

Appendix H: Evidence on HRT and Gallbladder Disease

H

There are several theoretical reasons to expect a causal link between estrogens and gallbladder disease. In particular, estrogens increase the risk of gallstone formation. Gallstones form in the gallbladder, a muscular sac in the abdomen that stores and releases bile, a substance that aids in fat digestion. Gallstones are solidified bile. Bile is highly saturated with cholesterol, and it is thought that estrogen raises the concentration of cholesterol in bile, increasing the risk of stone formation (2). Thus, one would expect an increased prevalence of gallstones and symptomatic gallbladder disease in estrogen users (1 1).¹

Tables H-1 to H-4 summarize the clinical studies evaluating the relationship between gallblad-

der disease and HRT. A small number of studies have shown that the incidence of symptomatic gallbladder disease increases approximately two-fold in current users of oral estrogen replacement therapy. The first report of an association came from a case-control study conducted in the mid- 1970s by the Boston Collaborative Drug Surveillance Program, which showed an increased incidence of surgically confirmed gallbladder disease in current users of either oral contraceptive or oral estrogen replacement therapy (3).²

One of the two prospective cohort studies of estrogen replacement therapy and gallbladder disease found that women who were current or past users of noncontraceptive estrogen had an age-adjusted relative risk of symptomatic gallstone dis-

¹It is not known whether estrogens not taken by mouth would also increase the risk of gallstones. Some argue that estrogen taken by skin patch or injection would not increase the risk of gallstone formation because estrogen taken by nonoral routes does not pass directly from the intestine to the liver. By avoiding the first-pass effect on liver metabolism, nonoral routes of estrogen administration may reduce this increased risk. A study by D'Amato and colleagues compared the effect of 17-beta estradiol given by skin patch and estradiol valerate given by mouth on bile lipid levels in a postmenopausal woman (4). While both therapies increased the cholesterol level in the bile, only oral estrogen induced the formation of cholesterol crystals.

²The Boston Collaborative Drug Surveillance Program study was criticized for using hospitalized controls, one half of whom were being treated for fracture or some other orthopedic problem. One commentator has argued that, since women with osteoporosis are less likely to be taking estrogen replacement therapy, this design could have led to a spuriously low rate of estrogen use in the comparison group, compared with usual use in the cases, and thereby a falsely elevated relative risk (1).

TABLE H-1: Hormone Replacement Therapy and Gallbladder Disease: Case-Control Studies (page 1 of 2)

Author	Description of cases and controls	Number of cases and controls	Results ^a
Boston Collaborative Drug Surveillance Program (1974)	Cases were postmenopausal women 45 to 69 years old with a diagnosis of "cholelithiasis" or "cholecystitis" and subsequent cholecystectomy, who were admitted to general medical and surgical wards of 24 hospitals in the Greater Boston area between January and November 1972. Patients with diseases that might either contraindicate estrogen therapy or be related to their use were excluded. Controls were hospital patients without a diagnosis of gallbladder disease, venous thromboembolism, or breast tumors,	152 cases, 774 controls	Relative risk 2,5 (1.5-4,2), there was "no evidence of a relation with duration of use in postmenopausal estrogen users. "
Honore (1980)	Cases were 262 perimenopausal women (ages 41 to 60 years) with symptomatic gallbladder disease treated by cholecystectomy from 1975 to 1978 at a hospital in Newfoundland, Canada, and diagnosed pathologically as having cholesterol gallstones. A control group, matched for age, consisted of women treated surgically for diseases that have no known association with estrogen replacement therapy. Information on HRT use was obtained from a review of medical records.	262 cases; 290 controls	Relative risk 3.72 ($p < 0.005$). There was a significantly greater incidence of gallbladder disease in obese HRT users than in nonobese HRT users ($p < 0.05$),
Scragg (1984)	Cases were patients in 2 public hospitals in Adelaide, Australia with gallstone disease diagnosed by ultrasound or cholecystectomy between December 1978 and September 1980. Two control groups were used for comparison. Hospital controls were women who were hospitalized and had negative cholecystograms. Community controls were women from the community, matched to cases for age and area of residence.	200 cases, 234 hospital controls, 82 community controls	Mean duration of estrogen use was not substantially different between cases and both control groups
Kakar (1988)	Subjects were women ages 41 to 74 enrolled in a prepaid health plan in western Washington's Group Health Cooperative of Puget Sound. Cases were women who underwent gallstone surgery between January 1979 and September 1988. Controls were matched for sex, age, and residence with cases.	102 cases, 98 controls	Relative risk 1.18 (0.65-2.13) for users of 1 year or more vs nonusers. Standardization for the effects of age, race, obesity, parity, thiazide use, and diagnosis of high blood pressure did not alter appreciably the estimate of relative risk.

