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Original Article

Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer

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No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: To report our 15-year institutional experience of fertility-sparing treatment in young patients with early endometrial cancer (EC) treated by combined hysteroscopic resection and progestin therapy.
Methods: Twenty-eight patients (stage IA, G1 and 2 endometrioid EC) wishing to preserve their fertility were enrolled into this prospective study. Hysteroscopic resection was used to resect the tumor, endometrium adjacent to the tumor and myometrium underlying the tumor. Adjuvant hormonal therapy consisted of oral megestrol acetate or levonorgestrel intrauterine device for 6 months or more.
Results: After 3 months from the progestin start date, 25 patients (89.3%) showed a complete regression (median time to complete regression, 3 months [range, 3-9 months]), two (7.1%) showed persistent disease, while one patient (3.6%) presented with progressive disease and underwent definitive surgery (stage IA, G3 endometrioid). At 6 months, one of the two patients with persistent disease underwent definitive surgery (stage IA, G1 endometrioid), while the other one was successfully re-treated. Two recurrences were observed (7.7%) both involving the endometrium and synchronous ovarian cancer. The median duration of complete response was 94.5 months (range, 8-175 months). More than half of the responders (57.7%) attempted to conceive with 93.3% and 86.6% pregnancy and live birth rates, respectively.
Conclusion: The addition of a standardized three-step resectoscopy to progestin would seem to improve the efficacy of progestin alone. High pregnancy and live birth rates were observed in women attempting to conceive.

Keywords: Endometrial Neoplasms; Fertility Preservation; Hormonal Therapy; Hysteroscopy

INTRODUCTION

Twenty-five percent of endometrial cancer (EC) are diagnosed in premenopausal women and up to 5% in women aged less than 40 years. The current therapeutic standard in an early stage EC is preclusive of fertility and consists of staging total hysterectomy, bilateral salpingo-oophorectomy, and eventual pelvic and aortic lymphadenectomy [1,2].

When arising in women of childbearing age, EC usually presents with favourable prognostic features, that are: endometrioid hystotype, focal and well-differentiated (G1) lesion, absent or minimal myometrial invasion [1,3]. This profile corresponds to the type 1 EC, which correlates with the estrogen/progesterone receptor (PR) positive pattern. In young women wishing to preserve their fertility, the decision making process with respect to a conservative management must take into consideration different risks: the inherent oncologic risk of an inadequately staged/treated disease, the potential risk of a synchronous/metachronous ovarian cancer (OC), and an inherited genetic cancer risk. Furthermore, there is no consensus regarding the ideal EC conservative treatment or the eligible cases.

Fertility-sparing treatment modalities are mainly based on progestin therapy; an alternative approach to progestin alone combines operative hysteroscopy and hormonal therapy. Medroxyprogesterone acetate (MPA), megestrol acetate (MA), and, more recently, levonorgestrel intrauterine device (LNG-IUD) are the most commonly used progestins. The dose (for oral progestins), and duration of treatment are, however, not yet standardized. Finally, data on conservative strategy are still limited, mostly based on small retrospective series generally in the absence of long-term treatment outcomes [4,5].

In this paper, we report our 15-year institutional experience of fertility-sparing treatment in early EC together with an overview of the most recent literature data.

