **Vaginal bleeding** – *suspicious for serious condition before evaluation* **CIN and cervical cancer** **HIV/AIDS** – *current HIV using antiretroviral therapy, or current AIDS and using HAART* **Diabetes** – *NIDDM and IDDM, non-vascular disease* **Gallbladder disease** – *asymptomatic or treated with a cholecystectomy* **History of cholestasis** – *pregnancy-related* **Inflammatory bowel disease** **Sickle cell disease** **Raynaud's disease** – *secondary without lupus anticoagulant* **Non-liver enzyme-inducing antibiotics** **Highly active antiretroviral therapy (HAART)**
UKMEC Category 3 – Risks generally outweigh benefits[b]	**UKMEC Category 4 – Unacceptable health risk and should not be used**
Breastfeeding – *between 6 weeks and 6 months postpartum and fully or almost fully breastfeeding* **Postpartum** – *<21 days postpartum* **Smoking** – *aged ≥35 years and smoking <15 cigarettes per day, or stopped smoking <1 year ago* **Obesity** – *BMI 35–39 kg/m²* **Cardiovascular disease** – *multiple risk factors for arterial cardiovascular disease* **Hypertension** – *elevated blood pressure >140 to 159 mmHg systolic or >90 to 94 mmHg diastolic* **Family history of VTE in a first-degree relative aged <45 years** **Immobility (unrelated to surgery)** – *e.g. wheelchair use, debilitating illness* **Known hyperlipidaemias** – *e.g. familial hypercholesterolaemia* **Migraine headaches** – *without aura in women aged ≥35 years; or a past history of migraine with aura at any age* **Breast disease** – *past history of breast cancer and no evidence of recurrence for 5 years; carriers of known gene mutations associated with breast cancer (e.g. BRCA1); undiagnosed mass* **Diabetes** – *with nephropathy/retinopathy/neuropathy; or other vascular disease or diabetes of >20 years' duration (category given will depend on disease severity)* **Gallbladder disease** – *symptomatic medically treated or current* **History of cholestasis** – *past COC-related* **Cirrhosis** – *mild compensated disease* **Drugs which induce liver enzymes** – *e.g. rifampicin, rifabutin, St John's Wort, griseofulvin and certain anticonvulsants (i.e. phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)*	**Breastfeeding** – *<6 weeks postpartum* **Smoking** – *aged ≥35 years and smoking ≥15 cigarettes per day* **Obesity** – *BMI ≥40 kg/m²* **Cardiovascular disease** – *multiple risk factors for arterial cardiovascular disease* **Hypertension** – *blood pressure ≥160 mmHg systolic and/ or ≥95 mmHg diastolic; or vascular disease* **VTE** – *current (on anticoagulants) or past history* **Major surgery with prolonged immobilisation** **Known thrombogenic mutations** **Current and history of ischaemic heart disease** **Stroke** **Valvular and congenital heart disease** – *complicated by pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis* **Migraine headaches** – *with aura at any age* **Gestational trophoblastic neoplasia** – *when hCG is abnormal* **Breast disease** – *current breast cancer* **Diabetes** – *with nephropathy, retinopathy, neuropathy or other vascular disease, or diabetes of >20 years' duration (category given will depend on disease severity)* **Viral hepatitis** – *active disease* **Cirrhosis** – *severe decompensated disease* **Liver tumours** – *benign and malignant* **Raynaud's disease** – *secondary with lupus anticoagulant and thus a tendency to thrombosis*

[a]Age ≥40 years: women may use COC until age 50 years if there are no medical contraindications.[3]
[b]Definition of UKMEC 3 – the risks generally outweigh the benefits but the method can be considered for use with clinical judgement and/ or specialist referral if other methods are unacceptable.
AIDS, acquired immune deficiency syndrome; BMI, body mass index; CIN, cervical intraepithelial neoplasia; HAART, highly active antiretroviral therapy; hCG, human chorionic gonadotrophin; HIV, human immunodeficiency virus; IDDM, insulin-dependent diabetes; NIDDM, non-insulin-dependent diabetes; PID, pelvic inflammatory disease; STI, sexually transmitted infection; TB, tuberculosis; VTE, venous thromboembolism.

Evidence-based information for clinicians to consider before giving a first prescription of COC is given as recommendations numbered 1 to 39. Essential information to be given to all women at first prescription of COC is given as recommendations numbered 40 to 51.

EVIDENCE-BASED INFORMATION FOR CLINICIANS

Medical history before a first prescription of COC

1 In order to advise on eligibility for COC use, clinicians should take a clinical history including: medical conditions (past and present), drugs use (prescription, non-prescription and herbal remedies) and family history (Good Practice Point).

2 When considering a first prescription of COC, clinicians should specifically enquire about migraine and cardiovascular risk factors (smoking, obesity, hypertension, thrombophilia, previous venous thromboembolism and hyperlipidaemia) (Good Practice Point).

3 User preference and individual concerns about COC use should be addressed (Good Practice Point).

History taking and appropriate examination/tests allow clinicians to assess medical eligibility for COC use. A clinician should enquire about: medical conditions (past and present), family history and drug history (prescription,

non-prescription and herbal remedies). Knowledge of previous contraceptive use, sexual health and reproductive health will help tailor advice for each individual woman. The medical history should alert the clinician to conditions or risk factors that might be a strong or absolute contraindication to COC use. For example, cardiovascular disease is rare in women of reproductive age but potentially serious. Risk factors for cardiovascular disease [smoking, obesity, hypertension, thrombophilia, previous venous thromboembolism (VTE), hyperlipidaemia] should be specifically enquired about. A woman with multiple risk factors may need to avoid COC use, although individual risk factors would not necessarily contraindicate use (Table 2). In addition, migraine is common in women of reproductive age but may contraindicate COC use and should be enquired about.

	Category
Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes and hypertension)	UKMEC 3/4

Age

4 COC can be used from the menarche to age 50 years if there are no other risk factors (Grade C).

Use of COC peaks in women aged 20–24 years with few women aged over 40 years using COC.[13] Previous Guidance has supported the use of COC up to the age of 50 years by women with no risk factors.[3] An alternative non-oestrogen-containing contraceptive should be used from age 50 years.

Age	Category
(a) Menarche to <40 years	UKMEC 1
(b) ≥40 years	UKMEC 2

Smoking

5 Clinicians should be aware that there is a very small increased risk of MI with current COC use in *non-smokers* which increases further for *smokers* (Grade B).

6 Use of COC by women aged ≥35 years who smoke is not recommended (Grade B).

7 Use of COC may be considered by women aged ≥35 years who have stopped smoking for ≥1 year (Grade C).

Myocardial infarction (MI), VTE and stroke are rare in women of reproductive age, however smoking is an independent risk factor.[24–31] Compared to non-smokers, heavy smokers (≥15 cigarettes per day) have a three-fold increased risk of MI,[24] a two-fold increased risk of stroke[26,27] and twice the rate of death from all causes [rate ratio (RR) 2.14, 95% CI 1.81–2.53].[16] Previous studies showed that the increased risk of MI and stroke associated with COC use was confined to smokers.[16,26] However, two meta-analyses[32,33] report a very small increase in the risk of MI with COC use in non-smokers [odds ratio (OR) 1.84, 95% CI 1.38–2.44[32] and OR 2.48, 95% CI 1.91–3.22].[33] Case-control studies[25,34] identified a two-fold increase in the risk of VTE associated with smoking and COC use (OR 2.0, 95% CI 1.3–3.3).[25]

COC can be used by women aged <35 years who smoke.[20] Excess mortality in heavy smokers becomes apparent from the age of 35 years, accounting for 0.7 deaths per 1000 woman-years.[16] The use of COC by women aged ≥35 years who are heavy smokers poses an unacceptable health risk.[20] The excess risk of MI and stroke associated with smoking reduces after cessation.[35–37] Smoking cessation should be encouraged and supported.[38,39] In addition, the Clinical Effectiveness Unit advises that previous smokers aged ≥35 years may consider the use of COC if they have stopped smoking for ≥1 year.[20]

Smoking	Category
(a) Age <35 years	UKMEC 2
(b) Age ≥35 years	
(i) <15 cigarettes/day	UKMEC 3
(ii) ≥15 cigarettes/day	UKMEC 4
(iii) Stopped smoking <1 year ago	UKMEC 3
(iv) Stopped smoking ≥1 year ago	UKMEC 2

Obesity

8 Use of COC by women with a BMI ≥35 is associated with an increased risk of MI and VTE and is not generally recommended (Grade B).

