Venous Thromboembolism and Hormonal Contraception
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This is the second edition of this guideline. The first edition was published under the same title in 2004.

1. Purpose and scope

The Venous thromboembolism (VTE) includes deep vein thrombosis (DVT), pulmonary embolism and cerebral venous sinus thrombosis. Most data in relation to venous thrombosis and hormonal contraceptive use relates to DVT and pulmonary embolism. The true background incidence of VTE in women of reproductive age is often difficult to quantify but recent data suggest that the incidence has been underestimated and that it is more likely to be in the range of 50–100/100 000 woman-years. This is ten-fold higher than the widely quoted absolute risks for women of reproductive age who are not using contraception (5/100 000 woman-years). This increased incidence of VTE may in part be a result of improved study design, clearer diagnosis and definition of VTE. Despite this increase in background risk of VTE for women of reproductive age the absolute risk is still small.

There is synergism between genetic factors associated with 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). This guidance covers the VTE risk with hormonal contraception and the risk factors which are relevant when considering contraceptive choices and medical eligibility for contraceptive use. Categories for the safe use of hormonal contraception have been recently updated in the UK Medical Eligibility Criteria (UKMEC). In particular, categories relating to hormonal contraceptive use by obese women, women with systemic lupus erythematosus and antiphospholipid syndrome and current VTE are relevant for this guideline.

Non-randomised studies suggest an increased risk of VTE with combined hormonal (estrogen and progestogen) contraceptive use but confounding and bias cannot be excluded. The consistency of finding an increased risk among combined oral contraceptive users in most of the 20 or more studies examining the risk of VTE, compared with non-users, strongly suggests that the effect is real. There are fewer data on VTE risk with progestogen-only contraception and, although a lack of evidence does not necessarily suggest an absence of effect, it is generally accepted that progestogen-only methods of contraception are not associated with an increased risk of VTE.

Clinicians counselling women on hormonal contraceptive use should be able to convey the risk of VTE. Using appropriate language and written materials and providing a comparison of the risks and benefits may help women judge the level of risk that is acceptable to her. Although the relative risks of VTE do increase with combined hormonal contraceptive use, the absolute risk in women of reproductive age is very low.

2. Identification and assessment of evidence

Electronic searches were performed for: Medline (OVID Version 1996–2009), Embase (1996–2009), PubMed (1996–2009), the Cochrane Library (to 2009) and the US National Guideline Clearing House. Searches were performed using relevant medical subject headings and text words. The Cochrane database was searched for systematic reviews, meta-analyses and controlled trials relevant to venous thromboembolism and hormonal contraception. Previously existing guidelines from the Faculty of Sexual and Reproductive Healthcare (FSRH), the Royal College of Obstetricians and Gynaecologists (RCOG) and the World Health Organization (WHO) were also reviewed. Key publications were appraised according to standard methodology checklists before conclusions were considered as evidence. The clinical recommendations within this guidance are based on evidence whenever possible. Areas lacking in evidence were designated ‘Good Practice Points’.
3. Do combined hormonal methods of contraception (pill, patch and vaginal ring) increase the risk of venous thromboembolism?

The relative risk of venous thromboembolism is increased with all combined hormonal contraceptives (pills, patch and vaginal ring). Nevertheless, the rarity of venous thromboembolism in women of reproductive age means that the absolute risk remains small.

The relative risk of venous thromboembolism increases in the first few months after initiating combined hormonal contraception. This risk reduces with increasing duration of use but it remains above the background risk until the combined hormonal contraceptive is stopped.

Most combined hormonal contraception (oral pills, transdermal patch and intravaginal ring) contain a combination of ethinylestradiol and a progestogen. A newer combined oral contraceptive pill contains estradiol valerate instead of ethinylestradiol with a new progestogen dienogest. Long-term safety data regarding VTE risk for this combination of hormones is not yet available therefore the risks and benefits of use have to be assumed to be as for other combined oral contraceptives. Although much of the data on VTE risk and combined hormonal contraception is based on studies of oral methods the risk of VTE is considered to be the same for all hormonal contraceptive methods regardless of the mode of administration.

