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SURGICALLY CONFIRMED GALLBLADDER DISEASE, VENOUS THROMBOEMBOLISM, AND BREAST TUMORS IN RELATION TO POSTMENOPAUSAL ESTROGEN THERAPY

A Report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center

Abstract The possible influence of estrogen-containing drugs (mainly conjugated estrogens) on gallbladder disease, venous thromboembolism and breast tumors in postmenopausal women 45 to 69 years of age was explored in a large hospital survey. As compared with controls, the estimate of relative risk for cases of surgically confirmed gallbladder disease occurring in otherwise healthy women was 2.5 (95 per cent confidence limits: 1.5 and 4.2), and the estimated incidence rate attributable to estrogens was 131 per 100,000 women at risk per year. Significant associations between estrogens and idiopathic venous thromboembolism, newly diagnosed breast cancer or benign breast tumors were not present. (N Engl J Med 290:15-19, 1974)

FOR many years estrogen compounds have been used in the treatment of postmenopausal symptoms. Concern about their possible harmful effects has stemmed from at least three sources. In the first place, the estrogenic components of oral contraceptives are thought to be associated with idiopathic venous thromboembolism[1-4] and other acute thrombotic vascular conditions,[5] and it is possible that a similar relation holds for estrogens used after the menopause. Secondly, it is believed that some breast cancers may be estrogen-dependent, and that such dependence may be a function of age. Thus, observations that breast cancer and benign breast tumors appear to be either unrelated or negatively related to oral contraceptive use in younger women[4,6-8] do not rule out the possibility of an etiologic connection between estrogens and these diseases in older women. A third and more recent concern has been the identification of a relation between the use of oral contraceptives and gallbladder disease,[4] raising the question of whether a similar association may exist for estrogens used after the menopause.

In premenopausal women, the relations between oral contraceptive use and gallbladder disease, venous thromboembolism and breast tumors have recently been studied in a large hospital survey.[4] The same survey has been used to explore the influence of estrogen-containing compounds on the same entities in postmenopausal women.

Material and Methods

The surveyed population and the methods of data acquisition have been described.[4] Nurse monitors interviewed consecutive patients admitted to the general medical and surgical wards of 24 hospitals in the Greater Boston area between January and November, 1972. Patients who had been hospitalized during the previous three months were excluded. Also excluded were patients who were too ill for interview, or who escaped interview because they were hospitalized for less than 72 hours.

Shortly after admission, the patients were asked about smoking habits, alcohol, coffee and tea consumption, and whether they took medications during the previous three months for any of 26 indications (insomnia, high blood pressure, hormonal replacement, menopausal symptoms and so on). If they had, the drug and frequency and duration of use were recorded. However, information on exact dosage per capsule, tablet, liquid preparation or injection was not obtained. The patients were also asked about a past history of peptic ulcer, myocardial infarction, diabetes mellitus, arthritis, hypertension and rheumatic fever. In addition, all women were asked whether they had had a hysterectomy or had reached the menopause.

Patients were not asked if they had previously undergone cholecystectomy. Diagnoses (up to six per patient) were recorded after discharge. All information was edited, coded and stored on magnetic tape.

The following hospitals in Massachusetts participated in this study: Beth Israel Hospital, Beverly Hospital, Boston University Hospital, Boston Veterans Administration Hospital, Brockton Hospital, Cardinal Cushing Hospital, Emerson Hospital, Faulkner Hospital, Framingham Union Hospital, Lawrence Memorial Hospital, Leonard Morse Hospital, Malden Hospital, Marlboro Hospital, Mount Auburn Hospital, New England Medical Center Hospital, New England Memorial Hospital, Newton-Wellesley Hospital, Norwood Hospital, Quincy City Hospital, Salem Hospital, Sancta Maria Hospital, South Shore Hospital, Symmes Hospital, and Waltham Hospital. We are indebted to the staffs and administrations of these hospitals for co-operation, and especially to record-room personnel for their help.

