Use of clinicopathological factors to predict prognosis of fertility-sparing treatment for endometrial endometrioid carcinoma and atypical hyperplasia

XIAOBO ZHANG[1], XIAOYA ZHAO[1], CHEN WANG[1], SHANSHAN LU[1], YIQIN WANG[2], YIJIAO HE[2], JIANLIU WANG[2] and DANHUA SHEN[1]

Departments of [1]Pathology and [2]Obstetrics and Gynecology, Peking University People's Hospital, Beijing 100044, P.R. China

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Abstract. The incidence of endometrial endometrioid carcinoma (EEC) has been gradually increasing over the past decade. Fertility-sparing therapy with progestin is a treatment option for EEC or endometrial atypical hyperplasia (AH). The present study evaluated the role of numerous prognostic factors following fertility-sparing therapy for EEC or AH. Furthermore, the present study assessed the strength of various clinicopathological indicators for the prediction of treatment efficacy. A retrospective analysis was performed of patients with EEC and AH who received fertility-sparing therapy between August 2013 and September 2021 at Peking University People's Hospital (Beijing, China). Endometrial specimens were obtained from each patient after 3 months of treatment and at the end of the fertility-sparing therapy, before treatment efficacy and prognosis were evaluated using the χ^2 test. Furthermore, the protein expression levels of EEC biomarkers, such as estrogen receptor (ER), progesterone receptor (PR), paired box 2 (PAX2), PTEN and p53 were assessed using immunohistochemistry. The overall complete response (CR) rate of fertility-sparing treatment in the EEC group was 67.39% (31/46), whereas that in the AH group was 86.49% (32/37). The difference between the CR rates in the EEC and AH groups was statistically significant ($P<0.05$). There was no association between prognosis after treatment and ER, PAX2, PTEN or Ki-67 expression in the initially untreated AH or EEC groups. However, tissues with >50% positive PR expression were demonstrated to have a higher CR rate compared with those with ≤50% positive PR expression in both the EEC and AH groups. Furthermore, the PAX2-positive group tended to demonstrate higher CR rates compared with the PAX2-negative group in the patients with EEC. In conclusion, these data suggested that fertility-sparing therapy is effective for patients with EEC and AH who wish to remain fertile after treatment. Specifically, in the AH group, a higher proportion of patients achieved a CR whilst also achieving this more rapidly. Furthermore, PR was demonstrated to be a useful marker for the evaluation of EEC and AH.

Correspondence to: Professor Jianliu Wang, Department of Obstetrics and Gynecology, Peking University People's Hospital, 11 Xizhimen South Street, Xicheng, Beijing 100044, P.R. China
E-mail: wangjianliu1203@163.com

Professor Danhua Shen, Department of Pathology, Peking University People's Hospital, 11 Xizhimen South Street, Xicheng, Beijing 100044, P.R. China
E-mail: danhuashen@126.com

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Introduction

Uterine corpus cancer is the sixth most commonly diagnosed malignancy among women, with 417,000 new cases and 97,000 cases of mortality reported worldwide in 2020 (1). A total of 81,964 new cases and 16,607 cases of associated mortality were reported in China in 2020 (2). Endometrial endometrioid carcinoma (EEC) is the most prevalent subtype of uterine corpus cancer, accounting for ~75% of all cases (3). The incidence of EEC has been gradually increasing over the past decade worldwide (4). Atypical hyperplasia (AH) and endometrioid intraepithelial neoplasia (EIN) refer to the precursor lesions that occur prior to EEC. This terminology is used in the World Health Organization (WHO) Classification (2014) of Tumors of Female Reproductive Organs (3). In total, ~25% of all AH cases will typically progress into EEC (5). Furthermore, both AH and EIN have similar morphological features, the occurrence of which has been reported to be largely associated with long-term non-antagonistic estrogen. In total, ~14% of patients with EEC are women of child-bearing age (6). At present, a large proportion of fertile women will delay bearing children, which has been reported to have caused an increase in the number of nulliparous women diagnosed with EEC (7). In 1997, Kim *et al* (8) first reported that patients with EEC could conceive successfully after progestin treatment. Hormonal treatment with progesterone may also be a viable option in women with well-differentiated EEC or AH who wish to preserve their fertility. Fertility-sparing treatment is becoming more popular and is increasingly being used for

young women diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IA, grade 1 EEC of the uterus who wish to have children in the future (7,9).

Excessive exposure of the endometrium to estrogen has been reported to be one of the most important risk factors for EEC (10). Pathologically well-differentiated EEC typically presents with positive estrogen receptor (ER) and progesterone receptor (PR) expression, and is also associated with a good prognosis (11). Protein biomarkers, such as PTEN and paired box 2 (PAX2), have been reported to be useful for the differential diagnosis of EEC and AH (12).

