ORIGINAL ARTICLE

Prognostic factors of oncologic outcomes after fertility-preservative management with progestin in early-stage of endometrial cancer

Hyun Jin Roh[1]*, Hyung Joon Yoon[2]*, Dae Hoon Jeong[3], Tae Hwa Lee[4], Byung Su Kwon[2], Dong Soo Suh[2], Ki Hyung Kim[2]

[1]Department of Obstetrics and Gynecology, Ulsan University Hospital, Ulsan University College of Medicine, Ulsan, South Korea, [2]Department of Obstetrics and Gynecology, Pusan National University School of Medicine, and Biomedical Research Institute and Pusan Cancer Center, Pusan National University Hospital, Busan, South Korea, [3]Department of Obstetrics and Gynecology, Busan Paik Hospital, Inje University, Busan, South Korea, [4]Department of Obstetrics and Gynecology, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, South Korea

*Hyun Jin Roh and Hyung Joon Yoon contributed equally to this article

Background: The aim of this study was to evaluate efficacy of various fertility-preservative treatments with progestin and analyze prognostic factors in Stage 1A of endometrial cancer. **Materials and Methods:** This retrospective study involved four Korean university hospitals. Data were collected from 43 women who were under the age of 40 with presumed stage IA endometrial cancer determined by magnetic resonance imaging and treated from January 2014 to December 2017. All of the patients were administered hormonal therapy for fertility preservation. Twenty-five patients received oral progestin with a levonorgestrel-releasing intrauterine system (LNG-IUS) for 6–24 months, and 18 patients received high-dose oral progestin for the same period of time. Oncologic outcomes were evaluated. Prognostic factors for pathologic response to progestin were identified by logistic regression analysis. **Results:** Complete response (CR) was achieved by 72.1% of patients (31/43), and the average time to CR was 4.2 (Stable disease [SD] 3.4) months (range, 3–9 months). Partial response was achieved by 7.0% of patients (3/43), SD by 9.3% (4/43), and progressive disease by 11.6% (5/43). Of the CR patients, 41.9% (13/31) achieved pregnancy with the median follow-up period of 12.5 (SD 7.6) months (range: 3–50 months). No irreversible toxicity or therapy-associated death occurred. Multivariate analysis showed that high endometrial thickness ratio of pre- and posttreatment measured at 2 months from the treatment initiation (≥0.55, Odds ratio [OR]: 19.018; 95% confidence intervals (CI): 1.854–195.078; $P = 0.013$) and oral progestin without LNG-IUS (OR: 13.483; 95% CI: 1.356–134.069; $P = 0.026$) might be related with unfavorable prognostic factors for CR. **Conclusion:** This study shows that progestin-based fertility-preservative treatment might be a feasible option for stage 1A endometrial cancer. It also identifies that low endometrial thickness ratio and oral progestin with LNG-IUS combination therapy might be related with favorable response to hormonal treatment.

Key words: Early endometrial cancer, fertility preservation, progestin, prognostic factor, response rate

How to cite this article: Roh HJ, Yoon HJ, Jeong DH, Lee TH, Kwon BS, Suh DS, *et al*. Prognostic factors of oncologic outcomes after fertility-preservative management with progestin in early-stage of endometrial cancer. J Res Med Sci 2021;26:48.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in developed countries, and globally, the sixth most common female malignancy with an estimated 382,069 new cases and 89,929 deaths in 2018.[1] In South Korea, endometrial cancer is the third most common gynecologic malignancy, and there were an estimated 2,404 new cases and 319 deaths in 2015.[2] Although it is primarily a disease found in postmenopausal females, 4%-14% of the patients are <40 years old,[3] and recently, the incidence of endometrial cancer has increased in younger women due to the adoption of a western lifestyle, delayed childbearing, obesity, polycystic ovarian syndrome (PCOS), diabetes, dysfunctional uterine

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_103_20

Address for correspondence: Dr. Dong Soo Suh, Department of Obstetrics and Gynecology, Pusan National University School of Medicine, 179, Gudeok-Ro, Seo-Gu, Busan 49241, South Korea.
E-mail: dssuh@pusan.ac.kr

Submitted: 29-Jan-2020; **Revised:** 10-May-2020; **Accepted:** 23-Oct-2020; **Published:** 31-Jul-2021

bleeding with anovulation, and hypermenorrhea, and such incidence has been frequently related with endometrial hyperplasia and infertility.[4]

