

# Oral Contraceptives and Nonfatal Myocardial Infarction

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• We obtained information on 107 women younger than 46 years who were discharged from a hospital with a diagnosis of acute myocardial infarction. In the series 26 women were otherwise apparently healthy and potentially childbearing. Among these 26 women, 20 (77%) were taking oral contraceptives just prior to admission, and one was taking conjugated estrogens. Among 59 control women, 14 (24%) were taking oral contraceptives and one was taking conjugated estrogens. The relative risk estimate, comparing oral contraceptive users with nonusers, is 14 with 90% confidence limits of 5.5 and 37. All but two of the 26 women were cigarette smokers. While this illness is rare in most healthy young women, the risk in women older than about 37 years who both smoke and take oral contraceptives appears to be high.

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CONSIDERABLE concern about the possible increased risk of acute myocardial infarction (MI) in women taking oral contraceptives has resulted from the studies of Mann et al<sup>1,2</sup> published in the *British Medical Journal* in late May 1975 and from other reports.<sup>3,5</sup> This concern prompted us to carry out a case-control study to evaluate this relationship further. The study was done in cooperation with the Commission on Professional and Hospital Activities (CPHA), an organization that obtains demographic and discharge diagnosis information on approximately 40% of all acute-care hospitalizations in the United States. The reports of Mann et al<sup>1,2</sup> focused attention on the possible positive associa-

tion between oral contraceptives and MI; therefore, to avoid biases that may have resulted from the 1975 publications and the resultant publicity, we selected cases that were diagnosed prior to the Mann reports. The present communication describes the results in women younger than 46 years who were in apparent good health prior to their MI and who had no known medical condition that predisposed to the illness.

## SUBJECTS AND METHODS

### Cases

All women younger than 46 years who were hospitalized during the first six months of 1975 with a discharge diagnosis of MI (Hospital Adaptation of International Classification of Diseases, codes 410.0 to 410.4 and 410.9) were identified by hospital number from the computer files of CPHA. We considered for further study only those who survived the hospitalization; 954 such patients discharged from 621 hospitals were identified initially. (Data about these patients were not made immediately available to us because CPHA has an agreement with partici-

pating hospitals not to release any information without permission.)

For each patient who was so selected, CPHA sent a letter to the hospital administrators explaining the purpose of the study and asking if they were willing to participate by providing the patient hospital number and the name, last known address, and telephone number of the attending physician primarily responsible for the care of the patient. One hundred ninety-six hospitals (representing 40 states) with 308 cases of MI agreed to participate. To the physicians named we sent a letter explaining the purpose of the study and requesting that they identify each case by name, address, and telephone number (if available) and give written permission to obtain a copy of the discharge summary for the hospitalization of interest. There was a follow-up letter and telephone call when necessary to encourage cooperation. For those cases for which such permission was obtained, a discharge summary was requested from the record room of the admitting hospital; when received, it was reviewed for relevant medical information.

All women who had a discharge diagnosis of definite or probable acute MI and who were not immediately shown to have one of the exclusion conditions (listed later) were considered suitable subjects for further study. Women deemed suitable were sent a letter explaining in a general way the purpose of the study and indicating that they would be telephoned to obtain a medical interview. Neither oral contraceptives nor myocardial infarction were mentioned in the letters sent to patients.

### Controls

For each case, four control women of the same age (within two years) were selected from the files of CPHA. These women were discharged from the same hospitals

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at about the same time as the cases, having been admitted for acute illness (other than MI) or elective surgery. There was no follow-up if the physician did not respond to the initial letter. The procedure for identification and interview of control women was otherwise identical to that for the cases.

### Information Obtained

All women were interviewed by telephone using a standard questionnaire. Two experienced nurse interviewers carried out all of the interviewing. The following information relating to the period prior to the 1975 hospitalization was obtained: (1) birthdate, (2) race, (3) marital status, (4) husband's occupation, (5) number of pregnancies and live-born children, (6) weight and height, (7) history of past medical illnesses, (8) smoking, coffee, and tea consumption habits, (9) family history, (10) menstrual and contraceptive history, and (11) history of regular drug use within three months of hospitalization.

Among the 308 subjects with MI, 164 were not interviewed because the admitting physician could not be located (8), had not replied (70), or declined to participate (16); because the patient could not be located (22), declined to participate (3), or had died (15); or because of other reasons (30).