Morbid obesity [body mass index (BMI) >40 kg/m^2] is an independent risk factor for MI and VTE.[40,41] Case-control studies show an increased risk of MI and VTE with increased BMI.[25,34,42–47] The risk of MI in women with a BMI ≥27 kg/m^2 is further increased with COC use.[47] The risk of VTE is increased two-fold for women with a BMI >30 kg/m^2 (OR 1.9, 95% CI 1.1–3.1)[34] and there is almost a four-fold increase in risk of VTE with a BMI >35 kg/m^2 (OR 3.8, 95% CI 1.8–8.0).[34] Other factors such as waist–hip ratio may be more strongly related to MI risk than BMI.[48]

For women with a BMI 35–39 kg/m^2, the risks of COC use generally outweigh the benefits (UKMEC 3); and with a BMI ≥40 kg/m^2, COC use poses an unacceptable health risk (UKMEC 4).[20]

Obesity	Category
(a) BMI >30–34 kg/m^2	UKMEC 2
(b) BMI 35–39 kg/m^2	UKMEC 3
(c) BMI ≥40 kg/m^2	UKMEC 4

Hypertension

9 Use of COC is not generally recommended when blood pressure is consistently >140 mmHg systolic and/or > 90 mmHg diastolic (Grade C).

Women with hypertension are at an increased risk of MI[24] and stroke (haemorrhagic and ischaemic).[26,31,49] The use of COC has a negligible effect on blood pressure.[50,51] However, a cross-sectional survey found that blood pressure was significantly increased in COC users compared to non-COC users.[52] There is a further increased risk of MI in hypertensive women with COC use.[24,26,28,31,32,47,53–56] When blood pressure is

consistently >140–159 mmHg systolic or >90–94 mmHg diastolic the risks associated with COC use outweigh the benefits (UKMEC 3), and use poses an unacceptable health risk if the blood pressure is ≥160 mmHg systolic and/or ≥95 mmHg diastolic (UKMEC 4).[20]

Hypertension	Category
(a) Adequately controlled hypertension	UKMEC 3
(b) Consistently elevated blood pressure (i) systolic >140–159 mmHg or diastolic >90–94 mmHg	UKMEC 3
(ii) systolic ≥160 mmHg or diastolic ≥95 mmHg	UKMEC 4
(c) Vascular disease (e.g. coronary heart disease presenting with angina, peripheral vascular disease presenting with intermittent claudication, hypertensive retinopathy and transient ischaemic attacks)	UKMEC 4

	Category
Current and history of ischaemic heart disease	UKMEC 4

Venous thromboembolism

10 Use of COC by women with a personal history of VTE or known thrombogenic mutations is not recommended (Grade C).

11 Clinicians should be aware that the relative risk of VTE with COC use can increase up to five-fold, but in absolute terms the risk is still very low (Grade B).

12 A thrombophilia screen is not recommended routinely before prescribing COC (Grade C).

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

14 The interpretation of a thrombophilia screen should be undertaken in consultation with a haematologist or other expert and in combination with a detailed family history (Good Practice Point).

Personal history of VTE

There is evidence of synergism between underlying genetic causes of venous thrombosis (such as factor V Leiden mutation, prothrombin gene mutations, Protein C and Protein S deficiency, anti-thrombin III deficiency and antiphospholipid syndrome) and acquired risk factors (such as pregnancy, puerperium, hormonal contraceptive use, surgery, trauma, immobilisation and malignancy).[57]

VTE is uncommon in women of reproductive age. All COCs increase the risk of VTE.[41] The level of VTE risk may differ depending on which progestogen is used in the pill (Table 3).[41] Nevertheless, the absolute risk of VTE with COC use remains small.[25,44,58,59] Evidence suggests that COCs containing gestodene or desogestrel are associated with almost a two-fold increase in the risk of VTE compared to COCs containing norethisterone or levonorgestrel (adjusted OR 1.7, 95% CI 1.4–2.0).[44] Whether the apparent relationship between the type of progestogen and the increased VTE risk is explained by confounding or bias has been contested.[49,60, 61] However, desogestrel and gestodene may not counteract the thrombogenic effects of EE as well as levonorgestrel and norethisterone, and therefore an increased risk of VTE is biologically plausible.[62]

Presenting the risk of VTE in relative terms may sound alarming, and risks in absolute terms recognise the rarity of VTE in women of reproductive age (Tables 3 and 4). The increased risk of VTE associated with COC use is greatest in the first year of use. The increased risk returns to that of non-users within weeks of discontinuation.[63] Case-control studies show a reduction in VTE risk with increasing duration of use.[25,42,58] This may be due to a thrombophilia being 'unmasked' when starting COC.

Studies on VTE risk and COC use have included few women using COCs containing norgestimate (Cilest®).[42,64] Since norgestimate is metabolised to levonorgestrel the VTE risk may be similar to that of a levonorgestrel COC.[65,66]

A prescription monitoring study identified 13 cases of VTE in women using a drospirenone-containing COC (Yasmin®).[67] The incident rate of VTE was 13.7 cases per 10 000 woman-years.[67] Notably, all cases had another additional risk factor for VTE (such as thrombophilia, smoking, age >35 years, obesity, immobility, long haul flight). The Committee on Safety of Medicines suggested that the risk of VTE with drospirenone-containing COCs does not appear to differ from that of other COCs.[41]

Compared to women using a COC containing levonorgestrel, women using Dianette® (35 μg EE and 2 mg cyproterone acetate) may have up to a further four-fold increase in the risk of VTE (OR 3.9, 95% CI 1.1–13.4).[68,69]

Thrombogenic mutations and family history of VTE

A family history of VTE may alert clinicians to women who may have an increased risk of VTE.[70–73] The cause of the VTE may not be hereditary (e.g. pregnancy, immobility) and many women with a family history of VTE will never develop venous thrombosis.[74]

Women with reduced levels of the naturally occurring anticoagulants (anti-thrombin III, Protein C or Protein S) or factor V Leiden or prothrombin gene mutations (G20210A) are predisposed to VTE.[74,75] Indeed, women with factor V Leiden mutation can have up to a 35-fold increased risk of thrombosis with COC use.[76,77] Exposure to acquired risk factors, such as COC, may increase the risk but only for some women. The low incidence of VTE in women of reproductive age also means that even with such an increased risk the absolute risk is low (around three additional cases of VTE per year per 1000 pill users with factor V Leiden).[76]

Table 3 *Risk of venous thromboembolism (VTE) associated with combined oral contraception (COC) use and non-use*

Circumstance	Risk of VTE per 100 000 woman-years
For women not using COC and not pregnant	5
For women using a levonorgestrel- or norethisterone-containing COC (e.g. Microgynon 30®, Loestrin 20®, Loestrin 30®)	15
For women using a desogestrel- or gestodene-containing COC (e.g. Marvelon®, Mercilon®, Femodene®, Femodette®)	25
In pregnancy	60

Table 4 *Potential harms and benefits of combined oral contraception (COC) use in non-smokers*

