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CLINICAL ARTICLE

A Turkish Gynecologic Oncology Group study of fertility-sparing treatment for early-stage endometrial cancer☆

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ABSTRACT

Objective: To analyze the results of fertility-sparing treatment of early-stage endometrial cancer (EC) in patients treated at Turkish gynecologic oncology centers, and to present a review of the literature. *Methods:* Thirteen healthcare centers in Turkey were contacted to determine if they were eligible to participate in the study. Centers that were eligible and agreed to participate were sent a database form to record the demographic characteristics, clinicopathologic findings, and follow-up results for their EC patients. *Results:* Eleven Turkish healthcare centers provided data on 43 EC patients. Mean duration of treatment was 5 months and mean follow-up was 49 months. In total, 35 (81.4%) patients were tumor free following primary progesterone therapy. Mean time from the end of progesterone therapy to pregnancy was 10.6 ± 4.3 months (range, 3–18 months). Two patients had tumor recurrence during follow-up. The pregnancy rate among the 31 women who actively sought pregnancy was 41.9% (n = 13). *Conclusion:* Conservative management of early-stage EC in women of reproductive age using oral progestins was effective and did not compromise oncological outcome. Pregnancy in the study patients was achieved spontaneously and artificially.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in women. Approximately 20% of all women will be diagnosed with EC before menopause, and 5% of them will develop the disease before the age of 40 years [1]. The current therapeutic approach for early-stage EC includes total abdominal hysterectomy and bilateral salpingo-oophorectomy, pelvic washing, and lymphadenectomy (pelvic and aortic), depending on preoperative and intraoperative pathologic risk profiles. As such, the current standard of surgical treatment irreversibly destroys the reproductive capacity in women of reproductive age [1,2].

In contrast, women of reproductive age who wished to have children were treated with progestins and achieved successful full-term pregnancies [2]. Recent research has also shown that 60%–75% of young women with early-stage well-differentiated EC responded to progestational agents [2,3]. To date, conservative management has been experimented with anecdotally or in small series of selected young patients with early-stage EC. The aim of the present study was to analyze the results of fertility-sparing treatment of early-stage EC in patients treated at Turkish gynecologic oncology centers, and to present a review of the literature.

☆ The preliminary results of this study were presented as a poster at the 17th International Meeting of the European Society of Gynecological Oncology held in Milan, Italy, September 11–14, 2011.

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2. Materials and methods

In 2010, after gaining Institutional Review Board approval, 13 healthcare centers in Turkey were contacted to determine if they were eligible to participate in the study; 11 eligible centers provided data before the deadline. The remaining 2 centers did not meet the deadline and were excluded from the study. The centers that agreed to participate were sent a database form to record the following data: patient age; body mass index (BMI); marital status; gravidity; parity; abortions; history of infertility, coexisting medical diseases; family medical history; preoperative imaging results; diagnostic methods; disease stage and grade; presence of myometrial invasion; type, dose, and duration of progestin treatment; presence of tumoral regression; regression time; presence of lymph node dissection; method of conception (natural or in vitro fertilization/intracervical insemination); fetal outcome; presence of disease recurrence; and duration of follow-up. All of the patients had been carefully informed about the risks and benefits of the fertility-sparing treatment approach, and all of the participating healthcare centers obtained the consent of their patients.

Data were obtained from the patient files, pathology/cytology reports, and hospital records of each participating center. These data were sent to the principal investigators, who performed the final analysis of the data (A. Ayhan and P. Dursun). Owing to the retrospective nature of the data, the 1988 FIGO staging classification was used for the determination of the disease stage. Endometrial sampling—either biopsy or curettage—was performed at 1–4-month intervals, according to each center's protocol. Complete response was defined as the absence of cancer or hyperplasia on follow-up endometrial curettings. The time of the response to progestin, preservation of fertility (presence or absence of a uterus), and status of the disease at follow-up were evaluated.

Statistical analysis was performed using SPSS version 11.0 (IBM, Armonk, NY, USA) and descriptive statistical methods. The χ^2 or Fisher exact test and contingency table analysis were used for categorical data. Continuous variables were tested for significance using the t test. $P<0.05$ was considered statistically significant.

