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Endometrial adenocarcinoma in young-aged women: a Turkish population study

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Summary

Purpose of investigation: The present study aims to investigate the incidence, clinicopathological features, and experience of treatment outcomes of patients with endometrial adenocarcinoma (EC) at ≤ 40 years of age in a gynecologic oncology reference center in Ankara, Turkey. *Materials and Methods:* This retrospective study included 577 patients with EC, diagnosed and treated between 2007 and 2013. *Results:* The incidence of EC ≤ 40 years of age was 5.1% (n: 30). The mean age at diagnosis was 35.5 (range: 27-40). Most of the patients with EC were overweight or obese. However, 23% had normal body mass index (BMI). Infertility was seen as a risk factor in 38.4%. The mean duration of postoperative follow-up was 38.3 months with rates of disease persistence and recurrence 14.2% and 28.5%, respectively. *Conclusion:* The disease is diagnosed usually in its early stage and has a good prognosis. Appropriately selected patients with fertility desire have the opportunity to conceive with conservative management.

Key words: Endometrial adenocarcinoma; Gynecological cancer; Young women; Infertility; Obesity.

Introduction

The prevalence of endometrial adenocarcinoma (EC) in women at or below the 40 years of age is known to be distinct in different studies and is reported approximately between 2.9% and 14.4% [1-3]. Nulliparity, increased estrogen level, insulin resistance (with or without overt diabetes), hypertension, polycystic ovarian syndrome (PCOS), infertility, early onset of menstruation, and late menopause are mostly encountered causative factors for EC. However young women with the diagnosis of this disease are often obese or overweight with anovulation [4].

Menometrorrhagia with or without pain, intermenstrual bleeding, and the presence of risk factors may demonstrate cancer, and endometrial investigation is recommended. The disease is often well-differentiated and diagnosed frequently in early stage with limited myometrial invasion in young women [1, 4, 5].

Up to 20% of EC cases occur between 40 and 50 years and the remaining 75% occur in patients over 50 years. Thus endometrial sampling is recommended in patients with abnormal uterine bleeding at ≥ 35 or ≥ 40 years in different studies [3, 4, 6, 7].

EC is staged surgically according to International Federation of Gynecology and Obstetrics (FIGO) guidelines in 2009 [8]. The staging operation is composed of total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, and pelvic and para-aortic lymphadenectomy. Depending on disease stage and tumor grade, surgery, radiation therapy, hormone therapy, and chemotherapy are used either alone or sequentially [9]. A crucial point is the age of the women at the diagnosis when the fertility issue is extremely important. Administration of high-dose progesterone has been recommended in women with clinical Stage IA and grade-I tumors that request to preserve fertility [10].

The purpose of this retrospective study was to investigate the incidence and clinicopathological features of EC in women at or below 40 years of age in a tertiary gynecologic oncology reference center in Ankara, Turkey.

Materials and Methods

The present study was approved by the Institutional Review Board of Zekai Tahir Burak Women' Health Education and Research Hospital where the study was conducted. The medical records of 577 patients who received the diagnoses of EC and treated in the present center between 2007 and 2013 were reviewed retrospectively. Thirty of 577 EC patients were 40 years of age or younger. However 26 patients' records were reached. The upper limit of 40 years was used since it is known that in Turkey, the median age of menopause is 47 years [11] and the premenopausal symptoms, such as bleeding abnormalities that lead to endometrial sampling, are increasingly encountered over 40 years. However patients who are at or less than 40 years of age might be overlooked because of the low EC prevalence in this age group.

From the hospital records of the 26 patients, data related with age, past medical history, menstrual properties, weight, body mass

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index (BMI), gravida, and parity were evaluated. Moreover, result of the last Papanicolaou (Pap) smear, prediagnostic endometrial thickness, levels of CA-125 (cancer antigen-125), CA-199 (cancer antigen-199), CA-153 (cancer antigen-153), CEA (carcinoembryonic antigen), AFP (alpha-fetoprotein), endometrial sampling results, tumor grade, disease stage with findings in surgical specimens, treatment approaches, and postoperative follow-up periods were investigated.

The patients were staged according to FIGO 2009 guidelines with total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, and pelvic and para-aortic lymphadenectomy. The patients that refused the surgery due their fertility desire were staged clinically and treated with oral course of megestrol acetate 160 mg/day 1x1 for six months, with or without the levonorgestrel-containing intrauterine device (IUD).

Statistical Analysis

The descriptive statistical analysis was performed with SPSS version 20.

