



## Faculty of Sexual & Reproductive Healthcare Statement

### Venous Thromboembolism (VTE) and Hormonal Contraception

November 2014

#### **Background**

This statement updates and replaces the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 40 on the same topic. It summarises Faculty of Sexual and Reproductive Healthcare (FSRH) recommendations and relevant information found within FSRH clinical guidance.<sup>1-5</sup>

Hormonal contraceptives contain either a combination of estrogen and progestogen (combined hormonal contraceptives (CHC)), or progestogen alone (progestogen-only contraceptives). In the UK, the majority of combined hormonal contraceptives contain the synthetic estrogen, ethinylestradiol. A combined oral contraceptive (COC) product containing mestranol is also available, with 50µg of mestranol roughly equating to 35µg of ethinylestradiol. More recently, COC products have been introduced onto the market that contain the naturally occurring human hormone, estradiol, either as estradiol valerate or as estradiol hemihydrate.

Progestogens are often grouped according to the time they were first marketed as constituents of COCs and may be referred to by 'generation'.

Examples of progestogens according to their classified 'generation'

<b>Generation of progestogen</b>	<b>Examples of Progestogen</b>
First generation	Norethisterone, norethisterone acetate
Second generation	Levonorgestrel
Third generation	Desogestrel, gestodene, norgestimate
Fourth generation	Drspirenone, dienogest, nomegestrol acetate

This summary document examines the VTE risk associated with hormonal contraception and the relevant risk factors to consider when choosing a combined hormonal contraceptive.

## ***Risk of venous thromboembolism***

The term venous thromboembolism (VTE) includes deep vein thrombosis (DVT), pulmonary embolism, and cerebral venous sinus thrombosis. Most studies of venous thrombosis and hormonal contraceptive use relate to DVT and pulmonary embolism. The true background incidence of VTE in women of reproductive age is difficult to quantify but recently published figures suggest it is in the range of 2 per 10,000 women in 1 year.<sup>6</sup>

Concerns about the role of hormonal contraceptives in mediating thrombosis risk are not new and have been ongoing since the introduction of hormonal contraceptives in the 1960s. Non-randomized studies have consistently reported an increased risk of VTE associated with combined hormonal contraceptive use,<sup>7-19</sup> suggesting that this effect is real.

## ***What is the venous thromboembolism risk associated with different combined hormonal contraceptives (pill, patch and vaginal ring)?***

### Combined oral contraception

Data<sup>10;18</sup> suggest that COCs containing the 'third generation' progestogens gestodene or desogestrel are associated with an increased risk of venous thromboembolism (VTE) when compared with those containing the 'second generation' progestogens levonorgestrel or norethisterone. The first publications to show differences in VTE risk led to the 'UK pill scare' in 1995 and a reduction in oral contraceptive use with a corresponding increase in unintended pregnancies.<sup>20;21</sup>

Since the publications in the 1990s, debate has continued about the effect of newly introduced progestogens on VTE risk. Some studies have reported no increased risk for 'fourth generation' drospirenone-containing COCs;<sup>14,15;22</sup> others have demonstrated an increased risk along with other newer progestogens.<sup>12;13;23</sup> The biological mechanism is not fully understood but different progestogens appear to modify the thrombogenic effects of estrogen to different extents, for example, acquired resistance to activated protein C is more pronounced during use of COCs containing desogestrel than levonorgestrel.<sup>24</sup> Although bias and confounding cannot be excluded, the consistency of recent studies coupled with evidence supporting biological plausibility suggests that this is a true effect.

In 2013 the European Medicines Agency (EMA) initiated a review of the risk of VTE associated with use of CHC. This review concluded that there was good evidence to suggest that the risk of VTE associated with different COCs was influenced by progestogen type, with those containing levonorgestrel,

norethisterone or norgestimate having the lowest risk (5-7 per 10,000 women) and those containing drospirenone, desogestrel or gestodene having the highest risk (9-12 per 10,000 women).<sup>6</sup> The risk of VTE with use of CHC was therefore reported to range from 5-12 per 10,000 women years, compared with 2 per 10,000 non-users. However the EMA noted that the benefits of CHC use generally outweighed the risk of venous thrombosis, which is low overall and is lower than the VTE risk associated with pregnancy and the postpartum period (29 per 10,000 woman-years and 300-400 per 10,000 woman-years, respectively).<sup>25</sup> Despite evidence of more favourable effects on lipid profiles and carbohydrate metabolism, there is no evidence to suggest that the newer, less androgenic progestogens are any safer in terms of arterial thrombosis risk than older progestogens.<sup>26</sup>

A Cochrane review<sup>27</sup> examined the findings of 26 studies and concluded that the risk of VTE with use of 30-35µg ethinylestradiol oral contraceptives was similar, regardless of whether they contained gestodene, desogestrel, cyproterone acetate or drospirenone, but that these oral contraceptives were associated with a 50-80% increased risk than 30-35µg ethinylestradiol oral contraceptives containing levonorgestrel.