The standard surgical treatment for early-stage endometrial cancer has been either hysterectomy with lymph node dissection or primary radiotherapy, but fertility-sparing treatment with progestin might be applied after clinical staging and medical workups.[4] The 5-year survival rate of stage IA endometrial cancer currently exceeds 90%. Fertility-sparing progestin treatment is the preferred option for the treatment of early-stage endometrial cancer in young women; it has been demonstrated to have a better response rate and moderate pregnancy rate, and it also does not compromise progression-free survival (PFS) or overall survival (OS) of the disease.[4,5] However, there is a limited amount of reports for fertility-preservative treatment with hormonal therapy in early-stage endometrial cancer, and there is no prognostic factor to predict the response rate of hormonal therapy.

Therefore, the aim of this study was to evaluate efficacy of hormonal therapy for fertility preservation and analyze prognostic factors in Stage 1A endometrial cancer.

MATERIALS AND METHODS

Study design

Our study is a retrospective study which involved four Korean university hospitals. From January 2014 to December 2017, we selected women under the age of 40 years with presumed stage IA endometrial cancer determined by magnetic resonance imaging (MRI). Among them, we selected women who underwent hormonal therapy. A total of 43 women were selected, and we evaluated their oncologic outcomes by using mean value and standard deviation, and then, we identified prognostic factors of oncologic outcomes after fertility-preservative management in stage 1A endometrial cancer through logistic regression analysis.

Patients

Four university hospitals belonging to the Pusan-Inje-Koshin Study Group participated in this study. Forty-three patients who received fertility-preservative progestin treatment between January 2014 and December 2017 were included. A comprehensive pretreatment evaluation including dilatation and curettage (D and C), pelvic ultrasound, or pelvic MRI was performed. Patients with histologically confirmed endometrial cancer grade 1 or 2 of presumed stage IA determined by MRI were included. The study protocol was reviewed and approved by the Institutional Review Board of Pusan National University Hospital and by also those of the other three participating centers.

General clinicopathological characteristics and treatment

Patients' clinicopathological data obtained from their surgical, clinical, and medical records were reviewed and analyzed, including the clinical variables such as treatment method, histopathology, complications, body mass index, age, and medication history.

Twenty-five patients received oral progestin, mainly megestrol acetate (MA; 40–320 mg/day) or medroxyprogesterone acetate (MPA; 10–400 mg/day), with levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena; Bayer Schering Pharma Oy, Turku, Finland) for 6–24 months. Eighteen patients received high-dose oral progestin only for the same period. When the patient wanted to conceive, fertility treatment was started with no residual lesion evident on two consecutive D and Cs.

Evaluation of response and follow-up

After starting treatments, responses were assessed by three monthly D and C or hysteroscopic endometrial resections after patient counseling. Two months after treatment commencement, endometrial thickness was evaluated by transvaginal ultrasonography (TVUS). Pathologic response to progestin treatment was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR was defined as the absence of hyperplasia or cancerous lesions as a result of two consecutive D and Cs every 3 months; PR as a residual lesion with hyperplasia; SD as a residual cancer lesion; and PD as the presence of a higher grade lesion.

CR rate, adverse effects, OS, PFS, pregnancy rate, and recurrence rate were evaluated. During the follow-up period, progestin treatment was stopped after counseling for nonresponders, and hysterectomy was recommended. Adverse effects were evaluated using National Cancer Institute Common Toxicity Criteria version 2. Clinical follow-up was performed for 5 years from treatment commencement.

Statistical analysis

Variables were evaluated for clinical significance using the mean and standard deviation. Odds ratios (ORs) and their associated 95% confidence intervals (CIs) were used to analyze response rates (RRs) and clinicopathological predictors for pathologic response to progestin, and they were identified by logistic regression analysis. In the univariate analysis, we set confounders known as factors that increase the incidence of endometrial cancer including age, histologic grade, BMI, PCOS, metformin, diabetic mellitus (DM), and hypertension (HTN). We set predictors, which we expected to affect the prognosis of the disease, including the endometrial thickness before treatment, endometrial thickness after the treatment, according to

endometrial thickness ratio of pre -and posttreatment, and progestin combination therapy (progestin with LNG-IUS). The cut pointing value of each factor was set as the mean value of the samples. In multivariate analysis, the confounding factors were histological grade, endometrial thickness ratio, and progestin combination therapy, which were statistically significant in univariate analysis. The primary outcome was defined as not reaching the CR. The analysis was performed using IBM SPSS Statistics, version 25.0, (IBM SPSS Statistics, Armonk, New York, USA). All statistical tests were two sided, and statistical significance was accepted for $P < 0.05$. There were no missing data of the patients.

