Comparison of Histopathologic Features of Endometrial Cancer Based on Menopausal Status and Safety of Ovarian Preservation in Premenopausal Women

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Abstract- The aim of this study was to investigate the frequency of coexisting ovarian malignancy and to determine whether ovarian preservation is feasible in premenopausal endometrial cancer (EC) patients. The data of 251 patients with endometrioid type endometrial cancer were retrospectively reviewed. We classified patients into two groups based on menopausal status. Information regarding patient age, preoperative and intraoperative evaluations, pathology reports, and follow-up results were abstracted from medical records. Coexisting ovarian malignancy was detected in 2 (4.3%) of 46 patients in premenopausal group and in 11 (5.3%) of 205 patients in postmenopausal group. Both patients in premenopausal group with coexisting ovarian malignancy had lymph node involvement and grade 2 tumors, while 5 (45.4%) of 11 patients in postmenopausal group had lymph node involvement and 9 (81.8%) of 11 patients had grade 3 tumors. Incidence of coexisting ovarian malignancies in premenopausal women with EC should not be underestimated. Owing to that thorough preoperative evaluation and an extensive intraoperative evaluation is critical for the decision of preserving ovaries.

Introduction

Endometrial cancer (EC) is the most common type of gynecological malignancy in developed countries (1). Although carcinoma of the endometrium is traditionally considered as a postmenopausal disease, previous studies reported that approximately 20% of patients are diagnosed before menopause, and 5% of them will develop the disease before the age of 40 years (2). Premenopausal women with EC often have early stage, well-differentiated, limited myometrial invasive tumors and favorable prognosis than older patients (3,4).

Surgical staging policy including total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), and lymph node dissection has not been changed since 1998. BSO is typically performed, regardless of the age, to exclude occult ovarian metastasis and to decrease estrogen production. However, the removal of the ovaries brings some adverse effects like hot flashes, vaginal atrophy, sleep disorders, sexual dysfunction and as a result, oophorectomy decreases the quality of life in premenopausal women.

The incidence of ovarian metastasis in women with early stage EC has been reported approximately 5% by most studies in the literature (5,6). In another study, women with EC aged 45 years and younger, had 25% coexisting epithelial ovarian tumors and the authors concluded that careful preoperative and intraoperative evaluation of the adnexa is critical (7). Although several reports have demonstrated that ovarian preservation does not impact the survival rates especially in early stage EC, this issue remains controversial (8,9).

The aim of this study was to compare tumor characteristics of EC between premenopausal and postmenopausal women, and also estimate coexisting ovarian malignancy rates and evaluate the feasibility of ovarian preservation in premenopausal women with early-stage EC.

Materials and Methods

Patient data of histologically confirmed, primarily

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diagnosed endometrioid type endometrial cancer was retrospectively collected from the data registry of Ankara University Department of Obstetrics and Gynecology between 2010 and 2013. A total of 314 patients were initially identified from the hospital records during the study period, among whom, 251 patients with complete data included in the study. Forty-six patients were premenopausal, and 205 patients were postmenopausal.

Medical charts including admission and discharge notes, epidemiological data (age, gravity, and parity), clinicopathological factors (myometrial invasion, histological subtype, lymphovascular space invasion (LVSI), tumor grade, cervical invasion, dissected lymph node counts, lymph node metastasis and ovarian involvement) were analyzed.

All the surgeries were performed by the same group of surgeons. In postmenopausal group, all patients had BSO, while in premenopausal group 10 patients' ovaries were preserved and ovarian biopsies performed. Ovarian metastasis was differentiated from independent synchronous ovarian cancer by using Ulbright and Roth's diagnostic criteria (10). For this classification, the criteria were either a multinodular ovarian pattern (major criterion) or two or more of the following criteria like small ovaries (<5 cm), bilateral ovarian involvement, deep myometrial or vascular invasion, and tubal involvement. The stage of the tumor was identified by using the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system (11).

Statistical analysis was conducted using SPSS Version 12.0 (SPSS, Inc., Chicago, IL). Numerical data was presented as mean±standard deviation (SD), or median. Results for categorical variables are given as frequencies. The correlation between qualitative variables was evaluated by chi-square test and extension of Fisher's exact test. A P of <0.05 was accepted as statistically significant. Multivariate logistic regression analysis was used to assess the association between ovarian involvement and other tumor characteristics after adjusting for age and assess the relationship between metastatic or synchronous ovarian malignancies and menopausal status.