TABLE H-1: Hormone Replacement Therapy and Gallbladder Disease: Case-Control Studies (page 2 of 2)

Author	Description of cases and controls	Number of cases and controls	Results ^a
LaVecchia(1992)	Subjects were women admitted to one of four hospitals in Milan, Italy between 1987 and 1990. Cases were women, ages 23 to 74 (median age 54), who underwent cholecystectomy, and were discharged with the diagnosis of cholelithiasis or cholecystitis. Controls were women, ages 21 to 74 (median age 54), admitted for acute diseases other than digestive or hormonal diseases or those potentially influencing the use of female hormone preparations.	235 cases; 583 controls	Users of any duration: unadjusted relative risk: 1.7 (0.9-3,1) adjusted relative risk ^b : 1.9 (1 ,0-3.6) Use less than 2 years: unadjusted relative risk: 1.7 (0.8-3.6) adjusted relative risk ^b : 1.8 (0.9-4,2) Use 2 or more years: unadjusted relative risk: 1.3 (0.5-3.8) adjusted relative risk ^b : 1.5 (0,5-4.5) Less than 10 years since last use: unadjusted relative risk: 1.1 (0.5-2.7) adjusted relative risk ^b : 1.3 (0.5-3,3) Last use 10 or more years ago: unadjusted relative risk: 2.3 (1 ,0-5.3) adjusted relative risk ^b : 2.4 (1 ,0-5.1)

^aThe results are followed by 95% confidence intervals in parenthesis.

^b Relative risk was adjusted for age, education, area of residence, body mass index, parity, and age at menopause.

SOURCE: Office of Technology Assessment, 1995.

TABLE H-2: Hormone Replacement Therapy and Gallbladder Disease: Cross-Sectional Studies

Author	Description of study participants	Number of participants	Results ^a
Diehl (1980)	Subjects were obtained from a review of a sample of medical records from patients enrolled in the Family Health Center of the University of Texas Health Sciences Center at San Antonio. Gallbladder disease was defined as history of cholecystectomy, gallbladder surgery, or abnormal cholecystogram.	1,018 records	"No trends in the prevalence of gallbladder disease were seen in relationship to use of conjugated estrogens. Our failure to find associations with estrogen-containing drugs may be related to our inability to quantitate their cumulative use in our study population."
Petitti (1981)	Subjects were adult female twins who volunteered to undergo a health examination for a study. Subjects were considered to have gallbladder disease if they answered "yes" to the question, "Has a doctor ever told you that you have had gallstones or gallbladder trouble?"	868 female twins	Relative risk 2.0 (1.1-3.6) for history of physician-diagnosed gallbladder disease in estrogen users versus nonusers.
Pixley (1985)	Subjects were women aged 40 to 69 registered at two Oxford, England general practices. All subjects were screened with ultrasound for gallstones. Gallbladder disease was defined as cholelithiasis on ultrasound cholecystectomy.	632 women recruited from general practice registers and 130 vegetarians.	Study concludes "no association [of gallstones] was found with parity or use of exogenous estrogens." No further information or statistical analyses was provided on this issue.
Jorgensen (1988)	Subjects were a random sample of women from Copenhagen county, Denmark, ages 30, 40, 50, and 60 years, drawn in 1982 from the National Person Register. Subjects were examined and/or interviewed by telephone or mailed questionnaire. Examined patients received ultrasonography to identify current gallstone disease.	2,301 women	Odds ratio 1.02 (0.25-4.26) for current or past gallbladder disease in estrogen users versus nonusers. Odds ratio 1.86 (0.89-3.86) for estrogen users of 8 or fewer years versus users of more than 8 years.

