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).

Initially, S&D make a rather unusual complaint, namely that large observational studies nearly always find significant associations, even if the association is small. Is that really a critique? Meaning that if we had done a smaller study then the quality would improve? The quality in large samples is first of all that one is able to separate the contribution from different axes of OC use; the length of use, the estrogen dose, the progestogen type, the dose and the route of administration. Other scientists would consider this to be a strength rather than a weakness.

Conclusion

Scientific critique is always welcome, and bias and confounding in observational studies are difficult to exclude completely. Some of the suggestions made by S&D are theoretically valid but seem of little or no quantitative significance. When several large-scale, independent epidemiological studies generate the same results, one also has to consider the possibility that these results are actually true.

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Reply

We thank Professor Lidegaard for his comments.[1] As stated[2] with regard to his study,[3] "The investigators are to be congratulated for conducting such a large study that also adjusted for the confounder information assessable in the Danish registries". We also believe that additional subanalyses might improve the interpretability of the findings. We address Professor Lidegaard's comments in the paragraphs that follow.

Previous studies

Relevant references to studies of the risk of venous thromboembolism (VTE) in users of desogestrel and gestodene, as compared with levonorgestrel (LNG), were provided in our review,[4] and a further detailed consideration of the "large number of studies" at issue would fall outside the scope of this response. Readers interested in the topic may also wish to refer to the judgement of the High Court of Justice[5] in the UK. It is not primarily the court's conclusion that is of interest here but the comprehensive documentation of methodological details and arguments that were scrutinised during more than 12 weeks of hearings with expert witnesses on the strengths and weaknesses of all relevant studies on this topic published until 2002.

The Danish cohort study

Professor Lidegaard questions the relevance and quantitative impact of our criticisms.[4] In response, we first consider the validity of the diagnosis of VTE in the Danish registry data.

Validation

In their publication,[3] Lidegaard 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.[6] As indicated in our Letter to the Editor in this issue of the Journal,[7] Severinsen and colleagues[8] 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 Lidegaard 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 Lidegaard's sequence.

Left censorship

Lidegaard 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,[9] 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 Lidegaard 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. Lidegaard 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 1995[9] 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 Lidegaard'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 Lidegaard "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 study[6] Lidegaard 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 duration 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 Lidegaard. 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

Lidegaard 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.[6] 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. Lidegaard 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

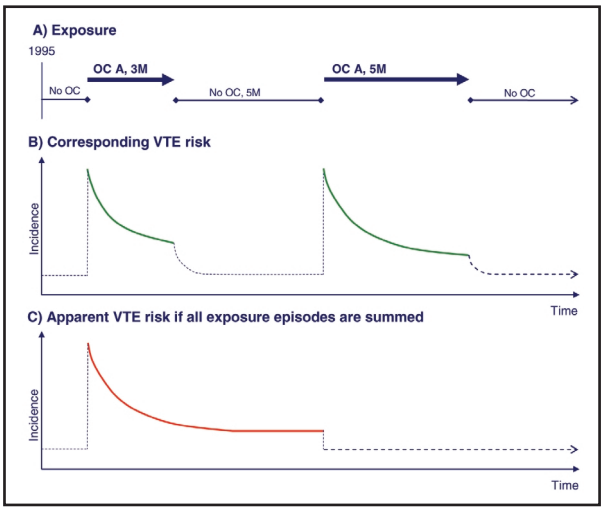

Figure 1 Time patterns of venous thromboembolism (VTE) occurrence based on a hypothetical example of two exposure episodes to the same oral contraceptive (OC), lasting 3 and 5 months (M), and separated by a 5-month interval of non-use: Real and apparent VTE risks if individual episodes of OC use are analysed separately or summed

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adjustment using time-trend data as a surrogate for obesity could possibly have reduced confounding, but it would not have eliminated it, especially since its effect in combination with other risk factors is multiplicative.

With regard to possible confounding from other sources, VTE was more frequently diagnosed in women who only completed primary school. Socioeconomic status was thus a determinant of VTE risk, and the possibility that this factor may have reflected detection bias was not evaluated. With regard to other potential confounders Lidegaard mentioned that allowance for treated diabetes, heart disease, hypertension and hyperlipidaemia did not affect the findings. Only heart disease and diabetes are risk factors for VTE; hypertension and hyperlipidaemia are not. As for other factors, the Danish study did not evaluate potential confounding due to a family history of VTE, recent surgery, trauma or immobilisation.

Confounding by indication

We stated that in the past there has been a general tendency to prescribe the most recently introduced OCs to women thought to be at increased risk of VTE. In a former publication[6] Lidegaard has agreed: "In many countries including Denmark … many gynecologists and general practitioners have prescribed these new pills to women at anticipated increased thrombotic risks". He has also stated that the risk of VTE conferred by "Family disposition, BMI, smoking, and years of schooling are probably the most important confounders to adjust for to account for prescribing bias".

Study size

We repeat that in the presence of systematic bias, a large study will more readily produce statistically significant results than a small one. Statistical significance, however, does not equate causation, and in a large study a biased or confounded association may nevertheless be "significant".

