Outcomes of ovarian preservation in a cohort of premenopausal women with early-stage endometrial cancer: A Korean Gynecologic Oncology Group study

Taek Sang Lee a,1, Jung-Yun Lee b,1, Jae-Weon Kim b,⁎, Sohee Oh c, Seok Ju Seong d, Jong Min Lee e, Tae Jin Kim f, Chi Heum Cho g, Seok-Mo Kim h, Chan-Yong Park i

a Department of Obstetrics and Gynecology, SMG–SNU Boramae Medical Center, Seoul, Republic of Korea
b Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Republic of Korea
c Department of Biostatistics, SMG–SNU Boramae Medical Center, Seoul, Republic of Korea
d Department of Obstetrics and Gynecology, Gangnam CHA Medical Center, CHA University, Seoul, Republic of Korea
e Department of Obstetrics and Gynecology, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea
f Department of Obstetrics and Gynecology, Cheil General Hospital, Seoul, Republic of Korea
g Department of Obstetrics and Gynecology, Dongsan Medical Center, Daegu, Republic of Korea
h Department of Obstetrics and Gynecology, Chonnam National University Hospital, Gwangju, Republic of Korea
i Department of Obstetrics and Gynecology, Gachon University Hospital, Incheon, Republic of Korea

HIGHLIGHTS
• Ovarian preservation was not associated with increased mortality, even after adjusting other covariates.
• This study suggests that ovarian preservation may be performed safely in young patients with early stage endometrial cancer.

ABSTRACT
Objective. The aim of this study was to evaluate the impact of ovarian preservation on the recurrence and survival rates of premenopausal women with early-stage endometrial cancer.

Methods. Using medical records of premenopausal women who received primary surgical treatment for stage I–II endometrial cancer, the demographics and survival rates were compared retrospectively for patients who had ovarian preservation and those who underwent bilateral salpingo-oophorectomy. Cox proportional hazards models with inverse probability of treatment weighting (IPTW) based on propensity score were performed to adjust for selection bias between the two groups.

Results. A total of 495 women were identified, including 176 patients who had ovarian preservation. The ovarian preservation group was younger (P < 0.001) and had an earlier year of diagnosis (P = 0.014), a lower prevalence of lymphadenectomy (P < 0.001), and a marginally significant association with lower tumor grade (P = 0.052). The Kaplan–Meier curve and the log rank test showed no difference in either recurrence-free survival (P = 0.742) or overall survival (P = 0.462) between the two groups. In a multivariate Cox model adjusted by IPTW and covariates, ovarian preservation had no effect on either recurrence (hazard ratio [HR], 0.73; 95% CI, 0.29–1.81) or overall survival (HR, 1.33; 95% CI, 0.43–4.09).

Conclusions. Ovarian preservation does not appear to be associated with an adverse impact on the outcomes of premenopausal women with early-stage endometrial cancer. The present study has useful implications for physicians counseling young women who want to preserve their ovaries.

Introduction

Endometrial cancer is the most common gynecologic malignancy in Western countries and its incidence in Asian countries, including Korea, is increasing [1,2]. A 2010 report on annual cancer statistics in Korea showed that approximately 37.0% of patients diagnosed with endometrial carcinoma were premenopausal women and 10.4% were under
the age of 40 [3]. The prognosis for endometrial cancer among premenopausal women tends to be favorable, with early-stage diagnoses and well-differentiated tumor grades being reported more frequently [4]. As a result, quality of life and fertility preservation are a matter of great interest in young endometrial cancer patients.

The current guidelines recommend surgical staging, including total hysterectomy, and bilateral salpingo-oophorectomy (BSO) for early-stage endometrial cancer regardless of age [5]. Routine BSO at the time of surgery is based on the concept of removing the occult, coexisting ovarian malignancy and estrogen production source. However, this decision should take into consideration the significant long-term morbidity and mortality of premature menopause [6]. Surgical castration may affect the quality of life for young women without coexisting ovarian cancer. In addition to the loss of fertility, early surgical menopause is known to be linked to increased risk of cardiovascular disease and osteoporosis in the future [7,8].