Newer synthetic hormones such as estradiol valerate, estradiol hemihydrate, dienogest, and nomegestrol acetate are being incorporated into COC products. Long-term safety data for these new formulations are not yet available. Therefore, the risks and benefits of use must be assumed to be as for other CHCs.<sup>28;29</sup>

#### Combined transdermal patch and vaginal ring

Long-term data on VTE risk with the combined ethinylestradiol and norelgestromin transdermal patch are limited. Those studies comparing the risk associated with transdermal patch use to oral contraceptives containing second generation progestogens have reported mixed results. Some observational studies of the transdermal patch have reported a similar level of venous thromboembolism (VTE) risk<sup>30-32</sup> to COCs containing second generation progestogens, whereas other studies have suggested an increased risk.<sup>33-35</sup>

There is less available data for the vaginal ring which contains ethinylestradiol and etonogestrel. A national registry-based study<sup>35</sup>, which sought to assess the risk of VTE in users of non-oral contraceptives, reported that compared to non-users use of the ring conferred a relative risk of 6.5 (95% CI 4.7-8.9) with a corresponding incidence rate of 7.8 per 10,000 exposure years. A prospective cohort study that examined the short and long-term cardiovascular risks associated with use of the combined vaginal ring, and COC in new users from the United States and five European countries, reported an incidence rate for the vaginal ring of 8.3 per 10,000 woman-years.<sup>36</sup>

In 2014 the Medicines and Healthcare Regulatory Authority (MHRA) produced updated advice for UK prescribers based on the EMA's estimates of VTE risk for

different products (see table 2).<sup>6</sup> The advice suggested a risk of 6-12 per 10,000 women over a year for CHCs containing norelgestromin or etonogestrel.<sup>6</sup>

Table 2: Risk of venous thromboembolism (VTE) associated with non-use, combined hormonal contraception (CHC) use over the course of 1 year (adapted from [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/11/news\\_detail\\_001969.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001969.jsp&mid=WC0b01ac058004d5c1))

	Risk of VTE per 10,000 healthy women over one year
Non contraceptive users and not pregnant	2
CHC containing ethinylestradiol plus levonorgestrel, norgestimate or norethisterone	5-7
CHC containing etonogestrel (ring) or norelgestromin (patch)	6-12
CHC containing ethinylestradiol plus gestodene, desogestrel or drospirenone	9-12

#### Cyproterone-containing combined oral contraceptives

Co-cyprindiol (brands in the UK include Dianette®, Clairette®, Cicafem® and Acnecin®) is a product containing the anti-androgen cyproterone acetate 2mg in combination with ethinylestradiol 35 micrograms. It is licensed for the treatment of acne that has not responded to antibiotics and while it can be used as a contraceptive, it should not be used solely for this purpose. Observational studies have suggested that cyproterone containing COCs may be associated with an increased risk of VTE compared with levonorgestrel COCs.<sup>12;13;37</sup> The VTE risk initially appeared to be four-fold higher than levonorgestrel COCs<sup>38</sup>, which conferred the highest VTE risk of all COCs available in the UK at that time. The Committee on Safety of Medicines (CSM) previously advised that co-cyprindiol should be discontinued 3-4 months after the complete resolution of symptoms.<sup>39</sup>

In 2008 the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM formerly the CSM) endorsed this advice but acknowledged that in women with severe hyperandrogenism symptoms usually recur when treatment is stopped.<sup>40</sup> The MHRA advised that for these women co-cyprindiol could be continued until symptoms are judged unlikely to recur and that in all women co-cyprindiol could be re-started at any time if acne or hirsutism recurs on stopping treatment.<sup>40</sup>

Following reported deaths from VTE in women prescribed co-cyprindiol in France, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted an evaluation of the risk of venous and arterial thromboembolism (VTE and ATE) associated with use of cyproterone-containing products.<sup>41</sup> A review of post-marketing data suggested that in some of the reported cases of death, women had been using Dianette as well as CHCs. In 2013 the PRAC<sup>42</sup> report concluded that the incidence of VTE is 1.5 to 2 times higher in users of co-cyprindiol than in users of levonorgestrel-containing COCs and that there may be similar risk to that associated with desogestrel / gestodene / drospirenone-containing COCs<sup>41</sup>.

