Retreatment with progestin for recurrence after complete response with fertility-sparing treatment in patients with endometrial cancer

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ABSTRACT

Objective To assess the outcomes of retreatment using progestin for recurrence after a complete response with fertility-sparing treatment in patients with early endometrial cancer.

Methods We retrospectively reviewed the data of patients with presumed stage IA, grade 1 endometrioid endometrial cancer who developed intra-uterine recurrence after a complete response with fertility-sparing treatment using progestin. Oncological and pregnancy outcomes were analyzed after repeated fertility-sparing treatment. Logistic and Cox regression analyses were performed to analyze the prognostic factors associated with a complete response with secondary fertility-sparing treatment and recurrence-free survival after secondary fertility-sparing treatment, respectively.

Results Fifty patients with a median age of 31 years (range 23–40) underwent secondary fertility-sparing treatment. With a median secondary progestin treatment duration of 9 months (range 3–55), the complete response rate was 78% (39/50) and no patients had extra-uterine spread of disease. Among the 26 (67%) patients who attempted to conceive after complete response, 10 became pregnant (3 spontaneous abortions, 7 live births). Eighteen (46.1%) patients had a second recurrence, with a median recurrence-free survival after secondary fertility-sparing treatment of 14 months (range 3–36); 15 patients received tertiary fertility-sparing treatment and nine (60%) achieved a complete response. Polycystic ovary on ultrasound (OR 5.82, 95% CI 1.1 to 30.6, p=0.037) was associated with an increased complete response rate with secondary fertility-sparing treatment. Multivariable analysis revealed that recurrence-free survival after initial hormonal treatment >6 months (HR 0.11, 95% CI 0.02 to 0.51, p=0.005) and pregnancy after secondary fertility-sparing treatment (HR 0.27, 95% CI 0.08 to 0.98; p=0.047) were significantly associated with longer recurrence-free survival after secondary fertility-sparing treatment.

Conclusions Repeated progestin treatment was associated with a 78% response rate and it was safe in patients with intra-uterine recurrent endometrial cancer. Thus, it might help preserve fertility after first and second recurrences.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited studies have assessed the oncological outcomes of retreatment with progestin for recurrence after complete response with fertility-sparing treatment in patients with endometrial cancer. This study aimed to evaluate the oncological and pregnancy outcomes of repeated fertility-sparing treatment using progestin in patients with first and second recurrent endometrial cancer.

WHAT THIS STUDY ADDS

⇒ Our results showed that repeated fertility-sparing treatment using progestin was effective and safe in patients with intra-uterine confined recurrent endometrial cancer, yielding a considerable live birth rate. Prolonged recurrence-free survival after hormonal retreatment was seen in the group with long-term recurrence-free survival after initial hormonal treatment and/or subsequent pregnancy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the rationale of hormonal retreatment in patients wishing to preserve fertility even after relapse.

INTRODUCTION

Endometrial cancer is one of the most commonly diagnosed cancers in women in developed countries.[1 2] It is the second most common gynecological cancer in South Korea, and its incidence has been increasing.[3 4] Endometrial cancer mainly occurs after menopause; however, 20–25% of women are diagnosed with endometrial cancer during their reproductive age.[5–7] Due to the recent delay in childbirth among women, >70% of young women aged <40 years are nulliparous at the time of diagnosis; therefore, increasing attempts have been made to preserve fertility.[8]

Fertility-sparing treatment using progestin has been selectively used in patients with grade 1 endometrioid endometrial cancer without myometrial invasion who strongly desire to preserve their fertility. The response rate to fertility-sparing treatment has been reported to be up to 85%; however, 9.5–40% of patients develop recurrence, with a median time to recurrence of 20 months (range 3–357) after achieving a complete response.[9–15] According to the current European Society of Gynecologic Oncology (ESGO) 2021 guidelines, fertility-sparing progestin retreatment can be

optional for intra-uterine recurrences only in highly selected cases under strict surveillance, although there is insufficient evidence regarding its efficacy (evidence level IV, recommendation grade C).[16]

In clinical practice, 63–73% of patients with relapse after initial fertility-sparing treatment prefer fertility-preserving treatment over surgery, including hysterectomy.[17 18] Thus far, limited studies have assessed the oncological outcomes of hormone retreatment in patients with recurrence. In addition, there are limited data on the predictive factors associated with response to secondary fertility-sparing treatment after recurrence and on the outcomes of tertiary fertility-sparing treatment for second recurrence. Therefore, this study aimed to evaluate the oncological and pregnancy outcomes of repeated fertility-sparing treatment using progestin in patients with first and second recurrent endometrial cancer after achieving a complete response with initial fertility-sparing treatment, and to identify the predictive factors associated with a response to secondary fertility-sparing treatment and recurrence-free survival.

