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IN FOCUS

The RATIO study: oral contraceptives and the risk of peripheral arterial disease in young women

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Summary. With regard to oral contraceptives, much research has concentrated on venous thrombosis and on the coronary and cerebral forms of atherosclerotic disease, while peripheral arterial disease (PAD) has received little attention. In this case-control study, we assessed oral contraceptive use and the risk of PAD in young women using a population-based case-control study. The women were 18–49 years of age, and had been admitted to a collaborating hospital between January 1990 and October 1995, and had a diagnosis of PAD. Participants were patients with PAD ($n = 152$), and control women ($n = 925$), identified by random digit dialing. The diagnosis of PAD was based almost exclusively on intra-arterial angiography. Patients and control subjects filled out the same structured questionnaire, which included questions on medical history, cardiovascular risk factors, and contraceptive use. The adjusted odds ratio for PAD in women using any type of oral contraceptives vs. no use, was 3.8 (95% CI 2.4–5.8). When first generation oral contraceptive use was compared with no use, the odds ratio was 8.7 (95% CI 3.6–21.3). For second and third generation oral contraceptives, the adjusted odds ratios (compared with non-users) were 2.6 (95% CI 1.4–4.9) and 3.0 (95% CI 1.4–6.6), respectively. This is the first study on oral contraceptive use and PAD in humans. All types of oral contraceptives were associated with an increased risk of PAD.

Keywords: epidemiology, oral contraceptives, peripheral arterial disease, risk factors.

The effects of combination oral contraceptives on cardiovascular health of women have been a subject of epidemiological research for more than 35 years [1,2]. These studies pointed to a link between oral contraceptive use and vascular complications, both venous and arterial. The recognition of these adverse vascular events associated with the use of oral contraceptives resulted in several modifications of the dose of estrogen and type of progestagen in combination preparations [3–6].

In 1995, several articles reported that users of third generation oral contraceptives containing gestodene or desogestrel had a twofold higher risk of venous thromboembolic disease than non-users [7–10]. It has been suggested that third generation oral contraceptives would be protective against arterial thrombosis by a favorable effect on the lipid profile: increasing high density lipoprotein (HDL)-cholesterol and lowering low density lipoprotein (LDL)-cholesterol [11,12]. Several studies have been aimed at the coronary and cerebral forms of atherosclerotic disease, but none at peripheral arterial disease (PAD) and its association with oral contraceptive use.

PAD is rare in young women. Co-morbidity in patients with premature onset of PAD is high, and it carries a poor prognosis, with a high incidence of vascular graft occlusion, amputation and death [13,14].

We conducted a case-control study among young women in the Netherlands to assess oral contraceptives as a risk factor for PAD, in which we also investigated dose of estrogen and type of progestagen.

Patients and methods

Study design

The RATIO study (Risk of Arterial Thrombosis In relation to Oral Contraceptives) is a multicenter, population based case control study. The study consists of three substudies for vascular diseases (stroke, myocardial infarction, and PAD) in relation to oral contraceptive use among women 18–49 years of age in the Netherlands. The results for myocardial infarction and stroke are reported separately. The study protocol was approved by the ethics committees of the participating hospitals (see Appendix).

Identification of patients

Women were eligible patients if they were aged 18–49 years, had been admitted to a collaborating hospital between January 1990 and October 1995, and had an angiographically confirmed

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diagnosis of PAD The end date was chosen because at that time several studies presented results of increased risk of venous thromboembolic disease in women, who used desogestrel and gestodene-containing oral contraceptives [15] Consequently, changes in prescription of oral contraceptives may have occurred which could have influenced the results All patients were identified by means of the local Hospital Registration Systems

PAD was diagnosed when patients presented typical symptoms of intermittent claudication (cramping pain of the calves or buttocks during exercise), and had an ankle–arm index in rest less then 0 90 with a decrease of more than 20% after exercise [16] Furthermore, all patients underwent intra-arterial angiography for evaluation of their chronic lower extremity ischemia The arteriograms were reviewed and scored by two radiologists Only patients with an atherosclerotic lesion and as a consequence a luminal diameter reduction of more than 50% were included for analyses This implies that only patients with atherosclerotic peripheral vessel disease were included and patients with only acute thrombotic or embolic occlusion (i e in the absence of atherosclerotic lesions locally), or patients with angiitis were excluded Also patients with a history of cerebral disease, coronary heart disease, or venous thromboembolic disease were excluded, because prescription of oral contraceptives is discouraged in these patients

