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Clinical features and outcome of 15 patients with recurrent endometrial cancer or atypical endometrial hyperplasia received primary fertility-sparing therapy followed by hysterectomy

Yuanting Li [a,1], Yiqin Wang [a,1], Yijiao He [a], Rong Zhou [a], Huiru Tang [b], Lijiang Xu [c], Mian He [d], Weili Li [e], Chunlin Chen [e], Weifeng Zhang [f], Jianliu Wang [a,*]

[a] Department of Gynecology and Obstetrics, Peking University People's Hospital, Beijing, China
[b] Department of Gynecology and Obstetrics, Peking University Shenzhen Hospital, Shenzhen, China
[c] Department of Gynecology and Obstetrics, The First People's Hospital of Foshan, Guangdong, China
[d] Department of Gynecology and Obstetrics, The First Affiliated Hospital, Sun Yat-sen University, Guangdong, China
[e] Department of Gynecology and Obstetrics, Nanfang Hospital, Guangdong, China
[f] Department of Gynecology and Obstetrics, Ningbo Women & Children's Hospital, Zhejiang, China

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ABSTRACT

Objective: To investigate the clinical features and outcome of recurrent endometrial cancer (EC) or atypical endometrial hyperplasia (AEH) patients who underwent hysterectomy after fertility-sparing therapy.
Methods: Clinical data was retrospectively collected for 15 recurrent endometrial cancer or atypical endometrial hyperplasia patients who underwent hysterectomy in six hospitals from 2003 to 2019. According to the indicators of hysterectomy, patients were divided into four groups: 7 patients who underwent direct hyesterectomy after the first relapse, 4 due to re-treatment failure, 1 after full term live birth, and 3 because of multiple recurrence. Clinical coexisting conditions, regimen and outcome of fertility-sparing therapy, pre- and post-operative pathological results, and prognosis were analyzed.
Results: (1) Fertility-spraring treatment was given to a total of 15 eligible patients, including 6 with EC and 9 with AEH. Median time interval from remission to recurrence was 12 months (range 3–92). Oral progestin-based medicine was the main fertility-sparing therapy in both primary treatment and re-treatment after recurrence. Six (6/8) patients received progestin combined with gonadotrophin releasing hormone agonist or metformin in three re-treatment groups. (2) Nine patients underwent hysterectomy and 6 staging surgery. Three patients had pathological upgrade after surgery. Five (5/10) EC patients had superficial myometrial invasion in postoperative pathology. All patients showed no evidence of disease in the median follow-up of 17 months (range 3–118). (3) Among seven patients who failed to re-treatment and had multiple recurrence, six were overweight/obesity and six had insulin resistance. Two of these patients had synchronous ovarian cancer in the postoperative pathology.
Conclusion: For the patients with recurrent EC or AEH after primary fertility-sparing therapy, overweight/obesity and insulin resistance might be the risk factors for re-treatment failure. Hysterectomy is recommended when patients had re-treatment failure or multiple recurrence; and generally the prognosis is favorable.

* Corresponding author. Peking University People's Hospital, No.11 South Main Street, Xicheng, Xizhimen, Beijing, 100044, PR China.
E-mail address: wangjianliu@pkuph.edu.cn (J. Wang).

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[1] Co-first authors.

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1. Introduction

Endometrial cancer (EC) has the second highest incidence among gynecological malignant tumors in China [1], and it is increasing every year. Endometrial cancer mainly occurs in postmenopausal women while around 7% of patients are between 20 and 44 years old [2]. At the same time, with the delay of childbearing, the incidence rises for nulliparous women who have strong fertility desire. Instead of hysterectomy, which generally leads to a permanent loss of fertility, fertility-sparing therapy becomes an important and necessary option to meet the patients' needs. At present, the efficacy of progestin-based fertility-sparing therapy is well established with the remission rate of 70%–90%. But up to 20%–40% of the patients relapse after remission. Recurrent patients are usually treated with hysterectomy. The aim of this study is to analyze clinical features and outcomes of recurrent endometrial cancer or atypical endometrial hyperplasia (AEH) patients who underwent hysterectomy after fertility-sparing therapy.