RESULTS

General patient characteristics

A total of 43 patients were enrolled in this study. Eighteen (41.9%) women received oral progestin alone and 25 (58.1%) women received oral progestin plus LNG-IUS. All 43 study subjects were nulligravida with a mean age of 32.1 (SD 4.9) years (range: 19–40) and mean BMI: 27.2 (SD: 6.4) kg/m^2 (range, 14.8–39.0). Twenty of the study subjects (46.5%) satisfied PCOS criteria and six (13.9%) had a history of metformin medication due to PCOS or DM [Table 1].

Table 1: General patient characteristics (*n*=43)

Characteristics	Total
Age (year), means (SD)	32.1 (4.9)
Histologic grade, *n* (%)	
1	36 (83.7)
2	7 (16.3)
BMI (kg/m^2), means (SD)	27.2 (6.4)
Comorbidity, *n* (%)	
PCOS	20 (46.5)
Metformin	6 (13.9)
DM	4 (9.3)
HTN	3 (6.9)
EM thickness (mm), means (SD)	6 (11.1)
Pretreatment	15.5 (5.5)
2 months after treatment	7.3 (5.1)
Endometrial thickness ratio (treatment/pretreatment)	0.52 (0.4)
Treatment, *n* (%)	
Oral progestin	18 (41.9)
Oral progestin+LNG-IUS	25 (58.1)

SD=Standard deviation; BMI=Body mass index; PCOS=Polycystic ovary syndrome; DM=Diabetes mellitus; HTN=Hypertension; EM=Endometrium; LNG-IUS=Levonorgestrel-releasing intrauterine system

Treatment outcomes

CR was achieved in 72.1% (31/43), and the average time to CR was 5.6 (SD: 2.7) months (range: 3–12 months). PR was achieved by 7.0% (3/43), SD by 9.3% (4/43), and PD by 11.6% (5/43) [Table 2]. The average follow-up was 22.5 (SD: 7.6) months (range: 6–36 months). Eighteen patients who received oral progestin therapy only recorded a 44.4% (8/18) CR rate and 25 patients who received oral progestin with LNG-IUS combination therapy recorded 92% (23/25) CR rate, respectively [Table 3].

Table 2: Oncologic outcomes after fertility-sparing treatment (*n*=43)

Outcome	Number of patients
Treatment response, *n* (%)	
CR	31 (72.1)
PR	3 (7.0)
SD	4 (9.3)
PD	5 (11.6)
Time to CR* (months), mean (SD)	5.6 (2.7)
Recurrence*, *n* (%)	9 (20.9)
Time to recurrence† (months), mean (SD)	12.5 (8.4)
Hysterectomy, *n* (%)	18 (41.9)

*Thirty-one patients achieve CR; †Seven patients recurred after achieving CR. CR=Complete response; SD=Standard deviation; PR=Partial response; SD=Stable disease; PD=Progressive disease

Adverse effects – Related risk factors

No significant adverse effect occurred during progestin treatment. The most common adverse effect was increased body weight (9.3%, 4/43), and this was followed by nausea and dyspepsia (7.0%, 3/43), headache (4.7%, 2/43), and breast pain (4.7%, 2/43). However, these adverse effects did not result in medication discontinuation, and there was no treatment-related death. There were no side effects of LNG-IUS such as uterine perforation, pelvic pain, or irregular bleeding which could be improved after 6 months of LNG-IUS use (data not shown).

Pregnancy outcomes and related risk factors

Of the 31 patients who achieved CR, 17 patients desired to conceive immediately. The spontaneous pregnancy rate was 23.5% (4/17) and the pregnancy rate with infertility treatment such as assisted reproductive technology (ART) was 52.9% (9/17). Six of the 17 (35.3%) pregnancies resulted in full-term deliveries and six were preterm deliveries (35.3% [6/17]). One resulted in spontaneous abortion (5.9% [1/17]). No remarkable maternal-fetal complication or anomaly was encountered [Table 4].