METHODS

Study Design and Patients

We retrospectively reviewed the data of patients with presumed stage 1A, grade 1 endometrioid endometrial cancer who developed intra-uterine recurrence after achieving a complete response with initial fertility-sparing treatment using progestin at Konkuk University Hospital from August 2005 to December 2020. This retrospective study was approved by the Institutional Review Board of Konkuk University Hospital (KUH1040065). Stage IA was defined as a tumor confined to the corpus uteri with no myometrial invasion according to the 1988 International Federation of Obstetrics and Gynecology (FIGO) staging system.[19] Recurrent disease was defined as atypical hyperplasia, endometrial intra-epithelial neoplasia, or endometrial cancer on follow-up endometrial biopsy.

The following patients underwent repeated fertility-sparing treatment: (1) those with initial clinical stage I, grade 1 endometrioid endometrial cancer with no myometrium invasion and who developed a relapse after achieving a complete response with fertility-sparing treatment; (2) those with recurrent disease confined to the uterine endometrium; (3) those aged <45 years with a strong desire to preserve fertility; (4) those without suspicious or metastatic disease on imaging; and (5) those who agreed to the consent form that fertility-sparing treatment was not the standard treatment for a recurrent setting. Patients who did not wish to preserve their fertility and wanted surgical staging, including hysterectomy, were excluded.

Treatment and Follow-Up

Patients with recurrent tumors who wished to preserve their fertility were administered oral medroxyprogesterone acetate or megestrol acetate with and without a concurrent levonorgestrel intra-uterine device. Follow-up endometrial biopsy was performed under dilatation and curettage or hysteroscopy every 3 months. The pathological response to repeat progestin treatment was classified as follows. Complete response was defined as the absence of hyperplasia or carcinoma on pathological examination. Partial response was defined as pathological improvement such as from endometrial cancer to atypical hyperplasia or from atypical hyperplasia to simple hyperplasia without atypia. Stable disease was defined as a residual endometrial cancer lesion or atypical hyperplasia/endometrial intra-epithelial neoplasia. Progressive disease was defined as increasing in grade or clinically progressive disease, including myometrial invasion, extra-uterine disease, or lymph node metastasis. After achieving a complete response with progestin retreatment, patients who wished to conceive immediately attempted to conceive. Those not planning to immediately conceive were administered maintenance therapy of a levonorgestrel intra-uterine device. For complete responders, follow-up was scheduled every 3 months for transvaginal ultrasonography and gynecologic examinations. Among the patients who developed relapse after achieving a complete response with secondary fertility-sparing treatment, only those who wanted to preserve their fertility and agreed to consent were administered tertiary fertility-sparing treatment.

Statistical Analyses

The mean and median values were compared using the Student's t-test or the Mann–Whitney U test to evaluate the normality of the distribution of variables. The χ^2 test was used to compare the frequency distribution of categorical variables. Body mass index (BMI) was categorized as $\geq 25\,kg/m^2$ and $<25\,kg/m^2$ by applying the criteria of the Korean Society for Obesity.[20]

Oncological outcomes and pregnancy outcomes were evaluated. The time from the date of achieving a complete response with initial fertility-sparing treatment to the date of first recurrence was defined as recurrence-free survival after fertility-sparing treatment. The time from the date of achieving a complete response with secondary fertility-sparing treatment to the date of second recurrence or to the last observation was defined as recurrence-free survival after secondary fertility-sparing treatment.