Disease	Rates per 100 000 women not using COC	Relative risk with COC use in non-smokers
Potential harms (risks)[a]		
Coronary artery disease[b]	1500	Very small increase risk
Ischaemic stroke[b]	100	Two-fold increase in ischaemic stroke
Venous thromboembolism (VTE)[c]	5	Three-fold increase with levonorgestrel and norethisterone COCs[e] Five-fold increase with desogestrel and gestodene COCs[e]
Breast cancer[d]	(1 in 9 women will develop breast cancer at some time in their lives. The estimated risk of developing breast cancer up to age 30 years is 1 in 1900, up to 40 years is 1 in 200 and up to age 50 years is 1 in 50)	Any increased risk likely to be small and will vary with age No increased risk above background risk 10 years after stopping COC
Cervical cancer	11	Small increase after 5 years and a two-fold increase after 10 years
Benefits		
Ovarian cancer	22	Halving of risk lasting for >15 years
Endometrial cancer	15	Halving of risk lasting for >15 years

[a]Potential harms: 1 in 100 000 risk of being affected by a disease is judged to be a negligible risk and equates to one person in a large UK town being affected. The perceived risk, however, can depend on how the information is given, and the seriousness and incidence of the disease. [b]Statistics from National Statistics (www.statistics.gov.uk). Prevalence of treated coronary heart disease and stroke recorded in general practice in England and Wales for women aged up to 54 years. [c]The relative risk of VTE associated with COC use increases three-fold but the absolute risk increases from 5 to only 25 per 100,000 women-years. [d]NHS Screening Programme (www.cancerscreening.nhs.uk). [e]All COCs increase the risk of VTE including those containing norgestimate, drospirenone and cyproterone acetate.

Thrombophilia screening

Most episodes of VTE occur in women who do not have a thrombogenic mutation. Routine thrombophilia screening prior to COC use is not recommended.[74] The use of thrombophilia screening for women considering COC use who have a family history of VTE is unclear. Women with a family history of VTE in a first-degree relative <45 years of age may indicate an increased likelihood of a hereditary thrombophilia. A negative screen may not exclude all types of thrombophilia. The interpretation of a thrombophilia screen is often difficult and if done should be performed in consultation with a haematologist or other expert.[74]

Other conditions

The use of COC by women with Raynaud's disease when associated with an underlying thrombogenic disorder [e.g. systemic lupus erythematosus (SLE)] poses an unacceptable health risk (UKMEC 4).[20] Although SLE itself is not included in UKMEC, two recent studies have shown that use of COC by women with SLE did not increase the incidence of flares. Women with high levels of anticardiolipin antibodies, lupus anticoagulant or previous thrombosis were excluded. Very few women with SLE developed thrombosis.[78,79] The risks of COC use by women who are immobile (due to causes other than surgery) may outweigh the benefits (UKMEC 3).[20]

Venous thromboembolism (VTE)	Category
(a) History of VTE	UKMEC 4
(b) Current VTE (on anticoagulants)	UKMEC 4
(c) Family history of VTE	
(i) First-degree relative aged <45 years	UKMEC 3
(ii) First-degree relative aged ≥45 years	UKMEC 2
(d) Major surgery	
(i) *With* prolonged immobilisation	UKMEC 4
(ii) *Without* prolonged immobilisation	UKMEC 2
(e) Minor surgery without immobilisation	UKMEC 1
(f) Immobility (unrelated to surgery) (e.g. wheelchair use, debilitating illness)	UKMEC 3

Venous thromboembolism (VTE)	Category
Known thrombogenic mutations	
(e.g. factor V Leiden; prothrombin mutation; Protein S, Protein C and anti-thrombin deficiencies)	UKMEC 4
Raynaud's disease	
(a) Primary	UKMEC 1
(b) Secondary	
(i) *Without* lupus anticoagulant	UKMEC 2
(ii) *With lupus* anticoagulant	UKMEC 4

Stroke

15 Clinicians should be aware that there is a very small increase in the absolute risk of ischaemic stroke with COC use (Grade B).

The annual incidence of ischaemic stroke in women aged <35 years is low (i.e. 3 per 100 000) but increases with age.[26] Mortality from haemorrhagic and ischaemic stroke is not increased with COC use.[16] A meta-analysis reported a two-fold increase in the risk of ischaemic stroke with the use of low-dose COCs.[33] A more recent case-control study found no increased risk of ischaemic stroke with current use of COCs containing <50 μg EE (OR 1.62, 95% CI 0.69–3.83).[80] There is no significant increase in risk of haemorrhagic stroke with COC use.[31]

	Category
Stroke (history of cerebrovascular accident)	UKMEC 4

Migraine

16 Use of COC by women of any age who have migraine with aura is not recommended (Grade B).

17 Use of COC by women ≥35 years of age who have migraine without aura is not generally recommended (Grade B).

The risk of ischaemic stroke is increased in migraine sufferers (OR 2.16, 95% CI 1.89–2.48).[81] Nevertheless, the absolute risk of stroke in women with migraine is low (17–19 per 100 000 woman years).[82] A meta-analysis[81] and case-control studies[26,27,30,83,84] found an increased risk of stroke in COC users with migraine, compared to COC users without migraine. Migraine with aura (which indicates ischaemia) is generally thought to be a greater risk for stroke. Symptoms of aura include homonymous visual disturbances, unilateral paraestheia and/or numbness, unilateral weakness and aphasia or unclassifiable speech disorder.[82] Visual symptoms progress from 'fortification spectra' (a star-shaped figure near the point of fixation with scintillating edges) to scotoma (a bright shape which gradually increases in size). Flashing lights do not constitute aura.[85] Aura occurs prior to the onset of headache.

UKMEC recommends that all women who suffer migraine *with* aura should not use COC as this poses an unacceptable health risk (UKMEC 4).[20] In addition, for women aged ≥35 years who suffer from migraine *without* aura the risks associated with COC use outweigh the benefits (UKMEC 3).[20] It is unclear if the risk of stroke with COC use is increased in women with a past history of migraine with aura and no recent episodes, and COC use in this situation is not generally recommended (UKMEC 3). Details about previous migraine with aura such as how long ago this occurred, how often and whether or not there have been recent episodes may be taken into account if considering COC use in women with a past history of migraine.

Headaches	**Category *initiation***
(a) Non-migrainous (mild or severe)	UKMEC 1
(b) Migraine	
(i) *Without* aura, age <35 years	UKMEC 2
(ii) *Without* aura, age ≥35 years	UKMEC 3
(iii) *With* aura, at any age	UKMEC 4
(c) Past history of migraine with aura at any age	UKMEC 3

Breast cancer

18 Clinicians should be aware that any increased risk of breast cancer with COC use is likely to be small, is in addition to background risk, and is reduced to no increased risk 10 years after stopping COC use (Grade B).

A meta-analysis of case-control studies showed an increased risk of breast cancer whilst using COC (RR 1.24, 95% CI 1.15–1.33).[86] This suggests a 24% increase in breast cancer risk above the background risk. A more recent population-based, case-control study found that current COC users appear to have no increased risk (RR 1.0, 95% CI 0.8–1.3) compared to never-users.[87] Any excess risk of breast cancer associated with COC use increases quickly after starting, does not increase with duration of use, and has gone within 10 years of stopping COC use.[86] Any excess risk does not appear to be influenced by family history (without BRCA mutations), age at first use, dose or type of hormone.[86,87] A large cohort study of 27 000 women with a family history of breast cancer reported no association between ever-use of COCs and breast cancer risk in women who had a first- or second-degree relative with breast cancer.[88] The risk of breast cancer in women with a genetic mutation is greater than in the general population, but most cases of breast cancer are sporadic. Women who are carriers of BRCA2 mutations have no additional increased risk of breast cancer with COC use (OR 0.94, 95% CI 0.72–1.24).[89] Carriers of BRCA1 had a small increase in risk (OR 1.2, 95% CI 1.02–1.4).[89] Other studies have found no risk or a decreased risk with BRCA mutations.[90–92]

Breast disease	**Category *initiation***
(a) Undiagnosed mass	UKMEC 3
(b) Benign breast disease	UKMEC 1
(c) Family history of cancer	UKMEC 1
(d) Carriers of known gene mutations associated with breast cancer (e.g. BRCA1)	UKMEC 3
(e) Breast cancer	
(i) Current	UKMEC 4
(ii) Past and no evidence of current disease for 5 years	UKMEC 3

Cervical cancer

19 Clinicians should be aware that there may be a very small increase in the risk of cervical cancer with COC use, which increases with increasing duration of use (Grade B).

