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Fertility-Sparing Treatment in Women with Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia/ Endometrial Cancer: A Tertiary Cancer Center Experience

Atipik Hiperplazi/Endometrioid İntraepitelyal Neoplazi/Endometrial Kanserde Fertilite Koruyucu Tedavi: Bir Üçüncül Kanser Merkezi Deneyimi

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The study was approved by the Research Ethics Committee of our institution (Approval number: 2020/182).

ABSTRACT

Objective: The present study aims to evaluate the oncological and obstetric outcomes after fertility-sparing treatment in patients with endometrial atypical hyperplasia (AH), endometrioid intraepithelial neoplasia (EIN), and endometrioid adenocarcinoma (EC). **Materials and Methods:** We retrospectively analyzed the records of patients with AH/EIN and EC who underwent fertility-preserving treatment in a tertiary gynecological cancer center between February 2014 and July 2020. The median follow-up was 52 (range, 6-75) months. **Results:** The complete response rate was 75.9%. All of the patients with EC (n=2) had stable disease after the treatment of 6 months. Twenty-two (81.5%) patients of 27 patients with AH/EIN had a complete response after the treatment of 6-12 months. Two of AH/EIN patients progressed to grade 1 endometrioid endometrial cancer, and 3 of AH/EIN patients had stable disease during the 6-month treatment period. The time to complete response was ≤6 months in 13 (59.1%) and >6 months in 9 (40.9%) patients in the AH/EIN group. One patient with AH/EIN after complete response became pregnant spontaneously and she gave a healthy birth. The recurrence rate was 9.1%. **Conclusion:** Fertility-sparing treatment modalities could be feasible in women with precursor lesions of endometrial carcinoma or low-grade endometrial cancer who want to preserve their fertility within close follow-up.

Keywords: Atypical hyperplasia; endometrial cancer; endometrioid intraepithelial neoplasia; fertility-sparing

ÖZET

Amaç: Bu çalışma, endometriyal atipik hiperplazi (AH), endometrioid intraepitelyal neoplazi (EIN) ve endometrioid adenokarsinom (EC) hastalarında fertilite koruyucu tedavi sonrası onkolojik ve obstetrik sonuçları değerlendirmeyi amaçlamaktadır. **Gereç ve Yöntemler:** Üçüncü basamak bir jinekolojik kanser merkezinde Şubat 2014 ile Temmuz 2020 arasında fertilite koruyucu tedavi uygulanan AH/EIN ve EC'li hastaların kayıtlarını geriye dönük olarak inceledik. Medyan takip süresi 52 (6-75) ay idi. **Bulgular:** Tam yanıt oranı %75.9 idi. EC'li hastaların tamamı (n=2) 6 aylık tedaviden sonra stabil hastalığa sahipti. AH/EIN'li 27 hastanın 22'sinde (%81,5) 6-12 aylık tedaviden sonra tam yanıt alındı. AH/EIN hastalarından ikisi grade 1 endometrioid endometrial kansere ilerledi ve AH/EIN hastalarının 3'ünde 6 aylık tedavi süresi boyunca stabil hastalık vardı. AH/EIN grubundaki 13 (%59.1) hastada tam yanıt alma süresi ≤6 ay ve 9 (%40.9) hastada >6 ay idi. Tam yanıttan sonra AH/EIN olan bir hasta spontan gebe kaldı ve sağlıklı bir doğum yaptı. Nüks oranı %9.1 idi. **Sonuç:** Endometrial karsinom veya düşük dereceli endometrium kanseri öncü lezyonları olan ve fertilitesini korumak isteyen kadınlarda fertilite koruyucu tedavi modaliteleri yakın takiple uygulanabilir.

Anahtar Kelimeler: Atipik hiperplazi; endometrial kanser; endometrioid intraepitelyal neoplazi; fertilite koruyucu

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Endometrial cancer (EC) is the second most common female genital tract cancer in the world, with approximately 382,069 of all new cases, leading to 89,929 deaths in 2018.[1] Although EC is most frequently diagnosed in women aged 55-64, approximately 7.1% of women with EC are between the ages of 20-44, and 70% of these women are nulliparous.[2,3] The precursor lesions of type I endometrioid adenocarcinoma are endometrial atypical hyperplasia (AH) and endometrioid intraepithelial neoplasia (EIN).