3.1 Combined oral contraception

Before the ‘pill scare’ in 1995, the risk of VTE among users of any brand of combined oral contraceptive with less than 50 micrograms of ethinylestradiol was considered to be the same. At this time the Committee on Safety of Medicines reported that combined oral contraceptives containing gestodene or desogestrel (third-generation pills) had a two-fold increase in the risk of VTE compared with those containing norethisterone or levonorgestrel (second-generation pills) (Table 1). This report was based largely on evidence from four non-randomised trials and therefore bias and confounding cannot be excluded.

Further studies since 1995 have supported these earlier findings.

Progestogen norgestimate is metabolised to levonorgestrel and is considered to have a VTE risk similar to that of second generation combined oral contraceptives, although data in support of this are limited.

A more recent Europe-wide surveillance study (EURAS) found a two-fold increase in the relative risk of VTE with combined oral contraceptive use compared with non-use. No difference in risk was identified between any brand of combined oral contraceptive, regardless of the progestogen (including those containing drospirenone).

Although there were some limitations in the EURAS study design, overall the data are good from over 58000 women with 142000 women-years of combined oral contraceptive exposure and low

<table>
<thead>
<tr>
<th>Population</th>
<th>VTE incidence/100 000 woman-years</th>
<th>Relative risk</th>
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</thead>
<tbody>
<tr>
<td>Non-pregnant non-users</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Levonorgestrel or norethisterone COC users</td>
<td>15</td>
<td>3-fold increase</td>
</tr>
<tr>
<td>Gestodene or desogestrel COC users</td>
<td>25</td>
<td>5-fold increase</td>
</tr>
<tr>
<td>Pregnant non-users</td>
<td>60</td>
<td>12-fold increase</td>
</tr>
</tbody>
</table>

Table 1. Risk table for combined oral contraceptive (COC) users and the risk of venous thromboembolism (Committee on Safety of Medicine data from 1999)
rate of loss to follow-up (2.4%). The absolute risk of VTE associated with combined oral contraceptive use in the EURAS study was ten-fold higher than those quoted in the earlier CSM data but this reflects the increase in the background risk. A large case–control study has suggested that, for women using combined oral contraceptives containing desogestrel or gestodene reducing the ethinylestradiol dose to 20 micrograms reduced the VTE risk by 18%.18

3.2 Cyproterone acetate-containing combined oral contraception

One combined oral contraceptive contains an anti-androgen, cyproterone acetate, with ethinylestradiol instead of a progestogen. This contraceptive is not licensed to be used solely as a contraceptive but it can provide contraception for women using it for the licensed indication (second-line treatment for severe acne or moderate to severe hirsuitism).21 There is some evidence that the use of this contraceptive is associated with a four-fold increase in the risk of VTE (OR 3.9; 95% CI 1.1–3.4).12,23 To date, no randomised trials have been performed, so confounding and bias cannot be excluded. Some of the additional risk may be due to inherent cardiovascular risks of women selected to be prescribed cyproterone acetate (for example women with polycystic ovary syndrome).21

3.3 Transdermal patch

Long-term data on VTE risk with the combined ethinylestradiol and norelgestromin transdermal patch are limited. EURAS reported the incidence of VTE in patch users to be 7.4/10 000 woman-years (74/100 000 woman-years).20 The confidence intervals were wide as the study included only 371 patch users. The summary of products characteristics suggests that the risk of VTE with patch use is slightly increased compared with that for a levonorgestrel contraceptive (OR 1.4; 95% CI 0.9–2.3) but this is not statistically significant.20

In a clinical trial (n = 3330 with 1704 woman-years of exposure) one case of non-fatal pulmonary embolism occurred during contraceptive patch use and one case of postoperative non-fatal pulmonary embolism was reported following contraceptive patch use.24 Follow-up in this study was short and few VTE events were observed and therefore it had limited power to detect differences in risk of VTE between the groups. Another study suggests that there is no increased risk of VTE patch use compared with combined oral contraceptive users. The study identified 68 cases of idiopathic VTE among 334 patch users (incidence rate 52.8/100 000 woman-years; 95% CI 35.8–74.9) similar to norgestimate users (41.8/100 000 woman-years; 95% CI 29.4–57.6). The age adjusted odds ratio comparing the two was given as 1.1 (95% CI 0.7–1.8).17

