HORMONE REPLACEMENT THERAPY, OTHER REPRODUCTIVE VARIABLES AND SYMPTOMATIC HIP OSTEOARTHRITIS IN ELDERLY WHITE WOMEN: A CASE–CONTROL STUDY

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SUMMARY

Background. Recent epidemiological studies suggest that post-menopausal hormone replacement therapy might reduce the risk of hip osteoarthritis (OA) in women. However, the association of the disorder with other reproductive variables is controversial. We addressed this issue in a population-based case–control study among 413 female cases and 413 age- and sex-matched controls.

Methods. A total of 413 women listed for hip replacement because of primary OA over an 18 month period were compared with an equal number of controls selected from the general population and individually matched for age and general practice. Information about reproductive variables was obtained by questionnaire administered at interview.

Results. The risk of hip OA was significantly elevated among women who had had an oophorectomy (OR = 1.9, 95% CI 1.0–3.7). After adjustment for body mass index, the presence of Heberden’s nodes, previous hip injury and past leisure sporting activity (all independent risk factors for hip OA), and for other reproductive variables, there was a non-significant, protective effect of long-term hormone replacement therapy, such that ≥ 5 yr of use was associated with a 40% reduction in risk (OR = 0.6, 95% CI 0.2–1.8). Paradoxically, short-term HRT use (up to 5 yr duration) was associated with an excess risk of hip OA (OR = 1.7, 95% CI 0.9–3.3). There was no association between the risk of hip OA and use of oral contraceptives, parity or hysterectomy.

Conclusions. These data are consistent with previous studies suggesting a protective effect of long-term hormone replacement therapy on the risk of hip OA. By contrast, an elevation of risk in short-term users was demonstrated. Our results also suggest that risk is increased among women who have undergone unilateral or bilateral oophorectomy. Studies are required to investigate the mechanisms underlying these associations.

KEY WORDS: Osteoarthritis, Hip, Hormone replacement therapy, Post-menopausal women, Oophorectomy.

Osteoarthritis (OA) is a common, often debilitating disorder, which accounts for a substantial majority of the 30 000 total hip arthroplasties carried out each year in England and Wales [1]. Epidemiological studies suggest differences in the incidence pattern with age in the two sexes: in women, incidence rates stabilize at the age of 60 yr, while in men incidence rates continue to rise, often into the seventh or eighth decade. This observation has prompted investigators to suggest a role for oestrogen in the aetiology of OA. Case–control and cohort studies suggest a protective effect of hormone replacement therapy (HRT) [2–6], but there have been relatively few studies examining the influence of other reproductive variables [7–11], and results have often been inconsistent. We therefore examined the relationship of HRT use, hysterectomy (with or without oophorectomy) and other reproductive variables to symptomatic hip OA, as part of a population-based case–control study.

SUBJECTS AND METHODS

The study area comprised two health districts in England (Portsmouth and North Staffordshire), which together had a combined population of ~1 million residents. They were selected for the following reasons: (a) they each have a centralized orthopaedic facility for the assessment and treatment of hip OA; (b) the local orthopaedic surgeons were willing to enter all patients into the study; (c) they have a diverse socioeconomic profile with inclusion of both affluent and deprived areas.

The detailed methods have been previously published [12]. In brief, a register was established in each district whereby the orthopaedic surgeons recorded all women aged 45 yr and over who were placed on the waiting list for primary total hip arthroplasty over an 18 month period. The medical records of each subject were reviewed, and the individual was excluded if she had suffered a hip fracture within the preceding year, fulfilled ACR criteria [13] for rheumatoid arthritis or modified New York criteria [14] for ankylosing spondylitis, or had a history of Perthes’ disease, congenital hip dislocation, slipped capital epiphysis or other established cause of secondary OA. Patients who lived outside the two districts under study were also excluded. The pelvic radiographs of each case were evaluated for the presence of OA using measurements of minimal joint space [15] and overall Kellgren/Lawrence score [16].

For each case, a control of the same sex and age (to within 4 yr) was selected from the list of the same general practice held by the county Family Health
Service Association. As almost everyone in the UK is registered with a general practitioner, such lists essentially enumerate the population. Controls were excluded using the same criteria as cases, and controls who declined to participate were replaced.

After giving informed consent, cases and controls completed a structured interviewer-administered questionnaire, enquiring about their medical history, lifestyle and leisure time activities. Information collected on reproductive variables included age at menarche and menopause, number of pregnancies, age at hysterectomy (if applicable) and whether one or both ovaries had been removed at the time (if known). Each woman was asked if she had ever taken HRT or oral contraceptives, and if so, for how long. Where required, information was validated by examination of general practice records. The questions about leisure activities covered participation in sports since leaving school, and the frequency and duration of other physically active pursuits (walking, cycling, gardening and dancing). Subjects were asked whether they had ever injured their hip badly enough to consult a doctor about it. Hip injuries were considered significant if they resulted in an inability to weight bear for at least 1 week, and had occurred at least 1 yr before the onset of hip pain. Measurements of body height and weight were made using portable scales and a stadiometer, and the hands of all subjects were examined for the presence of Heberden’s nodes (a marker for constitutional predisposition to generalized OA).