2. Methods

In this retrospective study, fifteen recurrent EC or AEH patients from six hospitals were included, who underwent hysterectomy after fertility-sparing therapy. Through established network, demographics, diagnosis, treatment and clinical results were extracted from patients diagnosed between November 2003 and May 2019. This study was approved by the ethics committee of Peking University People's Hospital (Ethics approval No. 2016PHB054-01). Informed consent and publication agreement were obtained from all the patients recruited.

Patients received fertility-sparing therapy if they met the following nine inclusion criteria: (1) $\leq$40 years old; (2) diagnosed with FIGO 2009 stage IA grade 1 EC or AEH; (3) lesion confined to the endometrium that was confirmed by pelvic MRI; (4) positive expression of estrogen receptor; (5) absence of myometrial invasion or extrauterine spread based on imaging; (6) no contraindications to oral progestin or pregnancy; (7) strong desire of fertility preservation; (8) fully informed consent; (9) willing to follow up.

Regimen of fertility-sparing therapy was progestin-based, medroxyprogesterone acetate (MPA) or megestrol acetate (MA). Gonadotrophin releasing hormone agonist (GnRHa) or metformin might be added according to patients' condition. Hysteroscopy was performed every three months to assess the lesion followed by pathological exam. Therapeutic response was determined according to current expert consensus [3]. Pregnancy was recommended as soon as comple response was achieved. For complete response (CR) patients without pregnancy plan in the near future, maintenance treatment with low-dose progestin was offered. Recurrence was defined as occurence with EC or AEH leision confirmed by pathology after CR. Staging hysterectomy was recommended for recurrent patients, which included total hysterectomy, ovariectomy and retroperitoneal lymphadenectomy, as well as postoperative adjuvant chemotherapy when necessary. If patients still had strong desire for fertility preservation and meet the former fertility-sparing indications, re-treatment was provided with above treatment regimen and follow-up approach.

Fertility-sparing treatment was terminated in any of the following situations, disease progression with proven evidence, not achieving complete response or multiple recurrence. For these patients, the same surgical treatment was recommended. Afterward, patients were followed up every 3–6 months for the first 2–3 years, and then every 6–12 months.

Coexistent medical conditions, treatment regimen, therapeutic response, surgical pathology and pregnancy outcome were evaluated. Patients were divided and analyzed according to the indications of hysterectomy. Obesity is defined as body mass index (BMI) $\geq$28 kg/m^2, and overweight is when BMI $\geq$24 kg/m^2. Homeostasis model assessment of insulin resistance (Homa-IR) index [fasting blood glucose (mmol/L) $\times$ fasting insulin (mIU/L)/22.5] is used to evaluate insulin resistance (IR) status, and patients with HOMA-IR $\geq$2.69 are considered to be insulin resistance [4].

3. Results

3.1. Patients' demographics

Fifteen eligible patients from six hospitals were included in the study, including seven patients from Peking University People's Hospital, four from Peking University Shenzhen Hospital, and one each from The First People's Hospital of Foshan, Nanfang Hospital, Ningbo Women & Children's Hospital and The First Affiliated Hospital, Sun Yat-sen University. Six patients were initially diagnosed with EC, and the other nine were AEH. The average age was 32 ± 4.2 years old and the average BMI was 26.5 ± 5.0 kg/m^2. The mean fasting blood glucose was 5.60 ± 0.81 mmol/L, and six patients (6/10) were combined with insulin resistance. Eight patients hadn't completed fertility (53.5%), and ten patients were nulliparous (66.7%). The fifteen patients were divided into four groups: 7 patients who underwent direct hyesterectomy after the first relapse, 4 due to re-treatment failure, 1 after full term live birth, and 3 because of multiple recurrence.

3.2. Primary fertility-sparing treatment and re-treatment

The primary fertility-sparing treatment and re-treatment is summarized in Table 1. All patients received initial oral progestin-based regimen (MPA 160–1000 mg/day or MA 160–300 mg/day) including one who was given MPA combined with GnRHa because of medical history of complex hyperplasia. Five patients (33.3%) received maintenance therapy (oral dydrogesterone 20 mg/d in the second half of menstruation cycle) after achieving complete response. The median recurrence interval is 12 (range 3–92) months. Pathologically, 10 (67%) patients were diagnosed with EC and 5 (33%) had AEH at recurrence. Eight of these recurrent patients still had fertility desire and were re-treated with oral progestin-based regimen. Two of them were given MPA combined with GnRHa or letrozole because of unsatisfactory response, and one was given GnRHa alone for abnormal liver function. There were more patients who received combined therapy with GnRHa (4/8 vs. 1/15) or metformin (3/8 vs. 0/15) in the re-treatment groups than in the primary treatment groups.