Therefore, the present study assessed the prognostic value of certain clinicopathological features and their protein marker expression profiles, specifically in women of childbearing age with EEC/AH. The ultimate aim was to evaluate if these protein markers were able to predict prognosis and provide guidance on the management of young women with EEC/AH. Furthermore, the present study evaluated these markers potential association with histological classification and prognosis following repeated conservative fertility-preserving treatments against EEC/AH.

Materials and methods

Case selection. In total, the cases of 83 patients, of whom 37 were initially diagnosed with AH and 46 were diagnosed with EEC, who were treated between August 2013 and September 2021 at Peking University People's Hospital (Beijing, China) were retrospectively analyzed. Endometrial biopsies had been collected from these patients, who were followed up ≥2 times. All patients had been treated using progestin and had undergone follow-up clinical examination using ultrasound every month. Furthermore, patients had undergone endometrial sampling using hysteroscopy or curettage to assess the endometrial response every 3 months. The follow-up duration was defined as the period from the initial treatment to the time of last observation. All pathological slides were carefully, independently, reviewed by two experienced gynecological pathologists. Before treatment, the absence of muscular infiltration, cervical invasion or extrauterine diffusion had been confirmed through inspection. The present study was approved by the Ethics Committee of Peking University People's Hospital (approval number 2016PHB054-01).

Pathological response evaluation

Pre-treatment biopsies evaluation. According to the criteria stated by the WHO Classification of Tumors of Female Reproductive Organs (3), EEC can be graded as grade 1, 2 or 3 using the FIGO grading criteria, exhibiting ≤5, 6-50 and >50% solid area (non-glandular and non-squamous growth area), respectively. AH is defined as a simultaneous change in epithelial cells (including enlarged nucleus and visible nucleoli) and increase in the number of endometrial glands (crowded gland architecture) within a morphologically defined region that is distinct from the surrounding endometrium of entrapped normal glands. AH size must be ≥1 mm.

Post-treatment evaluation. The patients underwent follow-up using endometrial sampling by hysteroscopy or curettage to assess endometrial changes every 3 months. According to Wheeler *et al* (13) and Chen *et al* (14), response to treatment based on the latest biopsy can be classified as follows: i) Complete response (CR), defined as a proliferative, secretory, inactive or atrophic endometrium without hyperplasia or atypia; ii) partial response (PR), defined as histological regression with decidual endometrial change; iii) stable disease (SD), defined as the persistence of EEC or AH/EIN in both the original and final specimens; iv) progressive disease (PD), defined as progression to lesions if the pre-treatment specimen showed AH whereas the latest specimen showed EEC, or if the original specimen showed grade 1 EEC whereas the latest specimen showed EEC grade 2 or 3; and v) recurrent disease (RD), defined as a CR to progestin treatment once or more according to a follow-up biopsy, but in which EEC/AH recurrence was subsequently identified. All pre-treatment and post-treatment evaluations were independently performed by two experienced gynecological pathologists. A consensus was considered to be reached if both observers agreed and a third pathologist would review it if both observers disagreed.

Histological and immunohistochemical analysis. All pathological specimens were fixed using 4% neutral formaldehyde (room temperature; 120 min), before the sample was conventionally dehydrated (graded alcohol series) and soaked, embedded in paraffin and sectioned (5 μm) for hematoxylin and eosin staining (room temperature; 10 min).

All immunohistochemical staining was performed according to the manufacturers' protocols. Formalin-fixed paraffin-embedded blocks were sectioned at 4 μm each and incubated with antibodies (37˚C; 20-30 min) against p53 (1:100; cat. no. ZM-0408; clone D0-7), ER (1:100; cat. no. ZM-0104; clone 6F11), PR (1:100; cat. no. ZM-0215; clone 16), PTEN (1:50; cat. no. ZM-0116; clone 6H2.1) and PAX2 (1:100; cat. no. ZM-0467; clone EP235) (all ZSGB-BIO Technology Co, Ltd.). Secondary antibody (HRP; cat. no. ZLI-9013; ZSGB-BIO Technology Co, Ltd.) incubation was 20-30 min at 37˚C. The presence of brown/yellow staining under a light microscope indicated positivity. PAX2, p53, ER, PR and PTEN positivity was present in the nucleus. ER and PR protein expression levels were assessed based on the intensity and the proportion of nuclear staining according to the area of positively stained nuclei, and were divided into two groups: >50 and ≤50% as estimated by a pathologist. p53 expression levels were used to divide cells into wild-type (sporadic or few cells positive) and mutant-type (>70% cells positive) (3). Positive PAX2 and PTEN expression was defined as >90% of EEC/AH having retained PTEN and PAX2 staining. Adjacent stromal cells or normal endometrial glands served as positive internal controls.