Although previous studies have demonstrated the risk of coexisting malignancy in patients with early-stage endometrial cancer [9–11], only a limited number of studies have described the long-term oncological outcomes of ovarian preservation. Several investigators, including our group, have shown that ovarian preservation does not impact the survival of early-stage endometrial cancer adversely [12–14]. However, uncertainty still remains about the safety of patients who have undergone ovarian preservation. In particular, a large number of clinicians think that they may not need to remove the ovaries in early-stage endometrial cancer. In a Korean survey, 68% of gynecologic oncologists stated that grossly normal-looking ovaries can be preserved in young patients with early-stage disease [15]. Our objective in this cohort study was to evaluate the impact of ovarian preservation on the recurrence and survival rates of premenopausal women with early-stage endometrial cancer.

Methods

Patient cohort

From January 1997 to December 2008, 1032 patients with endometrial cancer were identified in the tumor registries of 20 tertiary hospitals. These patients were screened for enrollment after obtaining the approval of the institutional review board. Advanced-stage (stage III/IV) patients, those with non-endometrioid histology, and postmenopausal women were excluded from the analysis. Consequently, 495 premenopausal women with early-stage endometrioid adenocarcinoma were identified. Ninety-eight cases in our previous study published in 2009 were also included [13].

Clinical data and pathologic information were collected, including age at diagnosis, year of diagnosis, stage, tumor grade, performance of lymphadenectomy or adjuvant treatment, and follow-up results for recurrence and survival. Age at diagnosis was categorized as follows: ≤ 35, 36–40, and ≥ 41. Year of diagnosis was categorized into 1997–2002 and 2003–2008. All patients were surgically staged using the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer [16]. Only patients with stages IA, IB, and II were included. Recurrence-free survival was measured from the date of diagnosis to the date of recurrence or censored at the date of last follow-up. Overall survival was calculated as the number of months from cancer diagnosis to the date of death. Patients who were alive at the last follow-up were censored.

Statistical analysis

Differences between the baseline characteristics of the ovarian preservation and BSO groups were compared using the chi-square test or Fisher’s exact test for categorical variables. The recurrence-free and overall survival curves were estimated using the Kaplan–Meier method and differences in survival between the groups were compared using the log rank test. To reduce the impact of treatment selection bias and potential confounding in an observational study, rigorous adjustment was performed for significant differences in the characteristics of patients using the weighted Cox proportional hazards models with the inverse probability of treatment weighting (IPTW) [17]. With this technique, weights for patients who underwent BSO were the inverse of (1-propensity score) and weights for patients who had ovarian preservation were the inverse of the propensity score. Multiple logistic-regression analysis was used to estimate the propensity scores. The following variables were included in the propensity score model: age, year of diagnosis, tumor grade, stage, and the performance of lymphadenectomy or adjuvant treatment. The discrimination of each propensity score model was assessed by means of the C statistic. In addition, for more rigorous adjustment to avoid selection bias and profile effects, a second Cox model was created with IPTW as the weights, the performance of BSO, and all pre-specified covariates. P-values less than 0.05 were considered significant and all statistical tests were two-sided. All statistical tests were performed using R, version 2.15.2 (Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/).

