

ORIGINAL ARTICLE / ORJİNAL MAKALE

The clinical and reproductive outcomes of endometrial intraepithelial neoplasia: experience of 117 cases

Endometrial intraepitelyal neoplazinin klinik ve repordüktif sonuçları: 117 vakanın deneyimi

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ABSTRACT

Aim: Hysterectomy is the suggested treatment for endometrial intraepithelial neoplasia since there is a high risk of coexisting endometrial adenocarcinoma in this subset of patients. However, fertility sparing treatment modalities can also be an option for patients with endometrial intraepithelial neoplasia who desire to preserve their fertility. In this study our aim was to evaluate the clinical and reproductive outcomes of endometrial intraepithelial neoplasia.

Materials and methods: We retrospectively analyzed the records of 117 patients with atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) in a tertiary gynecological cancer center. The median follow-up time was 54 (7-96) months.

Results: One hundred and one women underwent hysterectomy. The rate of coexistent endometrial carcinoma in women with AH/EIN was 33.7%. Sixteen women were treated conservatively. The complete response rate was 75% in patients after a treatment period of 12 months. Four of the patients in the infertile group had a successful live birth, 2 spontaneously and 2 with in vitro fertilization. Two patients in the fertile group had a successful live birth, 2 spontaneously.

Conclusion: Fertility sparing management is a feasible option for patients with atypical hyperplasia. However, it is crucial that there are high rates of coexisting endometrial cancer in these patients. Patients with AH/EIN should be followed up carefully for endometrial adenocarcinoma with regular endometrial samplings.

Keywords: Endometrial Hyperplasia, Endometrial Intraepithelial Neoplasia, Endometrial Cancer, Fertility-Sparing Treatment

Öz

Amaç: Histerektomi, endometrial intraepitelyal neoplazi için önerilen tedavidir, çünkü bu hasta alt grubunda endometrial adenokarsinom ile birliktelik riski yüksektir. Bununla birlikte, fertilesini korumak isteyen endometrial intraepitelyal neoplazili hastalar için fertilitte koruyucu tedavi modaliteleri de bir seçenek olabilir. Bu çalışmada amacımız endometriyal intraepitelyal neoplazinin klinik ve repordüktif sonuçlarını değerlendirmektir.

Gereç ve yöntem: Üçüncül bir jinekolojik kanser merkezinde atipik hiperplazi (AH)/endometrial intraepitelyal neoplazi (EIN) olan 117 hastanın kayıtlarını retrospektif olarak incelendi. Median takip süresi 54 (7-96) aydır.

Bulgular: Yüz bir kadına histerektomi yapıldı. AH/EIN'li kadınlarda eşlik eden endometriyal karsinom oranı %33,7 idi. On altı kadın konservatif olarak tedavi edildi. 12 aylık tedavi süresinden sonra hastalarda tam yanıt oranı %75 idi. İnfertil gruptaki hastaların 2'si spontan, 2'si tüp bebek ile olmak üzere 4'ü başarılı bir canlı doğum gerçekleştirdi. Fertil gruptaki 2 hasta spontan olarak başarılı 2 canlı doğum gerçekleştirdi.

Sonuç: Atipik hiperplazisi olan hastalar için fertilitte koruyucu tedavi uygulanabilir bir seçenektir. Bununla birlikte, bu hastalarda yüksek oranda birliktelik gösteren endometrial kanser oranları çok önemlidir. AH/EIN'li hastalar, düzenli endometrial örneklemeler ile endometriyal adenokarsinom açısından dikkatle izlenmelidir.

