Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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This guidance contains the revised version of Table 2, which corrects the version which was circulated with the October 2004 RCOG News.

VENOUS THROMBOEMBOLISM AND HORMONAL CONTRACEPTION

1. Aim

The aim of this guidance is to present evidence-based recommendations and statements on venous thromboembolism (VTE) and hormonal contraception.

2. Introduction

Hormonal methods are used by 29% of women in the UK aged 16–49 years who require contraception.[1] Most women opt for combined oral contraception (18%). Fewer women choose progestogen-only pills (5%), the progestogen-only injectable or implant (3%) or the levonorgestrel-releasing intrauterine system (1%). A further 2% use oral methods but are unclear whether these are combined or progestogen-only.

Use of combined oral contraception (COC) is associated with an increased risk of VTE.[2–4] However, less is known of the risks of VTE with progestogen-only methods.[5]

VTE encompasses deep-vein thrombosis (DVT), pulmonary embolism and cerebral venous sinus thrombosis. The incidence of VTE increases with age but it is uncommon in women of reproductive age (5–21 per 100 000 women per year).[6] Mortality from VTE is low and, in a 2003 population study, most deaths from VTE occurred in older women (aged 49–63 years) and were unrelated to hormonal contraceptive use.[7]

There is synergism between genetic causes of venous thrombosis (such as factor V Leiden mutation, prothrombin 20210A, protein C or protein S deficiency, antithrombin III deficiency) and acquired risk factors (such as antiphospholipid syndrome, pregnancy, contraceptive use, surgery, trauma, immobilisation and malignancy).[6]

Communicating risks, benefits and uncertainties requires the exchange of information and opinion between women and clinicians to allow women to make informed decisions. Risk tables may help explain degrees of risk.[8] A one in 100 000 risk is generally considered to be a 'minimal' risk. However, a woman's perception of risk depends upon how information is given, the seriousness of disease and its incidence. For example: the **relative** risk of VTE is increased three-fold with combined oral contraceptive use;[9] the **absolute** risk however, is small and thus increases from 5 to only 15 per 100 000 women years. Using appropriate language and written materials and providing a comparison of risks and benefits may help a woman judge the level of risk that is acceptable to her.

The association between COC and VTE is based on evidence from non-randomised trials and we cannot exclude confounding and bias. Absence of evidence regarding VTE and progestogen-only contraception does not equate to absence of effect.[10]

3. Identification and assessment of evidence

Electronic searches were performed for: Medline (Ovid version) 1996–2003; Embase (1996–2003); PubMed (1996–2003); the Cochrane Library (to 2003) and the US National Guideline Clearing House. Searches used relevant medical subject headings (MeSH) terms and text words. The Cochrane Library was searched for systematic reviews, meta-analyses and controlled trials. Previous guidance from the Royal College of Obstetricians and Gynaecologists (RCOG), the Faculty of Family Planning and Reproductive Health Care (FFPRHC) and the World Health Organization (WHO) was reviewed. Key publications were appraised according to standard methodological checklists before conclusions were considered as evidence.

The definitions of types of evidence used in this guideline originate from the US Agency for Health Care Research and Quality. Where possible, recommendations are based on and explicitly linked to the evidence that supports them. Areas lacking evidence were designated 'good practice points.'

4. Does combined oral contraception increase the risk of venous thromboembolism?

The relative risk of venous thromboembolism is increased with combined oral contraceptive use. Nevertheless, the rarity of venous thromboembolism in women of reproductive age means that the absolute risk remains small. **B**

The term 'combined oral contraception' is used here to describe monophasic preparations containing a low dose (20–35 micrograms) of ethinyl estradiol in combination with a progestogen. Progestogens include norethisterone and levonorgestrel: 'second generation'; desogestrel and gestodene: 'third generation'; and the newest progestogen, drospirenone: 'fourth generation'. The terms second, third or fourth generation can be confusing and will not be used further.[11]

4.1 Risk of venous thromboembolism

Combined oral contraceptives containing levonorgestrel or norethisterone are associated with a lower risk of venous thromboembolism than those containing desogestrel or gestodene. **B**