Results pooled from eight case-control studies suggested long-term COC use increased the risk of cervical cancer by up to four-fold in women who were positive for the human papillomavirus (HPV).[93] A systematic review of case-control and cohort studies that included women with invasive cancer and cervical intraepithelial neoplasia (CIN II or III) found that the risk of invasive and *in situ* cervical disease increases with increasing duration of oral contraceptive use.[94] This was apparent even in women who were HPV negative. COC use for >5 years increased the risk of invasive and *in situ* cervical disease by 10% (RR 1.1, 95% CI 1.1–1.2).[94] With ≥10 years of use, the risk is doubled (RR 2.2, 95% CI 1.9–2.4). An appraisal of this systematic review has, however, questioned any causal connection between long-term COC use and cervical cancer.[95] Women can be advised that COC use for <10 years is associated with a negligible risk of cervical cancer, but this may increase with duration of use. The National Health Service cervical cytology screening programme has reduced mortality from cervical cancer.[96] Women should be encouraged to take part in routine cervical screening and do not require different screening when using COC.[96]

Other cancers

Primary liver cancer is rare but COC use increases the risk depending on duration of use.[97]

Women with gestational trophoblastic neoplasia are advised against the use of hormonal contraception until serum concentrations of human chorionic gonadotrophin (hCG) are normal.[20,98]

Gestational trophoblastic neoplasia	**Category**
(a) hCG normal	UKMEC 1
(b) hCG abnormal	UKMEC 4

Potential drug interactions

20 Clinicians should consider the possibility of drug interactions when prescribing COC (Good Practice Point).

21 Liver enzyme-inducing drugs may reduce the efficacy of COC; therefore, if they are to be used long term, alternative contraceptives that are unaffected by enzyme-inducing drugs should be considered (Grade C).

22 If, after counselling, women using liver enzyme-inducing drugs still wish to use COC then a regimen with at least 50 μg EE should be used. In addition, barrier contraception is recommended while taking the liver enzyme-inducers and for 28 days after they are stopped (Good Practice Point).

23 A woman taking long-term non-liver enzyme-inducing antibiotics (≥3 weeks) does not require additional contraceptive protection when starting COC (Grade C).

24 Women using COC who are prescribed a short course (<3 weeks) of non-liver enzyme-inducing antibiotics should be advised to use additional contraceptive protection while taking the antibiotic and for 7 days after the antibiotic is stopped (Grade C).

Liver enzyme-inducing drugs

Liver enzyme-inducing drugs increase the metabolism of EE and progestogen, which can decrease the contraceptive efficacy of COCs.[99–103] If, after counselling, a woman taking a liver enzyme-inducing drug wishes to use COC then several unproven and unlicensed methods may improve COC efficacy[6,104–107] (e.g. 50 μg EE daily as a 20 μg COC plus a 30 μg COC). Additional contraceptive protection such as condoms is advised while taking the liver enzyme-inducing drug and for 28 days after this drug is stopped.[7,105] Shortening the hormone-free interval reduces ovarian follicular activity and may lower any potential risk of COC failure.[108,109]

Non-liver enzyme-inducing antibiotics

No study has reliably investigated if the efficacy of COC is reduced with concurrent antibiotic use. Short-term (i.e. <3 weeks) antibiotic use alters gut flora and reduces the enterohepatic circulation of EE. Gut flora recover after 3 weeks of antibiotic use. Although pregnancies have been reported in COC users taking antibiotics, this does not confirm direct causation. Nevertheless, the consequences of an unplanned pregnancy are such that a cautious approach is advised.[7] If a woman starting COC has been using a non-liver enzyme-inducing antibiotic for ≥3 weeks no additional contraceptive protection is required unless the antibiotic is changed and should be managed as for short courses (<3 weeks) of antibiotic use. Women using COC who are given a short course (<3 weeks) of non-liver enzyme-inducing antibiotics should be advised to use additional contraceptive protection while taking the antibiotic and for 7 days after the antibiotic is stopped. If there are fewer than seven active pills remaining in the pack the pill-free interval should be omitted.[7]

Other drugs

The bioavailability of drugs can be altered with concurrent COC use. This may have important clinical effects if serum drug concentrations are increased or decreased (e.g. theophylline, cyclopsorin, lamotrigine).[7,110–115]

Drug interactions	Category
Liver enzyme-inducing drugs (e.g. rifampicin, St John's Wort, griseofulvin, certain anti-convulsants, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, some anti-retrovirals)	UKMEC 3
Non-liver enzyme-inducing antibiotics	UKMEC 2

Potential non-contraceptive benefits to be considered

Dysmenorrhoea and menorrhagia

25 Clinicians should be aware that menstrual pain and blood loss may be reduced with COC use (Grade C).

Evidence to determine if COCs reduce primary dysmenorrhoea is poor.[116] A small, randomised, double-blind, placebo-controlled trial showed a significant reduction in menstrual cramps with COC use.[117] A COC was less effective than gonadotrophin-releasing hormone agonist in the relief of menstrual pain.[118]

Evidence to confirm that COC reduces menstrual blood loss is poor.[119] A small, randomised trial showed a 43% reduction in measured menstrual blood loss with COC use over two cycles.[120] Data from small prospective studies confirmed a reduction in menstrual blood loss and dysmenorrhoea in women using COC.[121] The Oxford Family Planning Association contraceptive study demonstrated that hospital referral for excessive periods, painful periods, irregular periods and other menstrual disorders was less common among women currently using COCs or stopping them within the previous 12 months than non-users.[122] Guidance from the Royal College of Obstetricians and Gynaecologists supports the use of COC in reducing menstrual blood loss.[123]

Ovarian cysts

26 Clinicians should be aware that the incidence of functional ovarian cysts and benign ovarian tumours is reduced with COC use (Grade B).

Case control and cohort studies suggest a reduction in the incidence of functional ovarian cysts[124–126] and benign ovarian tumours[127] for women using COC.

Ovarian and endometrial cancer

27 Clinicians should be aware that there is at least a 50% reduction in the risk of ovarian and endometrial cancer with COC use which continues for 15 or more years after stopping (Grade B).

A systematic review showed a reduced risk of ovarian cancer with COC use (high- and low-dose formulations).[128] The reduction in risk persisted for at least 20 years after cessation. Other studies[129,130] found that the risk of ovarian cancer is reduced by at least 50% with low-dose COC use. Mortality from ovarian cancer is reduced with increasing duration of COC use.[16] Studies suggest the reduction in ovarian cancer with oral contraceptives may also be present in women with genetic mutations that predispose them to ovarian cancer (e.g. BRCA1).[131,132]

Case-control studies[133,134] have reported that the risk of endometrial cancer is reduced by 50% with 50 μg COCs.

