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ORIGINAL RESEARCH

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Analysis of factors affecting the success of fertility preservation for early-stage endometrial carcinoma and atypical endometrial hyperplasia: a retrospective study from a single center

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Abstract

Background: To investigate the outcome of fertility preservation therapy in patients with early well-differentiated endometrial carcinoma (EC) and atypical endometrial hyperplasia (AEH). **Methods**: A retrospective analysis of the clinicopathological data and treatment outcomes of 31 cases of endometrial carcinoma (EC) and 93 cases of endometrial atypical hyperplasia (AEH) who were admitted to our hospital for fertility preservation from January 2013 to December 2020 was conducted. Univariate and multivariate analyses were used to evaluate the risk factors for complete response and recurrence. Statistical analysis was used to assess the effectiveness of both single drug and multi-drug combinations. **Results**: The total complete response (CR) rate was 92%. There was no significant difference between the two groups. The study revealed that patients with endometrial cancer who received high-efficiency progestin-based combination regimens experienced a significant reduction in treatment time (5.9 ± 3.3 *vs.* 3.1 ± 0.4 months, $p = 0.001$). The total pregnancy rate was 35%. Multivariate analysis showed irregular menstruation (odds ratio (OR) = 0.329, 95% confidence interval (CI) = 0.126–0.862, $p = 0.024$) and treatment time to complete response months (>6 months, OR = 0.254, 95% CI = 0.087–0.740, $p = 0.012$) were independent factors to reduce pregnancy rate. Furthermore, our findings indicated that there were no significant differences in complete response rate, recurrence rate and pregnancy rate between patients with grade-2 (G2) and patients with grade-1 (G1) EC ($p \geq 0.05$). **Conclusions**: Fertility preservation is safe and feasible for grade-2 endometrial carcinoma whereas Progestin-based combination therapy seems more effective than monotherapy for the treatment of fertility preservation.

Keywords

Endometrial cancer; Atypical endometrial hyperplasia; Female infertility; Fertility preservation

1. Introduction

Endometrial carcinoma (EC) is the most common gynecological malignancy in western countries and its occurrence is increasing globally [1]. While the majority of cases are found in postmenopausal women with a median age of 63 years, approximately 14% of diagnosis are made in women who have not yet reached menopause. [2]. The standard treatment (total hysterectomy and bilateral adnexectomy plus retroperitoneal lymph node dissection) for early EC may result in infertility [3]. As a result of the postponement of the age at which women have children, the implementation of China's two-child policy and other factors, there is an increasing demand in clinical practice for the preservation of reproductive function among older patients [4]. For this reason, fertility preservation treatments are becoming increasingly important for both clinicians and patients.

Several factors affect the success of fertility preservation, including the presence of muscle invasion, the level of histologic differentiation, insulin resistance (IR) and higher body mass index. Insulin resistance (IR) and higher body mass index are two of the important hallmarks of polycystic ovarian syndrome (PCOS) [5]. Currently, there is a scarcity of reports on this topic in China. In this study, we provide our center's findings on fertility preservation in young women with early grade 1 (G1) EC, grade 2 (G2) EC, and atypical endometrial hyperplasia (AEH) who had a strong desire to preserve their fertility.

2. Materials and methods

2.1 Patient selection

A retrospective analysis of the clinicopathological data and treatment outcomes of 31 cases of EC and 93 cases of AEH who were admitted to our hospital for fertility preservation from January 2013 to December 2020 was conducted. Inclusion criteria: ① Age ≤45 years old; ② Patients with a strong desire to preserve fertility and know the standard treatment of EC and AEH; ③ The pathological diagnosis was made by the pathologists of our hospital; ④ Stage I patients with localized lesions fully evaluated by clinical evaluation, and no suspicious metastasis in pelvic cavity or beyond; ⑤ Patients were fully aware of the risks of nursing care, signed the informed consent form, and had good compliance. Exclusion criteria: ① Less than one course of treatment; ② Incomplete clinical data; ③ Loss of follow-up.

