Oral Contraceptives and Venous Thromboembolism: A Case-Control Study Designed to Minimize Detection Bias

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Background: **Previous epidemiologic studies of venous thromboembolism and oral contraceptive use are susceptible to bias in the detection of venous thromboembolic events. This case-control study uses a unique design to minimize the influence of detection bias.**

Methods: **Nonpredisposed women younger than the age of 40 years who underwent pulmonary angiography, lower extremity venography, or lower extremity duplex Doppler sonography at a large urban hospital were classified into a case group or control group based on results of their diagnostic studies. Medical records were reviewed for a history of current oral contraceptive use.**

Results: **Fifty-seven women met the study criteria during the 11-year study period. Seven of 9 women in the case group and 17 of 48 women in the control group were currently using oral contraceptives (odds ratio 6.38; 95 percent confidence limits 1.19, 34.2).**

Conclusions: **The association previously noted between venous thromboembolism and oral contraceptive use is not due to bias in the detection of venous thromboembolic events. (J Am Board Fam Pract 1997;10:315-21.)**

Both case-control[1-16] and cohort[17-31] studies have consistently found an association between oral contraceptive use and venous thromboembolism, ie, deep vein thrombosis or pulmonary embolism. Relative risk estimates from these studies have ranged from about 2 to 11, with the largest cohort study indicating a relative risk of 4.2 (95 percent confidence limits of 2.1, 10.9) for idiopathic leg deep vein thrombosis.[19]

Careful evaluation of these epidemiologic studies reveals systematic, potentially serious sources of bias.[32,33] The most consistent and glaring weakness found in both case-control and cohort studies is the potential for bias in the detection of venous thromboembolism among patients using oral contraceptives compared with those not using oral contraceptives.[32]

Women using oral contraceptives undergo closer medical surveillance than women not using oral contraceptives, [17] and women using oral contraceptives and their physicians can be particularly prone to notice symptoms, suspect serious abnormalities, and order diagnostic tests. Because venous thromboembolism is so often clinically silent or misdiagnosed,[34-43] this greater likelihood for patients using oral contraceptives to undergo diagnostic testing can produce the appearance of a higher rate of events compared with women not using oral contraceptives, even when the actual rate is the same.

Unfortunately, none of the case-control or cohort studies published has been able to avoid this potential source of bias.[32,33] The cohort studies are not double-blind; the ordering of such tests as venograms, duplex Doppler studies, and pulmonary angiography can be influenced by the contraceptive method. In the case-control studies both the case groups and control groups are drawn from populations in which women using oral contraceptives are more likely than women not using oral contraceptives to undergo testing for venous thromboembolism, simply because of their contraceptive method.

The current study was undertaken to assess whether the association between oral contracep-

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tive use and venous thromboembolism persists when using a new case-control study design that limits such vulnerability to detection bias. Patients in this study were women who had contrast venography, pulmonary angiography, or duplex Doppler ultrasound examination to exclude or diagnose venous thromboembolism. Patients whose test results were positive made up the case group, and those with negative test results were the control group. By selecting for the control-group-only patients who have undergone testing (with negative results), the tendency to detect disease among women using oral contraceptives should apply to both control and case groups.

In the clinical encounter before performing such a diagnostic procedure, any tendency to observe and examine women using oral contraceptives more closely than women not using oral contraceptives would likely occur equally in the women who turn out to be in the case group and those who end up in the control group. Although women using oral contraceptives might be more likely than women not using oral contraceptives to undergo diagnostic testing, as long as this tendency does not differ between those in the case group and those in the control group, detection bias will not be introduced.

This study is the first to have used such a study design. An association between oral contraceptive use and venous thromboembolism that persists in this study would be strong evidence that the association noted in previous studies was not solely due to bias in the detection of venous thromboembolism. A finding of no association would suggest that the findings of previous studies might be a result of bias rather than of a real association.