A large, Swedish population, case-control study identified a 70% reduction in the risk of endometrial cancer for COCs with <40 µg EE (OR 0.3, 95% CI 0.1–0.9).[135] This protection was apparent after 3 years' use and continued for 15 or more years after discontinuation.[135] Mortality from endometrial cancer is decreased with COC use.[16]

Colorectal cancer

28 Clinicians should be aware that COC use is associated with a reduction in the risk of colorectal cancer (Grade B).

Studies on the risk of colorectal cancer with COC use are reassuring.[136–140] A meta-analysis identified an overall reduced risk of colorectal cancer (RR 0.82, 95% CI 0.74–0.92).[137]

Acne vulgaris

29 Clinicians should be aware that COCs can improve acne vulgaris (Grade A).

A Cochrane Review found that COCs can improve acne vulgaris.[141] Small randomised trials have shown significant reductions in acne lesions with COCs containing desogestrel,[142,143] levonorgestrel[143–146] and norgestimate.[147] Dianette® (35 µg EE and 2 mg cyproterone acetate) has anti-androgenic properties and is used to treat acne vulgaris. The risk of VTE may increase with Dianette use compared to other COCs and therefore it is not indicated solely as a contraceptive.[148] Dianette is a treatment option for women with severe acne, which has not responded to oral antibiotics, or for moderately severe hirsutism. It should be withdrawn 3–4 months after the treated condition has resolved.[148]

Miscellaneous non-contraceptive benefits

Evidence of the effects of COC use on bone density is conflicting but no studies found a reduction in bone density.[149–160]

Studies have indicated a reduction in benign breast disease with COC use, however results are limited due to confounding and bias.[161,162]

A meta-analysis identified a 30% reduction in the incidence of rheumatoid arthritis with COC use.[163] COC use does not significantly influence outcome in long-term rheumatoid arthritis.[164]

Other relevant information

Weight gain

30 Clinicians should be aware that there is no evidence of additional weight gain due to COC use (Grade A).

Studies have suggested small increases in weight with COC use, however a Cochrane Review did not support a causal association between COC and additional weight gain.[165]

Bleeding patterns

31 Clinicians should be aware that unscheduled bleeding can occur with COC use but in the absence of missed pills, vomiting within 2 hours of pill taking, severe diarrhoea or drug interactions it is not a measure of efficacy (Grade B).

32 Clinicians may wish to give women advice to alter the timing of the withdrawal bleeds but should be aware that this use is outside the terms of the product licences (Good Practice Point).

Clinicians should be aware of likely causes of unscheduled bleeding such as missed pills, sexually transmitted infections, pregnancy, malabsorption (due to drug interactions, vomiting within 2 hours of pill taking or severe diarrhoea). Several studies in a Cochrane Review[166] found unscheduled bleeding was more common in women using a 20 µg COC compared to COCs containing >20 µg EE. No link between serum steroid concentrations, unscheduled bleeding and loss of contraceptive efficacy has been established.[167,168]

Randomised trials report high user satisfaction when COCs are tricycled (pills taken for nine consecutive weeks before having a pill-free week).[169–172] Women can be advised to tricycle packets of COCs for a variety of reasons: to prevent or delay withdrawal bleeding, to reduce menstrual bleeding problems or to avoid withdrawal headaches. Use of COCs in this way is outside the product licence.[6]

Which examinations are needed before a first prescription of COC?

33 A blood pressure recording should be documented for all women prior to a first prescription of COC (Grade C).

34 BMI should be documented for all women prior to a first prescription of COC (Good Practice Point).

The WHO and UK *Selected Practice Recommendations for Contraceptive Use*[14,15] recommend examinations and tests that should be performed before providing contraception. Notably, breast, pelvic and genital examination, cervical cytology screening and routine laboratory tests including haemoglobin measurement are *not recommended* routinely as they do not contribute substantially to COC safety. A recording of blood pressure[15] and BMI should be documented for all women before a first prescription of COC. Guidance on standards for record keeping have been developed by the FFPRHC.[173]

When can COC be started?

35 Ideally COC should be started on the first day of menstruation but can be started up to and including Day 5 of the cycle without the need for additional contraceptive protection (Grade C).

36 COC can be started at any other time in the cycle if it is reasonably certain the woman is not pregnant but additional contraceptive protection, such as condoms, is required for the first 7 days (Grade C).

Ideally women should be encouraged to start COC on the first day of menstruation. Animal studies show that COC inhibits ovulation when started up to, and including, Day 6 of the menstrual cycle.[174] A randomised, single-blind study investigated ovarian follicle development and subsequent ovulation in women starting COC on Days 1, 4 or 7 of the menstrual cycle.[175] This trial supported findings from an earlier

Table 5 *When to start combined oral contraception (COC) in different circumstances (adapted from WHOSPR)*[14]

Circumstances for COC start	When to start COC	Additional contraceptive protection required
Women having menstrual cycles	Start COC up to and including Day 5 At any other time if it is reasonably certain that she is not pregnant	None For 7 days
Women who are amenorrhoeic	COC can be started at any time, if it is reasonably certain she is not pregnant	For 7 days
Postpartum (not breastfeeding)	Start COC on Day 21 postpartum if vaginal delivery and no additional risk factors for VTE If she is >21 days postpartum and her menstrual cycles have returned she can start COC as for other women having menstrual cycles If she is >21 days postpartum and her menstrual cycles have not returned treat as amenorrhoeic	None None or for 7 days For 7 days
Postpartum (breastfeeding)	If she is >6 months postpartum and her menstrual cycles have returned she can start COC as for other women having menstrual cycles (Women breastfeeding <6 weeks postpartum should not use COCs and between 6 weeks and 6 months COC can be started as for women who are postpartum and not breastfeeding – see above)	None or for 7 days
Post-abortion	She can start COCs within 7 days of surgical or medical abortion at gestations <24 weeks	None
Switching from other hormonal methods (other than the IUS)	COC can be started immediately if she has been using her hormonal method consistently and correctly, or if it is reasonably certain she is not pregnant. There is no need to wait for her next menstrual period If her previous method was an injectable or a implant (which inhibit ovulation), she can start COC any time up to when the repeat injection is due or the implant is removed	None None
Switching from a non-hormonal method (other than the IUD)	Start COC up to and including Day 5 of the menstrual cycle At any other time if it is reasonable certain that she is not pregnant	None For 7 days
Switching from IUD or IUS	COC can be started up to and including Day 5 after the start of menstrual bleeding. IUD/IUS can be removed at that time COC can be started at any other time, if it is reasonably certain she is not pregnant. Ideally the IUS/IUD can provide contraceptive protection until seven or more pills have been taken. The IUS/IUD can then be removed. If the IUD/IUS is removed at the time of starting COC then additional contraception is required for 7 days as ovulation still occurs for women using intrauterine methods	None For 7 days

COC, combined oral contraception; IUD, intrauterine device; IUS, intrauterine system; VTE, venous thromboembolism.

cohort study[8] that ovulation did not occur with a Day 5 start. Vaginal ultrasonography and serum progesterone were used to assess follicular activity and ovulation in 85 women. Ovarian follicular development occurred despite consistent COC use but no ovulation was identified.[169] The ovaries were quiescent by Day 21, even when starting COC on Day 7. In view of this evidence, and to increase flexibility in COC starting regimens, COC can be started up to, and including, Day 5 of the menstrual cycle without the need for additional contraception (Table 5).[15] This starting regimen is outside the terms of the product licence.[6]

A woman may start COC at any other time in the menstrual cycle if it is reasonably certain she is not pregnant. In this situation, additional contraception is required until seven consecutive pills have been taken. A clinician can be reasonably certain that a woman is not pregnant if she has no signs or symptoms of pregnancy and meets any of the following criteria:

- has not had intercourse since the start of the last normal menses[14]
- has been correctly and consistently using a reliable method of contraception[14]
- is within 7 days after the start of normal menses[14]
- is within 7 days post-abortion or miscarriage[14]
- is fully or nearly fully breastfeeding, amenorrhoeic and <6 months postpartum[14]
- is not breastfeeding and <3 weeks postpartum or has had no unprotected sex since delivery.

A pregnancy test, if available, adds weight to the diagnosis but only if 3 weeks have elapsed since the date of last intercourse.

Advice regarding starting COC in other circumstances, or when switching from another method of contraception, is summarised in Table 5.

What is the advice given for missed pills?

The terminology *late* pill is no longer used. A *missed pill* is a pill that is completely omitted from being taken. Missed pill guidance was updated in 2005[14,176] and is summarised in Figure 1.

