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Endometrial Hyperplasia with Conservative Treatment Using the Progestin or EP Agents, Compared to Cases that Worsen during Observation

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Abstract

A total of 157 patients were included in this study, comprising 147 with simple Endometrial Hyperplasia (EH) and 10 with complex EH. All patients treated cyclically with progestin or Estrogen-Progestin (EP) exhibited regression of EH after 3 or 4 treatment courses. The relapse rate in patients treated cyclically with progestin was significantly lower than that in those treated with EP for simple EH ($P < 0.01$). Five cases progressed to EIN over lesions in the 43 follow-up cases of simple EH, and two progressed to those lesions in the five follow-up cases of complex EH, respectively. Loss of PTEN expression was observed in relapse cases, suggesting a potential association with relapse. For EH without atypia, particularly in PTEN-null (+) cases, conservative treatment with progestin or EP is recommended to prevent progression to endometrial carcinoma.

Keywords

Endometrial Hyperplasia, Progestin, EP, PTEN-Null

1. Introduction

Endometrial Hyperplasia (EH) is a non-physiological, pre-cancerous, and non-invasive proliferation of the endometrial tissue characterized by glandular architectural changes and an endometrial gland-to-stroma ratio exceeding 1:1 [1] [2].

The incidence of EH among premenopausal women increases with age, reaching as high as 121 and 270 cases per 100,000 woman-years in South Korean women aged 46 - 50 years and U.S. women aged 45 - 49 years, respectively [3]. Most cases of EH develop in the context of chronic estrogen exposure unopposed by progestins [2]. Additionally, the overproduction of estrogen by adipose tissue in obese women contributes to an increased risk of EH and Endometrial Carcinoma (EC) [4] [5].

Approximately 80% of EH without atypia regress spontaneously, while 3% - 10% may progress to EH with atypia, and 1% - 5% may develop into EC if left untreated [6]-[8]. Various treatment options for EH without atypia have been reported [9], with progestins being the most commonly used therapy [10]-[12]. Levonorgestrel (LNG)-Impregnated Intrauterine Devices (IUDs), a second-generation progestin, have demonstrated higher efficacy compared to conventional oral progestins such as Medroxyprogesterone Acetate (MPA) [13]-[15]. Oral contraceptives, namely EP, may also be considered, especially when fertility preservation is desired after conservative management [16].

On a molecular level, mutations in the Phosphatase and Tensin Homolog (PTEN) tumor suppressor gene have been reported in 35% - 83% of endometrioid ECs and up to 63% in Endometrial Intraepithelial Neoplasia (EIN), suggesting that PTEN loss may play a role in early endometrial carcinogenesis [17]. A relationship between PTEN loss and progestin treatment in EIN has also been documented [18]. Furthermore, the well-known tumor suppressor gene p53 is reported to regulate PTEN transcription [19], and PTEN, in turn, inhibits the degradation of p53 [20].

Therefore, in the present study, EH without atypia cases were conservatively treated with cyclic progestin or EP, and patients who did not wish to receive drug treatment were only monitored. The response rate and relapse rate were examined in the treatment group, and the progression of lesions in the non-treatment group over the medium to long term. We also examined the immunohistological expression of the tumor suppressor genes PTEN and p53 in some relapsed and progressive cases.

2. Materials and Methods

Patient Selection

From January 2014 to December 2023, cases were included in which abnormal bleeding or endometrial thickening was observed, and endometrial biopsy revealed a diagnosis of EH without atypia. A total of 157 patients were retrospectively collected and included in the study [mean age: 45.8 ± 8.6 years (range: 23 - 79 years); 147 with simple EH and 10 with complex EH].

The diagnosis of EH without atypia was primarily based on the WHO 2020 classification [21]. However, considering that the biological responses of simple and complex EH may differ, the diagnosis and classification were divided into simple EH and complex EH, as outlined in the WHO 2003 classification [22]. Other di-

agnoses included EIN and EC, which were diagnosed according to the WHO 2020 guidelines [21].

