RESEARCH ARTICLE

Analysis of Endometrial Cancer in Premenopausal Women: Single-Centre Experience

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Abstract

BACKGROUND/AIMS: To evaluate the clinocopathological characteristics, treatment, and survival of premenopausal women with endometrial cancer (EC).

MATERIALS AND METHODS: The study sample retrospectively included 107 women under 50 years of age who had undergone surgical treatment for EC at a single centre.

RESULTS: We identified 107 premenopausal women with EC. Their median age was 46 (range: 34-49) years, and their mean body mass index was 33 (range: 19-65) kg/m². Fifty-nine women (55.1%) were nulliparous and 22 women (20.5%) reported a history of polycystic ovary syndrome. There were ninety-one (85%) young women (premenopausal) having <50% myometrial invasion (MI), sixteen women (15%) having ≥50 MI and ninety women (84.2%) with grade 1 or 2 endometrioid histology, and seventeen women (15.8%) with grade 3 endometrioid histology. Ninety-five (88.8%) women had stage 1-2 disease (1-2 early disease) and 12 (11.2%) women had stage 3-4 (advanced-stage) disease.

CONCLUSION: <50% MI, grade 1-2 and early stage (stage 1-2) endometrioid type EC were more common in young premenopausal patients. Additionally, most of the patients were obese and nulliparous in this age group.

Keywords: Endometrial cancer, premenopausal women, CA125, LVSI, adjuvant treatment

INTRODUCTION

Endometrial cancer (EC) is the most common cancer of the female reproductive system worldwide.[1] EC is mostly diagnosed in the postmenopausal period, and the median age at diagnosis is 62 years. However, up to 14% of patients with EC are diagnosed during the premenopausal period.[2] Women of advanced age with EC are often diagnosed via endometrial sampling early in the course of their disease with the common complaint of postmenopausal bleeding. However, irregular bleeding is common in the premenopausal age group and the diagnosis of EC may be delayed.[3] Chronic ovulation results in a thickening of the endometrial tissue due to unopposed estrogen and this is a risk factor for EC. Other risk factors for EC in premenopausal women include obesity, hypertension, nulliparity, impaired glucose intolerance, polycystic ovary syndrome (PCOS), menstrual irregularities, and a history of infertility.[4] Obesity increases the release of estrogen from adipose tissue in premenopausal women, significantly increasing the risk of EC. The risk of AK cancer increases three-fold in women who exceed normal body weight by 9-23 kg and ten-fold in women with an excess of 23 kg over the normal body weight.[5]

Young age, histologic endometrioid type grade 1 or 2, and low stage are good prognostic factors for EC.[6] Premenopausal EC is associated with 5-year survival rates of over 95% and good prognoses in premenopausal patients.[7] The standard treatment for EC is hysterectomy, bilateral salpingo-oophorectomy, possible lymphadenectomy, and omentectomy. Endometrioid endometrial carcinoma (EEC) accounts for 70% to 80% of

Ayhan and Yıldırım. Premenopausal Women and Endometrial Cancer

Cyprus J Med Sci 2023;8(2):153-157

all ECs.[8] Few published studies have investigated those patients with premenopausal EEC, and most such studies have had small sample sizes. We aimed to assess the clinical, pathologic, and prognostic factors associated with EEC in premenopausal patients aged <50 years.

