

Risk of Venous Thrombosis With Use of Current Low-Dose Oral Contraceptives Is Not Explained by Diagnostic Suspicion and Referral Bias

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Background: The magnitude of the relative risk of venous thrombosis caused by low-dose oral contraceptive use is still debated because previous studies might have been affected by diagnostic suspicion and referral bias.

Methods: We conducted a case-control study in which the effect of diagnostic suspicion and referral bias was excluded. The study was performed in 2 diagnostic centers to which patients with clinically suspected deep vein thrombosis of the leg were referred. History of oral contraceptive use was obtained before objective testing for thrombosis. Young females with an objective diagnosis of deep vein thrombosis were considered case patients, and those who were referred with the same clinical suspicion but who had no thrombosis served as control subjects. Participants were seen between September 1, 1982, and October 18, 1995: 185 consecutive patients and 591 controls aged 15 to 49 years with a first episode of venous thrombosis and without malignant neoplasms, pregnancy, or known inherited clotting defects.

Results: The overall odds ratio for oral contraceptive use was 3.2 (95% confidence interval [CI], 2.3-4.5); after adjustment for age, family history of venous thrombosis, calendar time, and center, the odds ratio was 3.9 (95% CI, 2.6-5.7). In the idiopathic group (120 patients and 413 controls, excluding recent surgery, trauma, or immobilization), the odds ratio for oral contraceptive use was 3.8 (95% CI, 2.5-5.9); after adjustment, the odds ratio was 5.0 (95% CI, 3.1-8.2).

Conclusions: In this study, in which patients and controls were subject to the same referral and diagnostic procedures, we found similar relative risk estimates for oral contraceptive use as in previous studies. We conclude that diagnostic suspicion and referral bias did not play an important role in previous studies and that the risk of venous thrombosis with use of current brands of oral contraceptives still exists.

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SEVERAL developments have generated renewed interest in the risk of venous thromboembolism associated with the use of oral contraceptives.¹ Results of recent large case-control studies²⁻⁵ in different parts of the world show that the relative risk of venous thromboembolism associated with low-dose oral contraceptive use is still elevated 3- to 4-fold. The risk is reported³⁻⁶ to be even higher for use of preparations containing newer progestins. In addition, females who carry the factor V Leiden mutation and use oral contraceptives have a venous thrombosis risk that might be elevated 30-fold or more⁷ compared with nonusers without such a mutation.

Although most physicians accept the reality of the association between oral contraceptive use and venous thromboembolism, most also think that the reported risks may be overestimated because of diagnostic suspicion and

referral bias.⁸⁻¹³ The mechanism of these biases is that physicians would more readily suspect venous thrombosis in oral contraceptive users than in other patients, or, as stated in a textbook^{14(p1283)} about hemostasis and thrombosis, "knowledge that the patient with leg pain is taking the oral contraceptive pill could easily sway the examining physician to make a clinical diagnosis of deep-vein thrombosis." If physicians preferentially diagnose or refer females taking oral contraceptives, the risk of thrombosis associated with oral contraceptive use will be overestimated. This view is echoed in a recent review¹⁵ wherein the risk of venous thrombosis with oral contraceptive use is accepted but judged to be too high.

Calculations of the risk-benefit of screening for the factor V Leiden mutation or other thrombophilic tendencies, and discussions about the risk-benefit of newer "third-generation contracep-

PARTICIPANTS AND METHODS

STUDY SETTINGS

The 2 centers (the Academic Medical Centre of the University of Amsterdam and the Amsterdam Thrombosis Service and Laboratory for General Practitioners, Amsterdam, the Netherlands) have offered a diagnostic service for patients with clinically suspected deep vein thrombosis of the legs for general practitioners and other physicians since 1982 for the larger part of Amsterdam.¹⁷⁻¹⁹ Females were included in the study from September 1, 1982, until October 18, 1995, at which date the Committee on Safety of Medicines in the United Kingdom issued a statement about the differential risk of oral contraceptive types.²⁰ This was covered extensively in the European media and could have led to a change of prescription patterns after October 1995.

