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 found 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 “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 documented discharge diagnoses as reported”, and that they 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

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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 (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 at the time was in the order of 0.22 (proportion of short-term users who were recorded within the first 3 months of 1995) = 0.22 x 0.5 x 0.5 = 0.055 or 5.5%. 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 during their short-term use in the beginning of 1995 would have had a substantial influence on our estimates.

Next 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.

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 risk of venous 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 of concern was a national Danish cohort study.2

Several comments need to be addressed regarding the validity of the registry-recorded diagnoses. In a previous validation study it was shown that only according to the last 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 during their short-term use in the beginning of 1995 would have had a substantial influence on our estimates.

Next 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.

The vast majority of these studies have found a consistent higher risk with OCs containing desogestrel and gestodene than for OCs containing LNG. Nevertheless, some studies found a possible differential effect of different progestogens to influence women’s VTE risk. 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 consistent 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 conclusion, 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 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,” showing that 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 between 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 with time effect of 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 an increased risk of VTE should preferably be prescribed newer OCs, in particular OCs containing drospirenone. Our data demonstrate the opposite. The studies excluded 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 as one of the 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 this is not in line with our previously shown general trend towards unhealthy 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

References


3 Van, Hyuckydam Vlieg A, Helmerhorst FM, Vandenvreubecke JP, Doggen C, Rosendaal FR. Effects of oestrogen 5% and progestogen type on
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is wrong. We went through all the VTE diagnoses during the period 1994–1998 in women aged 15–44 years and found 10% with an uncertain diagnosis (this was clearly stated in the paper).

Validation

In their publication,3 Lidégaard and his colleagues “clearly stated” that “the registry approach did not permit us to evaluate the validity of each included diagnosis of VTE” and that they relied on the “final discharge diagnosis as reported”. The statement now made, that they went through all the VTE diagnoses … and found 10% with an uncertain diagnosis…1 is misleading: that estimate was made in an earlier study.4 As indicated in our Letter to the Editor in this issue of the Journal,7 Severinsen and colleagues have now reported that in Denmark registry-recorded diagnoses of VTE were incorrect in at least 40% of cases aged 50–64 years (in 40% the diagnosis could be ruled out, and in 5% it was uncertain) – or about 29% in female hospital-ward cases. It is unlikely that the discrepancy with the 10% rate of “uncertainty” identified by Lidégaard can be explained by age, and it obliges him to verify the diagnoses in his study. If VTE was incorrectly diagnosed as commonly as is suggested by Severinsen’s data, the interpretation of the small risk estimates must be questioned.

The remainder of our response follows Lidégaard’s sequence.

Left censorship

Lidégaard acknowledges that left censorship may have distorted the data for LNG more than for drospirenone. In fact, since drospirenone was only introduced in Denmark in 2001, for this compound there was no left censorship, and no distortion. Desogestrel and gestodene were introduced in Denmark in the first and second half of the 1980s, respectively, whereas LNG has been available since the first half of the 1970s. In addition, the market shares of desogestrel and gestodene were more or less stable between 1995 and 2005,7 while the use of LNG declined. Inevitably, therefore, the distorting effect of left censorship was more marked for LNG than for desogestrel or gestodene.

While Lidégaard acknowledges left censorship, his calculation of its potential impact is misleading for a number of reasons. Here, however, we confine our response just to one of them. Lidégaard states that “about a half per cent” of “short-term levonorgestrel users” were misclassified. This misses the point. In the first study year (1995) all long-term users (100%) were misclassified as short-term users. As approximately 14% of the total LNG exposure stems from 19957 it has to be assumed that in that year approximately 57 000 woman-years of LNG use were classified as short-term use (0.14 × 411 099; see Table 2 in Lidégaard’s publication). This number probably represents more than 60% of the total short-term exposures (0.22 × 411 099; Table 1). We therefore disagree with Lidégaard “that it is very unlikely” that this misclassification “had a substantial influence” on the risk estimates.

Risk of VTE among short-term OC users

As the duration of oral contraceptive (OC) use was misclassified, the risk of VTE for short-term users was underestimated in the Danish study. In an earlier study3 Lidégaard observed a three-fold higher relative risk increase for the first year of use relative to the following years. That study identified VTE from the same source (the Danish patient registry) but the information on OC use was derived from a different source: it was reported by the patients, and there was no left censorship. Moreover, it is not only short-term use that is at issue: in a valid comparison similar durations of use, whether short- or long-term, should have been compared among users of the different OCs.

Total vs current duration of OC use

With regard to the total durations of all episodes of OC use versus duration of the current episode only, we reiterate that multiple studies have demonstrated that the risk of VTE is no longer increased within a few months of stopping current use. It is only the duration of such use that is relevant. The need to have data on all episodes of OC use is not in order to sum all durations, but in order to be able to compare starters with starters, re-starters with re-starters, and switchers with switchers, as illustrated in Figure 1.

A comparison along these lines would also minimise any “bias due to attrition of susceptible individuals”,1 mentioned by Lidégaard. In addition, the requirement that starters should be compared with starters could readily have been met in the Danish study. Had follow-up commenced in 2001, the study would have started after the introduction of all the relevant progestogens and had women who used OCs between 1995 and 2000 been excluded, for practical purposes that objective would have been accomplished.

Confounding by obesity and other risk factors

Lidégaard claims that he has documented that there was “no significant difference in the frequency of adiposity in users of different types of OC.”1 In his study he had no data on obesity,3 and his claim is based on data from a different study covering the time from 1994 to 1998,8 Those data do not preclude the possibility that preferential prescribing of selected OCs occurred after 1998, and there is evidence that it did occur. In a recent study, drospirenone – a progestogen that is also an aldosterone antagonist – was preferentially prescribed to women with a high body mass index (BMI).10 That study also demonstrated that the combination of obesity with other risk factors (e.g. family history) led to a multiplicative increase in the risk of VTE. Since the Danish study lacked data on BMI, confounding from that source was not ruled out. Lidégaard acknowledges the increase in the prevalence of obesity that occurred between 1995 and 2005,1,11 as well as the decline in the use of LNG.9 He nevertheless claims that adjustment for calendar year eliminated confounding due to obesity. Both the increase in obesity and the decline in the use of LNG were substantial. Thus