Statistical analysis. Statistical analysis was performed using SPSS 25 (IBM Corp.). The measurement data are presented as the count and percentage [n (%)]. The association between the clinicopathological features and patient outcome was assessed using the χ^2 test. All statistical tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinicopathological characteristics. Clinicopathological and outcome data were collected from 46 women with EEC and 37 women with AH. Patient age at diagnosis ranged

Table I. Relationship between clinicopathological features and prognosis of patients after treatment.

Clinicopathological feature	Total, n	CR, n	No CR, n	P-value
Age, years				0.342
≤35	45	36	9	
>35	38	27	11	
BMI				0.883
<25	26	20	6	
≥25	57	43	14	
Pathological type				0.043
EEC	46	31	15	
AH	37	32	5	
CR duration (<6 Months)				
EEC	46	16	30	<0.001
AH	37	28	9	

CR, complete response; BMI, body mass index; EEC, endometrial endometrioid cancer; AH, endometrial atypical hyperplasia.

from 19 to 44 years, with a median age of 32.6 years. The duration of clinical follow-up ranged from 4 to 98 months, with a median follow-up time of 37 months. In total, 5 patients abandoned progestin treatment, as a CR was not achieved within a given period of time (15-24 months), and instead opted for a hysterectomy. All patients received multiple cycles of high-dose progestin treatment (number of treatment cycles, 2-8). All but 5 patients were receiving progestin treatment continuously during the follow-up period. The detailed clinicopathological features of the EEC and AH groups are presented in Table I.

Comparison of outcomes between patients with EEC and patients with AH after repeated fertility-preserving treatments. According to the aforementioned definition of post-treatment evaluation, the overall CR rate in the EEC group was 67.39% (31/46). In total, 16 patients reached CR in <6 months and 30 patients reached CR in >6 months. Furthermore, 6 patients achieved PR and 8 patients demonstrated SD. Moreover, one patient experienced PD. Among the 31 patients who achieved CR, 7 patients experienced RD. In terms of patients with RD, 4 patients achieved CR, whereas 3 patients gave up fertility preservation treatment and underwent a hysterectomy. Figs. 1 and 2 show representative hematoxylin and eosin staining images of EEC and AH sections after fertility-preserving treatment.

The overall CR rate in the AH group was 86.49% (32/37), where 28 cases reached CR in <6 months and nine cases required >6 months. There were 3 cases of PR and 2 patients demonstrated SD. Among the 32 patients who achieved CR, 5 patients (15.63%) experienced RD. In the RD group, 3 cases reached CR and 2 cases reached SD. PD cases were not observed (Table I).

The CR rate of patients with EEC (67.39%) was significantly lower compared with that in AH patients (86.49%) (P=0.043; Table I). Furthermore, the CR rate in the EEC and AH groups at 6 months was statistically significant (P=0.000) and the CR rate in the AH was higher. The time required by the AH group to reach CR was significantly shorter compared with that in EEC group (Table I). Among the 46 cases of EEC, 36 cases were grade 1 and 10 cases were grade 2 (Table II). In the grade 1 EEC group, 26 cases achieved CR, 4 cases were PR and 6 cases were SD. In the grade 2 EEC group, 5 cases were CR, 2 cases were PR and 1 case was PD. SD was demonstrated in 2 cases. The CR rate of patients with grade 2 EEC (50.0%) was markedly lower compared with that of patients with grade 1 EEC (72.22%) (Table II). All patients were alive at the last follow-up (Fig. 3).

Relationship between pre-treatment biomarker expression and prognosis in the different groups. All patients with EEC and AH demonstrated positive PR and ER expression in 10-100% of the tumor cells before treatment and were divided into the following two groups: ≤50 and >50%. In EEC, there were 9 cases with ≤50% ER expression and 37 cases with >50% ER expression (Table II). For PR expression in EEC, 6 cases demonstrated ≤50% expression and 40 cases demonstrated >50% expression. In patients with AH, 10 cases presented with ≤50% ER expression and 27 cases presented with >50% ER expression. There were 5 cases with ≤50% PR expression and 32 cases with >50% PR expression. In EEC, 34 cases demonstrated PAX2-negative staining, whereas 12 cases demonstrated PAX2-positive staining. There were also 24 PTEN-negative cases and 22 PTEN-positive cases. The p53-mutant type was found in 1 case and the p53 wild-type was found in 45 cases (P=0.326) in EEC group. In the grade 2 EEC group, 2 cases demonstrated ≤50% PR expression and 8 cases demonstrated >50% PR expression. A total of 3 cases demonstrated PAX2-negative staining, whereas 7 cases demonstrated PAX2-positive staining.