^a The results are followed by 95% confidence Intervals in Parentheses unless otherwise specified

SOURCE: Office of Technology Assessment, 1995

TABLE H-3: Hormone Replacement Therapy and Gallbladder Disease: Prospective Cohort Studies

Author	Description of study participants	Size of cohort	Results ^a
Petitti (1 988)	Subjects were women 18 to 54 years old at time of entry into the Walnut Creek (California) Contraceptive Drug Study cohort between December 1968 and February 1972. Women who ever used oral contraceptives were excluded from this analysis. Women with a previous cholecystectomy were also excluded from this analysis. Results of 10 to 13 year followup are presented. Patients were examined at initiation of study and followed by examination, questionnaire and/or reexamination. Cases were women who underwent cholecystectomy for cholelithiasis or cholecystitis.	16,638 women	All ever users: unadjusted relative risk 2.4 (1 .7-3.2) age-adjusted relative risk 2.1 (1 .5-3.0) past users ^b : unadjusted relative risk 1.8 (1.1 -2.9) age-adjusted relative risk 1.6 (1.1 -2.5) current users: unadjusted relative risk 3.1 (2.2-4.9) age-adjusted relative risk 2.7 (1 .8-4.0) There was no evidence of a relationship of incidence of cholecystectomy with duration of estrogen use.
Grodstein (1 993)	Subjects were postmenopausal U.S. registered nurses who were enrolled in the Nurses Health Study. Information on postmenopausal estrogen use and cholecystectomy was gathered by mailed questionnaires every two years. Duration of follow-up was 8 years.	54,845 postmenopausal women	Current users: risk-factor adjusted relative risk 2.1 (1.9-2.4) Current users of 10 years or more. risk-factor adjusted relative risk 2.6 (2.2-3.1) Current users of 1.25 mg CEE per day or more: risk-factor adjusted relative risk 2.4 (2.0-2.9) Past users of less than 2 years duration. relative risk 1.4 adjusted for recency of use Past users of 10 or more years: relative risk 1,7 adjusted for recency of use Most recent use 1 to 2.9 years ago. risk-factor adjusted relative risk 1.6 (1.2 to 2.0) Most recent use 5 or more years ago. risk-factor adjusted relative risk 1.3 (1.1 to 1.6)

^aThe results are followed by 95% confidence intervals in parenthesis

^b Author notes that "We reviewed the medical records at the 39 past estrogen users who had cholecystectomies after 1977 and discovered that 12 Of them had reinitiated estrogen use after 1977 and before their hospitalization for gallbladder disease When those 12 women were removed from the cases that had been considered past users, the age-adjusted relative risk of gallbladder disease in past users decreased to 1.1 (95% confidence interval 0.7-1.8) When these 12 women were added to the current users, this relative risk estimate for current use increased to 3.9 (95% confidence interval 2.6-5 .9. As study subjects who never experienced cholecystectomy and who initiated estrogen use after followup could not be relocated, these risk estimates were biased downward for past estrogen use and upward for current estrogen use "

KEY: CEE = conjugated equine estrogen

SOURCE Office of Technology Assessment, 1995

TABLE H-4: Hormone Replacement Therapy and Gallbladder Disease: Randomized Trial

Author	Description of study participants	Duration of study	Results
Nachtigall (1979)	Subjects were 84 pairs of postmenopausal inpatients at Goldwater Memorial Hospital in New York City, a hospital for chronic diseases, matched for age and diagnosis. Treatment group received 2.5 mg CEE daily with 10 mg medroxyprogesterone acetate for 7 days each month. Control group received placebos.	10 years	Incidence of cholelithiasis ^a in treatment group: 4/84 (0.48%) Incidence of cholelithiasis control group: 2/84 (0.24%) P>=0.05 (nonsignificant)

^a Author did not define "cholelithiasis."