2.2 Eligibility criteria

Endometrial cancer was diagnosed by diagnostic curettage (DC) or hysteroscopy. The enrolled patients had endometrioid adenocarcinoma as the pathological type. All cases were confirmed by senior pathologists in our hospital. It is important to note that only a portion of the patients had immunohistochemistry p53 testing. The individuals included in this study were exclusively diagnosed with endometrioid adenocarcinoma (negative p53). The p53 test was only conducted in cases where there was morphologic indication of serous carcinoma.

Prior to commencing fertility preservation, the patient underwent a comprehensive assessment that included transvaginal ultrasound, whole-abdominal computed tomography (CT), pelvic Magnetic Resonance Imaging (MRI) and chest CT. These diagnostic procedures were performed to detect the possible presence of metastases outside the uterus. The median follow-up was 42 months.

2.3 Study setting

Of the 124 patients, 13 (1 EC, 12 AEH) were treated with a levonorgestrel-releasing intrauterine device (Mirena) alone, and the rest 111 patients were all treated with oral progesterone. Treatment with oral progestin was divided into two groups, either monotherapy or combination therapy, as follows: (1) Single drug therapy: Medroxyprogesterone acetate (MPA) (250 mg/d) or Megestrol acetate (MA) (160 mg/d); (2) Multidrug combination: MPA (250 mg/d) or MA (160 mg/d) in combination with other agents (Gonadotropin-Releasing Hormone Agonist (GnRHa) or levonorgestrel-releasing intrauterine system (LNG-IUS) or Metformin). For some patients with AEH cases, combination therapy was used, because most of these patients have comorbidities such as obesity, diabetes or polycystic ovarian syndrome.

Throughout the course of treatment, patients had regular monitoring of their biochemical and blood coagulation levels due to the potential risks of liver damage and thrombosis associated with high dose progestins medication. Furthermore, curettage or hysteroscopy were conducted at three-month intervals. In the case of any abnormal uterine bleeding outside the treatment evaluation point, ultrasound examination or further MRI was done. Pregnancy was encouraged after efficacy was assessed as complete response (CR).

2.4 Sample estimation

According to literature reports, efficacy evaluation was divided into five categories: complete response (CR), partial response (PR), stable disease (SD) and disease progression (PD) and Recurrence (R) [6–8]. The specific definition is as follows: (1) CR: No endometrial adenocarcinoma and endometrial hyperplastic lesions were observed, and the glands were completely atrophied and degenerated with deciduous edematous interstitial fluid. (2) PR: Endometrial glands were less crowded, but papillae and cribi form structures were still present whiles the atypia of glandular epithelium was reduced. (3) SD: Endometrioid adenocarcinoma or endometrial atypical hyperplasia still existed. (4) PD: The histopathologic grade of the tumor increased, cell atypia increased, and new definite muscular infiltration alongside vascular and/or nerve invasion showed in histopathology; Or imaging findings of myometrium infiltration, extrauterine lesions, or distant metastasis, or lymph node metastasis. (5) R: After complete remission, endometrioid adenocarcinoma or endometrial atypical hyperplasia reappeared in the pathological tissue.

2.5 Data analysis

Continuous data were expressed as mean ± (Standard Deviation (SD)) and were compared between groups using the student's t test. Categorical data were compared between groups by using the χ^2 test and expressed as the relative risk. Significant difference between groups was considered if the p value was less than 0.05. The χ^2, Fisher exact test was used for statistical analysis with SPSS software (Inc., Chicago, IL, USA), version 23.0.

3. Results

3.1 Clinical characteristics of patients

The clinical features of patients at baseline are summarized in Table 1. The median follow-up time was 33.5 months. The onset mean age ± SD of the EC group was slightly younger than the AEH group (29.26 ± 4.09 *vs.* 31.94 ± 5.30, p = 0.012). The most prevalent complications were infertility (53/124, 42.7%) followed by diabetes mellitus or insulin resistance (DM/IR) (20/124, 16.1%). In the EC group, 19 cases were classified as EC-G1 and 12 cases were classified as EC-G2. Furthermore, all patients who were tested for estrogen receptor (ER) and progestins receptor (PR) yielded positive results. Notably, the EC group included three (3) patients who had superficial muscle infiltration as determined by MRI. This indicates that the cancer's depth is less than half of the muscle layer. The three patients explicitly expressed their desire for fertility preservation and were well cognizant of the potential hazards, hence they underwent fertility preservation treatment. Among the three patients with superficial muscle layer invasion, one had a CR whiles two relapsed and received radical surgical treatment. Out of the two patients

who received surgical treatment, one exhibited stage Ib while the other exhibited stage III.

