Original Article

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Evaluation of the Safety of Ovarian Preservation at Early Stage of Endometrial Cancer in Premenopausal Women

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Abstract

Background: Endometrial cancer usually occurs at postmenopause stage of life but its incidence in younger patients is increasing in the last decades. The objective of the study was to evaluate the ovarian preservation in the early stage of endometrial cancer.

Methods: In this cross-sectional study, 174 patients with endometrial cancer who underwent Total Abdominal Hysterectomy (TAH) and Bilateral Salpingo-oophorectomy in 5 years were included.

Results: The results showed that 51.1% of the patients were at stage IA, 28.7% at stage IB, 6.9% at stage II, 11.5% at stage III and 1.7% at stage IV of endometrial cancer when they underwent surgery. One patient (1.12%) at stage IA of endometrial cancer, one patient (2%) at stage IB and one patient (8.3%) at stage II had micrometastasis in ovaries, and 8 patients (40%) at stage III and 2 patients (66.6%) at stage IV had micrometastasis and co-existing tumor.

Conclusion: In conclusion, findings revealed the high safety of ovarian preservation in endometrial cancer at earlier stages of the endometrial cancer with low risk of ovarian involvement.

Keywords: Endometrial neoplasms, Hysterectomy, Fertility preservation, Salpingo-oophorectomy

Introduction

Cancer is one of the most important public health concerns, which is the second cause of death in many countries of the world following cardiovascular diseases (1), and the burden of cancer is increasing worldwide, especially in less developed countries, which have more populations (82% of the world's population) (2).

Endometrial cancer is the most common cancer in the female genitourinary system by the mean age of 61 (3); however, 20-25% of patients are premenopausal and about 5% of patients are younger than 40 years old (4), and also 70% of endometrial cancers are localized (5). Early diagnosis of endometrial cancer in younger females usually has a good prognosis and better survival because of earlier stage and lower grade in time of diagnosis and treatment (6). Endometrial cancer in younger age warns more about cancer associated with Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome (7). The standard treatment of endometrial cancer is Total Abdominal Hysterectomy (TAH), Bilateral Salpingo-oophorectomy (BSO) and staging (8-10). Therefore, because of the possibility of endometrial cancer at younger age and lack of estrogen due to TAH-BSO surgery, conservative treatments to preserve fertility may be safe and do not increase the cancer related mortality (11). However, this study aimed to assess the ovarian involvement in patients with endometrial cancer who underwent TAH and BSO.

Materials and Methods

This cross-sectional study included 174 patients with endometrial cancer who underwent TAH and BSO from 2010 to 2015 in two hospitals, affiliated to Tehran University of Medical Sciences, Tehran, Iran. In this study, all patients were analyzed in the mentioned period. All patients had documented pathology of endometrial cancer, confirmed by two pathologists. The staging system was from the cancer committee of the International Federation of Gynecology and Obstetrics (FIGO, 2019)(12).

Total para-aortic and pelvic dissection was performed for patients with the following criteria: (a) pelvic lymphadenopathy, (b) gross adnexal involvement, and (c) grade 2 or 3 lesions with outer one-third myometrial invasion (13,14).

Ultrasound and Magnetic Resonance Imaging (MRI) with and without contrast was performed before surgery and both ovaries and uterus were evaluated for pathology after surgery in all patients (15,16).

This study had been approved by the ethics committee of Tehran University of Medical Sciences. Moreover, all the ethical codes on human subjects were followed as well. Patients' information was kept confidential and was reported as aggregated data. All the participants signed the informed consent form related to the study.

Quantitative variables were reported as mean (range) and qualitative variables as number (percentages). To examine the relationship between qualitative variables, likelihood-ratio Chi-square test was applied. Data was analyzed using Stata software, version 14 (Stata Corp, College Station, TX, USA). The P-value of less than 0.05 was considered statistically significant.

Results

The data of 174 patients were analyzed. The mean age of the patients was 44 years old (minimum 24 years and maximum 66 years). Half of the patients (50.6%) had a chief complaint of abnormal uterine bleeding. The mean parity of patients included 4 pregnancies, 3 live births, 1 abortion and all of the patients were Iranian.

As it is displayed in table 1, 13.8% of the patients had diabetes mellitus and 22.4% had hypertension. Eight percent were smokers, whereas 4% were confirmed cases of breast cancer before diagnosing endometrial cancer and they were treated by total mastectomy. The most pathologic sign detected in ultrasound before surgery was endometrial thickening in 36.7% of cases.

Table 1. Frequency distribution of demographic and clinical variables in the study

Variables		N(%)
Total	174	100%
Age (*yr*)	Mean (Range)	44(24-66)
Smoking status	Ever	14(8%)
	Never	160(92%)
Chief complaint	Postmenopausal bleeding	88(50.6%)
	Abnormal uterine bleeding	78(44.8%)
Diabetes mellitus	Yes	24(13.8%)
	No	150(86.2%)
Hypertension	Hypertensive	39(22.4%)
	Normotensive	135(77.6%)
Breast cancer	Yes	7(4%)
	No	167(96%)

All patients had documented pathology for endometrioid adenocarcinoma of the endometrium.

