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Use of Postmenopausal Hormones and Risk of Myocardial Infarction

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SUMMARY **Information was collected by mail survey about myocardial infarction (MI), use of female hormones after menopause, and coronary risk factors from 121,964 registered nurses ages 30–55 years. One hundred twenty-three women with a known type of prior menopause reported hospitalization for MI. Overall, use of female hormones by these women was very similar to that of control women matched for age and type of menopause. Compared with nonusers, the relative risk (RR) for women who had ever taken female hormones was 0.9 (95% confidence limits 0.6–1.2), and for current users the RR was 0.7 (0.5–1.1). For women with bilateral oophorectomy, the RR for current users was 0.4 (0.2–0.8). These data imply that, at present, a decision to prescribe postmenopausal hormones should be based primarily on weighing possible benefits from the relief of menopausal symptoms against known or suspected risks of other diseases, particularly uterine cancer in women with an intact uterus.**

ORAL CONTRACEPTIVE users have a substantially increased risk of myocardial infarction (MI)[1, 2] over nonusers. However, conflicting results have been reported about the role of noncontraceptive estrogens. In two case-control studies of older postmenopausal women, use of female hormones was not associated with hospitalization for MI,[3, 4] while in a case-control study of women 39–45 years of age, current users appeared to have a rate of hospitalization for MI seven times that of nonusers.[5, 6]

This retrospective study evaluates the association between postmenopausal hormone use and reported hospitalization for MI among registered U.S. nurses.

Methods

Subjects

Married female nurses ages 30–55 years (in 1976) and residing in 11 of the larger U.S. states were identified from the American Nurses' Association 1972 membership file. In 1976, questionnaires were mailed to them requesting information on various health-related items, including whether they had been hospitalized for MI, their menopausal status, and their use of female hormones other than oral contraceptives. Dates of diagnosis and of menopause were requested, as well as information on duration of hormone use. Of the 172,413 women who presumably received questionnaires, 121,964 (71%) completed and returned them.

Among the respondents were 318 women who reported hospitalizations for MI, of whom 156 were premenopausal on the date of their hospitalization, 37 were perimenopausal (i.e., were hospitalized in the year their menopause occurred and could not be classified with certainty as to menopausal status at MI), and two did not specify a type of menopause. The remaining 123 women were hospitalized after their reported date of menopause and also indicated the type of menopause. Of these, 25 reported natural menopause, 50 reported hysterectomy with retention of at least one ovary, and 48 had bilateral oophorectomy.

For each case, 20 control women without a history of MI were selected randomly from respondents having the same year of birth as the index case and the same type of menopause before the date of hospitalization of the case.

The information reported included duration of female hormone use after menopause, but not dates of use. For cases, female hormone use was defined as

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current at the date of hospitalization for MI if the reported duration of use was at least as long as the duration of the interval between menopause and the hospitalization. Duration of use for current users was the interval between menopause and hospitalization. Other risk factors were considered positive if reported to be present at any time before hospitalization. For controls, current use of female hormones and the presence of risk factors were defined with respect to the date of hospitalization for MI of the case with whom the control subject was matched.

The strength of the association between postmenopausal hormone use and MI was evaluated by estimating the relative risk (RR, calculated as the exposure odds ratio) of hospitalization for MI for women who were users of female hormones compared with women who had never used female hormones. Effects of potential confounding factors were controlled by individually calculating RRs after stratifying by the relevant variables.[7] For each RR, 95% confidence intervals were computed.[8] Finally, the RR for MI after female hormone use, adjusted for all potential confounders, was computed using multiple logistic regression analysis.[9] For duration of use of female hormones, the differences between cases and controls adjusted for age at menopause were derived by summing weighted stratum-specific differences. The significance of this difference was tested by a generalization of the paired t test.[10]

Results

Overall, female hormone use after menopause was not appreciably different in cases and controls: 64 cases (52%) and 1390 controls (57%) had used hormones at some time (ever users), and 32 cases (26%) and 825 controls (34%) were current users at the time of the relevant case's hospitalization for MI (table 1). There was no indication that past or current users of female hormones were more likely to be hospitalized for MI than nonusers. Compared with women who had never used female hormones, the estimated RR of reported hospitalization for MI, adjusted for age by combining data across age strata,[7] is 0.7 (95% confidence limits 0.5–1.1) for current users and 0.9 (0.6–1.2) for ever users.