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Selection of Patients

In the present study, 5339 consecutively monitored postmenopausal women, 45 to 69 years of age, were considered: 61 patients (1.1 per cent) who reported using estrogens only sporadically were excluded from the analyses that follow. Also excluded were patients with diseases, other than gallbladder disease, venous thromboembolism and breast tumors, that might either contraindicate therapy with estrogens or be related to their use. These included women with discharge diagnoses of cardiac disease, hypertension, other vascular diseases, peptic ulcer, blood dyscrasias, severe or chronic inflammatory bowel disease, disorders involving the breast or genitourinary system (except for cystocele and rectocele), any neoplasia, any chronic debilitating disease and obesity. Patients taking anticoagulants, antineoplastic drugs, cardiovascular drugs, insulin or oral hypoglycemics, or steroid drugs other than estrogens were also omitted, as were those giving a history of peptic ulcer, myocardial infarction or diabetes. A history of hypertension, without a corresponding discharge diagnosis or history of antihypertensive therapy, was not considered a criterion for exclusion. Instead, this factor was evaluated in the analyses.

Gallbladder Disease

All postmenopausal women, 45 to 69 years of age, with a discharge diagnosis of "cholelithiasis" or "cholecystitis" (or both) were identified from the computer files. Each discharge summary was evaluated without knowledge of drug intake. Only patients who had a cholecystectomy during the monitored admission were evaluated further. Of 436 patients identified, 284 were excluded (101 who were clinically diagnosed but did not come to surgery, 14 because of severe obesity, and 169 because of other associated conditions that met the exclusion criteria), leaving 152 patients who were apparently otherwise healthy and had surgically confirmed gallbladder disease.

Venous Thromboembolism

All postmenopausal women, 45 to 69 years of age, with a discharge diagnosis of "phlebitis," "thrombophlebitis" or "pulmonary embolism" were identified. Of 105 women with these diagnoses, 87 were excluded for reasons given in Table 1, leaving 18 who seemed otherwise healthy and who were judged to have "idiopathic venous thromboembolism." The diagnoses in all 18 patients were sufficiently convincing to justify the use of heparin and warfarin, and in seven patients with pulmonary embolism, evidence for the diagnosis was based either on filling defects on the lung scans (five), angiography (one) or surgical exploration and biopsy (one).

Breast Tumors

All postmenopausal women, 45 to 69 years of age, with a discharge diagnosis of "breast cancer," "benign breast disease" or "chronic cystic disease of the breast" were identified. Patients who had a biopsy-proved breast tumor that was diagnosed for the first time during the monitored admission were selected for analysis. Of 345 patients identified, 115 were excluded because they had recurrent breast cancer, and 127 met other exclusion criteria, leaving 103 patients who seemed otherwise healthy and who had surgically confirmed breast tumors. Among these, there were 51 newly diagnosed cases of cancer of the breast, and 52 benign breast tumors (fibrocystic disease in 37, fibroadenoma in five and miscellaneous tumors in 10 — lipoma, fibrolipoma, benign duct ectasia, or unspecified benign tumors).

Controls

Apart from women with discharge diagnoses of gallbladder disease, venous thromboembolism and breast tumors, there were 4392 postmenopausal women, 45 to 69 years of age, who were admitted to the collaborating hospitals. Of these, 3618 met one or other of the exclusion criteria, and the control group ultimately selected comprised all otherwise healthy women who were admitted to the hospitals because of acute illnesses, elective surgery or orthopedic treatment. This group consisted of 774 patients, and their primary diagnoses are listed in Table 2. When adjusted for age, distributions of estrogen use were similar for each of the diagnostic categories.

Table 1. Reasons for Exclusion of Cases of Venous Thromboembolism.