When pills are missed, the inhibitory effects on the ovaries may be reduced sufficiently for ovulation to occur.[177,178] However, studies have suggested that missed pills are much more common than reported without jeopardising effectiveness.[179,180] The risk of pregnancy following missed pills depends on many factors including *how many* pills were missed and *when* they were missed. The risk of pregnancy is greatest when pills are missed at the beginning or the end of a packet (when the usual seven pill-free days are extended) as efficacy may be reduced.[11] Reassuringly ovulation is a rare event after only 7 days of pill taking.[10] Therefore, after taking seven pills at least seven can be missed (such as occurs in the pill-free week) without the need for additional contraception or emergency contraception. It is for this reason that pills missed in Weeks 2 and 3 of pill taking are unlikely to result in a loss of efficacy (Figure 1). Advice to use condoms for 7 days when pills are missed in Weeks 2 and 3 of pill taking may therefore be overcautious. Nevertheless, this advice is given in case further pills are missed. The need for emergency contraception if condoms are known to have failed in these situations will need to be considered individually.

Most evidence for missed pill advice is from studies of pills containing 30–35 μg EE. Evidence is limited on the pregnancy risk when missing pills contain ≤20 μg EE, but theoretically the pregnancy risk may be higher and a more cautious approach is advised when missing these COCs.

Figure 1 relates to 21-day pill regimens with active,

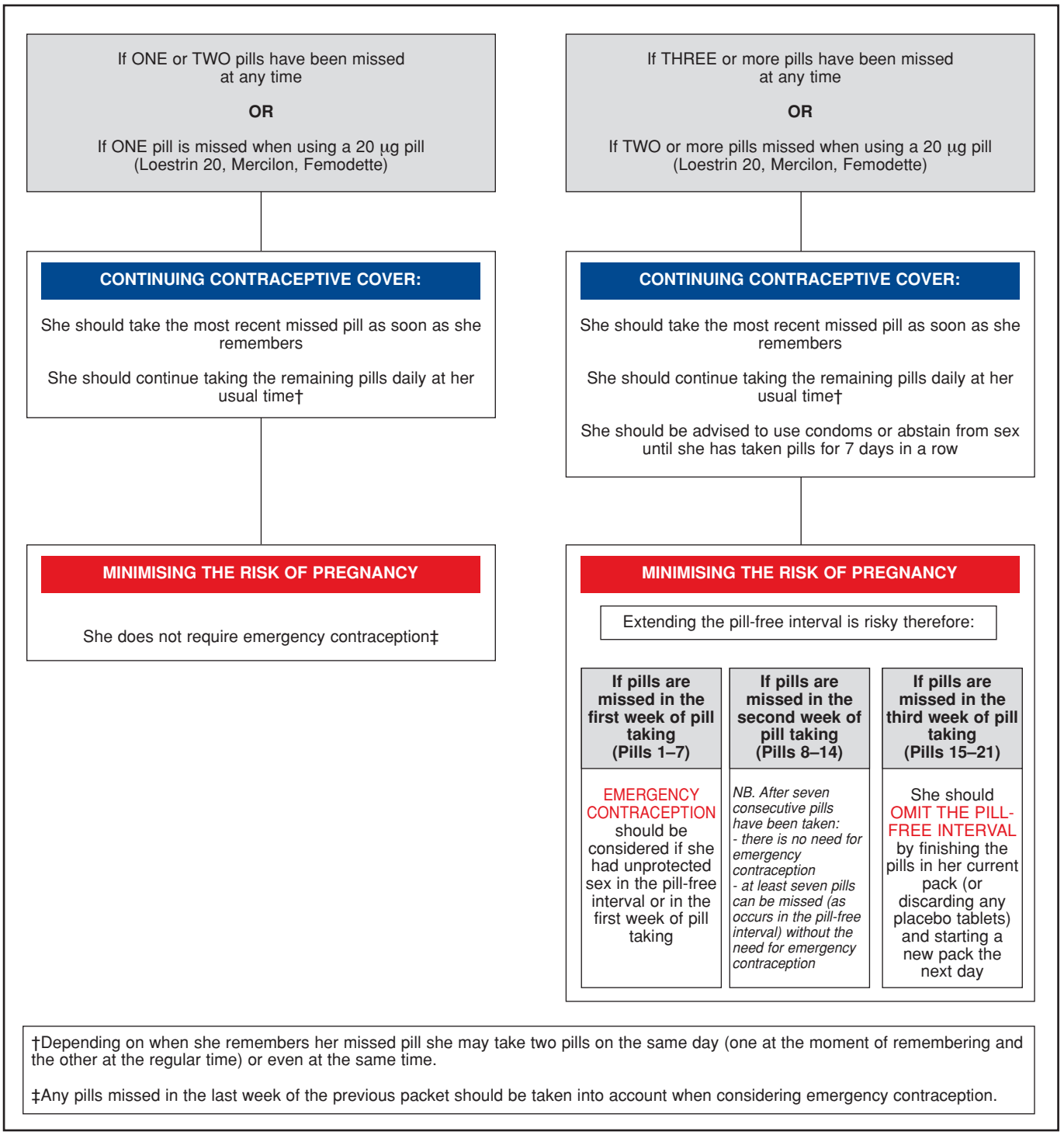

Figure 1 *Advice for women missing combined oral contraceptive pills*

hormone-containing pills being missed. Everyday regimens, which include seven inactive placebo pills, are rarely used in UK practice. For women using everyday regimens, the 'missed pill rules' must be modified accordingly.

Which pill is suitable for women being given a first prescription of COC?

37 A monophasic COC containing 30 μg EE with norethisterone or levonorgestrel is a suitable first pill (Grade C).

There are few direct, comparative data available to identify the best, first-line COCs. The rationale for advising a monophasic COC with 30 μg EE and norethisterone or levonorgestrel as a first pill is outlined.

- There is no evidence to support the use of biphasic or triphasic COCs.[181,182]
- Norethisterone- and levonorgestrel-containing COCs may have a lower risk of VTE than COCs containing desogestrel and gestodene.[63]
- Efficacy of 20 and 30 μg EE COCs is similar[183] but unscheduled bleeding is more common with 20 μg COCs.[166,183]

A retrospective survey showed that women were most likely to miss pills in the week following the pill-free interval,[180] however everyday pills have not been shown to improve compliance.

Other pills may be considered as second-line pills after trying a first pill.

What follow-up arrangements are appropriate for women being given a first prescription of COC?

38 A follow-up visit 3 months after a first prescription of COC allows an assessment of blood pressure, further instruction and assessment of any problems (Good Practice Point).

39 In the absence of special problems, women can be given up to 12 months' supply of COC at follow-up and encouraged to return at any time if problems arise (Grade C).

A follow-up visit 3 months after the first prescription of COC is advised to allow blood pressure to be rechecked, re-instruction given and an assessment of any problems. Women may be offered up to 12 months' supply of COC at the follow-up appointment. A yearly routine follow-up visit, plus advice to return at any time if there are problems, is recommended.[15]

EVIDENCE-BASED INFORMATION FOR WOMEN

What information should be given to all women when receiving a first prescription of COC?

Potential harms and benefits

40 At first prescription of COC all women should be informed that:
- **COC use is safe for the majority but can be associated with rare but serious harms**
- **there is a small increase in the risk of blood clots with COC use**
- **there is a very small increase in the risk of heart attack and stroke with COC use**
- **any increased risk of breast cancer is likely to be small and returns to no increased risk 10 years after stopping COC**
- **there may be a very small increase in the risk of cervical cancer that increases with increasing duration of use**
- **the risk of ovarian and endometrial cancer is halved with COC use and this continues for at least 15 years after stopping (Grade B).**

How to take the pill

41 Women should be advised to start COC on the first day of menstruation but it can be started up to and including Day 5 of the cycle without the need for additional contraceptive protection (Grade C).