STUDY ASSESSMENT

At presentation, a medical history, including use of oral contraceptives, was obtained by nurses using an existing questionnaire before clinical evaluation and diagnostic tests were performed. The medical history included questions about recent surgery, immobilization, trauma, pregnancy, puerperium, and malignant neoplasms. A personal and family history of venous thrombosis was also obtained, and medication intake, use of oral contraceptives, use of sex corticosteroids other than oral contraceptives, and a previous diagnosis of coagulation abnormalities were recorded routinely by the nurses. After completion of the forms, participants were seen by a physician, and diagnostic investigations were performed by technicians. The diagnostic tests used were serial impedance plethysmography or real-time B-mode ultrasound supplemented, if necessary, by contrast venography. In most participants, serial impedance plethysmography or real-time B-mode ultrasound examination was performed on days 1, 2, 7, and 10 and 3 months after referral.¹⁷⁻¹⁹

PARTICIPANTS

During the study period, 1374 females aged 15 to 49 years were seen at the 2 centers. We excluded those without clinical symptoms (those who were seen because of a history of familial thrombosis or fear of recurrence [$n = 73$]), those

with venous thrombosis at sites other than the legs (eg, chest symptoms, suggesting pulmonary embolus without leg symptoms [$n = 51$]), those with a history of previous deep vein thrombosis or pulmonary embolism ($n = 253$), and those already known (at their first visit) to have inherited clotting defects (eg, antithrombin, protein C, or protein S deficiency or the factor V Leiden mutation [FV R506Q]) ($n = 14$). Females were also excluded if they did not have complete data on oral contraceptive use at the first visit or did not have an objective diagnosis after serial impedance plethysmography and real-time B-mode ultrasound examination or for miscellaneous reasons ($n = 63$). For the present analysis, females were also excluded if they were pregnant, postpartum, or postabortum (until 30 days after delivery [$n = 137$]); were known to have malignant neoplasms ($n = 57$); used other sex corticosteroids ($n = 34$); or had other risk factors, eg, intravenous drug use or nephrotic syndrome ($n = 8$). The described categories are not mutually exclusive.

In the final analysis, we included 776 females (185 patients and 591 controls). We subdivided these females into those with idiopathic thrombosis and those in whom other risk factors were present, ie, recent surgery, recent trauma, or recent immobilization.

Because the choice of oral contraceptives might have been affected by the perception of an increased risk through a family history of venous thrombosis, which could lead to prescription bias, we also took family history into account. We considered family history to be positive when the referred females reported venous thrombosis in 1 or more relatives.

STATISTICAL ANALYSIS

Statistical analysis consisted of calculating odds ratios and their confidence intervals. Multivariate analysis by unconditional logistic regression was used to adjust for possible confounders, eg, age, family history of venous thrombosis, time of first visit (calendar time), and center. Age and calendar time were entered as continuous variables (in years); for age and calendar time, use of a categorized dummy variable model led to only trivial differences for the estimators of interest. Family history and center were entered as dichotomous variables. Finally, we analyzed the thrombotic risks associated with use of different brands of oral contraceptives.

tives," become fruitless when one cannot trust the risks derived from epidemiological studies.

To overcome these and other biases, the ideal control group in a case-control study is a so-called phenocopy of the disease group: (a group of) persons who originally sought care with similar signs and symptoms as potential case patients. This ensures that the control group consists of individuals who were subject to the same referral process as patients. That situation is reached when the final diagnosis is made at the end of clinical evaluation by objective means that are completely independent from exposure and original clinical presentation.¹⁶ We found such a situation in the diagnostic procedures of 2 referral centers for patients with clinically suspected deep vein thrombosis. Physicians at both centers evaluated patients who were referred by general practi-