3.3. Surgical treatment and follow-up outcomes

Surgical procedures, pre- and post-operative pathology comparison, and follow-up outcomes are shown in Table 2. Nine patients underwent total or subtotal hysterectomy and 6 received staging surgery. The post-operative pathological examination showed that 12 (80%) had been consistent with pre-operative diagnosis and 3 had pathological upgrade after hysterectomy, including two from AEH to EC and one from EC stage Ia to IIIc. And in the patients with recurrent EC, 5 (5/10) had myometrial invasion, although none myometrial infiltration was observed at preoperative imaging assessment. Ovarian masses were found in three patients, two of which were confirmed to be synchronism ovarian endometrioid adenocarcinoma/borderline tumor, and one was benign ovarian cyst. Ultrasonography and MRI also indicated that one patients had suspicious enlargement of lymph nodes, while no metastasis of lymph node was found after surgery.

Seven patients (case 1–7) chose direct hysterectomy after the first relapse, 6 (6/7) of which had consistent pre- and post-operative pathology including 4 patients with EC, 1 patient with AEH and one with no lesion (AEH in recurrent biopsy pathology) (Table 2). All of the four patients with EC had myometrial infiltration.

Four patients (case 8–11) suffered failure to re-treatment and received staging hysterectomy. Three of them had consistent pre- and post-operative pathology, while the other one had pathological upgrade from AEH to EC (Table 2). And two of the three EC patients (confirmed by postoperative pathology) had myometrial infiltration. In addition, primary ovarian tumor were found in two patients, including one ovarian endometrioid adenocarcinoma IC2 (left ovary) and one ovarian borderline endometrioid adenocarcinoma (bilateral ovaries), and one of them was diagnosed with Lynch syndrome by gene testing (patient 9).

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Table 1
The primary treatment and re-treatment summary of fifteen patients.

Group	No	Age (y)	Initial pathology	Primary treatment	Recurrence interval (month)	Recurrent pathology	Re-treatment	Interval between recurrence and surgery (m)
Without retreatment	1	40	AEH	MA 3 m PR, 6 m CR	9	AEH	–	<1
	2	36	AEH	MA 4 m CR	3	AEH	–	<1
	3	37	AEH	MA 5 m CR, maintenance therapy	44	AEH	–	3
	4	32	AEH	MA 2–10 m PR, 13 m CR, maintenance therapy 5 m	42	EC IaG1	–	<1
	5	24	EC IaG1	MPA5m CR, maintenance therapy 3 m	5	EC IaG1	–	<1
	6	28	EC IaG1	MA 2 m CR	92	EC IaG1	–	<1
	7	32	AEH	MA 6 m CR, maintenance therapy	11	EC IaG1	MA 20d	<1
Failure to re-treatment	8	28	AEH	MPA 8 m CR, maintenance therapy	12	AEH	MPA6-10 m NR, MPA+ letrozole 3 m PR, GnRHa2m PR, EC undetermined	15
	9	34	AEH	MA 3 m PR, 6 m PR (CH), maintenance therapy	12	EC IaG1	irregular treatment for 10 m ,MA 5 m NR, GnRHa3-6m NR	22
	10	28	EC IaG1	History of CH (MA), MPA+GnRHa3m PR, 6 m CR	58	EC IaG1	MPA+ GnRHa(2 injections)4 m NR	4
	11	33	EC IaG1	MPA2m NR, 6 m PR, 10 m CR	4	AEH	unknown treatment, 8–10 m NR	10
Fertility completed	12	28	EC IaG1	MA 11 m CR	15	EC IaG1	GnRHa 3 m PR, 6 m CR	32
Multiple recurrence	13	34	AEH	MA 3 m CR, maintenance therapy	15	AEH, EC undetermined	MA 5 m CR	–
					16	AEH, cancer not excluded	MA4m PR, 10 m CR, maintenance therapy (levonorgestrel-releasing intrauterine device, LNG-IUD)	–
					19	EC IaG1	MA 2 m	2
	14	33	EC IaG1	MPA 3 m PR, 17 m CR	10	EC IaG1	MPA+GnRHa 4 m CR	
					30	ECIaG1	–	<1
	15	36	AEH	Contraceptive 3 m PR, MPA 3 m CR	13	AEH	MPA 4 m CR	
					8	EC IaG2	MPA 1 m	2

EC, endometrial cancer; AEH, atypical endometrial hyperplasia; MPA, medroxyprogesterone acetate; MA, megestrol acetate; GnRHa, gonadotrophin releasing hormone agonist; CH: complex hyperplasia; CR, complete response; PR, partial response; NR, no response MA MPA.