No death was recorded at the end of follow-up. A total of 114 patients (91.9%) achieved CR. 28 patients (90.3%) achieved CR in the EC group with a mean treatment time of 5.2 months, and 86 patients (92.5%) achieved CR in the AEH group with a mean treatment time of 5.2 months. There was no statistically significant difference between the two groups ($p = 0.7$) (Table 1).

3.2 Monotherapy *vs.* combination therapy

Treatment with oral progestins was divided into two groups, either monotherapy or combination therapy, as follows: (1) Single drug therapy: Medroxyprogesterone acetate (MPA) (250 mg/d) or Megestrol acetate (MA) (160 mg/d); (2) Multi-drug combination: MPA (250 mg/d) or MA (160 mg/d) in combination with other agents (GnRHa or LNG-IUS or Metformin). The results showed that, treatment with progestin-based combination therapy in the EC group, significantly shortened the time to CR (5.9 ± 3.3 *vs.* 3.1 ± 0.4 months, $p = 0.001$) (Table 2).

3.3 Pregnancy-associated factors

Among the 124 patients, 82 patients retained their intention to have children after successful fertility treatment, the remaining 42 patients either experienced ineffective treatment or gave up pregnancy plan.

The study recorded 44 pregnancies that resulted in favorable outcomes, yielding a pregnancy rate of 35%. Univariate analysis showed that compared with the non-pregnant group, the pregnant group had a lower mean age (29.4 ± 4.1 *vs.* 31.7 ± 3.9, $p = 0.01$), a higher proportion of menstrual regularity (72.7% *vs.* 47.4%, $p = 0.019$), and a higher proportion of CR at 6 months (79.5% *vs.* 57.9%, $p = 0.034$) (Table 3).

Further multivariate analysis showed irregular menstruation (OR = 0.329, 95% CI = 0.126–0.862, $p = 0.024$) and treatment time for CR >6 months (OR = 0.254, 95% CI = 0.087–0.740, $p = 0.012$) were independent factors to reduce pregnancy rate.

3.4 EC-G1 *vs.* EC-G2 efficacy

There was no statistically significant differences in CR rate, recurrence rate and pregnancy rate between EC-G1 and EC-G2 patients ($p \geq 0.05$) (Table 4).

3.5 Natural pregnancy (NP) *vs.* assisted reproductive technology (ART)

Patients were divided into two groups: the NP group and the ART group based on their mode of pregnancy. The results showed that, the rate of pregnancy in the ART group was slightly higher than that in the natural pregnancy group (61.4% *vs.* 44.7%, $p = 0.132$), but the difference was not statistically significant. In addition, there was no increased risk of recurrence in ART group (15.9% *vs.* 13.2%, $p = 0.725$). It was also found that the gestation time in the ART group was slightly shorter than that in the NP group, but the difference was not statistically significant (9.6 ± 6.0 *vs.* 9.8 ± 9.2, $p = 0.93$) (Table 5).

4. Discussion

Fertility preservation therapy is crucial in managing endometrial tumors in young women. However, there has been disagreement and debate regarding its recommended use and treatment plan.

To begin, with regards to age, previous pertinent criteria restricted the age range to individuals who were 40 years old or less. However, Chinese experts concur that individuals between the ages of 41 and 45 who wish to preserve their fertility may consider undergoing fertility preservation treatment provided they have been thoroughly evaluated and informed about the potential drawbacks, such as limited treatment efficacy, disease progression and associated risks [6]. In our study, we observed a total of 9 individuals who were above the age of 40. All of these patients were diagnosed with AEH (atypical endometrial hyperplasia). Out of these patients, only 1 pregnancy resulted in a favorable outcome. Hence, caution should still be exercised while dealing with patients between the ages of 41 and 45.