These estimates were essentially unaltered after adjusting individually for potential confounding variables by combining data over appropriate strata. The variables included were histories of cigarette smoking, elevated cholesterol, hypertension, diabetes, angina pectoris, parental MI before age 50 years, type of menopause, obesity, year of hospitalization, and state of residence. Including these variables (other than state of residence) in a logistic regression analysis also yielded similar estimates for the association of use of postmenopausal hormones with MI, with an RR of 0.7 (0.4–1.1) for current users and an RR of 0.8 (0.6–1.3) for ever users.

Among women who reported a bilateral oopherectomy, however, a significantly decreased risk of MI was apparent for those who were current users of female hormones (table 2). (Of the cases, 16 were current users and 14 never users; and of the controls 523 were current users and 182 never users.) This association persisted after adjustment for the other risk indicators noted above. For ever use among women who had undergone bilateral oophorectomy, the RR was 0.6 (0.3–1.1).

Overall, the mean duration of use of postmenopausal hormones was somewhat longer for cases than for controls (table 3). The differences after adjustment for age at menopause were smaller than the crude differences, being only 0.9 years for current users (p = 0.09) and 1.2 years for ever users (p = 0.005).

Female hormone use among women without predisposing factors for MI other than cigarette smoking was not associated with a greater risk of hospitalization for MI. Stratification by cigarette smoking did not materially alter the RR estimates, nor did such

TABLE 1. *Relative Risk of Myocardial Infarction Among Postmenopausal Women According to Age and Female Hormone Use After Menopause*

Age (years) in 1976		Female hormone use after menopause*		
		Ever	Current†	Never
Total	MI patients	64	32	56
	Controls	1390	825	1048
	RR	0.9	0.7	1.0‡
33–45	MI patients	13	7	20
	Controls	333	211	320
	RR	0.6	0.5	1.0‡
46–49	MI patients	27	15	17
	Controls	565	357	359
	RR	1.0	0.9	1.0‡
50–55	MI patients	24	10	19
	Controls	492	257	369
	RR	0.9	0.8	1.0‡
	Overall RR estimate adjusted for age	0.9	0.7	1.0‡
	95% confidence limits	0.6–1.2	0.5–1.1	

*Subjects with unknown use excluded (three cases and 22 controls).
†Current use is a subset of ever use.
‡Reference category.
Abbreviations: RR = relative risk; MI = myocardial infarction.

TABLE 2. *Relative Risk (with 95% Confidence Limits) of Myocardial Infarction Among Postmenopausal Women According to Type of Menopause and Current Female Hormone Use*

Type of menopause	RR* (95% CL)	n†
Natural	1.3 (0.5–3.4)	6
Surgical: ≥ 1 ovary retained	1.0 (0.5–2.2)	10
bilateral oophorectomy	0.4 (0.2–0.8)	16

*RR adjusted for age at MI.
†Number of cases who were current users of hormones.
Abbreviations: RR = relative risk; MI = myocardial infarction.

TABLE 3. *Duration of Female Hormone Use After Menopause According to Age at Menopause*

Age (years) at menopause		Female hormone use: Ever* Duration (years) (mean ± SEM)	N	Female hormone use: Current Duration (years) (mean ± SEM)	n
< 30	MI cases	12.7 ± 3.0	9	17.7 ± 4.9	4
	Controls	10.4 ± 1.2	41	15.0 ± 1.5	14
30–34	MI cases	10.6 ± 2.1	9	12.2 ± 4.8	3
	Controls	6.6 ± 0.5	117	8.9 ± 0.7	57
35–39	MI cases	7.0 ± 1.9	10	11.0 ± 3.2	4
	Controls	6.2 ± 0.3	233	8.4 ± 0.3	121
40–44	MI cases	4.7 ± 0.7	17	4.7 ± 0.9	9
	Controls	4.0 ± 0.1	416	5.0 ± 0.2	248
≥ 45	MI cases	2.5 ± 0.3	18	2.6 ± 0.3	12
	Controls	2.3 ± 0.1	583	2.5 ± 0.1	384
Overall (crude)	MI cases	6.6 ± 0.8	63	7.0 ± 1.2	32
	Controls	4.1 ± 0.9	1390	4.8 ± 0.1	824

*Subjects with unknown duration of use excluded.
Abbreviation: MI = myocardial infarction.

stratification indicate modification of the effect of female hormone use by smoking. For women without predisposing factors who had bilateral oophorectomy and currently used female hormones, the RR was 0.3 (0.1–0.8), based on nine exposed cases.