Table 2
Surgical procedures, pathology and follow-up outcomes of fifteen patients.

Group	No.	Age (y)	Initial pathology	Surgical type	Recurrent pathology	Postoperative pathology	Myometrial infiltration	Pathology before and after surgery	Postoperative management	Prognosis	Follow-up time(m)
Without retreatment	1	40	AEH	TH	AEH	No lesions	–	Consistent	–	NED	9
	2	36	AEH	TH	AEH	AEH	–	Consistent	–	NED	30
	3	37	AEH	TH	AEH	EC IaG1	–	Upgrade[a]	–	NED	11
	4	32	AEH	Staging surgery	EC IaG1	EC IaG1 Ovarian inclusion cyst (right ovary)	Superficial	Consistent	–	NED	9
	5	24	EC Ia G1	TH	EC IaG1	EC IaG1	Superficial	Consistent	–	NED	53
	6	28	EC IaG1	TH	EC IaG1	EC IaG1	Superficial	Consistent	–	NED	25
	7	32	AEH	Staging surgery	EC IaG1	EC IaG1	Superficial	Consistent	–	NED	3
Failure to retreatment	8	28	AEH	TH	AEH	AEH	–	Consistent	–	NED	70
	9	34	AEH	Staging surgery	EC IaG1	EC IaG1; ovarian endometrioid adenocarcinoma IC2 (left ovary)	Superficial	Consistent	Four courses of chemotherapy	NED	5[b]
	10	28	EC IaG1	TH+BSO(preserving partial left ovary)	EC IaG1	EC IaG1; ovarian borderline endometrioid adenocarcinoma (bilateral ovaries)	–	Consistent	–	NED	22
	11	33	EC IaG1	TH	AEH	EC IaG1	Superficial	Upgrade[a]	–	NED	118
Fertility completed	12	28	EC IaG1	(CR)subtotal hysterectomy	EC IaG1	No lesions	–	Consistent	–	NED	3
Multiple recurrence	13	34	AEH	Staging surgery	EC IaG1	EC IIIc G1	–	Upgrade[a]	Six courses of chemotherapy	NED	5[b]
	14	33	EC IaG1	Staging surgery (preserving bilateral ovaries)	EC IaG1	EC IaG1	–	Accord	–	NED	26
	15	36	AEH	TH	EC IaG2	EC Ia	–	Accord	–	NED	61

TH, total hysterectomy; BSO: bilateral salpingooophoreclomy; EC, endometrial cancer; AEH, atypical endometrial hyperplasia; NED: no evidence of disease.
[a] Upgrade: pathological type upgrades (AEH before while EC after), or pathological stage upgrades.
[b] Follow-up time: duration between last course of chemotherapy and the last follow-up.

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One patients (case 12) got pregnant via in vitro fertilization (IVF) after complete remission resulted from re-treatment and underwent prophylactic hysterectomy after a term live birth; and there was no lesion in uterus and placenta in postoperative pathology.

Three patients (case 13–15) underwent hysterectomy because of multiple recurrence. Two of the three had consistent pre- and post-operative pathology with EC. The other one (case 13) upgraded to EC IIIc G1 with metastasis to pelvic lymph nodes and parametrial tissue, and was given six courses of postoperative adjuvant chemotherapy. During the follow-up period of 17 months (range 3–118), all 15 patients were alive and showed no evidence of disease.

