Risk of VTE among users of oral contraceptives

We have recently reviewed two studies,[1] a cohort study conducted in Denmark,[2] and a case-control study conducted in The Netherlands,[3] in which it was claimed that the risk of venous thromboembolism (VTE) among users of oral contraceptives (OCs) containing desogestrel, gestodene, drospirenone and cyproterone is greater than among users of levonorgestrel-containing OCs. We concluded that in both studies the comparisons among the progestogens were not valid due to methodological limitations.

The Danish study linked prescription data recorded in one national registry to hospital discharge diagnoses of VTE recorded in another registry. The investigators stated that in an earlier validation study 10% of the diagnoses documented between 1994 and 1998 "were uncertain". In the study under review they acknowledged that they relied on the "final discharge diagnoses as reported", and that they were unable to "evaluate the validity of each included diagnosis of [VTE]".[2]

Since publication of our review new information has come to light that bears on the validity of the registry-recorded diagnoses. In a cohort study that included 27 178 men and 29 876 women aged 50–64 years, Severinsen and her colleagues examined the medical records of 1100 cases of registry-recorded VTE.[4] The diagnosis was incorrect in 25% of cases diagnosed in hospital wards, and in 69% of cases diagnosed in emergency departments; the latter cases constituted 41% of the total. Incorrect diagnoses were more commonly recorded among women than among men. A stratified analysis did not show an impact of age on diagnostic precision.

It is difficult to reconcile the findings of Severinsen *et al*. with the assumption that the diagnosis was uncertain in about 10% of the cases of VTE,[2] even though that estimate was made among women of fertile age. Based on the wording used by the authors it can be assumed that the VTE incidence rates among the compared OCs were based on all VTE diagnoses – including VTE diagnosed in emergency departments. If so, Severinsen's results suggest that the diagnosis was not only uncertain, but in at least 40% of the cases it was wrong. If the analysis was based only on hospital ward cases, the diagnosis was incorrect in about 29% of the female patients.

Relative to levonorgestrel the relative risks for the compared OCs were small (<2), and the major diagnostic imprecision suggested by Severinsen's data would be sufficient to nullify the findings. It obliges Lidegaard to verify the diagnoses in his study.

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Statements on funding and competing interests
Funding None identified.
Competing interests The authors presently consult, and in the past have consulted, with manufacturers of products discussed in this letter.

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Critique of a Danish cohort study on hormonal contraception and VTE

Thanks to Samuel Shapiro and Jürgen Dinger (S&D) for their altruistic interest in and concern for possible bias and confounding in two recently published studies on use of oral contraceptives (OCs) and the risk of venous thromboembolism (VTE), as detailed in their review article[1] in the January 2010 issue of the *Journal of Family Planning and Reproductive Health Care*. One of the two studies under discussion was a national Danish cohort study.[2]

The two authors' concern is to question whether bias and confounding could explain how different types of progestogens in OCs seem to play a differential role in the risk of VTE. However, S&D don't stop with questioning. They actually conclude first that the results of both studies are invalid, and second that the best scientific evidence (taking all studies into account) is that the progestogen type in the combined OC has no influence on the risk of VTE.

These rather bombastic conclusions necessitate a validation of each of their points of concern for the Danish cohort study.

Control for duration of use

S&D correctly state that the risk of VTE is highest during the first months of use. It is also correct that some (in fact few, however) short-term users of OC with levonorgestrel (LNG) might have used the pill for a longer period (before our study window started in 1995), namely the small fraction of the LNG short-term users beginning their short use in the beginning of 1995. While this potential left censoring bias could influence users of OC with LNG more than users of OC with drospirenone, it also applies to users of the third-generation progestogens, desogestrel and gestodene. However, the risk estimates for third-generation OCs was 82% and 86% higher than the risk estimates for OCs with LNG, a risk ratio even higher than for OCs with the fourth-generation drospirenone. That should not be the case, if the concern of S&D had any substantial significance. The magnitude of misclassification of the short-term LNG users was in the order of 0.22 (per cent of short-term users) × 0.023 (proportion of short-term users who were recorded within the first 3 months of 1995) = 0.005 or about a half per cent. In addition, we stratified for (adjusted for) length of use when comparing the different types of progestogens, thereby eliminating all other differences (other than the small fraction of short-term users starting their short-term use in 1995) concerning length of use between different OC types. Therefore, it is very unlikely that this small misclassification of short-term users starting their short-term use in the beginning of 1995 would have had a substantial influence on our estimates.

Thereafter S&D argue that the risk in short-term users of OCs with LNG should have been three times higher than for long-term users. Our analysis demonstrated, however, that the risk among short-term users (all products considered together) was about 50% higher in the first year. Not more. With these national cohort data, their calculation, anticipating this three-fold difference, is far too high.

As indicated in our paper,[2] a large number of studies with different designs have assessed a possible differential effect of different progestogens to influence women's VTE risk. The vast majority of these studies have found a consistently higher risk with OCs containing desogestrel and gestodene than for OCs containing LNG.

So the present two new studies are in accordance with the available scientific evidence. In addition, the different impact of the different progestogens on the so-called Activated Protein C sensitivity ratio gives us a probable mechanism through which these different progestogens exert their differential influence on the coagulation system.

In conclusion, well-sized and well-conducted newer epidemiological studies consistently find a higher risk of VTE with the newer progestogen types as compared with the older types. The fact that differently designed studies conducted at different times in different countries find the same differential risk between different progestogen types increases the probability that this difference is real and not due to bias and confounding as S&D suggest.

Next S&D argue that when operating with length of use one has to consider only the length of the last use. Had we done so, S&D could have argued that our missing data on previous use had flawed our effort to exclude bias due to attrition of susceptible individuals, as this attrition is in effect according to the total length of use and not only according to the last length of use.

Confounding

Next S&D argue that our missing control for obesity (BMI) "was a major defect in the Danish study". Now, adiposity is a well-established risk factor for VTE. A risk factor is, however, not the same as a confounder, which in addition to being a risk factor also has to be associated with use of OCs in general, and differentially with different OC types, if the considerations of S&D are to be valid. The fact is that there is no association between OC use and adiposity, and no significant difference in the frequency of adiposity in users of different types of OC (as documented in our paper).[2] Therefore, the increased risk of VTE in users of OC with third- and fourth-generation OCs as compared with OCs containing LNG cannot be explained by our missing control for adiposity.

Conversely, it is true that the frequency of adiposity increased in the general population during the study period. Therefore we adjusted our estimates for calendar year, thereby eliminating this potential time-trend bias.

S&D further speculate that women at an increased risk of VTE should preferentially be prescribed newer OCs, in particular OCs containing drospirenone. Our data demonstrate the opposite. The use of medication for hypertension, diabetes, hyperlipidaemia and heart disease was actually lower in users of drospirenone than in users of LNG. Consequently, this speculation does not seem to be very relevant.

Finally, S&D postulate that the decreasing risk of VTE with increasing length of education was unexpected, and therefore an indicator of selection bias, women educated for a short time being more prone to be diagnosed with VTE in case of symptoms than women with a longer education. This assumption is unlikely. All diseases I am aware of (with the one exception of multiple sclerosis), including thrombotic diseases, decrease in frequency with increasing length of education. Referral to hospital and subsequent diagnostic investigations are free in Denmark. Therefore, there is no reason to believe in any selection bias according to length of education. As our trend confirms a previously proven general trend towards unhealthier lifestyle and more morbidity with decreasing length of education, this finding only strengthens the validity of our results.

Other issues

S&D postulate that the diagnoses in the National Register of Patients have not been validated. This