Discussion

In this study, use of postmenopausal hormones did not appear to increase risk of nonfatal MI among women 33–55 years of age, and indeed appeared to decrease this risk significantly among those with bilateral oopherectomy. This finding was essentially unaffected by a history of cigarette smoking. These results differ from those reported for contraceptive estrogens, in that oral contraceptives increase the risk of MI,[1, 2] and the effect may be greater among users of oral contraceptives who are cigarette smokers.[1, 2]

Adjusting for the effects of calendar year in which the MI occurred, geography, age, type of menopause and other predisposing factors for MI in addition to cigarette smoking did not materially affect the results.

The existence of selection bias could not be assessed directly, but respondents and nonrespondents were similar with regard to age, state of residence, employment status and type, and educational status. Further, rates of female hormone use and hospitalization for MI were similar among respondents to the first and subsequent mailings (up to three), suggesting that willingness to respond early was not associated with female hormone use or MI among those who did respond.

Random inaccuracies in reporting MI among users and nonusers, or random misclassification of female hormone use, would have altered RR estimates toward unity. Among 48 cases for whom the diagnosis of MI was confirmed by examination of discharge summaries, the RRs were virtually identical to those for the entire case group.

With regard to information provided on female hormone use, it is possible that cases and controls with the same actual use (or nonuse) recall and record this differently, leading to a systematic bias that could produce either a spurious positive or negative association between hormone exposure and risk of MI. We cannot examine this issue in these data, but we believe that, in general, subjects are more likely to remember and report, and perhaps mistakenly exaggerate, an exposure to a possible risk indicator for their disease. In any event, such a bias cannot be invoked to explain the absence of any association in the present study.

The results of classification of female hormone use are based on reported duration of use after menopause, but exact dates of use are unknown. Women were classified as current users if they reported a duration of use at least as long as the interval between menopause and hospitalization for MI, which might overestimate the proportion of current users. The definition was based on the assumption that use began at menopause.[11] No individual information on dosage or type of hormone preparation was available, although conjugated estrogens were the most commonly used preparations among the total study group.

In two other studies,[3, 4] use of female hormones after menopause did not appear to increase the risk for MI. However, most women in these latter studies were at least 50 years of age, and if these preparations affect coronary risk in younger women but not in older women, no effect of female hormone use would have been observed.

Jick et al.[5, 6] observed that, among women 39–45 years of age without predisposing conditions for MI, current users of noncontraceptive female hormones appeared to have a substantially increased risk of hospitalization for MI compared with nonusers. In that study,[5] 14 patients with MI and 21 controls were postmenopausal; among them, seven cases and four controls were current users of noncontraceptive female hormones, giving an estimated RR for hospitalization for MI of 4.2 for current users compared with nonusers, a barely significant difference. In the current study, among the 23 cases and 557 controls who were comparable in age and risk factor status to those of Jick et al., the estimated RR is 0.6, which is not significantly different from 1.0 (i.e., no effect). Thus, all reported data are consistent with the hypothesis that use of female hormones has no effect on risk of MI among postmenopausal women.

Information from these studies of noncontraceptive female hormone use in relation to MI is insufficient to allow firm conclusions. However, oral contraceptive use is strongly associated with increased risk of idiopathic venous thromboembolism, with the effect apparently related to dose.[12] On the other hand, postmenopausal female hormone use is associated only weakly, if at all, with venous thromboembolism.[12] Noncontraceptive female hormones may differ from oral contraceptives in their effect on the circula-

tory system because of lower estrogen doses in medications usually prescribed for the relief of menopausal symptoms.[13] This suggestion is supported by data from other studies. In the Coronary Drug Project,[14, 15] high-dosage (5-mg) conjugated estrogens increased risk of recurrent MI in male survivors of MI while lower doses (2.5 mg) had no such effect, although there was an increase in thromboembolic phenomena at each dose, with the greater increase, as compared with placebo, being in the high-dosage group. Further, in another study of oral contraceptive use in relation to thromboembolic disease, risk appeared to increase with increasing estrogen content of the oral contraceptives.[16]

Recent reports indicate that oral contraceptives and postmenopausal estrogens probably have different effects on blood lipids.[17-20] It appears that postmenopausal estrogen use is associated with lowered LDL and VLDL cholesterol and triglyceride levels, but with increased HDL cholesterol,[17, 19] whereas the oral contraceptive effects are more complex and vary with the estrogen dose and type of progestagen used.[18] In general, cholesterol (LDL and VLDL) and triglyceride values tend to be elevated among oral contraceptive users compared with nonusers.[18-20]

