Use of combined oral contraception and risk of venous thromboembolism

The BMJ today publishes the findings of a large UK observational study by Vinogradova et al looking at the association between combined oral contraception (COC) and risk of venous thromboembolism (VTE). The authors conducted two nested case-control studies utilising data from the UK QResearch and Clinical Practice Research Datalink (CPRD) databases. Women aged 15-49 years with a first diagnosis of VTE in 2001-13 were matched with controls by age, practice and calendar year. A total of 10,562 cases of VTE and 42,034 controls were included in the study. Odds ratios for incident VTE and the use of combined oral contraceptives in the previous year were adjusted for confounding factors. Results were combined across the two datasets using a meta-analysis technique.

The study found that current exposure to any COC was associated with an increased risk of VTE (adjusted odds ratio 2.97, 95% confidence interval 2.78 to 3.17) compared with no exposure in the previous year.

Odds ratios for VTE associated with current exposure to ethinylestradiol (EE) COC containing desogestrel (4.28, CI 3.66 to 5.01), gestodene (3.64, CI 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96), and cyproterone (4.27, CI 3.57 to 5.11) were significantly higher than those for COC containing levonorgestrel (2.38, CI 2.18 to 2.59), norethisterone (2.56, CI 2.15 to 3.06) and norgestimate (2.53, CI 2.17 to 2.96).

These figures are broadly in line with those published by the Medicines and Healthcare Regulatory Authority (MHRA) in 2014, based on the European Medicines Agency (EMA) 2013 review of the available evidence. [1,2] The MHRA estimates that, compared with non-users of COC, users of COC containing EE plus desogestrel, gestodene or drospirenone have a 4.5 to 6 fold increase in VTE risk. Users of COC containing EE plus levonorgestrel, norethisterone or norgestimate have around 2.5 to 3.5 times the risk of non-COC users. The EMA’s Pharmacovigilance Risk Assessment Committee advises that the risk of VTE in users of cyproterone-containing COC is likely to be similar to that with COC containing desogestrel, gestodene and drospirenone.[3] Current Faculty of Sexual and Reproductive Healthcare (FSRH) guidance reflects these risks.[4]
All the EE COC in this study increase the risk of VTE. In line with current data used to inform MHRA and FSRH statements, EE COC containing desogestrel, gestodene, drospirenone and cyproterone are associated with a greater increase in VTE risk than those containing levonorgestrel, norethisterone or norgestimate.

Vinogradova et al were unable to derive the VTE incidence for the unexposed population from either database. They therefore used figures from a large Danish cohort to estimate the background VTE risk for non-users of COC at just over four VTE events per 10,000 women per year. This figure was used to estimate the absolute number of additional VTE events that would be attributable to use of the various COC preparations. Thus, amongst levonorgestrel-containing COC users, the authors estimate that there would be an extra 6 VTE events per 10,000 users per year and an extra 14 for desogestrel and cyproterone COC.

These estimates for absolute numbers of VTE events are slightly higher than those quoted by the MHRA, who use a lower figure (2 per 10,000 women per year) for the background VTE risk amongst women that are not exposed to COC. It is important to note that the VTE risk amongst COC users relative to the risk in non-COC users is very similar in this study to that given by the MHRA for all COC studied, and that absolute numbers of VTE events in COC users are small. [2,4]

The number of additional VTE events occurring in COC users is small.

Previous evidence has suggested that VTE risk is highest in the four months following initiation of COC.[4] This was not confirmed by the current study. No significant effect of EE dose on VTE risk was observed with the COC studied.

This new study, in a UK setting, adds weight to the existing evidence relating to the relative increase in risk of VTE conferred by different combined oral contraceptives. It has the major advantages of its large size, the use of recent data and the extensive consideration of confounding factors. It is limited by its observational nature, the reliance on COC prescribing data (rather than data relating to actual COC use) and the fact that it cannot control for prescribing bias. Additionally, VTE events initially recorded in General Practice may not always have been subsequently confirmed. The study findings are in line with the current MHRA and FSRH figures and are not anticipated to change current UK practice recommendations.

When considering prescription of any COC, clinicians must consider whether a woman has any condition (such as obesity or a family history of VTE) that increases her risk of VTE. Clear guidance is provided by the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC). Some conditions will contraindicate COC use. [5,6]

The risk of VTE associated with COC should be made clear to a woman considering COC use, so that she can judge the level of risk that is acceptable to her. She should also be made aware that effective methods of contraception are available that do not confer an increased VTE risk. Prescription of a COC with a lower VTE risk should
be considered first line. However, an individual woman’s experience of non-contraceptive benefits and nuisance side effects associated with COC containing different progestogens may influence choice of COC type.

Some of the COC studied are commonly described as “newer”. However we now have over 12 years of clinical experience of use of even the “newest” of the COC considered (EE/drospirenone).

It is important to note that VTE risk increases markedly during pregnancy (29 per 10,000 women) and particularly in the weeks immediately after pregnancy (300-400 per 10,000 women). [4] The small increase in the risk of VTE amongst users of COC, which prevents pregnancy, must therefore be considered in the context of the greater risk amongst women who are pregnant, or have recently given birth.

**COC offers highly effective contraception and is widely used by women in the UK. The number of VTE events associated with COC use is small, and VTE is fatal in only about 1% of these cases.**[7] The findings of this study do not change current prescribing advice. COC use should be avoided if a woman has significant risk factors for VTE. A COC with a lower VTE risk should be considered first line. Women should be fully informed regarding potential risks of COC, and encouraged to be vigilant for symptoms of VTE. Clinicians should make women aware of alternative effective contraceptive methods that do not increase VTE risk.

4. Faculty of Sexual and Reproductive Healthcare Statement on Venous Thromboembolism (VTE) and Hormonal Contraception, November 2014 http://www.fsrh.org/pdfs/FSRHSStatementVTEandHormonalContraception.pdf