3. Results

Data for 47 patients with EC were collected from 11 centers; however, data from 4 patients were excluded because the records were incomplete. Therefore, final analysis was performed using data from 43 patients. The mean age of the patients was 31 ± 5.7 years (range, 21–43 years). Mean BMI was 28.5 (range, 21–41). In all, 19 (44.2%) patients were diagnosed via dilatation and curettage, 9 (20.9%) were diagnosed via hysteroscopy and biopsy, and 15 (34.9%) were diagnosed via Pipelle or suction curettage. In total, 41 (95.3%) patients were characterized as endometrioid and endometrioid with squamous differentiation (Table 1). One patient had Stage IA ovarian cancer concomitant with Stage IA EC. Among the patients, 34 (79.1%), 8 (18.6%), and 1 (2.3%) had grade 1, grade 2, and grade 3 disease, respectively. All of the patients underwent preoperative imaging via MRI or CT, or both. In all, 38 (88.4%) patients had Stage IA disease and 5 (11.6%) had Stage IB disease, based on preoperative imaging results. All Stage IB patients had very limited or suspicious myometrial invasion according to preoperative imaging results.

Laparotomic or laparoscopic pelvic and/or para-aortic lymph node dissection was performed in 8 (18.6%) patients and all were tumor free. Hysteroscopic/resectoscopic tumoral resection was performed in 4 (9.3%) patients. In all, 29 (67.4%) patients were treated with megestrol acetate and 14 (32.5%) were treated with medroxyprogesterone acetate (MPA). Mean duration of progesterone treatment was 5 months (range, 2–12 months). In total, 7 (16.3%) patients were treated with an intrauterine progesterone system for 3 months, in addition to oral progesterone therapy.

Thirty-five (81.4%) patients were tumor free following primary progesterone therapy, whereas tumors were persistent in 8 (18.6%) patients. Mean time from the completion of progesterone therapy to pregnancy was 10.6 ± 4.3 months (range, 3–18 months). In total, 13 (30.2%) patients became pregnant during follow-up, whereas 30 (69.8%) did not. Twelve patients were single and/or not trying to conceive at the time of treatment or follow-up; therefore, the pregnancy rate among the 31 patients who were actively seeking pregnancy was 41.9%. Conception occurred naturally in 2 (15.4%) patients and via assisted reproductive technologies in 11 (84.6%) patients. Two patients each had 2 full-term pregnancies and 1 patient became pregnant 3 times after being diagnosed with EC.

Mean follow-up duration was 49 months (range, 5–156 months). Two patients had recurrence in the uterine cavity 24 months ($n=1$) and 48 months ($n=1$) after the initial diagnosis and subsequently underwent hysterectomy. During follow-up there were no tumor-related deaths.

Table 1
Histologic types of the patients ($n=43$) included in the study.

Histologic type	No. (%)
Endometrioid carcinoma	39 (90.7)
Endometrioid carcinoma with squamous differentiation	2 (4.6)
Endometrioid carcinoma with stage Ia endometrioid ovarian carcinoma	1 (2.3)
Mucinous carcinoma	1 (2.3)

4. Discussion

As the number of younger women with EC increases, fertility-sparing treatment is receiving more attention among both clinicians and patients. EC in women of reproductive age poses a therapeutic dilemma for clinicians, especially when treating those who wish to preserve their fertility. EC in women of reproductive age usually presents as a well-differentiated endometrioid adenocarcinoma and an estrogen-dependent tumor. The prognosis in this group of patients with well-differentiated EC and no myometrial invasion is excellent, and the 5-year survival rate following primary therapy exceeds 93% [3].

Kelly and Baker [4] published one of the earliest reports on the successful use of progestational agents in the treatment of patients with advanced or recurrent EC in 1961. Ehrlich et al. [5] conducted an extensive review of the literature on progesterone receptors and response to progestin therapy in EC, and reported that the clinical response rate to progestin therapy was 72% for progesterone-positive tumors and 12% for progesterone-negative tumors. Unfortunately, owing the present study's retrospective nature, hormone receptor status was not investigated.