In a second study, an increased risk of VTE was noted for current patch users compared with current combined oral contraceptive users (OR 2.4; 95% CI 1.1–5.5).25

A third study reported a similar two-fold increased risk of VTE with patch use.26 Follow-up of patch users is continuing.27

3.4 Intravaginal ring

The combined hormonal vaginal ring (2.7 mg ethinylestradiol and 11.7 mg etonorgestrel) provides a serum concentration of ethinylestradiol of around 15 micrograms/day.28 The incidence of serious adverse events with the use of the vaginal ring is very low in all studies. Although cases of DVT have been reported in vaginal ring users, there is insufficient epidemiological data available to ascertain the relative risks of VTE associated with use compared with other combined methods. In a study comparing haemostatic variables in vaginal ring and combined oral contraceptive users, the activity of antithrombin, protein C and factor VII was higher in vaginal ring users. The clinical significance of these coagulation changes is unknown.29
3.5 Duration of use

The risk of VTE is highest in the 4 months following initiation of combined hormonal contraception.\textsuperscript{30} The risk reduces and remains stable thereafter.\textsuperscript{7,16,31,32} Although the risk of VTE is high in the first few months of combined oral contraceptive use and then falls, it remains higher than that of non-users until the contraceptive is stopped.

4. Do progestogen-only methods of contraception (pill, injectable, implant and intrauterine system) increase the risk of venous thromboembolism?

Progestogen-only pills, injectable, implants and the levonorgestrel-releasing intrauterine system do not appear to be associated with an increased risk of venous thromboembolism.

Although limited by the small numbers of women using progestogen-only contraceptives (oral or injectable), data from a WHO study suggests that there is little or no increase in the risk of VTE with use.\textsuperscript{9} The odds ratio for progestogen-pill users was 1.74 (95% CI 0.76–3.99) and for progestogen-only injectable users 2.19 (95% CI 0.66–7.26). A recent case–control study found no increased risk of thrombosis with progestogen-only methods.\textsuperscript{19}

A study using the General Practice Research Database showed a non-significant association between exposure to progestogens alone and VTE (relative risk 2.4; 95% CI 0.8–6.5).\textsuperscript{33}

No specific evidence was identified concerning the risk of VTE with the use of progestogen-only implants, the levonorgestrel-releasing intrauterine system or progestogen-only emergency contraception.

The desogestrel-only pill has not been associated with an increased risk of VTE but data are limited.\textsuperscript{34} A randomised controlled, double-blind trial of a desogestrel-only pill and a levonorgestrel-only pill did not identify any alterations in haemostatic parameters.\textsuperscript{35} Larger studies are required to confirm absence of risk.

There is no evidence to suggest that use of progestogen-only emergency contraception (levonorgestrel 1.5 mg) is associated with an increased risk of VTE.

5. What conditions which may increase the risk factors of VTE are relevant when assessing the medical history of women considering use of hormonal contraception?

The United Kingdom Medical Eligibility Criteria for Contraceptive Use provides consensus-based recommendation for the use of contraception. A clinical history should be taken to identify any relevant medical conditions which may influence contraceptive choice.
The United Kingdom Medical Eligibility Criteria for Contraceptive Use (UKMEC) update categories from the previous UKMEC and provide consensus-based recommendations to allow couples to select the most appropriate method of contraception without imposing unnecessary restrictions. For the majority of women, the use of hormonal contraception is safe; however, some medical conditions can contraindicate the use of particular methods (Table 3).

A clinical history should identify any conditions which fall within the categories 3 or 4 for use of hormonal contraception. Since progestogen-only methods do not increase the risk of VTE most of the risk assessment relates to combined hormonal contraceptive use. The UKMEC is a complete and comprehensive document outlining the safe use of contraception and clinicians are encouraged to use the current version, available on the Faculty of Sexual and Reproductive Healthcare website at www.fsrh.org.uk.