tioners or specialists. At entry, a nurse completed a questionnaire about the patient's antecedents and risk factors, including current oral contraceptive use. At the end of the visit, an objective diagnosis was made by ultrasound examination, plethysmography, or venography. We included females with objectively confirmed diagnoses of deep vein thrombosis as patients (approximately one third of the referred total) and the remainder as controls. The diagnostic situation at these facilities removes all possibility of diagnostic suspicion and referral bias and even interviewer or patient recall bias: future patients and controls are referred by the same physicians with the same diagnostic suspicion; oral contraceptive use is established without knowledge of the final diagnosis; and the final diagnosis is made by means that are independent of diagnostic suspicion, clinical presentation, or use of

Table 1. Clinical Risk Factors of Participants With and Without Deep Vein Thrombosis

Clinical Risk Factors	Participants, No. (%)*		
	With Deep Vein Thrombosis	Without Deep Vein Thrombosis	Total
Surgery	34 (18.4)	104 (17.6)	138 (17.8)
Trauma	22 (11.9)	56 (9.5)	78 (10.1)
Immobilization	9 (4.9)	18 (3.0)	27 (3.5)
None (idiopathic)	120 (64.9)	413 (69.9)	533 (68.7)
Total	185 (100)	591 (100)	776 (100)

*Percentages do not add to 100 owing to rounding.

oral contraceptives. Therefore, a difference in use of oral contraceptives between patients and controls in this design cannot have resulted from selective diagnosis or referral. If it is true that these biases would have resulted in too high estimates in previous studies, we expect lower relative risks in the present study.

RESULTS

The study group consisted of 185 patients with deep vein thrombosis of the legs and 591 controls. The median age of the entire group was 38 years. A total of 529 participants (68.2%) were referred by their general practitioner, the others by various specialists. Distribution between the 2 diagnostic centers was 2:1 (514 participants [66.2%] visited the Academic Medical Centre and 262 participants [33.8%] visited the Amsterdam Thrombosis Service); furthermore, 173 participants (22.3%) had a positive family history of venous thrombosis. We subdivided the participants into those with idiopathic thrombosis and those with other possible risk factors, ie, recent surgery, recent trauma, or recent immobilization (**Table 1**). About two thirds of all participants had none of these risk factors.

TOTAL GROUP

At referral, 55.1% (102/185) of the patients and 27.6% (163/591) of the controls used oral contraceptives (**Table 2**). The odds ratio for current oral contraceptive use was 3.2 (95% confidence interval [CI], 2.3-4.5). After adjustment for age, family history, center, and calendar time (time of first visit), the odds ratio was 3.9 (95% CI, 2.6-5.7).

IDIOPATHIC GROUP

When we restricted the analysis to participants without 1 of the major risk factors for venous thrombosis, the odds ratio became slightly higher: 3.8 (95% CI, 2.5-5.9), which increased to 5.0 (95% CI, 3.1-8.2) when adjusted (**Table 3**).

POSSIBLE CONFOUNDERS

Given the possible effect of the variables—age, family history of venous thrombosis, calendar time, center, and re-

Table 2. Current Use of Oral Contraceptives Among Participants With and Without Deep Vein Thrombosis and Their Adjusted and Unadjusted Odds Ratios*

	Participants, No.		
	With Deep Vein Thrombosis	Without Deep Vein Thrombosis	Total
Oral contraceptive use	102	163	265
No oral contraceptive use	83	428	511
Total	185	591	776

*Crude odds ratio, 3.2 (95% confidence interval, 2.3-4.5); adjusted odds ratio, 3.9 (95% confidence interval, 2.6-5.7), in logistic model with age, family history of venous thrombosis, calendar time, and center.

Table 3. Current Use of Oral Contraceptives Among Participants* With and Without Idiopathic Deep Vein Thrombosis and Their Adjusted and Unadjusted Odds Ratios†

	Participants, No.		
	With Idiopathic Deep Vein Thrombosis	Without Idiopathic Deep Vein Thrombosis	Total
Oral contraceptive use	76	128	204
No oral contraceptive use	44	285	329
Total	120	413	533

*After exclusion of participants with possible other clinical risk factors for venous thrombosis, eg, surgery, trauma, or immobilization.

