ORIGINAL INVESTIGATION

Low-Dose Oral Contraceptive Use and the Risk of Myocardial Infarction

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Background: Studies of oral contraceptives (OCs) containing 50 µg or more of estrogen suggest an increased risk of myocardial infarction (MI) among current users, particularly if they smoke heavily.

Objective: To assess whether use of the newer lower-dose OCs increases the risk of MI.

Methods: A case-control study was conducted from January 1985 through March 1999 in 75 hospitals in the greater-Boston and greater-Philadelphia areas. Data on OC use and MI risk factors were obtained by interview from 627 women with a nonfatal first MI (cases) and 2947 female hospital controls younger than 45 years.

Results: The overall odds ratio (OR) for current OC use relative to never used was 1.3 (95% confidence interval [CI], 0.8-2. 2). The OR was elevated, 2.5 (95% CI, 0.9-7.5), among heavy smokers (≥25 cigarettes per day) but close to 1.0 among lighter smokers (OR=0.8) and nonsmokers (OR=1.3). For current OC use together with heavy smoking relative to nonuse and nonsmoking, the OR was 32 (95 % CI, 12-81), considerably greater than that for heavy smoking alone, 12 (95% CI, 8.6-16). The ORs did not vary according to the type of formulation or the dose of estrogen; there were too few users to assess the new 20-µg preparations. Past OC use was unrelated to risk.

Conclusion: Current use of low-dose OCs in the United States is unrelated to an increased risk of MI among nonsmokers and light smokers, but users who smoke heavily may be at greatly increased risk.

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SOON AFTER oral contraceptives (OCs) were first marketed in the 1960s, case reports linked their use to the occurrence of myocardial infarction (MI).[1] By the late 1970s epidemiological studies had established that the risk of MI was increased among women using OCs, particularly if they smoked heavily.[2,3] The preparations assessed in these studies contained 50 µg or more of estrogen combined with a fixed dose of progestin. The relative risk estimates ranged from about 2 to 5 for the overall comparison of current OC users to nonusers, and the increase was much greater, about 20- to 30-fold, for OC users who smoked heavily relative to women who did not use OCs and were nonsmokers.[4-6]

Over the years, OC manufacturers have progressively lowered the doses, developed new progestins, and devised new types of formulations, such as triphasic preparations that release different doses of estrogen and progestin over the course of the menstrual cycle.[7-10] To assess whether the newer preparations are safer than earlier formulations, we carried out a large case-control study of OC use and the occurrence of first MI in young women.

RESULTS

Table 1 gives the distributions of age, region of the hospital, interview year, and potential MI risk factors among the cases and controls. Cigarette smoking, hypertension, diabetes mellitus, elevated serum cholesterol level, high body mass index, and positive family history of MI occurred more commonly among the cases.

As given in **Table 2**, the overall OR for current OC use relative to never used (hereafter, never-use) was 1.3 (95% confidence interval [CI], 0.8-2.2). The ORs for current OC use among women younger than 30 years and women aged between 30 and 34 years were 3.0 and 2.1, respectively. However, in those age groups and in all other age categories, the ORs for current OC use were compatible with 1.0. Eighty percent of current users had used OCs for 10 years or longer: the OR was 1.9 (95% CI, 0.7-5.0) for less than 10 years of use and 1.3 (95% CI 0.7-2.3) for 10 or longer.

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PARTICIPANTS AND METHODS

From January 1985 through December 1998 our central office telephoned collaborating hospitals every week to identify women younger than 45 years who had been admitted with a definite or possible first MI; 50 hospitals in Massachusetts and Rhode Island (the greater Boston area) and 25 in Pennsylvania, New Jersey, and Delaware (the greater Philadelphia area) participated. The physicians of potential cases were telephoned for details of the diagnosis and for permission to contact the patients for an interview. Potential control subjects, female patients younger than 45 years who had never had an MI, were drawn from the medical and surgical wards of the collaborating hospitals; they were identified from admission lists or from patient files on the wards. Interviews were conducted between January 1985 and March 1999. Among the potential cases, the participation rate was 79.4% (5.2% physician refusals, 8.5% patient refusals, and 6.9% died, too ill for interview, or could not be located). Among the potential controls, the participation rate was 83.9% (2.0% physician refusals, 10.7% patient refusals, and 3.4% died, too ill for interview, or could not be located).