A levonorgestrel- or norethisterone-containing combined oral contraceptive should be advised as a pill of first choice. However, after counselling, a woman may choose a desogestrel- or gestodene-containing combined pill. **B**

Epidemiological studies show a three- to five-fold increase in the risk of VTE with COC use, which does not appear to be related to the dose of ethinyl oestradiol (when less than 50 micrograms is used) but to the type of progestogen.[12,13] Meta-analyses provide further support for this increased risk.[4,14] COCs containing gestodene or desogestrel are associated with an almost two-fold increase in the risk of VTE compared with COCs containing norethisterone or levonorgestrel (adjusted OR 1.7, 95% CI 1.4–2.0).[4] The apparent relationship between progestogen type and risk of VTE[3] may be due to confounding or bias, inherent in observational studies.[15,16] However, this increased risk has biological plausibility (section 4.8).[17]

Evidence level IIa

The relative risk of venous thromboembolism increases in the first 4 months after starting combined oral contraception. This risk decreases with increasing duration of use, although it remains above that of non-users. After discontinuation, VTE risk falls to that of non-users within 3 months. **B**

A WHO study found an increased risk of VTE within 4 months of starting COC.[3] No change in risk of VTE occurred with increasing duration of use and the VTE risk returned to that of non-users within 3 months of stopping.[3] Data are conflicting regarding duration of COC use and VTE

Evidence level IIa

risk.[12,13,18,19] Further analysis of WHO Collaborative Study data showed an increased risk with duration of COC use.[3] However, four case–control studies have shown a decreasing risk of VTE with increasing duration of use (although remaining above that of non-users).[12,13,18,20] The risk of VTE appeared more than ten times higher in the first year of use than in later years. However, this was only evident for women with thrombophilia.[21] One possible reason for this effect may be the unmasking of underlying undiagnosed thrombophilia. A reanalysis of the Transnational Study data showed that levonorgestrel and norethisterone-containing COCs had a lower risk of VTE with increasing duration of use.[13] After adjustment, the rate ratio for VTE was 6.6 (95% CI 2.5–17.8) for less than 1 year of use, decreasing to 1.3 (95% CI 0.5–3.7) for more than 5 years of use.[13] Similar effects were identified for desogestrel and gestodene-containing COCs (adjusted rate ratio 14.6, 95% CI 6.0–35.1) for less than 1 year's use and 4.2 (95% CI 1.3–13.6) for over 5 years' use. A decreasing risk with increasing duration of COC use is further supported by a case–control study published in 2002.[18]

Evidence level IIa

4.2 Relative and absolute risks

Describing risk in **relative** terms may sound more alarming than in **absolute** terms. The risk of VTE in non-users is low (5 per 100 000 woman years). This increases to 15 per 100 000 woman years with COCs containing levonorgestrel or norethisterone and to 25 per 100 000 woman years with COCs containing desogestrel or gestodene.[22] Thus, venous thromboembolism is uncommon in women of reproductive age and despite a five-fold increase in risk for women using gestodene- or desogestrel-containing COCs, the absolute risk remains small (Table 1).

Evidence level IIa

Table 1. Risk table for combined oral contraceptive (COC) users and risk of venous thromboembolism[22]

	Relative risk	Absolute risk per 100 000 woman-years
Not using COC		5 in 100 000
COC containing levonorgestrel or norethisterone	3-fold increase	15 in 100 000
COC containing gestodene or desogestrel	5-fold increase	25 in 100 000
Pregnancy	12-fold increase	60 in 100 000

4.3 Mortality associated with COC use

A case–control study suggested that the probability of death due to VTE for women not using COC was five per million per year.[23] Three large cohort studies[8,24,25] have shown that long-term oral contraceptive use is not associated with an increase in mortality.

