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Pregnancy and oncologic outcomes after fertility-sparing management for early stage endometrioid endometrial cancer

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HIGHLIGHTS

- Pregnancy after fertility-sparing management can be successful.
- Grade 2 endometrial cancer might be a poor prognostic factor of fertility outcomes.
- Pregnancy itself slows the recurrence of endometrial cancer after complete remission.

ABSTRACT

Objective Hormonal management is an alternative treatment for preserving fertility in patients with presumed early stage endometrioid endometrial cancer. This study aimed to define the pregnancy and oncologic outcomes and factors of successful conception after hormone therapy for endometrioid endometrial cancer.

Methods We retrospectively analyzed patients presumed to have stage IA, grade 1–2 endometrioid endometrial cancer who underwent fertility-sparing treatment. Concurrent medroxyprogesterone and levonorgestrel-release intra-uterine devices were used for treatment. The pregnancy outcomes and oncologic outcomes were compared between the pregnant and non-pregnant groups.

Results Seventy-one patients presumed to have stage IA, grade 1–2 endometrioid endometrial cancer had complete remission, and 49 of them tried to conceive. Twenty-two (44.9%) patients became pregnant; the total number of pregnancies was 30. These pregnancies resulted in seven abortions (23.3%), one pre-term birth (3.3%), and 20 full-term births (66.6%). The total live birth rate was 66.6 % (20/30). The median duration of hormonal treatment was 11.9 months (range 4–49) and 12.0 months (range 3–35) in the pregnant and non-pregnant groups, respectively. On multivariate analysis, age, body mass index, treatment duration, medroxyprogesterone dose, and number of dilatation and curettage biopsies were not significantly associated with pregnancy failure, but the association with grade (OR 6.2, 95% CI 1.0 to 38.9; P<0.05) was statistically significant. The median disease-free survival duration was 26 months (range 20–38) and 12 months (range 4–48) in the pregnant and non-pregnant groups, respectively (P<0.05, log-rank test).

Conclusions A lower grade might be a positive factor for future pregnancy. Moreover, successful pregnancy might be a factor in preventing recurrence.

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in the USA and Europe.[1 2] Its incidence in Korea is rising gradually.[3–5] Endometrial cancer is common in post-menopausal women, but its incidence has been gradually increasing in pre-menopausal women in recent years. Early detection is possible because symptoms such as vaginal bleeding are common in early endometrial cancer.[1 3 6 7] In this regard, fertility-sparing therapy in fertile women with early stage EC has recently been enforced.[8] The gold standard EC management is hysterectomy and bilateral salpingo-oophorectomy with or without pelvic/para-aortic lymph node dissection.[9] However, for younger patients with early stage endometrioid EC who want to preserve fertility, this operation would decrease their quality of life and remove any chance of pregnancy.

For these patients, fertility-sparing management with medroxyprogesterone acetate and levonorgestrel-release intra-uterine devices has been recommended in several studies.[10–16] Oral medroxyprogesterone acetate use and levonorgestrel-release intra-uterine device insertion can prevent progression of endometrial cancer and induce endometrial regression.[17] Patients were advised to try to conceive immediately after complete response following medroxyprogesterone acetate treatment if pregnancy was desired. Although there have been some reports of pregnancy outcomes in these patients, there has been little research into what factors are associated with successful pregnancies.[18–21] The aim of this study was to define the pregnancy outcomes and factors of successful conception after hormone therapy for endometrioid endometrial cancer. Moreover, the oncologic outcomes were compared between the pregnant and non-pregnant groups.

METHODS

We retrospectively analyzed patients with presumed stage IA, grade 1–2 endometrioid EC patients who underwent fertility-sparing treatment between

