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Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen

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Summary

Recent concern about the safety of combined oral contraceptives (OCs) with third-generation progestagens prompted an examination of data from a population-based case-control study (Leiden Thrombophilia Study). We compared the risk of deep-vein thrombosis (DVT) during use of the newest OCs, containing a third-generation progestagen, with the risk of "older" products. We also investigated the influence of family history of thrombosis, previous pregnancy, age, and the thrombogenic factor V Leiden mutation.

We selected 126 women with DVT and 159 controls aged 15–49 (mean age 34.9) and premenopausal and found, as compared with non-users, the highest age-adjusted relative risks to be that for an OC containing desogestrel and 30 µg ethinyloestradiol (relative risk [RR] 8.7, 95% CI 3.9–19.3). We found lower relative risks for all other types of OC, ranging from 2.2 to 3.8. In a direct comparison, users of the desogestrel-containing oral contraceptive had a 2.5-fold higher risk (95% CI 1.2–5.2) than users of all other OC types combined. The relative risk for the desogestrel-containing OC was similar among women with and without a family history—ie, preferential prescription because of family history cannot explain our findings. Nor could the excess risk be explained by previous pregnancy, and it was highest in the youngest age categories, where we would expect most new users. The age-adjusted RR for the desogestrel-containing contraceptive was 9.2 (3.9–21.4) among non-carriers of the factor V Leiden mutation and 6.0 (1.9–19.0) among carriers of the mutation. This latter risk is superimposed on the 8-fold increased risk of venous thrombosis for carriers

of the factor V Leiden mutation. The risk of carriers using the desogestrel-containing OC as compared with non-carrier non-users will therefore be increased almost 50-fold.

Use of low-dose OCs with a third-generation progestagen carries a higher risk of DVT than the previous generation of OCs. The absolute risk of DVT associated with these OCs seems to be especially high among carriers of the factor V Leiden mutation and among women with a family history of thrombosis. However, the higher risk associated with OC with a third-generation progestagen compared with previous generations was also present in women without factor V Leiden and with no family history.

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See Editorial page 1569 and Commentary page 1570

Introduction

Since the early 1960s it has been known that oral contraceptives (OC) increase the risk of venous and arterial thrombosis. Efforts to reduce the risk by decreasing the oestrogen content have proved successful.^{1–4} Third-generation progestagens were introduced in an attempt to lower further the risk of cardiovascular side-effects. These new progestagens include desogestrel, gestodene, and norgestimate.^{5,6} Since these progestagens had less androgenic metabolic effects and did not adversely affect the lipid profile, it was thought that they might carry a lower risk of cardiovascular diseases than older progestagens such as levonorgestrel, lynoestrenol, and norethisterone.^{5,7}

There is no evidence yet from studies with clinical endpoints that these new progestagens do reduce the risk of cardiovascular diseases. Most studies of combined OCs containing the new progestagens have been small comparative trials on surrogate endpoints such as coagulation pattern and fibrinolytic and lipid levels in healthy young women.^{3,7}

Uncertainty about the safety of the newest low-dose OCs prompted us to reanalyse data from a case-control study. We focused on the possibility that OCs with a low dose of ethinyloestradiol and a third-generation progestagen would carry a greater risk of venous thrombosis than OCs containing similar doses of ethinyloestradiol but other progestagens. We also looked for alternative explanations, by investigating the effect of a

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positive family history of venous thrombosis, a history of pregnancy, and age. A positive family history of deep-vein thrombosis (DVT) might lead to a preferential prescription of a new low-dose OC. Women who have ever been pregnant have been exposed to higher oestrogen levels and might differ in other aspects from those who were never pregnant. Duration of use may also be a factor so we did an analysis among the youngest women, most of whom will be new users.

Factor V Leiden mutation, which leads to resistance to activated protein C and is commonly found among patients with venous thrombosis (20% carriers), displays a strong interaction with use of OCs, all types combined. In non-carriers who use OCs the risk of thrombosis is increased 4-fold, but the risk rises to 30–50 fold in users of OCs who also carry the factor V Leiden mutation.⁸

Patients and methods

The patients and methods have been described previously.^{8,9} We invited 474 consecutive patients (both sexes) with a first episode of proven DVT, diagnosed objectively between Jan 1, 1988 and Dec 31, 1992, who were aged less than 70 and who were not known to have malignant disorders. Patients had been selected from the files of three anticoagulation clinics in the Netherlands, which monitor anticoagulant treatment in all patients within a well-defined geographical area. For each thrombosis patient we invited one age and sex matched healthy control.