Logistic regression analysis was performed to analyze the factors associated with a complete response with secondary fertility-sparing treatment. Survival curves were analyzed using the Kaplan–Meier method and statistical significance was assessed using the log-rank test. Cox regression analysis was performed to identify the factors associated with recurrence-free survival after secondary fertility-sparing treatment. Variables with p values <0.1 on univariate analysis and clinically significant factors were considered for inclusion in the multivariate logistic regression model. Statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS Statistics version 17.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Patient Characteristics

In total, 156 patients with grade 1 endometrioid endometrial cancer confined to the endometrium were administered initial fertility-sparing treatment using progestin; 112 (72%) patients concurrently used levonorgestrel intra-uterine devices, with a median treatment duration of 13 months (range 3–39). Of these, 131 (84%, 131/156) patients achieved a complete response with initial fertility-sparing treatment. After a complete response, 55 (42%) patients developed recurrence with a median recurrence-free survival (the time from the date of achieving complete response with initial fertility-sparing treatment to the date of first recurrence) of 26 months (range 3–141), and imaging studies to evaluate disease extent showed no

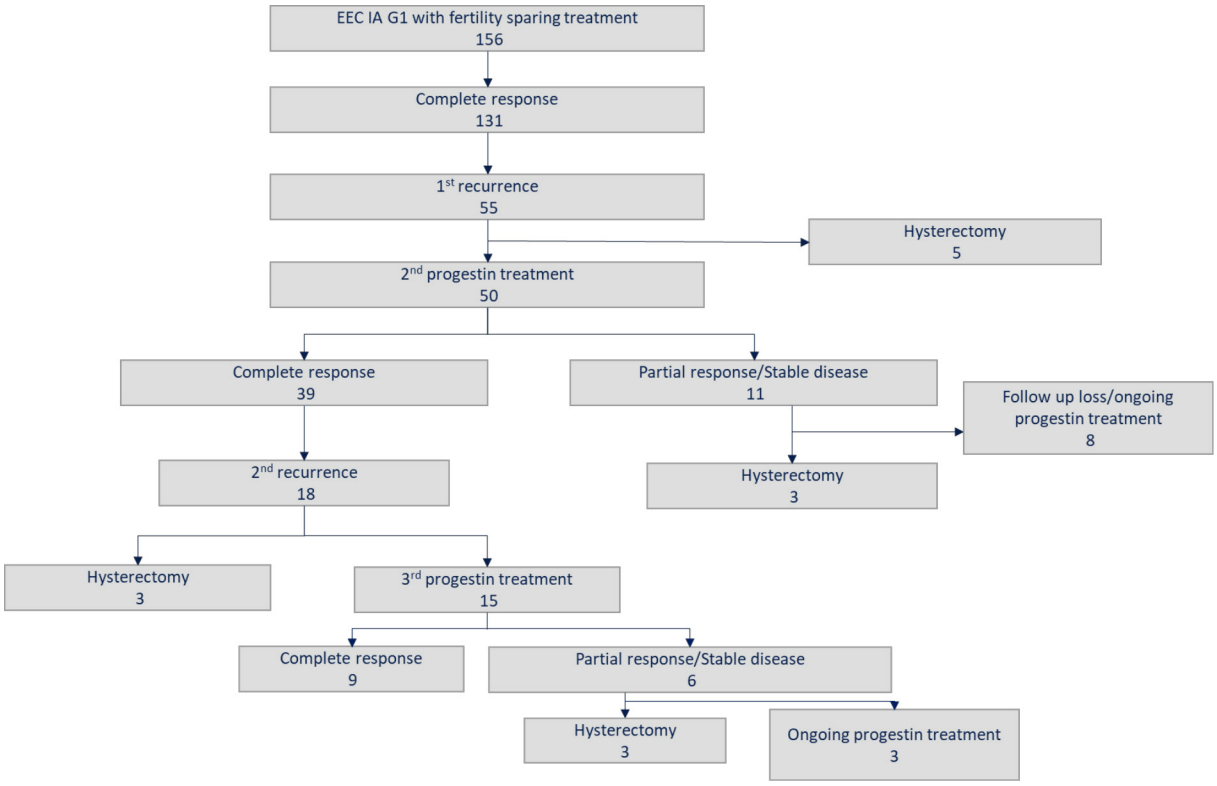

Figure 1 Flow chart of patients undergoing progestin retreatment.

extra-uterine recurrence. Five patients underwent definitive surgery immediately after recurrence (see Online Supplemental Table S1). Of these, two were diagnosed with stage 1A, grade 1 endometrial cancer, and the remainder had atypical hyperplasia/endometrial intra-epithelial neoplasia. In total, 50 patients underwent secondary fertility-sparing treatment (Figure 1).