MATERIALS AND METHODS

From December 2001 to March 2016, at the Gynecologic Oncology Department of the National Cancer Institute of Naples, 43 women aged 18 to 40 years, clinically diagnosed with early stage EC and wishing to preserve their fertility, were screened for fertility-sparing management. Primary and secondary outcome measures were respectively complete regression and recurrence rates, and pregnancy and live birth rates. Approval was obtained from the Institutional Ethics Committee, and the trial was subsequently registered at EU Clinical Trials Register (EudraCT 2010-018581-23). A pre-treatment oncologic and reproductive counseling were included in the screening workup. Patients were enrolled if they met the criteria listed in **Table 1**. Hysteroscopic resection (HR) was performed using a 5 mm cutting loop electrode to resect (1) the tumor lesion, (2) the endometrium adjacent to the tumor, (3) the myometrium underlying the tumor. The hysteroscopic procedure is further detailed in our previous paper [6]. If final pathology confirmed a G1 endometrioid EC with no myometrial invasion and PR positivity at immunohistochemistry, hormone therapy was started 1 week after HR. All histological slides were reviewed by two pathologists specializing in gynecologic oncology. A diagnostic laparoscopy (including surface ovarian biopsies and peritoneal cytology) was incorporated in the enrollment workup of the last 22 patients. Fifteen patients (34.8%) were excluded after the screening phase (two for positive cancer family history; eight for moderately (G2)/poorly (G3) differentiated EC; five for myometrial infiltration at magnetic resonance [MR]).

Table 1. Enrollment criteria for fertility-sparing treatment of EEC

Inclusion criteria
18–40 years
Pathological diagnosis of G1 EEC with PR ≥50% positivity at IHC
No radiologic (TVS; abdomen-pelvis MR; CXR) evidence of
myometrial/cervical invasion
retroperitoneal lymph node involvement
ovarian tumors
distant metastasis
CA-125 serum levels <35 IU/mL
No contraindication for adjuvant progestin treatment
Strong desire to preserve fertility
Written acceptance of an informed consent including availability for completing the follow-up program and definitive surgery after complete childbearing
Exclusion criteria
History of previous/concomitant cancer*
Patient belonging to a family with the Lynch II/HNPCC syndrome
BRCA mutation
Multifocal tumor

CA-125, cancer antigen 125; CXR, chest-X-ray; EEC, endometrioid endometrial cancer; G1, well-differentiated; HNPCC, hereditary non-polyposis colorectal cancer; IHC, immunohistochemistry; MR, magnetic resonance; PR, progesterone receptor; TVS, transvaginal ultrasonography.

*Except for adequately treated skin basal cell or *in situ* cervical cancer.

Adjuvant hormonal therapy consisted of oral MA (six patients, 22%) or LNG-IUD (21 patients, 78%). MA was started at 40 mg daily and increased gradually according to patient's tolerance to the recommended total dose of 160 mg daily for 6 months. LNG-IUD, releasing 20 mcg of levonorgestrel daily, was planned to be *in situ* for at least 6 months. Three months after starting progestin therapy, patients entered the follow-up phase undergoing: 3-monthly general and gynecological examinations, transvaginal ultrasonography (TVS), serum cancer antigen 125 (CA-125) and diagnostic hysteroscopy; an abdomen-pelvis computed tomography (CT) was performed at 6 months and 6-monthly thereafter. After 2 years, patients still in complete regression and wishing to maintain their reproductive potential were followed through 6-monthly general and gynecological examinations, TVS, serum CA-125, and diagnostic hysteroscopy. Patients in complete regression after hormone treatment were encouraged to conceive with or without assisted reproduction technology (ART). In the case of conception, pregnant patients were followed according a routine obstetrical schedule, with a follow-up visit 3 months after delivery. Women who successfully completed childbearing or who failed in their attempts to conceive were encouraged to undergo definitive surgery (total abdominal hysterectomy and bilateral salpingo-ophorectomy [TAH-BSO]).

Complete regression was defined as no evidence of residual EC or atypical hyperplasia (AH) at follow-up endometrial sampling. Time until complete regression was measured from the progestin start date. Partial regression was defined as the presence of AH during follow-up endometrial sampling, persistent disease if no evidence of disease regression was observed within 6 months from progestin initiation, and progressive disease if higher than stage IA (according to 1988 staging system of The International Federation of Gynecology and Obstetrics [FIGO]) and/or G2-3 EC was diagnosed during follow-up. Recurrence was defined as the presence of EC or AH during follow-up after an endometrial sample showing disease regression. Time to recurrence was measured from the date of complete regression. Patients showing persistent, progressive or recurrent disease were planned to undergo definitive surgery.