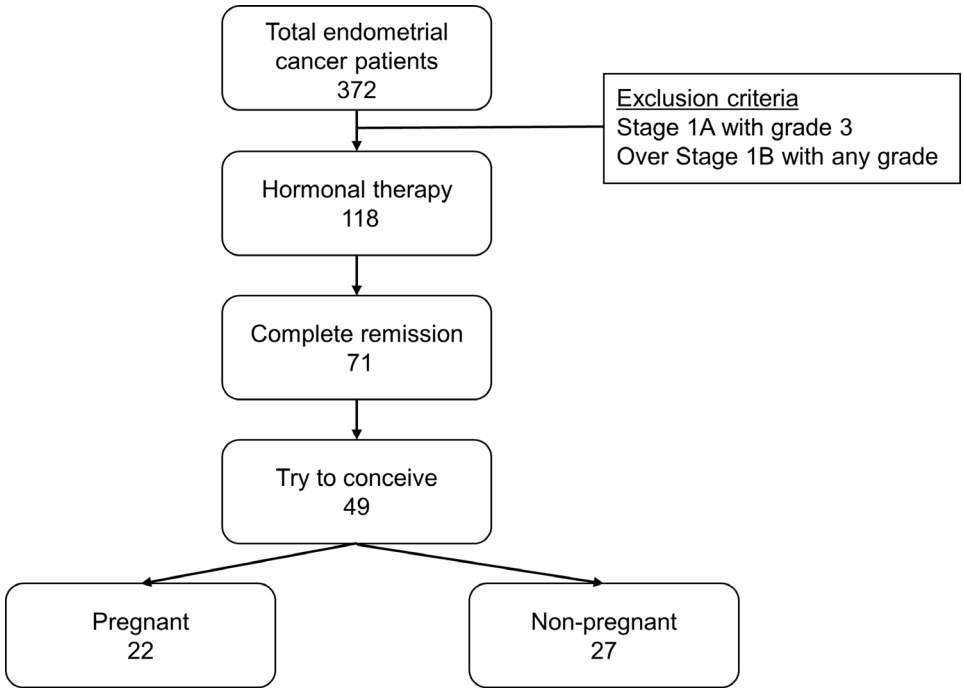

Figure 1 Outcome of patients with endometrial cancer after hormone treatment.

January 2005 and December 2017. Our institutional review board approved this study (KUH1040065).

Patients

Patients with endometrioid endometrial cancer were selected by pathologic confirmation with dilatation and curettage biopsy (D&C). Our gynecologic oncology pathologist reviewed all pathology slides, even those from outside hospitals. All patients underwent a full workup, such as abdominal-pelvis CT, abdominal-pelvis with liver coverage MRI, positron emission tomography-CTscan, mammography, cancer antigen (CA) 125, and other laboratory tests. After workup, patients who were presumed to have stage IA endometrioid endometrial cancer with grade 1 or 2 were included. Myometrial invasion was evaluated with MRI. Combination of T2-weighted imaging with contrast-enhanced T1-weighted imaging including dynamic contrast-enhanced MR imaging can provide appropriate information for the assessment of myometrial invasion.[22] Endometrial cancer was staged with the International Federation of Gynecology and Obstetrics (FIGO) system.[23] Hormonal therapy was used for those who wanted to preserve fertility and had presumed stage IA, grade 1 or 2 endometrioid endometrial cancer. Several studies are proposed to treat stage IA, grade 2 endometrioid endometrial cancer for fertility-sparing.[24–27] Patients with non-endometrioid histology or presumed stage IA, grade 3 or over stage IB endometrial cancer with any grade were excluded.

Management and Follow-up

Hormonal treatment was started with oral medroxyprogesterone acetate 500 mg once daily. In addition, levonorgestrel-release intra-uterine devices were inserted at the beginning of treatment. Follow-up for D&C was done every 3 months with transvaginal ultrasound and CA-125 tests.[28 29] Levonorgestrel-release intra-uterine devices were changed every 3 months after D&Cs. Complete remission was confirmed if carcinoma was absent on pathology. Persistent disease was defined as no regression within 6 months from the initial treatment. Progressive disease was defined as a FIGO stage or grade upgrade that occurred during follow-up. Increasing the medroxyprogesterone acetate dose to 1000 mg was considered if the patient had 6 to 9 months of persistent disease in follow-up D&Cs. Recurrence was diagnosed if carcinoma was observed on pathology after complete remission.[30] An anti-adhesive medication (poloxamer) was used in the endometrial cavity every time D&C was performed.[31 32] Treatment was stopped when two serial evaluations revealed no evidence of carcinoma on pathology. Hormone treatment and levonorgestrel-release intra-uterine device insertion were terminated if a patient with complete remission wanted to conceive. During fertility treatment or the conception trial period, follow-up was scheduled every 3 months for a general gynecologic examination and transvaginal ultrasound. Endometrial pathology was obtained if the patient had symptoms or abnormal examination results. Surgery was recommended after childbearing or when the patient did not want to get pregnant anymore. Patients with persistent disease for more than 12 months, progressive disease, or recurrent disease were strongly recommended to undergo surgery.