Of the 198 eligible patients admitted during the study period, 20 women died between diagnosis of PAD and the start of the study in 1996 Of the remaining 178 patients, 13 could not be located despite extensive efforts Therefore, 165 questionnaires were submitted from which 152 (92%) were returned

Control women

This project included three types of arterial disease, i e ischemic stroke, myocardial infarction and PAD, which are reported separately We proceeded to include one large control group to which each of the three groups of patients was contrasted The population-based group of control women was identified by random digit dialing (RDD) [17] In this method, random telephone numbers are dialed, and households are ascertained for eligible (age, sex) individuals, who are subsequently asked to participate Since age, area of residence and calendar year were potential confounding factors, we wished to be able to adjust for these variables as efficiently as possible The control women were recruited in the same geographic areas as the women of the three patient groups combined (six areas of residence widely distributed over the country) and control questionnaires were assigned an index year corresponding to the event years of the three patient groups combined (1990–95) The control group may therefore be seen as a sample of the population that is stratified on age, area of residence and calendar year, and therefore adjustment for these factors is appropriate For the control women, six questionnaires with index years 1990–95 were available to compare the questions concerning oral contraceptive use, history of hypertension, diabetes, hypercholesterolaemia and current smoking for each index year with the patients The index date of each control woman was the first of July of the index year Each control woman completed one questionnaire for one index date

A total number of 1259 eligible women were reached by random digit dialing Control women in the older age groups were oversampled to minimize the age difference between the patients and the control women Because the upper age limit was fixed on 49 years of age, oversampling in the older age group was achieved by increasing the lower age limit from 18 years to 35 years of age, during the final months of control recruitment Of these 1259 controls, 220 (17%) refused to participate The reasons for refusal were no interest (81%) or lack of time (19%) So a questionnaire was sent to 1039 control subjects who were eligible and free of prior cardiovascular disease, 925 questionnaires were returned (73%) To achieve optimal participation in the patient and control group we firstly submitted the questionnaires, and when not returned one telephone call was made to ask why the questionnaire was not returned

Data collection

Patients and control women were asked to fill out the same structured questionnaire comprising questions on demographic characteristics, medical history of cardiovascular risk factors, obstetric history, oral contraceptive use, medication, and a family history of vascular disease Color photographs of all oral contraceptive pills marketed in the Netherlands were used to help women recall specific brands of oral contraceptives used Current oral contraceptive use was defined as use within 1 month before the index date

Oral contraceptives were divided into four categories according to the type of progestagens (i) first generation oral contraceptives, containing lynestrenol and norethisterone, (ii) second generation oral contraceptives, containing levonorgestrel, (iii) third generation oral contraceptives, containing desogestrel or gestodene and (iv) oral contraceptives containing other types of progestagens

Smoking was defined as having smoked in the year before the index date Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2) Obesity was defined as a body mass index $\geq 27\,3\,kg\,m^{-2}$ Women were classified as hypertensive, diabetic or hypercholesterolaemic when they reported a physician's diagnosis or were taking medication for these conditions before the index date Family history of cardiovascular disease was defined as the presence of myocardial infarction, stroke or PAD under 60 years of age in first degree relatives

Statistical analysis

We calculated univariate odds ratios as estimates of the relative risk of PAD with the use of the various categories of oral contraceptives Odds ratios and 95% confidence intervals (95% CI) were calculated by unconditional logistic regression models, and adjusted for the stratification factors age, area of

residence and calendar year In addition, odds ratios were adjusted for putative confounding factors, i e smoking, hypercholesterolaemia, diabetes, hypertension and alcohol use, by multivariate models To allow a fair comparison of third vs second generation progestagens, we limited analyses to oral contraceptives containing 30 μg ethinylestradiol To evaluate the effect of estrogen dose without the influence of the progestagen type we limited analyses to oral contraceptives containing levonorgestrel We also conducted subgroup analyses to assess the possibility of interaction between use of oral contraceptives and major cardiovascular risk factors, such as smoking, diabetes, hypertension, hypercholesterolemia, and obesity In the remainder of the text, all odds ratios are adjusted for the stratification factors age, area of residence and calendar year, unless additional adjustment is mentioned