The treatment approaches for simple and complex EH cases were as follows: patients requesting conservative management with chemical curettage were recommended to undergo progestin therapy, especially for slightly older patients, or EP therapy for slightly younger patients. Patients who did not wish to undergo treatment were included in the follow-up group, based solely on their own wishes. Patients who preferred to avoid drug therapy and opted for follow-up observation were advised to undergo endometrial re-examination after 3 - 6 months. EH patients with uterine fibroids or other complications who requested a total hysterectomy underwent Total Laparoscopic Hysterectomy (TLH).

Figure 1 and Figure 2 show the flowcharts for simple EH and complex EH, respectively.

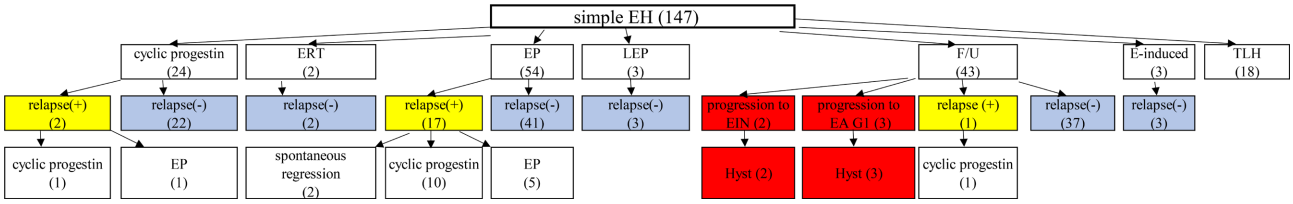

Figure 1. Flowchart of the study in simple EH. A total of 147 cases were included. Twenty-four cases were treated conservatively with cyclic progestin, 54 cases with EP, and 43 cases were managed with observation alone.

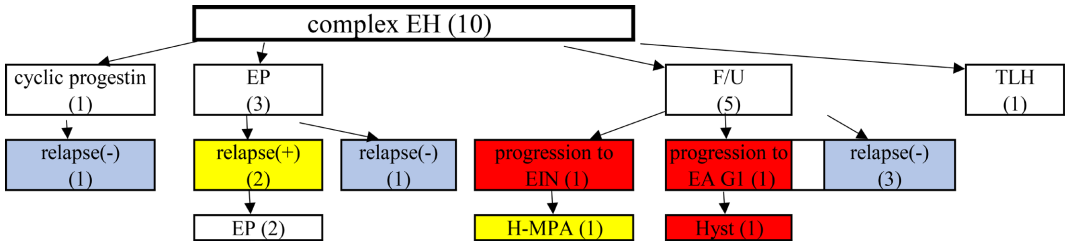

Figure 2. Flowchart of the study in complex EH. A total of 10 cases were included. One case was treated conservatively with cyclic progestin, three cases with EP, and five cases were observed without intervention. One patient who progressed to EIN after F/U was treated with high-dose MPA and whole-wall curettage.

Group 1 (Cyclic Progestin Group):

Typically, patients receive either Medroxyprogesterone Acetate (MPA, 10 mg/day) or dydrogesterone (10 mg/day) for 10 - 14 days each month. They undergo 3 - 4 treatment courses. If withdrawal bleeding does not occur with progestin alone, Estrogen Replacement Therapy (ERT) is initiated. ERT involves administering conjugated estrogens (1.25 mg/day, Days 1-21) along with MPA (10 mg/day, Days 14-21).

Group 2 (EP Group):

For patients with EH who request EP therapy, 3 - 4 courses of medium-dose EP [ethinylestradiol (0.05 mg) and norgestrel (0.5 mg), administered on Days 1-21] are administered monthly, followed by an endometrial examination for assessment. Patients requesting Low-dose EP (LEP) are prescribed ethynylestradiol (0.02 mg)

and norethisterone (1 mg) in the same manner.

Group 3 (Follow-up Group):

Patients who opt out of drug therapy and prefer observation are advised to undergo endometrial re-examination after 3 - 6 months.

Group 4 (Total Hysterectomy Group):

Patients with EH accompanied by uterine fibroids or other complications who request surgical treatment undergo Total Laparoscopic Hysterectomy (TLH).

Group 5 (Possible Estrogen-Induced Group):

Three cases of simple EH, suspected to be caused by estrogen monotherapy prescribed by local physicians, were observed. The lesions resolved promptly after discontinuation of estrogen therapy.

