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Original Article

Clinicopathologic characteristics and treatment features of women with the incidental diagnosis of endometrial adenocarcinoma during infertility follow-up in Ankara, Turkey

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ABSTRACT

Objective: The aim of this study was to investigate the clinical and laboratory features of patients with the incidental diagnosis of endometrial adenocarcinoma (EC) during infertility work-up, with special attention given to treatment approaches, recurrence rate, and fertility outcome.
Material and Methods: The medical records of 577 patients who were diagnosed with EC and treated between 2007 and 2013 were included in the study. Out of 577 EC patients, 5.1% ($n = 30$) were ≤ 40 years of age. However, 10 patients had a history of infertility and had been diagnosed during evaluation for infertility. Patients' clinical and laboratory data were reviewed retrospectively.
Results: The mean age at diagnosis was 34.3 ± 4.5 years and the mean duration of infertility was 5.1 ± 4.7 years. Immediate staging surgery was performed on three patients. The others were treated with oral megestrol acetate and/or a levonorgestrel-containing intrauterine device (IUD) for 6 months. The mean duration of postoperative or postdiagnostic follow-up was 44.7 ± 25.9 months. The disease persistence and recurrence rates were 11.1% and 22.2%, respectively. Two patients achieved pregnancy naturally or by assisted reproductive technology (ART) trial.
Conclusion: The investigation of patients during infertility work-up provides an opportunity to evaluate the endometrium and its malignancies in young women, when the disease is in its early stage and symptom free. The standard surgical treatment for early-stage EC is total hysterectomy with bilateral salpingo-oophorectomy. However, conservative management of early stage EC with progestational drugs, especially in young patients who wish to preserve their fertility, is acceptable with the possibility of future pregnancies.

Introduction

The prevalence of endometrial adenocarcinoma (EC) in women ≤ 40 years of age has been shown to be distinct in different studies and is reported to be roughly between 2.9% and 14.4% [1–3]. The incidence of EC in infertile women is not clear, even though it is known that women undergoing infertility treatment have increased risk of EC [4,5]. Genetic factors, nulliparity, insulin resistance (with or without overt diabetes), and hypertension also play a role in EC genesis. However, young women diagnosed with EC are often obese or overweight with anovulation [6]. Polycystic ovarian syndrome (PCOS), thyroid hormone imbalance, increased prolactin (PRL) levels, hyperandrogenism, hypercortisolism, etc. may result in ovulatory diseases with progesterone insufficiency and unopposed estrogenic stimulation, which increases the susceptibility of women to EC.

Abnormal uterine bleeding is the major complaint of women with EC. Heavy menstruation or irregular spotting leads to early perception of an abnormality by the women themselves. However, in its early stages, EC might be indolent with no apparent symptoms. Most of the women undergo gynecological examination and transvaginal ultrasonography in infertility clinics, perhaps for the first time, and routine investigations sometimes reveal endometrial pathologies that need further evaluation.

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EC is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines of 2009 [7]. The staging operation is composed of total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, and pelvic and paraaortic lymphadenectomy. A crucial point is the age of the women at diagnosis, since the fertility issue is extremely important. However, these patients usually have favorable prognosis with more frequent Grade I tumors and limited myometrial invasion [8,9]. Thus administration of high-dose progesterone has been recommended in women with clinical Stage IA and Grade I tumors who want to preserve their fertility [10]. In spite of high-dose progesterone therapy, the recurrence rate of EC is 50% [11,12]. As a result, the management of infertile women with EC necessitates a frequent multidisciplinary approach with oncologic surgeons and endocrinologists.