In patients with AH, 10 cases presented with ≤50% ER expression whilst 27 cases showed >50% ER expression (Table II). There were 5 cases showing ≤50% PR expression and 32 cases showing >50% PR expression. Patients with either EEC or AH showing >50% positive PR expression

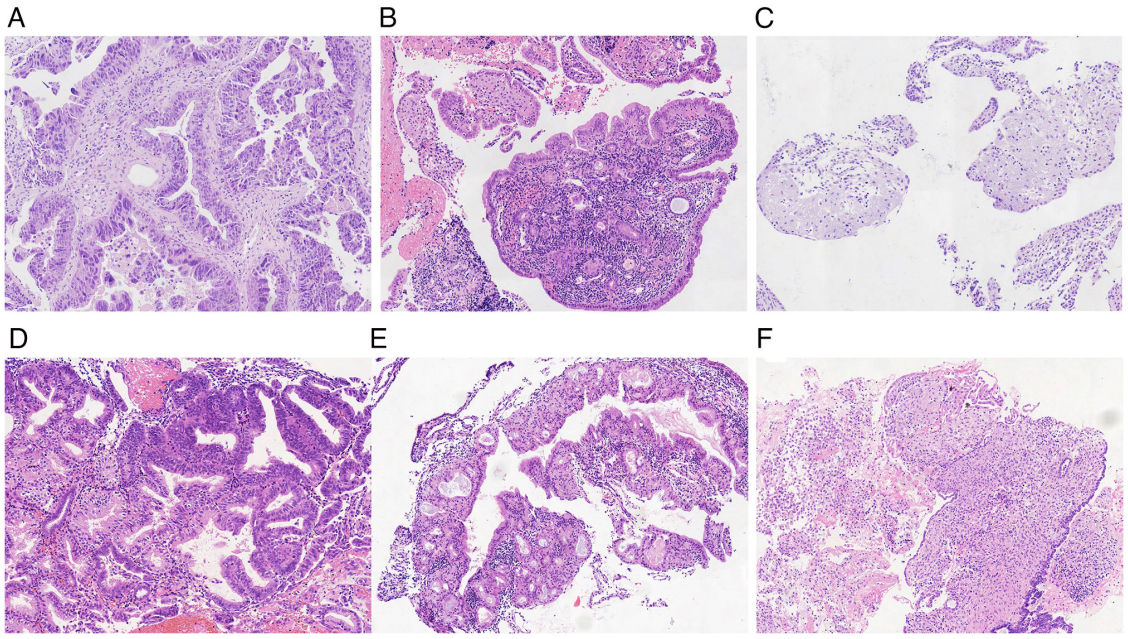

Figure 1. Representative hematoxylin and eosin staining images of endometrial endometrioid carcinoma sections after fertility-preserving treatment. (A and D) Stable disease demonstrating cribriform and papillary architecture and severe nuclear atypia, with focal stroma deciduloidosis clearly observed (magnification, x200). (B and E) Partial response demonstrating a small lesion (<1 mm) with gland crowding and mild nuclear atypia (magnification, x100). (C and F) Complete response demonstrating glands atrophied without nuclear atypia and extensive decidual-like changes in the stroma (magnification, x100).