Methods

The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. Women younger than 40 years who underwent (1) lower extremity contrast venography, (2) pulmonary angiography, or (3) duplex scanning (real-time B-mode sonography with concomitant use of color-enhanced Doppler flow imaging) of the lower extremity at University Hospital in San Antonio from January 1983 to May 1994 were singled out from the Radiology Department "Special Procedures" log books. Women undergoing ventilation-perfusion lung scanning were not included because of concerns about the poor sensitivity and limited predictive value of this procedure.[39,44]

Patients were excluded from the study based on the following criteria established before the study was conducted. Patients were excluded if their diagnostic study finding was indeterminate, if they were premenarchal, if they had a known condition predisposing to venous thromboembolism, or if there was no clear indication of whether the patient had taken oral contraceptives in the 30 days before the procedure. Predisposed patients were excluded because such conditions often contraindicate oral contraception.

For patients who underwent more than one procedure, the venogram or pulmonary angiogram was preferred as the index procedure. For patients who underwent duplex Doppler studies on more than 1 day, the first study that had positive findings for deep vein thrombosis was used as the index procedure. If none of multiple duplex Doppler studies had positive findings, then the first study was used.

The outpatient and inpatient medical records of all patients were reviewed to ascertain current use of oral contraceptives, defined (prior to conducting the study) as any use within 30 days of the index procedure. This information was obtained without knowledge of the results of the radiologists' rereadings (see below); however, the reviewer (JPR) was not blinded to the original radiologic readings or to the study hypothesis.

Demographic information was abstracted from the medical record. Symptoms, signs, and laboratory abnormalities related to venous thromboembolism were recorded as noted or not noted at the time of examination. In addition, whether the patient was obese, smoked cigarettes, and was taking any current medications was recorded.

All available original films and duplex Doppler studies were independently reread by a radiologist who was unaware of either the patients' exposure history or the original interpretation of the study. Study results were classified, based on standardized criteria, as positive for acute thrombosis or embolism, negative for acute thrombosis or embolism, or indeterminate. Pulmonary angiograms reread for this study were considered to have positive findings if a persistent filling defect was seen within any of the pulmonary arteries in more than one projection. Venograms were considered to have positive findings only when filling

defects were seen within the deep venous system. Duplex Doppler sonograms were considered to have positive findings when there was noncompressibility of a deep vein, a color-flow filling defect, a distended vein, and an absence of Doppler flow signals.

Where the rereading was in conflict with the original reading, additional radiologists who had no knowledge of the patient's contraceptive history were recruited to provide additional readings until two blinded readings were in agreement according to the predetermined criteria. Patients with venograms, Doppler sonograms, or angiograms diagnostic of deep vein thrombosis or pulmonary embolism were classified as the case group, and patients with negative study results were classified as the control group.

Case and control groups were compared in univariate analyses with regard to current oral contraceptive use, race or ethnicity, obesity, current cigarette smoking, signs and symptoms, and number of signs and symptoms recorded (as an index of severity). The chi-square statistic was used to test for significant differences between case and control groups with regard to categorical variables. When one or more cells in these analyses contained expected counts of less than five, a two-tailed Fisher exact test was used. A Student *t*-test was used to test for differences in continuous variables.

The relative risk of venous thromboembolism with current oral contraceptive use compared with that without current use was estimated by calculating the crude odds ratio. Ninety-five percent confidence limits for the odds ratio were calculated using Wolff's method.[45] Logistic regression analysis was performed with venous thromboembolism as the dependent variable and oral contraceptive use, age, Hispanic ethnicity, obesity, and smoking as independent variables. Because ethnicity, obesity, and smoking appeared to be noted inconsistently in the medical records, regression analysis with only oral contraceptive use and age as dependent variables was also performed.