Total hysterectomy is the definitive treatment of AH/EIN, and it also provides an evaluation of a possible concurrent carcinoma. While the standard treatment for EC is a total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy, this may not be a suitable approach for patients who desire future fertility.[4] Several studies have indicated that progestin-based conservative treatment is safe and feasible in patients with AH/EIN and low-grade endometrioid EC who have a strong desire to maintain their fertility.[2] Optimal management of patients with AH/EIN or EC who desire future fertility is unknown. In reproductive-aged women, progestin-based therapy may be used with either megestrol acetate (MA) or levonorgestrel-releasing intrauterine system (LNG-IUS), with a complete response rate of 50-80% and a recurrence rate of 24-40%.[5] Therefore, giving the opportunity to conceive by offering fertility-sparing options while providing adequate treatment for their cancers is a crucial issue.

In this study, we aimed to evaluate the oncological and obstetric outcomes after fertility-sparing treatment in patients diagnosed with AH/EIN and low-grade endometrioid EC.

METHODOLOGY

We retrospectively analyzed the records of patients with AH/EIN and EC who underwent fertility-preserving treatment in a tertiary gynecological cancer center between February 2014 and July 2020. Clinical, demographic, and histopathological data were obtained from institutional electronic medical records. Additionally, up-to-date fertility data obtained through telephone interviews.

Inclusion criteria were: aged <45 years, pathologically confirmed either AH/EIN or well-differentiated (grade 1) EC on dilatation and curettage (D&C), having a strong desire to preserve fertility, disease limited to the endometrium on magnetic resonance imaging (MRI), absence of pathologic lymph nodes and extrauterine involvement on MRI, no contraindications to medications or pregnancy. Fertility functions were evaluated prior to treatment to detect any irreversible infertility disease.

Patients who met the inclusion criteria were fully counseled about the disadvantages and possible risks of the treatments. Informed consent was obtained before treatment after discussion of the possible risks of the treatments in obedience to the declaration of Helsinki. Patients were initially treated with oral MA 160mg/day, with insertion of an LNG-IUS and with combination of MA and LNG-IUS. The patients underwent follow-up with pelvic examination, transvaginal ultrasonography, and endometrial sampling every 3-6 months. Endometrial sampling was taken by D&C biopsy, or Pipelle aspiration biopsy, or hysteroscopy guided biopsy. The response was evaluated pathologically and pathologic slides were reviewed by experienced gynecologic pathologists.

Outcomes were categorized as oncological and obstetrical. Oncological results were evaluated as complete response (CR), stable disease (SD), and progressive disease (PD). Complete response is defined as a normal endometrium without hyperplastic or cancerous lesions. Stable disease is defined as no change after treatment, and progressive disease as a progression from atypical hyperplasia to carcinoma, or progression in degree or stage in cancer after 6 months of treatment. The recurrent disease was defined as a relapse after complete response. Patients who gave up treatment within the first 3 month and underwent hysterectomy were excluded from the study. Obstetric results included pregnancy and live birth rates.

Patients with CR were encouraged to conceive and, if necessary, referred to an assisted reproductive technology department. Surgery was recommended for patients who had persistent disease, progressed or recurrent disease, and completed their fertility. The

study was approved by the Research Ethics Committee of our institution (Approval number: 2020/183).

All statistical analyses were performed using Statistical Package for the Social Science (IBM SPSS, Version 25.0. Armonk, NY: IBM Corp.) for Windows software. Median, mean, standard deviation, frequency and ratio values were used for descriptive statistics. Mann-Whitney U test was used to analyze quantitative data. The $\chi 2$ test or Fisher's exact test were used to analyze categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

Records of 37 patients with AH/EIN, and 2 patients with EC were analyzed. Ten patients were excluded from the study because they underwent hysterectomy without completing their medical treatment. The flow diagram is shown in Figure 1. The mean age was 36.66 ± 4.07 years, the median gravida was 0 (range, 0-3), and the median parity was 0 (range, 0-3), the mean body mass index (BMI) was 29.7 ± 4.52 kg/m^2. Approximately 35% of them were smokers. Characteristics of the patients were documented in Table 1. None of the patients with endometrial cancer had myometrial invasion on MRI. The median follow up was 52 (range, 6-75) months. Eighteen patients were treated with oral MA only, 3 patients with LNG-IUS only and 8 patients with combination of MA + LNG-IUS.