For the present analysis we selected only premenopausal women, aged 15–49 (mean age: 34.9), who were at the time of their thrombosis (or similar date for a control) not pregnant, nor in the puerperium, had not had a recent miscarriage, and had not used injectable progestagens.⁸

Information on the type of OCs used at the time of the thrombosis (or index date in the control) was obtained from the interview supplemented with data from the hospital discharge letter. This led to complete information on OC type in 95% of the 174 users.

We limited the analysis to types of OCs for which sufficient cases and controls were available (ie, 5 or more case and controls). We left out of the analysis a total of 20 cases and 10 controls who used the following preparations: monophasic 30 µg ethinyloestradiol and gestodene, 50 µg mestranol and norethisterone, 35 µg ethinyloestradiol and cyproterone acetate, biphasic ethinyloestradiol and desogestrel, and ethinyloestradiol and lynoestrenol. We also discarded data from 9 women (cases) in whom the type of OC remained unknown. Thus 29 cases and 10 controls were left out of the analysis.

Because the choice of OC might have been influenced by the perception of an increased risk known through a family history of venous thrombosis, we took family history into account. We called a family history "positive" when venous thrombosis was reported in one or more parents or siblings by the patient or control.

Presence of the mutant factor V Leiden gene was determined¹⁰ by technicians who did not know if the sample was from a patient or a control or from an OC user or non-user.

We analysed data from 285 women (126 cases and 159 controls) on current use of OCs at their thrombosis or index date. The OC types were classed as: (1) monophasic, containing 30 µg ethinyloestradiol and 150 µg desogestrel; (2) monophasic, containing 30 µg ethinyloestradiol and 150 µg levonorgestrel; (3) monophasic, containing 50 µg ethinyloestradiol and 125 µg or 250 µg levonorgestrel or 1000 µg lynoestrenol; (4) triphasic, containing ethinyloestradiol and levonorgestrel or norethisterone; or (5) monophasic, containing 35 µg or 37.5 µg ethinyloestradiol and 1000 µg norethisterone or 750 µg lynoestrenol.

To assess the risk of different types of OC among factor V Leiden positive and negative cases, we used the complete control group as a reference for frequency of OC use, because at the time these contraceptives had been prescribed for the women in our study factor V Leiden was unknown. The complete control

Type of OC		Cases/controls	RR
Amount of ethinyloestradiol	Type of progestagen		
30 µg	Desogestrel	37/15	8.7 (3.9–19.3)
30 µg	Levonorgestrel	20/18	3.8 (1.7–8.4)
50 µg	Levonorgestrel or lynoestrenol	8/6	3.4 (1.1–10.7)
Triphasic (30–40 µg)	Levonorgestrel or norethisterone	7/11	2.2 (0.8–6.5)
35 µg	Norethisterone	8/5	3.8 (1.2–12.5)
37.5 µg	Lynoestrenol		
No OCs		46/104	1.0

29 cases and 10 controls using types of rarely used OC for which no meaningful analysis was possible, or for whom the type of OC used was unknown, were left out of this analysis

Table 1: Numbers of cases and controls and age-adjusted RR (95% CI) for DVT according to type of OC used at time of thrombosis

group thus represents the best estimate of the population use of the various types of OCs.

Although the original data were age-matched we did an unmatched analysis. Because of the inclusion criteria and the age cut-off, many pairs were no longer intact in the database for this analysis. Since the analysis was restricted to the matching factor sex, we adjusted for confounding by the other matching factor (age) by controlling for age by logistic regression. Age was entered as a continuous variable (in years); use of a categorised dummy variable model led only to trivial differences for the estimators of interest.

Results

Table 1 shows the number of cases and controls using the various OC types and age-adjusted relative risks (RR, all relative to non-users). The highest RR of 8.7 was for the desogestrel-containing monophasic OC. For all other types of OC the RR was between 2.2 and 3.8. Too few women were using contraceptives containing gestodene or norgestimate to permit meaningful conclusions. Direct comparison of two OCs with identical oestradiol content (30 µg ethinyloestradiol) but with a different progestagen (ie, desogestrel *vs* levonorgestrel) revealed a 2.2-fold increased risk associated with desogestrel (95% CI 0.9–5.4). When we compared the OC containing desogestrel and 30 µg ethinyloestradiol with all other types combined the age-adjusted RR was 2.5 (1.2–5.2).

A family history of thrombosis was present in 41 cases and 23 controls (RR=2.9 [1.6–5.1]), indicating a higher baseline risk in women with a positive family history. When we restrict the analysis to patients and controls with a positive family history, the age-adjusted RR (*vs* non-users) for the desogestrel-containing product was 7.2 (1.2–42.1) and for the levonorgestrel-containing product it was 3.9 (0.6–24.6). For women with a negative family history, the RRs were 8.0 (3.2–20.1) and 3.3 (1.3–8.5) respectively.