3.4. Risk factors for patients who had multiple recurrence or failure to re-treatment

Risk factors for patients with multiple recurrence and failure to re-treatment are shown in Table 3. Six patients were diagnosed with obesity or overweight and six were with insulin resistance. For the 7 patients, the median time interval of primary treatment was 4.7 (range 3–17) months. While receiving re-treatment, ovarian tumors were found in two patients (case 9 and 10) who showed no response to re-treatment at the 4-month and 12-month follow-up and the postoperative pathology turned out to be synchronous primary carcinomas. One of them was diagnosed with Lynch syndrome by gene testing (case 9). As for the patient with a third recurrence (case 9 and 10), each treatment interval to complete remission was three, five and ten months, respectively, and finally the patient was diagnosed with EC IIIc G1 with metastasis to pelvic lymph nodes, and parametrial tissue.

4. Discussion

Fertility-sparing therapy is not the standard treatment for endometrial cancer while young patients with endometrial cancer usually face the dilemma of standard cancer treatment and fertility desire. A meta-analysis reported that hysterectomy rate was 48.5% (397/818) in EC and AEH patients who were ≤45 years old [5]. The rate was relatively high because that it included patients who were given short-term progestin before hysterectomy. Hysterectomy rate were 7.1% (2/8, in EC patients) and 6.25% (in AEH patients) in other two studies [6,7], which was consistent with our result (7.4%). This study analyzed fertility-sparing regimen, surgical treatment outcomes including pre- and postoperative pathology and prognosis for patients who had hysterectomy with recurrent EC or AEH, for clinical practice reference.

4.1. Indication of hysterectomy for recurrent EC or AEH patients

It is recommended by the European Society of Gynecological Oncology (ESGO) that re-treatment with progestin was effective for those complete responders who experienced recurrence [8]. Park et al. reported 85% (28/33) recurrent patients achieved complete response to retreatment [9]. A retrospective study suggested that among the 41 recurrent patients after CR, the complete response rate was 82.6% (19/23) in the second-round fertility-sparing treatment and there was no significant difference in the treatment duration to CR between the primary and retreatment groups (6.0 vs 5.8 months, respectively). Especially, two patients received a third-round treatment after the second recurrence and also achieved CR [10]. Yamagami et al. reported that complete response rates in the primary and retreatment groups were 98.5% (53/54) and 96.4% (27/28), respectively [11]. In this study, one patient achieved CR at the second-round conservative treatment and had a full-term delivery. Therefore, remission and pregnancy is possible in recurrent EC or AEH patients who received retreatment if they meet indications of fertility-sparing treatment. But evaluation of risk and willingness of patients should be considered at first.

In the study, indications of hysterectomy for recurrent EC or AEH patients are as follows, no desire of fertility preservation, live birth accomplished, failure to re-treatment and multiple recurrence. All of the four patients in the group of failure to retreatment had high BMI or insulin resistance condition. It suggests that insulin resistance and overweight may compromise the treatment efficacy to progestin. Some literature suggested that insulin resistance and overweight were associated with longer therapeutic duration [12,13]. Therefore, patients with these conditions may be at higher risk of failure to fertility-sparing treatment and thus require surgery consideration earlier. In addition, ovarian cyst were found in two patients on imaging assessment, whose endometrial pathology at the 4-month and 12-month follow-up showed no response to re-retreatment. Signorelli et al. reported that two patients had simultaneous ovarian tumor despite negative ovarian assessment on MRI imaging and laparoscopic exploration [14]. Thus, treatment failure might related with possible ovarian cyst and it's essential to evaluate the risk of ovarian tumor and extra-uterine metastasis during treatment. Prompt surgical exploration is necessary when extra-uterine lesions is highly suspected. Multiple recurrence is another proper indication for hystrectomy. Time to complete remission extended gradually in one patient (case 13), and the tumor finally progressed to IIIc stage. It reminds us multiple recurrent patients may have poor efficacy, and high risk of relapse. Although the mortality rate was very low in early-stage EC patients, one patient died from multiple recurrence with simultaneous endometrial cancer, ovarian tumor and primary peritoneal carcinoma [15]. Therefore, patients with recurrence, especially multiple recurrence, were at high risk when insisting on fertility-sparing treatment. In consideration of the possibility of tumor progression and indeterminate efficacy, we recommend surgery for multiple recurrent patients.

Table 3
Risk factors of seven patients who had multiple recurrence or failure to re-treatment.