Results

A total of 251 patients with endometrioid type EC were analyzed for this study. The mean age at the time of diagnosis was 59.7 years (range: 25-86). In postmenopausal group, all patients had hysterectomy and bilateral salpingo-oophorectomy, while in premenopausal group 10 patients had only hysterectomy and had bilateral ovarian biopsies plus lymphadenectomy when indicated. Pelvic±paraaortic lymphadenectomy was performed in 35 of 46 (76%) patients in premenopausal group and 188 of 205 (91.7%) in postmenopausal group. Pelvic or paraaortic lymph node involvement was associated with statistically higher grade, myometrial invasion, and lymphovascular space invasion rates.

FIGO stage distribution, histologic grades, myometrial invasion rates, lymphovascular space invasion ratios, cervical involvement rates, dissected lymph node counts, lymph node metastasis rates are summarized in Table 1. In premenopausal group, the Grade 1, Grade 2 and Grade 3 rates were 43.4%, 45.6%, 10.8%, respectively, while in postmenopausal group G1, G2 and G3 rates were 18.5%, 56.5%, and 24.8%. In postmenopausal group, tumor grade was statistically higher (P<0.05).

In premenopausal group, lymphovascular space invasion was significantly lower than postmenopausal group (21.7% vs. 42.0%, P<0.05). The deep myometrial invasion was significantly higher in the postmenopausal group compared with the premenopausal group, 48.3% vs. 26.1% respectively. Cervical involvement ratios were similar between two groups.

Features of all cases with ovarian involvement had summarized in Table 2. Coexisting ovarian malignancy was detected in 4.3% (n=2) of the premenopausal patients, and both cases were unilateral, one of this cases was metastatic, and the other was synchronous due to final pathologic results. Both tumors were grade 2, and myometrial invasion rates were >50%. Only pelvic lymph node involvement was noted in metastatic case, while both pelvic and paraaortic lymph node involvement was reported in the synchronous case. In postmenopausal patients, the rate of ovarian involvement was in 11 patients (5.3%), all of them were the endometrioid type, metastatic tumors and 8 of them were bilateral. Two of that cases (18.1%) had myometrial invasion less than 50%, 9 of that cases (81.8%) had >50% myometrial invasion. Three of 11 (27.2%) had grade 2 tumors, while 8 cases had grade 3 (72.7%). Whole 11 cases had lymphovascular space invasion, and 5 of the cases (45.4%) had pelvic and/ or paraortic lymph node metastasis.

Table 1. Clinical and pathological characteristics of the patients

		Premenopausal	Postmenopausal	*P*
		(n=46)	(n=205)	
Stage	1A	29 (63.0)	97 (47.3)	
	1B	9 (19.5)	68 (33.1)	
	2	4 (8.6)	15 (7.3)	
	3A	0 (0)	5 (2.4)	
	3B	0 (0)	2 (0.9)	
	3C	4 (8.6)	16 (7.8)	
	4A	0 (0)	0 (0)	
	4B	0 (0)	2 (0.9)	
Oophorectomy	NO	10 (21.7)	0 (0)	
	YES	36 (78.2)	205 (100)	
Ovarian involvement	NO	34 (95.6)	194 (94.6)	0.517
	YES	2 (4.3)	11 (5.3)	
LVSI	NO	36 (78.2)	119 (58)	0.011
	YES	10 (21.7)	86 (42)	
Grade	1	20 (43.4)	38 (18.5)	0.01
	2	21 (45.6)	116 (56.5)	
	3	5 (10.8)	51 (24.8)	
Myometrial invasion	NO	5 (10.8)	11 (5.3)	0.017
	<50	29 (63)	95 (46.3)	
	>50	12 (26)	99 (48.2)	
Cervical invasion	NO	40 (86.9)	178 (86.8)	0.222
	YES	6 (13)	27 (13.1)	
Dissected LN	NO	11 (23.9)	17 (8.2)	0.162
	YES	35 (76)	188 (91.7)	
LN metastasis	NO	30 (85.7)	163 (86.7)	
	PELVIC	4 (11.4)	15 (7.9)	0.762
	PARAAORTIC	1 (2.8)	10 (5.3)	0.659

LVSI: Lymphovascular space invasion; LN: Lymph node

Table 2. Features of all cases with ovarian involvement

	Age	Menopausal status	Myometrial invasion	Grade	Ovarian involvement	Pelvic LN	Positive Pelvic LN	Pao LN	Positive Pao LN
#1	38	Premenopausal	<50	2	Unilateral	131	4	6	0
#2	50	Premenopausal	>50	2	Unilateral	22	2	10	1
#3	56	Postmenopausal	>50	3	Bilateral	0	0	0	0
#4	58	Postmenopausal	>50	3	Bilateral	25	5	12	0
#5	58	Postmenopausal	>50	2	Bilateral	23	0	0	0
#6	62	Postmenopausal	>50	3	Unilateral	43	0	9	0
#7	62	Postmenopausal	>50	3	Bilateral	19	12	4	4
#8	62	Postmenopausal	>50	3	Bilateral	32	2	0	0
#9	64	Postmenopausal	<50	2	Unilateral	56	0	21	0
#10	67	Postmenopausal	<50	3	Bilateral	12	0	0	0
#11	71	Postmenopausal	>50	3	Bilateral	46	4	15	8
#12	76	Postmenopausal	>50	2	Unilateral	19	0	0	0
#13	78	Postmenopausal	>50	3	Bilateral	14	10	0	0