^b Author notes "These findings, however, should be interpreted with Caution Since the power of the test differences was generally low due to the small sample size."

SOURCE: Office of Technology Assessment, 1995

ease of **approximately 2.1**, while current users had a relative risk of 2.7 (16) (table H-3). The other cohort study found, after adjusting for confounding factors, a relative risk of cholecystectomy of 2.6 in long-term current estrogen users. The only controlled clinical trial of estrogen use and gallbladder disease found doubled the incidence of gallbladder disease in HRT users (12) (table H-4). This difference did not reach statistical significance, which may be due to the small number of women who participated in this study.

Some studies of symptomatic gallstone disease, however, have found no effect of estrogen use on gallbladder disease (9). The differences among studies may be due to differences in the doses of estrogens used by participants, the average duration of use of estrogen, or the small numbers of persons involved in these studies (14). These studies also were either case-control studies or cross-sectional studies, which may have biased their outcomes.

Although the strongest evidence, including the prospective cohort studies of the issue, points to an elevated risk of symptomatic gallstone disease among current users, it is less certain whether the risk of symptomatic gallstone disease remains elevated in those who have ceased estrogen therapy. The studies to date have not found a statistically significant relationship between past use and gallstone disease.

Although empirical studies have found an increase in symptomatic episodes, hospitalization, and gallbladder removal (cholecystectomy) among current estrogen users, they have failed to detect an increased prevalence of gallstones among estrogen users using imaging techniques capable of detecting silent gallstones (6,11,17). The failure to find increased incidence of asymptomatic gallstones raises the possibility that the studies examining symptomatic disease may be subject to surveillance biases (i.e., estrogen-treated women are seen more frequently by their doctors and are therefore more likely to be diagnosed and undergo surgery) (1).

Studies have not been able to consistently demonstrate an increased risk of gallbladder disease with increased duration of use of estrogen replacement therapy (3, 16, 16a). Results from the Nurses Health Study cohort demonstrated an increased risk with duration of use in current users, but little or no effect of duration in past users (16a) (table H-3).

The results from the Nurses Health Study also showed an increased risk with larger doses of estrogen (16a). This result is consistent with an earlier cohort study of oral contraceptive users that found an increase in risk with increasing dose (19).

The addition of progestins is unlikely to mitigate estrogen-induced increases in gallbladder

disease, since progestins also promote gallstone formation (11).

On the basis of the studies outlined in tables H-1 to H-4, including the cohort studies of this issue(16), OTA adopted a base case assumption that the risk of symptomatic gallbladder disease would be elevated by a factor of 2.5 while a woman is on HRT. The risk would subside to that of the general population of women at the time that HRT ceases. We believe that the possible values of the relative risk of symptomatic gallbladder disease due to current HRT range from 1.0 (best case) to 3.0 (worst case).

The definitive treatment for gallbladder disease is cholecystectomy, a standard surgical procedure that is rarely fatal (13). For this analysis, we have assumed that gallbladder disease results in health care costs for surgical removal of the gallbladder and hospitalization. We have assumed, however, that gallbladder disease does not affect the years of life lived.

OTA's sensitivity analysis shows that our assumptions about the risk of gallbladder disease in HRT users does not affect the outcome of the analysis greatly, since gallbladder disease affects health care costs but not years of life lived.