5.1 Current or previous VTE

Women with current venous thromboembolism or previous venous thromboembolism should be advised against the use of combined hormonal contraception as this poses an unacceptable health risk.

For women with current venous thromboembolism on anticoagulants or previous venous thromboembolism the use of progestogen-only contraception is safe.

The UKMEC includes pill, patch and vaginal ring under the heading of combined hormonal contraception therefore the same categories would apply for all. These will be referred to as combined hormonal contraception unless otherwise specified. For women with a current VTE on anticoagulants or previous VTE the use of combined hormonal contraception is not advised (UKMEC 4, unacceptable health risk).

For women with a current VTE and on anticoagulants the benefits of using any progestogen-only contraceptive (pills, implant, injectable and the levonorgestrel-releasing intrauterine system) outweighs any risks (UKMEC 2). Although there is a small risk of haematoma with use of progestogen-only implant or injectable in women using anticoagulants, the risk is small. For women with a previous history of VTE the benefits of progestogen-only contraceptive use outweigh the risks (UKMEC 2).

There is no evidence of haematoma formation or haemorrhage at the time of insertion of intrauterine contraception or subdermal implants in women using anticoagulants which causes harm. The levonorgestrel intrauterine system can be used to manage menorrhagia associated with anticoagulant use.

5.2 Family history

The use of combined hormonal contraception by women with a family history of VTE in a first-degree relative aged under the age of 45 years is not recommended.
A family history of VTE may alert clinicians to women who may have an increased risk of VTE themselves.37–41

Nevertheless, a family history alone cannot identify with any certainty an underlying thrombophilia. For women with a family history of VTE in a first-degree relative aged under the age of 45 years, the risks of using a combined hormonal contraception may outweigh the benefits (UKMEC 3).4

Notably, some young women considering combined hormonal contraceptive use may not yet have a first-degree relative who has reached the age of 45 years to allow a relevant family history of VTE to be excluded. A lack of exclusion should not lead to combined hormonal contraception being denied. Progestogen-only methods may be used regardless of family history.

5.3 Known thrombogenic mutations

For women with a known thrombogenic mutation the use of combined hormonal contraception poses an unacceptable health risk.

Women with reduced levels of naturally occurring anticoagulant (anti-thrombin III, protein C or protein S) or factor V Leiden who use combined oral contraceptives have up to a five-fold increase in the risk of VTE compared with non-users without this deficiency.41,42

Women with factor V Leiden can have up to a 35-fold increase in the risk of VTE with combined oral contraceptive use.43

Not all women with a thrombogenic mutation will develop a VTE and most VTEs occur in women without the defect. Nevertheless, if a woman has an identified thrombogenic mutation the risks of VTE are high enough to advise that the use of combined hormonal methods poses an unacceptable health risk (UKMEC 4).4

Progestogen-only methods do not increase the risk of VTE above that associated with the thrombogenic mutation itself and these methods can be used without further increasing the risk of VTE.

5.4 Post-pregnancy use

For women who are postpartum and not breastfeeding, combined hormonal contraception (pill, patch or vaginal ring) should not be initiated before day 21 postpartum.

All hormonal contraception can be safely initiated immediately following a first- or second-trimester termination of pregnancy.

In the first 3 weeks postpartum, coagulation and fibrinolytic factors have not returned to their prepregnancy state and therefore the risk of VTE is still greater than in nonpregnant women. In view of this fact, the risks of using combined hormonal contraception before day 21 postpartum usually outweigh the benefits (UKMEC 3).4 Nevertheless, from day 21 postpartum, the benefits of combined hormonal use for women who are not breastfeeding outweigh the risks (UKMEC 1 unrestricted use). In terms of considering VTE risk, progestogen-only methods can be started any time postpartum as they do not pose an increased risk. For recommendations on start times for individual progestogen-only methods in women who are postpartum and breastfeeding or not breastfeeding please see the UKMEC4. In terms of VTE risk, all hormonal methods of contraception can be commenced immediately following first- or second-trimester termination of pregnancy up to 24 weeks of gestation.
5.5 Smoking

For women aged over 35 years who are current smokers or who have stopped smoking less than 1 year ago, the use of combined hormonal contraception is not recommended.

