INTRODUCTION

The average age of onset of menopause in the U.S. population is 51 years.1 Vasomotor instability and hot flashes are among the first symptoms of decline of endogenous estrogen levels. Hormone replacement therapy (HRT), estrogen or estrogen plus progesterone, has been used to alleviate these symptoms. Important to note are the long-term effects of menopause as a risk factor for osteoporosis. One of the documented side effects of HRT is an increased risk of calculous gallbladder disease,2-4 the subject of this review.

EPIDEMIOLOGY

Cholelithiasis is the pathologic state of stones or calculi within the gallbladder lumen. Based on ultrasound examinations of a representative U.S. sample in the Third National Health and Nutrition Examination Survey (NHANES III), it is estimated that 14.2 million women age 20-74 years have gallbladder disease.5 There were 700,000 cholecystectomies in the year 1996.6 The annual cost of the disease is over $6.5 billion, which is second only to gastroesophageal reflux disease (GERD) among digestive diseases. In 1998, 1143 deaths were attributed to gallbladder disease.7

Age is a major risk factor for gallstones, and this risk increases sharply after age 40. Women have a higher risk of gallbladder disease than men of the same age. The female-to-male ratio of gallbladder disease falls with increasing age, suggesting a possible hormonal effect. Most gallstones are asymptomatic. Complications of gallstones include biliary colic, acute cholecystitis, choledocholithiasis, cholangitis, gallbladder cancer, and acute pancreatitis. Most studies have used the presence of gallstones on ultrasound or cholecystectomy as a marker for gallbladder disease.

In humans, 75-80% of gallstones are cholesterol stones, and approximately 10-25% are bilirubin pigment stones. Each type has a particular pathophysiology. The pathophysiology of cholesterol stones has been described in three steps: supersaturation of bile, crystallization, and stone growth.

Cholesterol is insoluble in water. It is made soluble in bile by the detergent action of bile salts and phospholipids. Factors that increase cholesterol in bile or decrease bile acids cause supersaturated bile. This tilts the balance toward cholesterol insolubility. In addi-
tion, alterations of biliary mucus, related to the presence of mucin glycoproteins, and the lack of gallbladder acidification promote crystallization of cholesterol in supersaturated bile. Gallbladder hypomotility and bile stasis also play a part in stone growth.8

HORMONE REPLACEMENT THERAPY

The risks and benefits of HRT have been a question of great interest over the past few years. Risks include venous thromboembolism, breast cancer, gallbladder disease, and endometrial cancer (in the setting of unopposed estrogen use). Clinical studies demonstrate that HRT reduces the risk of colorectal cancer and osteoporosis.9,10

Cardiovascular disease risk and HRT has been an area of uncertainty. Data from the Women’s Health Initiative (WHI) has shown that estrogen-plus-progesterin HRT imparts no cardiovascular benefit and leads to some increased risk of cardiovascular disease and thromboembolic events.11

The two WHI trials randomized postmenopausal, post-hysterectomy women to conjugated estrogen alone or conjugated estrogen plus progesterone in women with an intact uterus.12 Both trials were placebo-controlled with follow-up periods of 7.1 and 5.6 years, respectively. The results showed a greater risk of gallbladder disease or surgery with estrogen (hazard ratio [HR], 1.67; 95% CI, 1.35-2.06) than with estrogen plus progesterone (HR, 1.59; 95% CI, 1.28-1.97) (Table I).12 Among women receiving estrogen alone, there were 78 events per 10,000 person-years, which is an excess of 31 events per 10,000 women annually. Among women receiving estrogen plus progesterone, there were 55 events per 10,000 person-years, which is an excess of 20 events per 10,000 women.

| CEE Trial | Estrogen, No. (%) (n=4141) | Placebo, No. (%) (n=4235) | HR (95% CI) | P value*
| --- | --- | --- | --- | ---
| Follow-up time, mean (SD), y | 7.1 (1.6) | 7.1 (1.6) |  | 
| Global gallbladder procedure/disease† | 228 (0.78) | 143 (0.47) | 1.67 (1.35-2.06) | <0.001
| Global gallbladder procedure | 197 (0.67) | 113 (0.37) | 1.82 (1.45-2.30) | <0.001
| Cholecystectomy | 192 (0.65) | 104 (0.34) | 1.93 (1.52-2.44) | <0.001
| Other biliary tract procedures | 27 (0.09) | 24 (0.08) | 1.18 (0.68-2.04) | 0.56
| Global gallbladder disease | 223 (0.76) | 130 (0.43) | 1.79 (1.44-2.22) | <0.001
| Cholecystitis | 186 (0.63) | 107 (0.35) | 1.80 (1.42-2.28) | <0.001
| Cholelithiasis (gallbladder or biliary calculi) | 197 (0.67) | 110 (0.36) | 1.86 (1.48-2.35) | <0.001

CEE = conjugated equine estrogens; E + P = estrogen plus progestin; CI = 95% confidence intervals; HR = hazard ratios.

* P values from Cox proportional hazards analyses stratified by age and randomization status in the Women’s Health Initiative

† Events include the first of any diagnosis of gallbladder disease including cholecystitis or calculi, as well as biliary tract procedures.