Table 1 shows the basic characteristics of the 50 patients undergoing secondary fertility-sparing treatment. Eight had atypical hyperplasia/endometrial intra-epithelial neoplasia and 42 had endometrioid endometrial cancer at recurrence. Forty patients (80%) received medroxyprogesterone acetate and 10 (20%) received megestrol acetate, with a median secondary fertility-sparing treatment duration of 9 months (range 3–55); 33 (66%) patients concurrently used levonorgestrel intra-uterine devices with a median treatment duration of 8 months (range 3–24).

Oncological Outcomes to Secondary and Tertiary Fertility-Sparing Treatment and Subsequent Pregnancy Outcomes

The oncological outcomes of secondary and tertiary fertility-sparing treatment are shown in Table 2. The complete response rate with secondary fertility-sparing treatment was 78% (39/50), which was not significantly different between the endometrial cancer and atypical hyperplasia/endometrial intra-epithelial neoplasia groups (76.2% (32/42) vs 87.5% (7/8), p=0.43). There were no cases of progressive disease during secondary fertility-sparing treatment. Among the 11 patients who did not achieve a complete response with secondary treatment, three underwent hysterectomy. All patients who underwent surgery were diagnosed with stage 1A, grade 1 endometrial cancer limited to the endometrium (see Online Supplemental Table S1). The total median follow-up time for patients undergoing secondary fertility-sparing treatment was 43 months (range 3–141), with no deaths. Among the 26 patients who attempted to conceive after a complete response with secondary fertility-sparing treatment, 10 (38%) patients became pregnant, with three (30%) spontaneous abortions and seven (70%) live births (Table 2).

Eighteen patients (46.1%, 18/39) had a second recurrence, with a median recurrence-free survival after secondary fertility-sparing treatment (time from the date of achieving a complete response with secondary fertility-sparing treatment to the date of second recurrence) of 14 months (range 3–36). Imaging studies in all patients with a second recurrence showed no extra-uterine recurrence. All three patients who underwent hysterectomy (see Online Supplemental Table S1) were stage IA, grade 1 endometrial cancer, and none showed extra-uterine spread of disease. The remaining 15 patients (12 with endometrial cancer and 3 with atypical hyperplasia/endometrial intra-epithelial neoplasia) underwent tertiary fertility-sparing treatment. Nine (60%) patients achieved a complete response, with a median tertiary fertility-sparing treatment duration of 11 months (range 3–28). Online Supplemental Table S2 shows a summary of the results of tertiary fertility-sparing treatment in 15 patients. Nine patients who achieved a complete response survived without evidence of disease at the time of last contact, with a median follow-up duration of 37 months (range 5–123). Among the six patients who did not achieve a complete response, three were undergoing fertility-sparing treatment and three underwent hysterectomy (two with endometrial intra-epithelial neoplasia and one with grade 1 endometrial cancer without myometrium invasion). There were no cases of progressive disease during tertiary fertility-sparing treatment. Among the six patients who tried to conceive after a complete response with tertiary fertility-sparing treatment,

Table 1 Basic characteristics of patients with recurrence undergoing secondary fertility-sparing treatment (n=50)

Characteristics		
Age at diagnosis (years)	Median (range)	31 (23–40)
BMI (kg/m^2)	Median (range)	25.7 (18.0–46.3)
>25	n (%)	24 (48)
≤25	n (%)	26 (52)
Polycystic ovary on TV-US		
Yes	n (%)	25 (50)
No	n (%)	25 (50)
Time from initial FST to CR (months)	Median (range)	12 (3–35)
RFS (months)	Median (range)	26 (3–141)
Progestin type at secondary FST		
MPA	n (%)	40 (80)
500 mg/day	n (%)	27 (68)
1000 mg/day	n (%)	11 (28)
1500 mg/day	n (%)	2 (4)
MA	n (%)	10 (20)
40–80 mg/day	n (%)	2 (20)
160–320 mg/day	n (%)	8 (80)
Concurrent use of LNG-IUD during secondary FST		
Yes	n (%)	33 (66)
No	n (%)	17 (34)
Maintenance treatment after initial FST		
Yes	n (%)	14 (28)
No	n (%)	36 (72)
Pathology at recurrence		
AH/EIN	n (%)	8 (16)
EC	n (%)	42 (84)

