JOURNAL REVIEW

Another flawed database analysis of VTE risk and hormonal contraceptives

Lidegaard Ø, Nielson LH, Skovlund CW, *et al*. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. *BMJ* 2012;**344**:e2990

This is basically a companion paper to the one published last year in the *British Medical Journal*,[1] which concentrated on the pill and was comprehensively criticised in the January 2012 issue of this Journal,[2] to which readers are referred. This analysis, also from the Danish registry, looks at the Evra® patch, NuvaRing®, Implanon® and the levonorgestrel-releasing intrauterine system (Mirena® IUS). All the previous issues of confounding, lack of information regarding smoking, body mass index and family history, and not comparing like with like, apply here.

It is important to compare new users with new users, as a well-established fact is that the risk of venous thromboembolism (VTE) is highest in the first 6 months of use of estrogen-containing contraceptives. It is therefore important to look at the launch dates of contraceptive products. NuvaRing was launched in Denmark in late 2001/early 2002, while the EVRA patch was launched there in September 2003. Meanwhile, combined oral contraceptive pills (COCs) containing levonorgestrel have been in use since the 1970s, and those containing norgestimate since the mid-1980s. Thus, since the study period began in 2001, all users of NuvaRing and Evra must have been new users, and so also more likely to be first-time users/women with risk factors. Meanwhile, the users of the comparator COCs were more likely to be long-term users and therefore at lower risk, since the high-risk women in those groups will have been weeded out within the first 6 months of use – before the study began (i.e. attrition of susceptibles). The effect of duration of use is most clearly seen with NuvaRing in Table 4, where compared with non-users of hormonal contraceptives, the relative risk becomes appreciably lower with increasing duration of use, declining from 8.36 for <1 year of use to 3.83 for use of 1–4 years. In addition, the numbers in each duration category are small, leading to random variability. For the patch (six exposed women) and the implant (five women) not even the overall numbers are adequate.

With regard to the two progestogen-only methods under study, not surprisingly neither was associated with a significantly increased risk of VTE – progestogen-only methods have not been implicated in VTE risk, since this is related to estrogen. Indeed, progestogen-only methods are advised (in preference to estrogen-containing methods) for women with risk factors for VTE.[3] However, in the abstract, the authors misleadingly state that "the relative risk was increased in women who used subcutaneous implants" and yet their relative risk of 1.4 had a confidence interval (CI) of 0.6–3.4 (i.e. not even approaching statistical significance). For the IUS, not only was the relative risk not increased, it was significantly decreased at 0.6 (95% CI 0.4–0.8). This has no biological plausibility and simply highlights the lack of credibility of the analysis.[4]

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Competing interests Anne Szarewski has received honoraria, consultancy fees and conference sponsorship from Bayer Schering (formerly Schering HealthCare), Schering Plough (formerly Organon), Janssen-Cilag and Wyeth. Diana Mansour has received honoraria, consultancy fees and conference sponsorship from Bayer Schering (formerly Schering HealthCare), Schering Plough (formerly Organon), Janssen-Cilag, HRA Pharma and Wyeth.

Provenance and peer review Not commissioned; internally peer reviewed.

J Fam Plann Reprod Health Care 2012;**38**:166. doi:10.1136/jfprhc-2012-100393

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2 **Dinger J**, Shapiro S. Combined oral contraceptives, venous thromboembolism, and the problem of interpreting large but incomplete datasets. *J Fam Plann Reprod Health Care* 2012;**38**:2–6.

3 **Blanco-Molina MA**, Lozano M, Cano A, *et al.* Progestin-only contraception and venous thromboembolism. *Thromb Res* 2012;**129**:e257–e262.

4 **Szarewski A**, Mansour D. Rapid response re: Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. http://www.bmj.com/content/344/bmj.e2990/rr/584507 [accessed 14 May 2012].