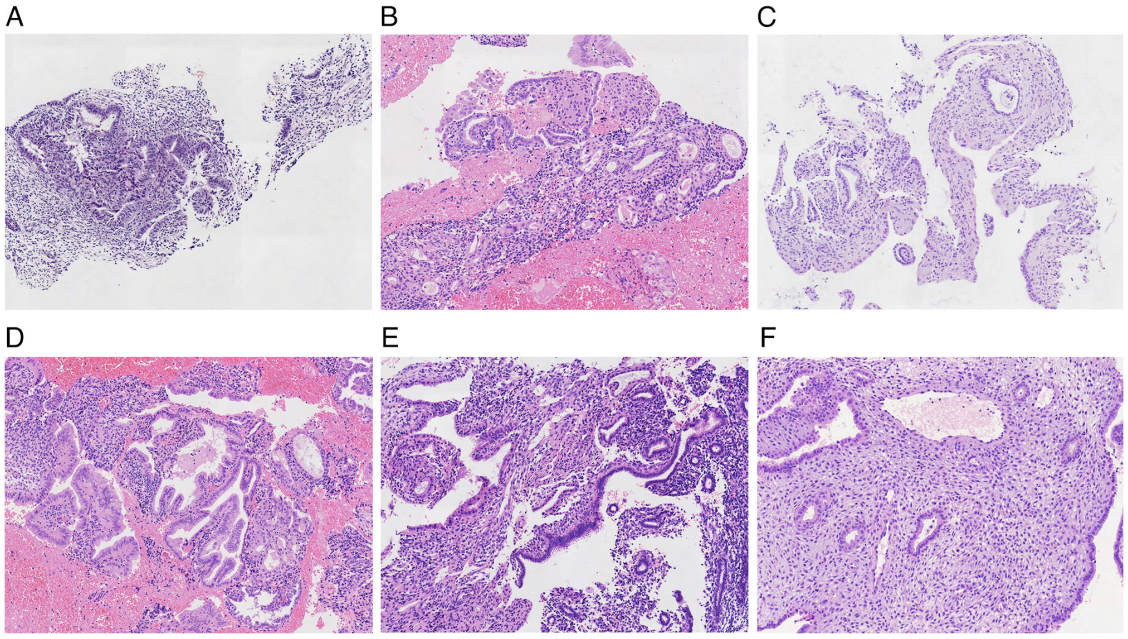

Figure 2. Representative hematoxylin and eosin staining images of atypical hyperplasia after fertility-preserving treatment. (A and D) Stable disease demonstrating a small lesion (>1 and <2 mm), cribriform architecture and dense glandular hyperplasia, with moderate nuclear atypia. (A) x100 and (D) x200 magnification. (B and E) Partial response demonstrating gland crowding without nuclear atypia. (B) x100 and (E) x200 magnification. (C and F) Complete response, demonstrating glands atrophied without nuclear atypia, with extensive decidual-like changes in the stroma. (C) x100 and (F) x200 magnification.

had higher CR rates compared with the ≤50% positive PR groups. The relationship between prognosis after treatment and PR expression in the initially untreated AH/EEC groups was significantly different (P=0.012; P=0.010; Table II). A total of 23 PAX2-negative cases were demonstrated whereas 14 PAX2-positive cases were demonstrated (Table II). There were 27 PTEN-negative cases and 10 PTEN-positive cases. The p53 mutant type was found in one case, whereas 37 cases had the p53 wild-type in the EEC groups. The relationships between prognosis after treatment and ER, PTEN and PAX2 expression in the pretreatment AH/EEC groups were not significantly different. The relationship between prognosis and p53 expression in the EEC groups were not significantly different. In the AH groups, p53 IHC test was not performed. Representative immunohistochemical results for the EEC and AH cases before treatment are presented in Fig. 4.

Table II. Association between pathological subtype/expression of biomarkers and prognosis of patients after treatment.

A, EEC pathological grade

Parameter	Total, n	CR, n	No CR, n	P-value
Pathological grade				0.185
I	36	26	10	
II	10	5	5	

B, EEC biomarkers

Parameter	Total, n	CR, n	No CR, n	P-value
ER				>0.999
≤50%	9	6	3	
>50%	37	25	12	
PR				0.010
≤50%	6	1	5	
>50%	40	30	10	
PAX2				0.070
Negative	34	20	14	
Positive	12	11	1	
PTEN				0.603
Negative	24	17	7	
Positive	22	14	8	
p53				0.326
Mutant	1	0	1	
Wild-type	45	31	14	

C, AH biomarkers

Parameter	Total, n	CR, n	No CR, n	P-value
ER				0.110
≤50%	10	7	3	
>50%	27	25	2	
PR				0.012
≤50%	5	2	3	
>50%	32	30	2	
PAX2				>0.999
Negative	23	20	3	
Positive	14	12	2	
PTEN				>0.999
Negative	27	23	4	
Positive	10	9	1	

CR, complete response; EEC, endometrial endometrioid cancer; AH, endometrial atypical hyperplasia; ER, estrogen receptor; PR, progesterone receptor; PAX2, paired box 2.