†Crude odds ratio, 3.8 (95% confidence interval, 2.5-5.9); adjusted odds ratio, 5.0 (95% confidence interval, 3.1-8.2), in logistic model with age, family history of venous thrombosis, calendar time, and center.

ferral by general practitioners or other specialists—on the relation of oral contraceptive use and venous thrombosis, we analyzed these variables in more detail.

Age

The odds ratio for current oral contraceptive use was 3.2 (95% CI, 2.3-4.5) in the total group and 3.8 (95% CI, 2.5-5.9) in the idiopathic group. After adjustment for age, these odds ratios increased to 3.8 (95% CI, 2.6-5.6) and 5.2 (95% CI, 3.2-8.3), respectively.

Family History

Fifty-two (28.1%) of 185 patients and 121 (20.5%) of 591 controls had a positive family history for venous thrombosis. When analyzing the total group of participants with a positive family history for venous thrombosis, the age-adjusted odds ratio for oral contraceptive use was 2.5 (95% CI, 1.2-5.2); for the group of participants with no family history of venous thrombosis, this odds ratio for oral contraceptive use was 4.3 (95% CI, 2.7-6.8). The odds ratios became 3.7 (95% CI, 2.5-5.5) in the total group and 5.0 (95% CI, 3.1-8.2) in the idiopathic group after adjustment for age and family history.

Table 4. Patients and Controls Taking Selected Types of Oral Contraceptives and Their Adjusted Odds Ratios

Type of Oral Contraceptive and Amount of Ethinyl Estradiol	Type of Progestin	Patients, No.	Controls, No.	Odds Ratio (95% CI)*
Monophasic, 50 µg	Lynestrenol, Levonorgestrel, or Norethisterone	8	7	8.7 (2.9-25.8)
Monophasic, 30 µg	Levonorgestrel	18	28	3.7 (1.9-7.2)
Triphasic, 30-40 µg	Levonorgestrel	8	14	3.7 (1.4-9.6)
Monophasic, 30 µg	Desogestrel	22	29	4.9 (2.5-9.4)
Monophasic, 30 µg	Gestodene	5	4	5.2 (1.3-20.6)
Monophasic, 20 µg	Desogestrel	6	1	24.7 (2.8-213.5)
No oral contraceptives	...†	83	428	Reference

*CI indicates confidence interval. Odds ratios were adjusted for age, family history of venous thrombosis, calendar time, and center.

†Ellipses indicate not applicable.

Calendar Time

Because of possible differences in referral, prescription, and management patterns over time, we adjusted for calendar time. The odds ratios became 3.8 (95% CI, 2.6-5.6) in the total group and 5.1 (95% CI, 3.2-8.3) in the idiopathic group when we adjusted for age and calendar time.

Center

The age-adjusted odds ratios for oral contraceptive use in the total group were 5.1 (95% CI, 3.1-8.2) for the Academic Medical Centre and 2.4 (95% CI, 1.3-4.6) for the Amsterdam Thrombosis Service. The odds ratios became 4.0 (95% CI, 2.7-5.8) in the total group and 5.2 (95% CI, 3.2-8.3) in the idiopathic group when we adjusted for age and center.

Referral by General Practitioners

When only those who were initially referred by general practitioners and not by other specialists were analyzed, the odds ratio (adjusted for age, family history, center, and calendar time) was 3.9 (95% CI, 2.4-6.3). The odds ratios became 4.2 (95% CI, 2.9-6.3) in the total group and 5.4 (95% CI, 3.3-8.9) in the idiopathic group when we adjusted for age and referral by general practitioners.