Prognostic factors for treatment response with progestin

Univariate analysis adjusted for clinicopathologic prognostic factors including age, histologic grade, BMI, PCOS, metformin, DM, HTN, endometrial thickness before treatment, endometrial thickness after 2 months of progestin treatment, according to endometrial thickness ratio of pre-and posttreatment, and treatment method (oral progestin with or without LNG IUS) showed that histologic grade (II) (OR: 7.43; 95% CI: 1.12–49.24; $P = 0.038$), endometrial thickness after treatment (≥7 mm) (OR: 8.00; 95% CI: 1.65–38.79; $P = 0.010$), endometrial thickness ratio

Table 3: Oncologic outcomes after oral progestin only/ oral progestin+levonorgestrel-releasing intrauterine system (*n*=43)

Outcome	Number of patients
Oral progestin only	18
Treatment response, *n* (%)	
CR	8 (44.4)
PR	1 (5.6)
SD	4 (22.2)
PD	5 (27.8)
Oral progestin+LNG-IUS	25
Treatment response, *n* (%)	
CR	23 (92)
PR	2 (8)
SD	0
PD	0

LNG-IUS=Levonorgestrel-releasing intrauterine system; CR=Complete response; PR=Partial response; SD=Stable disease; PD=Progressive disease

Table 4: Pregnancy outcomes after fertility-sparing treatment (*n*=17)

Outcome	Number of patients
Clinical pregnancy, *n* (%)	
Spontaneous	4 (23.5)
ART	9 (52.9)
Pregnancy outcome, *n* (%)	
Full-term delivery	6 (35.3)
Preterm delivery	6 (35.3)
Spontaneous abortion	1 (5.9)

ART=Assisted reproductive technology

after 2 months of progestin treatment (≥0.55) (OR: 10.50; 95% CI: 2.08–53.14; $P = 0.004$), and treatment method oral progestin without LNG-IUS (OR: 8.00; 95% CI: 1.65–38.79; $P = 0.010$) were unfavorable prognostic factors for CR. In addition, multivariate analysis adjusted for statistically significant prognostic factors ($P < 0.05$) in the univariate analysis including histologic grade, endometrial thickness ratio of pre- and posttreatment, and treatment method (oral progestin with or without LNG IUS) showed that high endometrial thickness ratio (≥0.55) (OR: 19.018; 95% CI: 1.854–195.078; $P = 0.013$) and oral progestin without LNG-IUS (OR: 13.483; 95% CI: 1.356–134.069; $P = 0.026$) might be related with an unfavorable response to progestin treatment [Table 5].

DISCUSSION

In the current study, we investigated the efficacy of hormonal treatment in early endometrial cancer and prognostic factors in patients with early-stage endometrial cancer who requested fertility-preservative progestin treatment. We showed that CR rate of 72.1% and PR rate of 7% were reached after hormonal therapy. In terms of treatment modality, oral progestin therapy alone achieved a CR rate of 44.4% and oral progestin with LNG-IUS combination therapy achieved a CR rate of 92%; the combination therapy was found to be more efficient. In addition, multivariate analysis showed that the combination therapy might be related with a favorable response to hormonal treatment. In multivariate analysis, low endometrial thickness ratio, measured before and after hormonal treatment, was also associated with a favorable response to hormonal treatment.

Since the early 1980s, several reports were issued on conservative progestin-based treatment for early-stage endometrial cancer in young women.[4,5] According to published studies, oral progestin has been the most frequent type of fertility-preservative treatment in early-stage endometrial cancer.[6] Recent review articles and related studies have reported the mean CR rate ranging from 66.7% to 79.7%.[7,8] It is the treatment that has been proven to be somewhat effective and thus has been widely used. In addition, in a recent study, the effectiveness of combination therapy using oral progestin with LNG-IUS in patients with early-stage endometrial cancer has been reported. In a Korean study on the effect of combined hormone therapy using oral progestin with LNG-IUS in patients with early endometrial cancer who desired fertility preservation,[9] the CR rate was 87.5%, and this was achieved approximately 9.8 months after the treatment initiation. Unfortunately, in the present study, oral progestin (MA: 40–320 mg/day) therapy alone had a 44.4% CR rate, which was lower than the response rate reported in other studies. Yet, oral progestin (MPA: 100–500 mg/day) with LNG-IUS had a 92% CR rate, higher than that of other studies. Therefore, when considering hormone-based fertility preservation treatment, it would be safe to prefer combination therapy to oral progestin therapy alone.