MATERIALS AND METHODS

The records of those patients who had undergone treatment for EC in the gynecologic oncology clinic of the University of Health Sciences City Hospital between January, 2007 and January, 2018 were evaluated retrospectively. Ethics committee approval was obtained from Ankara Zekai Tahir Burak Training and Research Hospital Non-Interventional Clinical Research Ethics Committee under the Declaration of Helsinki (approval number: 2018/20). Written informed consent for the use of medical information for investigative intent was obtained. Clinical information was obtained from our institution's electronic medical records. This study's sample included a total of 107 women under 50 years of age with EC who had undergone surgical treatment for endometrioid-type EC (EEC) according to their final pathology reports. We excluded those patients older than 50 years with endometrioid-type EC, those with non-endometrioid-type EC, and those with the presence of synchronous malignancies according to their final pathology reports. Women under 50 years of age with a follicle-stimulating hormone (FSH) levels <30 IU/L and/or an irregular menstrual cycle were considered premenopausal and included in this study. Women who had not had menstrual bleeding within 6 months to 1 year and whose serum FSH levels were >30 IU/L were considered menopausal and were excluded from this study.[9] Additionally, those receiving neoadjuvant chemotherapy or primary radiation therapy and those with incomplete medical records were excluded. The following data were collected retrospectively from the files and electronic data of the patients in this study: age, date of operation, International Federation of Gynaecology and Obstetrics (FIGO) stage, menopausal status, preoperative cancer antigen (CA125) levels, lymphovascular space invasion (LVSI) status, type of surgical treatment, lymphadenectomy status, presence of recurrence (loco-regional, retroperitoneal, distant), adjuvant treatment received (radiotherapy, chemotherapy, and chemo-radiotherapy), brachytherapy history, time to recurrence, survival status, and follow-up period until January, 2018. Prior to 2014, all patients diagnosed with EC underwent staging surgery, which included hysterectomy, bilateral salpingo-oophorectomy, and systematic retroperitoneal (pelvic and para-aortic) lymphadenectomy. Starting in 2014, retroperitoneal lymphadenectomy was performed according to the results of intraoperative frozen section analysis for those women who met the Mayo Clinic Criteria.[10] LVSI is defined as the presence of tumour cells within the lymphatics or capillaries.[11] We followed up the patients every 3 months for the first 2 years, twice a year for the next 3 years, and once a year for the next 5 years. Pelvic examinations were performed at each outpatient visit. Disease-free survival (DFS) was defined as the time interval between surgery and the first recurrence of EC. Overall survival (OS) was defined as the time from surgery to death or the last outpatient visit.

Statistical Analysis

Cox regression analysis was used to identify independent prognostic factors for DFS and OS. The Kaplan-Meier method was used for survival analysis. A p-value <0.05 was accepted as being statistically significant. Statistical calculations were performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

We identified 107 women according to the inclusion criteria. Their median age was 46 (range: 34-49) years. Their median follow-up duration was 58.0 (range: 12-144) months. The patient demographic and clinicopathological characteristics are summarized in Table 1. Their mean body mass index (BMI) was 33 (range: 19-65) kg/m^2; 57% of the patients had a BMI ≥30 kg/m^2. Fifty-nine women (55.1%) were nulliparous. Thirty (35.5%) had a history of irregular menstrual cycles. Twenty-two women (20.5%) reported a history of PCOS. Twenty-three women (21.4%) had diabetes, and twenty-one women (19.6%) had hypertension. Their FIGO stages are presented in Table 1. Histologic grades 1, 2, and 3 of the disease were reported in 74 (69.2%), 16 (15%), and 17 (15.8%) patients, respectively. Ninety-one women (85%) had <50 myometrial invasion (MI), and sixteen women (15%) had ≥50 MI. Ninety-five (88.8%) women had stage 1-2 disease (1-2 early disease) and 12 (11.2%) women had stage 3-4 (advanced-stage) disease. There were 29 patients (27.1%) with EC who had undergone total hysterectomy ± bilateral salpingo-oophorectomy only. Lymphadenectomy was performed in 78 patients (72.9%). Eighty-seven patients (81.3%) did not receive adjuvant treatment. Twenty patients (14.9%) received postoperative adjuvant therapy, eight patients (7.2%) received chemo-radiotherapy, and four patients (3.6%) received only chemotherapy. In the entire cohort, the 5-year DFS and OS rates were 96.4% and 98.2%, respectively. Results of the univariate analysis results for the demographic and clinic-pathological characteristics associated with DFS are presented in Table 2. Univariate analysis revealed that DFS was significantly lower among those patients with stage 3-4 disease (p<0.001), grade 2-3 histology (p<0.001), and those with the presence of LVSI (p=0.002) and lymph node metastasis (p<0.001) (Table 2). Univariate analysis revealed that OS was significantly lower among those patients with stage 3-4 disease (p=0.004), grade 2-3 histology (p=0.007), and those with the presence of LVSI (p=0.018) and lymph node metastasis (p<0.001). The multivariate analysis revealed no independent predictors for prolonged DFS or OS.

