Noncontraceptive Estrogens and Nonfatal Myocardial Infarction

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• **We obtained information on 107 women younger than 46 years discharged from a hospital with a diagnosis of acute myocardial infarction. In the series there were 17 women aged 39 to 45 years who were otherwise apparently healthy and had had a natural menopause, hysterectomy, or tubal ligation or whose spouse had had a vasectomy. Among them, nine (53%) were taking noncontraceptive estrogens just prior to admission. Among 34 control women, four (12%) were taking estrogens. The relative risk estimate, comparing estrogen users with nonusers, is 7.5, with 90% confidence limits of 2.4 and 24. All but one of the 17 MI subjects were cigarette smokers. While this illness is rare in most healthy young women, the risk in women older than about 38 years who both smoke and take estrogens appears to be substantial.**

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RECENTLY we carried out a study of the epidemiology of nonfatal acute myocardial infarction (MI) in women younger than 46 years 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. In the preceding article, we describe a strong association between oral contraceptive use and MI.

Many of the women who were interviewed were not candidates for oral contraceptives since they had had a natural menopause, hysterectomy, or tubal ligation or their husband had had a vasectomy. We report on the relationship of noncontraceptive estrogens to acute MI in this latter group of women. The analyses were restricted to those women who were in apparent good health prior to their MI and who had no known medical condition that predisposed to the illness nor any known contraindication to estrogen treatment.

SUBJECTS AND METHODS

The methods of this study are detailed (see p 1403). Cases of nonfatal MI and controls discharged from a hospital during the first six months of 1975 were identified from the computer files of CPHA. Patients were interviewed by telephone following a procedure that involved permission from the hospital of entry, the attending physician, and the patient herself. The obtained information included standard vital statistics, smoking habits, drug intake, and menstrual and contraceptive history.

Information sufficient to classify patients according to whether there had been a sterilization procedure in the family was obtained in 107 cases and 165 controls. For most subjects, the information was obtained from the discharge summary or by interview. In a few, information was received directly from the attending physician. Among the 107 MI subjects, there were 47 who had had a natural menopause, hysterectomy, or tubal ligation or whose spouse had had a vasectomy. Seventeen of these women could not be located and were, therefore, not interviewed. Among the 165 controls, 89 had had a natural menopause or the woman or her spouse had been sterilized surgically; all were interviewed.

RESULTS

Among the 30 MI subjects and 89 controls who were interviewed, 17 MI subjects and 61 controls were apparently healthy prior to hospitalization and had no known medical condition that predisposed to MI or any known contraindication to estrogen treatment. The youngest MI subject was 39 years old; therefore, the analyses were restricted to women aged 39 to 45 years inclusively. The distribution of admitting diagnoses among the control women was as follows: hemorrhoids, appendicitis, and hernia, six; musculoskeletal disorders, six; skin disorders, five; benign tumors, five; other gastrointestinal disorders, five; other, seven.

Among the 17 MI subjects, nine (53%) gave a history of estrogen use at the time of admission. The corresponding rate for the controls was

Table 1.—Estrogen Use Among Women With MI and Controls Aged 39 to 45 Years*

	Estrogen Users	Nonusers	Total
Women with natural menopause or hysterectomy			
Cases	7	7	**14**
Controls	4	17	**21**
Women with tubal ligation or whose spouse had had vasectomy			
Cases	2	1	**3**
Controls	0	13	**13**

*Maximum likelihood estimate of relative risk is 7.5; approximate 90% confidence limits are 2.4 and 24; two-sided $P=.002$. MI indicates myocardial infarction.

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

No. of Cigarettes per Day	MI Cases	Controls
None		
Never smoked	1	15
Ex-smoker	0	3
1-14	2	2
15-25	9	12
26-40	4	2
≥41	1	0
Total	**17**	**34**

*MI indicates myocardial infarction.

4/34 (12%). To control for confounding by the type of sterilization present, we stratified subjects into two categories: (1) those women who had had a natural menopause or hysterectomy and (2) those women who had had a tubal ligation or whose husband had undergone vasectomy (Table 1). The maximum likelihood estimate of the relative risk after stratification[1] was 7.5 comparing estrogen users with nonusers, with approximate 90% confidence limits[2] of 2.4 and 24 and a two-sided P value of .002 from the Mantel-Haenszel test.[3]

Among the cases, six women used conjugated estrogen (Premarin), one used piperazine estrone sulfate (Ogen), and two used an unknown estrogen preparation. Among the controls, three used conjugated estrogen and one used an unknown estrogen preparation. The duration of estrogen use (in users) averaged 2.6 years in the cases and 1.7 years in the controls.