RESULTS

Twenty-eight patients, aged 25 to 40 years, with EC limited to the endometrium were enrolled. Nineteen patients (67.8%) showed a ≥25 kg/m^2 body mass index (BMI). EC diagnosis was performed during investigations for infertility in 11 cases (39.3%), and abnormal uterine bleeding in the remaining 17 cases (60.7%). Thirteen patients (46.4%) have had no previous pregnancies; 11 (39.3%) referred one or more spontaneous abortions, the remaining four (14.3%) have had babies, wishing further pregnancies. Dilation and curettage (D&C, 53.6%) and hysteroscopic biopsy (46.4%) were performed for the histological diagnosis. Twenty-six patients (93%) presented with a ≤2 cm, and two (7%) with a >2 cm tumor diameter; all but one (G2) showed a G1 endometrioid histotype. In particular, the G2 patient, although fully informed about her higher risk of recurrence, decided to undergo a conservative treatment as well. All patients were submitted to HR. Diagnostic laparoscopy was performed during the same surgical session in the last 22 patients and was negative in all, both in terms of ovarian surface biopsies and peritoneal cytological abnormalities. The first six patients were surgically treated on a day-surgery basis, while the last 22 (additional laparoscopy) with a median hospital stay of 2 days (range, 2 to 3 days), with no perioperative complications. Pathological examination of hysteroscopic surgical specimens confirmed the endometrioid histotype, grade, PR ≥50% positivity, and the absence of myometrial invasion in all cases. The first six patients (21.4%) received oral MA for 6 months, while a LNG-IUD was placed to the subsequent 22 patients (78.6%). In particular, the duration of LNG-IUD varied depending on pregnancy desire. Complete responders not wishing to conceive after the first 6 months were encouraged to keep LNG-IUD *in situ* (median 18 [range, 3 to 60]). **Table 2** reports demographics, clinical-pathological characteristics, and conservative treatment pattern.

The compliance to treatment and follow-up was good and both hormonal therapies were well tolerated with no cases of treatment interruption. The median follow-up from the end of treatment was 92 months (range, 6 to 172 months). After 6 months from the progestin start date, 25 patients (89.3%) showed a complete regression (median time to complete regression, 3 months [range, 3 to 9 months]), two (7.1%) showed persistent disease, while one patient (3.6%) had already presented with progressive disease at 3 months. Two of the non-responders (cases 13 and 20) underwent definitive surgery: the final pathology showing a stage IA (intramucous) G1 endometrioid, and a stage IA (with myometrial invasion) G3 endometrioid EC, respectively. The latter non-responding patient (case 27), due to her strong desire to preserve fertility, refused the proposed definitive surgery and was re-treated with repeated HR and LNG-IUD. Eight months from the endometrial complete response to re-treatment, she was found to have bilateral ovarian masses and underwent definitive surgery with a diagnosis of stage IIB G1 endometrioid OC and endometrial AH. Patient of case 12, 41 months from complete response, was found to have an ovarian mass and treated by definitive surgery, showing a stage IA G1 endometrioid OC and a synchronous asymptomatic endometrioid G1 intramucous EC. A complete response was observed at the 3-month hysteroscopy in 25 patients, and in one further patient (case 27) after re-treatment, with an overall complete response rate of 92.8%, increased to 96.3% when only G1 patients are considered. The median duration of complete response was 94.5 months (range, 8 to 175 months). Fifteen complete responders (57.7%) attempted to conceive: 14 (93.3%) achieved at least one pregnancy and 13 (86.6%) gave birth to a healthy child. In particular, 11 patients (73.3%) underwent ART: nine of these had one live born infant, one had two spontaneous abortions, and another one had no pregnancies. The remaining four patients, who did not

Table 2. Demographics, clinicopathologic characteristics, and conservative treatment of endometrial cancer