DISCUSSION

EC is usually diagnosed in postmenopausal women, but there is a significant proportion of ECs diagnosed in premenopausal women younger than 50 years of age. Premenopausal EC may be difficult to diagnose because irregular vaginal bleeding can frequently be as a result of menstrual irregularities and hormonal disorders.[11] Age is in important prognostic factor in EC patients. Young patients with EC have more favourable prognoses than older patients. For this reason, it is important to diagnose and treat the premenopausal EC age group. In this study, we evaluated patients under 50 years of age with EC at a single centre over a period of 12 years. The major findings of our study included that premenopausal EC is associated with better clinicopathological prognostic characteristics, including earlier stages, lower tumour grades, less MI, and the absence of LVSI and lymph node involvement. Recent studies have shown that patient age, advanced FIGO stage, high grade, deep MI, the presence of cervical stromal invasion, and the presence of LVSI increase the risk of extrauterine disease and nodal metastases and that these factors are associated with poor prognosis.[12-14] Benedetti Panici et al.[15] demonstrated that older age was a significant poor prognostic factor for OS and cancer-specific survival. The authors showed that being aged ≥65 years among EC patients was a poor prognostic factor, associated with their tumour grade and tumour stage, in terms of OS (5-year OS 92.1% for patients <65 years old vs. 78.4% for patients ≥65 years old). Premenopausal patients had better

Cyprus J Med Sci 2023;8(2):153-157

Ayhan and Yıldırım. Premenopausal Women and Endometrial Cancer

Table 1. The demographic and clinicopathological characteristics of all patients (n=107)

Characteristics	Values, n (%)
Age (years), median	46 (34-50)
BMI	33 (19-65)
Baseline serum Ca125 (IU/mL)	28 (2-1,100)
Surgical treatment	
TAH + BSO	29/107 (27.1%)
TAH + BSO + staging	78/107 (72.9%)
Grade	
1	74/107 (69.2%)
2	16/107 (15 %)
3	17/107 (15.8 %)
Depth myometrial invasion, (n %)	
<%50	91/107 (85%)
≥%50	16/107 (15%)
Primary tumour diameter (cm), median	3 (0.1-8)
Peritoneal cytology, (n %)	
Positive	5/107 (4.7%)
Negative	102/107 (95.3%)
Cervical stromal invasion	
Yes	10/107 (93%)
No	97/107 (99.6%)
Adnexal involvement	
Yes	8/107 (7.5%)
No	99/107 (92.5%)
Number of LNs removed	45 (0-96)
Pelvic	31 (0-61)
Paraaortic	14 (0-40)
Stage	
1A	83/107 (77.6%)
1B	5/107 (4.7%)
2	7/107 (6.5%)
3A	3/107 (2.8%)
3B	-
3C	4/107 (3.7%)
4	5/107 (4.7%)
No additional treatment	87107 (81.3%)
Adjuvant treatment	
Brachytherapy only	6/107 (6.1%)
EBRT	1/107 (0.9%)
EBRT + brachytherapy	1/107 (0.9%)
Chemo-radiation	8/107 (7.2%)
Chemotherapy only	4/107 (3.6%)
Recurrence rates	5/107 (4.6%)
Status	
Alive	104/107
Died	3/107
Median follow-up time (months)	32 (3-68)

LN: Lymph node, LVSI: Lympho vascular space invasion, EBRT: External beam radiotherapy, TAH: Total abdominal hysterectomy + bilateral salpingo ooferectomy

prognoses in the presence of early stage and less MI. EC tends to have prognostically favourable histologic types, such as well-differentiated endometrioid type endometrial adenocarcinoma.[16,17] Lau et al.[18] found that perimenopausal EC patients had low-risk features, such as low-grade tumours, lymph node status, less MI, and endometrioid histology. Previous studies have revealed good prognostic features for ECs in the perimenopausal age group such as early stage, low grade, endometrioid histology, and less depth of MI.[4,19] We found that low-risk features, such as early-stage disease, less MI, and lower grade were more common in premenopausal patients with EC.

The PORTEC-1 study showed that patient age, histological grade, and deep MI were poor prognostic factors in terms of the recurrence and outlook for early-stage EC. They found a three-fold higher rate of recurrence among those patients aged ≥60 years.[12] Similarly, the Gynaecological Oncology Group-99 study found that age-related prognosis was worse in the older age group.[10] In our study, similar to postmenopausal status, the presence of lymph node metastasis, advanced stage, tumour size >2 cm, LVSI, and grade 2-3 differentiation were significantly associated with both shorter DFS and OS among premenopausal patients with EC.

Type 1 tumours are more common and are specifically more common during the premenopausal period. They are associated with clinical conditions which cause increased estrogen levels, as well as endometrioid-type EC with a better prognosis.[19] Type 2 ECs, on the other hand, are generally more aggressive, of the serous papillary or clear cell EC types, and are relatively rare in the postmenopausal period.[20]

According to the literature, the rate of early-stage (stage 1-2) EC is about 84.2-91% during the premenopausal period.[15,16] In our study, the rate of early-stage disease (stage 1-2) was 88.8%, which is similar to the findings of previous reports. Biler et al.[21] reported that high grade EC in younger patients had worse prognosis. Our study found that high-grade EC was associated with shorter DFS and OS.