AH, atypical hyperplasia; BMI, body mass index; CR, complete remission; EC, endometrial cancer; EIN, endometrial intra-epithelial neoplasia; FST, fertility-sparing treatment; LNG-IUD, levonorgestrel intra-uterine device; MA, megestrol acetate; MPA, medroxyprogesterone acetate; RFS, recurrence-free survival (time from achieved date of CR with initial fertility-sparing treatment to first recurrence date); TV-US, transvaginal ultrasonography.

four (66%, 4/6) became pregnant. All four pregnancies were full term.

Variables Predicting A Complete Response with Secondary Fertility-Sparing Treatment and Longer Recurrence-Free Survival

Table 3 shows the results of logistic regression analyses for predicting a complete response with secondary fertility-sparing treatment. Polycystic ovary on transvaginal ultrasonography (OR 5.82, 95% CI 1.1 to 30.6, p=0.037) was significantly associated with a complete response with secondary fertility-sparing treatment after univariate analysis. Table 4 shows the results of Cox proportional hazards regression analyses for recurrence-free survival after secondary fertility-sparing treatment. Recurrence-free survival after initial fertility-sparing treatment >6 months (HR 0.11, 95% CI 0.02 to 0.51, p=0.005) and pregnancy after secondary fertility-sparing treatment (HR 0.27, 95% CI 0.08 to 0.98, p=0.047) were significantly associated with longer recurrence-free survival after secondary fertility-sparing treatment according to multivariate analysis. Online Supplemental Figure S1 shows the recurrence-free survival after secondary fertility-sparing treatment of 39 patients according to recurrence-free survival and pregnancy. The median recurrence-free survival after secondary fertility-sparing treatment was 9 months (range 5–14) and 36 months (range 12–61) in the recurrence-free survival after initial fertility-sparing treatment ≤6 months and >6 months groups, respectively (p=0.002, log-rank test). The median recurrence-free survival after secondary fertility-sparing treatment was 18 months (range 5–30) and 36 months (range 22–49) in the non-pregnant and pregnant groups after secondary fertility-sparing treatment, respectively (p=0.061, log-rank test).

DISCUSSION

Summary of Main Results

In the present study the complete response rate with secondary fertility-sparing hormonal treatment was 78% in patients with intra-uterine recurrence after achieving a complete response with initial fertility-sparing treatment for early endometrial cancer. A considerable pregnancy rate (38%, 10/26) and live birth rate (70%, 7/10) were obtained for these responders. In addition, tertiary hormonal treatment for the second recurrence was effective (60%, 9/15). No patients undergoing fertility-sparing treatment showed extra-uterine spread of disease during progestin retreatment and follow-up. Therefore, progestin retreatment can be considered an option for young patients with intra-uterine recurrence who want to maintain fertility after relapse.

Results in the Context of Published Literature

Limited studies have assessed oncological outcomes of repeated hormone treatment in patients with endometrial cancer with relapse after fertility-sparing treatment (see Online supplemental table S3).[17 18 21–24] According to these studies, the complete response rate with secondary fertility-sparing treatment ranges from 76% to 98% for recurrent disease, and the complete response rate was 78% (39/50) after secondary fertility-sparing treatment in our study, consistent with the results of previous studies.[17 18 21–24] In a multicenter study,[17] six pregnancies, including all live births, were reported in five patients after achieving a complete response after recurrence. In our study we reported 10 pregnancies including seven live births after a secondary complete response. Moreover, there were no cases of progressive disease during secondary fertility-sparing treatment in our study. Thus, our findings support the recommendation of the current ESGO guidelines that allow repeated fertility-sparing treatment for patients with intra-uterine recurrence after initial fertility-sparing treatment.