Case	Age (yr)	BMI (kg/m^2)	Previous pregnancy	Diagnostic method	Tumor diameter (cm)/grade	Surgical approach	Adjuvant HT (mo)
1	40	24.8	SFTM	HSC	≤2/G1	HR	Oral MA (6)
2	39	25.0	-	HSC	≤2/G1	HR	Oral MA (6)
3	38	26.3	-	D&C	≤2/G1	HR	Oral MA (6)
4	36	27.3	SFTM	D&C	≤2/G1	HR	Oral MA (6)
5	37	31.0	SFTM	D&C	≤2/G1	HR	Oral MA (6)
6	38	25.4	-	D&C	≤2/G1	HR	Oral MA (6)
7	37	23.3	1 SFTM	HSC	≤2/G1	HR and LPS	LNG-IUD (18)
8	39	28.5	1 SFTM	HSC	≤2/G1	HR and LPS	LNG-IUD (24)
9	39	26.3	2 SFTM	HSC	≤2/G1	HR and LPS	LNG-IUD (60)
10	39	48.0	1 NFTD	HSC	≤2/G1	HR and LPS	LNG-IUD (60)
11	37	23.5	2 NFTD	D&C	≤2/G1	HR and LPS	LNG-IUD (30)
12	40	24.2	-	HSC	<2/G1	HR and LPS	LNG-IUD (24)
13	28	53.5	1 NFTD	HSC	≤2/G1	HR and LPS	LNG-IUD (6)
14	26	27.3	-	D&C	≤2/G1	HR and LPS	LNG-IUD (60)
15	40	24.8	1 SFTM	HSC	≤2/G1	HR and LPS	LNG-IUD (60)
16	38	25.4	-	D&C	≤2/G1	HR and LPS	LNG-IUD (6)
17	33	27.3	-	HSC	≤2/G1	HR and LPS	LNG-IUD (9)
18	35	26.3	1 SFTM	D&C	≤2/G1	HR and LPS	LNG-IUD (6)
19	25	24.5	-	D&C	≤2/G1	HR and LPS	LNG-IUD (24)
20	39	24.3	-	HSC	>2/G2	HR and LPS	LNG-IUD (3)
21	39	25.0	-	HSC	≤2/G1	HR and LPS	LNG-IUD (60)
22	36	28.7	1 SFTM	D&C	≤2/G1	HR and LPS	LNG-IUD (14)
23	36	28.3	1 SFTM	D&C	≤2/G1	HR and LPS	LNG-IUD (24)
24	38	26.3	-	D&C	≤2/G1	HR and LPS	LNG-IUD (6)
25	37	31.0	1 SFTM	D&C	≤2/G1	HR and LPS	LNG-IUD (18)
26	38	30.1	1 NFTD	D&C	≤2/G1	HR and LPS	LNG-IUD (12)
27	35	23.2	-	HSC	≤2/G1	HR and LPS	LNG-IUD (18)
28	30	20.9	-	D&C	≤2/G1	HR and LPS	LNG-IUD (6)

BMI, body mass index; D&C, dilation and curettage; HR, hysteroscopic resection; HSC, hysteroscopy; HT, hormonal therapy; LNG-IUD, levonorgestrel intrauterine device; LPS, laparoscopy; MA, megestrol acetate; NFTD, normal full-term delivery; SFTM, spontaneous first-trimester miscarriage.

undergo ART, had each one live born infant. Among 24 women who did not show persistent, progressive, or recurrent disease, definitive surgery was performed in eight women at the time of caesarean section, in 11 at completion of the 5-year follow-up, while the remaining five women have so far refused. The oncologic and reproductive outcomes are detailed in **Table 3**. To date, all patients are alive with no evidence of disease.

DISCUSSION

In the present paper, we report about our institutional prospective series of early-stage EC patients who were selected for fertility preservation, and treated by combined HR and progestin therapy. This is the largest series of EC treated by such a combined approach, and that with the longest follow-up published so far (**Table 4**) [7-12]. In our experience, this strategy, in young women with intramucous G1 EC, resulted in a complete regression rate of 96.3% (26/27), with a recurrence rate of 7.7% (2/26). Therefore, 85.7% (24/28) of our patients achieved a durable complete response, with a median duration of 95 months (range, 9 to 175 months). Since the achievement of pregnancy is the most important indicator of the success of uterine preservation, the observed 93.3% pregnancy rate and 86.6% live birth rate among women who tried to conceive, represent remarkable results.