Of the cases and controls with a positive family history 17% (11/64) carried the factor V Leiden mutation while the mutation was found in only 8% (18/221) of cases and controls without a family history. When we adjusted for all these variables jointly, by entering age, factor V Leiden mutation, and family history in a logistic model, the RRs associated with the various OCs remained essentially the same and the 2-fold higher risk for desogestrel persisted when we contrasted the desogestrel-containing OC to the levonorgestrel-containing one.

Further adjustment for history of pregnancy did not change the estimates. Among women who have never been pregnant RRs of 20.8 (4.8–90.2) for the desogestrel OC and 7.7 (1.8–32.9) for the levonorgestrel product

Type of OC		Cases		RR	
Amount of ethinyloestradiol	Type of progestagen	Factor V positive	Factor V negative	Factor V positive	Factor V negative
30 µg	Desogestrel	8	29	6.0 (1.9-19.0)	9.2 (3.9-21.4)
30 µg	Levonorgestrel	3	17	1.9 (0.4-8.5)	4.2 (1.8-9.7)
50 µg	Levonorgestrel or lynoestrenol	1	7	1.8 (0.2-16.3)	3.9 (1.2-12.9)
Triphasic (30-40 µg)	Levonorgestrel or norethisterone	1	6	1.0 (0.1-9.4)	2.6 (0.8-8.0)
35 µg	Norethisterone	2	6	4.1 (0.7-24.0)	3.8 (1.1-13.6)
37.5 µg	Lynoestrenol	1	1	1.0	1.0
No OCs	...	10	36	1.0	1.0

29 cases and 10 controls using types of rarely used OC for which no meaningful analysis was possible, or for whom the type of OC used was unknown, were left out of this analysis.

Table 2: Numbers of factor V positive and factor V negative cases and age-adjusted RR (95% CI) for DVT with total control group as reference population, according to type of OC used at time of thrombosis

(both with similar amounts of ethinyloestradiol) were found. Among ever-pregnant women we found RRs of 5.1 (1.7-15.3) and 3.0 (1.0-9.6), respectively, compared with non-users.

When we restricted the analysis to the youngest women, where most new users will be found, we found the highest risks for the desogestrel-containing OC, relative to levonorgestrel. Among women aged 15-19 the risk of the desogestrel-containing OC was 7-fold higher than that of the levonorgestrel-containing product; among women aged 20-24 the risk was 4-fold higher.

Table 2 shows age-adjusted RRs for factor V Leiden carriers and non-carriers. We must stress that the risk of the OC is superimposed on the baseline risk.⁸ The baseline risk is much higher (8-fold) in carriers of the factor V Leiden mutation than among non-carriers, so that the RR of 6.0 (1.9-19.0) leads to a much larger overall effect in factor V positives than in the factor V negatives (RR 9.2 [3.9-21.4]). The risk of carriers who use the desogestrel-containing OC, compared with non-carrier, non-users, will therefore be increased almost 50-fold. Contrasting the different OC groups, we found that, relative to 30 µg ethinyloestradiol OCs with levonorgestrel, the newer progestagen carries a 3.5 (0.8-15.9) higher risk among factor V positives (age-adjusted analysis) and only a 2.1 (0.8-5.3) higher risk among factor V negatives. Table 2 shows that the combined RR of all other types of progestagen is lower in factor V positives.

We found no factor V Leiden positive controls who used OCs, and 4% carriers among non-users controls. Among the cases, the factor V Leiden mutation was present in 22% of non-users, also in 22% of users of desogestrel-containing OCs and in 15% of levonorgestrel (30 µg ethinyloestradiol) containing OCs. Even though the absence of mutant gene carriers among the users of OCs in the controls render analysis with an interaction term in a regression model impossible, these data again point to a high risk associated with the combination of factor V Leiden carriership and use of a desogestrel-containing OC.

Discussion

We found that a new low-dose OC with a third-generation progestagen has a higher risk of DVT than OCs with previous generations of progestagens. This effect is enhanced by factor V Leiden mutation and by a family

history of venous thrombosis. However, neither factor V Leiden nor the family history explains all of the excess risk of a third-generation progestagen, since the risk was also increased in women without the factor V Leiden mutation and without a family history of thrombosis.

In this study almost all of the combined OCs with third-generation progestagens contained desogestrel. OCs containing gestodene, norgestimate, or 20 µg ethinyloestradiol were not or only rarely used in the Netherlands during the time period of the investigation. Hence, our conclusions focus on desogestrel but are not necessarily limited to OCs containing this third-generation progestagen.