Anahtar Kelimeler: Endometriyal Hiperplazi, Endometriyal İntraepitelyal Neoplazi, Endometriyal Kanser, Fertilitte Koruyucu Tedavi

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INTRODUCTION

Endometrial cancer (EC) is the second most common female genital tract cancer in the world. The precursor lesions of endometrioid adenocarcinoma are endometrial atypical hyperplasia (AH) and endometrioid intraepithelial neoplasia (EIN). The new classification, WHO 2014, accepted by the International Society of Gynaecological Pathologists, divided hyperplasia into two groups: benign hyperplasia and atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) (1). The WHO 2014 schema is more likely to successfully identify precancerous lesions than the WHO 94 classification. Atypical hyperplasia is the least common type; however, it is the most strongly associated type with endometrial cancer (2). The probability of AH to progress to type 1 endometrial carcinoma was reported to be 29% previously (3). Also, in numerous series the coexistence of endometrial carcinoma in the hysterectomy specimens of the women with a diagnosis of AH was reported as %17 to %64 (4). According to these data the recommended treatment for AH/EIN is hysterectomy with or without bilateral salpingo-oophorectomy. Additionally, sentinel lymph node mapping should be performed for detecting sentinel lymph node, because of the possibility of coexisting endometrial cancer (5). However up to 5% of women with AH and endometrial carcinoma diagnosed before 40 years of age (6). Subfertility is a common problem of this group of patients since subfertility and endometrial neoplasia share some common risk factors such as polycystic ovarian syndrome, chronic anovulation, obesity, hyperinsulinemia and insulin resistance (3). Additionally, there is a subgroup of patients who may choose to be treated conservatively regardless of reproductive concerns and some of the patients are not fit enough for surgical treatment (7). In these patients who wish to be treated conservatively the most commonly studied treatment modality is oral progestins. In the literature there are several studies

showing that these patients can be treated safely with oral progestins even though five deaths reported previously due to progression of the disease or a synchronous malignancy failed to be diagnosed (3). The type and the dosage of the progestin is unclear as well as the duration of the treatment but most commonly studied oral progestins were megestrol acetate (MA) and medroxyprogesterone acetate (MPA).

In this retrospective cohort study our aim was to report clinical and reproductive outcomes of patients diagnosed to have AH/EIN at our institution and treated either with hysterectomy or conservatively by oral progestins.

METHODS

Women with a diagnosis of AH/EIN were detected from clinical database. Diagnosis and the response to treatment were based on either endometrial dilatation and curettage (D&C) or hysteroscopy. All of the pathological specimens were evaluated by the same gynecologic pathologists at our institution according to WHO criteria (8). The final pathology report of the women who proceeded to hysterectomy as initial treatment are evaluated. A management plan was programmed for all of the women who desired to be managed conservatively and all of the women were followed by our gynecologic oncology department. The selected progestin regimen was MA for all of the women with a daily dose of 160 mg. After 3 months and 6 months of treatment the women underwent endometrial sampling. Additionally, women underwent multiple biopsies at variable intervals after the complete remission achieved. Complete response was defined as absence of any endometrial hyperplastic or neoplastic pathology. The stable disease was defined as the persistence of AH/EIN after 6 months of treatment, and progression was defined as the endometrial carcinoma detected during follow up. In cases of stable disease and progression surgical treatment recommended to the patients. Assisted reproductive technologies

were offered to patients who desired to conceive but could not get spontaneously pregnant within six months. The pregnant women were followed up in perinatology department. Women underwent multiple biopsies at variable intervals after the delivery. Routine hysterectomy was not performed after pregnancy. For the conservatively treated group the primary outcome was the response rate in the first 12 months. Secondary outcome of interest was the fertility outcomes of patients who desired to conceive. All of the women were informed about the potential risks of conservative management of the AH/EIN. A written informed consent was obtained from the patients who wanted to be treated conservatively.

All statistical analyses were performed using Statistical Package for the Social Science (IBM SPSS, Version 25.0. Armonk, NY: IBM Corp.) for Windows software. Continuous data were described using medians and ranges; categorical variables were described using frequencies and proportions.

RESULTS

Records of 117 patients with AH/EIN were analyzed. The flow diagram is shown in Figure 1.