Results

A total of 495 patients were included in this study. 176 had ovarian preservation and 319 underwent BSO. The baseline characteristics of the two groups are shown in Table 1. The ovarian preservation group was younger (P = 0.001) and had an earlier year of diagnosis (P = 0.014), a lower prevalence of lymphadenectomy (P < 0.001), and a marginally significant association with lower tumor grade (P = 0.052). After adjustment by IPTW, there is no significant difference in variables between the two groups. Reasons for ovarian preservation were listed under two categories based on a review of the medical charts. First, clinicians decided to preserve grossly normal-looking ovaries in young women as per the patients’ desire. In 110 cases, at least one ovary was preserved for this reason. Second, endometrial cancer was found incidentally after the operation. In 63 cases, only a hysterectomy was performed as the preoperative diagnosis was a benign disease such as endometrial hyperplasia, leiomyoma, or adenomyosis. No additional surgery was performed to remove these ovaries. A clear reason for ovarian preservation could not be identified for three patients. In 71 patients, only one ovary was preserved based on surgeon’s discretion considering the risk of occult metastasis despite grossly-normal-looking finding.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Ovarian preservation (n = 176)</th>
<th>BSO (n = 319)</th>
<th>P-value</th>
<th>Adjusted by IPTW P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤ 35</td>
<td>80 (45.5%)</td>
<td>36 (11.3%)</td>
<td>&lt;0.001</td>
<td>0.871</td>
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<tr>
<td>36–40</td>
<td>45 (25.6%)</td>
<td>35 (11.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 41</td>
<td>51 (29.0%)</td>
<td>248 (77.7%)</td>
<td></td>
<td></td>
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<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997–2002</td>
<td>48 (27.3%)</td>
<td>57 (17.9%)</td>
<td>0.014</td>
<td>0.822</td>
</tr>
<tr>
<td>2003–2008</td>
<td>128 (72.7%)</td>
<td>262 (82.1%)</td>
<td></td>
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<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>131 (75.6%)</td>
<td>251 (78.7%)</td>
<td>0.052</td>
<td>0.192</td>
</tr>
<tr>
<td>2</td>
<td>40 (22.7%)</td>
<td>52 (16.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (1.7%)</td>
<td>16 (5.0%)</td>
<td></td>
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<tr>
<td>Stage</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>IA</td>
<td>159 (90.3%)</td>
<td>283 (88.7%)</td>
<td>0.622</td>
<td>0.503</td>
</tr>
<tr>
<td>IB</td>
<td>6 (3.4%)</td>
<td>17 (5.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11 (6.3%)</td>
<td>19 (6.0%)</td>
<td></td>
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<tr>
<td>Lymphadenectomy</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<td>101 (57.4%)</td>
<td>77 (24.1%)</td>
<td>0.620</td>
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<td>Yes</td>
<td>75 (42.6%)</td>
<td>242 (75.9%)</td>
<td></td>
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<td>Adjuvant treatment</td>
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<td></td>
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<td>0.065</td>
</tr>
<tr>
<td>No</td>
<td>157 (89.2%)</td>
<td>265 (83.1%)</td>
<td>0.504</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (10.8%)</td>
<td>54 (16.9%)</td>
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</tr>
</tbody>
</table>

Abbreviations: BSO, bilateral salpingo-oophorectomy; IPTW, inverse probability of treatment weighting.
The median follow-up duration was 49.0 months (range = 6–208 months). The Kaplan–Meier curves and the log rank test showed no difference in either recurrence-free survival (P = 0.742) or overall survival (P = 0.462) between patients who underwent ovarian preservation and BSO (Fig. 1). Five-year overall survival was 94.5% for those who had ovarian preservation, compared with 97.8% for patients who underwent BSO. In addition, 10-year overall survival was 94.5% for those who had ovarian preservation, compared with 91.3% for patients who underwent BSO.

Table 2 shows the characteristics of 12 patients who experienced recurrences. Of the 495 patients, 12 (2.4%) had recurrences. Of the 176 patients who had ovarian preservation, four (2.3%) were diagnosed with recurrences. Adnexal recurrence was suspected in just one of the patients with recurrence, based on imaging study findings. Furthermore, we did not find any subsequently developed ovarian cancer in patients who underwent ovarian preservation. Of the 319 patients who underwent BSO, eight patients (2.5%) were diagnosed with recurrences. Distant recurrences were found in seven out of 12 of the cases with recurrence.