The data were analysed by conditional logistic regression, and the results summarized as odds ratios (OR) with 95% confidence intervals (CI). Odds ratios are presented both unadjusted and adjusted for the presence of Heberden’s nodes (absent/possible/definite), body mass index (BMI) (in thirds of the distribution) and previous hip injury.

RESULTS

We identified 579 women aged 45 yr and over who were consecutively listed for total hip arthroplasty in Portsmouth and North Staffordshire over the 18 month study period. A total of 472 fulfilled criteria for entry to the study as cases, the main reasons for exclusion being inflammatory arthritis (40 women) and residence out of the area (52 women): 424 (90%) of the eligible cases agreed to participate. The two main problems with control recruitment were general practitioner refusal to allow their patient to be approached (13%), and refusal by the women themselves (28%). Thirteen women from 11 matched pairs were pre-menopausal and these pairs were excluded from the analysis. This report is based on the remaining 413 case–control pairs who provided complete information on the main risk factors under study.

The ages of the cases ranged from 66.2 to 77.3 yr with a median of 72.4 yr. The minimum joint space on plain radiography was ≤1.5 mm in 86% of the case series, and 95% had at least grade 3 osteoarthritic change, according to the Kellgren and Lawrence grading system.

Obesity, hip injury, leisure activity and Heberden’s nodes have all been shown to be significant (P < 0.05) risk factors for hip OA in this study [12]. Among the women included in this analysis, the risk in the highest third of the distribution of BMI was 1.6 (95% CI 1.1–2.3) when compared with the lowest third. Previous hip injury was associated with a 3-fold increase in the risk of hip OA (OR 3.0, 95% CI 1.5–6.1) and those women participating in three or more physically active leisure pursuits during their youth also had an increased risk of hip OA in later life (OR 1.6, 95% CI 1.0–2.5).

Eighty-one women (10%) had ever taken HRT, while only eight women (1%) were taking HRT at the time of their interview. In those women who had ever used HRT, 59 (74%) had taken it for <5 yr, nine (11%) had taken it for between 5 and 9 yr, and 12 (15%) had taken it for 10 yr or longer. A total of 21% of women who had undergone oophorectomy had ever used HRT: 13% for <5 yr and 8% for >5 yr. In those women who reported both hip pain and HRT use (52 women), 19 had started HRT before the onset of pain, while hip pain pre-dated HRT prescription in 32 individuals. The two events were simultaneous in one woman. The median age at menarche of both the cases and their controls was 14 yr, and the median age at menopause was 50 yr in both groups. Eighty-two women (10%) had used the oral contraceptive pill and 100 (13%) had undergone an oophorectomy. In these women, the majority (63; 63%) had both ovaries removed. The prevalence of previous hysterectomy was 21%.

Table I shows the relationship between these reproductive variables and the risk of hip OA. After adjustment for potential confounders and other reproductive variables, short-term (<5 yr) HRT use was associated with an excess risk of hip OA (OR 1.7, 95% CI 0.9–3.3); longer term use showed a weak protective effect (OR 0.6, 95% CI 0.2–1.8). When we divided the group according to whether HRT was started before or after the onset of hip pain, a protective effect of short-term (<5 yr duration) HRT was demonstrated in women who had started HRT at the same time as, or before, hip pain began (OR 0.5, 95% CI 0.2–1.2), while in women who commenced HRT after the onset of hip pain, a non-significant increased risk of OA was again observed (OR 1.3, 95% CI 0.7–2.5). Long-term (>5 yr) HRT was protective in both groups (OR 0.5, 95% CI 0.2–1.5 for women whose therapy pre-dated pain; OR 0.2, 95% CI 0.0–0.8 for women starting long-term therapy after the onset of hip pain). The risk of hip OA was increased in women who had undergone oophorectomy (OR 1.9, 95% CI 1.0–3.7). Age at menarche, age at menopause and number of pregnancies were not significantly associated with risk of hip OA.

DISCUSSION

We have demonstrated that surgical oophorectomy is associated with an increased risk of symptomatic hip OA. In addition, our results accord with those of
previous studies, in showing that long-term HRT use is associated with a reduced risk of the disease. Short-term use of HRT, however, was associated with an increased risk of OA, which may reflect the prescription of HRT to women who present with hip pain. Other risk factors included high BMI, high level of leisure physical activity and previous hip injury, but adjustment of the risks associated with surgical oophorectomy and HRT for these other factors did not alter them appreciably.

Our study has certain limitations. This is a study of end-stage hip OA among women referred for total hip replacement. If women seeking medical care (and hence receiving hip replacement) were also more likely to take HRT, we might have detected a spurious positive association of HRT with end-stage hip OA. Alternatively, it is possible that HRT might have been more frequently prescribed to women having hip pain, a possibility supported by our observation that 62% of women who had undergone hysterectomy and oophorectomy, rather than hysterectomy alone. By contrast, the prevalence of post-menopausal oestrogen use was relatively low, with a corresponding constraint on statistical power. However, these figures accord with estimates that HRT is ever used by 15% of eligible UK women, and used for more than a few years in only 5% [17]. In particular, HRT use in women who had undergone oophorectomy was surprisingly low; previous surveys have suggested a prescription rate of 30% for any duration of HRT use [18]. We were unable to validate subjects' reports of oophorectomy at the time of hysterectomy, although in this age group it is more likely that oophorectomy had occurred without the subject being aware, than the reverse. We have no reason, however, to suspect that the accuracy of information about HRT use and oophorectomy differed systematically between cases and controls, and therefore we would expect any errors to obscure rather than exaggerate associations with OA.