To evaluate the potential bias introduced from the physicians who did not respond, we telephoned 14 of these physicians, chosen at random, to determine the reasons for no response. The most common reasons were failure to be able to identify the patient and simple non-follow-up of our initial letter. In only one instance did the private physician have knowledge of the patient's contraceptive history. (The patient used oral contraceptives.)

### RESULTS

On 144 MI subjects and 165 controls younger than 46 years and originally selected from the computer files, sufficient information was obtained from the discharge summary or other sources to define their status.

Among the 144 cases, 37 had been misclassified, ie, they did not, in fact, represent women younger than 46 with a discharge diagnosis of acute MI. Twelve women were excluded from further analyses because they gave a history of a serious chronic illness or an illness that contraindicates oral contraceptive use: recent cancer, 2; chronic myocardiopathy, 2; severe coronary disease with coronary angiography, 3; recurrent ve-

Table 1.—Oral Contraceptive Use Among Women With MI and Controls by Age\*

Age, yr	Oral Contraceptive Users	Non-users	Total
27 to 37			
MI cases	5	1	6
Controls	8	7	15
38 to 40			
MI cases	5	1	6
Controls	2	11	13
41 to 43			
MI cases	4	2	6
Controls	1	18	19
44 to 45			
MI cases	6	2†	8
Controls	3	9†	12

\*MI indicates myocardial infarction. Maximum likelihood estimate of relative risk is 14; approximate 90% confidence limits are 5.5 and 37; two-sided  $P=.000004$ .

†One woman was taking conjugated estrogens.

Table 2.—Cigarette-Smoking Status Among Women With MI and Controls\*

No. of Cigarettes per Day	MI Cases	Controls
None		
Never smoked	2	32
Ex-smoker	0	6
1-14	3	6
15-25	6	8
26-40	10	6
≥41	5	1
Total	26	59

\*MI indicates myocardial infarction.

nous thromboembolism, 1; stroke, 1; other, 3.

After these exclusions, there remained 95 cases of MI. Among these, 47 gave a history of natural menopause or surgical sterilization (in themselves or their spouse). Among the remaining 48 MI subjects, 22 gave a history of predisposing illness—past MI, toxemia of pregnancy, or treated hypertension, diabetes, angina, or a combination of these. The results in this group will be reported separately.

Among the 165 controls, seven were excluded because they gave a history of serious chronic illness or an illness that contraindicates oral contraceptive use, and an additional 89 gave a history of natural menopause or surgical sterilization. Among the remaining 69 controls, ten gave a history of predisposing illness.

After all exclusions, there remained 26 MI subjects and 59 controls who were apparently healthy pre-

menopausal women (prior to admission). Among these women there was no apparent contraindication to oral contraceptive use nor had there been a surgical sterilization that would have made oral contraceptive use unnecessary. The distribution of admitting diagnoses among the control women is as follows: hemorrhoids, appendicitis, and hernia, 13; musculoskeletal disorders, 13; benign skin tumors, 5; other benign tumors, 5; other gastrointestinal disorders, 3; other diagnoses, 20.

Among the remaining 26 MI subjects, 20 (77%) gave a history of oral contraceptive use in the three months prior to admission. The corresponding frequency in the controls was 14/59 (24%). To control for possible confounding by age, we stratified subjects into four age categories—27 to 37, 38 to 40, 41 to 43, and 44 to 45 years—such that each category included approximately one fourth of the cases (Table 1). The maximum likelihood estimate of the relative risk after age stratification<sup>6</sup> is 14, comparing oral contraceptive users with nonusers, with approximate 90% confidence limits<sup>7</sup> of 5.5 and 37 and a two-sided  $P$  value of .000004 using the Mantel-Haenszel test.<sup>8</sup>

One of the MI subjects and one of the controls gave a history of taking conjugated estrogens at the time of admission. One control had stopped using oral contraceptives about ten weeks prior to admission. The remainder of the oral contraceptive users among MI subjects and controls were taking the drug at the time of hospitalization. The duration of oral contraceptive use adjusted for age averaged 6.7 years in the MI subjects and 8.8 years in the controls. Of the six MI subjects who were not using oral contraceptives at the time of hospitalization, four gave a history of oral contraceptive use in the past. The corresponding figure for the controls is 16/45 (36%).