Very limited information is available on the oncological outcomes of tertiary fertility-sparing treatment for second recurrence in

Table 2 Oncological and pregnancy outcomes of patients undergoing fertility-sparing treatment using progestin

Variables		Initial FST (n=156)	Secondary FST (n=50)	Tertiary FST (n=15)
Duration of FST, months	Median (range)	13 (3–36)	9 (3–55)	11 (3–28)
Time from each FST to CR, months	Median (range)	12 (3–36)	6 (3–52)	9 (3–19)
Response rate				
CR rate	n (%)	131 (84%)	39 (78%)	9 (60%)
PR/SD rate	n (%)	20 (13%)	11 (22%)	5 (33%)
PD rate	n (%)	5 (3%)	0	0
Recurrence after achieving CR				
Recurrence rate	n (%)	55 (42%)	18 (46%)	0
RFS, months	Median (range)	26 (3–141)	14 (3–36)	
Pregnancy rate				
Attempts to conceive	n (%)	80 (61%)	26 (66%)	6 (66%)
Total number of pregnancies	n (%)	31 (38%)	10 (38%)	4 (66%)
Live births	n (%)	30 (97%)	7 (70%)	4 (100%)
Abortions	n (%)	1 (3%)	3 (30%)	0

CR, complete response; FST, fertility-sparing treatment; PD, progressive disease; PR, partial response; RFS, recurrence-free survival; SD, stable disease.

patients with endometrial cancer (see Online supplemental table S3). Chen et al reported a complete response rate of 70% with tertiary fertility-sparing treatment in 10 patients with a second recurrence.[22] In another study,[24] two patients achieved a complete response (66%, 2/3) with tertiary fertility-sparing treatment. In our study, 15 patients with a second intra-uterine recurrence underwent tertiary fertility-sparing treatment. Among them, nine (60%) achieved a complete response resulting in four live births, and no patients showed extra-uterine spread of disease during follow-up. Despite limited evidence, it is suggested that fertility-sparing treatment plays a role in second or more recurrences. Further studies with a larger number of patients are needed.

Several studies have shown that the response rate is higher with combined oral progestin/levonorgestrel intra-uterine device than with single treatment during initial fertility-sparing treatment.[25 26] Kim et al reported an 87.5% complete response rate in 16 patients with early endometrial cancer using a combined oral progestin/levonorgestrel intra-uterine device.[25] In a prospective study, the complete response rate was 37.1% in 35 patients with combined oral progestin/levonorgestrel intra-uterine device at 6 months follow-up. Given the short treatment duration, the authors suggested that complete response rates may be much higher if treatment is continued for up to 9 or 12 months.[26] In our study, 66% (33/50) of patients received a combined oral progestin/levonorgestrel intra-uterine device for secondary fertility-sparing treatment at the discretion of the physician, expecting higher efficacy. However, concurrent use of levonorgestrel intra-uterine devices was not significantly associated with a complete response with secondary fertility-sparing treatment. The exact reason for this is unknown, but it may be due to the small sample size or secondary treatment rather than primary treatment. Future randomized trials are necessary to confirm this finding.

In the present study, polycystic ovary on transvaginal ultrasonography, which is a classic clinical feature of polycystic ovarian syndrome, was associated with a complete response with secondary fertility-sparing treatment. Polycystic ovarian syndrome is characterized by chronic anovulation and hyperandrogenism in reproductive age and is related to infertility, metabolic disorders, and endometrial cancer.[27] Similar to our study, a meta-analysis by Koskas et al[28] also found a higher response rate in the presence of infertility. Although the exact mechanism is unclear, one possible reason is that chronic anovulation in a polycystic ovary results in high estrogen levels and insufficient progesterone levels; these progestin-naïve conditions increase tissue compliance to progestin.[27] Further research is warranted in this area.

Long recurrence-free survival after initial fertility-sparing treatment appears to have a positive impact on the prognosis of patients with recurrent endometrial cancer. In the present study, patients who relapsed after 6 months of initial fertility-sparing treatment showed longer recurrence-free survival after secondary fertility-sparing treatment than those who relapsed within 6 months. Although we did not evaluate the expression of progesterone receptor (PR)/estrogen receptor (ER), PR expression has been positively correlated with response to progestin therapy and good prognosis.[29] In a previous study, the overall response in patients with PR-positive and PR-negative tumors was 37% and 8%, respectively.[30] In responders to progestin treatment it is believed that the effectiveness of first-line therapy also affects that of second-line therapy, depending on the downregulating nature of PR/ER. Therefore, patients who are expected to have a short recurrence-free survival after secondary fertility-sparing treatment should be followed up more carefully after achieving a complete response.