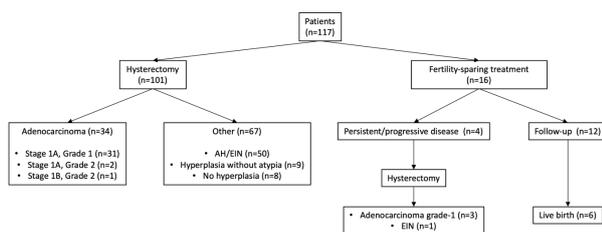


Figure 1. Flow-chart of the study participants (AH, atypical hyperplasia; EIN, endometrial intraepithelial neoplasia).

One hundred and one women underwent hysterectomy. The final pathology was stage 1A, grade 1, endometrioid adenocarcinoma in 31 patients; stage 1A, grade 2, endometrioid adenocarcinoma in 2 patients; stage 1B, grade 2, endometrioid adenocarcinoma in 1 patient; AH/EIN in 50 patients; hyperplasia without

atypia in 9 patients; and no hyperplasia in 8 patients. The rate of coexistence of endometrial carcinoma in women with AH/EIN was 33.7%. The median follow-up time was 54 (7-96) months. No adjuvant therapy was given.

Sixteen women were treated with oral progestins. Baseline characteristics of the patients with AH/EIN who underwent fertility-sparing treatment were shown in Table 1. The median age of the patients who underwent fertility-sparing treatment was 34 (24-39) years, and the median follow up time was 30 (7-86) months. The complete response rate was 75% in patients after a treatment period of 12 months. Eleven (68.8%) of the patients were infertile. Five patients who have at least one live birth did choose to be managed conservatively. Four of the patients underwent a hysterectomy in their first year of follow up; 3 from the fertile group for endometrial adenocarcinoma and 1 from the infertile group for persistence of the disease and patients desired for operation. Four (40%) of the patients from the remaining 10 patients in the infertile group had a successful live birth, 2 spontaneously and 2 with in vitro fertilization. Two patients in the fertile group had a successful live birth, 2 spontaneously.

Table 1. Baseline characteristics of the patients with AH/EIN who underwent fertility-sparing treatment (n=16).

	n	%
Age (years)	34 (24-39)	
Gravida	0 (0-1)	
Parity	0 (0-1)	
BMI (kg/m²)	30.66 ± 2.64	
Initial symptoms		
Irregular genital bleeding	3	18.8%
Menstrual abnormality	2	12.5%
Infertility	11	68.8%
Live birth	6	

Data are expressed as number (%), mean ± SD or median (range). AH, atypical hyperplasia; BMI, body mass index; EIN, endometrioid intraepithelial neoplasia.

DISCUSSION

Premenopausal women diagnosed with AH/EIN often seek fertility-sparing treatment for their disease. Our study suggests that fertility-sparing treatment using oral progestins is a feasible option for these patients. On the other hand, it is crucial that there are high rates of coexisting endometrial cancer in these patients. The Society of Gynecologic Oncology recommends that exclusion of a concurrent carcinoma is necessary in all patients with a new diagnosis of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia (9, 10). In this cohort, 101 women underwent hysterectomy. The rate of coexistence of endometrial carcinoma in women with AH/EIN was 33.7%. Erturk et al. reported that endometrial cancer rate in patients with AH was 32.6% in their study including 189 patients (11). A retrospective evaluation of 169 endometrial intraepithelial neoplasia patients by Vetter et al. showed that of these patients, 87 (51.5%) had a final diagnosis of endometrial intraepithelial neoplasia/other benign disease, whereas 82 (48.5%) were ultimately diagnosed with endometrial cancer (12). Similar findings were found by Robbe et al. They reported that a coexisting endometrial carcinoma was present in 25 of 39 patients (64.1%) (4).