Results

Table 1 summarizes the characteristics and risk factors of 152 patients with PAD and 925 control subjects The age of the patients varied between 25 and 49 years of age (mean 44 years) Control women were 18–49 years of age (mean age 38 years) Compared with control women, patients had a lower education level and more often reported a history of hypertension, hypercholesterolemia or diabetes A high percentage (92%) of the patients was current smoker at the time of diagnosis Patients more often reported a family history of cardiovascular disease

Table 2 shows the use of different types of oral contracep tives We found 78 patients (51%) and 348 control women (38%) who were current users of oral contraceptives Thirty-four (22%) patients used second generation oral contraceptives and 14 (9%) used third generation oral contraceptives, compared with 173 (19%) and 110 (12%), respectively, in the control group Two control women used hormone replacement therapy

Table 1 Baseline characteristics of young women with peripheral arterial disease (PAD) and control women

	PAD patients ($n = 152$)	Control subjects ($n = 925$)
Age (mean SD)	43 7 (5 8)	38 1 (8 3)
Education		
Primary school or less	(87)	278 (30)
Secondary school	45 (30)	390 (42)
Higher education or university	10 (7)	252 (27)
History of hypertension	45 (30)	56 (6)
History of hypercholesterolemia	30 (20)	24 (3)
History of diabetes	18 (12)	13 (1)
Body mass index (mean SD)	24 2 (4 3)	23 5 (3 9)
Cigarette smoking		
Never	9 (6)	305 (33)
Former	3 (2)	222 (24)
Current	139 (92)	394 (43)
Family history of cardiovascular disease	96 (63)	311 (34)

SD standard deviation Data are number (%) unless otherwise indicated Totals may differ due to missing data

Table 2 Oral contraceptive use in young women with peripheral arterial disease (PAD) and control women

	PAD patients ($n = 152$)	Control women ($n = 925$)
Oral contraceptive use		
All types	78 (51)	348 (38)
First generation	15 (10)	31 (3)
Second generation	34 (22)	173 (19)
Third generation	14 (9)	110 (12)
Other*	11 (7)	28 (3)
Type unknown	4 (3)	6 (1)
No oral contraceptive use	74 (49)	568 (61)
Use unknown	0	7 (1)
Hormone replacement therapy	0	2 (0)

Data are numbers (%) unless otherwise indicated *Including oral contraceptives containing cyproterone norgestimate and progestagen only

The risk of PAD in women currently using any type of oral contraceptives was almost fourfold increased compared with non-users (OR = 3 8, 95% CI 2 4–5 8, adjusted for stratification factors) Further adjustment for putative confounding factors did not affect the estimate

Table 3 shows the adjusted odds ratios for PAD in relation to oral contraceptive use stratified for age categories The risk was clearly elevated in all three age categories

Women who used first generation oral contraceptives had an almost ninefold increased risk of PAD compared with women who did not use oral contraceptives, odds ratio 8 7 (95% CI 3 6–21 3) (Table 4) Compared with non-users, the adjusted odds ratio for PAD in women who used second generation oral contraceptives containing 30 μg ethinylestradiol was 2 6 (95% CI 1 4–4 9) The odds ratio for third generation oral contraceptives with the same amount of ethinylestradiol was 3 0 (95% CI 1 4–6 6) The risk of third generation oral contraceptives containing 30 μg ethinylestradiol did not differ from that of second generation oral contraceptives with the same amount of estrogen (OR 1 1, 95% CI 0 5–2 5) The results did not change when risk estimates were additionally adjusted for putative confounders

The use of oral contraceptives containing higher doses of estrogen (= 50 μg), was associated with an adjusted odds ratio for PAD of 19 8 (95% CI 7 7–51 1) This was much higher than the odds ratio of preparations with low dose estrogens (<50 μg),

Table 3 Odds ratios (95% CI) for peripheral arterial disease (PAD) in relation to oral contraceptive use by age categories

Age (years)	PAD patients ($n = 152$) OC use/no use	Control subjects ($n = 925$)† OC use/no use	OR* (95% CI)
<40	25/7 (78)	249/223 (53)	3 2 (1 4–7 5)
40–44	18/21 (46)	45/125 (26)	2 5 (1 2–5 1)
>45	35/46 (43)	54/220 (20)	3 1 (1 8–5 3)

OC oral contraceptives Data are numbers (%) unless otherwise indicated *Adjusted for stratification factors (area of residence and calendar year) † Nine control women were left out of the analysis oral contraceptive use was unknown in seven women and two women used hormone replacement therapy

Table 4 Adjusted odds ratios (95% CI) peripheral arterial disease (PAD) in relation to different types of progestagens