Of the 17 MI subjects, 16 (94%) were cigarette smokers at the time of admission. The corresponding rate for the controls was 16/34 (47%). 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.) It is apparent that there is a strong correlation between MI and smoking in these subjects.

Weight and height were used to calculate Quetelet's index[4] (weight divided by height squared). The mean values of this index did not differ substantially between cases and controls (2.45 and 2.71, respectively).

Among the 17 MI subjects, two (12%) reported a family history of acute MI or stroke in at least two close blood relatives (parents or siblings). The corresponding figure for the controls was 5/34 (15%). Among the 17 MI subjects, 16 (94%) were married and 16 (94%) were white. The corresponding rates for the controls were 97% and 97%. When the discharge summaries were reviewed, 16/17 cases of MI (94%) had evidence sufficient to satisfy the diagnostic criteria set by the World Health Organization.[5]

COMMENT

The present data provide substantial evidence that noncontraceptive estrogens increase the risk of acute MI in women younger than 46 years. The results are similar to those obtained for oral contraceptives in women of the same age range. As noted in the preceding article, the illness is rare in healthy women younger than about 38 years. Furthermore, it occurs almost exclusively in cigarette smokers. In this series, 16 of 17 women with MI were cigarette smokers; in the previous series, 24 of 26 MI subjects were smokers. This extremely strong association between smoking and MI in young women is in great contrast with the absence of such a strong relationship between those in whom stroke[6] or venous thromboembolism develops.[7]

Using the results of the preceding article, together with US census figures,[8] we estimate roughly that the annual risk of nonfatal MI among healthy women aged 39 to 45 years who both smoke and use estrogens is approximately one per 750. This estimate is similar to the estimate of about one per 600 obtained for otherwise healthy women of the same age who both smoke and use oral contraceptives (see p 1405).

A family history of arterial disease has been reported as a risk factor for MI in young women (p 1403).[9] In contrast to the findings with oral contraceptives (p 1403),[9] this association was not noted in the current series. The reason for this difference is not apparent to us.

The results of this study in young women are substantially different from those reported for estrogens in older women, for whom no overall positive association between estrogens and MI was found (relative risk of 0.97).[10] (That study included only one otherwise healthy woman with MI younger than 46 years, and she was an estrogen user.) This great difference in the risk of MI for estrogen users comparing younger and older women indicates that the epidemiology of this illness is substantially different in the two groups. This argument is reinforced by the observation that the illness is almost exclusively confined to cigarette smokers in younger women, whereas for older women smoking appears to play little, if any, role in the cause of MI.[11]

In view of present results and those reported for oral contraceptives, it appears prudent for women between the ages of 39 and 45 years to avoid any estrogen use if they smoke or have conditions that predispose to MI, such as diabetes or hypertension.

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References

1. Gart JJ: Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed margins. *Biometrika* 57:471-475, 1970

2. Miettinen O: Estimability and estimation in case referent studies. *Am J Epidemiol* 103:226-235, 1976.

3. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22:719-748, 1959.

4. Goldbourt U, Medalie JH: Weight-height indices: Choice of the most suitable index and its association with selected variables among 10,000 adult males of heterogeneous origin. *Br J Prev Soc Med* 28:116-126, 1974.

5. *Ischaemic Heart Disease Registers: Report of the Fifth Working Group.* Copenhagen, World Health Organization, 1971.

6. Oral contraception and increased risk of cerebral ischemia or thrombosis, Collaborative Group for the Study of Stroke in Young Women. *N Engl J Med* 288:871-878, 1973.

7. Lawson DH, Davidson JF, Jick H: Oral contraceptive use and venous thromboembolism: Absence of an effect of smoking. *Br Med J* 2:729-730, 1977.

8. *United States Census of Population.* Bureau of the Census, 1970.

9. Mann JI, Vessey MP, Thorogood M, et al: Myocardial infarction in young women with special reference to oral contraceptive practice. *Br Med J* 2:241-245, 1975.

10. Rosenberg L, Armstrong B, Jick H: Myocardial infarction and estrogen therapy in post-menopausal women. *N Engl J Med* 294:1256-1259, 1976.

11. Miettinen OS, Neff RK, Jick H: Cigarette-smoking and nonfatal myocardial infarction: Rate ratio in relation to age, sex and predisposing conditions. *Am J Epidemiol* 103:30-36, 1976.