Fertility-sparing treatment should be considered because patients with AH/EIN are candidates for a conservative approach. Comprehensive evaluation prior to fertility-sparing treatment is the key to success. All patients should undergo detailed evaluation to exclude myometrial invasion and to confirm the diagnosis. Although there is no established standard for treatment, most patients will benefit from progestins. The current literature reported that remission rates ranged from 42% to 100% (13-17). However, these studies are inhomogeneous in terms of many factors such as the type, dose, the duration of treatment time and follow-up time, type of progestin used, progestin therapy indications, pathologic distributions, demographic characteristics, and response

definitions. In 2018 Guillon et al conducted a systematic review and meta-analysis including 1604 patients and they observed that the remission rate was 0.75 (95% CI, 0.73–0.77), and also operative hysteroscopy for endometrial sampling was associated with higher remission rates (OR 2.31; 95% CI, 1.10–4.84; P=0.03) (17). In our study, complete response rate was 75% at one year. In a meta-analysis, Fan et al. reported the complete remission rate was 95.3% in patients with grade 1 stage IA endometrial cancer who underwent hysteroscopic resection followed by progestin therapy (18). In a series of 110 patients, He et al. reported that a complete response of 84% was noted after fertility-preserving retreatment in patients with recurrence of atypical endometrial hyperplasia and endometrial cancer (19). The relapse rate was 38% after fertility-preserving retreatment. They also reported that among the 21 patients who achieved complete response, 12 patients had a desire for fertility, among whom 8 patients had a successful pregnancy (66.7%, 8/12) and 6 patients experienced term birth (1 patient with natural pregnancy, and 5 patients with assisted reproductive technology). In our study, 4 patients in the infertile group had a successful live birth (2 spontaneously and 2 with in vitro fertilization), and 2 patients in the fertile group had a successful live birth (2 spontaneously). Ohyagi-Hara et al. published a retrospective study on 27 patients with endometrioid adenocarcinoma/complex atypical hyperplasia and showed that complete response was achieved in 81.8 % (9/11) of complex atypical hyperplasia cases and 68.8 % (11/16) of grade 1 endometrioid adenocarcinoma, and 5 patients (4 complex atypical hyperplasia and 1 grade 1 endometrioid adenocarcinoma) became pregnant and had 9 live births (20). The importance of fertility-sparing treatment in patients with AH/endometrial cancer has been denoted by Tamauchi et al in 2017. They reported a high rate of complete response using high-dose Medroxyprogesterone acetate. Complete response rates for the initial treatment were

89% for grade 1 endometrial cancer and 93% for AH. During their study period, a total of 14 pregnancies were recorded with 10 live births.

The possibility of recurrence cannot be excluded. In our cohort, no recurrence occurred. Ayhan et al. reported that the recurrence rate of the EIN patients was 7.4% (21). Therefore, after live birth or giving up future fertility, hysterectomy could be recommended to patients with AH/EIN or EC even if they have a complete response. Additionally, careful preoperative assessment of the adnexa is mandatory in young women with AH/EIN or EC. Among all synchronous cases of EC and ovarian cancer, approximately 15% may have normal-appearing ovaries (22, 23). There was no adnexal pathology in our patients who underwent hysterectomy. In a population-based study including endometrial cancer patients, synchronous ovarian malignancies were found in 14% of women who are younger than 45 years of age, compared with in 2% of women aged over 45 years (24).

Limitations of the presented study are the retrospective design. Due to the retrospective nature of the study, we could not reach the data concerning additional medication (metformin etc.) history, adverse effects of drugs used, or patients' weight gain, which may influence the study results. On the other hand, the strength of our study is that patient follow-up was up to 96 months.

CONCLUSION

Uterine preservation is a feasible option in women with precursor lesions of endometrial carcinoma who want to preserve their fertility within close follow-up. Assisted reproductive technology could help patients to become pregnant after fertility-sparing treatment. It is recommended for clinicians to evaluate patients with a multidisciplinary team.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Declaration

Ethical permission was obtained from Istanbul University, Istanbul Medical Faculty Ethical Committee for this study. Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: BG, HS, YS, MA, ÇT, Design: BG, EED, FK, ST, Supervising: YS, ST, MA, ÇT, Financing and equipment: BG, EED, DV, Data collection and entry: BG, EED, DV, FK, HS, Analysis and interpretation: BG, HS, DV, Literature search: FK, YS, ST, MA, Writing: BG, EED, YS, HS, DV, ÇT, Critical review: MA, ÇT

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