The investigation of endometrial pathologies of infertile women is warranted since the incidence of infertility is approximately 15% in high-income and 9–30% in low-income countries [13] and many endometrial pathologies cause structural or functional inabilities [14]. Subtle endometrial pathologies without any symptoms may be noticed easily by blind endometrial sampling or by direct visualization via hysteroscopy. However, the diagnosis of EC may be overlooked if endometrial evaluation is postponed and an assisted reproductive technology (ART) trial is performed in the case of endometrial abnormality upon routine ultrasonographic investigation. Thus, endometrial sampling before an ART trial is reasonable in women with longstanding estrogenic stimulation and endometrial irregularity despite the absence of symptoms [5].

In this study, we aimed to evaluate the clinical and laboratory aspects of patients that incidentally were diagnosed with EC during investigations for infertility and focused on the aforementioned points in terms of etiology, treatment approaches, and course of the disease.

Materials and methods

The present study was approved by the Institutional Review Board of Zekai Tahir Burak Women' Health Education and Research Hospital, Ankara, Turkey where the study was conducted. The medical records of 577 patients who had been diagnosed with EC and treated in our tertiary reference center between 2007 and 2013 were reviewed retrospectively. Thirty out of the 577 EC patients were $\leq$ 40 years of age. However, 10 patients with a history of infertility had been diagnosed during evaluation for infertility.

From the hospital records of these 10 patients, data related to age, past medical history, cycle property, symptoms, weight, body mass index, cause of infertility, duration of infertility, and history of previous ART trials were reviewed. Furthermore, the results of the last Papanicolaou smear, endometrial thickness on transvaginal ultrasonography, cycle Day 3 follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, PRL, thyroid stimulating hormone, free triiodothyronine, and free thyroxine levels were collected. The pathological reports of diagnostic endometrial sampling with respect to histologic diagnosis and tumor grade were checked. The cancer antigen-125 (CA-125), CA-199, CA-153, carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) levels were evaluated after the diagnosis of EC. Data related to treatment, disease stage, and findings in surgical specimens were browsed and processes were evaluated.

The patients were staged surgically according to the FIGO 2009 guidelines with total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, and pelvic and paraaortic lymphadenectomy or clinically due to their fertility preferences. All of the patients on whom staging surgery was not performed were treated with a 6 month oral course of megestrol acetate 160 mg/d 1 $\times$ 1 (Megace 160 mg pill, Haupt Pharma Regensburg GMBH, Regensburg, Germany) with or without the levonorgestrel-containing intrauterine device (IUD) (Mirena levonorgestrel-releasing intrauterine system, Bayer Schering Pharma Oy, Turku, Finland).

Statistical analysis

The descriptive statistical analysis was performed with SPSS for Mac version 20 (SPSS for Mac Inc., Chicago, IL, USA). Values are presented as mean $\pm$ standard deviation (SD) and range.

Results

In the study population, there were 12 nulligravid patients (40%) of whom eight (66%) were infertile and 14 nulliparous patients (46%), while two (14%) had experienced recurrent pregnancy loss, and 10 patients (33%) were infertile and diagnosed during infertility workup. Table 1 presents the profile of patients with EC and infertility (Table 2).

Patients were diagnosed incidentally by endometrial sampling because of abnormal visualization of the endometrial cavity during transvaginal ultrasonography or office hysteroscopy. However, when they were asked after the diagnosis of EC about their periods or previous symptoms, it was understood that three had pelvic pain with oligomenorrhea, four had a recently noticed menometrorrhagia, and two had pelvic pain with hypermenorrhea. There was only one patient who had had no apparent symptoms.

The mean age at diagnosis was 34.3 $\pm$ 4.5 years (range, 28–40 years) and the mean duration of infertility was 5.1 $\pm$ 4.7 years (range, 1–18 years). Three patients had at least one ART trial before the diagnosis and three had ART trials after the medical therapy for EC. The mean weight at diagnosis was 77.7 $\pm$ 9.7 kg.

The last Papanicolaou smear (Pap test) was reported to be normal in five patients and the other five patients had inflammatory reactive alterations. The mean value of the endometrial thickness was 22.41 $\pm$ 18.9 mm on transvaginal ultrasonography. Based on the Rotterdam 2003 criteria [15], PCOS was diagnosed in seven patients (70%).