The complete response rate was 75.9% in patients after a treatment period of 6-12 months. All of the patients with EC (n=2) had stable disease after the treatment of 6 months, and 2 patients underwent hysterectomy. The final pathology result of these 2 patients was International Federation of Gynecology and Obstetrics (FIGO) stage 1A, grade 1 endometrioid endometrial cancer. Twenty-two (81.5%) patients of 27 patients with AH/EIN had complete response after the treatment of 6-12 months. Two of AH/EIN patients progressed to grade 1 endometrioid endometrial cancer during the 6-month treatment period and underwent hysterectomy. Three of AH/EIN patients had a stable disease during the 6-month treatment period and underwent hysterectomy. The final pathology of these patients was AH/EIN. There was no statistical difference according to relation between

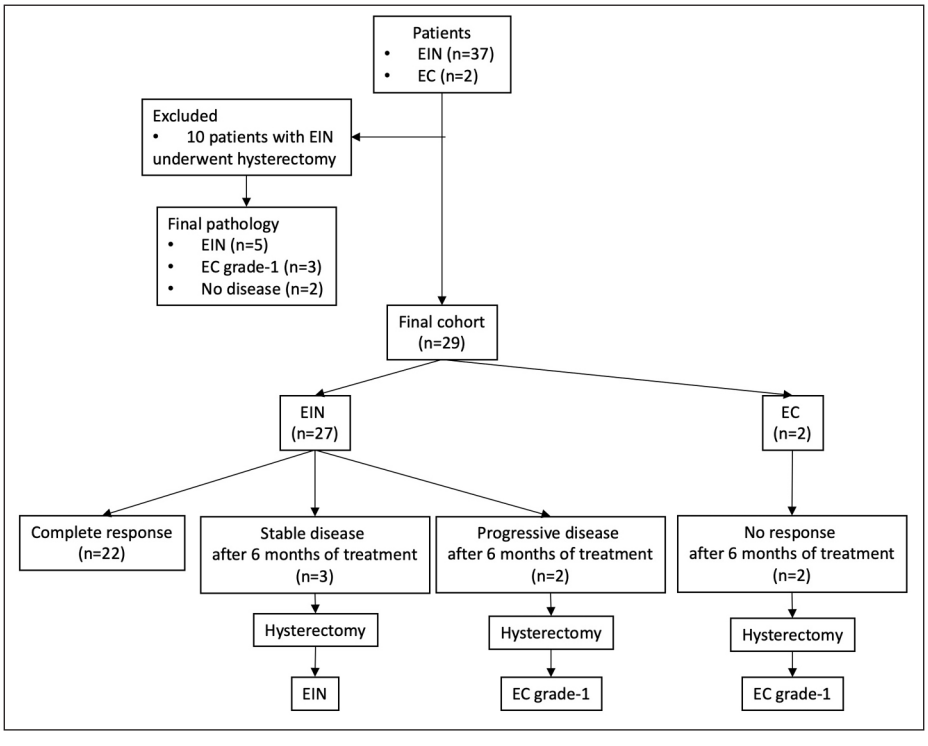

FIGURE 1: Flow-chart of the study participants (EC, endometrial cancer; EIN, endometrial intraepithelial neoplasia).

TABLE 1: Baseline characteristics of the patients with atypical hyperplasia/endometrioid intraepithelial neoplasia and endometrial cancer.

	All patients (n=29)	AH/EIN (n=27)	EC (n=2)
Age (years)	36.66 ± 4.07	36.44 ± 4.03	39.5 ± 4.95
Gravida	0 (0-3)	0 (0-3)	0
Parity	0 (0-3)	0 (0-2)	0
BMI (kg/m^2)	29.7 ± 4.52	29.23 ± 4.2	36.15 ± 4.74
Smoking	10 (34.5%)	10 (37%)	-
Comorbidity			
Hypertension	1 (3.4%)	1 (3.7%)	-
Insulin resistance	3 (10.3%)	2 (7.4%)	1 (50%)
Diabetes mellitus	1 (3.4%)	1 (3.7%)	-
Initial symptoms			
Irregular genital bleeding	11 (37.9%)	10 (37%)	1 (50%)
Menstrual abnormality	8 (27.6%)	7 (25.9%)	1 (50%)
Infertility	1 (3.4%)	1 (3.7%)	-
Other	9 (31%)	9 (33.3%)	-
Treatment response			
Complete response	22 (75.9%)	22 (81.5%)	-
Stable disease	5 (17.2%)	3 (11.1%)	2 (100%)
Progressive disease	2 (6.9%)	2 (7.4%)	-
Recurrence	2(9.1%)	2(9.1%)	-
Time to complete response (months)			
≤ 6		13/22 (59.1%)	-
> 6		9/22 (40.9%)	
Pregnancy	1 (3.4%)	1 (3.7%)	-