In response to the PRAC report, the MHRA issued updated advice for health professionals in the UK<sup>42</sup>:

- The benefits of co-cyprindiol outweigh the risks in women of reproductive age for the treatment of:
  - Skin conditions related to androgen sensitivity (for example, severe acne with or without seborrhoea)
  - Hirsutism
- Co-cyprindiol provides effective contraception in these women. An additional hormonal contraceptive should not be used in combination with co-cyprindiol.
- The need to continue treatment should be evaluated periodically by the treating physician.
- The risk of VTE is rare but this remains an important side effect, and healthcare professionals should themselves be vigilant for signs and counsel patients to remain vigilant for signs and symptoms.

#### Duration of use

The risk of VTE is highest in the four months following initiation of CHC<sup>43</sup> or when restarting after a break of at least one month. The risk then reduces over the next year and remains stable thereafter.<sup>14;19;44-46</sup> Although the risk is high in the first few months of CHC use and then falls, it remains higher than in non-users.

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

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

C A personal history of VTE or having a known thrombogenic mutation represents an unacceptable health risk to CHC use.

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

C A thrombophilia screen is not recommended routinely before prescribing CHC

**Do progestogen-only methods of contraception (pill, injectable, implant and intrauterine system) increase the risk of VTE?**

There are fewer data on VTE risk with progestogen-only methods of contraception and, although a lack of evidence does not necessarily suggest an absence of effect, data<sup>12:47</sup> do not generally support an increased risk.

Data from a WHO study suggested that there was little or no increased risk of VTE associated with use of oral or injectable progestogen-only methods.<sup>47</sup> The odds ratio for progestogen-only pill (POP) users was 1.74 (95% CI 0.76-3.99) and for progestogen-only injectable users 2.19 (95% CI 0.66-7.26).<sup>47</sup> More recently a case-control study<sup>48</sup> reported a 3.6-fold (95% CI, 1.8- to 7.1-fold) increased risk of venous thrombosis associated with use of the injectable compared with nonusers of hormonal contraceptives. A meta-analysis of eight observational studies, designed to investigate the risk of VTE associated with progestogen-only methods, noted that from the small amount of available data the relative risk of a VTE event for users of the progestogen-only injectable was increased compared with non-users (2.67 (95% CI, 1.29 to 5.53)).<sup>49</sup> However, the studies included in the analysis had small sample sizes and bias and confounding cannot be excluded.

Norethisterone and norethisterone acetate have been shown to be partly metabolised to ethinylestradiol.<sup>50:51</sup> At an oral dose of 5mg a conversion ratio of about 0.4+/-0.4 was found. This approximated to equate to an oral dose equivalent of 4µg of ethinylestradiol per 1mg of norethisterone, although the authors noted that they could not rule out individual variations.<sup>51</sup> While therapeutic doses of norethisterone used for gynaecological treatment should perhaps be prescribed with care in women with risk factors or contraindications to estrogen, POPs in the UK only contain 350µg of norethisterone, and therefore this conversion is not likely to be clinically significant.

The progestogen-only injectable Noristerat® contains norethisterone enanthate (NET-EN). The degree of conversion to ethinylestradiol after intramuscular injection (IM) of NET-EN is unknown. However, if the conversion rate is assumed to be the same as for oral administration then levels similar to a combined oral product would be expected during the first 4 weeks of use (personal communication with Bayer Healthcare Pharmaceuticals). An open label one-way crossover pharmacokinetic study designed to assess the *in vivo* formation of EE following administration of IM NET-EN is currently ongoing.

No statistically significant increased risk has been observed for the levonorgestrel intrauterine system<sup>35:48</sup> or the progestogen-only implant.<sup>35</sup>

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

**B** Progestogen-only methods of contraception do not appear to be associated with an increased risk of venous thromboembolism.

**What conditions increase the risk of VTE in women considering hormonal contraception?**

There is synergism between acquired risk factors associated with venous thrombosis, such as, CHC use, antiphospholipid syndrome, pregnancy, surgery, trauma, immobilisation, malignancy<sup>52</sup> and high altitude<sup>53</sup>, and genetic factors, such as, factor V Leiden mutation, prothombin 20210A, protein C or protein S deficiency, and antithrombim III deficiency. The use of hormonal contraceptives, in particular CHC, in women with such conditions may negatively affect the balance of risk and therefore contraindicate the use of such methods.

The UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) provides consensus-based recommendations to allow health professionals and individuals to select the most appropriate method of contraception, without imposing unnecessary restrictions. On the balance of the available evidence and consensus opinion of experts, conditions are assigned one of four categories for each category of contraceptive method (see table 3).

Table 3: Definitions of UK Medical Eligibility Criteria categories for contraceptive use<sup>54</sup>

UKMEC Category	Definition
1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
4	A condition which represents an unacceptable health risk if the method is used.

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 CHC use. UKMEC is updated following each update of the World Health Organisation Medical Eligibility Criteria (WHOMECE). Health professionals should refer to the current version of UKMEC, available via the FSRH website [www.fsrh.org](http://www.fsrh.org)

Summary of UKMEC categories relevant to VTE risk

	CHC	POP	DMPA/NET-EN	PO Implant	LNG-IUS	Cu-IUD
History of VTE	4	2	2	2	2	1
Current VTE (on anticoagulants)	4	2	2	2	2	1
Family history of VTE in a first degree relative aged under 45	3	1	1	1	1	1
Family history of VTE in a first degree relative aged 45 or over	2	1	1	1	1	1
Major surgery with prolonged immobilisation	4	2	2	2	2	1
Major surgery without prolonged immobilisation	2	1	1	1	1	1
Minor surgery without immobilisation	1	1	1	1	1	1
Immobility unrelated to surgery (e.g. wheelchair use, debilitating illness)	3	1	1	1	1	1
Known	4	2	2	2	2	1



thrombogenic mutation (Factor V Leiden, Prothrombin mutation, Protein S, Protein C, and Antithrombin deficiencies)						
BMI ≥ 30-34kg/m <sup>2</sup>	2	1	1	1	1	1
BMI ≥ 35kg/m <sup>2</sup>	3	1	1	1	1	1
Smoking aged < 35 years	2	1	1	1	1	1
Smoking less than 15 cigarettes/day aged >35years	3	1	1	1	1	1
Smoking > 15 cigarettes/day aged >35years	4	1	1	1	1	1
Aged > 35 and stopped smoking < 1 year ago	3	1	1	1	1	1
Aged >35 and stopped smoking a year or more ago	2	1	1	1	1	1
Postpartum (non breastfeeding) <sup>1</sup>						
<21 days	3	1	1	1	1	1
≥ 21 days	1	1	1	1	1	1

<sup>1</sup> WHOMECS<sup>55</sup> and USMEC<sup>56</sup> are more restrictive than UKMEC depending on whether there are other risk factors

While the advantages of using the progestogen-only implant, injectable and intrauterine methods generally outweigh the theoretical or proven risks in women who are anticoagulated, the CEU would advise ensuring that coagulation has been monitored recently. FSRH guidance<sup>57</sup> advises that there is generally no need to alter anticoagulant therapy if the woman is anticoagulated within the target therapeutic range. A community setting for fitting implants and intrauterine contraceptives is generally appropriate providing there are no other risks, for example, severe vasovagal reaction. However, it is recommended that an experienced clinician performs the procedure with careful attention to haemostasis, and application of a pressure bandage following implant procedures. Subcutaneous administration of the progestogen-only injectable (Sayana-Press®) can be considered as an alternative to IM injection, although any advantage in terms of bleeding is currently unproven.

While women with reduced levels of naturally occurring anticoagulants (anti-thrombin III, Protein C or Protein S) factor V Leiden, or prothrombin gene mutations (G20210A) are predisposed to VTE<sup>58</sup> FSRH guidance<sup>1</sup> does not recommend the need for routine thrombophilia screening prior to use of CHC, as a negative screen may not exclude all types of thrombophilia.

√ The United Kingdom Medical Eligibility Criteria for Contraceptive Use provides consensus-based recommendations for the use of contraception. A clinical history should be taken to identify any relevant medical conditions which may influence contraceptive choice.

C A thrombophilia screen is not recommended routinely before use of CHC

## **Summary**

Although the relative risk of VTE does increase with CHC use, the absolute risk in women of reproductive age is very low. Other hormonal contraceptives do not appear to be associated with an increased risk of VTE, although more evidence is required, particularly for high risk groups. Clinicians advising women on hormonal contraceptive use should be able to convey the risk of VTE and provide information on overall risks and benefits to help women judge the level of risk that is acceptable to them.

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