Statistical Analysis

The primary outcome was to compare the pregnant and non-pregnant groups in terms of all possible factors that might be associated with pregnancy success such as age, tumor grade, treatment duration, time of remission, progestin dose difference, number of D&Cs, and endometrial thickness on transvaginal ultrasound. The secondary outcome was to compare the pregnancy and oncologic outcomes between the two groups. Depending on the normality of the distribution of continuous variables, the Student's t-test or the Mann-Whitney U test was used to compare the mean values of the two groups. The χ^2 test was used to compare the frequency distribution of categorical variables. We performed univariate

Table 1 Basic characteristics of patients with early-stage endometrial cancer who were in remission and attempting to conceive

		Total (n=49)	Pregnant (n=22)	Non-pregnant (n=27)	P values
Age of initial treatment, years	Median (range)	37 (28–45)	37 (29–41)	37.0 (28–45)	0.68*
BMI, kg/m^2	Median (range)	22.7 (18.5–43.5)	22.0 (19.2–43.6)	23.5 (17.9–46.3)	0.26*
Parity	n (%)				0.16†
0		44 (89.8)	18 (81.8)	26 (96.3)	
1≤		5 (10.2)	4 (18.2)	1 (3.7)	
Presumed grade	n (%)				0.083†
G1		37 (75.5)	19 (90.5)	18 (66.7)	
G2		11 (22.4)	2 (9.5)	9 (33.3)	
PCO on ultrasonography	n (%)	33 (67.3)	15 (71.4)	18 (66.7)	0.72‡
Time of MPA treatment duration, months	Median (range)	12.2 (3–49)	11.9 (4–49)	12.0 (3–35)	0.93*
MPA dose					0.46‡
500 mg once daily	n (%)	33 (67.3)	17 (51.5)	16 (48.5)	
1000 mg once daily	n (%)	16 (32.7)	10 (62.5)	6 (37.5)	
Time to complete remission, months	Median (range)	6 (3–33)	6 (3–27)	9 (3–33)	0.32*
Initial CA 125	Median (range)	18 (3.9–58.9)	18.0 (11.4–58.9)	18.0 (3.9–55.7)	0.32*
CA 125 at the end of treatment	Median (range)	13.9 (1.2–30.1)	13.9 (1.2–30.1)	13.2 (6.3–29.7)	0.30*
Number of D&Cs	Median (range)	4 (2–7)	4 (2–7)	4 (2–7)	0.51*
Initial endometrium, mm	Median (range)	9.0	9.7 (4.4–18.0)	8.0 (3–18)	0.32*
Endometrium at the end of the treatment, mm	Median (range)	4 (2.3–10)	4.3 (2.3–7.0)	4.0 (2.5–10)	0.91*
Superficial myometrium invasion in MRI					0.67†
Yes	n (%)	6 (14.0)	4 (66.7)	2 (33.3%)	
No	n (%)	37 (86.0)	20 (54.1)	17 (45.9)	
Recurrence	n (%)	18 (36.7)	4 (18.2)	14 (51.9)	0.007†
Time of treatment end to recur, months	Median (range)	15.0 (4–48)	26.0 (20–38)	12.0 (4–48)	0.001§

*Mann-Whitney U test.
†Fisher's exact test.
‡χ^2 test.
§Log-rank test.
BMI, body mass index; CA, cancer antigen; D&C, dilatation and curettage; MPA, medroxyprogesterone acetate; PCO, polycystic ovary.

analyses to identify factors associated with pregnancy failure. Variables yielding values of P<0.1 by univariate analysis and clinically significant factors were considered for inclusion into a multivariate logistic regression model. The time from the end of treatment to recurrence or to the last observation was defined as disease-free survival. Survival curves were calculated using the Kaplan-Meier method, and statistical significance was assessed with the log-rank test. In this study, P<0.05 was considered significant. Statistical analysis was performed with the SPSS software package, version 17.0 (Chicago, IL, USA).