	No.	BMI(kg/m^2)	HOMA-IR*	Initial pathology	Primary treatment (m)	Recurrent pathology	Re-treatment (m)	Ovarian cyst
Failure to retreatment	8	28.3	3.85	AEH	8	AEH	15	–
	9	34.4	13.45	AEH	6	EC Ia G1	11	8 and 11 m, left ovarian cyst by ultrasound
	10	29.1	8.02	EC IaG1	6	EC Ia G1	4	0 and 2 m, left and right ovarian cyst by ultrasound
	11	25.4	3.52	EC IaG1	10	AEH	10	–
Multiple recurrence	13	23	40.0	AEH	3	AEH, EC undetermined	5	–
						AEH, cancer not excluded	10	
						EC Ia G1	2	
	14	35.4	6.75	EC Ia G1	17	EC Ia G1	4	–
						EC Ia G1	–	
	15	33.2	-#	AEH	3	AEH	4	–
						EC Ia G2	1	

EC, endometrial cancer; AEH, atypical endometrial hyperplasia; CR, complete response; PR, partial response; NR, no response; PD, disease progression.
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4.2. Consistency between hysteroscopic biopsy and hysterectomy pathology

Hysteroscopic and hysterectomy pathology were consistent in 80.0% patients (12/15) in this study. Three patients had pathological upgrading, including one with direct hysterectomy, one with failure to retreatment and one with multiple recurrence. Zakhour et al. suggested 19% (16/46) had disease progression among 46 patients who underwent hysterectomy [16]. Chen et al. reported that in 14 patients underwent hysterectomy, 14.3% had pathological upgrade [17]. A meta-analysis reported that consistency rate between hysteroscopic biopsy and hysterectomy pathology in EC patients was 89% [18]. Compared with literature, the consistency rate in this study was lower while disease progression rate was higher. The reasons may result from the cohort was relatively small, patients enrolled in the study were recurrent cases who generally have poor treatment efficacy; and the interval between last hysteroscopy and hysterectomy surgery was quite long (38.6 days on average), during which disease might progress.

It is also worth noting that five patients had myometrial infiltration in ten recurrent EC patients who actually did not meet the fertility-sparing indications. Currently pelvic MRI is recommended to detect myometrial infiltration while its accuracy is influenced by many factors, like skills of radiologists, image resolution and images change due to hysteroscopic resection. It's difficult to accurately evaluate minimal or superficial myometrial infiltration with current technology. A prospective study reported that nineteen patients underwent hysterectomy because of recurrence or poor efficacy and seven of them were diagnosed with myometrial infiltration [19]. This study also confirmed that recurrent patients were at high risk of myometrial infiltration and lead to poor efficacy. Before starting fertility-sparing therapy, imaging examination and sufficient materials from suspicious lesions are essential for evaluating suspicious myometrial infiltration.

4.3. Oncological safety after hysterectomy

In this study, all patients showed no evidence of the disease during the observation period (median 17 months, range 3–118 months). It suggested patients who underwent hysterectomy after fertility-sparing therapy had favorable prognosis. In a population-based study, among 638 patients with EC stage Ia, only seven experienced recurrence and their recurrence-free survival varied (8–50 months) [20]. Chen et al. reported that one in fourteen non-responder experienced vaginal recurrence 4 years after hysterectomy [17]. The likely reasons that no recurrence occurred during the follow-up period in the study are most patients were in early-stage, with tumor confined to uterus and no distant metastasis. Nevertheless, with only five months' follow-up time for the one IIIc EC case, long-term outcome is not yet known. Despite the general favorable prognosis, late recurrence might occur even after surgery. Adjuvant therapy according to postoperative pathological stage and close follow-up are necessary. Long-term follow-up is required to clarify the relationship between fertility-sparing therapy and prognosis.

5. Conclusion

Gynecologists should always consider the indication and timing of hysterectomy during the fertility-sparing treatment. Termination of conservative treatment should be base on comprehensive evaluation including risk factors, pathological response, times of recurrence and patients' desire. Patients with initial recurrence could receive second-round conservative treatment with close follow-up. Surgery is recommended for patients with risk factors such as insulin resistance and obesity, multiple recurrent, indeterminate oncological safety and less fertility opportunity. Hysteroscopic pathology is the current basic approach to assess the treatment response. However, hysteroscopic and post-hysterectomy pathology are not always consistent, especially in evaluation of myometrial infiltration. So comprehensive accessment by imaging and hysterescopy should be obtained before fertility-sparing treatment. Hysterectomy usually provides good prognosis for patients with recurrent EC or AEH while more research is needed to evaluate its long-term safety.

