Postmenopausal estrogen replacement therapy and increased rates of cholecystectomy and appendectomy

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Abstract

Background: Several studies have indicated that estrogen may prime inflammatory and nociceptive pathways, leading to symptoms that mimic cholecystitis. We set out to confirm the relation between recent estrogen use and cholecystectomy in postmenopausal women and to test the novel hypothesis that a similar relation exists for appendectomy.

Methods: We developed a retrospective cohort using prescribing and surgical procedure information from health administrative databases for approximately 800 000 female residents of Ontario who were over 65 years of age between July 1, 1993, and Mar. 31, 1998. We compared the incidence of cholecystectomy and appendectomy among women recently prescribed estrogen replacement therapy, levothyroxine and dihydropyridine calcium-channel antagonists (DCCA) using age-adjusted Cox proportional hazards models. Patients were followed for a mean of 540 (standard deviation [SD] 449) days.

Results: Compared with women taking DCCA, those who had recently begun taking estrogen were significantly more likely to undergo cholecystectomy (age-adjusted risk ratio [aRR] 1.9, 95% confidence interval [CI] 1.6–2.2) and appendectomy (aRR 1.8, 95% CI 1.1–3.0). No significant difference in either outcome measure was found between the levothyroxine users and the DCCA users.

Interpretation: This study identifies an increased risk of cholecystectomy and appendectomy among postmenopausal women who have recently begun estrogen replacement therapy.

Estrogen has been associated with a variety of inflammatory and pain syndromes. Associations between postmenopausal estrogen replacement therapy and pancreatitis,[1] systemic lupus erythematosus,[2] asthma,[3] temporomandibular pain[4] and general abdominal pain[5] have been reported. A recent randomized controlled trial, the Heart and Estrogen–Progestin Replacement Study (HERS), identified an increased risk of gallbladder disease among postmenopausal women given hormone replacement therapy.[6] In a large prospective study involving postmenopausal women hormone replacement therapy more than doubled the risk of cholecystectomy.[7] Everson and colleagues[8] observed an increased risk of cholecystectomy among men treated with diethylstilbestrol (DES) but, upon postsurgical pathological examination, found no association between DES and gallstones.

It appears that estrogen primes inflammatory[9] and nociceptive[10] pathways. Moreover, estrogen is associated with several markers of systemic inflammation[9,11,12] as well as substance P receptor gene expression.[13] A recent study examining nociception in monkeys whose ovaries had been removed demonstrated a small, yet statistically significant, increase in pain sensitivity to thermal stimuli upon administration of estradiol.[14]

These findings suggest, first, that estrogen use may lead to either acalculous cholecystitis or symptoms that mimic cholecystitis more often than to actual gallstone formation and, second, that estrogen may also be associated with an increased

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Research

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risk of other surgical procedures because of its priming effect on the inflammatory and nociceptive pathways. We therefore set out to confirm the relation between recent estrogen use and cholecystectomy in postmenopausal women and to test the novel hypothesis that a similar relation may exist for appendectomy.

Methods

We created a retrospective cohort by linking universal health administrative databases covering over 800 000 female residents of Ontario who were more than 65 years of age between July 1, 1993, and Mar. 31, 1998. Patients were included if they had been prescribed estrogen, levothyroxine (a different long-term endocrine replacement therapy) or a long-acting dihydropyridine calcium-channel antagonist (DCCA) (representing a distinct class of drugs not known to induce significant systemic inflammation).

The Ontario Drug Benefits Plan database was used to identify the medication each patient was prescribed during the observation period. This database is maintained by the Ontario Ministry of Health and includes encrypted patient identifiers, prescription dates and drug information for all residents of Ontario aged 65 years or older. Patients who received medication from any of the 3 groups during the 180 days before cohort entry were excluded so that only new users of the medications would be included.

The primary outcomes of interest were the incidences of cholecystectomy (Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures [CCP][15] codes 63.1, 63.11, 63.12, 63.13 and 63.14) and primary (nonincidental) appendectomy (CCP code 59.0). Cholecystectomies and primary appendectomies were identified using the Canadian Institute for Health Information Discharge Abstract Database. This database records discharge information for all patients admitted to Ontario acute care hospitals. Patients were excluded if they had undergone cholecystectomy or appendectomy during the 2 years before study entry.

Each patient's sex, age at study entry and date of death (if applicable) were taken from Ontario's Registered Persons Database.