Follow-up and monitoring

Groups 1 and 2 are monitored through regular outpatient visits every four weeks from the start of treatment. After completing three or four courses, transvaginal ultrasound and a second endometrial biopsy are performed to evaluate treatment efficacy and determine whether the patient is cured.

Pathological and immunohistochemical examinations

All endometrial samples were fixed in 10% buffered formalin. As previously mentioned, since the biological responses of simple and complex EH may differ, the diagnosis and classification are divided into simple EH and complex EH based on the WHO 2003 criteria [22]. The other categories include EIN, and EC is diagnosed according to the WHO 2020 guidelines [21].

Due to budget limitations, immunohistochemical examinations were performed on specimens from a limited number of cases. We conducted a retrospective analysis of PTEN expression using specimens from cases of EH that relapsed or progressed to EIN or more severe conditions during follow-up. The immunostaining method and evaluation were as follows, as previously reported [23]. Each tissue section was mounted on a silane-coated glass slide, deparaffinized, and then soaked for 15 minutes at room temperature in 0.3% hydrogen peroxide/methanol to block endogenous peroxidase activity. The sections were incubated overnight at 4˚C with primary antibodies against PTEN (Dako, used at a 1:200 dilution) and p53 (DO-7, Dako, used at a 1:200 dilution), following microwave antigen retrieval. Afterward, the slides were washed, incubated with an appropriate secondary biotinylated immunoglobulin (Vastatin ABC kit, Vector Laboratories, Inc., Burlingame, CA), and the signal was detected through sequential addition of avidin peroxidase and 3,3′-diaminobenzidine. Cases in which PTEN-positive specimens contained ductal cells lacking PTEN expression were classified as PTEN-null (+). The intensity of p53 expression in ductal cells was evaluated as follows: negative, weakly positive, and positive.

Microsatellite Instability (MSI) testing was performed on some cases that progressed to EC. MSI testing involves amplifying the microsatellite regions by PCR and determining whether the tumor is MSI-High or not based on the waveform obtained through capillary electrophoresis (SRL Inc., Japan).

Outcome measures

The primary outcome measures were the regression of hyperplasia one month after progestin or EP treatment, or at 3 - 6 months in the follow-up groups. Cases in which EH recurred during follow-up were classified as relapse (+), and drug therapy that was substantially different from the previous treatment was resumed. For patients who wished to have children, the number of pregnancies and deliveries after treatment was also examined.

Statistical analysis

As for mean age, BMI and observation time, tests of differences in mean values were performed using IBM SPSS software (version 24, IBM Corp, Armonk, New York) with the Mann-Whitney U method. As for regression, relapse and progression rate of each group, the chi-square tests were also performed using the above software. A p-value greater than 0.05 was considered statistically significant.

3. Result

The mean ages at first diagnosis, BMI, and observation time for each group of simple EH are shown in Table 1. Although there were no statistically significant differences, the mean ages in the EP and LEP groups tended to be younger compared to the cyclic progestin and ERT groups. This is thought to be due to a tendency to prescribe EP or LEP therapy to relatively younger patients. The mean ages at first diagnosis, BMI, and observation time for each group of complex EH are also presented in Table 2. All patients who underwent cyclic progestin therapy or TLH were in their 30s and tended to be younger than patients in the other groups.

Table 1. Summary of outcomes of treatment and follow-up for simple EH.

		Cyclic progestin (24)	ERT (2)	EP (54)	LEP (3)	F/U (43)	E-induced (3)	TLH[a] (18)
Simple EH (147)	Mean age at the first diagnosis	46.0 ± 6.0		42.5 ± 5.7		48.9 ± 11.4	60.3 ± 8.7	50.1 ± 6.1
	BMI	23.7 ± 4.8		24.0 ± 3.8		24.7 ± 4.5	21.8 ± 2.1	25.4 ± 3.4
	Observation time (yr)	6.7 ± 3.1		4.7 ± 3.1		5.5 ± 3.3	(−)	(−)
	Regression of EH	24 (100%)	2 (100%)	54 (100%)	3 (100%)	37 (86%)	3 (100%)	
	Relapse (−)	22 (92%)	2 (100%)	37 (69%)	3 (100%)	37 (86%)	3 (100%)	
	Relapse (+)	2 (8%)[c]	0 (0%)	17 (31%)	0 (0%)	1 (2%)	0 (0%)	
	Progression to EIN[d]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)	
	Progression to EA G1[e]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (7%)	0 (0%)	

[a]TLH was performed due to complications such as uterine fibroids. [b]After estrogens were discontinued. [c]Significantly lower than the EP-treated group ($P < 0.01$, by the chi-square test). [d]Endometrial intraneoplasia. [e]Endometrial carcinoma, well-differentiated endometrioid carcinoma, located within the endometrium.