The results of a recent meta-analysis have reported that patients who received hysteroscopic endometrial resection followed by hormone therapy achieved the highest CR rate.[10] In our study, of the patients receiving combined therapy using oral progestin with LNG-IUS, four patients received combined hormone therapy after hysteroscopic endometrial resection and their CR rate achieved 100%. We identified that the combination of hysteroscopic endometrial resection and hormonal therapy was the most effective in spite of the small number of patients. We suggest that hormonal treatment after hysteroscopic endometrial resection seems to be the most effective as a fertility-preservative treatment in early-stage endometrial cancer; still, further studies are warranted.

In terms of fertility outcome, pregnancy with a good oncologic outcome is an ultimate goal of fertility-sparing treatment in oncologic patients. According to one Korean study,[11] 70 patients had attempted to conceive, with 44 receiving treatments for infertility including ovarian

Table 5: Unfavorable prognostic factors for complete response (*n*=43)

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (year)						
<32	1 (references)	-				
≥32	0.970	0.228-4.151	0.970			
Histologic grade						
I	1 (references)	-		1 (references)	-	
II	7.429	1.121-49.244	**0.038**	4.446	0.405-48.785	0.222
BMI (kg/m^2)						
<27.5	1 (references)	-				
≥27.5	1.600	0.393-6.509	0.511			
PCOS						
No	1 (references)	-				
Yes	0.962	0.237-3.899	0.956			
Metformin						
No	1 (references)	-				
Yes	1.852	0.265-12.947	0.535			
DM						
No	1 (references)	-				
Yes	1.852	0.265-12.947	0.535			
HTN						
No	1 (references)	-				
Yes	2.700	0.154-47.392	0.497			
EM thickness before treatment (mm)						
<15	1 (references)	-				
≥1	1.429	0.326-6.257	0.636			
EM thickness after treatment (mm)						
<7	1 (references)	-				
≥7	8.000	1.650-38.790	**0.010**			
EM ratio (after treatment/before treatment)						
<0.55	1 (references)	-		1 (references)	-	
≥0.55	10.500	2.075-53.142	**0.004**	19.018	1.854-195.078	**0.013**
Treatment						
Oral progestin+LNG-IUD	1 (references)	-		1 (references)	−1.356-134.069	**0.026**
Oral progestin	8.000	1.650-38.790	**0.010**	13.483		

Bold numbers indicate *P*<0.05. OR=Odds ratio; CI=Confidence interval; BMI=Body mass index; PCOS=Polycystic ovary syndrome; DM=Diabetes mellitus; HTN=Hypertension; EM=Endometrium; LNG-IUD=Levonorgestrel-intrauterine device

hyperstimulation. Fifty-one (73%) of 70 women who tried to conceive were successful and 46 (66%) gave birth to 58 live neonates. In our study, 17 patients attempted pregnancy: four patients received treatment for infertility and 13 patients successfully became pregnant. A pregnancy rate of 76.4% (13/17) was achieved, which was similar to the previous Korean study. The hormone-based fertility-preservative treatment seems to be effective in terms of fertility outcome.

Recent attempts have been made to identify radiologic indicators and prognostic factors for predicting response to progestin. Ushijima *et al*. reported that CR patients showed significantly thinner endometrium 6.5 (SD 3.5) mm after 8 weeks of treatment and 4.2 (SD 1.4) mm after 16 weeks by TVUS.[12] Sato *et al*. supported Ushijima's report, stating that endometrial thickness after 8 (≤8 mm) and 16 (≤5 mm) weeks of MPA treatment in patients with endometrial cancer grade 1 showed significant correlations with CR after progestin treatment.[13] In the current study, we analyzed three types of radiologic parameters, namely endometrium thickness before treatment (≥15 mm) (OR: 1.429; 95% CI: 0.326–6.257; *P* = 0.636), endometrial thickness after 2 months of progestin treatment (≥7 mm) (OR: 8.000; 95% CI: 1.650–38.790; *P* = 0.010), endometrium thickness ratio of pre- and posttreatment (≥0.55) (OR: 10.500; 95% CI: 2.075–52.142; *P* = 0.004) by univariate analysis, and endometrial thickness ratio (OR, 14.551; 95% CI, 1.127–47.928; *P* = 0.040) by multivariate analysis might be significantly related with favorable factors for CR. These findings might be useful in predicting treatment response to progestin before D and C which is usually performed 3 months after treatment commencement, making treatment decisions regarding dose escalation, and adding LNG-IUS to follow-up plans.