Pregnancy appears to prolong the disease-free period in patients with endometrial cancer after achieving a complete response with

Table 3 Univariate logistic regression analysis for predicting complete response achievement with secondary fertility-sparing treatment

Variables	Univariate analysis	
	OR (95% CI)	P values
Age at diagnosis (years)	1.14 (0.8 to 1.4)	0.297
BMI (kg/m^2)		
≤25	1.00	
>25	0.64 (0.2 to 2.5)	0.520
Pathology at recurrence		
EC	1.00	
AH/EIN	2.2 (0.2 to 20.0)	0.488
Polycystic ovary on TV-US		
No	1.00	
Yes	5.82 (1.1 to 30.6)	0.037
Progestin type at secondary FST		
MPA	1.00	
MA	1.77 (0.3 to 9.5)	0.507
Concurrent use of LNG-IUD during secondary FST		
No use	1.00	
Use	0.75 (0.2 to 3.3)	0.704
Time from the start of initial FST to CR		
≤6 months	1.00	
>6 months	0.60 (0.1 to 2.6)	0.497
RFS		
≤6 months	1.00	
>6 months	0.68 (0.1 to 6.5)	0.738

AH, atypical hyperplasia; BMI, body mass index; BMI, kg/m^2, Korean Society for the Study of Obesity: normal BMI 18.5–23; overweight 23–25; obesity >25; CR, complete response; EC, endometrial cancer; EIN, endometrial intra-epithelial neoplasia; FST, fertility-sparing treatment; LNG-IUD, levonorgestrel intra-uterine device; MA, megestrol acetate; MPA, medroxyprogesterone acetate; RFS, recurrence-free survival; TV-US, transvaginal ultrasonography.

fertility-sparing treatment. The mean disease-free survival in our previous study including 118 patients with early endometrioid endometrial cancer treated with fertility-sparing treatment was significantly longer in the pregnant group (26 months) than in the non-pregnant group (12 months).[31] These findings are similar to those reported by Fan et al, who reported relapse rates of 16.7% and 40.6% in the pregnant and non-pregnant groups, respectively.[32] This effect was also observed in cases of secondary fertility-sparing treatment. In our study, multivariate analysis showed that recurrence-free survival after secondary fertility-sparing treatment was significantly longer in the pregnant group than in the non-pregnant group. Pregnancy itself seems to lower the rate of endometrial cancer recurrence due to prolonged exposure to high levels of endogenous progesterone.[31] During delivery and postpartum, the decidua of the endometrium is totally evacuated. It is equivalent to curettage and has some therapeutic effect on endometrial lesions to prevent recurrence.[32] Therefore, it is thought that the disease-free survival is prolonged even in patients with relapse during pregnancy after achieving a complete response with secondary fertility-sparing treatment. It is therefore recommended to try to conceive immediately after achieving a complete response with secondary fertility-sparing treatment in recurrent cases.

Strengths and Weaknesses

This study is one of the largest studies focusing on progestin retreatment for recurrence after achieving a complete response with fertility-sparing treatment in endometrial cancer with a relatively long follow-up period. Thus, further analyses were performed to evaluate the prognostic variables and predictable variables for repeated fertility-sparing treatment. Moreover, treatment outcomes of tertiary fertility-sparing treatment for second recurrence and pregnancy outcomes were also reported.

However, this study has several limitations. First, it was a retrospective study conducted at a single center so the regimens and protocols may differ from those of other institutions. Moreover, the treatment of these patients may be very heterogeneous as patients received a large variety of oral and intra-uterine progestin combinations, and these have not been used with other medications such as metformin or aspirin. Second, not all recurrent cases were treated with repeated fertility-sparing treatment. Third, some patients (10%, 5/50) were lost to follow-up after initiation of retreatment, which might have affected our outcomes. Last, we could not evaluate the expression of ER and PR as well as the molecular classifications, which are prognostic factors for endometrial cancer.[29 33–35]

Implications for Practice and Future Research

This study provides the oncological and pregnancy outcomes of secondary and tertiary hormonal therapy in women with recurrent endometrioid endometrial cancer after fertility-sparing treatment, which support the rationale for hormonal retreatment of patients wishing to preserve fertility even after relapse. Furthermore, this study provides objective data by providing the results of analysis of factors related to achieving a complete response and recurrence.