Group	No. of Cases	
Total screened		105
Exclusion categories		
Past history of thrombophlebitis, pulmonary embolism or varicose veins	17	
Postoperative or post-traumatic thrombophlebitis or pulmonary embolism	13	
Other reasons (diabetes, cardiovascular disease, cancer, chronic debilitating disease, severe obesity)	57	
Total excluded		87
Case of "idiopathic" thromboembolism		18

Results

In the overall series of 926 cases and controls, there were 98 women who used estrogen-containing compounds (10.6 per cent). Of the latter, 85 used conjugated estrogen tablets (Premarin). The remaining 13 patients used stilbestrol (five), ethinylestradiol (two), or an unspecified estrogen-containing drug (six).

The following factors appeared to be unrelated to estrogen use: hospital, parity, marital status, smoking and history of hypertension or hysterectomy.

The rate of estrogen use, as expected, dropped sharply with age, and in the controls, fell from 20 per cent at 45 to 49 years to 1.4 per cent at 65 to 69 years (Table 3).

Gallbladder Disease

The rates of estrogen use by five-year age intervals for patients with gallbladder disease and controls are shown in Table 3. Apart from women 65 to 69 years of age, there was an excess of estrogen use in the cases as compared to the controls at all ages. The summary risk ratio estimate is 2.5,[9] with 95 per cent confidence limits of 1.5 and 4.2.[10] The summary chi-square for this result is 14.1 ($p<0.001$).[9]

Duration of use was compared between cases and controls who used estrogens. Duration of use increased with increasing age but was similar at all ages in the cases and the controls. However, there were only 13 patients, all below 55 years of age, who used estrogens for less than 12 months.

Idiopathic Venous Thromboembolism and Breast Tumors

Table 4 gives the rates of estrogen use in cases of venous thromboembolism, breast cancer and benign

Table 2. Primary Diagnoses in 774 Controls.

Diagnosis	No. of Cases
Fractures & other traumatic injuries	216
Nontraumatic orthopedic diseases	172
Cystocele or rectocele (or both)	100
Diseases of eye & ear	81
Respiratory infections	76
Hemorrhoids	52
Inguinal & femoral hernias	43
Dental disease	34
Total	774

Table 3. Distributions of Cases of Surgically Confirmed Gallbladder Disease and Controls According to Estrogen Use by Five-Year Age Intervals.*

AGE (YR)	GROUP	ESTROGEN USERS	NONUSERS	TOTALS
45-49	Cases	12 (34%)	23	35
	Controls	22 (20%)	87	109
50-54	Cases	15 (25%)	44	59
	Controls	24 (12%)	169	193
55-59	Cases	5 (17%)	25	30
	Controls	11 (7%)	155	166
60-64	Cases	3 (14%)	18	21
	Controls	4 (2%)	160	164
65-69	Cases	0	7	7
	Controls	2 (1%)	140	142

*Summary risk ratio = 2.5; $\chi_1^2 = 14.1$; $p<0.001$; 95% confidence limits = 1.5-4.2.

breast tumors and in controls. Since the age distributions in the four series differ, the overall rates have been standardized for age by the direct method, with the 774 controls as the standard population. In relation to the control series, in which 8 per cent of the patients used estrogens, the adjusted rates among the cases were 14 per cent for venous thromboembolism, 9 per cent for breast cancer and 8 per cent for benign breast tumors. The only suggestion of a difference is the group with venous thromboembolism, in which three of 18 patients (and two of seven with pulmonary embolism) used estrogens. This result, however, is far short of statistical significance.

Division of the benign breast tumors into fibrocystic disease, fibroadenoma and other tumors did not give suggestive evidence of association, either positive or negative, between estrogens and these entities.

With only three estrogen users among the 18 patients with venous thromboembolism, duration of use could not be evaluated. Duration of use in the cases of breast cancer and benign breast tumors was similar to that of control users.

ESTIMATES OF INCIDENCE

For reasons previously published,[4] we estimate that the 24 collaborating hospitals serve a population of about 1,300,000 persons in the metropolitan Boston area, which has a population of approximately 2,800,000. Census data indicate that women between the ages of 45 and 69 years represent about 14 per cent of this population. Thus, we estimate that there were approximately 177,000 women in this age group in the catchment population of the surveyed hospitals.