The mean values $\pm$ SD of cycle Day 3 FSH, LH, estradiol, PRL, thyroid stimulating hormone, free triiodothyronine, and free thyroxine levels were: 5.5 $\pm$ 1.2 mIU/mL, 9.5 $\pm$ 5.3 mIU/mL, 62.09 $\pm$ 18.5 pg/mL, 23.1 $\pm$ 20.9 ng/mL, 1.8 $\pm$ 0.7 uIU/mL, 3.5 $\pm$ 0.4 pg/mL, and 1.3 $\pm$ 0.3 ng/dL, respectively.

The endometrial sampling results revealed Grade I EC in four, Grade II EC in one, complex atypical hyperplasia (CAH) with Grade I EC in two, CAH with Grade I EC could not be excluded in two, and complex hyperplasia without atypia with Grade I EC could not be excluded in one patient.

The mean values $\pm$ SD of the CA-125, CA-199, CA-153, CEA, and AFP levels after the diagnosis of EC were: 31.9 $\pm$ 24.2 U/mL, 29.7 $\pm$ 71.2 U/mL, 19.6 $\pm$ 9.8 U/mL, 0.9 $\pm$ 0.7 ng/mL, and 1.9 $\pm$ 1.1 ng/mL, respectively. Elevations of the CA-125 and CA-199 tumor markers above the current cut-off value were diagnosed in five and two patients, respectively.

The mean duration of postoperative or postdiagnostic follow-up was 44.7 $\pm$ 25.9 months (range, 3–75 months). Only one patient who was under medical treatment dropped out of the regular postoperative check visits 3 months after the diagnosis.

Three of the patients (P1, P2, P3) elected to have immediate surgical staging instead of progesterone therapy. In the permanent pathology evaluation: P1 had architectural Grade I, nuclear Grade II, Stage IB, EC with deep myometrial invasion and lymphovascular space involvement (LVSI), and had postoperative adjuvant

Table 1
Profile of patients with endometrial adenocarcinoma (EC) diagnosed on infertility investigations.

Patient	Age (y)	Duration of infertility (y)	Infertility cause	BMI (kg/m^2)	Previous pregnancy	ART history	PCOS	Medical illness	Diagnosis
1	28	1	OD	24	G0P0	−	+	−	P&C
2	31	3	Recurrent abortion	22	G3P0A3	+ (PD)	−	Multiple myomectomy operations	H/S
3	38	3	OD	41	G0P0	−	+	HT, Cushing's syndrome, multiple myoma	P&C
4	40	5	Recurrent abortion	21	G2P0A2	−	−	Impaired fasting glucose, decreased protein S and protein C activity, PRL > 20 ng/mL	H/S
5	39	6	OD	28	G0P0	+ (PD&AD)	+	Metabolic syndrome, multiple myoma	H/S
6	34	18	OD	20	G0P0	+ (PD&AD)	+	Multiple myoma, PRL > 20 ng/mL	H/S
7	33	5	OD	24	G0P0	−	+	−	H/S
8	30	3	OD	32	G0P0	+ (AD)	+	−	H/S
9	30	2	Unexplained	26	G0P0	−	−	Hypothyroidism	H/S
10	40	5	OD	26	G0P0	Unknown	+	Hypothyroidism	P&C

A = abortus; AD = after the diagnosis; BMI = body mass index; G = gravida; H/S = hysteroscopy; HT = hypertension; OD = ovulatory disorder; P = parity; P&C = probe curettage; PCOS = polycystic ovarian syndrome; PD = previous the diagnosis; PRL = prolactin.

Table 2
Treatment and clinical course of 10 patients with endometrial adenocarcinoma (EC) detected on infertility investigations.