Most data on smoking and thrombosis relate to arterial rather than venous thrombosis and are in relation to risk of myocardial infarction. Compared with non-smokers, light smokers (fewer than 15 cigarettes/day) have almost a two-fold increased risk of myocardial infarction and heavy smokers (more than 15 cigarettes/day) have a four-fold increased risk (RR 4.3; 95% CI 2.6–6.9).44

The use of combined hormonal contraception in heavy smokers appears to increase the risk 20-fold (RR 20.8; 95% CI 5.2–83.1). Other studies support increasing risk of VTE with increasing amount smoked.45,46 The risks of stroke, myocardial infarction and VTE increase with increasing age and mortality from cigarette smoking increases from age 35 years. Smokers who are aged over 35 years should be advised against the use of combined hormonal contraception (UKMEC 3 for women who smoke fewer than 15 cigarettes/day and UKMEC 4 for women smoking 15 or more cigarettes/day, respectively). The use of progestogen-only methods in women who smoke are unrestricted.4

5.6 Obesity

For women with a body mass index of 35 kg/m² or greater, the risks of combined hormonal contraception may outweigh the benefits.

Obesity is an independent risk factor for cardiovascular disease and VTE. Case–control studies suggest that combined oral contraceptive users who are obese are more likely to experience VTE than users who are not obese.16,19,37–39 Combined oral contraceptive users who are obese have a five- to eight-fold increased risk of VTE compared with non-users and up to a ten-fold increase in risk compared with that of non-users who are not obese. The absolute risk of VTE in women with increased body mass index (BMI) is still low. The National Institute for Health and Clinical Excellence (NICE) classification of obesity I, II and III depends on the BMI.50 For women with obesity I (BMI 30.0–34.9 kg/m²), the benefits of using combined hormonal contraception generally outweigh the risks (UKMEC 2).4 For women with obesity II (BMI 35.0–39.9 kg/m²) and obesity III (BMI 40 kg/m² or more) the risks of combined hormonal contraception may outweigh the benefits (UKMEC 3). However, use may be considered with expert clinical judgment and/or referral if other methods are unavailable or unacceptable. Progestogen-only contraception may be used safely regardless of weight.4

5.7 Surgery and other conditions leading to immobilisation

Combined hormonal contraception should be discontinued and an alternative estrogen-free method used at least 4 weeks before major elective surgery where immobilisation is expected but does not need to be discontinued before minor surgery without immobilisation.

The benefits of using combined hormonal contraception outweigh risks for women having minor surgery where immobilisation is not expected or for major surgery without prolonged immobilisation. For women undergoing major elective surgery with prolonged immobilisation, the use of combined hormonal contraception poses an unacceptable health risk (UKMEC 4).4

A woman should be encouraged to use a method of contraception (such as progestogen-only methods) which does not increase the risk of VTE and does not need to be discontinued before surgery. When the use of combined hormonal contraception has not been discontinued before surgery (for example, in an emergency procedure) thromboprophylaxis guidelines should be followed. This includes the use of mechanical or pharmacological thromboprophylaxis.
5.8 Other conditions which may predispose to venous thromboembolism

For women with medical conditions which may predispose to venous thromboembolism, the risks associated with use of combined hormonal contraceptives must be weighed against the benefits, including pregnancy prevention.

Women with inflammatory bowel disease are not at an inherent increase in risk of VTE and should be offered the same contraceptive choices as other women.45,51

In women who are immobilised owing to disease exacerbation or major surgery, however, stopping combined hormonal contraception and providing an alternative method of contraception is recommended.

Women with varicose veins and superficial thrombophlebitis are not at an increased risk of VTE and can therefore use any method of contraception.4 Women with varicose veins may use all hormonal methods (UKMEC category 1 unrestricted use). For women with superficial thrombophlebitis use of progestogen-only methods is unrestricted (UKMEC category 1 unrestricted use) and the benefits associated with the use of combined hormonal methods outweigh any risks (UKMEC category 2).