Results

During the 11-year study period, 234 women younger than 40 years of age underwent pulmonary angiography, lower extremity venography, or lower extremity duplex Doppler sonography because of suspicion of deep vein thrombosis or pulmonary embolism. One hundred seventy-seven patients were excluded from the sample, primarily because of predispositions to venous thromboembolism (Table 1).

Table 1. Patients Excluded from the Study, by Reason for Exclusion.

Condition	Number of Patients
Pregnancy	30
Chart not located	29
Previous venous thromboembolism	23
Postpartum*	21
Uncertain oral contraceptive history	13
Cancer	11
Trauma*	8
Immobilization*	7
Surgery*	7
Diabetes mellitus	7
Chronic renal failure	6
Systemic lupus erythematosus	5
Morbid obesity	3
Nephrotic syndrome	2
Chronic osteomyelitis	1
Paraplegia	1
Sickle cell disease	1
Intravenous drug abuse and sepsis	1
Indeterminate study results	1
Total	177

*Within 30 days before the index diagnostic procedure.

Of the remaining 57 patients, 24 had lower extremity duplex Doppler sonograms, 28 had venograms, and 5 had pulmonary angiograms. Films could be located for rereading for 46 patients (80.7 percent). Based on the blinded rereadings of the diagnostic studies, 1 patient was reclassified into the control group rather than the case group. (Notes from the original reading of this patient's duplex Doppler study indicated the test result was considered positive because of the patient's oral contraceptive exposure.)

The basis for ascertainment of oral contraceptive use was a chart note written before the diagnostic procedure for 54 patients (94.7 percent). For three patients the history of contraceptive use was recorded in a note after the procedure was completed.

Characteristics of the case groups and control groups are displayed in Table 2. Little information about marital status or parity was available. Although those in the case group were more likely to be Hispanic and to be obese, these differences were not statistically significant. The most common findings were leg pain (82.5 percent),

Table 2. Characteristics of Women in the Case Group and Control Group.

Variable	Case (n = 9) No. (%)	Control (n = 48) No. (%)	Test of Significance	Crude Odds Ratio (95% CL)
Age, years (mean ± SD)	27.2 (± 8.12)	30.3 (± 5.60)	$t = 1.08$, $P = 0.307$	—
Hispanic ethnicity	7/9 (77.8)	21/48 (43.8)	Fisher exact test (2-tail), $P = 0.16$	3.50 (0.65, 18.9)
Obesity noted	5/9 (55.6)	16/48 (33.3)	Fisher exact test (2-tail), $P = 0.266$	2.50 (0.59, 10.6)
Current smoking noted	3/9 (33.3)	11/48 (22.9)	Fisher exact test (2-tail), $P = 0.674$	1.68 (0.36, 7.85)
Current oral contraceptive use	7/9 (77.8)	17/48 (35.4)	—	6.38 (1.19, 34.2)

CL - confidence limits.

swelling (70.2 percent), edema (66.7 percent), and tenderness (57.9 percent). Only one finding—a difference in leg circumference greater than 1.0 cm—was more common among the patients in the case group ($P = 0.007$).

Of the 57 patients, 9 had positive study results and were thus in the case group, whereas 48 had negative study results (control group). Seven of the 9 case patients and 17 of the 48 control patients were currently using oral contraceptives, with a resultant odds ratio of 6.38 and 95 percent confidence limits of 1.19 and 34.2. Neither adjustment for age alone nor multivariate adjustment materially affected the odds ratio (Table 3).

When the patients whose films could not be located for rereading were excluded, the odds ratio rose to 9.29, falling just short of statistical significance (95 percent confidence limits 0.985 and 87.5). With exclusion of the three patients whose oral contraceptive history was recorded after the index procedure was performed, the odds ratio was essentially unchanged (6.34; 95 percent confidence limits 1.18 and 34.2).