Furthermore, in certain patients with conditions outside of the established criteria, fertility preservation therapy yielded satisfactory outcomes following comprehensive assessment. Fertility preservation therapy is considered safe and practical for patients with superficial muscle infiltration according to published guidelines [9].

For patients with superficial muscle infiltration, there are some guidelines that consider fertility preservation therapy to be safe and feasible, but a comprehensive assessment is required to exclude lymph node metastasis and other risk factors [9]. In a multicenter retrospective study in South Korea [9], a total of 23 patients diagnosed with early endometrial cancer, characterized by G1 and superficial invasion, were selected for the study. Out of these patients, 17 (73.9%) obtained complete remission (CR). Out of the 11 individuals that attempted pregnancy preparation, 5 successfully achieved it. In our study, we had 3 patients with superficial muscle infiltration, and out of those, 2 patients showed progression. Thus, we hypothesize that patients displaying imaging signals of superficial muscle infiltration are more susceptible to disease progression.

Furthermore, an increasing data of clinical evidence indicates that intermediate differentiation (G2) is not a complete contraindication [10, 11]. According to certain authors, the CR rate was 96% and the rate of recurrence was 22% in 11 patients with grade 2 (G2) undergoing fertility conservation therapy. These rates were similar to those observed in patients with grade 1 endometrial cancer (EC-G1) and atypical endometrial hyperplasia (AEH). However, it took a longer time to achieve CR in the G2 patients compared to the EC-G1 and AEH patients (8 months *vs.* 6 months *vs.* 4 months, respectively; $p = 0.046$). Additionally, the pregnancy rate was 75% (6 out of 8 patients). Our study also examined the efficacy and safety of fertility preservation therapy for EC-G2 patients. However, further evidence-based research is required to establish its usefulness. Furthermore, we propose that the utilization of combination therapy may yield superior results.

Oral therapy with medroxyprogesterone acetate (400–600 mg/day) or megestrol acetate (160–320 mg/day) is recom-

TABLE 1. The clinical characteristics of patients with EC and AEH.

	Early well-differentiated EC (n = 31)	AEH (n = 93)	*p* value
Age (yr) (mean)	29.26 ± 4.09	31.94 ± 5.30	
≤35 yr, n (%)	4 (12.9)	28 (87.1)	0.012
>35 yr, n (%)	27 (30.1)	65 (69.9)	
Pregnancy history	7 (22.6)	39 (41.9)	0.053
Delivery history	2 (6.5)	28 (30.1)	0.008
Age of menarche ($\bar{x}$ ± S, yr)	13.6 ± 1.0	13.5 ± 1.1	0.963
CA125 ($\bar{x}$ ± IU/mL)	17.7 ± 8.6	30.3 ± 66.8	0.281
AMH ng/mL			
<1.1	5 (33.3)	10 (29.4)	0.784
The time to CR ($\bar{x}$ ± S, mon)	5.2 ± 3.1	5.2 ± 3.5	
≤6 mon	18 (64.3)	61 (70.9)	0.670
>6 mon	10 (35.7)	25 (29.1)	
BMI	24.35 ± 6.12	25.01 ± 4.97	
<25 kg/m^2, n (%)	5 (16.1)	13 (14.1)	0.760
≥25 kg/m^2, n (%)	26 (83.9)	80 (85.9)	
Tumor differentiation			
G1, n (%)	19 (61.3)	NA	NA
G2, n (%)	12 (38.7)	NA	
Superficial muscle infiltration	3 (9.7)		
ER, PR status			
Positive, n (%)	16 (51.6)	13 (13.9)	
Negative	0	0	0.587
NA, n (%)	15 (48.4)	80 (76.1)	
p53 gene gstatus			
Wild type, n (%)	7 (22.6)	5 (5.4)	
Mutant, n (%)	0	0	0.563
NA, n (%)	24 (77.4)	88 (94.6)	
Complications			
History of infertility, n (%)	10 (32.3)	43 (46.2)	0.173
PCOS, n (%)	5 (16.1)	10 (10.8)	0.427
DM/IR, n (%)	4 (12.9)	16 (17.2)	0.573
Complete response rate, n (%)	28 (90.3)	86 (92.5)	0.703