Evidence level IIa

4.4 Norgestimate-containing COC

Few studies have investigated the risk of VTE with a norgestimate-containing COC (Cilest®, Janssen-Cilag). The Transnational Study[23] included 46 women (18 cases with VTE and 28 controls without VTE) using a norgestimate-containing COC. A Danish National Study[18] included 18 women with VTE who had used norgestimate-containing COC and 118 women without VTE using a norgestimate-containing COC. The risk of VTE in users of norgestimate-containing COC was OR 1.4 (0.8–2.5). Norgestimate is metabolised to levonorgestrel and may have a similar VTE risk to levonorgestrel-containing COCs but there are insufficient data to support this hypothesis.[26,27]

Evidence level IIb

4.5 Drospirenone-containing COC

Drospirenone with ethinyl oestradiol is marketed in the UK as Yasmin® (Schering Health). No evidence was identified regarding the VTE risk associated with this COC. To date, the Netherlands Pharmacovigilance Centre has reported five cases of VTE in women using this COC.[28]

Evidence level IV

4.6 Combined transdermal contraceptive system

A transdermal contraceptive system Evra® (Janssen-Cilag) received its UK product licence in 2003. Each 2-cm^2 patch delivers 150 micrograms norelgestromin (17-deacetyl norgestimate) and 20 micrograms ethinyl oestradiol daily into the systemic circulation.[29,30] Norelgestromin is the primary active metabolite of norgestimate (which has been administered orally with ethinyl oestradiol, providing safe effective contraception).[31] A pulmonary embolism was diagnosed in one contraceptive patch user[32] but the patch had been used up until the time of major surgery. No clinically significant alterations in relevant laboratory parameters have been identified with contraceptive patch use. Inevitably, there are limited long-term safety data and case reporting will provide evidence on VTE risk.

4.7 Cyproterone acetate

Dianette® (Schering Health) contains 35 micrograms ethinyl oestradiol with 2 mg cyproterone acetate (a progestogen with anti-androgenic properties). Dianette® is not licensed as a contraceptive but for treatment of acne or hirsutism. A case–control study used data from the General Practice Research Database and, after adjustment for body mass index (BMI), smoking and androgenic disorders, showed a four-fold increase in the risk of VTE with Dianette® compared with a COC containing levonorgestrel (OR 3.9, 95% CI 1.1–13.4).[33] Duration of use did not affect this risk. A combined nested cohort analysis and case–control study support this level of risk but no randomised trials have been performed thus confounding and bias cannot be excluded.[34] The Committee on the Safety of Medicines (CSM) advises: "Dianette is not indicated solely as a contraceptive; it 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".[35]

Evidence level IIa

4.8 Biological plausibility

Alterations in coagulation and fibrinolysis have been reported with oral contraception.[36] In deciding whether or not a causal relationship exists between hormonal contraception and VTE risk, account must be taken of the evidence of COC exposure before VTE, the consistency of findings between studies and agreement with laboratory research (biological plausibility).[15]

A review of 17 comparative and two cross-sectional studies identified no differences in haemostatic factors thought to be related to VTE risk between COCs containing gestodene or desogestrel and those containing levonorgestrel or norgestimate.[37] However, small randomised trials investigating resistance to the natural anticoagulant action of activated protein C,[38] found that levonorgestrel- or norethisterone-containing COCs produced less acquired activated protein C resistance than gestodene- or desogestrel-containing COCs. Desogestrel-containing COCs have been shown, in randomised, double-blind trials, to have a more pronounced effect on the coagulation system than levonorgestrel-containing COCs. This may be explained by less effective compensation for the thrombotic effect of ethinyl oestradiol.[39] Randomised, crossover trials have identified a stronger antioestrogenic effect of levonorgestrel compared with desogestrel.[40] Thus, it may not be the progestogen itself which increases the risk of VTE but desogestrel or gestodene may counteract the prothrombotic effects of ethinyl oestradiol less than levonorgestrel or norethisterone.

Evidence level Ib

4.9 Cerebral sinus thrombosis

A case–control study identified an increased risk of cerebral venous sinus thrombosis with oral contraceptive use (OR 13, 95% CI 5–37).[41] Further data suggest an increased risk with COCs containing desogestrel or gestodene compared with other COCs.[42]

Evidence level IIa

5. Does progestogen-only contraception increase the risk of venous thromboembolism?

5.1 Progestogen-only contraception

Progestogen-only pills, injectables and levonorgestrel implants do not increase the risk of venous thromboembolism.