CONCLUSIONS

Repeated fertility-sparing treatment using progestin was effective and safe in patients with intra-uterine confined recurrent endometrial cancer, yielding a considerable live birth rate. Prolonged recurrence-free survival after secondary fertility-sparing treatment was seen in the group with long-term recurrence-free survival after initial fertility-sparing treatment and/or subsequent pregnancy. Although the hormonal treatment response rate of the second recurrence seemed to be lower than that of the first recurrence, even in the case of failure there was no extra-uterine disease and was successfully salvaged. Therefore, it may provide an opportunity for young patients who want to preserve their fertility after the first and second recurrence under close surveillance. Future studies should focus on the role of tertiary or higher-line fertility-sparing treatment in second or more recurrences and on finding more effective treatment strategies, including immune checkpoint inhibitors,

Table 4 Univariate and multivariate Cox proportional hazards regression analysis for recurrence-free survival after secondary fertility-sparing treatment

Variables		Total (n=39)	Univariate analysis			Multivariate analysis		
			HR	95% CI	P values	HR	95% CI	P values
Age at diagnosis, years	Median (range)	32 (23–40)	0.97	0.88 to 1.07	0.548			
BMI, kg/m^2								
≤25	n (%)	22 (56)	1.00					
>25	n (%)	17 (44)	0.487	0.16 to 1.49	0.206			
Polycystic ovary on TV-US								
No	n (%)	17 (44)	1.00					
Yes	n (%)	22 (56)	1.44	0.54 to 3.85	0.470			
Progestin type at secondary FST								
MPA	n (%)	30 (77)	1.00					
MA	n (%)	9 (23)	0.77	0.27 to 2.20	0.630			
Concurrent use of LNG-IUD at secondary FST								
No use	n (%)	15 (38)	1.00					
Use	n (%)	24 (62)	1.24	0.47 to 3.27	0.670			
Time from start of secondary FST to CR, months								
≤6	n (%)	21 (54)	1.00					
>6	n (%)	18 (46)	1.14	0.44 to 2.96	0.786			
Maintenance treatment after secondary FST								
No	n (%)	29 (74)	1.00					
Yes	n (%)	10 (26)	1.208	0.43 to 3.39	0.720			
RFS, months								
≤6	n (%)	5 (13)	1.00			1.00		
>6	n (%)	34 (87)	0.15	0.04 to 0.61	0.008	0.11	0.02 to 0.51	0.005
Pathology at recurrence								
AH/EIN	n (%)	6 (15)	1.00					
EC	n (%)	33 (85)	1.57	0.36 to 6.87	0.552			
Pregnancy after secondary FST								
No	n (%)	29 (74)	1.00			1.00		
Yes	n (%)	10 (26)	0.32	0.09 to 1.12	0.075	0.27	0.08 to 0.98	0.047

AH, atypical hyperplasia; BMI, body mass index; CR, complete response; EC, endometrial cancer; EIN, endometrial intra-epithelial neoplasia; FST, fertility-sparing treatment; LNG-IUD, levonorgestrel intra-uterine device; MA, megestrol acetate; MPA, medroxyprogesterone acetate; RFS, recurrence-free survival; TV-US, transvaginal ultrasonography.

based on molecular classification and predictive biomarkers in non-responders.

Contributors AJL: Conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing - original draft, writing - review and editing. S-HS: Conceptualization, investigation, methodology, formal analysis, resources, supervision, visualization, writing - original draft, writing - review and editing. NRK: Investigation, validation, writing - review and editing. EJY: Investigation, validation, writing - review and editing. KAS: Investigation, validation, writing - review and editing. SJL: Validation, writing - review and editing. JYL: Validation, writing - review and editing. TJK: Validation, writing - review and editing. S-BK: Data curation, resources, writing - review and editing. S-HS acts as guarantor.

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