Data are more consistent in pointing to a protective effect of HRT on the risk of OA. Among women in Framingham who had ever used HRT, there was a 30% reduction in the risk of radiographic knee OA [3]. As in our study, there was also an excess risk of knee OA among those women who had used HRT short term (<1 yr), although this was non-significant. Four other studies have suggested that HRT might

![Table 1](https://example.com/table1.png)

**Table 1**

Risk of hip OA among women according to selected reproductive risk factors

<table>
<thead>
<tr>
<th>Risk of hip OA</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Unadjusted OR (95% CI)</th>
<th>Confounder adjusted† OR (95% CI)</th>
<th>Mutually adjusted‡ OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>No</td>
<td>365</td>
<td>375</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>46</td>
<td>36</td>
<td>1.5 (0.9, 2.6)</td>
<td>1.6 (0.8, 2.9)</td>
</tr>
<tr>
<td>Ovaries removed</td>
<td>None</td>
<td>330</td>
<td>348</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>One or both</td>
<td>59</td>
<td>41</td>
<td>1.5 (1.0, 2.4)*</td>
<td>1.9 (1.0, 3.7)*</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>1</td>
<td>82</td>
<td>73</td>
<td>1.2 (0.7, 2.0)</td>
<td>1.2 (0.7, 2.1)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>102</td>
<td>131</td>
<td>0.8 (0.5, 1.2)</td>
<td>0.8 (0.5, 1.3)</td>
</tr>
<tr>
<td></td>
<td>3 or more</td>
<td>176</td>
<td>154</td>
<td>1.2 (0.8, 1.9)</td>
<td>1.2 (0.7, 2.1)</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>No</td>
<td>321</td>
<td>331</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>91</td>
<td>81</td>
<td>1.1 (0.8, 1.6)</td>
<td>0.8 (0.5, 1.3)</td>
</tr>
<tr>
<td>HRT taken</td>
<td>No</td>
<td>365</td>
<td>376</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>46</td>
<td>35</td>
<td>1.4 (0.9, 2.3)</td>
<td>1.4 (0.8, 2.4)</td>
</tr>
<tr>
<td>Duration of HRT</td>
<td>0</td>
<td>365</td>
<td>375</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Up to 5 yr</td>
<td>36</td>
<td>23</td>
<td>1.7 (0.9, 2.9)</td>
<td>1.7 (0.9, 3.3)</td>
</tr>
<tr>
<td></td>
<td>5 or more yr</td>
<td>9</td>
<td>12</td>
<td>0.8 (0.3, 2.0)</td>
<td>0.6 (0.2, 1.8)</td>
</tr>
</tbody>
</table>

†Adjusted for BMI, Heberden's nodes, previous hip injury and leisure activity.
‡Adjusted for BMI, Heberden's nodes, previous hip injury, leisure activity and all other reproductive variables.
*P < 0.05.
protect against the initiation or progression of OA at the hip or knee [4–6, 19]. In the largest of these, current oestrogen use was shown to retard the development of OA at the hip [19].

Our finding that short-term HRT use was positively associated with hip OA may have occurred by chance. Alternatively, there may be aspects of the lifestyle of women who take HRT for short periods (mostly to relieve vasomotor symptoms perimenopausally) which predispose them to the disease.

The indications for long-term HRT tend to be different. A large proportion of women in the UK who take long-term oestrogen replacement do so because of osteoporosis, a disorder which has been inversely associated with OA in several studies [20]. This may be because of differing metabolic influences on the two disorders, OA being more common in ‘bone formers’ and osteoporosis in ‘bone losers’; or it may reflect contrasting environmental and lifestyle risk factors for the diseases. Either way, the reduced risk of hip OA in women receiving long-term HRT could result from selection into such treatment of women who were already predisposed to OA.

Another possibility is that oestrogen retards the development of OA through an influence on cartilage or bone metabolism. Oestrogen receptors are found in articular cartilage, and oestrogen is known to have complex effects on the growth hormone/IGF-I axis. Also, HRT reduces bone turnover in post-menopausal women and could help stabilize OA by slowing subchondral bone remodelling.

In conclusion, our observations add to other epidemiological studies in suggesting that oestrogen deficiency in post-menopausal women is associated with an increased risk of hip OA, and that the post-menopausal use of HRT, if continued for > 5 yr, might reduce this risk. Paradoxically, however, short-term HRT use was associated with an excess risk of hip OA. The mechanisms through which oestrogen might exert its effects remain unclear, and observations for OA at different articular sites do not appear consistent. Further research should address both these issues and include the collection of data on the indications for HRT use in cases and controls.

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