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Original Article

Fertility preservation in early-stage endometrial cancer and endometrial intraepithelial neoplasia: A single-center experience

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ABSTRACT

Objective: The purpose of this study was to define the pregnancy and oncologic outcomes after fertility-sparing treatment of atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) and early-stage endometrioid endometrial cancer (EEC).
Materials and methods: The retrospective cohort study included patients who had applied to Başkent University's Ankara Hospital between January 2007 and October 2018 with either AH/EIN (n: 27; Group A) or EEC (n: 30; Group B), and who had the desire to preserve their fertility. The medical records of all patients included in the study were reviewed retrospectively from the hospital records.
Results: There were 2 (7.4%) and 5 (16.7%) recurrences, whereby one patient from Group A and two patients from Group B underwent staging surgery. In Group A, 8 patients attempted pregnancy after their treatment and 4 of them (50%) became pregnant, while 3 of them (37.5%) had a live birth. In Group B, there were 17 patients who wanted to become pregnant following treatment of the disease; 8 of them (47%) became pregnant after treatment, 5 of them (16.6%) had a live birth, 1 experienced intrauterine exitus (at 21st gestational week, 350 g), and 2 currently have ongoing pregnancies.
Conclusion: Hysteroscopic resection of visible lesions and full endometrial curettage prior to hormonal therapy as a fertility-preserving approach for women of reproductive age with endometrial malignancies can achieve promising oncologic and obstetric responses.

Introduction

Although atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) and endometrial cancer (EC) are usually observed in postmenopausal women, they may also develop, albeit rarely, in women under 40 years of age [1]. The incidence of AH/EIN and EC in this age group has increased in recent years [2]. As a result of this, the number of AH/EIN and EC patients who desire to preserve their fertility has also been increasing. Therefore, fertility-sparing treatment approaches have become important in the treatment of endometrial AH/EIN and EC.

The National Comprehensive Cancer Network (NCCN) published a new guideline on this subject in light of the increasing interest in fertility-sparing management for EC [3]. The patient selection criteria for fertility-sparing management of AH/EIN and EC were stated in detail in this guideline and four criteria must be met: 1) patient diagnosis of well-differentiated (grade 1) endometrioid adenocarcinoma; 2) lesion confined to the endometrium on transvaginal ultrasonography (TVUS) or preferably magnetic resonance imaging (MRI); 3) no metastasis; 4) no contraindications to pregnancy. Additionally, patients should be thoroughly informed that fertility-sparing management is not a standard of care for EC treatment.

Standard treatment of both AH/EIN and EC includes total abdominal hysterectomy with bilateral salpingo-oophorectomy [4]. However, these approaches may not be appropriate for patients who want to preserve their fertility; this patient group may prefer more conservative management of AH/EIN and EC to preserve fertility. In the literature, there are several conservative treatment approaches for fertility-sparing treatment of AH/EIN and EC, including systemic hormonal therapy with progestins alone, hormonal therapy after the hysteroscopic resection of focal lesions, and the levonorgestrel-releasing intrauterine device (LNG-IUD) [5–7].

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In this study, we aimed to define the obstetric and oncologic outcomes after fertility-sparing treatment of AH/EIN and early-stage endometrioid endometrial cancer (EEC).

Materials and methods

Study cohort and design

This retrospective cohort study included patients visiting Başkent University's Ankara Hospital between January 2007 and October 2018 with AH/EIN (n: 27) or EEC (n: 30) who were younger than 45 years of age and who had the desire to preserve their fertility. Prior to selecting a fertility-sparing treatment for patients aged 40 and older, an ovarian reserve test was performed with measurements of antral follicle count, serum anti-Müllerian hormone level, and day 2 serum follicle-stimulating hormone level. The criteria for inclusion in the study were as follows: 1) patient diagnosis of well-differentiated (grade 1) EEC or AH/EIN; 2) lesions being confined to the endometrium as confirmed by pelvic MRI or by TVUS if MRI was contraindicated; 3) no metastatic disease as confirmed by chest imaging (chest X-ray), or if an abnormality was seen then chest computed tomography without contrast or whole-body PET/CT if metastasis was suspected in selected patients or other imaging based on symptomatology and clinical concern for metastatic disease; 4) no contraindications for pregnancy and/or progestin therapy; and 5) patients using only megestrol acetate following the four-step management method. Patients' data were retrieved from the medical records. This study was approved by Başkent University's Institutional Ethical Committee.

In our clinic, following a diagnosis of EC or AH/EIN by endometrial biopsy performed with probe curettage or under direct visualization during in-office hysteroscopy, all patients of reproductive age who met the inclusion criteria were informed about both current standard therapies regarding their condition and fertility-sparing approaches, as well as the possible risk of recurrence and progression following these procedures. In our center, EIN is diagnosed according to the criteria of Baak et al. from 2005 [8]. All patients were thoroughly informed that fertility-sparing is not the standard of care for either disease.