Table 2. Summary of outcomes of treatment and follow-up for complex EH.

		Cyclic progestin (1)	EP (3)	F/U (5)	TLH[a)] (1)
Complex EH (10)	Mean age at the first diagnosis	33	46.0 ± 1.5	49.0 ± 9.9	36
	BMI	20.6	28.2 ± 2.6	25.1 ± 3.9	21.8
	Observation time (yr)	8	8.0 ± 1.6	5.4 ± 2.4	(−)
	Regression of EH	1 (100%)	3 (100%)	3 (60%)	
	Relapse (−)	1 (100%)	1 (33%)	3 (60%)	
	Relapse (+)	0 (0%)	2 (67%)	1 (20%)	
	Progression to EIN	0 (0%)	0 (0%)	1 (20%)	
	Progression to EA G1	0 (0%)	0 (0%)	1 (20%)	

[a)]TLH was performed due to complications of uterine fibroids.

All patients treated with cyclic progestin, ERT, EP, or LEP exhibited regression of simple EH on endometrial examination following the scheduled treatment (Table 1). In some cases, relapse of endometrial hyperplastic lesions was observed during subsequent routine follow-up. The incidence of relapse in patients treated with cyclic progestin (2/24, 8 %) was significantly lower than in those treated with EP (17/54, 31%) for simple EH ($P < 0.01$, Table 1).

Among the follow-up cases, two progressed to EIN, and three progressed to EC, specifically well-differentiated (G1) EA (Table 1). In three cases of simple EH believed to be induced by estrogen administration, the lesions resolved promptly after discontinuation of estrogen therapy (Table 1).

In ten complex EH cases treated with either cyclic progestin or EP, all exhibited regression following the scheduled treatment. However, two cases treated with EP experienced relapse (Table 2). No cases progressed to EIN among the complex EH cases treated with cyclic progestin or EP. During follow-up, one case progressed to EIN and another to EA, grade 1 (Table 2).

Among the 54 cases of simple EH in the EP treatment group, only 5 patients expressed a desire to have children. Following treatment, 2 of these patients achieved normal pregnancies and delivered babies, while 1 experienced a tubal pregnancy and subsequently underwent salpingectomy.

The number of cases examined for PTEN expression was limited. A representative example of PTEN-null expression in complex EH is shown in Figure 3. Among relapse cases of EH, 4 out of 5 (80%) exhibited PTEN-null (+) status. Additionally, initial specimens from EH cases that progressed to EIN or EA G1, as well as other EIN and EA G1 cases, all demonstrated PTEN-null (+) expression (see Table 3).

The cases in which EH progressed to EIN and EC are summarized in Table 4. Five cases of simple EH and two cases of complex EH developed EIN or EA G1

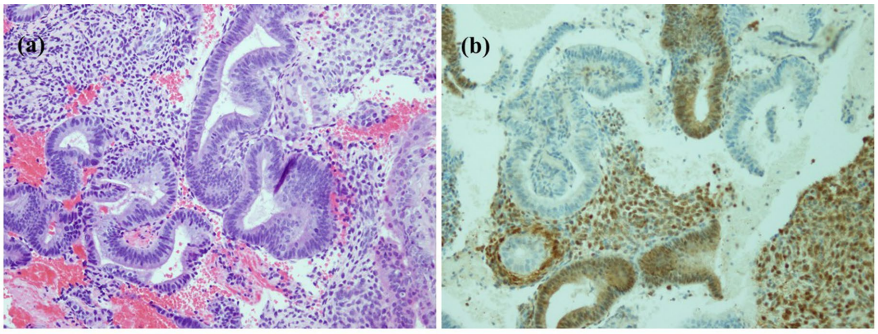

Figure 3. Typical case of complex EH. Hematoxylin and Eosin (H&E) staining (a) and immunohistochemical findings of PTEN expression (b) before treatment. Back-to-back glands were observed (a) (magnification × 100), and some glands showed PTEN loss (b) (sABC × 100).