Discussion

In 1983, endometrial carcinoma was divided into type I and type II by Bokhman, according to the relationship between endometrial carcinoma and estrogen, and histopathological and epidemiological characteristics (15). Type I cancer was EEC and defined as being hormone-associated tumors, which responded well to progestin therapy and were associated with a good prognosis, with a 5-year survival rate of 81%. Type II cancer was serous carcinoma, which was not considered in the

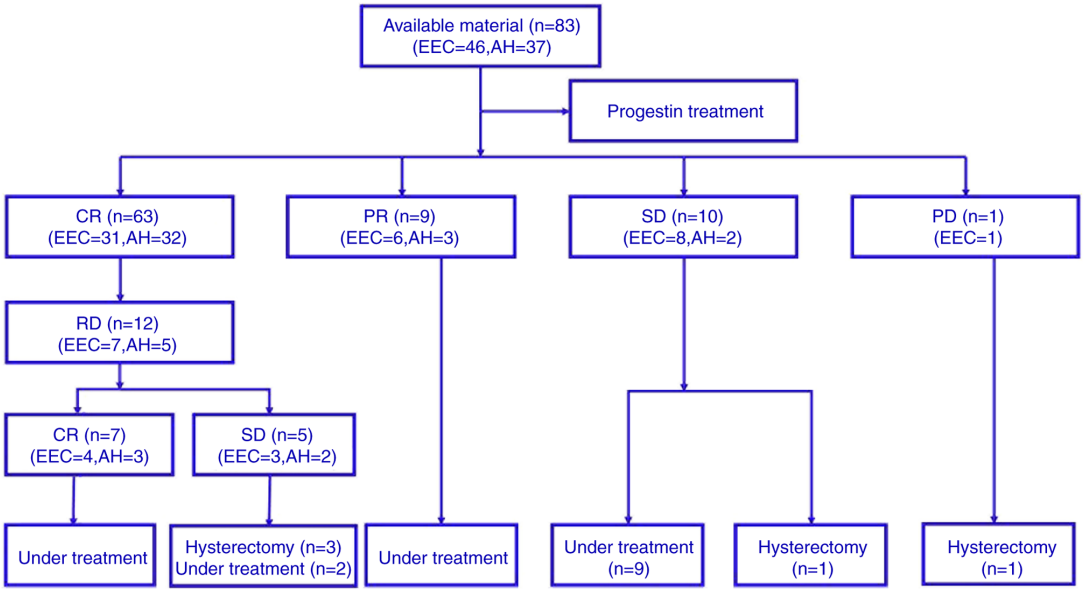

Figure 3. Responses after progestin treatment of all patients in the present study. EEC, endometrial endometrioid carcinoma; AH, atypical hyperplasia; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RD, recurrent disease.

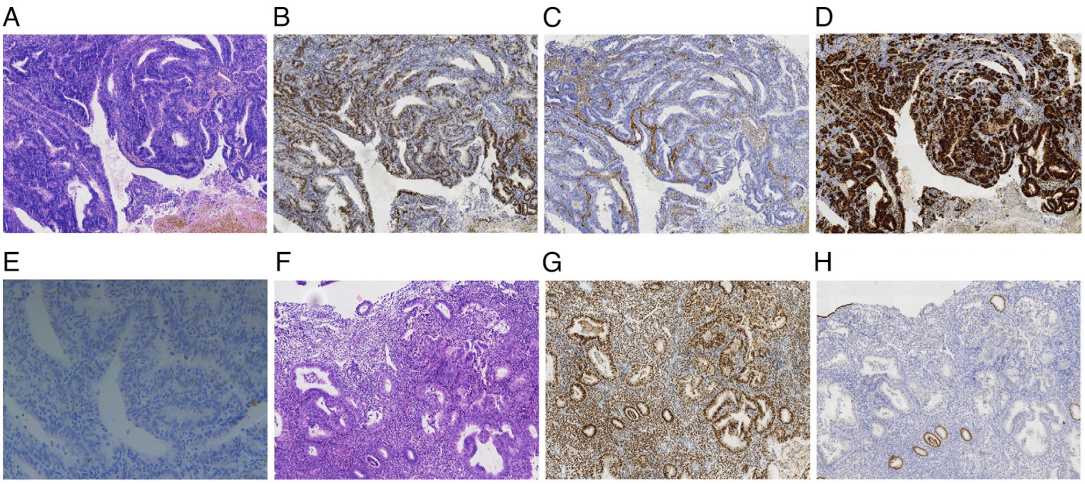

Figure 4. Differential immunohistochemical staining profiles before treatment for EEC and AH. (A) Representative image of grade 1 EEC (hematoxylin and eosin; magnification, x100). (B) Representative image of positive ER expression in an EEC biopsy before treatment (magnification, x100). (C) Representative EEC biopsy image of negative PTEN expression before treatment, but with positive PTEN expression in stroma cells (magnification, x100). (D) Representative image showing strongly positive PR expression in an EEC biopsy before treatment (magnification, x100). (E) Representative image showing p53 scattered (wild-type) expression in an EEC biopsy before treatment (magnification, x200). (F) Representative AH biopsy image (hematoxylin and eosin; magnification, x100). (G) Representative image showing positive ER expression in a pre-treatment biopsy (magnification, x100). (H) Representative AH biopsy image showing negative PAX2 expression before treatment, but positive PAX2 expression could be observed seen in the adjacent normal epithelium (magnification, x100). EEC, endometrial endometrioid carcinoma; AH, atypical hyperplasia; ER, estrogen receptor; PAX2, paired box 2.