Among the 26 MI subjects, 24 (92%) were cigarette smokers at the time of admission. Among the 59 controls, 21 (36%) were smokers. The distribution of cases and controls according to the amount smoked per day is given in Table 2. (Standardization for age was not necessary because smoking was not related to age within this age span.) There is a strong correlation

between MI and smoking in these subjects; the relative risk estimate for smokers of >25 cigarettes per day relative to never-smokers is 34.

Among the 26 MI subjects, 18 (69%) were smokers using oral contraceptives; two used oral contraceptives in the absence of smoking, and six smoked without using oral contraceptives. The corresponding figures for the controls are 4/59 (7%), 10/59 (17%), and 17/59 (29%).

Weight and height were used to calculate Quetelet's index<sup>9</sup> (weight divided by height squared). The mean values of this index did not differ substantially between cases and controls (2.52 and 2.40, respectively).

Among the 26 MI subjects, nine (35%) gave a positive family history of acute MI or stroke in at least two close blood relatives (parents or siblings). The corresponding figure for the controls was 6/59 (10%). Among the 26 MI subjects, 22 (85%) were married and 24 (92%) were white. The corresponding figures for the controls are 78% and 95%, respectively. The discharge summaries were reviewed by an experienced cardiologist (H. Emerson Thomas, Jr, MD), who had no knowledge of the results. Among the 26 MI subjects, evidence sufficient to satisfy the diagnostic criteria for MI set by the World Health Organization<sup>10</sup> was present in 22 (85%). Among the 20 MI subjects using oral contraceptives, 15 stopped using them immediately after the MI, four had stopped by the time of interview in 1977, and one has continued using the drug.

#### Estimates of Incidence Rates

The incidence rate of nonfatal MI among the otherwise healthy, potentially childbearing women in various exposure categories was roughly estimated from the data obtained in the present study together with US census data<sup>11</sup> and data obtained in a 1972 survey study in the greater Boston area carried out by our group.<sup>12</sup>

The number of women living in the United States in 1975 for the four age categories (27 to 37, 38 to 40, 41 to 43, and 44 to 45 years) are estimated to be 16, 3.5, 3.5, and 2.4 million, respectively. We estimate from the data in this study that about 50% of women in each age category were postmenopausal or that the woman or her

spouse had been sterilized surgically. We estimate the proportion of women in the general population with predisposing illness, eg, treated diabetes or hypertension, to be about 4%, 5%, 7%, and 11% for the four age categories, respectively.<sup>12</sup> We further estimate that about 45% of women smoked and that the use of oral contraceptives among potentially childbearing women was 40%, 20%, 10%, and 10%, respectively, for the four age categories.<sup>12</sup> Finally, it is assumed that the cases described in this section are representative of the cases originally identified on the CPHA tape with respect to pattern of oral contraceptive use and age and that these, in turn, are representative of cases occurring at large in the country.

No MI subjects were nonsmokers who did not take oral contraceptives, and, therefore, we estimate that the incidence rate of nonfatal MI for such women who are otherwise healthy and have no predisposing condition is near zero. For women who had one exposure or the other but not both, the annual age-specific risks for each of the four age categories are estimated to be about 1 per 190,000 (aged 27 to 37 years), 1 per 47,000 (aged 38 to 40 years), 1 per 23,000 (41 to 43 years), and 1 per 16,000 (44 to 45 years). The corresponding risks for women who both smoked and used oral contraceptives are estimated to be about 1 per 8,400, 1 per 920, 1 per 540, and 1 per 250, respectively.

#### COMMENT

The present data provide strong evidence that oral contraceptives increase the risk of nonfatal acute myocardial infarction in otherwise healthy women with no predisposing medical conditions. Our results, however, should be viewed in the context of other important findings that have emerged from this study. First, the illness is rare in such women younger than about 38 years. Therefore, even with a large relative risk among oral contraceptive users, the absolute risk in these women is likely to be small. Second, in contrast to stroke<sup>13</sup> and venous thromboembolism,<sup>14</sup> acute MI in otherwise healthy premenopausal women is almost exclusively an illness of cigarette smokers. Therefore, we estimate that among non-

smokers the risk of nonfatal MI attributable to oral contraceptives (or any other cause) is extremely small. The risks for women who smoke and also use oral contraceptives, however, are substantially larger, ranging from an estimated one per 8,400 annually in women aged 27 to 37 years to one per 250 for women aged 44 to 45 years.