Table 3 demonstrates the cumulative hazards of adverse outcomes in patients receiving either ovarian preservation or BSO using unadjusted and adjusted multivariable analyses. Unadjusted Cox regression models showed that ovarian preservation had no effect on either recurrence (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.25–2.72) or death (HR, 1.64; 95% CI, 0.44–6.12). In addition, after the outcomes of patients who underwent ovarian preservation or BSO were adjusted with IPTW, there was no significant difference in recurrence (HR, 0.90; 95% CI, 0.39–2.12) or death (HR, 1.70; 95% CI, 0.64–4.54) between the two groups. Similarly, a Cox model with IPTW as the weights, treatment effect (ovarian preservation or BSO), and pre-specified covariates (age, year of diagnosis, tumor grade, stage, and the performance of lymphadenectomy or adjuvant treatment) also showed that ovarian preservation did not increase the risk of recurrence (HR, 0.73; 95% CI, 0.29–1.81) or mortality (HR, 1.33; 95% CI, 0.43–4.09) significantly more than BSO. The C statistic of the propensity score was 0.741 in all patients. Detailed results for other covariates in this multivariable Cox model are described in Table 4. Tumor grade and stage were the most significant prognostic factors for recurrence and survival in our cohort.

Discussion

We compared the recurrence-free and overall survival rates of patients who underwent ovarian preservation and BSO. Ovarian preservation was not associated with increased mortality in our cohort, even after adjusting other covariates.

Previous studies have reported inconsistent results on the incidence of coexisting ovarian malignancy in early-stage endometrial cancer, with a range of 5–29% reported in the literature [9,10,18–22]. This discrepancy may be due to various sample sizes, the characteristics of patients, and differing study regions. In addition, the proportion of synchronous primary tumors and metastatic tumors is altered by the pathologic criteria. Walsh et al. demonstrated that there is a high rate of synchronous tumors in patients with early-stage endometrial cancer.
of coexisting malignancy of 25% among women with endometrial cancer aged 24–45 and recommended caution when considering ovarian preservation in young endometrial cancer patients [18]. This high rate should be interpreted with caution as the authors did not provide information about intraoperative gross extraterine spread, which is one of the most significant predictors of ovarian involvement [9]. Our results suggest that the overall rate of a coexisting ovarian malignancy in endometrial cancer is approximately 7% [9]. This is within the range reported by most other investigators [10,19–21]. In addition, we emphasized that the risk of coexisting ovarian malignancy is minimal in endometrial cancer patients that present with no evidence of intraoperative extrauterine disease (below 1%) [9]. A recent study of Asian countries demonstrated that the frequency of coexisting ovarian malignancy in patients with clinical stage I endometrial cancer is lower than expected [11,23]. Pan et al. reported that approximately 2% of a dataset of 976 patients with clinical stage I endometrial cancer is lower than expected [11,23]. Pan et al. reported that approximately 2% of a dataset of 976 clinical stage I endometrial cancer patients had ovarian metastases or synchronous ovarian primary cancers [23]. Akbayir et al. showed that a high predictive value of the intraoperative examination for the diagnosis of benign/normal ovaries is accurate [11]. These results suggest that ovarian preservation may be performed safely in young endometrial cancer patients after careful intraoperative inspection of the adnexa.

Although previous reports have examined the frequency of ovarian metastasis in young women with endometrial cancer, only a limited number of studies have evaluated the long-term oncologic outcomes of ovarian preservation [12–14,24]. Richter et al. reported that the BSO group had lower recurrence rates than the ovarian preservation group for stage I endometrial cancer patients [24]. However, only 20 patients were included in the ovarian preservation group. In contrast, Wright et al. demonstrated that ovarian preservation did not have an impact on adverse outcomes such as cancer-specific survival (HR, 0.58; 95% CI, 0.14–2.44) and overall survival (HR, 0.68; 95% CI, 0.34–1.35) [12]. In addition, Koskas et al. reported the safety of ovarian preservation in a homogenous group with grade I endometrial adenocarcinoma limited to the endometrium [14]. The study showed that cancer-related death did not occur in patients with ovarian preservation. In particular, death related to heart disease or diabetes occurred only in patients who underwent BSO.