Our nurse-interviewers interviewed patients in person in the hospital or by telephone at home after discharge. They administered standard questionnaires to obtain information on demographic factors, OC use, and MI risk factors that included cigarette smoking, hypertension, diabetes mellitus, elevated serum cholesterol level, height and weight, and family history of MI. We found previously that information obtained in our case-control studies by in-person and telephone interviews was relatively similar, as were the results.[11,12] In this study patients interviewed in the hospital were shown pictures of OC pills and packets to aid recall; patients interviewed at home by telephone were not. For 104 women who reported current OC use (ie, in the month before admission), who were willing for us to contact the prescribing physician, and whose physician responded, we compared self-report of current OC use and the product used with the report of the physician. In all but one instance the physician's report indicated that the patient was a current OC user. There was concordance on the product name for 84% of the comparisons; concordance was 86% for hospital interviews (52 women) and 81% for the telephone interviews (42 women).

CASES

We obtained the discharge summaries of 90% of the potential cases, of which 98% met the criteria for inclusion after review by the study's physician-investigator (S.S.): pathologic Q waves with evolution, or any 2 of the following: other electrocardiographic changes with evolution, typical history of chest pain, elevated cardiac enzyme levels, or angiographic evidence of coronary occlusion. After exclusion of 25 cases that did not meet the enrollment criteria, there were 627 cases; 88% were white.

CONTROLS

From the pool of 3668 potential controls, we selected 2947 patients whose hospital admission was for a nonmalignant condition that we judged was unrelated to OC use. Thus, for example, patients admitted for cardiovascular disease or deep vein thrombosis were ineligible. The diagnoses were documented by review of discharge summaries. The selected controls were admitted for trauma or orthopedic disorders (1100 patients), acute infection (913 patients), or a wide range of other conditions (934 patients), most of which affected fewer than 50 controls; 90% were white. The rates of current OC use (use within the month before admission) in the 3 diagnostic categories among the controls, adjusted to the overall age-distribution of the controls, were 8.3%, 7.1%, and 9.0%, respectively; the rates of past OC use (use that ended at least a month before admission) were 63.6%, 66.6%, and 65.3%, respectively.

STATISTICAL ANALYSIS

The relative risk for MI among OC users was estimated by the odds ratio (OR) obtained by multiple logistic regression.[13] Terms were included for age, region, interview year, type of interview (telephone or hospital), cigarette smoking, drug-treated hypertension, drug-treated diabetes mellitus, history of an elevated serum cholesterol level, body mass index (measured in kilograms per meters, squared), menopausal status, and history of MI before the age of 60 years in a parent or sibling. Reduced models with terms for only age, region, and interview year were used when there were fewer than 5 current OC users among either the cases or controls.

For past OC use (Table 2), the overall and age-specific ORs were close to 1.0 and not statistically significant. The OR did not vary according to the duration of use: for less than 5, 5 to 9, 10 to 14, and 15 years or longer of OC use, the ORs were 1.0, 0.9, 1.0, and 1.0, respectively.

Hypertension is a contraindication to OC use. Among 140 cases and 238 controls with drug-treated hypertension, only 1 case (0.7%) and 5 controls (2.1%) were current OC users. The numbers were too small for informative estimation of the OR.

Table 3 gives current OC use according to levels of cigarette smoking. The OR for current OC use among heavy smokers (≥25 cigarettes per day) was elevated, 2.5, but not statistically significant (95% CI, 0.9-7.5). Among nonsmokers and smokers of 1 to 24 cigarettes per day, the ORs were close to 1.0 and not statistically significant.

Table 4 gives data on the joint effect of current OC use and heavy cigarette smoking relative to nonuse of OCs (the combined category of never and past use) and nonsmoking. Past OC users were combined with never-users because past use was unrelated to the risk of MI. The OR for current OC use among nonsmokers, 1.6, was compatible with 1.0. The ORs for current OC use together with smoking 1 to 24 cigarettes per day, 3.4 (95% CI, 1.4-8.0), did not differ materially from that for smoking 1 to 24 cigarettes per day in the absence of OC use, 4.7 (95%CI, 3.6-6.1). By contrast, the estimate for current OC use and heavy smoking together, 32 (95% CI, 12-81), was considerably larger than the estimate, 12 (95%