NA: non-available; EC: Endometrial carcinoma; AEH: Atypical endometrial hyperplasia; CR: Complete response; BMI: Body mass index; ER: Estrogen receptor; PR: Progesterone receptor; PCOS: Polycystic ovary syndrome; DM/IR: Diabetes mellitus/Insulin resistance; AMH: anti-mullerian hormone; G1: well differentiated; G2: moderately differentiated; CA125: Cancer Antigen 125.

mended for fertility-sparing treatment. The effectiveness of different progestin therapies and the use of medication combinations is still a subject of controversy [12]. Medroxyprogesterone is the standard medication used at our center. However, it is frequently unavailable. The literature shows that patients with incomplete remission after 9 months who are treated with progestins combined with GnRHa, have a high remission rate [13]. The utilization of a combination of GnRHa (gonadotropin-releasing hormone agonists) and aromatase inhibitors in endometrial cancer patients who are obese has demonstrated a favorable long-term response rate (100%, 6/6) lasting between 3 to 6 months. Additionally, this treatment approach has resulted in a high proportion of successful pregnancies and live births [14].

TABLE 2. Comparison of efficacy between monotherapy and combination therapy.

	EC (n = 30)		*p* value	AEH (n = 81)		*p* value
	Single[a] (n = 22)	Combine[b] (n = 8)		Single[a] (n = 70)	Combine[b] (n = 11)	
CR	21 (95.5)	6 (75.0)	0.166	64 (91.4)	11 (100)	0.590
CR at 3 m (n)	12 (54.5)	6 (75.0)	0.419	43 (61.4)	8 (72.7)	0.738
Time to achieve CR (mon)	5.9 ± 3.3	3.1 ± 0.4	0.001	5.2 ± 3.7	5.2 ± 3.8	0.968
Recurrence	4 (18.2)	1 (12.5)	0.993	7 (10.3)	0 (0)	0.585

CR: Complete response; EC: Endometrial carcinoma; AEH: Atypical endometrial hyperplasia.
Single[a]: MPA 120–250 mg/d or MA 120–320 mg/d;
Combine[b]: MPA 120–250 mg/d (MA 120–320 mg/d) + metformin/GnRHa/LNG-IUS.

TABLE 3. Factors associated with pregnancy in EC and AEH.

	Successful pregnancy (n = 44)	Unsuccessful pregnancy (n = 38)	*p*
Age ($\bar{x}$ ± S)	29.4 ± 4.1	31.7 ± 3.9	0.010
BMI ($\bar{x}$ ± S kg/m^2)	23.8 ± 4.0	24.7 ± 5.0	0.375
Menstrual history			
Regular (%)	32 (72.7)	18 (47.4)	0.019
Irregular (%)	12 (27.3)	20 (52.6)	
Ovarian hypofunction			
No	36 (81.8)	31 (80.6)	0.978
Yes	8 (18.2)	7 (19.4)	
DM/IR			
No	38 (86.4)	30 (78.9)	0.373
Yes	6 (13.6)	8 (21.1)	
Pathology			
EC	11 (25.0)	14 (36.8)	0.245
AEH	33 (75.0)	24 (63.2)	
Intrauterine adhesions			
Yes	3 (6.8)	6 (15.8)	0.195
No	41 (93.2)	32 (84.2)	
CR (6 mon)			
Yes	35 (79.5)	22 (57.9)	0.034
No	9 (20.5)	16 (42.1)	
Pregnancy way			
Natural pregnancy	17 (38.6)	21 (55.3)	0.134
ART	27 (61.4)	17 (44.7)	
The pregnancy time ($\bar{x}$ ± S, mon)	9.2 ± 5.3	9.9 ± 7.9	0.778

BMI: Body mass index; DM/IR: Diabetes mellitus/Insulin resistance; CR: Complete response; ART: Assisted reproductive technology; EC: Endometrial carcinoma; AEH: Atypical endometrial hyperplasia.

TABLE 4. Comparison of the efficacy between EC-G1 and EC-G2.