Results

Based on the present data, there were 30 patients that had the diagnoses of EC at or less than 40 years of age with the incidence of 5.1%. The minimum age at diagnosis was 27 years (mean: 35.5, range: 27-40) and the mean weight was 78.4 kg (range: 64-98). Table 1 presents the clinical data of all patients with accompanying medical illnesses.

There were 12 nulligravid patients (46.2%), eight of which were infertile, 14 multigravid patients (53.8%) 12 of which had given at least one birth, and 14 nulliparous patients (53.8%) two of which had recurrent pregnancy loss. Infertility was seen as a risk factor only in ten patients (38.4%).

Twenty patients (76.9%) had a primary symptom of menometrorrhagia, three (11.5%) had pelvic pain, and two had (7.6%) pelvic pain with hypermenorrhea. There was only one patient without apparent symptom and her diagnosis was made after endometrial sampling due to increased endometrial thickness on the transvaginal ultrasonographic evaluation shortly after her menstruation.

On the preoperative diagnostic workup, only two patients had adnexal mass; one patient with bilateral 5x6 cm solid-cystic ovarian and the other patient with right ovarian cystic mass. The Papanicolaou tests (Pap test) were evaluated in 22 patients (84%). Eleven patients' tests (50%) were reported as normal and the other ten patients (45%) with an inflammatory reaction. Only one patient (4%) had the presence of abnormal glandular cells on the Pap test evaluation. The mean thickness of the endometrium on transvaginal ultrasonography was 15.8 mm (range: 7 - 57 mm). PCOS was diagnosed in seven patients (26%) according to the Rotterdam 2003 criteria [12].

Endometrial sampling revealed grade-I endometrioid EC in 12 patients (46%). Up to 23% (n= 6) of patients' pathologic diagnoses were complex atypical hyperplasia (CAH) with grade-I EC could not be excluded. Two patients' biop-

Table 1. — *Clinical details of all patients.*

		No. of patients	Percentage
Age (27-40 yrs)	40	8	30.7%
	30-39	16	61.5%
	< 30	2	7.6%
BMI	Low (< 20)	-	0%
	Normal (20 - 25)	6	23%
	Overweight (25 - 30)	13	50%
	Obese (> 30)	4	15.3%
	Morbid-obese (> 40)	3	11.5%
Gravida	0	12	46.2%
	I	1	0.38%
	> I	13	50%
Parity	0	14	53.8%
	I	3	11.5%
	> I	9	34.6%
Medical history			
	Hypothyroidism	5	19.2%
	Hypercortisolism	3	11.5%
	HT	1	3%
	Impaired fasting glucose	1	3%
	Hyperprolactinemia	2	7.6%
	Rhemoid arthritis	1	3%
	Decreased protein C, S activity	1	3%
Symptom	Menometrorrhagia	20	76.9%
	Pain with hypermenorrhea	2	7.6%
	Pain	3	11.5%
	None	1	3.8%
PCOS	+	7	26.9%
Infertility	+	10	38.4%
Cervical cytology	Normal	11	50%
	Inflammatory/reactive	10	45.4%
	AGC	1	4.5%
CA-125	> 35 u/ml	8	30.7%
CA-199	> 37 u/ml	2	7.6%
CA-153	> 38 u/ml	0	-
Endometrial sampling			
	GI EC	13	50%
	GII EC	3	11.5%
	GIII	1	3.8%
	CAH with GI EC could not be excluded	6	23%
	CH with GI EC could not be excluded	1	3.8%
	CAH	2	7%
Initial treatment	Surgery	19	73%
	Medical	7	26.9%
2nd course treatment	Surgery	3	42.8%
	Medical	1	14.2%
Histology at staging			
	Endometrioid	17	77.2%
	Endometrioid with focal clear cell component	1	4.5%
	Endometrioid with serous and clear cell components	1	4.5%
	Serous	1	4.5%
	No tumor	2	9%
Surgical Stage	IA	16	80%
	IB	3	15%
	IIIC2	1	5%
Adjuvant therapy	RT	3	12.5%
	CT	1	4.1%
Follow-up (months)	≤ 24	7	26.9%
	25 - 48	11	42.3%
	> 48	8	30.7%

BMI: body mass index (kg/m^2); PCOS: polycystic ovarian syndrome; CA- : cancer antigen; HT: hypertension; G: grade; EC: endometrial adenocarcinoma; CAH: complex atypical hyperplasia; CH: complex hyperplasia; RT: radiotherapy; CT: chemotherapy.

sies (7%) were reported as CAH. Another patient that had an endometrial polyp extending throughout the vaginal lumen resulted in an adenomyoma with components of complex hyperplasia without atypia with grade-I EC that could not be excluded. Three patients, one with villoglanduler differentiation, had grade-II endometrioid EC. Two other patients, one with grade-I endometrioid and the other with grade-III EC, also had focal clear cell and serous and clear cell components. There was only one patient with serous EC.