The most critical step in fertility-sparing treatment is patient selection. A recent review suggests that only well-differentiated early-stage (low grade) EC patients (Stage IA, grade 1) without myometrial invasion or extrauterine involvement should be selected for conservative therapy; however, some researchers reported that patients with grade 2 lesions or myometrial invasion have successfully undergone fertility-sparing treatment. Nevertheless, an important consideration is that such treatment fails more frequently in such cases [6,7].

Kaku et al. [3] reported that 9 out of 12 women (75%) with EC had an initial response to MPA treatment, as evidenced by negative follow-up endometrial curettage. Moreover, the majority of initial responders remained disease-free during follow-up. Kim et al. [7] reported 7 patients treated at their institution and reviewed 14 cases from the literature. In all, 13 out of 21 patients (62%) had an initial response and 3 later delivered (23%) a total of 6 viable infants [7]. Randall and Kurman [8] reported 12 patients with well-differentiated EC who were treated with progestin; the regression rate was 75% and 33% of the women with disease regression delivered healthy, full-term infants. The disease persistence rate was 25% and the nonresponders—the majority with Stage IA disease—underwent surgical treatment. All of the patients were alive and healthy without evidence of progressive disease. These

findings and those of the present study suggest that second-line aggressive treatment can be used in women who want to maintain their fertility, but this remains controversial.

In 2010, Serkanli and Ayhan [9] reviewed the results of 231 cases published between 1966 and 2009. The overall response rate to fertility-sparing therapy in the 231 patients was 75.3% (n = 174). Among the 174 patients who responded to primary treatment, 57 (32.7%) had recurrence. Overall, 57 (24.7%) of the 231 patients failed to respond to primary treatment; in other words, 50.6% (117/231) of patients had complete and long-term response without recurrence. Furthermore, there were only 4 (1.7%) deaths due to EC among the patients who underwent fertility-sparing treatment [9].

A review of the literature was performed that included studies conducted with more than 10 cases (n = 263; Table 2). The mean initial response and disease persistence rates were 71% (range, 18%–100%) and 21% (range, 0%–58%), respectively; the mean pregnancy rate among the women who attempted to conceive was 46% (range, 13%–83%); and the mean overall recurrence rate was 33% (range, 0%–67%) with a mean recurrence-free period of 32 months (Table 2). In the present study, the overall response and persistence rates after progesterone therapy were 81.4% and 18.6%, respectively, confirming that adequately evaluated early-stage EC in women of reproductive age can be treated successfully with progestin without compromising oncological safety.

Although there is consensus concerning the use of progestin as a fertility-sparing approach in the treatment of early-stage EC, debate continues about the type, dose, duration, and the route of progestin administration. MPA is the most commonly used progestin for fertility-sparing treatment; however, megestrol acetate, hydroxyprogesterone acetate, 17a-hydroxyprogesterone caproate, oxyprogesterone acetate, norethindrone, gonadotropin-releasing hormone agonists, aromatase inhibitors, a levonorgestrel-releasing intrauterine system, and selective estrogen receptor modulators were also reported to be similarly effective [1,3,8,9]. In the present study, megestrol acetate was the most commonly used drug, followed by MPA.

EC treatment response rates range from 57% to 76%, and the recurrence rate ranges from 11% to 50%. Such variations are probably due to differences in drugs and dosage used, duration of treatment, and tumoral factors. The reported daily dose of megestrol acetate ranges between 10 and 400 mg, versus 200 and 800 mg for MPA [10]. In the present study, the daily megestrol acetate dose was 80–320 mg, versus 20–40 mg for MPA. Ushijima et al. [10] conducted a prospective study that aimed to determine an accurate complete response rate for MPA treatment of EC at a fixed dose of 600 mg d^{-1} for 26 weeks; the complete response rate was 55% and the recurrence rate was 57%.