REFERENCES

1. Barrett-Connor, E., "Putative Complications of Estrogen Replacement Therapy: Hypertension, Diabetes, Thrombophlebitis, and Gallstones," *The Menopause. Biological and Clinical Consequences of Ovarian Failure: Evolution and Management*, S. Korenman (ed.) (Norwell, MA: Serono Symposia, USA, 1990).
2. Bennion, L., Ginsberg, R., Garnick, M., et al., "Effects of Oral Contraceptives on the Gallbladder of Normal Women," *New England Journal of Medicine* 294(4): 189-192, 1976.
3. Boston Collaborative Drug Surveillance Program, "Surgically Confirmed Gallbladder Disease, Venous Thromboembolism, and Breast Tumors in Relation to Postmenopausal Estrogen Therapy," *New England Journal of Medicine* 290(1):15-19, 1974.
4. D'Amato, G., Cavallini, A., Mesa, C., et al., "Serum and Bile Lipid Levels in a Postmenopausal Woman After Percutaneous and Oral Natural Estrogens," *American Journal of Obstetrics and Gynecology* 160:600-601, 1989.
5. Diehl, A.K., Stern, M. P., Ostrower, V. S., et al., "Prevalence of Clinical Gallbladder Disease in Mexican-American, Anglo, and Black Women," *Southern Medical Journal* 73(4):438-443, 1980.
6. Everson, R., Byar, D., and Bischoff, A., "Estrogen Predisposes to Cholecystectomy but not to Stones," *Gastroenterology* 82(1):4-8, 1982.
- 6a. Grodstein, F., Colditz, G. A., Stampfer, M. J., "Prospective Hormone Use and Cholecystectomy in a Large Prospective Study," *Obstetrics and Gynecology* 83(1):5-11, 1993.
7. Honore, L. H., "Increased Incidence of Symptomatic Cholesterol Cholelithiasis in Perimenopausal Women Receiving Estrogen Replacement Therapy: A Retrospective Study," *Journal of Reproductive Medicine* 25(4):187-190, 1980.
8. Jorgenson, T., "Gall Stones in a Danish Population: Fertility Period, Pregnancies, and Exogenous Female Sex Hormones," *Gut* 29:433-439, 1988.
9. Kakar, F., Weiss, N., and Strite, S., "Non-Contraceptive Estrogen Use and the Risk of Gallstone Disease in Women," *American Journal of Public Health* 78(5):564-566, 1988.
10. La Vecchia, C., Negri, E., D'Avanzo, B., et al., "Oral Contraceptives and Non-Contraceptive Oestrogens in the Risk of Gallstone Disease Requiring Surgery," *Journal of Epidemiology and Community Health* 46(3):234-236, 1992.
11. Mack, T., and Ross, R., "A Current Perception of HRT Risks and Benefits," *Osteoporosis: Physiological Basis, Assessment, and Treatment*, H.F. DeLuca and R. Mazess (eds.) (New York, NY: Elsevier Science Publishing Co., Inc., 1990).

12. Nachtigall, L.E., Nachtigall, R. H., Nachtigall, R. D., et al., "Estrogen Replacement Therapy II: A Prospective Study in the Relationship to Carcinoma and Cardiovascular and Metabolic Problems," *Obstetrics & Gynecology* 54(1):74-79, 1979.
13. Nahrwold, D.L., "Acute Cholecystitis," *Textbook of Surgery: The Biological Basis of Modern Surgical Practice*, 14th Ed., D.C. Sabiston, Jr., (ed.) (Philadelphia, PA: W.B. Saunders Co., 1991).
14. Petitti, D., "Gallbladder Disease and Use of Noncontraceptive Estrogens," *Geriatric Medicine Today* 9(3):56-63, 1990.
15. Petitti, D. B., Friedman, G.D., and Klatsky, A. L., "Association of a History of Gallbladder Disease with a Reduced Concentration of High-Density-Lipoprotein Cholesterol," *New England Journal of Medicine* 304(23): 1396-1398, 1981.
16. Petitti, D., Sidney, S., and Perlman, J., "Increased Risk of Cholecystectomy in Users of Supplemental Estrogen," *Gastroenterology* 94:91-95, 1988.
17. Pixley, F., Wilson, D., McPherson, K., et al., "Effect of Vegetarianism on Development of Gall Stones in Women," *British Medical Journal* 291:11-12, 1985.
18. Scragg, R. K., McMichael, A.J., and Seemark, R. F., "Oral Contraceptives, Pregnancy, and Endogenous Oestrogen in Gall Stone Disease - A Case-Control Study," *British Medical Journal* 288: 1795-1799, 1984.
19. Strom, B., Tamragouri, R., Morse, M., et al., "Oral Contraceptives and Other Risk Factors for Gallbladder Disease," *Clinical Pharmacology and Therapy* 39:335-341, 1986.