B

Few studies have been large enough to quantify the risk of VTE associated with the use of progestogen-only contraception (POC). A hospital-based, case–control study by WHO[5] in Africa, Asia, Europe, and Latin America evaluated the risks of cardiovascular disease with the use of oral and injectable POC. A total of 1137 women with VTE and 9997 control subjects were recruited. Cases and controls were matched for age, BMI and live births. Cases were more likely to have other cardiovascular risk factors (hypertension, diabetes, or rheumatic heart disease) or to be smokers. No significant increase in odds ratio for VTE was identified with the use of any progestogen-only method. The odds ratio for progestogen-only pill-users was 1.74 (95% CI 0.76–3.99) and for women using progestogen-only injectables (OR 2.19, 95% CI 0.66–7.26). Although limited by small numbers, the data suggest that there is little or no increase in risk of VTE associated with use of oral or injectable progestogen-only methods.

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There is little evidence available on the etonorgestrel implant or levonorgestrel-releasing intrauterine system and the risk of venous thromboembolism.

✓

Only one woman in the WHO Study[5] was using a levonorgestrel-only implant (Norplant®). A post-marketing study evaluated the safety of levonorgestrel-only implants in developing countries.[43] It included 7977 women with over 95% completing 5 years of follow-up. Only one levonorgestrel-only implant-user developed a DVT and no increase in mortality was identified. No data were identified regarding the etonorgestrel-only implant (Implanon®). Similarly, there is little evidence regarding the levonorgestrel-releasing intrauterine system.

Further evidence supporting no increased risk of VTE with POC is provided by a 1999 case–control study (adjusted RR 1.3, 95% CI 0.3–6.8).[44] However, high-dose progestogens (used primarily for menstrual disorders) appear to be associated with an increased risk of VTE (adjusted RR 5.3, 95% CI 1.5–18.7). Reanalysis of data from the WHO Collaborative Study[45] also showed an increase in VTE risk with therapeutic progestogens (OR 5.92, 95% CI 1.16–30.1). However, small numbers have resulted in wide confidence intervals.[46]

Although COCs containing desogestrel have been found to have an increased risk of VTE compared with those containing levonorgestrel or norethisterone, the new desogestrel-only pill, Cerazette® (Organon) has not been associated with an increased risk. However, data are limited. A randomised, controlled, double-blind trial of desogestrel-only and levonorgestrel-only pills did not identify any clinically significant alterations in haemostatic parameters;[47] however, larger studies are required to confirm absence of risk.

Evidence level IIa

5.2 Progestogen-only emergency contraception

No evidence is available on the risk of venous thromboembolism, if any, associated with progestogen-only emergency contraception.

✓

Progestogen-only emergency contraception is the only hormonal emergency contraceptive currently available in the UK. It comprises two 0.75-milligram levonorgestrel tablets, to be taken as a single dose within 72 hours of unprotected sex.[48] A case–control study investigated VTE risk associated with the previous combined emergency contraceptive (Yuzpe method) and no increase in VTE risk was noted.[49] No evidence was identified on the VTE risk associated with progestogen-only emergency contraception but it is likely to be negligible.

6. Medical eligibility for hormonal contraceptive use

Assessing medical eligibility before prescribing allows contraception to be provided appropriately and safely without introducing unnecessary medical barriers. C

The WHO *Medical Eligibility Criteria for Contraceptive Use* (WHOMEC)[50] provides systematically developed, evidence-based recommendations to facilitate selection of the most appropriate method of contraception without unnecessary medical barriers. **Eligibility**, rather than **ineligibility** (or contra-indication), is described. (WHO category 1: 'unrestricted use'; WHO category 2: 'benefits generally outweigh risks'; WHO category 3: 'risks usually outweigh benefits'; WHO category 4: 'unacceptable health risk'). Eligibility criteria for combined contraception (oral and transdermal) and progestogen-only, relevant to VTE, are summarised in Table 2. The 2004 update of WHOMEC[51] includes transdermal combined contraception and the vaginal oestrogen-progestogen ring under the category for COC. The WHOMEC was developed using a rigorous systematic process to appraise and grade evidence.[52] A nested case–control study investigated the risk of VTE in women with acute medical conditions (e.g. lower limb fracture, surgery, cancer, or having invasive endoscopy) using COC.[53] The risk of VTE was increased compared with women without acute conditions (RR 17, 95% CI 6.5–46.0).