In general, the impact of progestins on EC cells becomes apparent as early as 10 weeks following the start of treatment. Reifenstein [11] recommends an initial period of exposure of 12 weeks or more before evaluating response. Moreover, 16% of patients were treated using a progesterone-releasing intrauterine device (IUD) in addition to oral progesterone therapy in the present study. Perri et al. [12] reported positive results with progesterone-releasing IUD treatment, both alone and together with oral progesterone [12]. Recent studies report that levonorgestrel IUD treatment effectively suppresses hyperplastic endometrium. Although the efficacy of progestin IUD treatment for EC remains unclear, it may be an alternative to progestin therapy during the observation period in patients who do not presently wish to conceive. Furthermore, progestin IUD treatment may also reduce the duration of high-dose systemic progestin treatment and the incidence of its associated complications [10,12]. On the other hand, hysteroscopic resection was also used as an adjunctive treatment method in 10% of patients in the present study—a similar approach as the one reported by Laurelli et al. [13]; however, the procedure is experimental and peritoneal dissemination of tumoral cells into the peritoneal cavity is theoretically an important associated risk of this treatment approach [3,9,14]. In the present study, overall 27.9% of the evaluated patients treated with progesterone for fertility preservation had either pelvic/para-aortic lymph node dissection or hysteroscopic resection of tumor. The real effect of these interventions on the oncological outcome of the patients is not known and patients should be informed about the risk and benefits of these interventions.

Approximately 33% of young patients with EC who undergo fertility-sparing treatment experience recurrence (the recurrence rate ranged from 11%–50%) [9]; this rate is much higher than that associated with standard treatment of early-stage EC. As such, patients who receive fertility-sparing treatment must be monitored closely, and emergent, definitive surgery might be necessary following childbirth. Nonetheless, it is not clear what should have been done for patients with persistent disease or recurrent patients who underwent a fertility-sparing approach. In patients with a strong desire to maintain their fertility, treatment with high-dose progestins could be an option, and the risks and benefits must be discussed with these patients; however, definitive surgery is also a possibility in such cases [9].

Randall and Kurman [8] reported a series of nonresponders who underwent surgical treatment, the majority with Stage IA disease; all patients were alive and healthy without evidence of disease progression. In the present study, 2 patients who underwent definitive surgery had recurrence, and the tumors in both patients were limited and in the uterine cavity. The present study may suggest a second fertility-sparing attempt although there is an ongoing debate on this

Table 2
Summary of studies with more than 10 cases.

Reference	No.	Mean follow-up, mo.	Response rate, % [a]	Persistence rate, % [b]	Pregnancy rate, %	Recurrence rate, % [c]	Mean recurrence time, mo.
Duska et al. [17]	12	26	100	0	33	16	Not reported
Gotlieb et al. [6]	13	–	100	0	46	46	–
Imai et al. [18]	15	–	53	–	13	20	–
Kaku et al. [3]	12	31.5	75	25	22	22	12
Niwa et al. [19]	12	56	100	0	70	67	43.5
Randall and Kurman [8]	14	39	75	25	25	0	–
Ushijima et al. [10]	22	48	55	14	55	57	47
Signorelli et al. [20]	11	98	18	46	36	33	32
Ota et al. [21]	12	53	42	58	75	66	28
Hahn et al. [22]	35	39	63	34	83	41	12
Peri et al. [12]	27	57	89	11	52	62	40
Eftekhar et al. [23]	21	48	86	14	28	17	36
Minig et al. [24]	14	54	57	28	64	14	36
Present study	43	49	81	19	42	5	36
Total	263	50	71	21	46	33	32

[a] Response rate after initial treatment.
[b] Persistence rate after initial treatment.
[c] Recurrence rate after long-term follow-up.

subject. Cormio et al. [15] reported that distant metastasis occurred in patients who underwent fertility-sparing treatment. Ferrandina et al. [16] reported 1 conservatively managed patient with early-stage disease and disease progression following a full-term pregnancy. As such, patients should be informed about the risks and benefits of fertility-sparing treatment.

Only 2 (15.4%) patients conceived spontaneously in the present study and the remaining patients used a method of assisted reproductive technology (ART). This high rate of ART use might be related to the distress of the patients and their physicians with regard to oncological outcome. Furthermore, the unknown effects of fertility associated medications on primary endometrial malignancy need to be clarified.

The present study has some limitations; namely, its lack of a central pathology review, lack of hormone receptor status, and its retrospective, multicenter design.

In conclusion, conservative management with oral progestins in young patients with early-stage EC was effective and did not compromise oncological outcome. Patients in the present study achieved pregnancy both naturally and via artificial techniques. Further prospective studies with larger numbers are needed to more clearly delineate the efficacy of fertility-sparing treatment of EC.

Conflict of interest

The authors have no conflicts of interest to declare.

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