RESULTS

A total of 118 patients with presumed stage IA, grade 1–2 endometrioid endometrial cancer were treated with medroxyprogesterone acetate/levonorgestrel-release intra-uterine devices. Of these, 71 (60.17%) patients showed complete remission. Twenty-two of 71 patients in complete remission who did not try to conceive were not married or had no plan to conceive, and none of them received hysterectomy. They were maintained on an levonorgestrel-release intra-uterine device and followed-up every 3 months after complete remission following medroxyprogesterone acetate treatment. Of these 22 patients, five had recurrence and four underwent repeat medroxyprogesterone acetate therapy, with complete remission after re-treatment until the time of final analysis in this study. One patient did not return to our institution after recurrence was diagnosed. Forty-nine patients with complete remission tried to conceive after hormonal treatment. Among them, 22 patients became pregnant (Figure 1). The basic patient characteristics are listed in Table 1. The median age of the pregnancy success group was 37 years (range 29–41), and that of the non-pregnant group was 37 years (range 28–45). Grade 1 endometrial cancer was diagnosed in 19 (90.5%) and 18 (66.7%) patients in the pregnant and non-pregnant groups, respectively. The median time of remission in the pregnant and non-pregnant groups was 6 months (range 3–27) and 9 months (range 3–33) (P=0.32), respectively. The median duration of treatment was 11.9 months (range 4–49) and 12.0 months (range 3–35) in the pregnant and non-pregnant groups, respectively. In the pregnant and non-pregnant groups, 17 (51.5%) and 16 (48.5%) patients, respectively, took medroxyprogesterone acetate 500 mg once daily; 10 (62.5%) and six (37.5%)

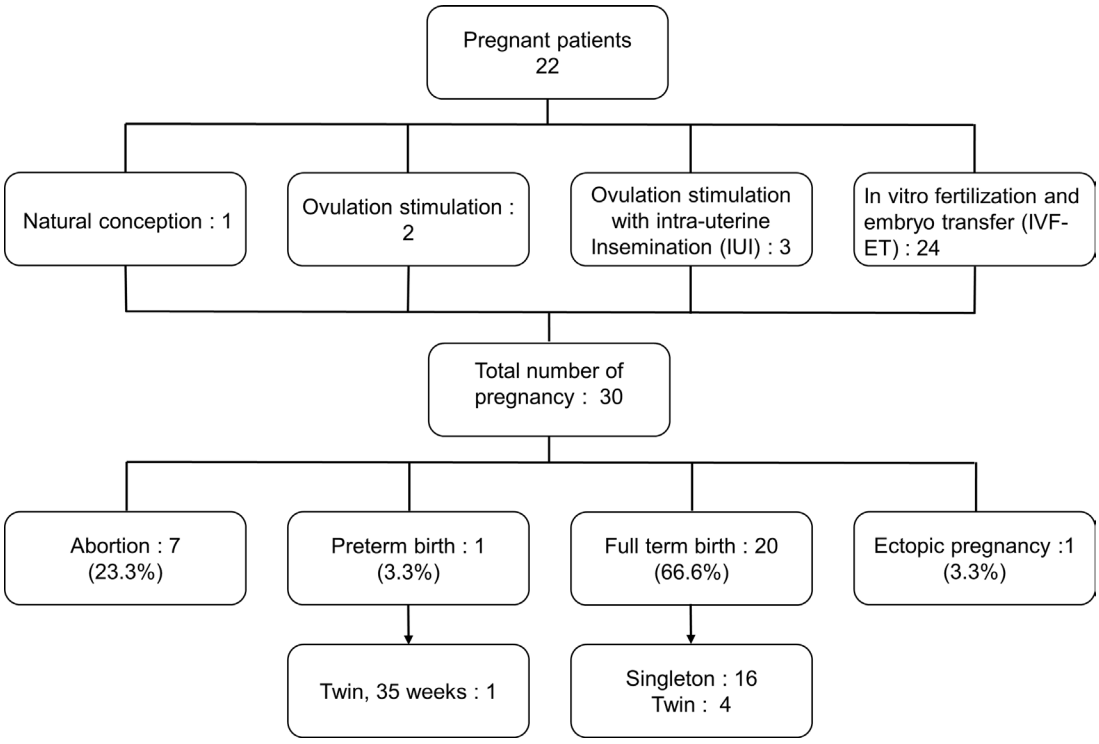

Figure 2 Pregnancy outcomes of 22 patients who successfully conceived. IUI, intra-uterine insemination; IVF-ET, invitro fertilization and embryo transfer.

patients, respectively, changed to 1000 mg (P=0.46). The median time from the end of treatment to successful pregnancy was 7.67 months (range 0–44), and the median time from the end of treatment to delivery was 17.17 months (range 10–54).