6.1 Current or previous venous thromboembolism

Women with current venous thromboembolism should not use hormonal contraception. C

Women with a personal history of venous thromboembolism should not use combined oral contraception but may use progestogen-only methods. C

For women with current VTE, WHOMEC recommends that COC should not be used (WHO 4) and the risks of using any progestogen-only method usually outweigh any benefits (WHO 3).[50] Women with a previous history of VTE should be advised against COC (WHO 3). However, women with a previous history of VTE can be advised that the benefits of using any progestogen-only method generally outweigh the risks (WHO 2).

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6.2 Postpartum

A woman who is less than 21 days postpartum should not use combined oral contraception. C

Combined oral contraception can be used after day 21 postpartum if a woman is not breastfeeding. C

The progestogen-only pill, implant or injection can be used safely before day 21 postpartum, even if a woman is breastfeeding. C

WHOMEC[50] suggests that risks of COC use before 21 days postpartum usually outweigh benefits (WHO 3). By 3 weeks postpartum, coagulation and fibrinolysis are normalised and the benefits of COC use for women who are not breastfeeding outweigh risks (WHO 1). Combined oral contraceptives affect the quality and quantity of breast milk and are not advised for breastfeeding

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women.[54] The benefits of progestogen-only pills, injectables and progestogen-only implants outweigh the risks, even if commenced before 21 days postpartum (WHO 1).

Table 2. WHO categories for hormonal methods of contraception in relation to venous thromboembolism: adapted from the WHO Medical Eligibility Criteria for Contraceptive Use[51]

WHO Category 1: unrestricted use		WHO Category 2: benefits outweigh risks	
COC	**POC**	**COC**	**POC**
Postpartum ≥ 21 days in non-breastfeeding women Immediately after first- or second-trimester TOP Minor surgery without immobilisation Varicose veins	Postpartum < 21 days in non-breastfeeding women (injectable and implant)[a] Immediately after first-trimester TOP Immediately after second-trimester TOP (excluding LNG-IUS) BMI ≥ 30 Family history of VTE in a first-degree relative Major surgery without prolonged immobilisation Minor surgery without immobilisation Varicose veins Superficial thrombophlebitis Sickle cell disease	Obesity BMI ≥ 30 Family history of VTE in a first-degree relative Major surgery without prolonged immobilisation Superficial thrombophlebitis Sickle cell disease	Immediately after second-trimester TOP (LNG-IUS) History of VTE Major surgery with prolonged immobilisation Known thrombogenic mutations (factor V Leiden; prothrombin mutation; protein S, protein C and antithrombin deficiencies)
WHO Category 3: risks outweigh benefits		**WHO 4: unacceptable health risk**	
COC	**POC**	**COC**	**POC**
Postpartum < 21 days in non-breastfeeding women	Current VTE < 4 weeks postpartum for LNG-IUS insertion[b]	History of VTE Current VTE Major surgery with prolonged immobilisation Known thrombogenic mutations (factor V Leiden; prothrombin mutation; protein S, protein C and antithrombin deficiencies)	–

[a] WHOSPR suggests depot medroxyprogesterone acetate and progestogen-only implants should not be used before 6 weeks postpartum;
[b] Owing to risk of perforation and not to VTE risk; COC = combined oral contraception; LNG-IUS = levonorgestrel-releasing intrauterine system; POC = progestogen-only contraception; TOP = termination of pregnancy; VTE = venous thromboembolism (which includes deep vein thrombosis and pulmonary embolism); WHO = World Heath Organization; WHOSPR = WHO Selected Practice Recommendations

6.3 Post-abortion

Combined oral contraception can be commenced immediately following first- or second-trimester abortion. **C**