Applying the age-specific rates of estrogen use in the controls to this catchment population yields an estimate of about 16,500 women receiving estrogens. On the basis of these figures, we estimate the incidence rate of surgically proved gallbladder disease to be approximately 87 per 100,000 per year in otherwise healthy women, 45 to 69 years of age, who do not take estrogens, and 218 per 100,000 per year in those who do. The incidence rate attributable to estrogens is thus about 131 per 100,000 per year. Similar calculations for idiopathic thromboembolism, breast cancer and benign breast tumors yield incidence rates in nonusers of about 11, 35, and 32 per 100,000 per year, respectively. As indicated above, there was no significant evidence that the incidence rates for the latter three diseases were higher in the estrogen users. Among an estimated 6300 women using estrogens for five or more years, there were no patients with thromboembolism, only two with breast cancer and only three with benign breast tumors.

Table 4. Estrogen Use in Patients with Idiopathic Venous Thromboembolism, Breast Cancer and Benign Breast Tumors, and in Controls by Five-Year Age Intervals.

AGE (YR)	ESTROGEN USERS/CASES OF VENOUS THROMBOEMBOLISM	ESTROGEN USERS/CASES OF BREAST CANCER	ESTROGEN USERS/CASES OF BENIGN BREAST TUMOR	ESTROGEN USERS/CONTROLS
45-49	1/3	0/5	3/11	22/109
50-54	1/7	1/13	5/28	24/193
55-59	0/3	3/9	0/3	11/166
60-64	0/2	0/9	0/5	4/164
65-69	1/3	0/15	1/5	2/142
Total	3/18	4/51	9/52	63/774
Age-standardized rate*	14%	9%	8%	8%
Significance†	p>0.2	p>0.2	p>0.2	

*Standardization by direct method with controls used as the standard population.
†All p values computed with age taken into account.[9]

DISCUSSION

Gallbladder Disease

The present findings show that the risk of gallbladder disease appears to be higher in postmenopausal women who use estrogens than in those who do not. The result is highly significant, and chance is an unlikely explanation of the findings. In addition, factors such as age, parity, obesity or prior hysterectomy do not appear to explain the association.

It is unlikely that physicians selectively diagnosed and performed cholecystectomies in estrogen users, or that the interviewers selectively elicited a history of estrogen use in patients with gallbladder disease, since there was no awareness of the hypothesis. In addition, other data in the survey do not give any evidence of an association between estrogen use and various other diseases leading to abdominal surgery.

The results are in accord with those reported for oral contraceptive users,[4] and the relative risks are of similar magnitude, being 2.0 for oral contraceptives and 2.5 for estrogens.

In contrast to users of oral contraceptives,[4] in whom the risk of gallbladder disease appeared to be highest after six to 12 months of use, there was no evidence of a relation with duration of use in postmenopausal estrogen users. One possible explanation for this discrepancy may be that a duration effect could have been missed in this study because of the small number of women who had been using estrogens for less than 12 months.

In the present study, information on prior cholecys-

tectomy was not obtained. In the Framingham study, it has been estimated that perhaps 10 to 15 per cent of women 50 to 62 years of age have gallbladder disease,[11] and the prevalence of prior cholecystectomy might be 7 to 12 per cent. Presumably, if such women could have been excluded from the control series, the effect should have been to increase the relative risk. Possibly, such removal might also have uncovered a relation with duration of use. However, if these assumptions are incorrect, one point is worth stressing: even if 12 per cent of the controls had previously undergone cholecystectomy and had been excluded, and even if the unlikely assumption is made that none of the excluded women had used estrogens, the net effect would have been to reduce the relative risk from 2.5 to not less than 2.0, and the association would still have been highly significant.