Patient	Endometrial sampling	Initial treatment	Follow-up (mo)	Treatment outcome	ART	Pregnancy after diagnosis	Clinical course	Final diagnosis
1	CAH + AG-I EC could not be excluded	Surgery	70	CR	−	−	CR	AG-I, NG-II, stage IB EC with deep myometrial invasion and (+) LVSI AT: Radiotherapy
2	CAH + AG-I EC could not be excluded	Surgery	25	CR	−	−	CR	AG-I, NG-II, stage IA EC with (+) LVSI AT: None
3	CAH + AG-I EC	Surgery	42	CR	−	−	CR	Simple atypical hyperplasia without EC
4	NG-II EC	6 Mo MA	19	Persistence at 6^{th} mos. Scheduled for surgery	−	−	CR	AG-I, NG-II, stage IB EC with (+) LVSI AT: Radiotherapy
5	CH without atypia & NG-I EC could not be excluded	6 Mo MA	63	Recurrence in the form of CAH at 18^{th} mo after failed ART trial. Scheduled for surgery	+	−	CR	AG-I, NG-I, stage IA EC without LVSI AT: None
6	NG-I EC	6 Mo MA and LNG-IUD	24	Abortion after ART trial at 12^{th} mo. Scheduled for surgery	+	G1P0A1	CR	AG-I, NG-I, stage IA EC without LVSI AT: None
7	NG-I EC	6 Mo MA and LNG-IUD	75	CR	−	G2P2 (Spontaneous)	CR	Clinical Stage IA
8	CAH + NG-I EC	6 Mo MA and LNG-IUD	51	CR	+	G2P1	Recurrence in the form of CAH at 36^{th} mo. Second course of medical therapy. CR	Clinical Stage IA
9	NG-I EC	6 Mo MA and LNG-IUD	75	CR	Not yet	−	CR	Clinical Stage IA
10	NG-I EC	6 Mo MA and LNG-IUD	3	Unknown	Unknown	Unknown	Unknown	Clinical Stage IA Dropped out

A = abortion; AG = architectural grade; ART = assisted reproductive technology after EC diagnosis; AT = adjuvant therapy; CAH = complex atypical hyperplasia; CR = complete response; G = gravida; LNG-IUD = levonorgestrel-containing intrauterine device; LVSI = lymphovascular space involvement; MA = megestrol acetate; NG = nuclear grade; P = parity.

radiotherapy; P2 had architectural Grade I, nuclear Grade II, Stage IA, EC with LVSI, and had no postoperative adjuvant therapy; and P3 was diagnosed with simple atypical hyperplasia without EC. Her previous tissue biopsy had revealed CAH with Grade I EC.

Three other patients (P4, P5, P6) with suspected malignancies were administered 6 months of oral progesterone therapy. Only one of them used the levonorgestrel-containing IUD in addition to oral progesterone. At the 6^{th} month, P4 had disease persistence confirmed by tissue biopsy and underwent surgery. She had architectural Grade I, nuclear Grade II, Stage IB, EC with LVSI, and underwent adjuvant radiotherapy. P5 had ART trial that resulted in failure and at the 18^{th} month underwent surgery due to disease recurrence in the form of CAH in the endometrial biopsy. P6 had elected surgery at the 12^{th} month after aborting her ART pregnancy. P5 and P6 had architectural and nuclear Grade I, Stage IA, EC without LVSI, and they had no adjuvant therapy.

The staging surgeries of six patients revealed that the whole endometrial cavity was affected by the tumor in two patients (Stage IA and Stage IB). The isthmus was invaded by the tumor in three patients (2 Stage IB and 1 Stage IA) without cervical involvement. There was no adnexal involvement. Two patients, one with bilateral, had follicular cysts > 3 cm. Peritoneal washings were negative for malignant cells. Omentectomy evaluations revealed chronic inflammation in one and mature adipose tissue in five patients. Appendectomies were performed in all of the patients, which revealed obliteration in one and periappendicitis in another patient. The LVSI was seen in only three patients with Stage IA and Stage IB disease. The mean collected pelvic and paraaortic lymph node count was 71.8 ± 26 (range, 37–111). Three patients had multiple myoma uteri in the uterine specimens and another one had a history of three myomectomy operations. One of the operated patients had metabolic syndrome, one had Cushing's syndrome with morbid obesity and hypertension, and one had impaired fasting glucose levels with decreased protein S and protein c activity.