Candidates for conservative management are generally considered women younger than 40 years with limited to the endometrium, well-differentiated, endometrioid EC, with no evidence of extrauterine spread, who are highly motivated to maintain their reproductive function [1,3].

Table 3. Oncologic and reproductive outcomes of endometrial cancer patients conservatively treated

Case	Oncologic outcome at 6 mo	Relapse (mo)	Second cancer (mo)	Attempting to conceive	Pregnancy	Follow-up (mo)	Current status
1	CR	-	-	-	-	172	NED*
2	CR	-	-	-	-	171	NED
3	CR	-	-	-	-	161	NED*
4	CR	-	-	Yes	1 NFTD	156	NED*
5	CR	-	-	Yes (ART)	1 NFTD	150	NED
6	CR	-	-	Yes (ART)	1 NFTD	144	NED*
7	CR	-	-	Yes (ART)	2 SFTM	116	NED*
8	CR	-	-	-	-	110	NED*
9	CR	-	-	Yes (ART)	-	105	NED*
10	CR	-	-	-	-	103	NED*
11	CR	-	-	-	-	100	NED*
12	CR	Endometrial (41)	Ovarian (41)	-	-	98	NED*
13	Persistence	-	-	-	-	95	NED*
14	CR	-	-	Yes	1 NFTD	92	NED*
15	CR	-	-	-	-	92	NED*
16	CR	-	-	Yes (ART)	1 NFTD	91	NED*
17	CR	-	-	Yes (ART)	1 NFTD	87	NED*
18	CR	-	-	Yes	1 NFTD	84	NED*
19	CR	-	-	Yes	1 NFTD	79	NED*
20	Progression†	-	-	-	-	78	NED*
21	CR	-	-	-	-	76	NED
22	CR	-	-	Yes (ART)	1 NFTD	73	NED*
23	CR	-	-	Yes (ART)	1 SFTM, 1 NFTD	57	NED*
24	CR	-	-	Yes (ART)	1 NFTD	56	NED*
25	CR	-	-	Yes (ART)	1 NFTD	50	NED
26	CR	-	-	Yes (ART)	1 NFTD	37	NED*
27	CR‡	Endometrial (8)	Ovarian (8)	-	-	32	NED*
28	CR	-	-	-	-	6	NED

ART, assisted reproduction technology; CR, complete regression; NED, no evidence of disease; NFTD, normal full-term delivery; SFTM, spontaneous first-trimester miscarriage.

*Submitted to definitive surgery. †Definitive surgery at 3 months. ‡After re-treatment of persistent disease at 6 months.

Table 4. Literature review of early, well-differentiated, endometrioid endometrial cancer conservatively treated by combined hysteroscopic resection and progestin therapy

Study	No.	Resectoscopic technique	Adjuvant treatment (mg/day)	Oncologic outcome at 6 mo	Relapse	DFI (mo)	Pregnancy (no. of patients)	Live births	Follow-up (mo)	Current status
Mazzon et al. (2010) [12]	6	Three steps*	MA (160)	CR	-	NA	4	5	21–82	NED
Shan et al. (2013) [11]	14	EER	MA (160-200)	11 CR, 3 PD	3	10–24	2	1	15–66	13 NED, 1 AWD
Marton et al. (2014) [10]	2	EER	MPA (400) or LNG-IUD	CR	2	13–15	2	2	NR	NR
Arendas et al. (2015) [7]	2	Two steps*	MPA (300) or cyclic MPA (20–100)	CR	1	48	1	1	48–57	NED
De Marzi et al. (2015) [8]	3	Three steps*	MA (160) or LNG-IUD	CR	1	6	1	1	8–37	NED
Wang et al. (2015) [9]	6	Three steps*	MA (160)	CR	-	NA	3	3	26–91	NED
Present study	27	Three steps*	MA (160) or LNG-IUD	26 CR, 1 PD	2	8–41	14	13	6–172	NED