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Table 1. Selected Factors Among 627 Cases of First Myocardial Infarction (MI) and 2947 Control Subjects*

Factor	Cases	Controls†
Age, y		
<35	15.2	32.5
35-39	26.8	32.8
40-44	58.1	34.7
Region		
Greater Boston, Mass	73.4	81.8
Greater Philadelphia, Pa	26.6	18.2
Interview year		
1985-1988	23.1	30.1
1989-1993	37.6	35.9
1994-1999	39.2	34.0
Current smoking (cigarettes per day)		
None	23.8	62.2
1-24	39.1	27.0
≥25	37.0	10.1
Drug-treated hypertension	22.3	10.1
Drug-treated diabetes mellitus	12.8	2.1
Elevated serum cholesterol level	26.2	10.3
Body mass index, kg/m^2		
<26	38.9	49.0
26-29	23.0	21.2
≥30	37.6	28.7
MI in a parent or sibling		
<60 y	33.2	14.9
≥60 y	21.9	20.3

*Data are given as percentage of participants.
†Percentages for current cigarette smoking, drug-treated hypertension, drug-treated diabetes mellitus, elevated cholesterol level, body mass index, and the occurrence of an MI in a parent or sibling are standardized to the age distribution of the cases.

Table 2. Current and Past Oral Contraceptive (OC) Use Overall and According to Age Among 627 Cases of First Myocardial Infarction and 2947 Controls Subjects*

	OC Use			
Age	Current	Past	Never	Total
<30 y				
Cases	8	9	3	**20**
Controls	90	135	52	**277**
OR	3.0	1.3	Reference	
95% CI	0.4-23	0.2-8.7		
30-34 y				
Cases	15	45	15	**75**
Controls	89	426	167	**682**
OR	2.1	1.1	Reference	
95% CI	0.8-5.2	0.5-2.3		
35-39 y				
Cases	7	103	58	**168**
Controls	37	650	279	**966**
OR	1.2	0.7	Reference	
95% CI	0.4-4.1	0.5-1.1		
40-44 y				
Cases	6	255	103	**364**
Controls	21	715	286	**1022**
OR	0.5	1.1	Reference	
95% CI	0.1-1.5	0.8-1.5		
All Women				
Cases	**36**	**412**	**179**	**627**
Controls	**237**	**1926**	**784**	**2947**
OR	1.3	1.0	Reference	
95% CI	0.8-2.2	0.8-1.2		

*OR indicates odds ratio; CI, confidence interval; and reference, reference category.

CI, 8.6-16), for heavy smoking in the absence of OC use; the difference between the 2 estimates was of borderline statistical significance ($z=1.94$, $P=.05$).

Table 5 gives data on the type of OC formulation used, the dose of estrogen, and the type of progestogen in formulations containing less than 50 µg of estrogen. The most commonly used formulations were fixed-dose combination products (an estrogen with a progestogen); the most common estrogen dose was 30 or 35 µg; and the most commonly used progestogen was norethindrone. For the overall comparison of current OC use to never-use, all ORs for the various categories considered were compatible with 1.0 except that for OCs containing norethindrone, for which the OR was 2.5 (95% CI, 1.1-5.8). For the joint effect of current OC use with cigarette smoking relative to nonuse and nonsmoking, the ORs ranged from 17 to 110, all were statistically significant, and all were compatible with a uniform value. The numbers of current OC users were small in some categories, particularly for the type of progestogen in the OC and for the joint effect of OC use with heavy smoking, and 95% CIs were wide. There were too few users of the lowest-dose preparations, 20 µg (1 case and 12 controls) for separate analysis.

The ORs for current OC use relative to never-use were consistent across interview year and study center. The results were similar regardless of the method of interview: for current OC use relative to never-use, the OR was 1.4 (95% CI, 0.5-3.6) based on hospital interviews and 1.1 (95% CI, 0.6-2.1) based on telephone interviews; the corresponding estimates for current OC use and heavy smoking together relative to nonuse and non-

Table 3. Current and Past Oral Contraceptive (OC) Use According to Cigarette Smoking Among 627 Cases of First Myocardial Infarction and 2947 Control Subjects*

Current Cigarette Smoking	OC Use			
	Current	Past	Never	Total
None				
Cases	11	91	47	**141**
Controls	158	1171	491	**1820**
OR	1.3	0.8	Reference	
95% CI	0.6-3.0	0.6-1.3		
1-24 Cigarettes per day				
Cases	8	166	71	**245**
Controls	66	562	211	**839**
OR	1.3	1.0	Reference	
95% CI	0.6-3.0	0.7-1.5		
≥25 Cigarettes per day				
Cases	17	154	61	**232**
Controls	13	191	74	**278**
OR	2.5	1.1	Reference	
95% CI	0.9-7.5	0.7-1.8		

*OR indicates odds ratio; CI, confidence interval; and reference, reference category.