TYPE OF ORAL CONTRACEPTIVES

Complete information about oral contraceptive type was available for 70.9% of 265 users. Only a few (5%-6% of all patients and controls) still used preparations with ethinyl estradiol, 50 µg, which had high relative risks (**Table 4**). All others used low-dose "subfifty" oral contraceptives. The adjusted odds ratio for monophasic levonorgestrel-containing oral contraceptives with ethinyl estradiol, 30 µg (3.7), was similar to our overall estimate (3.9) (Table 4). The odds ratio for the triphasic levonorgestrel preparation was also the same but with a wider CI because of smaller numbers. The odds ratios for all third-generation monophasic contraceptives were higher. In a direct comparison of monophasic third-generation (desogestrel- or gestodene-containing) oral contraceptives with monophasic levonorgestrel-

containing oral contraceptives, the crude odds ratio was 1.5 (95% CI, 0.7-3.2). After adjustment for age, family history, center, and calendar time, the odds ratio was 1.9 (95% CI, 0.8-4.5). The highest odds ratio was for the monophasic third-generation oral contraceptive containing desogestrel, 150 µg, and ethinyl estradiol, 20 µg (Table 4). Of the 6 patients, 1 had Schönlein disease and 1 had hypertension and diabetes. In 2 patients, the family history of venous thrombosis was positive. This risk profile was not different from that of the other patients wherein several long-term ailments that are not direct risk factors for venous thrombosis were present. In our analysis, we had already removed all females with known hereditary clotting defects when they presented for diagnostic tests (see "Participants and Methods" section); otherwise, the odds ratio for this contraceptive would have been even higher. This indicates that preferential prescribing cannot completely explain the high odds ratio. A high odds ratio for this (20 µg) preparation has also been found in 2 other studies.^{5,21} This high odds ratio is similar to the high relative risk for all third-generation contraceptives in new users (first-time users) in the World Health Organization study²² and probably reflects the combination of a "starter" and a "third-generation" effect.²³

COMMENT

In this case-control study within a large database of referred females, in which the referral and diagnostic strategies for patients and controls were the same, we found that use of currently available oral contraceptives increases the risk of venous thrombosis 3- to 5-fold. This finding is fully consistent with that of earlier observations.^{2-4,7-10,24-34}

Diagnostic suspicion and referral bias is hypothesized to be the result of the awareness of females and their physicians of the association between oral contraceptive use and venous thrombosis.^{8-14,31-34} Females who use oral contraceptives would seek health care more readily for certain symptoms than nonusers. General practitioners would more readily refer females with complaints of the leg for diagnostic workup when they are using oral contraceptives. Physicians seeing these referred patients would be more likely to thoroughly investigate them and to apply objective diagnostic meth-

ods. As a result, females who use oral contraceptives might be more frequently and intensely investigated than are those who do not use oral contraceptives. Therefore, the association with oral contraceptive use would seem stronger than it actually is.^{8-14,31-34}

The situation at the diagnostic centers in which we enrolled patients and controls removes all possibility of diagnostic suspicion and referral bias and even interviewer or patient recall bias. The main difference between our study and previous studies is the choice of control group. In previous studies, only patients with venous thrombosis were referred because of diagnostic suspicion: controls were not referred, and this difference in referral might have led to a difference in oral contraceptive use. In principle, patients in our study were referred similar to those in previous studies, but, unlike in previous studies, controls were referred in the same way as patients because of the same diagnostic suspicion. Any referral selection as to use of oral contraceptives thus was the same in future patients and controls. Furthermore, both centers in the present study formed the basis of several comparative diagnostic investigations, with high sensitivity and specificity¹⁷⁻¹⁹ of the tests used. The diagnostic facilities have operated for more than 10 years under the same protocol, emphasizing the necessity of objective diagnosis in deep vein thrombosis.¹⁷⁻¹⁹ Given the high sensitivity and specificity that were attained, the amount of misclassification will be minimal. In the present study, a substantial proportion of referred females (20%-30%) eventually had an objective diagnosis of deep vein thrombosis. If diagnostic suspicion and referral biases had affected previous studies, we had expected to find clearly lower odds ratios in the present study. However, we still found a 3- to 5-fold increased risk, with reasonably small confidence intervals. Therefore, we conclude that diagnostic suspicion and referral bias did not affect previous studies to the extent that has been suggested.

