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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