A total of 22 patients became pregnant, and there were a total of 30 pregnancies (Figure 2). One pregnancy was due to natural conception, two by ovulation stimulation, three by ovulation stimulation with intra-uterine insemination, and 24 by in vitro fertilization and embryo transfer. The outcomes of the 30 pregnancies included seven (23.3%) abortions, one (3.3%) preterm birth, 20 (66.6%) full-term births, and one (3.3%) ectopic pregnancy. The total number of live births was 25, including five twins. Incompetent internal os of cervix occurred in one case. An emergency cervical cerclage operation was performed at 21 weeks, followed by a full-term normal spontaneous delivery. Cesarean section was performed in eight cases, and vaginal delivery occurred in 12 cases.

All 27 non-pregnant patients who had undergone IVF-ET tried but failed to conceive after complete remission.

Table 2 shows the logistic regression analyses for predicting pregnancy failure after fertility-sparing hormonal therapy. Age (OR 1.05, 95% CI 0.9 to 1.2; P=0.47), body mass index (BMI) (OR 1.12, 95% CI 0.3 to 3.5; P=0.85), and polycystic ovary on ultrasound (OR 0.8, 95% CI 0.2 to 2.7; P=0.72) were not statistically significant. Moreover, treatment time (OR 0.83, 95% CI 0.26 to 2.6; P=0.75), complete remission time (OR 1.8, 95% CI 0.5 to 5.6; P=0.31), medroxyprogesterone acetate dose (OR 1.5, 95% CI 0.4 to 5.3; P=0.47), and number of D&Cs (OR 1.6, 95% CI 0.5 to 5.0; P=0.42) were not statistically significant. However, endometrial cancer histologic grade (OR 6.2, 95% CI 1.0 to 38.9; P<0.05) was statistically significant after multivariate analysis.

The total recurrence rate was 36.7% (18/49). The pregnant group had a recurrence rate of 18.2% (4/22), and the non-pregnant group had a recurrence rate of 51.9% (14/27) (P<0.05) (Table 1). In the pregnancy group, one had recurrence before pregnancy, and the other three had recurrence after delivery. The mean disease-free survival time was 26 months (range 20–38) and 12 months (range 4–48) in the pregnant and non-pregnant groups, respectively (P<0.05, log-rank test) (Figure 3). Table 3 describes the patients who had recurrence. Four patients in the pregnancy group had recurrence. One patient (No. 1 in Table 3) had recurrence before pregnancy. After her first complete remission, she tried invitro fertilization and embryo transfer for 16 months, but relapse was confirmed during the procedure. After achieving complete remission for 3 months, she successfully conceived 3 months after the end of the treatment. She delivered a full-term singleton by vaginal delivery. Another three patients experienced recurrence after delivery, and two of them underwent surgery because they no longer desired fertility. Fourteen patients failed to become pregnant and experienced recurrence. Four of them underwent surgery, one had progression of disease, and the others did not want to preserve fertility. All the patients with recurrence are alive. Six have persistent disease and are attempting re-treatment with hormonal therapy. A second recurrence occurred in two patients, and they are being re-treated with a third trial of hormonal therapy.

DISCUSSION

In this study, the pregnancy rate was considerably high. We found that tumor grade was related to successful pregnancy and that age, BMI, polycystic ovaries on ultrasonography, time to complete remission, duration of hormonal treatment, and number of D&Cs were not related. The oncologic outcomes showed that patients who

Table 2 Univariate and multivariate logistic regression analysis for predicting pregnancy failure after fertility-sparing hormonal treatment for early endometrial cancer