42 Women can start COC at other times in the menstrual cycle if is reasonably certain that they are not pregnant but additional contraceptive protection is required for the first 7 days (Grade C).

43 Women should be encouraged to take one pill every day, at around the same time, for 21 consecutive days (Grade C).

44 Women should be advised that if all pills are taken consistently and correctly a COC is >99% effective at preventing pregnancy, even during the routine seven hormone-free days (Grade B).

45 Missing pills is not encouraged but women can be reassured that if one pill in the packet is missed at any time then contraceptive protection is not lost. If more pills are missed and they are unsure what to do they should seek help (Grade C).

Situations where efficacy may be reduced

46 Women should be advised that if vomiting occurs within 2 hours of taking COC another pill should be taken as soon as possible (Grade C).

47 Women should be informed that if they are prescribed antibiotics (non-liver enzyme-inducing) then additional contraceptive protection such as condoms should be used during the treatment and for 7 days after the antibiotic is stopped. If fewer than seven active pills are left in the pack after antibiotics are finished the woman should omit the pill-free interval (or discard any inactive pills). After using the same antibiotic for ≥3 weeks additional contraception is no longer required (Grade C).

Other information

48 Women should be encouraged to continue with the first COC for at least 3 months before considering an alternative (Good Practice Point).

49 Women should be given information on symptoms, which should prompt immediate medical consultation such as warning signs of VTE and new headache (Good Practice Point).

50 Women can be advised about practising safer sex with the use of condoms in addition to COC (Good Practice Point).

51 Women should be provided with appropriate written and verbal instructions regarding rules for missed pills, vomiting within 2 hours of taking a pill, severe diarrhoea, the use of new medication and when to seek help (Good Practice Point).

Long-term COC use is safe for the vast majority of women.[16–18] COC use is associated with both serious health risks and 'nuisance' side effects (Table 4). There are important potential harms that *all women* should be informed about when receiving a *first prescription* of COC. Women should also be advised of serious side effects that warrant immediate medical consultation. Specific concerns may also be raised at the first discussion but may be raised at future follow-up consultations. Advice on missed pills is summarised in Figure 1. Women who vomit within 2 hours of taking COC should repeat the dose as soon as possible.[14] The general advice for women using COC who have persistent vomiting or severe diarrhoea for more than 24 hours is to follow the instructions for missed pills.

Additional contraceptive protection, such as condoms, is advised when COC users start or change any non-liver enzyme-inducing antibiotic. Additional contraceptive protection is required during the antibiotic treatment and after the antibiotics have stopped until seven consecutive pills have been taken. If there are fewer than seven active pills remaining in the pack, the pill-free interval should be omitted.[7]

A randomised trial showed improvement in cycle

control after the initial 3 months of COC use.[184] Women should be encouraged to use COC for at least 3 months before considering an alternative regimen.

Advice should be given about the use of condoms to reduce the risk of sexually transmitted infections when using COC although this does not affect COC safety.

Women should be given written information such as the fpa leaflet on *Your Guide to the Combined Pill*,[185] which provides information on what to do when a pill is missed. A randomised trial conducted in a primary care setting[186] found that a widely available fpa leaflet was associated with a three-fold increase in good pill knowledge at follow-up. Women should be aware of appropriate local and national helplines providing advice on contraception and sexual health and be invited to re-attend services at any time should they have concerns about their contraception.

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This Guidance was developed by the Clinical Effectiveness Unit (CEU) on behalf of the Faculty of Family Planning and Reproductive Health Care (FFPRHC). CEU Guidance is developed in collaboration with the Clinical Effectiveness Committee (CEC) of the FFPRHC. Our process of Guidance development makes use of a multidisciplinary group of professionals and includes clinicians working in family planning, sexual and reproductive health care, general practice and other allied specialties. The multidisciplinary group also includes user representation. In addition to the multidisciplinary group involvement in the development of Guidance, drafts of CEU Guidance are peer reviewed independently by members of the CEC and a representative from FFPRHC Council. CEU Guidance is also available on the Faculty website (www.ffprhc.org.uk). Any comments about CEU Guidance can be made directly to the CEU at ceu.guidance@abdn.ac.uk.

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Evidence tables relating to this Guidance are available on request from the CEU. These summarise relevant published evidence on first pill prescription, which was identified and appraised in the development of this Guidance. The clinical recommendations within this Guidance are based on evidence whenever possible.

	Grades 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

Electronic searches were performed for: MEDLINE (CD Ovid version) (1996–2006); EMBASE (1996–2006); PubMed (1996–2006); The Cochrane Library (to April 2006) and the US National Guideline Clearing House. The searches were performed using relevant medical subject headings (MeSH) terms and text words. The Cochrane Library was searched for systematic reviews, meta-analyses and controlled trials relevant to a first prescription of COC. Previously existing guidelines from the Faculty of Family Planning and Reproductive Health Care, the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization and reference lists of identified publications were also searched. Similar search strategies have been used in the development of other national guidelines. Selected key publications were appraised according to standard methodological checklists before conclusions were considered as evidence. Evidence was graded as above, using a scheme similar to that adopted by the RCOG and other guideline development organisations.

Discussion Points for First Prescription of Combined Oral Contraception

The following discussion points have been developed by the FFPRHC Education Committee.

Discussion Points

1 Discuss and consider the evidence-based advice a clinician would give a 36-year-old client considering combined oral contraception (COC) use with a body mass index (BMI) of 29, whose blood pressure on the last two occasions has been 130/90.

2 In deciding which COC to use, a woman needs to think about risks and benefits carefully. Discuss how best to explain 'risk' to a patient.

3 In helping women feel comfortable with COC use, discuss any health benefits COC may offer.

Questions for First Prescription of Combined Oral Contraception

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

Indicate your answer by ticking the appropriate box for each question	***True***	***False***
1 Women requesting COC should be advised that it has no effect on risk of breast cancer.	☐	☐
2 The pregnancy risk may be higher when 20 μg pills are missed compared to 30 μg pills.	☐	☐
3 COC may be prescribed to a woman with a BMI of 34 as the benefits generally outweigh the risks.	☐	☐
4 Women should be routinely advised that COC is associated with potential weight gain.	☐	☐.
5 According to the WHO *Medical Eligibility Criteria*, the risks of COC use outweigh the benefits when there is a history of pregnancy-related cholestasis.	☐	☐
6 The risk of venous thromboembolism (VTE) rises with increasing duration of use of COC.	☐	☐
7 The benefits outweigh the risks of prescribing COC to a woman who is taking anticoagulants for a history of VTE.	☐	☐
8 Women who suffer from migraine with aura can use COC provided they are aged less than 35 years.	☐	☐
9 If vomiting occurs within 4 hours of taking COC another pill should be taken.	☐	☐
10 It is acceptable practice to offer women a 12-month supply of COC at routine follow-up visits.	☐	☐

Answers

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

KEY POINTS ON FIRST PRESCRIPTION OF COMBINED ORAL CONTRACEPTION

Combined oral contraception (COC) can be used safely by the majority of women from menarche to age 50 years when no other risk factors are present. User preference and concerns should be considered when counselling about the benefits, potential harms, and correct use of COC.

Implications for clinical practice from this updated Guidance:
- Blood pressure and BMI should be recorded before a first prescription of COC.
- A monophasic pill with 30 μg (micrograms) of ethinylestradiol and levonorgestrel or norethisterone should be chosen first line.
- Women should be counselled that the risk of MI with COC use is very small but is increased for non-smokers and smokers.

