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 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 compared 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 This suggests 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 participants.

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

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References


Critique of a Danish cohort study on hormonal contraception and VTE

Thanks to Samuel Shapiro and Juergen 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 thromboembolism (VTE), as detailed in their review article1 in the January 2010 issue of the Journal of Family Planning and Reproductive Health Care. One of the two studies being 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 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 (including 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 first use in 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 during the study period. Therefore we adjusted our estimates for calendar year, thereby eliminating this potential time-trend bias.

S&D further speculate that at an increased risk of VTE should preferably be prescribed newer OCs, in particular OCs containing drospirenone. Our data demonstrate that in the long run, the users of OCs for hypertension, diabetes, hyperlipidaemia and heart disease was actually lower in users of LNG 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 in Denmark as 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 a result, the very significant, in accordance with the available scientific evidence.

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 among the 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 (defined as users of different types of OC (as documented in our paper). 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. Therefore, S&D further speculate that at an increased risk of VTE should preferably be prescribed newer OCs, in particular OCs containing drospirenone. Our data demonstrate that in the long run, the users of OCs for hypertension, diabetes, hyperlipidaemia and heart disease was actually lower in users of LNG than in users of LNG. Consequently, this speculation does not seem to be very relevant.
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