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P values	OR (95% CI)	P values
Age	1.05 (0.9 to 1.2)	0.47	1.05 (0.8 to 1.3)	0.69
BMI				
Normal to over weight	1			
Obesity	1.12 (0.3 to 3.5)	0.85		
Grade				
1	1			
2	4.75 (0.9 to 25.0)	0.06	6.2 (1.0 to 38.9)	<0.05
PCO in ultrasonography	0.8 (0.2 to 2.7)	0.72		
Operation history	0.98 (0.3 to 3.0)	0.97		
Medical history	0	0.99		
Initial CA 125	0.97 (0.9 to 1.0)	0.3		
Superficial myometrium invasion	0.76 (0.1 to 4.2)	0.75		
Endometrial mass size				
<1 cm	1			
>1 cm	0.8 (0.09 to 6.0)	0.77		
Treatment time				
≤9 months	1			
>9 months	0.83 (0.26 to 2.6)	0.75		
Remission months				
≤6 months	1			
>6 months	1.8 (0.5 to 5.6)	0.31		
MPA dose				
500 mg, once daily	1			
1000 mg, once daily	1.5 (0.4 to 5.3)	0.47		
Number of D&Cs				
≤3				
>3	1.6 (0.5 to 5.0)	0.42		
Initial endometrium thickness	0.9 (0.8 to 1.0)	0.31		
≤10 mm				
>10 mm	0.31 (0.07 to 1.2)	0.097	0.23 (0.4 to 1.0)	0.06
End of treatment endometrial thickness				
<4 mm				
≥4 mm	0.71 (0.2 to 2.2)	0.57		

BMI, kg/m^2 (Korean Society for the Study of Obesity: normal BMI 18.5–23; overweight 23–25; obesity >25).
BMI, body mass index; CA, cancer antigen; D&C, dilatation and curettage; MPA, medroxyprogesterone acetate; PCO, polycystic ovary.

achieved pregnancy had recurrence later than the patients who did not conceive.

There are very sparse data regarding the factors for successful pregnancy after fertility-preserving hormonal treatment in patients with early endometrioid endometrial cancer. Osamu et al compared the clinicopathological variables between a pregnancy group (n=45) and a non-pregnancy group (n=53) after medroxyprogesterone acetate treatment for well-differentiated endometrial cancer or atypical endometrial hyperplasia. They discussed pregnancy-related factors: recurrence before conception, endometrial thickness during ovulation, and the age at which pregnancy was attempted.[21]

In our study, tumor grade seemed to be an important factor. We think complete remission in patients with endometrial cancer endometrial status grade 2 is different from those with grade 1.[24] Complete remission in grade 1 endometrium is more responsive to progestin; that is, the normal shape of the endometrium recovers better. Although there is no precise mechanism explaining how the grade affects the pregnancy success, several researchers have suggested that the plasminogen activator inhibitor type 1 level is higher in grade 2/3 endometrial cancer than in grade 1 endometrial cancer.[33–35] Plasminogen activator inhibitor type 1 is an inhibitor of tissue plasminogen activators and urokinase plasminogen

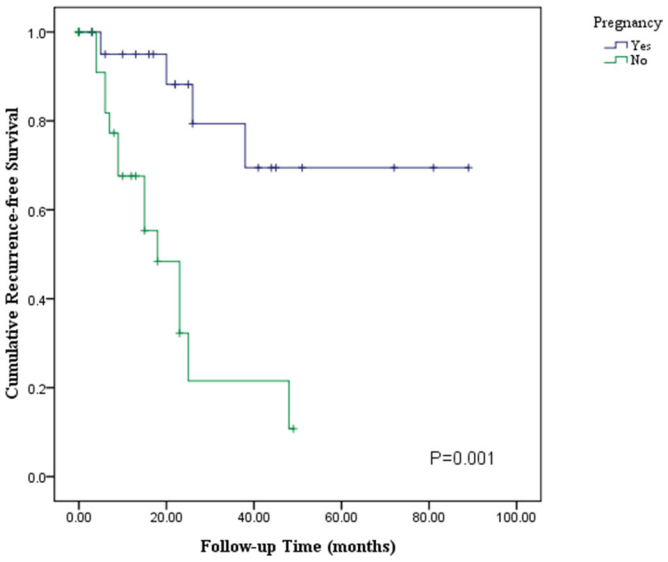

Figure 3 Recurrence-free survival of 49 patients with stage 1A, grade 1–2 endometrial cancer who had complete remission due to initial hormonal treatment according to pregnancy status.

activators that can inhibit the fibrinolytic system. The higher the PAI-1 level, the more likely it is to form thrombus. This is a known association with poor prognostic cancer characteristics. Its genetic mutation is associated with thrombophilia, which is related to infertility.[36] Because a higher grade of endometrial cancer has a higher PAI-1 level and has a higher probability of thrombus, pregnancy failure might be related to a higher grade because of the higher PAI-1 level.