Sickle-cell disease is a chronic, inherited, haematological condition that can be complicated by vaso-occlusion by poorly deformable erythrocytes. An observational study comparing hormonal (combined and progestogen-only) and barrier contraception in women with sickle-cell disease showed no significant difference in haemostatic variables.52

A case–control study showed a reduction in painful sickle-cell crises with use of a progestogen-only injectable (depot medroxyprogesterone acetate).53

The benefits of using any type of hormonal contraception by women with sickle-cell disease outweigh the risks.4 In women with sickle-cell disease, there is a high risk of pulmonary hypertension41 and, in this situation, combined hormonal contraception would not be recommended.

Women with systemic lupus erythematosus (SLE) are at an increased risk of heart disease, stroke and VTE. Nevertheless, very few women with SLE will go on to develop VTE.45,50 Use of combined hormonal contraception by women with SLE and positive or unknown antiphospholipid antibodies poses an unacceptable health risk (UKMEC 4).36 A UKMEC category 3 is given for use of progestogen-only methods of contraception for women with SLE and positive or unknown antiphospholipid antibodies which suggests that the risks may outweigh the benefits. However, progestogen-only contraceptive may be used in this situation based on individual risks and with liaison between contraceptive and SLE specialists.4

6. Is screening for thrombophilia recommended before prescribing hormonal contraception?

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

Most episodes of VTE occur in women who do not have a thrombogenic mutation. Routine population screening for thrombophilia is not recommended.7 Based on a hypothetical model, a UK based cost-effectiveness analysis published in 2005 found that selective screening (based on the presence of personal or family history of VTE) was more cost-effective than universal screening.56 However, in terms of avoiding clinical adverse events, selective screening prevented fewer clinical adverse events (1/10000) compared with universal screening (3/10000) prior to prescribing hormonal contraception.55
A recent systematic review of the literature concluded that, because the absolute risk of each thrombolipophilia cannot be determined, asymptomatic first-degree relatives may not be identifiable and the association of genetic thrombolipophilia in the development of VTE is not clearly established, screening does not offer any clinical benefit.39

References

34. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. New Product Review: Desogestrel-only pill (Cerazette) [www.ffprhc.org.uk/pdfs/Cerazette%20CEC%20Approved%2029.04.05.pdf].


49. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Sexual and Reproductive Health for Individuals with Inflammatory Bowel Disease (Update 2009) [www.fsrh.org.uk].


55. Faculty of Family Planning and Reproductive Healthcare. Clinical Effectiveness Unit. First prescription of combined oral contraception [www.ffprhc.org.uk/admin/uploads/FirstPrescCombOralContJ an06.pdf].


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: Development of RCOG Green-top Guidelines (available on the RCOG website at www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes). 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 within the appropriate health services.

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. Once adapted for local use, these guidelines are no longer representative of the RCOG.

<table>
<thead>
<tr>
<th>Classification of evidence levels</th>
<th>Grades of recommendations</th>
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<tbody>
<tr>
<td>1++  High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias</td>
<td>A At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++ and directly applicable to the target population; or</td>
</tr>
<tr>
<td>1+  Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias</td>
<td>A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results</td>
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<tr>
<td>1–  Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias</td>
<td>A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or</td>
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<tr>
<td>2++  High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
<td>Extrapolated evidence from studies rated as 1++ or 1+</td>
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<td>2+  Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
<td>A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or</td>
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<tr>
<td>2–  Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
<td>Extrapolated evidence from studies rated as 2++</td>
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<tr>
<td>3  Non-analytical studies; e.g. case reports, case series</td>
<td>D Evidence level 3 or 4; or</td>
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<tr>
<td>4  Expert opinion</td>
<td>Extrapolated evidence from studies rated as 2+</td>
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Good practice point

Recommended best practice based on the clinical experience of the guideline development group
This Guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: Dr S Brechin MRCOG, Aberdeen and Ms JE Allerton, Somerset.

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

The guidelines review process will commence in 2013 unless otherwise indicated.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health series.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient’s case notes at the time the relevant decision is taken. Once adapted for local use, these guidelines no longer represent the views of the RCOG.