Risk of venous thromboembolism in users of non-oral contraceptives
Statement from the Faculty of Sexual and Reproductive Healthcare

New data
A paper published in May 2012 in the British Medical Journal\(^1\) has reported new data on non-oral hormonal contraceptives and risk of venous thromboembolism (VTE).

Key findings
- The combined (estrogen and progestogen containing) contraceptive patch and combined vaginal ring appeared to be associated with an increased risk of VTE compared with non-users of hormonal contraception.
- VTE risk also appeared increased in ring and patch users compared with users of combined oral contraceptives (COCs) containing levonorgestrel.

Synopsis
The study\(^1\) was a retrospective cohort study. VTE cases from 2001-2010 were identified from a Danish national registry and confirmed by prescription data. The cohort included all non-pregnant women aged 15-49 years free of previous thrombotic disease or cancer. Information on age and education of the cohort cases was obtained from four Danish national data sources. The data sources did not contain information on body weight, family history of VTE, smoking or past contraceptive use.

The study included 1,626,158 women contributing to 9,429,129 women-years of observation. Over the observation period there were 5287 first time VTE diagnoses (8.1 per 10,000 women years according to the authors).

Current use of COCs containing levonorgestrel was found to confer a relative risk (RR) of VTE of 3.2 (95% Confidence Interval [CI] 2.7-3.8). Compared with non-users of hormonal contraception, use of the patch gave a RR of 7.9 (CI: 3.5-1.7) and for the ring a RR of 6.5 (CI: 4.7-8.9). There were 6178 women years of observation for the patch during which there were 6 confirmed events of VTE (9.7 per 10,000 exposure years). For the ring there were 39 confirmed VTE events from the 50334 women-years of observation (7.8 per 10,000 exposure years).

Compared with users of levonorgestrel-containing COCs, patch users were found to have an adjusted relative risk of 2.3 (CI: 1.0-5.2) and ring users an adjusted relative risk of 1.9 (CI: 1.3-2.7).

The authors stated that there was an increased risk of VTE with the progestogen-only implant but this increase was not significant (RR 1.4 [CI: 0.6-3.4]). A reduced risk was observed among users of the levonorgestrel-releasing intrauterine system (RR 0.6 [CI: 0.4-0.8])
CEU response
The paper adds to a large body of evidence on the risk of VTE associated with use of combined hormonal contraceptives (2-14). While the data from this study suggest higher relative risk rates than previously cited for other combined hormonal contraceptives, the risk is far lower than the risk of VTE associated with pregnancy or the postpartum period (see table 1). Women should be reassured that the absolute risk of VTE associated with combined hormonal contraception is low.

The risk of thrombosis associated with the transdermal patch in comparison to combined oral contraceptives has been investigated previously with conflicting results. The findings of this study suggest the risk of VTE is two fold greater for women using the patch compared to women using combined oral contraceptives containing levonorgestrel (RR 2.3 [CI: 1.0-5.2] or norgestimate (RR 2.2 [CI:1.0-5.0]). As these confidence intervals contain the value of 1, the increased risk could be a chance finding. The finding is similar to that of other studies (15;16) which similarly found a two fold increased risk of VTE in women using the transdermal patch compared to women using combined oral contraceptives containing norgestimate. However there are also data which suggest no significant increased risk in comparison to COC use(17;18).

Published data in relation to the risk of VTE associated with the vaginal ring is limited. A large, controlled, prospective, open-label observational trial looking at the risk of VTE associated with the contraceptive ring has been undertaken but to date the results have only been presented in poster format. The study by Lidegaard et al(1) appears to suggest that the risk is twice that of women using levonorgestrel-containing COCs (RR 1.9 [CI:1.3 to 2.7]). This finding is perhaps surprising given that it is a lower dose method, with serum hormone levels almost half that of oral contraceptive use.

As with previous observational studies investigating VTE risk, there are confounders and bias which may limit the ability to draw any firm conclusions from the findings. The main limitations of the Lidegaard study(1) are its:

- Retrospective nature
- Reliance on registry data
- Lack of ability to adjust for factors such as BMI, family history of VTE, smoking, duration of current and past contraceptive use

The CEU would advise that whilst these results are interesting, they should be viewed with caution and that this analysis should not change current practice.

Prescribing of CHC should be in line with current guidance from the CEU on CHC and the UK Medical Eligibility Criteria for Contraceptive Use. When prescribed appropriately the benefits of using combined hormonal contraception (CHC) generally outweigh the risks of VTE.
Although the paper stated there was an increased VTE risk in women using the progestogen-only implant, this was not significant and the CEU would continue to advise that there is no evidence that progestogen-only methods increase the risk of VTE.

**Practical advice for practitioners**

- Health professionals should be aware the risk of VTE amongst COC users is approximately twice that of non-users (average across all brands studied). The risk of VTE associated with newer progestogens such as desogestrel, drospirenone and gestodene has, in several but not all studies been found to be higher than the risk associated with levonorgestrel-containing pills and up to six times that of non-contraceptive users. However women should be aware that the absolute risk for all combined hormonal contraceptives is still very low.

- Women starting combined hormonal contraception should be offered a levonorgestrel-containing combined oral contraceptive as a first line option.

- In addition to considering the risk of VTE, health professionals prescribing CHCs should take into account the individual woman’s personal preference, risk factors, any contraindications, potential non-contraceptive benefits and experience with other contraceptive formulations.

**Table 1:** Risk of venous thromboembolism (VTE) associated with combined oral contraception (COC) use, pregnancy and non-use

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of VTE per 10,000 women years</th>
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<tbody>
<tr>
<td>Non contraceptive users and not pregnant</td>
<td>4-5&lt;sup&gt;(19)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oral contraceptive users</td>
<td>9-10&lt;sup&gt;(9)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>29&lt;sup&gt;(9)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immediate Postpartum period</td>
<td>300-400&lt;sup&gt;(20)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Reference List**


2. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared...


(12) Jick H, Kaye JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before