Surgical management process prior to hormonal therapy

In our center, if patients prefer a fertility-sparing approach, we perform the hysteroscopic resection of visible lesions and full endometrial curettage prior to progestin treatment for all patients as a four-step surgical management method. We perform this procedure as follows: 1) hysteroscopic visualization of the uterine cavity, detection of the lesion(s), and removal of the superficial endometrial tissue to preserve the basal layer of the endometrium; 2) checking of the other sides of the uterine wall using sharp curettage; 3) suction curettage of spilled tissue with negative pressure via Karman's cannula and vacuum aspirator; 4) repeated hysteroscopy before the end of the procedure for any possible residual lesions and assessment of possible injury of the basal layer of the endometrium (endometrial basal layer was recognized by definite signs of punctuation specifying the presence of glandular tissue). There was no visible residual lesion or injury of the basal layer. All specimens were separately sent for pathologic examinations, which were performed by the same expert gynecopathologist. The entire four-step minimal invasive surgical management procedure prior to hormonal therapy was performed under general anesthesia by the same gynecologic oncology surgeon (AA). Hysteroscopic evaluation was performed carefully with low pressure (maximum pressure of 80 mmHg) to avoid adverse effects on the incidence of positive peritoneal washings [9]. There were no intraoperative or postoperative complications.

Post-surgical hormonal therapy

In our clinic, following the four-step surgical management method, all of the patients were given megestrol acetate (Megace 160 mg pill, Haupt Pharma Regensburg GmbH, Regensburg, Germany) at 160 mg daily and/or LNG-IUD. The study only included patients who were given megestrol acetate for analyses performed in a uniform group of patients. Although fertility-sparing treatments were applied to a total of 32 patients with AH/EIN and 37 with EEC at our center in this period, only 27 patients with AH/EIN and 30 with EEC who were given megestrol acetate were included in the study. The medical treatment was administered over a three-month period to AH/EIN patients and over a six-month period to EC patients.

Follow-up

After minimal invasive surgical management and medical treatment, patients underwent hysteroscopic evaluation and endometrial biopsies at three, six, twelve, and twenty-four months. If the disease was persistent, the dosage of megestrol acetate was increased to 320 mg per day. Patients were followed via clinical history (i.e. abnormal uterine bleeding), as well as through physical examinations and TVUS every three months during the first two years and then every six months thereafter. If the disease remained stable for one year after the administration of progestin therapy, or if there was a recurrence of the disease, patients were then offered hysterectomy with salpingo-oophorectomy.

Outcomes

The outcomes were classified as either oncologic or obstetric. The oncologic outcomes were assessed as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and recurrent disease (RD). Complete response is defined as no residual disease, partial response is defined as regression to EIN from EEC, stable disease is defined as no regression after treatment, progressive disease is defined as progression to EC from EIN or a grade or stage increase of EC, and recurrent disease is defined as the recurrence of the disease after complete response to therapy. The obstetric outcomes included pregnancy and delivery rates.

Statistical analysis

Statistical analysis of the findings was conducted using the software SPSS 22.0 for Mac (IBM Corp., Armonk, NY, USA). Descriptive statistics for both parametric and non-parametric variables were expressed in terms of median, ranges, and interquartile ranges.

Results

The median ages of AH/EIN patients (Group A) and EEC patients (Group B) were 34 and 32 years, respectively. Demographic characteristics of patients are summarized in Table 1.

Oncologic outcomes

The median follow-up time was 50.3 (range: 11–100) and 55.5 (range: 6–133) months in Group A and B, respectively. Complete response (CR) was obtained from 92.6% (25/27) and 73.3% (22/30) of patients in Groups A and B, respectively.

Table 1
Demographic characteristics of the patients.

	AH/EIN (n: 27)	Range/SD	EEC (n: 30)	Range/SD
Age (median)	34	20–43/6.2	32	20–45/5.1
BMI (mean)	28.8	22–41/9	30.8	23–40/4.7
Previous pregnancy (n)	7		3	
Previous live birth (n)	6		1	
Complaint at first exam				
Abnormal bleeding	12 (44.4%)		16 (53.3%)	
Pregnancy desire	15 (55.6%)		14 (46.7%)	

Abbreviations: BMI: body mass index, AH/EIN: atypical hyperplasia/endometrial intraepithelial neoplasia, EEC: early-stage endometrial cancer.

