Hormone Replacement Therapy and Gallstone Disease: A Real Association

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Cholelithiasis is the most common form of benign gallbladder disease. Cholesterol gallstones occur more frequently in women than in men in all parts of the world. The role of female sex hormones in the pathogenesis of gallstones is well established [1]. The sex difference starts at puberty, continues throughout the fertile period and diminishes after menopause [1].

Observational studies indicate a 2- to 4-fold increased risk for gallbladder disease related to estrogen therapy (table 1). The Nurses’ Health study found an increased risk of cholecystectomies among participants taking postmenopausal hormones, with a relative risk (RR) of 2.1 for current hormone users. Higher risks were associated with longer duration of use (RR 1.4 and RR 1.7 for past users of <2 years and ≥10 years’ duration, respectively) and higher doses (RR 1.3 for users of 0.3 mg daily of estrogen compared to RR of 2.4 for users of 1.25 mg or more daily) [2]. Mamdami et al. [3] also reported an increased risk of cholecystectomies among Canadian women who recently started using estrogen. The Atherosclerosis Risk in Communities (ARIC) study group also demonstrated that both current and former users of hormone replacement therapy (HRT) had a significantly increased risk of gallbladder disease [4]. Two recently conducted randomized controlled trials among women that examined gallbladder disease outcome after HRT – the Heart and Oestrogen/Progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI) Postmenopausal Hormone Trial – also unequivocally confirmed that oral estrogen use is causally associated with gallbladder disease, and the magnitude of effect is not influenced greatly by the presence or absence of progestins [5, 6].

Yet another study by Hart et al. [7] from the UK also confirms previous reports that the use of HRT is positively associated with an increased risk of symptomatic gallstones. This first European study also shows that the risk of gallstones appeared greater with an increasing duration of use of HRT.

The strengths of this study include the fact that it was a properly conducted investigation with radiological and/or surgical/pathological confirmation of gallstones, appropriate exclusions and selection of age-matched controls. Despite these advantages, the study has several weaknesses/limitations as also discussed by the authors. The study is unable to provide an answer on the effect of dose of estrogen on occurrence of symptomatic gallstones. The results of the study apply only to symptomatic gallstones but not to the clinically silent gallstones. It is also not clear whether HRT influences the natural history of clinically silent gallstones by making them symptomatic. Estrogen use has been shown to cause inflammation or pain or both, thus resulting in an intensification of symptoms [1, 8, 9]. The same mechanism can cause clinically silent gallstones to become symptomatic. However, this issue needs to be examined prospectively by performing abdominal ultrasonography of the subjects at the time of inclusion into the study. Though there are no ethical issues with ultrasound examination in...
healthy subjects, it would require extensive efforts and financial inputs. Finally, authors were unable to validate the self-reported use of HRT by the participants.

Most gallstones are composed of cholesterol. Super-saturation of bile with cholesterol, bile stasis and destabilization of bile are required for the formation of cholesterol gallstones. Similar mechanisms of cholesterol gallstone formation may operate in women taking HRT. Estrogens increase cholesterol saturation of bile, alter bile acid composition (by lowering the chenodeoxycholate pool and by increasing the cholic acid pool) and decrease bile flow [10]. Addition of progestins in HRT may contribute to gallstone formation by causing gallbladder and intestinal hypomotility [1, 11].

HRT is indicated for reducing menopausal symptoms, especially vasomotor and urogenital symptoms, and in improving quality of life. HRT may also be beneficial in osteoporosis prevention near the menopause. However, with the publication of the WHI study in July 2002, a dramatic fall in the use of HRT was observed. The study was stopped early because analysis did not find the expected benefit in preventing hip fracture and colorectal cancer were outweighed by the increased risk of breast cancer, stroke, and deep vein thrombosis [12]. Recent analyses of the WHI data and other randomized controlled trials have now unified much of the data on HRT and have greatly changed the risk-benefit ratio; the benefits outweigh the risks for most women if HRT is initiated in the perimenopausal period [13, 14].

The potential side effects and risks associated with HRT, including symptomatic gallstones, can be reduced by: (1) using lower doses of HRT [15], (2) minimizing or eliminating systemic progestogens, e.g. low-dose vaginal estrogen preparations for genitourinary symptoms [16], (3) initiating HRT in symptomatic women near menopause (there are now robust data in support of the ‘critical therapeutic window’ hypothesis that estrogen is cardioprotective if initiated around the menopause when there are still vascular estrogen receptors responsive to exogenous HRT), (4) women harboring asymptomatic gallstones should not receive estrogens because of possibility of developing cholecystitis, and (5) HRT should only be continued for women as long as distressful symptoms remain.

### Table 1. Evidence of association between estrogen use and gallstones

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study population</th>
<th>Outcome measure</th>
<th>Risk of development of benign gallbladder disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td>current users</td>
</tr>
<tr>
<td>Grodstein et al.</td>
<td>USA</td>
<td>postmenopausal nurses</td>
<td>cholecystectomy</td>
<td>†</td>
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<tr>
<td>Mamdani et al.</td>
<td>Canada</td>
<td>postmenopausal women</td>
<td>cholecystectomy</td>
<td>†</td>
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<tr>
<td>Boland et al.</td>
<td>USA</td>
<td>healthy men and women</td>
<td>gallbladder disease</td>
<td>†</td>
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<tr>
<td>Hart et al.</td>
<td>UK</td>
<td>healthy women</td>
<td>symptomatic cholelithiasis</td>
<td>†</td>
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<td><strong>Randomized controlled trials</strong></td>
<td></td>
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<td></td>
<td>current users</td>
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<tr>
<td>Simon et al.</td>
<td>USA</td>
<td>postmenopausal women with known coronary artery disease</td>
<td>documented biliary tract surgery</td>
<td>†</td>
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<tr>
<td>Cirillo et al.</td>
<td>USA</td>
<td>healthy postmenopausal women</td>
<td>gallbladder disease and related procedures</td>
<td>†</td>
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### References