Table 3. PTEN-null (+) in the initial biopsies in the relapsed, progressed cases, and EIN and G1 cases.

	PTEN-null (+)	PTEN-null (−)
Relapsed cases of EH (simple 4; complex 1)	4/5 (80%)	1/5 (20%)
EH cases, progressed to EIN (2) or EA G1 (1)[a)]	3/3 (100%)	0/3 (0%)
EIN (2)	2/2 (100%)	0/2 (0%)
EA G1 (2)	2/2 (100%)	0/2 (0%)

[a)]EIN, intraepithelial neoplasia, EA G1, endometrioid adenocarcinoma, well-differentiated; initial specimens in EH cases that progress to EIN or EA G1.

Table 4. Summary of the cases in which precancerous lesions developed into EIN and endometrial cancer.

Cases	age	BMI[a)]	Initial diagnosis[b)]	Follow-up time[c)] (yr)	Final diagnosis[d]	Notes[e)]		
						PTEN	p53	MSI
1	61	22.2	simple EH	1 Y →	EIN	PTEN-null(+)	ND	ND
2	54	27.3	simple EH	0.5 Y → complex EH 0.5Y →	EIN	PTEN-null(+)	p53(+)	ND
3	53	21.9	simple EH	1 Y → complex EH 3 Y →	EA G1	PTEN-null(+)	ND	ND
4	50	23.1	simple EH	1 Y 2 Y ⇢	EA G1	ND	p53(+/-)	MSI(-)
5	40	30.8	simple EH	1 Y 7 Y ⇢	EA G1	ND	p53(+/-)	MSI(-)
6	29	37.2	complex EH	3 Y → complex EH 2 Y →	EIN	ND	p53(+/-)	ND
7	60	20.8	complex EH	1 Y →	EA G1	ND	p53(+/-)	MSI(-)

[a)]BMI, body mass index; [b)]initial diagnosis, simple EH, simple endometrial hyperplasia, complex EH, complex endometrial hyperplasia; [c)]Follow-up times; → visited our hospital every 3-6 months; ⇢ no symptoms and has not visited our hospital.
[d)]final diagnosis, EIN, endometrial intraneoplasia; G1, endometrial carcinoma, well-differentiated.
[e)]PTEN-null(+) in the initial specimnes; ND, not determined; p53 expression in the final specimens; MSI, microsatellite instability.

over a period of 1 to 8 years. Among the 7 cases with EIN and EA G1, six patients who did not wish to pursue fertility preservation underwent a total hysterectomy. One patient with EIN who desired fertility preservation was treated conservatively

with high-dose MPA (600 mg/day) and whole-wall curettage and achieved a pathological complete remission six months later, in the manner previously reported [23]. PTEN null (+ status was observed in all three examined cases. A representative image showing p53 expression in EIN is presented in **Figure 4**. MSI was not detected in any of the three cases of EA G1.

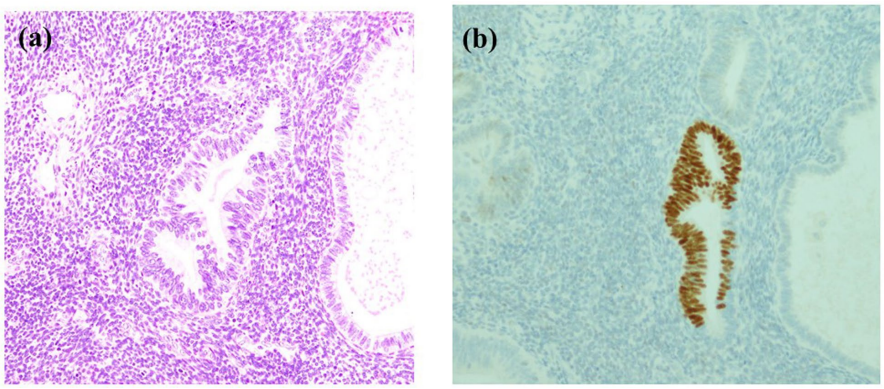

Figure 4. Case 2 of EIN from **Table 4**. H&E staining (a) and immunohistochemical findings of p53 expression at hysterectomy (b). Atypical glands were identified (a) (magnification × 100), and p53 was positive in the glands (b) (sABC × 100).