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smoking were 31 (95% CI, 8.0-117) and 21 (95% CI 5.9-77), respectively.

COMMENT

This study suggests that current OC use has little or no influence on the risk of a nonfatal first MI among women who do not smoke or who smoke fewer than 25 cigarettes a day. However, current use seems to increase the risk among smokers of 25 or more cigarettes per day, and we estimate that current OC use together with heavy smoking increases the risk of MI to a level about 30 times that of nonsmokers who do not use OCs. As in previous studies,[2,3,14] past OC use was not associated with an increase in the risk of MI and there was little, if any, influence of the duration of OC use. There was little variation in risk according to the type of formulation (fixed-dose combined or triphasic) or the estrogen dose (<35 µg, 35-49 µg, or ≥50 µg). However, only one case used a preparation containing 20 µg of estrogen and we were unable to assess the effect of these low-dose preparations.

The results of a recent case-control study of British and European women suggested that use of OCs containing the so-called third-generation progestogens, notably gestodene and desogestrel, was not associated with an overall increase in the risk of MI, whereas second-generation progestogens were.[15] However, another British study[16] found no overall increase for either second- or third-generation pills. In the present study third-generation pills were not commonly used. The overall effect of OCs, and of OC use together with heavy smoking, did not vary by the type of second-generation progestogen used. However, the numbers of current OC users of any particular type tended to be small and CIs were wide.

Four recent reports have provided information on OCs containing less than 50 µg of estrogen. Sidney et al[17] assessed 271 cases and 993 controls from 2 population-based case-control studies of US women. The overall relative risk estimate for current OC use was 0.94. There was no interaction with cigarette smoking. However, there were only 12 current OC users among the cases, limiting the power of the study to assess this possibility, and heavy smoking was not considered. Lewis et al[15] conducted a hospital-based case-control study of MI among British and European women. Based on 182 cases and 635 controls, the OR for current OC use was 0.82 for third-generation OCs and 2.35 for second-generation OCs. The joint effect of OCs with smoking was not estimated, but the OR for current smoking among current OC users was 3.9 among users of third-generation OC products and 9.5 among users of second-generation OC products. The WHO Collaborative Study of Cardiovascular Disease and

Table 4. Joint Effects of Current Oral Contraceptive (OC) Use and Cigarette Smoking Among 627 Cases of First Myocardial Infarction and 2947 Control Subjects*

Current OC Use	Current No. of Cigarettes per Day	Cases	Controls	OR (95% CI)
No	None	138	1662	Reference (. . .)
Yes	None	11	158	1.6 (0.8-3.2)
No	1-24	237	773	4.7 (3.6-6.1)
Yes	1-24	8	66	3.4 (1.4-8.0)
No	≥25	215	265	12 (8.6-16)
Yes	≥25	17	13	32 (12-81)

*OR indicates odds ratios; CI, confidence interval; and reference, reference category.

Table 5. Current Oral Contraceptive (OC) Use Overall and by Smoking of 25 Cigarettes or More per Day According to OC Formulation Among 627 Cases of First Myocardial Infarction and 2947 Control Subjects*

	Current OC Use			Current OC Use and ≥25 Cigarettes per Day		
Formulation	Cases	Controls	OR† (95% CI)	Cases	Controls	OR‡ (95% CI)
Type of formulation						
Combined fixed dose§	20	153	1.3 (0.7-2.3)	11	10	37 (12-115)
Combined triphasic	9	71	1.6 (0.7-3.8)	2	2	18 (1.9-165)
Progestin only	1	1	. . .	1	1	. . .
Unknown	6	12	2.1 (0.5-8.1)	3	0	. . .
Estrogen dose in combined OC, µg						
≥50	4	20	1.5 (0.4-6.5)	3	3	17 (2.5-115)
35-49‖	13	108	1.8 (0.9-3.6)	3	4	30 (4.9-150)
<35	9	74	1.4 (0.6-3.3)	5	3	110 (19-630)
Progestogen in combined OC containing <50 µg of estrogen						
Norethindrone	11	68	2.5 (1.1-5.5)	3	2	88 (10-770)
Norethindrone acetate, ethynodiol diacetate, and norgestrel	5	57	0.9 (0.3-2.8)	2	2	22 (1.7-280)
Levonorgestrel	4	42	1.6 (0.5-5.2)	1	1	. . .
Desogestrel and norgestimate	2	15	1.5 (0.3-7.7)	2	2	80 (6.7-950)