The other four patients (40%) were treated with oral megestrol acetate and levonorgestrel-containing IUD for 6 months. Endometrial biopsy evaluations were performed thereafter at 3 month intervals. However, one of them dropped out of the follow-up in the 3rd month. Two patients were under levothyroxine supplementation due to Hashimato's disease. After treatment, one of the patients had two spontaneous pregnancies and deliveries. Another patient had two ART trials and had one delivery, and developed CAH in the 36th month. She was treated with a second course of medical therapy with the same protocol and is now disease free. The last patient has had no ART trial yet. The mean duration of postoperative follow-up was 51 ± 33.9 months in these four patients and three of them are still on close follow-up.

Disease persistence or recurrence was seen after oral therapy in the patients with Stage IB (P4) and Stage IA (P5). Another patient with Stage IA (P8) disease and treated with both oral and levonorgestrel-containing IUD had recurrent disease in the form of CAH. Thus, the rates of disease persistence and recurrence were reported to be 11.1% and 22.2% in the infertile patients with EC. Furthermore, the disease persistence and recurrence rates of the whole study population (n = 577) were reported to be 14.2% and 28.5%, respectively.

Discussion

Nowadays, the number of young women with EC is increasing in developing countries due to alterations of diet and lifestyle, such as increasing obesity and getting married in later reproductive years. The literature data presenting the increased incidence of EC in women ≤ 40 years of age leads to treatment challenges, especially in women who wish to preserve their fertility [1,2]. Fortunately, the prognosis of EC in this group of patients is known to be promising assuming the tumor is well differentiated and without myometrial invasion, with a 5-year survival rate of 93% [16].

The incidence of infertility is estimated to be between 8.5% and 20% in industrialized countries [17] and it is much more common than the 5% incidence of EC in women ≤ 40 years of age. Uterotubal peritoneal factors, ovulatory disorders, and unexplained infertility create the main components of the female infertility. Nevertheless, endometrial pathologies, such as CAH or EC may predispose patients to infertility [18] or vice versa [19]. Therefore, investigations during infertility work-up provide an opportunity to evaluate the endometrium and its pathologies in young women, when the disease is in its early stage and still symptom free.

Based on our data, the incidence of EC was 5.1% in women ≤ 40 years of age. Infertility, with the most frequently encountered ovulatory disorder, was a risk factor in 33% of EC patients (n = 10) at ≤ 40 years of age with the estimated incidence of 1.7%. Almost 70% of the patients with a history of infertility had Stage IA disease.

Based on previous reports in the literature, it is known that EC is most commonly encountered in overweight or obese women [20]. However, it is also clear that familial cancer syndromes (Lynch syndrome), nulliparity, history of infertility, insulin resistance, and PCOS with its altered hormonal milieu may contribute to the development of EC in normal weight women [21]. The mean body mass index in infertile women with EC was 26.4 ± 6.2 kg/m^2 in our study with the ratio of normal weight women at 50%. There was only one patient with morbid obesity. According to the preoperative diagnostic evaluations, increased endometrial thickness was the most remarkable sign for endometrial pathology necessitating probe curettage in three patients and hysteroscopy in seven patients. None of the patients had abnormal glandular cells in the Pap test. Day 3 hormone levels presented increased estrogen levels over 40 pg/mL in all patients with LH/FSH ratio > 2 in 60%. The accompanying conditions with EC were PCOS, hypothyroidism, hypercortisolism, hypertension, impaired fasting glucose levels, hyperprolactinemia, and history of previous ART trials. The presence of multiple myoma was also evidence that supported the estrogenic effect in three patients [22].