Conflicts of interest

The authors declare that they have no conflict of interest.

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References

[1]. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA A Cancer J. Clin.* 2016;66(2):115–132.
[2]. Corzo C, Santillan NB, Westin SN, et al. Updates on conservative management of endometrial cancer. *Obstet. Gynecol. Surv.* 2017;72(12):715–716.
[3]. Zhou R, Lu Q, Liu GL, et al. Expert consensus for fertility-sparing therapy in early-stage endometrial cancer. *Chin. J. Clin. Obstet. Gynecol.*. 2019;(4):369–373 [J].
[4]. Insulin resistance group of Chinese Diabetes Society. Expert guidance on insulin resistance assessment method and application. *Chin. J. Diabetes Mellitus.* 2018; 10(6):377–385 [J].
[5]. Harrison RF, He W, Fu SS, et al. National patterns of care and fertility outcomes for reproductive-aged women with endometrial cancer or atypical hyperplasia. *Am. J. Obstet. Gynecol.* 2019;221(5):474 e1–474 e11.
[6]. Falcone F, Laurelli G, Losito S, et al. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. *J. Gynecol. Oncol.* 2017;28(1):e2.
[7]. Li M, Song JL, Zhao Y, et al. Fertility outcomes in infertile women with complex hyperplasia or complex atypical hyperplasia who received progestin therapy and in vitro fertilization. *J. Zhejiang Univ. - Sci. B.* 2017;18(11):1022–1025.
[8]. Rodolakis A, Biliatis L, Morice P, et al. European society of gynecological Oncology task force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. *Int. J. Gynecol. Canc. Off. J. Int. Gynecol. Canc. Soc.* 2015;25(7):1258.
[9]. Park JY, Lee SH, Seong SJ, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. *Gynecol. Oncol.* 2013;129(1):7–11.
[10]. Wang Y, Yu M, Yang JX, et al. Prolonged conservative treatment in patients with recurrent endometrial cancer after primary fertility-sparing therapy: 15-year experience. *Int. J. Clin. Oncol.* 2019;24(6):712–720.
[11]. Yamagami W, et al. Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility? *J. Gynecol. Oncol.* 2018;29(2). e21-e21.
[12]. Yang, B, Yamagami W, Susumu N, et al, Insulin resistance and overweight prolonged fertility-sparing treatment duration in endometrial atypical hyperplasia patients. J. Gynecol. Oncol.. 29(3): p. e35..
[13]. Li M, Guo T, Cui R, et al. Weight control is vital for patients with early-stage endometrial cancer or complex atypical hyperplasia who have received progestin therapy to spare fertility: a systematic review and meta-analysis. *Canc. Manag. Res.* 2019;11:4005–4021.
[14]. Signorelli M, Caspani G, Bonazzi C, et al. Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. *BJOG An Int. J. Obstet. Gynaecol.* 2009; 116(1):114–118.
[15]. Gallos, ID, Yap J, Rajkhowa M, et al, Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am. J. Obstet. Gynecol.. 207(4): p. 266.e1-266.e12.
[16]. Zakhour M, Cohen JG, Gibson A, et al. Abnormal mismatch repair and other clinicopathologic predictors of poor response to progestin treatment in young women with endometrial complex atypical hyperplasia and well-differentiated endometrial adenocarcinoma: a consecutive case series. *BJOG An Int. J. Obstet. Gynaecol.* 2017; 124(10):1576–1583.
[17]. Chen M, Jin Y, Li Y, et al. Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. *Int. J. Gynaecol. Obstet.* 2016;132(1):34–38.
[18]. Visser NCM, Reijnen C, Massuger LF, et al. Accuracy of endometrial sampling in endometrial carcinoma: a systematic review and meta-analysis. *Obstet. Gynecol.* 2017;130(4):803–813.
[19]. Ushijima K, Yahata H, Yoshikawa H, 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(19):2798–2803.
[20]. Lyu T, Guo L, Chen XJ, et al. Ovarian preservation for premenopausal women with early-stage endometrial cancer: a Chinese retrospective study. *J. Int. Med. Res.* 2019;47(6):2492–2498.

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