This study has several limitations. First, the number of patients included was relatively small. Second, it is limited

by its retrospective design. Since it is a retrospective design, strict variable control could not be achieved. For this reason, external validity is somewhat low. Nevertheless, our study has an advantage in that it solely included the patients with endometrial cancer excluding atypical endometrial hyperplasia, and the number of patients was not critically small compared to other similar studies on fertility-preservation treatment for endometrial cancer. In addition, no other study has investigated the use of three different ultrasonographic methods for predicting treatment response to hormonal therapy in young women with early-stage endometrial cancer, and our study has shown that the only endometrial thickness ratio is significantly related with favorable factors for CR. These results suggest that the endometrial thickness ratio is the possibility of a noninvasive surrogate marker that can predict the response to hormone therapy, so initial endometrial thickness might be assessed prior to starting hormonal therapy for endometrial thickness ratio assessment after the treatment.

CONCLUSION

Our findings suggest that oral progestin plus LNG-IUS combination treatment in patients with a low endometrial ratio (<0.55) might be closely related to a favorable response in young women with early-stage endometrial cancer, which further emphasizes that these factors should be considered before counseling candidates with early-stage endometrial cancer for fertility-preservative treatment. Furthermore, this study contributes to the growing body of literature demonstrating the efficacy of hormonal treatment in early-stage endometrial cancer patients requiring fertility preservation. With further analysis with a larger number of patients, future findings on the hormonal therapy in early-stage endometrial cancer and prognostic factors that can predict the response of hormone therapy could innovatively suggest proper management direction for fertility-preservative therapy in early-stage endometrial cancer.

Acknowledgments

We would like to thank Editage (www.editage.co.kr) for English language editing.

Financial support and sponsorship

This study was supported by Biomedical Research Institute Grant (2019B011), Pusan National University Hospital.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Jung KW, Won YJ, Kong HJ, Lee ES, Community of Population-Based Regional Cancer Registries. Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2015. Cancer Res Treat 2018;50:303-16.
3. Gadducci A, Spirito N, Baroni E, Tana R, Genazzani AR. The fertility-sparing treatment in patients with endometrial atypical hyperplasia and early endometrial cancer: A debated therapeutic option. Gynecol Endocrinol 2009;25:683-91.
4. Papaioannou S, Tzafettas J. Anovulation with or without PCO, hyperandrogenaemia and hyperinsulinaemia as promoters of endometrial and breast cancer. Best Pract Res Clin Obstet Gynaecol 2010;24:19-27.
5. Shao R, Li X, Feng Y, Lin JF, Billig H. Direct effects of metformin in the endometrium: A hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma. J Exp Clin Cancer Res 2014;33:41.
6. Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, *et al*. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol 2003;102:718-25.
7. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: A literature review. Gynecol Oncol 2004;95:133-8.
8. Chiva de Agustín L, Lapuente Sastre F, Corraliza Galán V, Granados Galainena L, González Martín A, González Cortijo L, *et al*. Conservative management of patients with early endometrial carcinoma: A systematic review. Clin Transl Oncol 2008;10:155-62.
9. Kim MK, Seong SJ, Lee TS, Kim JW, Nam BH, Hong SR, *et al*. Treatment with medroxyprogesterone acetate plus levonorgestrel-releasing intrauterine system for early-stage endometrial cancer in young women: Single-arm, prospective multicenter study: Korean Gynecologic Oncology Group study (KGOG2009). Jpn J Clin Oncol 2012;42:1215-8.
10. Fan Z, Li H, Hu R, Liu Y, Liu X, Gu L. Fertility-preserving treatment in young women with grade 1 presumed stage IA endometrial adenocarcinoma: A meta-analysis. Int J Gynecol Cancer 2018;28:385-93.
11. Park JY, Seong SJ, Kim TJ, Kim JW, Kim SM, Bae DS, *et al*. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. Obstet Gynecol 2013;121:136-42.
12. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, *et al*. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007;25:2798-803.
13. Sato M, Arimoto T, Kawana K, Miyamoto Y, Ikeda Y, Tomio K, *et al*. Measurement of endometrial thickness by transvaginal ultrasonography to predict pathological response to medroxyprogesterone acetate in patients with grade 1 endometrioid adenocarcinoma. Mol Clin Oncol 2016;4:492-6.