HISTORY SHOULD INCLUDE ENQUIRY ABOUT

- Medical conditions (past and present)
- Specific enquiry about migraine and cardiovascular risk factors (smoking, obesity, hypertension, thrombophilia, previous VTE and hyperlipidaemia)
- Drug use (prescription, non-prescription and herbal remedies)
- Family history

EXAMINATIONS

- Blood pressure and BMI should be documented prior to a first prescription of COC
- A thrombophilia screen is not recommended routinely before prescribing COC

†Use of COC is NOT recommended for women in the following circumstances:

- Smokers aged ≥35 years
- Migraine with aura at any age
- Migraine without aura when aged ≥35 years
- BMI ≥35 kg/m2
- Blood pressure consistently >140–159 mmHg systolic or 90–94 mmHg diastolic
- Personal history of VTE or a thrombogenic mutation
- Personal history of cardiovascular disease or stroke
- When using long-term liver enzyme-inducing drugs

†For a detailed list please refer to Table 2 in the full Guidance document

POTENTIAL HARMS ASSOCIATED WITH COC USE SHOULD BE DISCUSSED

- All COCs increase the risk of VTE‡, MI and ischaemic stroke but the absolute risk is small.
- Any increase in the risk of breast cancer associated with COC use is likely to be small, is in addition to the background risk and is reduced to no increased risk 10 years after stopping.
- There may be a very small increase in the risk of cervical cancer with COC use, which increases with increasing duration of use.

POTENTIAL NON-CONTRACEPTIVE BENEFITS ASSOCIATED WITH COC USE CAN BE CONSIDERED

- Menstrual pain and blood loss may be reduced.
- The incidence of functional ovarian cysts and benign ovarian tumours is reduced.
- The risk of ovarian and endometrial cancer is reduced by at least 50% during use and for at least 15 years after stopping.
- The risk of colorectal cancer is reduced.
- Improvement in symptoms of acne vulgaris.

ABSOLUTE VTE RISK ASSOCIATED WITH COC USE AND NON-USE‡

Circumstance	Risk of VTE per 100 000 woman-years (absolute risk)
Women not using COC	5
Women using COCs containing norethisterone or levonorgestrel	15
Women using COCs containing desogestrel or gestodene	25
Women who are pregnant	60

INSTRUCTIONS FOR USE

- A monophasic COC containing 30 μg (micrograms) of ethinylestradiol with norethisterone or levonorgestrel is a suitable first pill.
- One pill should be taken daily for 21 days followed by 7 pill-free days. *Women may choose to take more than one packet of pills continuously followed by a 7-day pill-free interval*.
- COC may be started up to and including Day 5 of the menstrual cycle without the need for additional barrier contraception. *COC can be started at other times if it is reasonably certain a woman is not pregnant but additional barrier contraception is required for the first 7 days of pill taking*.
- If vomiting occurs within 2 hours of pill taking another pill should be taken as soon as possible. *With persistent vomiting or severe diarrhoea for >24 hours instructions for missed pills (see Figure) should be followed*.
- If taking antibiotics women should be advised to use condoms during antibiotic use and for 7 days after the antibiotic is stopped. *If there are fewer than 7 pills remaining in the packet the pill-free interval should be omitted. If a non-liver enzyme-inducing antibiotic has been used for ≥3 weeks additional barrier contraception is no longer required*.
- When used consistently and correctly, COC is >99% effective at preventing pregnancy. Missing pills is not encouraged but one pill can be missed any time without loss of contraceptive protection. Instructions for missed pills are outlined in the Figure.

FOLLOW-UP *(Women should be encouraged to use a COC for at least 3 months before considering an alternative)*

A follow-up at 3 months allows an assessment of blood pressure and problems and re-instruction if required. In the absence of special problems, a 12-month supply of COC can be given at follow-up. Women should be encouraged to return if any problems arise.

KEY POINTS ON FIRST PRESCRIPTION OF COMBINED ORAL CONTRACEPTION

ADVICE FOR WOMEN MISSING COMBINED ORAL CONTRACEPTIVE PILLS

If ONE or TWO pills have been missed at any time

OR

If ONE pill is missed when using a 20 µg pill (Loestrin 20, Mercilon, Femodette)

CONTINUING CONTRACEPTIVE COVER:

She should take the most recent missed pill as soon as she remembers

She should continue taking the remaining pills daily at her usual time†

MINIMISING THE RISK OF PREGNANCY

She does *not* require emergency contraception‡

If THREE or more pills have been missed at any time

OR

If TWO or more pills missed when using a 20 µg pill (Loestrin 20, Mercilon, Femodette)

CONTINUING CONTRACEPTIVE COVER:

She should take the most recent missed pill as soon as she remembers

She should continue taking the remaining pills daily at her usual time†

She should be advised to use condoms or abstain from sex until she has taken pills for 7 days in a row

MINIMISING THE RISK OF PREGNANCY

Extending the pill-free interval is risky therefore:

If pills are missed in the first week of pill taking (Pills 1–7)	If pills are missed in the second week of pill taking (Pills 8–14)	If pills are missed in the third week of pill taking (Pills 15–21)
EMERGENCY CONTRACEPTION should be considered if she had unprotected sex in the pill-free interval or in the first week of pill taking	*NB. After seven consecutive pills have been taken:* *– there is no need for emergency contraception* *– at least seven pills can be missed (as occurs in the pill-free interval) without the need for emergency contraception*	She should **OMIT THE PILL-FREE INTERVAL** by finishing the pills in her current pack (or discarding any placebo tablets) and starting a new pack the next day

†Depending on when she remembers her missed pill she may take two pills on the same day (one at the moment of remembering and the other at the regular time) or even at the same time.

‡Any pills missed in the last week of the previous packet should be taken into account when considering emergency contraception.

STEPS IN GUIDANCE DEVELOPMENT

STEP	TIME TAKEN
Formulation of **key clinical questions** by Clinical Effectiveness Unit (CEU). **Systematic literature review** involving searching electronic, bibliographic databases by CEU researchers. **Obtaining and reviewing** copies of the full papers of all relevant publications identified through the searches. **Formal, critical appraisal** of key papers and development of short evidence tables.	This process is completed in 8 weeks.
Draft One Guidance document is written, providing recommendations and good practice points based on the literature review.	The CEU must take overall responsibility for writing the Guidance document. The Multidisciplinary Group and other peer reviewers should highlight inconsistencies and errors or where the text is incomprehensible.
Multidisciplinary Group Meeting comprising stakeholders and including service user representation, representation from the Faculty of Family Planning and Reproductive Health Care Education Committee and, where possible, representation from the FFPRHC Clinical Effectiveness Committee (CEC) and FFPRHC Council.	A one-day meeting is held in Aberdeen with the Multidisciplinary Group to discuss the Draft One Guidance document.
Preparation of Draft Two Guidance document based on discussion at the Multidisciplinary Group. **Peer Review of Draft Two Guidance document** by the Multidisciplinary Group and the FFPRHC CEC. All **written feedback on the Draft Two Guidance document** is tabulated and the CEU response to these comments outlined.	The Multidisciplinary Group meeting is held at least 2 months before the Guidance deadline to allow time for development of further drafts.
Draft Three Guidance document is prepared based on written feedback and is sent to the Multidisciplinary Group and the FFPRHC CEC.	Only minor comments can be accepted at this stage.
The **Final Guidance document** is published by the FFPRHC.	Proof reading of the Guidance is then performed by three members of the CEU team independently and comments collated and sent back by the Unit Director. A pdf version of the Guidance is made available on the FFPRHC website.

FEEDBACK ON GUIDANCE

Feedback on First Prescription of Combined Oral Contraception can be sent directly to the CEU via e-mail (**ceu.guidance@abdn.ac.uk**).

You will receive an automated acknowledgement notice on receipt of your comments. If you do not receive this automated response please contact the Clinical Effectiveness Unit (CEU) by telephone (01224 553623) or e-mail (**ffp.ceu@abdn.ac.uk**).

The CEU is unable to respond individually to all comments received. However, the CEU will review all comments and provide an anonymised summary of comments and responses which, after being reviewed by the Clinical Effectiveness Committee, will be posted on the Faculty website at regular intervals.