Documentation of the oral contraceptive preparations the patients used was sparse. Of the 24 patients using oral contraceptives, 13 had specific preparations recorded. Twelve of these preparations contained 35 µg or less of estrogen per dose, and one preparation (Ovral) contained 50 µg of ethinyl estradiol per dose. Only 2 of the 7 patients in the case group who were using oral contraceptives had the brand or dosage documented; both of these patients were taking pills with 30 or 35 µg of estrogen.

Table 3. Association of Venous Thromboembolism With Current Oral Contraceptive Use: Odds Ratio (± 95 Percent Confidence Limits).

Crude	Age-Adjusted	Multivariate Adjusted*
6.38 (1.19, 34.2)	5.44 (0.930, 31.9)	6.85 (0.941, 49.9)

*Multivariate analysis = logistic regression using age, Hispanic ethnicity, smoking, and obesity as independent variables.

Discussion

Our study confirms a strong association between idiopathic venous thromboembolism and current oral contraceptive use. Using an innovative design to minimize bias in the detection of venous thromboembolism did not reduce or eliminate the observed association. Because control group as well as case group patients in the current study were women undergoing diagnostic procedures, any tendency toward more intense medical surveillance because of oral contraceptive exposure should apply equally to all patients. Although the current study is small, it addresses a troublesome and pervasive potential source of bias.

Other potential sources of bias should be acknowledged. The original, unblinded readings by radiologists could contribute to detection bias,[46] and we were unable to locate all the films for blinded rereadings. When patients with unlocated films were excluded from our analysis, however, the association between oral contraceptive use and venous thromboembolism was even stronger (odds ratio 9.29), albeit of borderline statistical significance.

Bias in the ascertainment of oral contraceptive exposure is another common problem for case-control studies.[32,46] Nearly all the histories of oral contraceptive use in our study

were recorded before the diagnosis was confirmed, minimizing both recall bias on the part of patients and interviewer bias on the part of physicians. Investigator bias in reviewing medical records is unlikely to be responsible for the study results, since the investigator's conscious bias with this study design was against finding an association. Nevertheless, a systematic method of ascertaining and recording oral contraceptive exposure before the patients' diagnostic study would strengthen the current study design.

The risk of venous thromboembolism is thought to be related to the dosage of estrogen,[10,47-49] and perhaps to the dosage and type of progestogen.[48-53] Most of the epidemiologic studies were performed when oral contraceptive estrogen dosages were higher, but our study adds to recent evidence that an elevated relative risk persists in the era of low-dose prescriptions.[52,53] Recent evidence suggests that 30 to 35 μg of estrogen does not elevate the risk of stroke,[54] but there is no such reassuring evidence about venous thromboembolism.

The absolute risk of venous thromboembolism is small, however: 10 to 30 cases per 100,000 women per year in women using oral contraceptives versus 4 per 100,000 in nonpregnant women not using oral contraceptives.[55] With only nine cases in 11 years from a large urban hospital, our study reinforces the understanding that venous thromboembolism is a rare event among nonpredisposed young women, even those taking oral contraceptives. The small risks of oral contraceptives must be placed in perspective, including weighing their noncontraceptive benefits, particularly since misunderstandings already cause unrealistic fear of oral contraceptives.[56]

The results of this study suggest directions for future research. The study design, using patients undergoing diagnostic procedures to form both the case and control groups, should be replicated in larger populations and in diverse settings. The study design should also be strengthened by collecting data on oral contraceptive use uniformly and prospectively, before the patients undergo the procedures. Films should be read without knowledge of the patient's contraceptive method. Such a study design would be unprecedented in its ability to guard against detection bias.

Adaptations of our study design could be used to investigate urgent questions about weaker associations, such as exogenous hormones and breast cancer.[57] The threat of detection bias could be reduced or eliminated in such studies by deriving the control group, as well as the case group, from women undergoing screening for breast cancer. Epidemiologic studies of these and other purported associations would be strengthened by techniques to reduce vulnerability to bias in the detection of adverse events. Although our study did not refute previous findings, detection bias is still a potential influence in many epidemiologic studies.

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