*OR indicates odds ratio; CI, confidence interval; and ellipsis, the value was not given if any cell was less than 2.
†Reference category is nonuse of OCs.
‡Reference category is nonuse of OCs and nonsmoking.
§Formulation contains estrogen and progestogen.
‖Group includes OC users of triphasic formulations first releasing 30 µg of estrogen and then releasing 40 µg of estrogen.

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Steroid Contraception[18] studied 188 cases and 480 controls from European countries in a hospital-based case-control study. The overall relative risk estimate for current use of OCs was 5.64 and it did not vary by estrogen dose (<50 µg or ≥50 µg). Current OC use together with smoking 10 or more cigarettes daily increased the risk by an estimated 22-fold. Dunn et al[16] studied 448 cases and 1728 controls in a general practice–based study of British women. The OR was 1.40 for current OC use. The ORs were compatible with 1.0 among smokers of 20 or fewer cigarettes per day and more than 20 cigarettes per day. Some of the variation in the relative risks for current OC use among the studies may well reflect variations in the coexistence of other risk factors among OC users.[14]

The results of the present study concerning OCs with less than 50 µg of estrogen are similar to those of earlier studies of higher-dose preparations,[4-6] and to the recent results of the WHO Collaborative Study of Cardiovascular Disease and Steroid Contraception,[18] in suggesting that OCs and heavy smoking together greatly increase the risk. In particular, we conducted an earlier study of MI (from July 1976 through June 1979) that used the same methods as the present study.[4] Almost all of the OCs used contained 50 µg or more of estrogen. We estimated that the joint effect of current use of OCs with smoking 25 or more cigarettes per day was to increase the risk of MI 39-fold.

Differential reporting, such as more complete reporting of OC use by cases than controls, is unlikely to explain the current findings. There is strong evidence that women report recent OC use reasonably accurately[19-22] and we found this to be so when we compared self-report with physician report for a sample of current OC users. In addition, if reporting by the cases had been more complete than that of the controls, one might expect to have seen increased ORs for current OC users who were nonsmokers or light smokers, or for past OC use; no such increases were observed. Major distortion from confounding is unlikely because the important risk factors for MI were considered. With regard to potential selection bias, the enrollment rates of cases and controls were satisfactory. The controls were selected to have diagnoses unrelated to OC use; that the selection was successful is supported by the observation of similar rates of current and past OC use across the major diagnostic categories. While there is little information available on the relation of low-dose OC use to the risk of MI, there is a large body of evidence on the older higher-dose pills. Results from our previous hospital-based case-control study of current OC use and first nonfatal MI, which used methods similar to those of the present study, were similar to those obtained from population-based case-control studies and follow-up studies.[2,3] Based on all of these considerations, selection bias seems to be an unlikely explanation for the present findings.

The newer lower-dose OCs have less adverse effects on serum lipid levels than earlier preparations.[7,8,23] However, the observation in epidemiologic studies that the effect of OCs is acute,[1-5] coupled with clinical evidence of clots in OC users who suffered MIs,[24] suggests that a thrombotic rather than an atherogenic mechanism is involved in OC-related MIs. The newer OCs generally have smaller effects than earlier pills on clotting factors. The overall effect still tends to be in the direction of increased clotting,[7,8,25] yet within normal ranges. How these changes relate to clinical events is unknown. The present evidence suggests that OC preparations that contain more than 20 µg of estrogen are safe for nonsmokers and smokers of fewer than 25 cigarettes per day. Whatever the mechanism, for the small subset of OC users who smoke heavily there is evidence to suggest a greatly increased risk of MI, just as was the case for older higher-dose preparations. The current warning on OC package inserts, that users of OCs should not smoke, is still appropriate.

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