

EDITORIALS



Fresh evidence confirms links between newer contraceptive pills and higher risk of venous thromboembolism

Important insights for women and their doctors

Susan S Jick *professor of epidemiology*

Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA 02421, USA

In this week's issue of *The BMJ*, Vinogradova and colleagues (doi:10.1136/bmj.h2135) report the results of a large study on the effects of combined oral contraceptives on the risk of venous thromboembolism, conducted in two large United Kingdom databases: the Clinical Practice Research Datalink (CPRD) and QResearch. The authors identified over 10 500 cases of VTE in women aged 15-49 years and around 42 000 matched controls to address the inconsistencies and limitations of earlier studies. Older oral contraceptives (those containing levonorgestrel or norethisterone) showed results consistent with previously published findings: current users of oral contraceptives are at increased risk of venous thromboembolism compared with non-users of similar age and health status. Relative to non-users, risks were increased by around 2.5-fold for users of older oral contraceptives.

Notably, Vinogradova and colleagues also looked at the newer oral contraceptives, such as those containing desogestrel, gestodene, and cyproterone, as well as the newest pill containing drospirenone, where data have been limited and the magnitude of effects on the risks of venous thromboembolism remains controversial. They found that the newer contraceptives increased risks by around 3.6- to 4.3-fold compared with non-use, and by around twofold compared with oral contraceptives containing levonorgestrel, norethisterone, or norgestimate. Combined, the results provide compelling evidence that these newer oral contraceptives are associated with a higher risk of venous thromboembolism than older options, despite attempts to develop safer hormonal contraceptives for women.

There is controversy surrounding the association between different oral contraceptives and risk of venous thromboembolism, which is due to the variability of case definition and inclusion criteria, and has led to divergent results.¹ Vinogradova and colleagues tried to address differences within previous study designs to help explain the range of results. The current study's size and design enabled the authors to analyse risks of venous thromboembolism in important subsets of

women: those treated with anticoagulants (about 52% of cases) and their controls, and those with idiopathic venous thromboembolism (about 52% of cases) and their controls (39% of eligible controls).

Odds ratios for each newer oral contraceptive compared with non-use were higher in analyses confined to women treated with anticoagulants, ranging from 6.0 for pills containing cyproterone to 6.5 for pills containing gestodene. These results are similar to those of a large study conducted by Lidegaard and colleagues in 2011,² where anticoagulation treatment was part of the case definition of venous thromboembolism. It is likely that the treated subset of women contained a higher proportion of true cases compared with the full set since anticoagulation is essential in the treatment of venous thromboembolism. The higher odds ratios in the treated groups are likely to be closer to the true effect because random case misclassification results in bias to the null.

Similarly, the higher risk estimates in analyses confined to idiopathic cases (that is, those with no other proximate cause such as recent surgery or lower limb injury) suggest that the effect associated with oral contraceptives is higher among women without strong risk factors or other causes of venous thromboembolism. Again, inclusion of cases with other proximate causes results in bias towards the null; therefore, the higher odds ratios are likely to be closer to the true effect.

This result is also consistent with findings of earlier studies where venous thromboembolism was restricted to idiopathic cases. In these restricted analyses in the current study, the odds ratio for current oral contraceptive use ranged from 4.0 in pills containing gestodene to 4.7 in pills containing cyproterone. It would be useful to see the odds ratios from analyses of women who were both idiopathic and had received anticoagulation treatment.

Perhaps of most importance to women and to prescribers is the relative risk of venous thromboembolism in users of the various oral contraceptives currently available. Vinogradova and colleagues compared the risks of venous thromboembolism in

women taking newer pills relative to older pills containing levonorgestrel. In subanalyses of women treated with anticoagulants, the risks associated with the newer oral contraceptives were around twofold higher than the risks associated with the older levonorgestrel pills. In subanalyses of idiopathic cases, the risks varied from about 1.4 to 1.9 for current use of the newer oral contraceptives compared with the levonorgestrel contraceptives. The risks did not materially vary by oestrogen dose or age.

Are risks of venous thromboembolism higher in the first few weeks of treatment? The Vinogradova study did not find differences in risk between short and long term users of the newer oral contraceptive preparations, although there was a suggestion of a differential effect in women taking pills containing levonorgestrel. These findings are consistent with those of Lidegaard and colleagues,² suggesting that new users of oral contraceptives are not, in general, at a materially increased risk of venous thromboembolism compared with longer duration users.

Vinogradova's comprehensive study addresses important questions about the risk of venous thromboembolism in women taking oral contraceptives, concluding that the risk associated

with newer pills is around twofold higher than the risk associated with older contraceptives. The risk varies according to case definition of venous thromboembolism, and does not seem to be materially higher for new users of oral contraceptives. These results, combined with those published in a similar study by Lidegaard and colleagues,² clarify inconsistencies in earlier studies and provide important guidance for the safe prescribing of oral contraceptives.

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- 1 Stegeman BH, de Bastos M, Rosendaal FR, et al. Different oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ* 2013;347:f5298.
- 2 Lidegaard O, Nielson LH, Skovlund CW, Skjeldestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study 2001-9. *BMJ* 2011;343:d6423.

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