The preoperative mean CA-125, CA-199, CA-153, CEA, and AFP tumor marker levels were 66.8 U/ml (range: 4.6 - 762.0), 22.1 U/ml (range: 0.6 - 209.5), 14.2 U/ml (range: 0.4 - 29.1), 1.4 ng/ml (range: 0.1 - 4.3), and 2.2 ng/ml (range: 0.8 - 5.3), respectively.

The disease stages at surgery were Stage IA (n= 16, 80%), Stage IB (n= 3, 15%), and Stage IIIC2 disease with para-aortic lymph node involvement (n= 1, 5%) respectively. Three of the infertile patients were surgically staged immediately after the diagnosis of EC according to patients' desire. The other three infertile patients were treated with six months of oral progesterone therapy. Only one of them used the levonorgestrel-containing IUD in addition to oral therapy. However staging surgery was the end point in these patients due to disease persistence at six months, disease recurrence in the form of CAH after assisted reproductive technology (ART) trial at 18 months and abortion after ART trial at 12 months, respectively. The other four patients who desired future fertility and grade-I, clinical Stage IA EC had no surgery and were treated with oral and progesterone containing IUD treatment with negative endometrial biopsy. After treatment, one of them dropped out from the follow-up at three months. One of the patients had two spontaneous pregnancies and deliveries. Another one had two ART trials and had one delivery, and developed CAH at 36 months . She was treated with a second course of medical therapy with the same protocol and is now disease-free. The last patient had yet no ART trial.

The entire endometrial cavity was affected by the tumor in five patients with isthmic invasion without endocervical canal entrapment. Moreover one patient with Stage IIIC2 disease had positive peritoneal washing, cervical stroma, and right adnexal invasion with omentum and sigmoid colon involvement. Omentectomy evaluations revealed normal adipose tissue in 18 patients and chronic inflammatory reaction in one patient. Appendectomy specimens demonstrated normal appendix tissue (n= 15), periappendicitis (n= 3), obliteration (n= 1), and lymphoid hyperplasia (n= 1). The lymphovascular space involvement was diagnosed in five patients with Stage IA (n= 1), IB (n= 3), and IIIC2 (n= 1) disease. The mean pelvic and para-aortic lymph node counts were 74.75 (range: 37 - 133). Only one patient with serous tumor had para-aortic lymph node involvement.

Two patients (9%) who had had biopsy proven EC had no malignancy in the hysterectomy specimens after staging. Endometrial sampling results of these patients were complex atypical hyperplasia with grade-I endometrioid EC and grade-I endometrioid EC, respectively. These patients were 31 *vs.* 40 years of age one with a history of infertility. The permanent pathology after staging surgery revealed simple endometrial hyperplasia with atypia and normal endometrium with bilateral mucinous cystadenoma in these patients.

The mean duration of postoperative follow-up was 38.3 months (range: 3-75). Only one patient on progesterone treatment dropped out from the regular check visits at three months. There are two patients in close follow-up with the pelvic lymphocyst formation after the staging surgery. Three patients with Stage IB disease had adjuvant radiotherapy. Another patient with serous tumor and positive para-aortic lymph nodes had adjuvant chemotherapy with carboplatin and paclitaxel.

Discussion

EC is more frequently seen in older, postmenopausal women. However women have changed their lifestyles in the last decades. Due to westernization of diet, getting married in later reproductive years, decreased attempts on childbearing and breast-feeding, increased use of oral contraceptives, and genetic tendency predispose the women more vulnerable to EC. The incidence of EC in young aged women at ≤ 40 years of age is reported to be roughly 5% and reaches as high as 14% in different studies [1-3]. The present authors found a 5.1% incidence of EC in young aged women at ≤ 40 years similar to literature. Moreover the incidence of infertility complicating the treatment decision was 1.7% in the present study.

The mean weight and the BMI values of the present patients supported the data in the literature related with the increased incidence of EC in overweight and obese patients with the effects of hyperestrogenism [13]. Nevertheless 23% patients with EC had normal BMI. The accompanying medical conditions with EC and normal BMI were nulliparity, PCOS, hypothyroidism, impaired fasting glucose levels, hyperprolactinemia, presence of myoma uteri and history of previous ART trials. Hypercortisolism and hypertension were the associated risk factors for EC in patients with higher BMI.