We have no explanation for the slightly longer duration of hormone use reported by cases. For current users, the adjusted difference of 0.9 year was not statistically significant, and although previously published studies provide few data, they suggest no marked differences in duration of use between women with and without MI.[3-5] It may be that whereas short-term use of hormones has no effect on MI risk, long-term use increases this risk. This seems unlikely, given that it is only currency, and not duration, of oral contraceptive use that increases the likelihood of MI. Further, the alterations of lipid levels noted above do not provide a mechanism for the long-term effects of hormone use; and although blood pressure is somewhat elevated in current users of oral contraceptives, this effect does not appear to be associated with duration of use.[21, 22] More precise information on duration of use and dosage from other studies would be helpful.

In conclusion, the current data show no positive association between postmenopausal hormone use and nonfatal MI. For women who have a bilateral oophorectomy, use of postmenopausal hormone supplements appears to confer significant protection against the risk of MI while the hormone is being used, although this finding needs confirmation in other studies. For the present, a decision to prescribe postmenopausal hormones should be based primarily on possible benefits from relief of menopausal symptoms weighed against known or suspected risk of other diseases, particularly uterine cancer for women with a uterus.[23] The potential cardiovascular risks and benefits of hormone use require the evaluation of additional data, including the association with fatal MI, for even a small effect will have an important public health impact, especially at older ages when MI becomes a more common cause of death.

Addendum

A recently completed case-control study of 447 women ages 30-49 years with a first MI and 1832 controls gives further support for the absence of a causal relationship between the use of noncontraceptive estrogens and MI.[24] The overall adjusted RR of current use was 1.0 (95% confidence limits 0.6-1.7), while duration of use was not associated with risk in any consistent manner.

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Detection of Residual Myocardial Function in Acute Transmural Infarction Using Postextrasystolic Potentiation

A Computerized Angiographic Study

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SUMMARY **Twelve subjects without clinical or hemodynamic heart failure, admitted for a first untreated anterior transmural myocardial infarction, were evaluated within the first 24 hours after the onset of symptoms. Pulmonary angiography was performed while a right ventricular extrastimulus was delivered every fourth beat at 50% of the RR interval to systematically analyze the basal and the postextrasystolic left ventricular frames. Left ventriculograms were quantitatively processed to determine the ejection fraction (EF) and the percentage of the end-diastolic circumference showing hypokinetic (%HK) or akinetic (%AK) areas. Left ventricular angiography was performed 1 month later in all cases at the same paced atrial heart rate to compare this final angiogram to the basal and the electrically induced postextrasystolic initial beats. During the 1-month period of the study none of these subjects had complications such as recurrent chest pain, heart failure or rhythm disturbances, and no drug administration was necessary.**

Comparing the basal cycle of the initial angiogram and the final cycle, a poor correlation was found between the corresponding values of EF ($r = 0.34$), %HK ($r = 0.38$) and %AK ($r = 0.48$). The correlations were much better when a comparison was made between the postextrasystolic cycle of the initial angiogram and the final cycle (EF, $r = 0.84$; %HK, $r = 0.96$; %AK, $r = 0.95$).

These results indicate that, from the first day after a TMI, the analysis of the postextrasystolic frame allows accurate estimation of the final left ventricular function and regional wall motion abnormalities. Postextrasystolic potentiation may be useful in the acute state of transmural infarction to discriminate potentially reversible ischemic from definitely jeopardized areas.

HEMODYNAMIC PATTERNS of transmural myocardial infarction (TMI) have been extensively evaluated. Most studies only take into account cardiac output and capillary wedge pressure. This approach is useful for recognizing high-risk patients,[1] especially using multivariate analysis.[2] Although overall and regional wall motion in acute TMI have been evaluated,[3-9] the information is far from complete.

Most studies define the acute state of TMI too broadly, i.e., from the first days to the first month after the clinical onset of symptoms.[3] The early evaluation of ejection fraction and extent of akinetic areas do not give reliable information about the possible early detection of residual myocardial function. Postextrasystolic potentiation (PEP) is effective in detecting residual potential contractile function in stable coronary artery disease,[10] but this has not been evaluated in man during the acute state of TMI.

The aim of our study was to quantitate, using computerized angiographic data, overall and regional left ventricular (LV) function and wall motion in the very acute (< 24 hours) state of TMI. During this early angiogram, the right ventricle is paced every fourth beat to systematically analyze the postextrasystolic

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