CORRESPONDENCE

Venous thromboembolism and oral contraceptives

Sir—We are pleased that 5 years after the first studies, R M C Herings and colleagues (July 10, p 127)[1] have confirmed the difference in venous thromboembolism risk between second and third generation oral contraceptives. The difference in risk is highest among the youngest women who were exposed to sex steroids for the first time, as suggested in two of the original studies.[2,3]

The investigators conclude that their data point to an interaction between types of oral contraceptives, and to an unidentified susceptibility factor that might be a prothrombotic mutation. Although the exact mechanism by which oral contraceptives cause venous thrombosis is unknown, we feel that progress was made by the finding of the interaction between oral contraceptive use and factor V Leiden in explaining venous thrombosis.[3,4] By analysing our data for type of oral contraceptives, we found that the age-adjusted relative risk for the desogestrel-containing oral contraceptive was 9·2 (95% CI 3·9–21·4) among non-carriers of factor V Leiden mutation and 6·0 (1·9–19·0) among carriers. This risk is, however, in addition to the eight-fold increased risk of venous thrombosis for carriers of the factor V Leiden mutation.

The risk for venous thrombosis is highest during initial oral contraceptive use, which suggests that some women are at immediate risk of thrombosis when exposed to oral contraceptives. This prompted us to re-analyse the data of the Leiden Thrombophilia Study.[5] Women were classified thrombophilic when they had deficiencies of protein C, protein S, or antithrombin, or mutations in factor V Leiden or prothrombin 20210 A. The risk of developing deep-vein thrombosis (DVT) was greatest in the first 6 months and the first year of use, and women who developed venous thrombosis during the early periods of use were likely to be thrombophilic. Of 109 women with DVT objectively diagnosed during oral contraceptive use, 37 were thrombophilic. Of 65 women in the control group who used oral contraceptives, ten were thrombophilic. Among women with thrombophilia, the risk of developing DVT during the first year of use, compared with prolonged use, was increased 11-fold (95% CI 2·1–57·3).

Variation in susceptibility in each woman is the key to finding an explanation of why oral contraceptives cause venous thrombosis.

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1 Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999, **354:** 127–28.
2 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995, **346:** 1589–93.
3 Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing third-generation progestagen. *Lancet* 1995; **346:** 1593–96.
4 Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet* 1994; **344:** 1453–57.
5 Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Women with inherited clotting defects have higher risk of venous thrombosis during the first year of use of oral contraceptives. *Arch Intern Med* (in press).

Sir—R M C Herings and colleagues[1] report a four-fold increased risk of thromboembolic disease among users of third-generation compared with second-generation combined oral contraceptives. This difference they report as highest among the youngest women who used oral contraceptives for the first time. We wonder whether the investigators or other readers can explain the very high rates of thromboembolic disease in all users of oral contraceptives in this study compared with results from previous studies.[2]

It was unclear to us whether identification of "women with first episodes of exclusive use of third—or second—generation drugs" allowed previous use of other varieties of oral contraceptives in that individual's lifetime. In other words, were they all new users of the combined oral contraceptive (never previously exposed), or had some used other types of combined oral contraceptive in the distant or recent past? This question is obviously important in view of the higher risk of thromboembolic disease within the first year of use of combined oral contraceptive.

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1 Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; **354:** 127–28.
2 Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998, **57:** 169–81.

Authors' reply

Sir—First, we must apologise for and correct several errors in our letter (see Department of Error, p 1478).

Our study was limited to episodes of first, exclusive use of third or second generation oral contraceptives among new users. Therefore, we first converted all prescriptions of oral contraceptives into episodes of exclusive use, on the basis of the numbers prescribed and dispensed cycles. Most women had more than one episode of contraceptive use, either

because they stopped taking oral contraceptives for a period of 1–2 years or they switched to other methods of contraception (<5%). To compare our data with those of others we need to extend our study to recurrent users. In the total population, including new and recurrent users, we saw 78 cases of DVT during 209 706 person-years use of second and third generation oral contraceptives. The overall incidence rate (new and recurrent users) was 3·7/10 000 person-years with 5·5/10 000 person-years (49/88 295) for users of third generation oral contraceptives and 2·4/10 000 person-years (29/121 411) for users of second generation oral contraceptives, giving a crude relative risk of 2·3 (95% CI 1·5–3·7). These rates and relative risk corroborate the initial findings cited by Vandenbroucke[1] and Walker[2] and their colleagues. Our results are also in line with Farmer and colleagues'[3] findings with respect to the major potential confounding role of age and calendar year. By contrast, we limited the number of confounders by restricting the exposure in our main analysis to new, exclusive users of second or third generation oral contraceptives. We controlled for age differences and date of initiation of oral-contraceptive use by including age and year of onset of use as continuous variables in our Poisson regression models. Our findings clearly show that the risk difference between third and second generation oral contraceptives is strongest among new, healthy users of third generation oral contraceptives.