The databases were linked through common encrypted patient-identifying numbers. Researchers using these databases have found that surgical procedures are coded with a high degree of accuracy.[16] There is very little missing information in the Ontario databases; other studies have found that less than 1% of the basic information about patients is missing in various provincial databases.[17]

We defined the duration of exposure as the period of continuous, exclusive enrolment in any of the study arms. Exposure started from the first prescription of a study medication during this period. Subjects were allowed to switch to different medications within the same drug class. We assumed that therapy was discontinued if it was not renewed within 180 days. Observation occurred from the date the study drug was started to 30 days following the last recorded prescription date. Observation ended when subjects underwent cholecystectomy or appendectomy in the respective analyses. Patients were censored if they were exposed to a drug from another study group, they temporarily or permanently discontinued their study drug, they died or the observation period ended.

Time-to-event analyses were conducted using Cox proportional hazards models that controlled for patient age at entry. The outcome variables for the 2 primary analyses were the incidence rates of cholecystectomy and appendectomy, respectively. We tested whether the proportional hazards assumption was violated by our model. In addition to the Cox model we also conducted sensitivity analyses using parametric survival models (gamma, log-logistic, log normal) that do not require a proportional hazards assumption.

Results

The average age at entry of the women in the estrogen group was 72.2 (standard deviation [SD] 5.8) years, as compared with 75.6 (SD 7.4) years for those in the levothyroxine group and 75.2 (SD 6.6) years for those in the DCCA group. During a total of approximately 136 000 person-years of follow-up the crude incidence rates of cholecystectomy per 10 000 person-years in the estrogen group (n = 30 232), the levothyroxine group (n = 22 294) and the DCCA group (n = 39 422) were 122.2, 59.9 and 61.1 respectively (Table 1); the corresponding crude incidence rates of primary appendectomy were 9.4, 5.8 and 5.3 per 10 000 person-years (Table 1). Relative to the DCCA users, the estrogen users were significantly more likely to undergo cholecystectomy (age-adjusted risk ratio [aRR] 1.9, 95% confidence interval [CI] 1.6–2.2) and primary appendectomy (aRR 1.8, 95% CI 1.1–3.0), whereas levothyroxine use did not increase the risk of cholecystectomy (aRR 1.0, 95% CI 0.9–1.2) or of primary appendectomy (aRR 1.1, 95% CI 0.7–1.9) (Table 1, Fig. 1). We conducted a sensitivity analysis by repeating the analyses on 5-year age groups (i.e., 65–69, 70–74, 75–79, 80–84, ≥ 85). A consistently elevated risk was noted for both cholecystectomy

Table 1: Surgical interventions in postmenopausal women by treatment group

	Treatment group		
Intervention	Estrogen replacement	Levothyroxine	DCCA
Cholecystectomy	*n = 30 232*	*n = 22 294*	*n = 39 422*
No. of events	346	234	420
Mean follow-up period (and SD), d	342 (376)	640 (454)	637 (447)
Total follow-up period, person-years	28 317	39 042	68 703
Crude incidence rate per 10 000 person-years	122.2	59.9	61.1
Age-adjusted risk ratio (and 95% CI)*	1.9 (1.6–2.2)	1.0 (0.9–1.2)	1.0
Appendectomy	*n = 30 565*	*n = 22 476*	*n = 39 796*
No. of events	27	23	37
Mean follow-up period (and SD), d	342 (377)	643 (455)	638 (448)
Total follow-up period, person-years	28 591	39 533	69 552
Crude incidence rate per 10 000 person-years	9.4	5.8	5.3
Age-adjusted risk ratio (and 95% CI)*	1.8 (1.1–3.0)	1.1 (0.7–1.9)	1.0

Note: DCCA = dihydropyridine calcium-channel antagonists, SD = standard deviation, CI = confidence interval.
*Derived from Cox proportional hazards model estimates.

and appendectomy among estrogen users in each age group.

Our analyses showed that, in fitting the Cox regression models, the proportional hazards assumption was not satisfied. Nevertheless, alternative sensitivity analyses using parametric survival models that do not require such assumptions yielded comparable results, including age-adjusted survival curves similar to those presented in Fig. 1.

Interpretation

The results of our study confirm the relation between recent estrogen use and cholecystectomy and identify an association between recent estrogen use and primary appendectomy in postmenopausal women.

Treatment with exogenous estrogen is complicated by numerous physiological and pathological responses. Estrogen use increases levels of C-reactive protein (a physiological marker of inflammation)[9,11,12] and has been associated with enhanced substance P receptor gene expression.[13] Such physiological changes may contribute to conditions associated with inflammation or pain, or both. The HERS study indicated that recipients of hormone replacement therapy may initially be at increased risk for cardiovascular disease.[6] The initial inflammatory effects of hormone replacement therapy may be contributory.[9] A similar initial detrimental effect has been reported for osteoarthritis of the hip.[18]

The primary limitations of this study involve insufficient characterization of the cohorts and potential confounding variables.