Ayhan et al.[22] revealed that LVSI is an independent predictor of both OS and DFS among low-risk EC patients. The 5-year OS rate for those patients who had EC without LVSI was significantly higher than that of those patients who were LVSI-positive EC (98.5% vs. 88.2%, respectively).[22] In our study, only 15% of premenopausal patients with EC had LVSI. The overall 5-year DFS and 5-year OS rates were 97.3% and 98.8% among the LVSI-negative patients, respectively.

Obesity is strongly associated with the development of EC in the premenopausal age.[5] Recent studies have reported that estrogen, insulin levels, adipokines, growth factors, and many interrelated inflammatory factors may explain the link between obesity and increased EC risk.[23] A recent meta-analysis found a strong association between obesity and EC. Furthermore, a 5 kg/m^2 increase in BMI was significantly associated with higher EC risk. Notably, the obesity rate (57%) was high in our study.[24]

Previous studies reported that EC is more frequently associated with nulliparity, diabetes and hypertension in the premenopausal age group.[25,26] We saw similar outcomes among those women in the premenopausal age with EC; 55.1% were nulliparous, 21.4% had diabetes, and 19.6% had hypertension. This may be due to the high prevalence of obesity in those patients with EC in the premenopausal age group.

Ayhan and Yıldırım. Premenopausal Women and Endometrial Cancer

Cyprus J Med Sci 2023;8(2):153-157

Table 2. Univariate analyses for disease free survival and overall survival in women <50 years with endometroid type endometrial carcinoma				
	5 years (DFS)	Univariate, (p)	5 years (OS)	Univariate, (p)
Grade				
1	100%	<0.001	100%	**0.007**
2-3	82%		89.4%	
Stage				
1-2	97.8%	<0.001	98.8%	**0.004**
3-4	62.5%		82.5%	
Myometrial invasion				
<50%	98.8%	<0.001	98.8%	**0.016**
>50%	67.7%		86.5%	
Tumour size				
<3 cm	98.2%	0.107	100%	0.056
>3 cm	90.3%		93%	
Peritoneal cytology				
Positive	-	0.056	80%	**0.017**
Negative	95.5%		97.7%	
LVSI				
Yes	81.3%	0.002	87.1%	**0.018**
No	97.2%		98.8%	
CS involvement				
Yes	65.5%	<0.001	81.8%	**0.002**
No	97.8%		98.8%	
CA-125 (IU/mL)				
<35	97.8%	<0.001	98.9%	**0.001**
≥35	65.5%		80%	
LN involvement				
Yes	-	<0.001	60%	**<0.001**
No	97.3%		98.6%	
Adnexal involvement				
Yes	87.3%	0.253	87.5%	0.097
No	95.3%		97.7%	
DFS: Disease free survival, OS: Overall survival, LN: Lymph-node, LVSI: Lympho vascular space invasion, CC: Cervical stromal				

Study Limitations

The main limitations of our study were its retrospective, single-centre design and its small sample size. Additionally, histopathological re-evaluation could not be performed. Despite these limitations, our study involved long-term follow-ups, and we believe that it is an important contribution to the literature in this field.

CONCLUSION

EC is uncommon in premenopausal patients, and it is usually early-stage, and it involves well-differentiated tumours. This age group has more favourable prognosis than elderly patients. In our study, obesity, diabetes, and hypertension rates were high, and EC risk could be reduced by changing dietary habits and lifestyles.

MAIN POINTS

• Obesity is associated with the development with EC in the premenopausal age.

• EC is uncommon in premenopausal patients and young patients.

• The absence of LVSI is a good prognostic indicator in premenopausal EC patients.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from Zekai Tahir Burak Training and Research Hospital Non-interventional Clinical Research Ethics Committee under the Declaration of Helsinki (approval number: 2018/20).

Informed Consent: Written informed consent for the use of medical information for investigative intent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: S.A., F.Y., Design: S.A., F.Y., Data Collection and/or Processing: S.A., Analysis and/or Interpretation: S.A., F.Y., Literature Search: S.A., Writing: S.A.

Cyprus J Med Sci 2023;8(2):153-157

Ayhan and Yıldırım. Premenopausal Women and Endometrial Cancer

DISCLOSURES

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