present study. However, the 5-year survival rate was reported to be 96% for patients with EEC with FIGO stage I (16). The National Comprehensive Cancer Network (NCCN) previously recommended (17) that patients should be included for repeated fertility-preserving treatments if they met the following conditions: i) Diagnosed with well-differentiated EEC; ii) lesions confined to the endometrium, assessed using ultrasound or MRI, with no suspicious metastatic lesions; iii) no contraindications for medications; and iv) have been informed that the fertility preservation option is not the standard treatment for endometrial cancer. If these conditions are met, a proportion of women of childbearing age can receive fertility-preserving treatment. With the rapid development of assisted reproductive technology, an increasing number of patients with EEC, especially those in the younger population, have the opportunity to achieve pregnancy and childbirth despite an EEC diagnosis.

Fertility-sparing management is being increasingly adopted for younger patients with EEC who wish to preserve their fertility. However, the CR rate of fertility-sparing therapy can vary significantly. Qin *et al* (18) performed a systematic review and meta-analysis to evaluate the efficacy of progestin treatment for endometrial cancer. The study identified 25 studies reporting a total of 445 cases. The CR rate of patients with EEC was 82.4%. However, Wang *et al* (19) reported that the

CR rates of patients with EEC and AH were 66.7 and 92.9%, respectively. These CR rates were slightly higher compared with the above reports demonstrated in the present study. The present study demonstrated that the CR rates of patients with EEC and AH were 67.39 and 86.49%, respectively. This may be due to the short duration of follow-up, in the present study, 10 patients were only treated for ~4 months and so the follow-up times were shorter.

In the present study, 16 patients in the EEC group demonstrated CR ≤6 months after treatment, whereas 28 cases in the AH group achieved CR ≤6 months. There was a statistically significant difference between the CR rates of the EEC and AH groups. The AH group demonstrated a higher CR rate and the time required for CR was also shorter compared with that in the EEC group. Therefore, it could be hypothesized that AH may be more receptive to progestin treatment compared with EEC, with superior curative effects and a shorter remission time. From the perspective of histopathology, AH is a precancerous lesion of EEC, where ~25% of AH cases progress to EEC (5). The lesion severity and size range (lesions <2 mm) of AH were weaker and smaller compared with those of EEC, which rendered the therapeutic effect and time required for CR shorter, which was consistent with their histological characteristics. Among the 46 cases of EEC in the present study, there were 36 cases with grade 1 and 10 cases with grade 2 EEC. The CR rate of patients with grade 2 EEC (5/10; 50.0%) was markedly lower compared with that of patients with grade 1 EEC (26/36; 72.22%); however, no significant difference was demonstrated between the two groups. These results indicated that there was no difference in the effect of treatment between these two groups and that progestin treatment was equally effective against EEC and AH. These results were consistent with those reported in previous studies (19,20) but were lower compared with the CR rate of 76.5% reported in the multicenter retrospective study by Park *et al* (21), which consisted of patients with stage Ia, grade G2-G3 EEC without muscular invasion. This suggested that fertility-preserving treatment could also be attempted in patients with grade 2 EEC. For patients who desire to preserve their fertility and meet all other conditions of progestin treatment, this may be a viable choice. However, the small sample size in the present study is a limitation. Larger sample sizes are required to validate the findings of the present study.

The 2018 NCCN guidelines recommended that if patients suffered from adverse events as a result of fertility-preserving treatment for 9-12 months and the disease was not in CR, then surgical treatment was indicated (17). However, at present, there is no absolute limit for the duration of use of fertility-preserving treatment. Previous studies have reported that the cumulative response rate gradually increases as the treatment time increases, where 10-13% patients require >12 months to achieve CR whilst not causing recurrence and/or affecting pregnancy outcome (22,23). The time to reach CR in the present study was a little longer compared with that reported in the aforementioned studies (21,24), which was especially the case in the EEC group, where 15 patients achieved CR in >6 months. The RD rates in the EEC and AH groups were 22.28% (7/31) and 15.63% (5/32), respectively. There was no significant difference between these two groups in this regard. Therefore, the treatment time was longer; however, the RD rate was not different, which suggested that the treatment was efficacious. Therefore, if patients wish to preserve their fertility and there are no contraindications to progestin treatment or severe lesions, such as muscular infiltration and metastasis, and they have been explicitly informed that this form of treatment may cause adverse effects, then fertility-preserving treatment time may be extended appropriately. In such cases, this therapy could continue, but the option to terminate treatment at any time should remain open in cases of emergency.