Conclusion

We are aware that *ex-post facto* criticism of studies conducted by others is easier than doing better oneself. We would welcome an opportunity to discuss with Professor Lidegaard details of additional subanalyses that might shed light on the issues raised in his publication, and in this correspondence. However, we reiterate that in our view the Danish comparison of selected progestogens with LNG was not valid.

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LNG may still be the best oral EC option

The last two issues of this Journal each included a commentary[1,2] on the progesterone receptor modulator (PRM), ulipristal acetate (UPA). Both commentaries concluded that UPA is more effective for emergency contraception (EC) than levonorgestrel (LNG). Now, as the key studies have been published, it is possible to assess the possible merits of providing UPA rather than LNG oral EC.

At present there remain good reasons to be cautious about the claims that UPA is the superior emergency contraceptive:

1. Both studies comparing LNG and UPA found no significant difference in pregnancy rates when used for EC. The recently published randomised controlled trial (RCT)[3] was designed as a non-inferiority study and a previous RCT[4] also showed non-inferiority for UPA. None of the studies were powered to provide the answer as to which is the better method of EC. There are two reasons why a non-inferiority design was chosen: (i) it is cheaper as a smaller sample size is required and (ii) it is all that is required for drug licensing. Analysis of the combined data of both studies showed that UPA showed significantly reduced pregnancy rates for UPA as compared to LNG. A meta-analysis does not replace a sufficiently powered single study such as the World Health Organization (WHO) multicentre RCT.[5] The WHO study also compared a PRM (10 mg mifepristone) with LNG. It was powered to find a difference but did not find one.
2. The primary outcome of the recently published RCT[3] was pregnancy rate, which was not statistically different for LNG and UPA. Pregnancy prevention rates are listed on ClinicalTrials.gov (No. NCT00551616) as a secondary outcome. The results were presented at a conference[6] but were not reported in the recent publication.[3] Pregnancy prevention rates are not observed but calculated and are much less robust than pregnancy. In theory, randomisation should have ensured that pregnancy risks in the LNG and UPA groups will have been similar, and different pregnancy prevention rates should also be apparent in different pregnancy rates. As we do not know if a power calculation was performed for secondary outcomes we cannot assess the likelihood of a type 1 error (i.e. finding something which is not there).

Even if UPA is more effective than LNG for EC used under trial conditions, there are good reasons (costs aside) to remain cautious about the use of UPA:

1. Post-implantation use of LNG has not been associated with any harm to an early pregnancy. This still needs to be shown for UPA.
2. Information provided on ClinicalTrials.gov (No. NCT00551616) explains that the recent[3] study specifically excluded women who intended to use hormonal or used contraception during the current cycle. While the same criteria were used for the WHO multicentre trial[5] it is unlikely that the use of hormonal contraception started at the time of LNG EC would reduce the effectiveness of EC or vice versa. This is important as there is a high risk of subsequent conception in the current cycle in women receiving EC.[7] In a commentary in the January 2010 issue of this Journal, Cameron and Glasier[8] appear to suggest that hormonal contraception can also be started at the time of UPA EC. This may not be the case, as there are at least theoretical reasons why the combination of a progestogen and a PRM at the same time might cancel each other out. As the use of hormonal contraception was specifically excluded in the recent RCT it is only possible to speculate how UPA and hormonal contraception affect each other. The serum half-life of UPA may only be 32.4 hours[9] but its biological effects last a lot longer. When given in the immediate pre-ovulation period it prevents ovulation for 5 or more days in 59% of cases.[10] Similarly, it might affect the effectiveness of hormonal contraception for an uncertain period of time. While we know that there are no adverse interactions between LNG and hormonal contraception, we cannot even estimate the effect of UPA on the effectiveness of 'quickstart' hormonal contraception and vice versa.
3. UPA is a cousin of mifepristone, and it is at least conceivable that women may access it under the pretext of EC with the intention of terminating an early pregnancy. UPA (30 mg) (ellaOne®) taken as EC does not appear to interrupt a pregnancy, and the same number of pre-EC pregnancies occurred in the UPA and LNG arms of the recently published RCT.[3] It will, however, not be long before it will become common knowledge that to get more than one dose of ellaOne one will need to present to more than one clinic. This may be an attractive proposition for women who cannot access a termination on the National Health Service. A drug that can induce abortions would also have a real value on the black market. To prevent this we should consider pregnancy testing prior to administration of ellaOne under direct supervision.

The purpose of EC is to prevent unplanned pregnancy. In most cases this can best be achieved if EC can be combined with ongoing contraception. As this has not been studied we do not know how the combination of UPA and hormonal contraception will affect the effectiveness of EC or ongoing contraception. At least for the combination of EC with LNG with an immediate depot medroxyprogesterone acetate (DMPA) start there is strong evidence of reduced pregnancy rates.[11] Even now for the purpose of prevention of unplanned pregnancy in women presenting for EC, LNG plus 'quickstart' DMPA remains the most evidence-based approach for women who do not wish to have an intrauterine device fitted.

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