Idiopathic Venous Thromboembolism

Although the excess of estrogen use in women with thromboembolism was not significant, numbers were too small categorically to rule out a causal relation. However, postmenopausal estrogen users appear to differ from premenopausal oral contraceptive users. In the current series, among an estimated 160,500 women 45 to 69 years of age who did not use estrogens, 15 cases of idiopathic venous thromboembolism were identified. This number is similar to the 11 cases previously identified from among an estimated 187,000 women, 20 to 45 years old, who did not use oral contraceptives.[4] By contrast, there were only three cases of idiopathic venous thromboembolism among an estimated 16,500 estrogen users as compared with 32 cases among approximately 47,000 users of oral contraceptives. It is apparent, therefore, that if estrogens do cause thromboembolism, the risk is likely to be considerably lower than that reported for oral contraceptives.

The failure to identify a strong association between estrogen use and idiopathic venous thromboembolism is surprising since this is the strongest association that has been reported in younger women using oral contraceptives.[1-4] One likely explanation is dosage. There is evidence in users of oral contraceptives that the risk of venous thromboembolism is related to the dose of the estrogenic component,[12] and it is possible that estrogen-related thromboembolism does not occur in postmenopausal women because of lower doses. Conjugated estrogens accounted for the majority of users in this study. Although exact doses were not known, postmenopausal symptoms are generally treated with doses of 0.3 to 1.25 mg per day. Comparisons of potency between conjugated estrogens, stilbestrol and other estrogens in human beings show variability from subject to subject.[13] However, a dose of 1.25 mg of conjugated estrogens would probably be equivalent to much less than the 50 to 80 μg of ethinylestradiol or mestranol present in the oral-contraceptive tablets currently in use.

The incidence rate of idiopathic venous thromboembolism estimated in this series was 11 per 100,000 per year. This is the first available estimate for women over the age of 45 years, and having regard for the size of the denominator, it can be considered reasonably stable. Thus, the general belief that the risk of venous thromboembolism increases with age is probably a function of a higher prevalence of predisposing diseases. This is borne out in this study since only 17 per cent of 105 patients with venous thromboembolism who were initially identified were considered to be otherwise healthy.

Breast Tumors

The results for breast cancer and benign breast tumors are reassuring. Once again, although the numbers in this study are insufficient categorically to rule out causal connections between estrogens and these diseases, the data suggest that if such connections do exist, they are unlikely to be strong. It is particularly encouraging that there is no suggestion of a higher risk even in long-term users. The results for breast cancer accord with those reported in relation to oral contraceptives.[4,6-8] As far as benign breast tumors in young women are concerned, oral contraceptives appear, if anything, to confer some protection.[4,6] In this study, lack of evidence of a protective effect may reflect small numbers, or it may be that estrogens in older women do not influence the disease in a manner analogous to that of oral contraceptives in younger women; or it is possible that a protective effect may not be conferred by low doses.

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NATURAL HISTORY OF HEROIN-ASSOCIATED NEPHROPATHY

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Abstract Of 14 black heroin addicts with massive proteinuria, 12 manifested a typical syndrome including edema, hypoalbuminemia and hypercholesterolemia. Renal biopsies obtained in 13 patients showed focal and segmental glomerular sclerosis in 11, typically (seven of 11 patients) associated with focal glomerular deposition of IgM and β_1C/β_1A globulin.

Deterioration of renal function was continuous and rapid, so that in all eight patients with follow-up examinations, uremia developed in six to 48 months. Although focal sclerosis may have other as yet unidentified causes (especially in children), its occurrence in 11 of 13 nephrotic heroin addicts biopsied in the absence of other systemic or renal disease indicates a causal relation to heroin abuse. The combination of focal glomerular sclerosis and IgM and β_1C/β_1A globulin localization in glomeruli is otherwise unusual, having been noted in only two of 400 adult renal biopsies originating from a general nephrology service. An undefined response of the addict to heroin or its vehicle may be responsible for the renal syndrome. (N Engl J Med 290:19-23, 1974)