The duration of hormonal treatment or complete remission was shown to have no effect on pregnancy. Therefore, if the duration of treatment is longer than expected, the physician can counsel the patient that pregnancy outcomes will not be significantly affected. However, if the patient has persistent disease without progression, there is still not a clear answer to how long we can continue the hormonal therapy. A recent study recommended extending the therapy for 9–12 months in this situation. A total duration of 3–36 months of progestin therapy has been reported in previous studies.[15 37]

Frequent D&C may adversely impact embryo placentation because of the destruction of the basal layer of the endometrium that can cause synechia and other inflammatory problems.[38] However, our study showed no difference in the number of D&Cs between the pregnant group (4, range 2–7) and the non-pregnant group (4, range 2–7; P=0.51). Even undergoing >3 D&Cs was not a barrier for pregnancy in univariate analysis. Kim et al suggested that D&C is more accurate than the office-based endometrial sample for response evaluation.[38] Clinicians may hesitate to perform D&C because frequent D&Cs may interfere with pregnancy. However, our result shows that frequent D&Cs do not affect pregnancy. These improved outcomes may reflect the use of anti-adhesive agents or a surgeon effect. The use of anti-adhesive material after D&Cs may be helpful in recovering the basal layer of the endometrium by reducing direct exposure of hematomas and fibroblasts in the early healing phase.[31 32 39] Using anti-adhesive materials might be a good technique to improve the chance of future pregnancy and might make it easier for the physician to perform D&C frequently if a patient has to undergo progestin treatment for a long time. The fact that the frequency of D&Cs does not affect future pregnancy allows physicians to choose D&Cs to evaluate the hormonal treatment response more accurately.

Age was not a significantly important factor in pregnancy success in this study. However, because of the small number of patients and because most patients were over 35 years old, this finding might not be meaningful. To confirm the association between age-related factors and pregnancy, we would have needed to test for ovarian function by testing the anti-müllerian hormone. Unfortunately, because this was a retrospective study, this test was not performed, so we could not compare ovarian function test results.

Pregnancy seemed to have a positive effect on the prognosis of endometrioid endometrial cancer. Park et al reported a recurrence rate of 20.5% (9/44) and 36.6% (26/71) in the pregnant and non-pregnant groups, respectively. The multivariate analysis also showed a significant improvement in recurrence-free survival (OR 0.25, 95% CI 95%, 0.11 to 0.56; P=0.001) in the pregnant group.[40] Similarly, the present study showed that recurrence in the pregnant group was lower than that in the non-pregnant group, and the time to recurrence was significantly longer in the pregnant group than in the non-pregnant group. Pregnancy itself provides prolonged exposure to endogenous progesterone, thus lowering the recurrence rate of endometrioid endometrial cancer.

Our institution had complete remission in 60% of patients after hormonal treatment, which is slightly higher than that in other reports. The complete response rate of hormonal treatment has been demonstrated in some studies to be about 53–55%.[15 41] However, unlike these studies, we performed concurrent treatment with medroxyprogesterone acetate and levonorgestrel-release intrauterine devices. Several studies demonstrate that the complete response rate is higher with dual treatment than with single treatment. Kim et al enrolled 16 patients with endometrioid endometrial cancer, and they were treated with combined oral medroxyprogesterone acetate and levonorgestrel-release intra-uterine devices. The overall complete remission rate was 87.5% (14/16), and the average time to complete remission was 9.8±8.9 months (range 3–35 months).[28] Hwang et al studied five patients with endometrioid endometrial cancer treated with combined oral medroxyprogesterone acetate and levonorgestrel-release intra-uterine devices, with a complete response in three out of five patients.[42] Thus, concurrent treatment might have a better response rate than single agent management. Future randomized trials are necessary to confirm this issue.