In this study, 76.9% of the patients had menometrorrhagia and the other 7.6% had hypermenorrhea with pelvic pain. However the patients with infertility had no recognized bleeding abnormality by themselves until detailed questioning after the diagnosis of EC due to endometrial irregularity on transvaginal ultrasonography or hysterosonography (H/S) during infertility work-up diagnosed. The diagnosis of EC may be difficult since the dysfunctional uterine bleeding is common in reproductive ages and the underlining pathology may be overlooked if the appropriate evaluation is not performed [14].

There are studies in the literature supporting increased endometrial pathology in the presence of endometrial glandular cells in the Pap test of women over 40 years age. The reproductive aged women have the increased possibility of desquamated endometrial cells on Pap tests due to cyclic alterations of the endometrium throughout the menstrual cycle. However the importance of the presence of these cells in respect to endometrial pathologies in women at ≤ 40 years of age is not known [15, 16]. Only one of the patients in this study had abnormal glandular cells on the Pap test evaluation and the 45% patients had inflammatory reactive alterations. Moreover the increased endometrial thickness was the most remarkable sign of endometrial pathology necessitating endometrial sampling or H/S in the preoperative diagnostic evaluation.

The endometrial sampling results and the endometrial pathologies diagnosed in the hysterectomy specimens are known to show 16% discrepancy [17]. The discrepancy rate was 9% in the present study which is much less than the literature. There were two patients with the diagnosis of no malignancy in the permanent pathology. However the preoperative tissue diagnosis was CAH with grade-I EC and grade-I EC, respectively. As suggested in the literature, these patients were accepted as having focal grade-I EC possibly on a polyp structure. Postoperative regular visits were recommended to these patients.

CA-125 levels have been clinically used for EC and increased levels correlate with the disease stage or histopathologic factors. Also it appears to predict the lymph node metastasis and advanced stage disease [18]. Elevation of CA-125 was diagnosed in 25% of patients with Stage IA and in all patients with Stage IB and IIIC2 disease. However there was only one patient with positive lymph node metastasis in the present study. The concurrent CA-199 value was increased in 6.2% and 33% in Stage IA and IB disease, respectively. The levels of CA-153, CEA or AFP levels were within normal levels in all patients.

In industrialized countries, the incidence of infertility is estimated between 8.5 - 20% [19] much more common than the 5% incidence of EC in young women. Thus evaluations during infertility work-up provide an opportunity to evaluate the endometrium and its pathologies in these patients, when the disease is in its early stage and symptom free. As mentioned in the literature conservative management of EC with oral progestational drugs in the early disease stage is effective without compromising oncological outcome in young women [20]. However there is no consensus concerning the type, dose, and duration of progesterone. The positive effects of combined treatment with oral and levonorgestrel-containing IUD are presented in the literature [21]. The oral progestational drug was megestrol acetate 1 x 160 mg for six months in the present patients. Furthermore only five patients (71.4%) had also used the levonorgestrel-containing IUD.

Dursun *et al.* reported the mean EC persistence and recurrence rates as 21% (range: 0% - 58%) and 33% (range: 0% - 67%), respectively, in their literature review [20]. The disease persistence and recurrence rates were 14.2% and 28.5% in the present study, similar with the literature. One of the patients had disease persistence confirmed by tissue biopsy at six months of therapy and she underwent surgery. Her definitive diagnosis was grade-II, Stage IB EC with lymphovascular space invasion (LVSI) and she had adjuvant radiotherapy. The second patient underwent surgery after a failed ART trial at 18 months due to disease recurrence in the form of CAH. Her definitive diagnosis was grade-I, Stage IA EC without LVSI and she had no adjuvant therapy. These two patients were treated only with oral progesterone therapy. Another patient with clinical Stage IA disease treated with oral progesterone and levonorgestrel-containing IUD had recurrent disease in the form of CAH at 36 months. She underwent a second course of therapy with the same regimen and is now disease-free.

The present study had some limitations. The retrospective nature of this study was one of the obstacles. Although there were infertile patients diagnosed during infertility work-up, the present results cannot present the EC incidence in the infertile women. Another limitation was that although familial cancer syndromes might predispose patients with normal BMI to EC and receptor status of the tumor affects the treatment outcome, the authors did not evaluate their patients with the genetic testing for Lynch Syndrome or the hormone receptor status.

In conclusion, it must be recognized that although the rate is low, young women are prone to EC as postmenopausal women and they are more frequently obese. The disease is noticed usually in early stage with well-differentiation. Diagnostic imaging adds benefits on gynecologic examination for the diagnosis of unexpected endometrial pathologies. The accompanying risk factors for EC should be questioned when dealing with young patients during infertility evaluations. Appropriately selected patients have change to conceive with conservative management after progesterone treatment.

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