One objection to the findings might be that the newest OCs have been preferentially prescribed to individuals with the highest risk of thrombosis (confounding by indication). This would mean that the excess risk might be paradoxical but expected and not a consequence of the type of OC. A factor that could lead to such preferential prescription is a positive family history of venous thrombosis. The excess risk was also present in women with a negative family history, however, and a logistic model which was adjusted for family history, factor V Leiden mutation, and age together showed the same relative risks for the various types of contraceptive. Besides family history and clotting defects, there are no generally accepted strong risk factors for DVT in healthy young people that could lead to preferential prescription patterns; smoking seems not a risk factor for venous thrombosis, and obesity and varicose veins are at most a weak risk.^{13,14} It therefore seems unlikely that preferential prescribing can explain the higher risk of DVT with an OC containing a third-generation progestagen, since prescribers cannot readily identify women at high risk.

Because pregnancy is a risk factor for thrombosis that might affect the same women who are "sensitive" to OCs, and since women who have been pregnant may use different brands of OC, we did an analysis adjusted for previous pregnancy (ever/never). This did not change the estimates.

A similar issue is whether part of the observed risk could have been brought about by differences between women who start oral contraception for the first time and those who have used them for some time. Among the youngest users (15-19 years), where most will be recent users, we again found the excess risk for the desogestrel-containing OC.

Our study took place within anticoagulation clinics that serve well-defined geographical areas in the Netherlands where patients with thrombosis are routinely monitored, and consecutive patients with a first objectively diagnosed DVT were enrolled. Therefore the study itself could not have introduced any change in referral patterns, diagnostic methods, or treatment.

We previously reported an interaction between OC use and factor V Leiden carriership which appeared to be synergistic.⁸ Our current data show that this synergy seems to a large part due to a positive interaction between a desogestrel-containing OC and factor V Leiden mutation. The number of carriers of this mutation, however, was small, especially among control users of OCs, which made an analysis of the interaction in an age-adjusted model impossible and also led to estimates with a considerable statistical uncertainty. The meaning of the finding is open to interpretation: on the one hand, it might simply imply that carriers of the mutation are at a

higher risk when using OCs because of a multiplication of risks. If so the factor V Leiden mutation would only indicate a subgroup with a higher baseline risk, such as family history. On the other hand, this finding might give a clue about the mechanism of the thrombogenic nature of these contraceptives and should prompt further research—first, to confirm the finding of a synergistic effect and second to study the effect of different types of OC on the haemostatic system, also in women without apparent genetic abnormalities since their risk too was increased by OCs containing a third-generation progestagen.

When we come to look back on the history of oral contraception it is certain that the decrease in the dose of ethinyloestradiol will be seen to have contributed to a reduced thrombotic risk, especially for arterial disease.^{3,13,14} However, the use of a third-generation progestagen does seem to have led to an unexpected and yet unexplained return of a higher risk of venous thrombosis.

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Efficacy of traction for non-specific low back pain: a randomised clinical trial

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Summary

Previous trials to assess the efficacy of lumbar traction for back pain have been methodologically flawed. To avoid these shortcomings, we conducted a randomised controlled trial in which high-dose traction was compared with sham traction. The sham traction was given with a specially developed brace that tightens in the back during traction. To the patient, the experience is that of traction. The patients and outcome assessor were blinded for the assigned treatment.

151 patients with at least six weeks of non-specific low back pain were randomised. Intention to treat analysis showed no differences between the groups on all outcome measures (patients' global perceived effect, severity of main complaints, functional status and pain); all 95%

confidence intervals included the value zero. The number of withdrawals from treatment, loss to follow-up, and protocol deviations was low. Consequently, the per-protocol analysis showed results similar to the intention to treat analysis. Subgroup analyses did not show any group for which traction might seem promising.

Our data do not support the claim that traction is effective for patients with low back pain.

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Introduction

Each year 5% of the population in industrialised countries experience an episode of low back pain (LBP)^{1,2} for which there is no consensus about treatment. The efficacy of many physiotherapeutic interventions is questionable.^{3–5} One of the treatment options is traction (motorised or manual), which can be combined with other techniques, such as massage, exercises, electrotherapy, or heat.³

The supposed mechanical effects of traction are vertebral separation and widening of the intervertebral foramen.^{6–9} These mechanisms suggest short-term rather than long-term effects or benefits.^{10,11} Part of the applied traction force is needed to overcome opposing forces, namely friction of the body on the table-top, muscle contraction, spinal curvatures, ligamentous resistance and

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