Progestogen-only contraception can be commenced immediately following first- or second-trimester abortion. **C**

WHOMEC[50] suggests that COC and POC can be commenced immediately following first- or second-trimester abortion. The benefits of hormonal contraception outweigh the risks (WHO 1). Two randomised trials have confirmed the safety of COC commenced immediately after early medical abortion.[55,56]

6.4 Smoking

Smokers over the age of 35 years should not use combined oral contraception but progestogen-only methods can be used. **B**

Three case–control studies[18,12,57] identified a two-fold increase in the risk of VTE associated with smoking (OR 2.0, 95% CI 1.3–3.3).[12] A large study compared mortality in relation to contraceptive use and smoking.[8] For all causes of mortality the rate ratio for death for women who had ever used COC was not increased (OR 0.89, 95% CI 0.77–1.02). However, this rate ratio doubled for women who smoked more than 15 cigarettes per day (rate ratio 2.14, 95% CI 1.81–2.53). The risks of stroke, myocardial infarction and VTE increase with age; therefore, smokers over the age of 35 years are advised against the use of COC (WHO 3).[50] However, progestogen-only methods can be used (WHO 1).[18]

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6.5 Body mass index

Women with a body mass index over 30 should first consider progestogen-only methods but combined oral contraception can be used after counselling. **B**

A BMI of 30.0–39.9 kg/m^2 constitutes obesity and a BMI greater then 40 kg/m^2 constitutes morbid obesity.[58] This is an independent risk factor for cardiovascular disease and VTE. Despite this, WHOMEC recommends that the benefits of COC use by women with a BMI greater than 30 kg/m^2 outweigh the risks (WHO 2).[50] No upper limit for BMI is given but additional risk factors should be considered. Case–control studies suggest that VTE risk increases with increasing BMI.[12,18,19] The risk doubled for women with a BMI over 30 (OR 1.9, 95% CI 1.1–3.1) and increased almost four-fold for a BMI over 35 (OR 3.8, 95% CI 1.8–8.0).[19] Two studies indicated that VTE risk increased up to five-fold for women with BMI over 30 (OR 5.1, 95% CI 3.8–6.9)[18] and, in another study, a six-fold increase was observed if the BMI was over 25 (OR 6.4, 95% CI 2.6–15.5).[12] Guidance from the FFPRHC suggests that, after counselling about alternatives, obese women may still choose to use COC.[11] Progestogen-only methods can be used safely (WHO 1: oral pill; WHO 2: injectable or intrauterine).[50]

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6.6 Surgery

Combined oral contraception should be discontinued at least 4 weeks before major surgery where immobilisation is expected. **C**

Progestogen-only methods need not be discontinued prior to surgery even when immobilisation is expected. **C**

Hormonal methods do not need to be discontinued before minor surgery without immobilisation. **C**

WHOMEC[50] considers that benefits of COC use outweigh risks for women having minor surgery without immobilisation or major surgery without prolonged immobilisation (WHO 1 and 2, respectively). For women undergoing major surgery with prolonged immobilisation, COC should not be used (WHO 4). However, there is no need to discontinue any progestogen-only method of contraception prior to major surgery, even when prolonged immobilisation is expected (WHO 2). The Scottish Intercollegiate Guideline Network (SIGN) guideline for prophylaxis of VTE addresses

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oral contraceptives, hormone replacement therapy and VTE risk.[59] The guideline acknowledges that the decision to discontinue COC preoperatively is controversial. The risk of postoperative VTE is increased from 0.5% in non-users to 1.0% for pill-users.[60] This small absolute risk must be balanced against the risks of discontinuing effective contraception. When indicated, COC should be discontinued at least 4 weeks before surgery and alternative contraception discussed.[11]

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6.7 Other conditions which may predispose to venous thromboembolism

Superficial venous thrombosis: WHOMEC[50] recommends that the benefits of COC and POC outweigh the risks in women with varicose veins and superficial thrombophlebitis (WHO 1 and WHO 2, respectively).