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

treatment method and the complete response rate (p=0.65) (Table 2). With respect to complete response, there were also no statistical difference according to age (≤35 vs >35 years), BMI (<30 vs ≥30 kg/m^2), pathologic diagnosis (AH/EIN vs EC) except for comorbidity of the patients. All the patients with comorbidity were found in the noncomplete responsive group (Table 2).

The time to complete response was ≤6 months in 13 (59.1%) and >6 months in 9 (40.9%) patients in the AH/EIN group. Eight patients with AH/EIN underwent in vitro fertilization treatment. One patient with AH/EIN after complete response became pregnant spontaneously and she gave a healthy birth. However, 8 months after delivery, the patient was diagnosed with AH/EIN and underwent hysterectomy, and the final pathology was AH/EIN. In addition, one of the AH/EIN patients with complete response was diagnosed with synchronous high-grade serous ovarian cancer in the left ovary and grade 1 endometrial cancer in the endometrium after 18 months of complete response during follow-up period. Therefore, the recurrence rate was 9.1%.

DISCUSSION

The incidence of EC has increased worldwide per year due to growing rates of women who postpone their births to advanced ages, having polycystic ovary syndrome, or suffering from obesity. The number of women who have a strong desire for fertility but have been diagnosed with low-grade EC or precursor lesions at this very moment should not be underestimated. We encounter progressively more patients in our institution who are faced with this challenging situation. Therefore, the data revealing the obstetric and oncological consequences of this difficult situation for both clinicians and patients are crucial.

TABLE 2: Univariate analysis of the patients for complete response after treatment.

	Complete response (n=22)	Not complete response (n=7)	*p*
Age (years)			
≤ 35	6 (27.3%)	3 (42.9%)	0.642
> 35	16 (72.7%)	4 (57.1%)	
BMI (kg/m$^{2)}$			
< 30	13 (59.1%)	1 (14.3%)	0.08
≥ 30	9 (40.9%)	6 (85.7%)	
Pathology			
AH/EIN	22 (100%)	5 (71.4%)	0.052
EC	0 (0%)	2 (28.6%)	
Comorbidity			
Yes	0 (0%)	5 (71.4%)	0.000
No	22 (100%)	2 (28.6%)	
Treatment			
MA	13 (59.1%)	5 (71.4%)	0.650
LNG-IUS	2 (9.1%)	1 (14.3%)	
MA + LNG-IUS	7 (31.8%)	1 (14.3%)	

Data are expressed as number (%).

AH, atypical hyperplasia; BMI, body mass index; EC, endometrial cancer; EIN, endometrioid intraepithelial neoplasia; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate.

There are many studies on MA and/or LNG-IUS as conservative therapy regimens for patients with AH/EIN/low-grade EC who wish to preserve their fertility, in the currently published papers. Chen et al. reported a 74% complete response rate and a 26% recurrence rate for EIN or FIGO Stage 1A patients using oral progestin-only for at least six months.[6] With acceptable complete response rates, it is noteworthy that there is a less complete response in obese patients in their study. Our findings are in agreement with these studies. The EC cohort had a mean age of 39.5 years, BMI of 36.1 kg/m^2, and 50% had comorbidities, representing a considerably older, fatter, and non-healthier cohort compared to the AH/EIN cohort in our analysis. Consequently, we obtained a complete response from most AH/EIN patients, while there was no treatment response in the EC cohort. We may speculate that older age, obesity, and accompanying diseases were important factors associated with achieving a complete response rate in treatment.