	PAD patients	Control subjects	OR (95% CI)*	OR (95% CI)†
Any oral contraceptive use	78	348	3 8 (2 4–5 8)	4 0 (2 5–6 3)
First generation use	15	31	8 7 (3 6–21 3)	9 3 (4 0–21 4)
Second generation use‡	20	94	2 6 (1 4–4 9)	2 4 (1 2–4 7)
Third generation use‡	13	91	3 0 (1 4–6 6)	3 3 (1 5–7 3)

OR relative to non users 74 patients and 568 control women *Adjusted for stratification factors (age, area of residence, and calendar year) †Adjusted for stratification factors, hypertension, diabetes mellitus, hypercholesterolemia smoking, and alcohol use ‡Analyses are restricted to oral contraceptives containing 30 μg ethinylestradiol Excluded were 23 women who used oral contraceptives containing 50 μg ethinylestradiol, 59 women who used second generation triphasic oral contraceptives, 17 women who used 20 μg ethinylestradiol and three women who used third generation triphasic oral contraceptives Eleven control women were excluded because of missing data of ethinylestradiol concentration

Table 5 Adjusted odds ratios (95% CI) for peripheral arterial disease (PAD) in relation to different doses of estrogens

	Patients (*n*)	Control subjects (*n*)	OR* (95% CI)
Estrogen dose			
50 μg ethinylestradiol vs no use†	2	10	3 1 (0 4–19 5)
30 μg ethinylestradiol vs no use†	17	94	1 6 (1 1–2 2)
30 μg vs 50 μg ethinylestradiol	17/2	94/10	0 6 (0 1–5 3)

*Adjusted for stratification factors (age, area of residence, and calendar year †OR relative to non-users 74 patients and 568 control women Analyses were restricted to oral contraceptives with 50 μg ethinylestradiol and 30 μg ethinylestradiol and only with the progestagen levonorgestrel

adjusted odds ratio 2 4 (95% CI 1 5–3 9) To evaluate the effect of estrogen dose without the influence of the progestagen type we limited the analysis to brands containing the progestagen levonorgestrel (Table 5) Users of oral contraceptives with 50 μg ethinylestradiol (and 125 μg levonorgestrel) had a 3 1-fold increased risk (95% CI 0 4–19 5) compared with non-users Users of oral contraceptives with 30 μg ethinylestradiol (and 150 μg levonorgestrel) had a 1 6-fold increased risk (95% CI 1 1–2 2) compared with non-users In a direct comparison of preparations with 30 μg and 50 μg ethinylestradiol the adjusted odds ratio was 0 6 (95% CI 0 1–5 3)

Table 6 shows odds ratios associated with oral contraceptive use among patients and control subjects with and without any of the classical cardiovascular risk factors Among non-users, smoking, hypertension, hypercholesterolemia and diabetes clearly increased the risk When combined with the use of oral contraceptives, the relative risks became very high among smokers (OR = 36), hypercholesterolaemic women (OR = 50), and diabetic women (OR = 40), indicating synergistic effects

Discussion

Results of the study

Our study is the first to investigate oral contraceptives as a risk factor for PAD We found that current users of oral contraceptives were at threefold increased risk for PAD in comparison with non-users When first, second and third generation pills were compared with non-users and analyzed separately, we found a highly elevated risk for first generation users, and an almost threefold increased risk for second and third generation

Table 6 Odds ratios for peripheral arterial disease (PAD) in relation to current use of combined oral contraceptives according to other risk factors

	No oral contraceptive use		Oral contraceptive use	
	Patients/controls	OR* (95% CI)	Patients/controls	OR* (95% CI)
Smoking				
No	5/338	1 (reference)	7/183	6 1 (1 5–25 0)
Yes	68/228	19 1 (7 2–50 5)	71/165	35 9 (13 5–95 9)
Hypertension				
No	47/532	1 (reference)	60/327	4 7 (2 8–7 8)
Yes	27/36	4 9 (2 5–9 5)	16/19	8 8 (3 9–19 8)
Hypercholesterolemia				
No	56/547	1 (reference)	64/344	3 8 (2 4–6 1)
Yes	17/20	4 4 (1 9–10 2)	13/3	49 9 (10 4–239 8)
Diabetes				
No	63/556	1 (reference)	69/345	4 1 (2 6–6 5)
Yes	10/11	16 9 (4 9–58 6)	7/2	40 1 (7 5–213 9)
Obesity				
No	52/476	1 (reference)	59/300	3 8 (2 3–6 3)
Yes	18/76	1 8 (0 9–3 5)	22/37	7 9 (3 6–17 6)