In a smaller randomized trial studying outcomes of combination estrogen and progestin therapy in postmenopausal women, one of the secondary outcomes studied was gallbladder disease. The Heart and Estrogen/progestin Replacement Study (HERS) included 2763 women with heart disease who were treated with placebo or equine estrogen (0.625 mg) plus medroxyprogesterone acetate (2.5 mg) hormone therapy. Gallbladder disease occurred in 3% of participants in the hormone treatment group (84/2763) versus 2.2% in the placebo group (62/2763), with a relative hazard of 1.38 (95% CI, 1.0-1.92). The authors also found that increasing the dose of estrogen correlated with increased risk of cholecystectomy. A hospital-based, case-control study of postmenopausal women conducted in Italy between 1985 and 1997 showed a correlation between the use of HRT and gallbladder cancer. The odds ratio was 3.2 with 95% CI, 1.1-9.3. The study based its findings on a small number of incident cases (31 cases of histologically confirmed gallbladder cancer) due to the rarity of gallbladder cancer; however, it is one of the few studies to show an epidemiological link between HRT and gallbladder cancer.

### PATHOPHYSIOLOGY

The mechanism of estrogen-induced gallstone disease is believed to arise from its ability to increase levels of biliary cholesterol while decreasing the relative level of bile acids (Table II). This increases cholesterol saturation in bile, predisposes to crystal, and, finally, gallstone nucleation and formation. Conjugated estrogen and progesterone have been shown to increase the lithogenic index of bile, increase biliary cholesterol secretion, stimulate cholesterol esterification, reduce nucleation time, and inhibit bile acid synthesis.

<table>
<thead>
<tr>
<th>Assignment in the Women’s Health Initiative Estrogen Trials</th>
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<tr>
<td><strong>E + P Trial</strong></td>
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<tr>
<td>Estrogen, Placebo, HR (95% CI)</td>
</tr>
<tr>
<td>No. (%) (n=4141) No. (%) (n=4235) P value*</td>
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<tr>
<td>5.7 (1.3) 5.6 (1.3)</td>
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<td>228 (0.55) 135 (0.35) 1.59 (1.28-1.97) &lt;0.001</td>
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<td>196 (0.47) 113 (0.29) 1.63 (1.29-2.06) &lt;0.001</td>
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<td>190 (0.46) 107 (0.28) 1.67 (1.32-2.11) &lt;0.001</td>
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<td>24 (0.06) 15 (0.04) 1.49 (0.78-2.84) 0.23</td>
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<td>223 (0.54) 130 (0.34) 1.61 (1.30-2.00) &lt;0.001</td>
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<td>192 (0.46) 117 (0.30) 1.54 (1.22-1.94) &lt;0.001</td>
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<tr>
<td>208 (0.50) 116 (0.30) 1.68 (1.34-2.11) &lt;0.001</td>
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Results showed an increased risk in women using HRT (estrogen and estrogen plus progesterone). The relative risk of cholecystectomy was 2.1 in the “ever-users” of HRT and 2.6 in long-term users of HRT (95% CI, 2.2-3.1). The authors also found that increasing the dose of estrogen correlated with increased risk of cholecystectomy.

Dietary Modification and Calcium and Vitamin D trials. including cholecystectomy. JAMA 2005;293:330-339. Copyright© 2005; American Medical Association. All rights reserved.
In a case study of a postmenopausal woman in whom a Kerr tube was inserted due to a lesion of the bile duct, D’Amato et al.21 administered 4 weeks of percutaneous 17beta-estradiol at a dose of 5 mg per day, which was followed by 6 weeks without treatment, and then by oral 17beta-estradiol 2 mg per day. Biliary cholesterol concentration increased after both methods of hormone administration, whereas bile flow increased and cholesterol crystals appeared after oral administration only.

In studies with prairie dogs, Tierney et al.22 reported that administration of exogenous estrogen slows sphincter of Oddi motility. In addition, another study of prairie dogs found progesterone to alter biliary flow.23 In comparison to control animals, progesterone-treated animals had impaired gallbladder filling and emptying.

The gallbladder has been shown to have both estrogen and progesterone receptors.24 In studies using female guinea pigs, the contractile response of the gallbladder was inversely related to the number of progesterone receptors. Oophorectomized animals treated with estrogen plus progesterone showed increased levels of progesterone receptors, and the concentration of receptors was inversely related to the contractile response to cholecystokinin.24 The mechanism of this decrease in contractility after treatment with progesterone has been investigated. G protein impairment is shown to play a role in mediating this effect,25 specifically via G13 protein.26

**CONCLUSION**

Multiple studies have reported on the relationship between the use of HRT and the occurrence of calculous gallbladder disease. Randomized clinical trials, prospective studies, case studies, observational...
studies, and animal-based experiments have been discussed in this review. Most reports describe a significant increase in the risk of gallbladder disease in individuals using HRT. Gallbladder disease is one of the factors to be considered when reviewing the risks and benefits of HRT prescribed for the postmenopausal patient.

The authors report no relevant financial relationships.

REFERENCES