Sickle cell disease: This chronic, inherited, haematological condition can be complicated by vaso-occlusion by poorly deformable erythrocytes. Fetal and maternal morbidity and mortality are associated with sickling crises. An observational study comparing hormonal (COC and POC) and barrier contraception in women with sickle cell disease showed no significant difference in haemostatic variables.[61] A case–control study showed a reduction in painful sickle cell crises with use of depot medroxyprogesterone acetate (DMPA).[62] WHOMEC advises that benefits of combined contraception and POC use by women with sickle cell disease outweigh the risks (WHO 2 and WHO 1, respectively).[50] An observational study identified pulmonary hypertension in 32% of patients with sickle cell disease.[63] Women with pulmonary hypertension should be advised against the use of combined contraception.[50]

Inflammatory bowel disease: WHOMEC[50] does not address inflammatory bowel disease. FFPRHC guidance suggests that women with inflammatory bowel disease should be offered the same contraceptive choices as other women.[64] Women who are immobilised due to disease exacerbation require counselling regarding stopping COC.

7. Is screening for thrombophilia needed before prescribing hormonal contraception?

Routine thrombophilia screening prior to hormonal contraceptive use is not recommended. C

A thrombophilia screen may be considered in a woman with a history of venous thromboembolism in a first-degree relative under the age of 45 years who, after counselling, still wishes to use combined oral contraception. C

A thrombophilia screen should be interpreted in consultation with a haematologist or other expert, in conjunction with a detailed family history. ✓

Approximately one in 3000 people have reduced levels of a natural anticoagulant (antithrombin III, protein C or protein S) and a predisposition to VTE.[65] As many as 1 in 20 people have Factor V Leiden or prothrombin gene mutation and a lesser degree of predisposition to VTE.[65,66] Antiphospholipid syndrome is less common, but is identified more often in women with recurrent miscarriage than in the general population.[65,67,68]

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Women with factor V Leiden mutation who use a COC have up to a 35-fold increased risk of VTE.[66] Even this degree of increase in relative risk results in a low absolute risk (around three additional cases of VTE per year per 1000 pill-users with factor V Leiden).[66]

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The 2004 update of WHOMEC advises that risks of COC use outweigh benefits for women with known thrombophilias (WHO 3).[51]

WHO *Selected Practice Recommendations for Contraceptive Use*[69] (WHOSPR) recommends

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examinations and tests which should be performed before providing different methods of contraception; but provides no guidance on screening for thrombophilias. Other sources do not advise routine thrombophilia screening prior to COC or POC use.[11,65]

WHOMEC recommends that women with a family history of VTE may use COC (WHO 2). Family history of VTE may alert clinicians to those women who have an increased risk[70,71] but regarding family history as a contraindication may unnecessarily deny COC to many women. Guidance on COC prescribing from the FFPRHC recommends that women with a family history of VTE in a first-degree relative under the age of 45 years should be advised that risks of COC might outweigh benefits.[11] Alternative contraception should be considered. If alternatives are unacceptable, a thrombophilia screen may help decision making. A thrombophilia screen may identify women who are carriers of thrombophilias but who may not necessarily develop DVT or pulmonary embolism. Such women may then be denied oestrogen-containing contraception. Conversely, a negative thrombophilia screen can be falsely reassuring. Therefore, interpretation of a thrombophilia screen is problematic and should be performed by a haematologist or other expert.[65]

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A personal history of recurrent miscarriage suggests the possibility of antiphospholipid syndrome, which predisposes to thrombosis, recurrent miscarriage or both.[65]

8. Summary

- For most women, COC is a safe method of contraception. Although the relative risk of VTE is increased, the absolute risk remains very small.
- Progestogen-only methods (pills, injectables, implant and intrauterine system) do not appear to be associated with increased risk of VTE. However, evidence regarding these methods is limited and absence of evidence does not equate to absence of risk.
- Heavy smoking, obesity and underlying thrombophilia increase the risk of VTE and these factors must be taken into account when making contraceptive choices.
- Women with previous VTE should be advised against the use of COC but a progestogen-only method may be used.
- There is no place for routine screening for thrombophilia prior to contraceptive prescribing.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

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