4. Discussion

For EH without atypia, conservative treatments such as cyclic progestin, continuous progestin, intrauterine progestin, and EP therapies have been employed, with reported high remission rates [9] [15] [16]. Considering fertility preservation, EP therapy may be preferable [16]. LNG-IUD is widely used worldwide to treat EH without atypia, but a recent systematic review reported that MPA was the most effective monotherapy, while adding metformin was even more effective [24]. In this study, since LNG-IUS is not covered by insurance for EH in Japan, and because "chemical curettage", which induces periodic bleeding, was also effective, relatively young patients with EH were treated with EP agents, while relatively older patients received cyclic progestin therapy. All patients treated with cyclic progestin, ERT, EP, or LEP demonstrated regression of simple and complex EH upon follow-up endometrial examination after the scheduled treatment. Post-treatment, two patients achieved normal pregnancies and delivered healthy babies.

Regardless of the method used, the relapse rate has been reported to be high [15] [25]. Some studies suggest that high estrogen levels following conservative treatment, high BMI, and premenopausal status may be factors predictive of relapse [15]. Increased expression of Progesterone Receptor (PR) B and decreased expression of PR A have been significantly correlated with relapse [25]. The latter study also reported that PTEN expression has not been associated with relapse. Although the number of cases was small, the proportion of PTEN-null (+) specimens before treatment in our relapse cases was higher than that in PTEN-null (+) EH cases, as previously reported [17], and may be related to relapse.

PTEN null (±) status may occur early in cancer progression and is often observed at the initial stages when EH worsens [17]. However, it has been reported that PTEN loss in EH occurs in approximately 40% of cases and shows little correlation with progression to EC [25] [26]. In cases where simple EH progressed to EIN or more advanced lesions, PTEN-null status was confirmed in all examined initial specimens. Additionally, initial specimens from relapsed EH cases exhibited PTEN loss more frequently than those from normal EH, which may be related to relapse. Conversely, overexpression of the tumor suppressor gene p53 was observed in only one case that progressed early to EIN, suggesting that p53 abnormalities may be associated primarily with rapidly progressing cases.

In the group that did not receive conservative treatment with progestin or EP agents, five cases of simple EH and two cases of complex EH progressed to EIN or more severe conditions over a period of 1 to 8 years. Even in cases diagnosed pathologically as EH without atypia, especially those with PTEN null (+) status, conservative treatment with progestin or EP should be considered to prevent progression to EC. The presence of PTEN-null status in EH without atypia prompts a recommendation for active treatment over observation, although PTEN immunohistochemistry has not been covered by medical insurance even in Japan.

5. Conclusions

A total of 157 patients were treated and followed up: 147 with simple EH and 10 with complex EH. All patients who received cyclic progestin or EP therapy experienced regression of EH for 3-4 months. However, relapse was observed, with significantly fewer relapse cases in the cyclic progestin group compared to the EP for simple EH. Among the follow-up cases, 5 of the 43 patients with simple EH progressed to EIN and EA G1, and 2 of the 5 patients with complex EH also progressed to EIN and EA G1. In cases of EH without atypia, especially in PTEN null (+) patients, conservative treatment with progestin or EP should be considered to prevent progression to EC.

Additional Information

Disclosures

Human Subjects: All participants in this study provided either consent or a waiver of consent. Written informed consent was obtained from the patient.

Ethical Approval: Written informed consent was obtained from the patient before writing this article. Ethical approval was obtained from our hospital's ethics committee before conducting this study (approval no. 24022903).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

EH	Endometrial Hyperplasia
EP	Estrogen and Progestin
EIN	Endometrial Intra-Neoplasia
PTEN	Phosphatase and Tensin Homolog
EC	Endometrial Carcinoma
LNG	Levonorgestrel
IUD	Intrauterine Device
MPA	Medroxyprogesterone Acetate
TLH	Total Laparoscopic Hysterectomy
BMI	Body Mass Index
F/U	Follow-Up
EA	Endometrial Adenocarcinoma
MSI	Microsatellite Instability
PR	Progesterone Receptor