As it is shown in table 2, 51.1% of the patients were at stage IA, 28.7% were at stage IB, 6.9% were at stage II, 11.5% were at stage III and 1.7% were at stage IV when they underwent surgery. In pathologic evaluation, 31.6% had myometrium invasion greater than 50%, 25.9% had para-aortic lymph node invasion and 32.7% had isthmus or cervical involvement.

The findings showed that one patient at stage IA (1.12%), one patient at stage IB (2%) and one patient (8.3%) at stage II of endometrial cancer had micrometastasis in ovaries, whereas 8 patients at stage III (40%) and 2 patients (66.6%) at stage IV had micrometastasis in ovaries with a co-existing tumor. Chi square test showed that there was a significant difference between disease stages and frequency of micrometastasis in ovaries ($p<0.001$) (Table 3).

Discussion

The standard treatment of endometrial cancer is TAH and BSO, and staging (8-10) but because estrogen deprivation imposes nearly lots of side effects on younger patients and decreases their quality of life, ovarian preservation in endometrial cancer, particularly in young patients at early stage of cancer may be beneficial (17).

BSO is considered somewhat safe; but it has some side effects in young patients including hot flushes, vaginal atrophy, increased cardiovascular disorder, osteoporosis and dementia (18-22).

There are two main risks in preserving ovaries in perimenopausal women. First, estrogen can stimulate microscopic foci of residual endometrial cancer, but in the study of Barakat *et al* (23), Hormone Replacement Therapy (HRT) with estrogen on 1236 women with history of endometrial cancer at early stages had no effect on mortality or recurrence of te cancer (absolute recurrence rate was 2.1% and the incidence of new malignancy was low). Second, the rate of coexisting ovarian tumors was reported to be 5% (24): however, in younger patients with an endometrial cancer, the risk of such tumors varies between 5-29% (24-26).

In a study by Walsh *et al* (25) on 102 patients at the age of 45 years or younger who underwent surgery for endometrial cancer, 25% had co-existing ovarian malignancies. In pathology report, 18 cases of co-existing ovarian malignancies out of 26 (69%) were detected in patients with grade 1 endometrial cancers, and 15 (58%) were detected in patients with inner myometrial invasion. In 15.7% of the patients, ovaries were preserved and all of them were at stage I. Also, 18.7% of these patients with preserved ovaries needed another operation in the next 50 months after the initial surgery due to adnexal abnormalities and because of

Table 2. Tumor specific characteristics of patients in the study

Variables		N (%)
Stages of endometrial cancer	IA	89(51.5%)
	IB	50(28.7%)
	II	12(6.9%)
	III	20(11.5%)
	IV	3(1.7%)
Myometrium invasion greater than 50%		55(31.6%)
Para-aortic lymph node involvement		45(25.9%)
Isthmus or cervical involvement with cancer		57(32.7%)

Table 3. Frequency of endometrial cancer patients who had micrometastasis in ovaries

Stages	Micrometastasis in ovaries		p value
	Yes	No	
IA	1(1.12%)	88(98.88%)	p<0.001, likelihood-ratio Chi2(4)= 34.0568
IB	1(1%)	49(99%)	
II	1(8.3%)	11(93.7%)	
III	8(40%)	12(60%)	
IV	2(66.6%)	1(33.4)	

the high rate of co-existing tumor (25%), younger patients were advised to undergo ovarian preservation. In the present study, just 1.1% of cases at stage IA and 2% at stage IB had micrometastasis in their ovaries which shows the high safety of ovarian preservation at early stages. Similarly, in Wright *et al*'s study (27) on 3269 women aged 45 or younger at stage I of endometrial cancer, it was shown that ovarian preservation in young premenopausal women at stage I is safe and not associated with an increase in cancer-related mortality. However, the 5-year survival at stage IA in both patients with and without ovarian preservation was reported to be 98%. Our results suggested that there is a linear relationship between the stage of the disease and micrometastasis in ovaries, which also significantly increases with the stage progression of the cancer.

Predictor factors for ovarian involvement during surgery are morphology of the ovaries, grossly involved lymph node confirmed by frozen section during surgery and tumor spreading (28,29). In the present study, risk of micrometastasis regardless of normal appearance of ovaries was just 2%.

However, our study showed high safety of ovarian preservation at early stages in patients with low risk of ovarian involvement in endometrial cancer (cases younger than 45 years for whom cancer doesn't invade serous membrane, with no family history of breast cancer or susceptibility to Lynch syndrome); however, the medical team should consult with the patients before surgery.

This study was conducted as a cross sectional one in two hospitals. Some similar studies with larger sample size in different ethnic groups and geographic areas with longer follow up should be conducted in order to be able to generalize the findings.

Conclusion

Findings show the high safety of ovarian preservation at earlier stages of endometrial cancer in patients with low risk of ovarian involvement (Cases younger than 45 years for whom cancer doesn't invade serous membrane, with no family history of breast cancer or susceptibility to Lynch syndrome).

Conflict of Interest

All authors declare no competing interest.

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