Numerous immunohistochemical markers have been used for the diagnosis of EEC and AH. In particular, PR and ER are reported to be commonly used markers for this disease (25). However, a previous study reported that as the normal endometrium progressed to the cancerous endometrium and the pathological grade and clinical stage increased, ER and PR expression decreased (3). ER and PR have been reported as potential targets, as progestins primarily mediate their effects through PR, but an imbalance between estrogen and progestin has been reported to be involved in the pathogenesis of EEC (26). Previous studies have reported that PR-positive patients with EEC have superior outcomes following fertility-preserving treatment (21,27). Raffone *et al* (27) reported that the CR rate of fertility-sparing therapy was 60% in PR-positive patients with EEC, whereas it was only 18.8% in PR-negative patients. A retrospective study previously performed by Travaglino *et al* (28) suggested that PR expression was a highly sensitive predictive marker for conservative EEC and AH treatment. These results were similar to those of the present study. In the present study, >50% ER positivity was not demonstrated to confer higher a CR rate compared with the CR rate demonstrated by the ≤50% ER positivity group in the EEC and AH groups. However, >50% PR positivity was found to confer a higher CR rate compared with a ≤50% PR positivity rate in the EEC and AH groups. This suggested that the expression of PR might have a prognostic implication. However, reports regarding the utility of hormone receptor expression for the prediction of the response to progestin therapy have been controversial, suggesting that there was no significant difference in the outcome between PR-positive and PR-negative patients (28). Therefore, a study using a larger sample is required for verification.

PAX2 is involved in the carcinogenesis of numerous cancer types through the regulation of cell proliferation and apoptosis. Loss of PAX2 protein expression has been frequently reported in EEC and AH (12). However, PTEN is a tumor suppressor, the expression of which can be lost through numerous mechanisms, including point mutations in EEC and AH (29). In the present study, PAX2 positivity was not demonstrated to confer higher CR rates compared with PAX2-negative findings among patients with EEC and AH. PAX2 protein expression was not significantly associated with prognosis in the EEC group. Similarly, an association between PTEN protein expression and prognosis was not demonstrated in the EEC and AH groups before treatment. This was not consistent with the data previously reported by Chen *et al* (14). In a previous meta-analysis or systematic review of fertility-sparing treatment of EEC or AH in young women, no clear predictive biomarkers which were associated with remission, recurrence or progression could be identified following multivariate analysis (30). However, the present study has certain limitations that should be discussed.

The present study was a single-center retrospective study. Therefore, it remains difficult to compare the effects of different interventions directly. Furthermore, the relatively small sample size reduced the scientific power of the conclusions. A larger sample, prospective study is required to verify the preliminary findings from the present study. Moreover, certain patients were under treatment until the last follow-up, which may have influenced the results of the present study. Therefore, longer term monitoring and increasing the frequency of evaluation would be of value in future studies.

In 2013, The Cancer Genome Atlas divided endometrial carcinoma into DNA polymerase epsilon mutations, microsatellite instability high mutant, low copy number and high copy number types based on the gene mutation spectrum ε mutant (31). Molecular typing can be used to more accurately estimate patient prognosis and guide treatment design; its introduction may contribute to the further selection of patients who are eligible for fertility-sparing treatment (32). The NCCN 2018 guidelines recommended the molecular typing of EEC for the first time (17). Integration of clinical pathology and molecular features is expected to be completed for early EEC risk stratification in patients and for guiding clinical decision making, which could deepen our understanding into the effects of fertility-sparing treatment for EEC and AH. Additional studies based on molecular classification will contribute to more accurate and individualized treatment strategies.

In summary, fertility-sparing treatment is relatively effective for patients with EEC and AH who wish to preserve their fertility. In the AH group, a higher proportion of patients achieved a CR whilst also achieving this more rapidly compared with those in the EEC groups PR may also have prognostic implications as it is a useful marker for the evaluation of EEC and AH.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

XBZ contributed to data acquisition and drafted and wrote the manuscript. XYZ, CW,SSL prepared the materials and aided in the analysis. YQW and YJH contributed to collection of clinical information. JLW and DHS designed and supervised the study. XBZ, JLW and DHS confim the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Peking University People's Hospital (approval no. 2016PHB054-01).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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