LN: Lymph node; Pao: Paraaortic

Discussion

Since 1998, total abdominal hysterectomy, BSO, and surgical staging are used for the optimal surgery method for EC, but using this method regardless of age causes climacteric symptoms, such as hot flushes, vaginal atrophy and predisposes cardiovascular disease, osteoporosis due to surgical menopause. The most

challenging point in the treatment of EC is choosing the best approach for younger patients. Due to the risk of coexisting ovarian malignancy, preserving ovaries should be approached cautiously.

We found the rate of ovarian involvement to be 4.3% in premenopausal patients with endometrial carcinoma, similar to results of a study conducted by Lin and colleagues (12). Previous studies in the literature

demonstrated conflicting results on the incidence of coexisting ovarian malignancy in younger endometrial cancer patients, with a range of 5-29% (13-15). Lee *et al.*, reviewed 260 patients and found a 7.3% coexisting malignancy rate, but this was only 0.97% in patients without any evidence of intraoperative gross extrauterine disease (15). Another study reviewed 178 cases and suggested that ovarian preservation does not affect disease recurrence or overall survival in clinical Stage I and II endometrial cancer (16). Lau *et al.*, also reported that ovarian preservation had no effect on recurrence rates and disease-free survival (17). On the other hand, in the postmenopausal group, ovarian involvement rate was found 5.3%. We did not find a significant difference in ovarian involvement rates between the premenopausal and postmenopausal group, similar to study conducted by Yamazawa and colleagues (18). They reported that there were no significant differences in ovarian malignancy rates due to menopausal status. Similar to that, Evans-Metcalf *et al.*, found that age is not an independent factor for coexistent ovarian malignancies (19).

Adnexal involvement in EC could be metastatic from the endometrial origin or from a synchronous ovarian malignancy. The rates of adnexal involvement in the premenopausal group were seen in two patients (4.3%). One of these cases had synchronous ovarian malignancy and in preoperative evaluation unilateral ovary was noted as grossly enlarged in ultrasound imaging. In the other case with metastatic ovarian involvement, preoperative evaluation was noted as normal, while intraoperative findings pushed surgeons to perform unilateral oophorectomy and send the specimen to frozen section investigation. Ultimately, synchronous or metastatic cancer risk should be evaluated in premenopausal patients similar to postmenopausal women with EC. Possible risks should be discussed with the patient in case of ovarian preservation decision, and extensive and careful preoperative and intraoperative evaluation of adnexa should be performed to eliminate concurrent malignancy risk.

In this study, we performed hysterectomy without bilateral salpingo-oophorectomy at 10 out of 46 premenopausal patients with EC. If the adnexa and peritoneal surfaces found macroscopically normal by the intraoperative evaluation, we determined not to excise ovaries. Two of 46 premenopausal patients with EC had adnexal involvement in our study. Both patients had deep myometrial invasion and grade 2 tumors. In the absence of poor prognostic factors such as deep myometrial invasion and grade 3 diseases, preserving

ovaries might be a judicious option. Pan *et al.*, reported that approximately 2% of endometrial cancer patients had adnexal involvement (20); while in another study authors reported a high predictive value of the intraoperative examination for the diagnosis of normal ovaries is accurate (21). Results from these studies claim that preserving ovaries might be performed after extensive intraoperative evaluation in premenopausal EC patients.

Our study has several limitations. First, this was a retrospective study, and all the information and data were collected from a single institution. Therefore we could not reach a larger sample size in the pre-menopausal group. Lastly, despite all the surgeries were conducted by the same group of surgeons, oophorectomy decision is not standardized. For this reason, ovarian preservation risks and results need to be discussed with patients.

In conclusion, the incidence of coexisting ovarian malignancies in young women with endometrioid type EC was approximately 5%. That risk has to be kept in mind, and patient needs to be informed about the possibility of concurrent malignancy. Salpingo-oophorectomy should be performed in cases with deep myometrial invasion, suspicion for ovarian or lymph node involvement. The risk of an occult disease underneath has worse results than surgical menopause, owing to that thorough preoperative evaluation and extensive intraoperative evaluation is critical for the decision of preserving ovaries.

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