In Group A, 2 patients had stable disease and both of them had surgical intervention. While one patient underwent hysterectomy, the other patient underwent surgical staging. The pathological results were AH and stage I endometrial cancer, respectively. There were two recurrences in Group A. One patient had wanted to continue oral progestin therapy for an additional six months despite this not being suggested therapy for her condition and the patient rejected surgical therapy. She achieved complete response after increased dosage of progestin therapy. The other patient chose surgical intervention after a failed effort to conceive and underwent staging surgery because her frozen section revealed endometrial cancer. A final pathology report revealed that she had stage I endometrial cancer (Table 2).

In Group B, there were 7 cases of stable disease (SD) and 1 partial response (regression to AH from EEC) after six months of progestin therapy. All of the patients with SD preferred surgical intervention. Six patients were diagnosed with stage 1 disease, whereas one patient had pelvic lymph node involvement. The patient with partial response following the second biopsy preferred staging surgery, whereupon her pathological result was stage 1 endometrial cancer. There were 5 recurrences in Group B; four of these patients were treated with re-administration of oral progestin therapy, whereas one underwent staging surgery. Her final pathology report revealed stage I disease (Table 2).

Obstetric outcomes

In Group A, 8 patients attempted pregnancy after their treatment. Four of the patients (50%) became pregnant and 37.5% (3/8) of them had a live birth. One of the pregnancies was terminated by abortion. Two of the pregnancies were achieved using intracytoplasmic sperm injection (ICSI), and there were two spontaneous pregnancies. All patients in Group A who attempted pregnancy after their initial treatments were nulliparous at the time of diagnosis.

In Group B, there were 17 patients who desired to become pregnant after treatment of the disease. Eight of the patients (47%) became pregnant after treatment and 29.4% (5/17) of them had a live birth, while 1 had intrauterine exitus (at the 21st gestational week, 350 g) and 2 had ongoing pregnancies (at 18 and 12 gestational weeks at the time of reporting). Four of these eight pregnancies were achieved with assisted reproductive techniques (1 ovulation induction, 3 ICSI). Only one patient in Group B who attempted pregnancy had a prior delivery at the time of diagnosis.

All of the patients who gave live birth requested close follow-up instead of staging surgery. No deaths or cases of Asherman syndrome were observed in any of the patients. The lack of Asherman syndrome was confirmed by hysteroscopic evaluation and TVUS during follow-up (Table 3).

During progestin therapy we did not observe any side effects of the medication, such as thromboembolic events, abnormal bleeding, or anemia. There was no significant difference of patients' body mass index (BMI) after completion of the treatment. None of the patients agreed to undergo hysterectomy after completion of their family planning.

Table 2
Oncologic outcomes.

	AH/EIN (n: 27)	EEC (n: 30)
Treatment time		
3 months	13	
6 months	13	18
6–12 months		11
>12 months	1	1
Response		
CR	25 (92.6%)	22 (73.3%)
PR	–	1 (3.3%)
SD	2 (7.4%)	7 (23.3%)
Recurrence	2 (7.4%)	5 (16.7%)
Complication	None	None

Abbreviations: H/S: hysteroscopy, CR: complete response, PR: partial response, SD: stable disease, AH/EIN: atypical hyperplasia/endometrial intraepithelial neoplasia, EEC: early-stage endometrial cancer.

Discussion

In the present study, we have reported the oncologic and obstetric outcomes of the fertility-sparing treatment of patients with AH/EIN and EEC at our institution. Our data are important because, in the literature, hysteroscopic resection prior to hormonal therapy has been performed with resection of the lesion either with or without the myometrium underlying the tumor [10,11]. We speculate that resection of the adjacent myometrium may lead to intrauterine adhesions during recovery, and therefore we resect the lesion using hysteroscopy and then gently perform sharp curettage for any possible residual lesions and suction curettage of spilled tissue with negative pressure via Karman's cannula and vacuum aspirator, without damage to the basal endometrial layer. As a result, our data showed a similar complete response rate compared to hysteroscopic resection (including the resection of the adjacent myometrium) combined with hormonal therapy [6,12], a lower recurrence rate than that of oral progestin therapy, and a higher recurrence rate than that of hysteroscopic resection (including the resection of the adjacent myometrium) according to the literature [6,12]. In addition, our obstetric outcomes are similar to and at times higher than those reported in the literature [6,10,13,14].

In the literature, there are many studies and meta-analyses of oral and local progestins as conservative treatments for AH/EIN and EEC patients desiring to preserve fertility [12,15–17]. The latest meta-analysis on different fertility-preserving managements in EEC reported that the pooled complete response rate for the group only using oral progestin was 76.3% and that the recurrence rate was

Table 3
Obstetric outcomes.

	AH/EIN (n: 27)	EEC (n: 30)
Pregnancy attempt	8 (8/23)	17 (17/27)
Pregnancy	4 (50%)	8 (47%)
Pooled live births	3/27 (11.1%)	5/30 (16.6%)
Live births in patients with pregnancy attempt	3/8 (37.5%)	5/17 (29.4%)
Ongoing	–	2
Technique		
Spontaneous	2	4
ART	2	4

Abbreviations: ART: assisted reproductive techniques, AH/EIN: atypical hyperplasia/endometrial intraepithelial neoplasia, EEC: early-stage endometrial cancer.