First, some recent cohort studies have suggested that the benefits of hormone replacement therapy observed in previous observational studies may owe more to confounding than to an actual beneficial effect of estrogen replacement,[19,20] since women taking hormone replacement therapy may represent a healthier cohort of subjects. The corollary is that the estrogen recipients in our study may have been healthier than the women in the other study groups, with fewer contraindications to surgical procedures. Since the relation between estrogen and cholecystectomy has already been established in a prospective study,[7] this potential selection bias may falsely increase the strength of the association in our study but is unlikely to account for it. Furthermore, primary appendectomy is generally an emergency procedure, and it is therefore unclear how better overall health status in the estrogen group would account for a higher incidence of surgery.

Second, the duration of observation was much shorter in the estrogen group, probably as a result of early discontinuation of the study drug relative to the other 2 groups. Despite the shorter duration of observation we found a significant relation between estrogen use and the primary outcomes.

Third, the estrogen group was younger at the outset than the other 2 groups; this age difference is larger than it first appears because the women in the estrogen group were followed for a shorter period. However, we controlled for age in our models, and the sensitivity analysis showed that the findings were highly consistent within 5-year age intervals. Sensitivity analyses using parametric survival models further confirmed our original findings.

Fourth, we are uncertain how similar the study groups were in other clinical characteristics associated with cholecystectomy or appendectomy. Although factors such as obesity, smoking, dyspeptic symptoms, diet, antibiotic use, alcohol consumption and coffee intake can influence the need for these procedures,[21,22] we cannot identify any reason why these factors would be substantially different between the study groups assessed.

Finally, our findings pertain to the relatively recent use of estrogen replacement therapy and may not be generalizable to postmenopausal women who have been receiving long-term therapy.

Controversy surrounding the benefit-to-risk profile of estrogen use in postmenopausal women continues. The results of our study are pathophysiologically consistent with multiple lines of evidence and suggest additional risks that have hitherto been unrecognized.

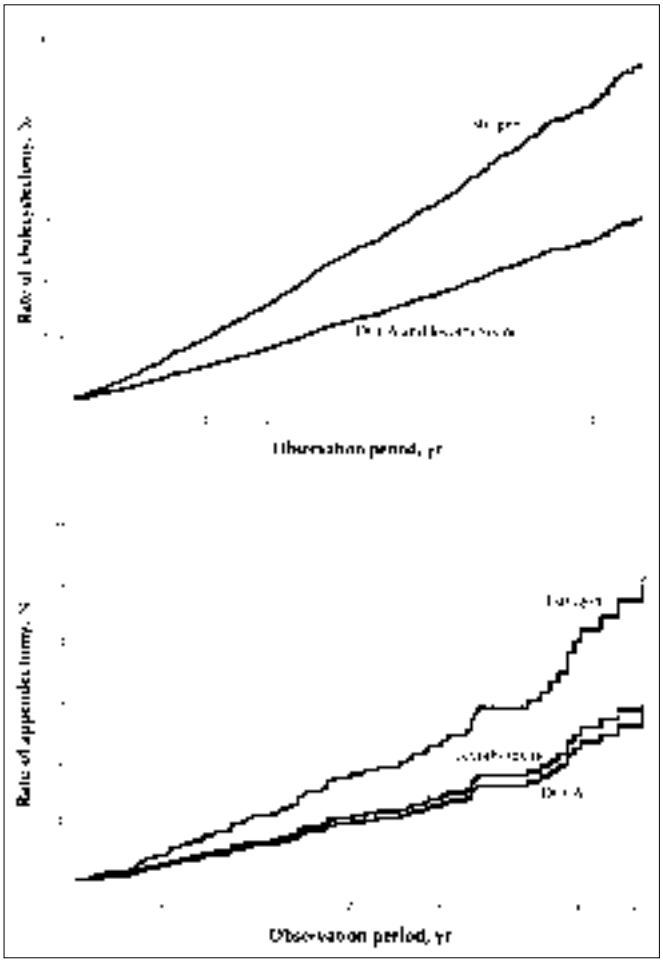

Fig. 1: Age-adjusted incidence rates of cholecystectomy (top) and appendectomy (bottom) among postmenopausal women receiving estrogen replacement therapy, levothyroxine and dihydropyridine calcium-channel antagonist (DCCA).

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Competing interests: None declared.

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