Our previous study reported the oncologic outcomes of 175 patients with ovarian preservation including all age groups and not considering menopausal status [13]. Seven of the 175 patients had recurrence, and no recurrences were observed in stage I patients with endometrioid histology. Most cases included in the study had endometrioid histology (92.6%), while most recurrences arise from non-endometrioid histologic subtypes. Despite the results being promising, the benefits of ovarian preservation could not be assessed precisely owing to the lack of a control group and because all age groups were included. The present study supports the findings of previous reports with performing the comparative study and focusing on only premenopausal women.

The standard surgical treatment for endometrial cancer includes a total hysterectomy and BSO, with pelvic and paraaortic lymphadenectomy as indicated [5]. The rationale behind performing BSO, even in young women, is based on two theoretical risks of leaving the ovaries in situ: First, the risk of coexisting ovarian malignancy cannot be excluded completely; and second, endogenous estrogen production from ovaries may activate potential residual microscopic foci of endometrial cancer. However, ovarian preservation did not adversely impact recurrence or survival rates in our study. This may be explained by the high rate of adverse risk factors for adjuvant treatment in cases that involved the ovaries. Therefore, adjuvant treatment, such as pelvic radiation, was performed on occult metastases and oncologic outcomes were not hampered, despite the possibility of occult ovarian involvement in the ovarian preservation group. Furthermore, the theory that endogenous estrogen may activate quiescent endometrial cancer cells after surgery is not supported by epidemiologic studies. Several studies, including a randomized controlled trial by the Gynecologic Oncology Group, failed to provide evidence of the risks of estrogen replacement therapy following endometrial cancer surgery [25–27]. Considering these recent results, the risk of reactivating cancer cells by endogenous hormonal stimulation appears to be negligible, particularly among women with early-stage endometrial cancer.

No prospective study on this issue has been designed and such a study is unlikely to perform a randomized controlled trial in the near future owing to ethical problems and the anticipated difficulty in patient recruitment. Under these circumstances, the results of this study carry weight as we included a sufficient number of ovarian preservation patients and compared the outcomes while attempting to reduce selection bias. Ovarian preservation is more likely when a clinician encounters a favorable case and a younger patient. Thus, selection bias should be controlled in order to compare the survival outcomes of the two groups. We
performed multivariable Cox modeling with IPTW to overcome the limitations of retrospective study. By doing so, we were able to avoid the possibility that the benefits of ovarian preservation were overestimated due to the selection of a lower-risk sample.

Our study has several potential limitations. First, although we attempted to reduce the significant bias inherent in retrospective studies by using IPTW, hidden bias still exists as propensity scores control only for selection bias. Second, a sufficient follow-up period was not achieved in some patients due to missing data in the medical records of tertiary hospitals. Third, the performance of lymphadenectomy and adjuvant radiotherapy had not been standardized in the current study. Fourth, recurrence or death did not occur in stage Ib disease, as only a small proportion of stage IB patients were included in this study. Lastly, the consequences of surgical menopause in young women, such as cardiovascular disease, osteoporosis, and quality of life, are not evaluated in this study.

In conclusion, our findings demonstrate that ovarian preservation does not appear to have an adverse impact on recurrence and survival rates in premenopausal women with early-stage endometrial cancer. This study has useful implications for physicians counseling patients who want to preserve their ovaries. To validate our results, further large-scale studies that consider both the potential consequences of premature surgical menopause and cancer-specific outcomes are necessary.

Conflict of interest statement
No potential conflicts of interest were disclosed.

Acknowledgment
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References