MASSIVE proteinuria as a complication of heroin addiction was recognized by McGinn and his co-workers.[1] Kilcoyne et al. noted focal membranoproliferative glomerulonephritis with IgM and complement deposition in seven of eight heroin addicts with the nephrotic syndrome.[2]

Renal biopsies in 14 "unselected" asymptomatic heroin addicts studied by Salomon and his co-workers showed a slight increase in the glomerular mesangium, mesangial deposits of IgM and basement-membrane localization of IgG.[3] Electron microscopical changes consisted of epithelial foot-process fusion and electron-dense deposits in the glomerular basement membrane. We present confirming evidence of the existence of a nephrotic syndrome associated with heroin abuse and describe its grim prognosis. In 13 of 14 proteinuric heroin addicts, renal biopsies were examined by light and immunofluorescence microscopy. Follow-up examinations were possible in eight patients, in all of whom uremia developed within six to 48 months of the detection of proteinuria.

Materials and Methods

Fourteen heroin addicts were admitted, because of proteinuria, to the medical service of either Kings County Hospital (12) or State University Hospital (one) between 1969 and 1973. One patient (Case 4, Tables 1 and 2) had one renal biopsy performed in another New York City municipal hospital in 1967 before his hospitalization here in 1970. All the patients were black men between the ages of 19 and 34 years, who admitted to heroin self-injection for one to 18 years before the onset of renal disease. Although attempts to quantitate the amount of heroin injected are approximations, the patients stated that their "habit" varied from five to 40 bags (street cost of $5 per bag) per day. Considerable variability in actual heroin content of a "bag" is noted in analyses performed by the Medical Examiner's office. In "good times" a bag may contain 60 mg or more of heroin whereas in periods of "panic" (shortage) measured heroin content may drop to 10 mg or less per bag. The heroin is mixed with milk sugar, quinine, mannose or other low-cost "white powder."

Table 1 lists the patients' age, daily consumption of heroin, duration of addiction before detection of proteinuria, quantitation of proteinuria, endogenous creatinine clearance, serum cholesterol and subsequent clinical course.

Percutaneous renal biopsy was performed in 12 patients, and open biopsy in one patient. Renal tissue was fixed in 10 per cent formalin or 4 per cent glutaraldehyde for subsequent light and electron microscopy. When available (11 of 14 patients), a portion of the biopsy core was frozen for immunofluorescence studies.

Fresh-frozen sections were exposed to fluorescein-isothiocyanate-labeled antiserums specific for the following human serum proteins: IgG,* IgA,† IgE,† IgM,† albumin,† fibrinogen† and β_1C/β_1A globulin† (the third component of complement). All antiserums gave a single line on immunoelectrophoresis.

In addition, unlabeled human‡ and rabbit* antiserums against Australia antigen were used in an indirect immunofluorescence test.

The preparations were viewed with a Leitz Ortholux-Orthomat fluorescence apparatus (200-watt high-pressure mercury lamp, UG1 transmission filter, K460 suppression filter, dark-field illumination).

A composite picture of drug experimentation (glue sniffing), habituation (barbiturates, lysergic acid diethylamide, amphetamines or cocaine) and finally heroin addiction could be drawn from the similar, if not superimposable, histories of each patient. Three patients had a recent history of icteric hepatitis. None of the patients were aware of any congenital, familial or acquired renal disease. Of the three patients with elevated antistreptolysin titers (Cases 8, 11 and 13), none recalled recent sore throat or respiratory infection.

In 12 of 14 patients, proteinuria was discovered during evaluation for the complaint of facial swelling or leg edema. The proteinuria was asymptomatic in two patients, one of whom (Case 9) was found to have a urinary protein loss of 9.1 g per 24 hours while hospitalized for viral hepatitis.

Results

At initial evaluation, two patients had end-stage renal failure with endogenous creatinine clearances of less than 10 ml per minute, two had severe reduction in glomerular filtration rate, with endogenous creatinine clearances of 23 and 30 ml per minute, and four others

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