This study has several limitations. First, this study was performed in a single center with a relatively small number of patients. However, fertility-preserving treatment is limited by age, cancer stage, and patient desire, so it is difficult to include a large number of patients from a single institution. The outcomes of the present study should be interpreted with caution and should be confirmed by large-scale research in the future. Second, retrospective chart review was the main method of this study. Because data for some key statistics could not be measured, selection bias may have occurred. Moreover, there were several patients lost to follow-up after complete remission, possibly affecting our results. Third, we were not able to study the expression of estrogen and progesterone receptors. Studies have suggested that positive estrogen and progesterone

Table 3 Data on patients with recurrent endometrial cancer after fertility-sparing management

No.	Age	Grade	Time of first remission (months)	Pregnancy	DFS (months)	Time of second remission (months)	Re-treatment	Surgery	Reasons of surgery	Remission/ persistent/ progression	Second recur	Second DFS	Alive/ death	Follow-up
1	30	G1	6	Yes	16	6	Yes	No		Remission	No		Alive	2 years
2	35	G1	12	Yes	12	6	Yes	Yes	Do not want fertility preserving	Remission	No		Alive	6 months
3	33	G1	3	Yes	24	9	Yes			Remission	No		Alive	3 months Trying to conceive
4	30	G1	27	Yes	37		No	Yes	Do not want fertility preserving	Remission	No		Alive	3 years
5	28	G2	6	No	18	6	Yes	No		Persistent	Yes	10	Alive	3 months Refused surgery Re-treat
6	32	G1	9	No	6	12	Yes	No		Persistent	Yes	11	Alive	3 months Re-treat
7	33	G2	15	No	4	–	No	Yes	Do not want fertility preserving	Remission	No		Alive	2 years
8	33	G1	9	No	48	3	Yes	No		Remission	No		Alive	5 months Trying to conceive
9	36	G1	9	No	9	4	Yes	No		Persistent	No	3	Alive	3 months Re-treat 1000 mg
10	38	G2	12	No	4		Yes	Yes	Progression disease	Remission	No		Alive	Chemotherapy #6 (paclitaxel/ carboplatin) 3 years
11	32	G1	12	No	23		Yes	No		Persistent	No		Alive	5 years treatment underway Refused surgery
12	31	G1	3	No	23	55	Yes	No		Remission	No		Alive	2 years
13	38	G1	3	No	6	6	Yes	No		Remission	No		Alive	6 months Trying to conceive
14	33	G1	9	No	7	10	Yes	No		Persistent	No		Alive	1 year treatment underway Refused surgery
15	31	G1	3	No	25	48	Yes	No		Remission	No		Alive	Trying to conceive and f/u loss
16	33	G1	33	No	15		No	Yes	Do not want fertility preserving	Remission	No		Alive	3 years
17	35	G1	12	No	15		No	Yes	Do not want fertility preserving	Remission	No		Alive	3 years
18	31	G1	6	No	9		Yes	No		Persistent	No		Alive	7 months treatment underway

DFS, disease free survival.

receptors are related to endometrial cancer prognosis.[43 44] One more limitation is that the grade reported through D&Cs does not completely reflect the grade after hysterectomy. Wang et al reported that the concordance of grade between D&C and hysterectomy was 35.2% (62/176), tumor grade after office based biopsy was upgraded 26% after hysterectomy, and D&Cs were upgraded by 10%.[45] In this study, 12.2% (6/49) of patients underwent hysterectomy after fertility sparing treatment. Five of six patients were presumed stage IA with grade 1 and the final stage was stage IA with grade 1 after hysterectomy. One patient out of six, who had presumed stage IA, grade 2 disease, experienced relapse 3 months after complete remission. After imaging work-up, ovarian metastasis could not be ruled out, and staging surgery was immediately performed. The final stage was IIIC1, grade 2, and six cycles of adjuvant chemotherapy (paclitaxel + carboplatin) were given. She has remained alive without disease for 3 years (briefly described in Table 3, No. 10). Of 118 patients in this study who received hormonal therapy to preserve fertility, 29 underwent hysterectomy after medroxyprogesterone acetate treatment, and the tumor grade was upgraded in 10.3% (3/29) after the final pathologic report. The number of patients who underwent hysterectomy was too small to be statistically compared.

In conclusion, the success rate of pregnancy after hormonal therapy in patients with early endometrioid EC was satisfactory. A higher EC grade was an independent factor associated with pregnancy failure. Moreover, the pregnancy success group had better oncological outcomes than the pregnancy failure group. A prospective study with a large cohort is needed to confirm our findings in the future.

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