The overall complete response rate of our study was 75.9%, and 24.1% of the cohort had persistent/progressive disease. In addition, 1 live birth occurred in 1 patient with AH/EIN after complete response. These findings were similar to those of Gunderson et al., with a 74.6% response rate and 25.4% of the cohort had persistent/progressive disease.[7] In their research, women with endometrial hyperplasia have a higher rate of complete response to hormone therapy, as in the present study. Additionally, in the systematic review of Gunderson et al., regarding 38 studies involving 315 subjects, the majority of women (63%; 201/315) could not become pregnant, and most of them were those with carcinoma (65.2%).[7]

Many studies have shown that the duration of treatment required for regression of endometrial pathology varies between 1-17 months, particularly in the first 4-6 months.[8-11] Our study findings are in line with the available published data which the duration of response to treatment ranges from 3 to 36 months, and the median response time is 6 months, leading to the conclusion that it is practicable to treat with progestins for up to 6-12 months without affecting obstetric and oncological outcome.

In the literature, response rates of women receiving fertility-sparing treatment ranged between 75% and 86%. In our study, complete response rate

was 75.9%, which is consistent with current available data.[7, 12-16] 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.

On the other hand, the possibility of recurrence cannot be excluded. In the current study, one live birth occurred in a patient with AH/EIN after complete response. However, after 8 months of delivery, the patient diagnosed with AH/EIN and underwent hysterectomy, and the final pathology was AH/EIN. In our cohort, the recurrence rate was 9.1%. Ayhan et al. reported that the recurrence rate of the EIN patients was 7.4%.[17] 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.

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.[18,19] In this study, one of the AH/EIN patients with complete response was diagnosed with high-grade serous ovarian cancer after 18 months of the treatment during follow-up period, and underwent debulking surgery. In the final pathology, synchronous high-grade serous ovarian cancer in the left ovary and low grade, endometrioid endometrial cancer in the uterus were reported. In a population-based study, 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.[20] Additionally, Morice et al. suggested that laparoscopic evaluation should be performed in patients with EC selected for conservative management to confirm the absence of extrauterine disease.[19] Double gynecologic cancer with primary cancers in two organs is relatively rare. Careful pretreatment assessment of the adnexa is mandatory in young women with endometrial cancer and with AH/EIN who desire fertility preservation and they should be counseled regarding the high rate of coexisting ovarian malignancy.

There was only 1 live birth in the study resulting in 3.4% pregnancy rate. This rate was lower than the rates in literature.[6,21] Our admission rate to in vitro fertilization for patient with complete response was 36.3% (8 of 22 patients). Sharing the same etiology of AH/EIN/EC and infertility might have resulted in that condition.

More detailed, well-designed and further studies are needed to clarify unresolved issues such as the most effective and safe drug, the most reliable biopsy methods and most appropriate follow-up intervals for the fertility preserving treatment management of gynecological oncology patients.

Limitations of the presented study are the retrospective design of a single-center study with small sample size. 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, patients' weight gain, or follow-up biopsy methods, which may influence the study results. On the other hand, the strength of our study is that the definitions of response to treatment were made more meticulously compared to most of the studies and patient follow-up was available for up to 75 months.

CONCLUSION

Fertility-sparing treatment modalities could be feasible in women with precursor lesions of endometrial carcinoma or low-grade endometrial cancer who want to preserve their fertility within close follow-up. Since histopathology, obesity, age, and comorbidities, therapy options may affect the treatment response, it is recommended for clinicians to evaluate patients diligently with a multidisciplinary team consisting of psychiatry, dietician, reproductive endocrinology, and gynecological oncology departments.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or mem-

bers of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Canan Kabaca, Esra Keleş Peker, Mine Güray Uzun, Uğur Kemal Öztürk;* ***Design:*** *Canan Kabaca, Burak Giray;* ***Control/Supervision:*** *Burak Giray, Mine Güray Uzun;* ***Data Collection and/or Processing:*** *Esra Keleş Peker, Uğur Kemal Öztürk;* ***Analysis and/or Interpretation:*** *Canan Kabaca, Esra Keleş Peker, Burak Giray;* ***Literature Review:*** *Canan Kabaca, Esra Keleş Peker, Mine Güray Uzun;* ***Writing the Article:*** *Canan Kabaca, Esra Keleş Peker, Mine Güray Uzun, Uğur Kemal Öztürk;* ***Critical Review:*** *Burak Giray, Uğur Kemal Öztürk.*

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