That diagnostic suspicion and referral bias might have led to an overestimation of the association between oral contraceptive use and venous thrombosis was hypothesized in the late 1960s.⁸⁻¹⁰ This bias was a theoretical concept that has never actually been shown to be present in case-control and follow-up studies of oral contraceptive use and venous thrombosis. It was hypothesized that this bias would mostly affect the risk estimates among patients with least-evident disease⁸ because the "clue" of oral contraceptive use might have been necessary for diagnosis. Therefore, in older studies, patients were classified by degree of certainty of the presence of thromboembolism. However, the association with oral contraceptive use was, if anything, higher among the definite and severe cases, which runs counter to the idea of diagnostic suspicion and referral bias,^{2,4,5,8-10} but was not totally conclusive. In the literature, we found 1 recent study³⁵ of similar design as ours but with much fewer patients (9 patients). A relative risk of 6.4 was found but with a large CI (95% CI, 1.2-34.2).³⁵

In our study, the odds ratio for oral contraceptive use in the total group of participants was between 3- and 4-fold. Statistical adjustment for age gave higher odds ratios for oral contraceptive use. In the idiopathic group

(ie, in which participants with other possible clinical risk factors, eg, surgery, trauma, or immobilization, were excluded), the odds ratio for oral contraceptive use was slightly higher, about 5-fold, a difference that has been documented previously.^{9,25} Only 5% to 6% of our study population still used older preparations containing ethinyl estradiol, 50 µg. Our results are fully in agreement with those of recent studies²⁻⁷ on the relation of low-dose oral contraceptive use and venous thrombosis, which in turn indicates that the findings in those studies were not affected by diagnostic suspicion and referral bias. Thus, risk estimates from several recent studies can be used for risk-benefit analyses on low-dose oral contraceptive use and should not be seen as overestimated. Comparing the results of our study with those of older studies¹ that show odds ratios between 2 and 11, it is also clear that the introduction of low-dose combined oral contraceptives may have led to some decrease in risk—because we also found higher risks for 50-µg preparations in our study—but that this decrease has been less than expected.

To address the possibility of another bias, the prescription bias, we removed from the present analysis females who were known to have inherited clotting defects, such as antithrombin, protein C, or protein S deficiency or the factor V Leiden mutation at their first visit. Furthermore, we adjusted for a positive family history, considered to be present when 1 or more relatives had an episode of venous thromboembolism in the past. This adjustment did not alter the estimators, which is consistent with previous findings⁶ and supports the conclusion that prescription bias is unlikely to affect the findings.

Recently, it has been shown that oral contraceptives containing a newer (third) generation of progestins (desogestrel and gestodene) have a higher relative risk of venous thrombosis compared with older progestin preparations (mainly vs levonorgestrel).³⁻⁶ Also, for this finding, the effect of diagnostic suspicion and referral bias was considered as an explanation.^{21,36-39} Although the numbers are small and the type of contraceptive was not known in all participants, the results of our study are compatible with an increased risk of third-generation (desogestrel and gestodene as progestins) and relative to second-generation (levonorgestrel as progestin) products.³⁻⁶ The excess in relative risk could not be explained by a positive family history of venous thrombosis, clotting defects, or age.⁶

In previous investigations,^{1,4,21,39} diagnostic suspicion and referral bias were the only biases that seemed impossible to overcome. In our study, in which patients and controls were subject to the same referral and objective diagnostic procedures, which also ruled out recall and information bias, we found that these biases do not play a major role in assessment of the venous thrombosis risk associated with oral contraceptive use. We conclude that the risk of deep venous thrombosis with use of current low-dose brands of oral contraceptives still exists.

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