	G1	G2	*p* value
CR (n)	15	10	0.760
CR at 3 m (n)	8	8	0.538
Recurrence (n)	2	2	0.567
Pregnancy (n)	6	4	0.657

G1: well differentiated; G2: moderately differentiated; CR: Complete response.

TABLE 5. Comparison of NP and ART.

	NP (n = 38)	ART (n = 44)	*p*
Number of pregnancies, n (%)	17 (44.7)	27 (61.4)	0.132
Number of births, n (%)	16 (42.1)	18 (40.9)	0.913
Gestation time ($\bar{x} \pm$ S, mon)	9.8 $\pm$ 9.2	9.6 $\pm$ 6.0	0.930
Recurrences, n (%)	5 (13.2)	7 (15.9)	0.725

NP: Natural pregnancy; ART: Assisted reproductive technology.

A Phase II trial of medroxyprogesterone acetate in combination with metformin showed a complete response rate of up to 97%. After period of 58 months of monitoring, the rate of recurrence was 13%, significantly lower than medroxyprogesterone acetate monotherapy. The combination therapy group had a 61% pregnancy rate and 45% live birth rate. Furthermore, it was observed that obese individuals were more inclined to experience positive outcomes from the combined therapy [15]. Our study revealed that patients in the EC group who received progestin-based combination regimens experienced a significant reduction in treatment time for CR (5.9 $\pm$ 3.3 *vs.* 3.1 $\pm$ 0.4 months, p = 0.001). Therefore, we conclude that combination therapy could be beneficial for patients by accelerating the time to remission. Nevertheless, there is currently a dearth of randomized controlled trials.

The general consensus is that the implementation of Assisted Reproductive Technology (ART) can positively impact the pregnancy rate. Numerous studies have indicated that ART has no influence on relapse. Our study's findings align with the majority of these studies [16–18]. Nevertheless, the impact of ovarian stimulation on estrogen levels above the normal physiological dose in the body, as well as its potential association with an increased risk of disease recurrence has not been uniformly concluded.

Our study comes with some limitations. Firstly, while having a sample size of over 100 patients, the data is derived solely from a single center. Furthermore, due to the extended duration and retrospective nature of our investigation, it is expected that there would be variations in the treatment plan, resulting in heterogeneity. Numerous obstacles remain in determining the precise and personalized selection of patients appropriate for fertility preservation treatment [19]. Endometrial cancer research has seen significant advancements with the introduction of molecular typing in recent years. For this reason, it is reasonable to believe that more patients suitable for fertility preservation therapy can be screened through integrated molecular typing.

5. Conclusions

We conclude that progestin-based combination therapy could be beneficial for patients by accelerating the time to remission. Our study also examined the efficacy and safety of fertility preservation therapy for G2-EC patients, and for those patients, we propose that the utilization of combination therapy may yield superior results.

ABBREVIATIONS

EC, Endometrial carcinoma; PCOS, Polycystic ovary syndrome; AEH, Atypical endometrial hyperplasia; LNG-IUS, Levonorgestrel Intrauterine System; MPA, Medroxyprogesterone acetate; MA, Metoprogesterone acetate; GnRHa, Gonadotropin-releasing hormone analogue; CR, Complete response; NP, Natural pregnancy; ART, Assisted reproductive technology; EC-G1, Low differentiated endometrial carcinoma; EC-G2, Moderately differentiated endometrial carcinoma; CI, confidence interval; OR, odds ratio; IR, insulin resistance; DC, diagnostic curettage; CT, computed tomography; MRI; pelvic Magnetic Resonance Imaging; PR, partial response; SD, stable disease; PD, disease progression; R, Recurrence; SD, Standard Deviation.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

XQQ, HHF—Investigation and data collection; DXH, XYW—Project administration; XQQ—Writing–original draft; YMS, LLC, GWW, XYW—Writing–review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Research has been performed in accordance with the Declaration of Helsinki. Ethics approval has been granted for this project by the ethics committee of Women's Hospital, School of Medicine, Zhejiang University (Ethical approved number: IRB-20200024-R). Informed consent was not required as deemed by the ethics committee of Women's Hospital, given this was a retrospective review of medical records.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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