*Odds ratios are relative to the reference category and are adjusted for stratification factors (age, area of residence, calendar year) Note totals may differ due to missing data

users Third generation oral contraceptives use resulted in a threefold increased risk (95% CI 1 4–6 6) The risk of oral contraceptives was even more elevated in combination with the presence of risk factors for PAD, i e smoking, hypertension, hypercholesterolemia and diabetes

Effect of other risk factors

Univariate analysis confirmed the established role of smoking as a major risk factor for peripheral vascular disease and of other cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes Only 12 of 152 women were non-smokers This indicates that smoking is a strong risk factor for PAD, and is in fact nearly a condition for its occurrence PAD is a rare disease in young women So, even though oral contraceptives increase risk in non-smokers this will lead to low probabilities of disease However, the combination of smoking and oral contraceptive use revealed an odds ratio of 35 9 (95% CI 13 5–95 9), which suggests a synergetic effect of these two factors Such an effect has previously been reported only for myocardial infarction and stroke [18–24]

Comparison of the results with earlier reports

Although there are no studies on oral contraceptive use and PAD in young women, both clinical and animal-experimental evidence suggests that female steroids have a direct effect on the arterial wall In 1964 Danforth demonstrated histological changes in the wall of arteries after administration of ovulation inhibitors Remarkably, most marked changes were found in the distal aorta [25] In 1970, Irey described microscopic changes in arteries in young women who used oral contraceptives [26] In 1977, Van Vroonhoven reported long-term use of oral contraceptive agents in 15 young women with atherosclerosis of the distal aorta [27] Several other animal-experimental studies correlated older oral contraceptive formulations containing high doses of potent synthetic estrogens and progestagens to increased risk of arterial thrombosis [28] One recently published study examined the effect of current low-dose oral contraceptives on arterial thrombosis and concluded that current oral contraceptive regimens did not increase the susceptibility of the artery wall to develop an occlusive thrombus In fact, there was a reduction in the incidence of thrombosis in the oral contraceptive animals compared with untreated control subjects [29] Our results do not support this experimental observation

Aspects of the design of our study

Our study was a nationwide multicenter population-based case-control study, and the first study to evaluate the relationship between the use of oral contraceptives and the risk of PAD in young women A unique feature of this study was the high proportion of oral contraceptive users in the patient and control group, 51% and 38%, respectively Taken together with the large number of patients and controls, this mostly resulted in precise estimates

In this study, data were collected by a self-administered questionnaire and we provided color photographs of all marketed pills However, we are confident that the presence of severe illnesses, or current pill use, will have been reported correctly in the majority of cases, because several studies which assessed the validity of self reported pill use [30], concluded that acceptably valid oral contraceptive histories were obtained with a self-administered questionnaire A more recent survey on the validation of cardiovascular risk factors also revealed a high agreement between questionnaire information and medical records [31]

We only compared current users of oral contraceptives with non-users (never users and past users combined), because previous studies reported that the adverse effects of combined oral contraceptives, platelet hyperactivity, blood pressure elevation, decreased glucose tolerance, and unfavorable lipid profile, disappeared when oral contraceptives are discontinued [2,32] However, all these studies included patients with myocardial infarction or patients with cerebral vascular disease, which are vascular diseases with a thrombotic component In our study, we included patients with PAD, which is of a more chronic (atheromatous) rather than an acute nature (thrombotic) However, we do not think that this division is absolute, nor that there are no similarities, with angina pectoris and claudicatio intermittens as an obvious example We believe that a view of all these arterial disease as manifestations of a similar disease etiology, consisting of an interplay between atherosclerotic and thrombotic phenomena, is not unusual For this reason, examining pill use in this context as it has been done in many studies on other vascular diseases, with an emphasis on current use, is not out of the ordinary Our study should be seen as a first step, demonstrating an association between oral contraceptive use and the occurrence of PAD

Subsequent studies will be necessary to extend our findings of this association into details, relating to duration of use, and look into the mechanism by which oral contraceptives induce PAD, for which assessment of duration of use may prove useful

Conclusion

The results of this study showed that current oral contraceptive use is associated with a threefold increased risk of PAD There was no difference between oral contraceptives containing second and those containing third generation progestagens

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Appendix

Participating centers

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