30.7% [12]. Although this conservative treatment method offers an acceptable complete response rate, the recurrence rate seems high [18]. Hence, clinicians have pursued new conservative therapeutic modalities for this patient group, including LNG-IUD with or without gonadotropin-releasing hormone agonist (GnRH-a) and hysteroscopic resection combined with progestin therapy [5,6,13,19]. The meta-analysis by Fan et al. on different fertility-preserving approaches in patients with EEC reported that the pooled complete response rate for hysteroscopic resection when combined with progestin therapy was 95.3% and that the recurrence rate was 14.1% [12]. However, in a recent study regarding hysteroscopic resection combined with progestin therapy for fertility preservation in EEC patients, the revealed complete response rate was 78.6%, whereas the recurrence rate was 6.5% [6]. In this study, Giampaolino et al. performed hysteroscopic resection following a three-step method according to the technique first described by Mazzon et al. [6,13]. In our series, we found a complete response rate similar to the outcomes of hysteroscopic resection combined with progestin therapy reported by Giampaolino et al. [6], as well as those reported for a group using only oral progestin by Fan et al. [12]. The recurrence rate in our study was lower than that reported in the meta-analysis by Fan et al. for the group only using oral progestin, which is similar to the result of the same meta-analysis for hysteroscopic resection combined with progestin therapy [12] and higher than the results of the three-step method presented by Giampaolino et al. [6]. We think that this low recurrence rate is tied to the hysteroscopic resection of possible microscopic cancer in the myometrium that could not be detected in any other way. However, we think there is a disadvantage to this three-step method, which is that although intrauterine adhesions affecting fertility have not been reported, one might speculate that the removal of the myometrium and basal endometrial layer may cause intrauterine adhesions that in turn cause infertility in this patient group, and we therefore think that the reason for intrauterine adhesions affecting fertility not being reported was the low number of EEC cases (n: 14) in their series. In our clinic, we perform the hysteroscopic resection of only visible lesions and full endometrial curettage prior to hormonal therapy because it does not harm the endometrial basal layer, and as a result we did not observe any intrauterine adhesion symptoms such as secondary amenorrhea affecting fertility in our all 30 of our EEC patients.

Pregnancy is one of the eventual goals of fertility preservation methods. There are many different pregnancy rates in the case series presented in the literature. Upon a meta-analysis of 34 observational studies, it was found that the live birth rates of patients with endometrial cancer and atypical complex endometrial hyperplasia were 28% and 26.3%, respectively [16]. In recent years, outcomes of hysteroscopic resection combined with progestin therapy have been published. The rates of live birth among the cumulative outcomes of endometrial cancer and atypical complex endometrial hyperplasia in these studies include those reported by Mazzon et al. [13], De Marzi et al. [10], and Falcone et al. [14] as 54.5%, 21.7%, and 50%, respectively. In a recent study of this topic by Giampaolino et al. [6], the pooled live birth rate was 14.5%; however, there were no pregnancies in the endometrial cancer group and all of the pregnancies were in the atypical complex endometrial hyperplasia group (18.2%). The live birth rates in our series appear to be lower compared to the literature. Despite this, however, in the AH/EIN group, 8 patients attempted pregnancy after their treatment, and 37.5% of them had a live birth. In the EEC group, 17 patients attempted pregnancy after their treatment; 47% (8/17) of them became pregnant and 29.4% (5/17) had live births, while 1 experienced intrauterine exitus (at 21st gestational week, 350 g) and 2 had ongoing pregnancies (at 18 and 12 gestational weeks at the time of reporting). Therefore, when we calculate the pregnancy rate in the patients who attempted pregnancy, our results are similar to or higher than the rates reported in the literature. Some of our patients were single in the follow-up period. The rest of our patients did not want to become pregnant immediately after their treatment or in the follow-up period.

The first limitation of this study is that it was a retrospective analysis of medical records. The second and most important limitation was that there was no control group, given that conservative treatments include only oral and local progestin and the technique of Mazzon et al. [13]. Despite these limitations, this study is strengthened by the definition of a new minimally invasive surgical management prior to hormonal therapy.

In conclusion, both oncological and obstetric outcomes are important for patients undergoing fertility preservation. These outcomes of fertility-sparing management should be mutually agreeable. In this context, hysteroscopic resection of visible lesions and curettage prior to hormonal therapy as a fertility-preserving approach for women of reproductive age with endometrial malignancies can achieve promising oncologic and obstetric responses. However, well-designed, prospective, larger clinical trials are required in order to better understand the feasibility of this method.

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Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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