The potential for a variety of biases in this study was substantial. A majority of hospitals did not choose to participate. To our knowledge, however, this decision was made independent of oral contraceptive use. About 20% of physicians did not respond at all to our request. In addition, a small proportion of physicians and patients declined to participate. Insofar as this behavior related to oral contraceptive use, bias could have been introduced. However, our evaluation of the reasons for nonresponse indicates that few physicians were aware of the contraceptive habits of their patients. As to the control group, similar concerns about bias are present; it is reassuring that the rate of oral contraceptive use is similar to that which would be expected based on results of our 1972 study<sup>12</sup> and other studies.<sup>13</sup> Some confounding may have been present from differences between cases and controls with regard to marital status, geography, or race, but these are likely to have had little influence on the results since the differences between cases and controls were small. The combined effect of all these biases seems unlikely to account for the large overall associations in the data.

Several approximations and assumptions were involved in the estimation of incidence rates. These approximations could easily have led to inaccuracies of 100% or more in the estimates. Despite the possibility of such inaccuracy, we believe these estimates provide useful information about the order of magnitude of the risks.

A family history of arterial disease has been reported as a risk factor for MI in young women.<sup>1</sup> This association was noted in our data and, along with an elevated serum lipid level (not measured in this study), may be an additional predisposing factor for the effect of oral contraceptives and

smoking on the risk of MI.

We are continuing to collect data on nonfatal MI for women with predisposing illnesses; the results will be reported later. In the meantime, the results of the present study, together with those of Mann et al<sup>1,2</sup> and those recently reported by the Royal College of General Practitioners<sup>15</sup> and Vessey et al,<sup>16</sup> leave little doubt that oral contraceptives increase the risk of MI in otherwise healthy women. Since multiple risk factors seem to act synergistically in this illness, it would seem prudent to withhold these drugs from women older than about 37 years with predisposing illness to MI, such as diabetes and hypertension, particularly if they smoke.

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*continued from page 1366*

Two circumstances peculiar to England coincided to fertilize the work that Monet and Pissarro had begun in France: the instability of the English weather, with the perpetually shifting lights and changing shadows, and the paintings of the English landscapists, Constable and Turner. But while Pissarro freely admits their debt to these two English painters, he also notes that they had "no understanding of the *analysis of shadow* . . . it is simply used as . . . a mere absence of light." It is this treatment of shadow as color and not as the mere absence of light (black) that advances the work of Constable and Turner. Renoir says it well: "A tree . . . has the *same* local color on the side where the sun shines as on the side where the shadow is. . . . The color of the object is the same, only with a veil thrown over it. Sometimes that veil is thin, sometimes thick, but always it remains a veil. . . . No shadow is black. It always has a color."

*Near Sydenham Hill* (cover), painted near the London suburb where Pissarro lived in 1870-1871, is Pissarro's winter and Impressionism's spring. The strongly-shadowed tree trunks, like the pilasters of a Renaissance painting, support an arch that opens onto a vista which disappears finally into infinity. For the Renaissance painters infinity

was marked by a set of lines which converged until they met and vanished at a point on the horizon. For Pissarro infinity is marked by a series of horizontal planes which also merge and vanish at the horizon, but in color rather than in line. For example, the first plane is boldly marked by the foreground fence cutting across the lower portion of the painting. Behind, the second plane is indicated by slightly paler green tones; it ends sharply at the railroad line just beyond the figure at left center. Beyond are the houses of Lower Norwood, their colors already muted by distance, and finally, on a hill are the cemetery and church tower, where the ground mists merge with and disappear into the infinity of the cloudy sky.

Still, Pissarro remained the realist. "He never composes a picture," said Duret, "and in his landscapes, never arranges nature. For him a landscape on canvas must be the exact reproduction of a natural scene and the portrait of some spot in the world that really exists." Emile Zola, the literary realist, had another kind of praise for Pissarro: "One hears . . . the deep voice of the soil, the powerful life of the trees. . . . There is a man hidden here, a straight and vigorous personality, incapable of falsehood, making of art a pure and eternal truth."—M. THERESE SOUTHGATE, MD

(*Near Sydenham Hill*, painted in 1871. Oil on canvas. 43.5×53.5 cm. Courtesy of the Kimbell Art Museum, Fort Worth, Tex.)