Despite being able to follow up drug use for most women since their childhood to detect first use of oral contraceptives, we cannot entirely exclude past use of oral contraceptives. However, any undetected past use would lead us to underestimate the relative risk we report. Differences between new and recurrent use were only recorded for third generation contraceptive (9·0/10 000 *vs* 3·8/10 000 person-years, and 2·4/10 000 *vs* 2·4/10 000 person-years for third and second generation oral contraceptives). Furthermore, the risk differences between third and second generation contraceptives declined from an eight-fold to a two-fold risk difference over time. Most thromboemboli were seen during the first year of use and virtually all thromboemboli occurred before the end of the second year of use. The risk in the first year of use was increased compared with long-term use for both second and third generation oral contraceptives. These data are in line with Kitty Bloemenkamp and colleagues' conclusions, although we have no data on genetic susceptibility.

Further research is necessary to ascertain the mechanisms behind the small but seemingly definite differences in risk attributable to the second and third generation oral contraceptives. A noteworthy conclusion is that women who have used these contraceptives for more than 1 year without an episode of DVT have safely run the gauntlet of modestly raised risk.

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1 Vandenbroucke JP, Helmerhorst FM, Bloemenkamp KWM, Rosendaal FR. Third generation oral contraceptive and deep venous thrombosis: from epidemiologic controversy to new insight in coagulation. *Am J Obstet Gynecol* 1997; **177:** 887–91.

2 Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998; **57:** 169–81.

3 Farmer RDT, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997; **349:** 83–88.

Sir—R M C Herings and co-workers[1] present high relative risks of developing venous thromboembolism (VTE) among first users of third-generation oral contraceptives compared with first users of second generation oral contraceptives. With an overall adjusted estimate of 4·2, the relative risk seems to be highest for women younger than 25 years (8·5), for duration of use of 1 year or more (8·1), especially in the absence of other disorders (14·1), and is apparently independent of the type of third generation progestagen used or the oestrogen content of the preparation. These findings were based on 27 women who developed VTE exposure to third generation and six women exposed to second generation oral contraceptives.

Several issues related to this analysis should be addressed, apart from the small number of cases. Although the investigators repeatedly referred to a base population of 450 000, it was unclear how many women were included in the calculations, and there was no mention of the exact numbers of non-cases in the cohort. The accrued total exposure time was 54 939 woman-years over 10 years. Little seems to have been done to validate the data. The data on exposure and outcome were derived from different sources, with exposure measured on a regional basis and outcome on a nationwide basis. Time periods were not clearly defined in the exposure database, for which data were apparently collected retrospectively for 1986–89. Although implicitly stated, it was not entirely clear that first users actually became first users within the time period assessed, nor whether the definition of first user related to continuous use. The issue of left-censoring was unclear, and women older than 16 years in 1986 may have used oral contraceptives before the database was established. Users of second generation pills might therefore have been misclassified as first-time users. Crude and adjusted risk ratios showed little differences, despite large differences in the age structures of cases and non-cases by generation and in other variables. Furthermore, duration of use seemed not to have been adjusted for.

We have shown the importance of previous exposure history and duration of use by use of a Cox's time-dependent regression model on a dataset of the transnational study, with additional information on lifetime use of oral contraceptives (hazard ratio of third *vs* second generation 0·79 [95% CI 0·50–1·26]).[2] For first-time users, taking into account duration of use, the hazard ratio is 1·23 (0·70–20·07). For previous users, the time-dependent model adjusts for full history of exposure, giving a hazard ratio of 0·64 (0·48–0·83). Our results do not support the suggestion that there is an increased risk of VTE in first-time users of third generation oral contraceptives compared with first-time users of second generation oral contraceptives.

Data selection, small numbers of cases, and not taking into account duration of use are likely to outweigh the potential influences of changing prescribing patterns on the risk estimates.

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1 Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; **354:** 127–28.

2 Lewis MA, MacRae KD, Kühl-Habich D, Bruppacher R, Heinemann LAJ, Spitzer WO, Transnational Research Group on Oral Contraception and the Health of Young Women. The differential risk of oral contraceptives: the impact of full exposure history. *Hum Reprod* 1999; **14:** 1493–99.