Serum CA-125 levels have been used clinically for EC and increased levels correlate with the disease stage or several histopathologic factors [23]. This appears to predict lymph node metastasis and advanced stage disease preoperatively [23,24]. Although the optimal CA-125 cut-off value for premenopausal patients with endometrial cancer was reported to be 105 U/m: in the literature [23], there were no patients with CA-125 values above this threshold level in our study. However, elevation of the CA-125 tumor marker above the current cut-off value of 35 U/mL was diagnosed in five patients (n = 3, Stage IA and n = 2, Stage IB EC) and elevated values were seen in patients with Stage IB disease, deep myometrial invasion, (+) LVSI and isthmic involvement. There was no patient with positive lymph node metastasis in our study and based on this data, we could not demonstrate any correlation with lymphatic involvement and preoperative CA-125 levels. Moreover, the concurrent CA-199 tumor marker was diagnosed above the current cut-off value of 37 U/mL in only two patients (n = 1, Stage IA and n = 1, Stage IB EC). The levels of CA-153, CEA, or AFP levels were within the normal range in all infertile patients with EC. The level of prolactin hormone, which was previously reported to have a positive correlation with the tumor stage and grade in EC [25], increased in only two patients.

As previously mentioned in the literature, conservative management of EC with oral progestational drugs in young patients with early stage disease is effective without compromising oncological outcome, with mean persistence and recurrence rates of 21% and 33%, respectively [26]. Furthermore, Wang et al [27] reported that the crude recurrence rate was 50%, and the 5-, 10-, and 15-year cumulative recurrence-free survival rates were 51.0%, 51.0%, and 34.0%, respectively, in their series, which was composed of young aged women with EC. They also drew attention to the substantial risk of late recurrences [27]. The disease persistence and recurrence rates of the whole study population (n = 577) were 14.2% and 28.5%, respectively, in our study. We operated on three patients immediately and treated the remaining seven patients medically according to the patients' desire in the infertile population (n = 10) with EC. The oral progestational drug was megestrol acetate in all patients with the same dose regimen. Only five patients also used the levonorgestrel-containing IUD. The rates of disease persistence and recurrence were reported to be 11.1% (1/9) and 22.2% (2/9) in the infertile patients with EC; however, the case number was small.

The preoperative endometrial sampling results and endometrial pathologies diagnosed in the hysterectomy specimens are known to show a 16% discrepancy [28]. There was only one patient with a diagnosis of no malignancy in the hysterectomy specimen. However, the preoperative tissue diagnosis was CAH with Grade I EC. As suggested in the literature, this patient was accepted as having focal Grade I EC possibly on a polyp structure and postoperative regular check visits were recommended to this patient.

The present study has some limitations. The retrospective nature of this study is one of the obstacles. Furthermore, it cannot present the EC incidence in the infertile women because this study was not conducted in a fertility clinic. We studied a group of women $\leq$ 40 years of age with the diagnosis of EC in our gynecologic oncology clinic and evaluated their clinical data. A history of diagnosis during the infertility work-up was seen in 10 of the 577 EC patients with an incidence of 1.7%. We roughly know the history of the ART trials prior to or after the diagnosis. What specific drugs and which treatment protocols had been used were not always clear. Another limitation was that we did not evaluate our patients with the genetic testing for Lynch syndrome, despite 50% of the women with EC being normal weight; nor were we aware of their hormone receptor status.

In conclusion, conservative management of EC, especially in young patients with fertility desire, is acceptable only after the patients are fully informed about the risks and benefits. Two patients in this study achieved pregnancy both spontaneously and with an ART trial. To the best of our knowledge, this study includes all the clear data related to patients' profiles and clinical properties with a sufficiently long duration of follow-up. Further prospective studies with larger numbers are needed to clearly delineate the EC incidence in infertile women and the efficacy of medical treatment instead of staging surgery in the early stages of the disease.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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