AWD, alive with disease; CR, complete regression; DFI, disease-free interval; EER, extensive endometrial resection; LNG-IUD, levonorgestrel intrauterine device; MA, megestrol acetate; MPA, medroxyprogesterone acetate; NA, not applicable; NED, no evidence of disease; NR, not reported; PD, persistent disease.

*Resection of the tumor and of a small layer of the myometrium below the lesion (two steps), and of the endometrium adjacent to the tumor (three steps).

D&C is associated with the lowest rate (<10%) of histological under-grading, and is still considered by some authors the elective diagnostic method in a fertility-sparing setting [3,13,14]. Hysteroscopic biopsy, however, is increasingly used for the diagnosis of EC. In the present series, both D&C or hysteroscopic biopsy were performed, with, in our hands, no high-grade tumors missed on the enrollment endometrial biopsy compared with the resectoscopic specimen. A potential increased risk of peritoneal spread during hysteroscopy caused by the use of liquid distension medium has been raised [15]. In a recent meta-analysis, although preoperative hysteroscopy resulted in a significantly increase of positive peritoneal

cytology, this was not confirmed in an early stage setting, and no impact on prognosis was observed [16]. In our series, there were no cases of positive peritoneal cytology among the 22 patients undergoing pre-treatment laparoscopy. Only one patient (3.5%) was included with intramucous G2 EC at pathological examination of hysteroscopic surgical specimen (**Table 3**). This patient showed progressive disease at 3 months, and underwent definitive surgery (stage IA with myometrial invasion G3 EC). Few studies have reported the outcomes of fertility-sparing treatment in patients with higher than low-grade intramucous disease [17,18]. Park et al. [17] reported a complete response rate in the 17 patients with intramucous G2-3 EC not significantly lower than that observed in G1 patients (76.5% vs 77.7%), nor higher was the recurrence rate (23.1% vs 30.4%). These results, however, are based on very limited numbers, and a conservative management of moderate-high grade disease should still be considered with caution.

Contrast enhanced MR is the most accurate method to detect myometrial involvement [19], but TVS has also yielded promising results when performed by experienced and dedicated sonographers [20]. In our series, the combined use of TVS and MR resulted very accurate, with pathological examination of hysteroscopic surgical specimens confirming the absence of myometrial invasion in all patients with no false negative cases at imaging examination. Therefore, in our experience, the HR does not seem to add a significant benefit, at least in terms of pathologic assessment.

Young EC patients are potentially (5% to 10%) harbouring a germ-line mutation in DNA mismatch repair (MMR) genes (Lynch II/hereditary nonpolyposis colorectal cancer [HNPCC] syndrome), characterized by increased lifetime risk for EC and OC (up to 60% and 24%, respectively) [21,22]. Current guidelines suggest that EC patients younger than 50 years should be routinely evaluated for Lynch II syndrome [21]. In our study, we excluded two women with a very suspicious cancer family history (with evidence of MMR mutation at subsequent genetic testing) and submitted them to conventional surgery. In fact, it is debatable whether an EC young patient with a MMR or a *BRCA1/2* mutation should not be offered a conservative management, since this should not be considered as a definitive treatment, and it should be followed by TAH-BSO after childbearing completion. In this perspective, fertility-sparing treatment may be also offered to patients at genetic high risk after appropriate counseling to be included in the pre-treatment workup even in the absence of a positive cancer family history.

In the past years [23,24], the risk of a synchronous OC (11% to 29%) in young EC patients has been likely overestimated, with lower incidence rates (3% to 4.5%) more recently reported [25,26]. In accordance with other authors [27,28], a pre-treatment laparoscopy was included in the study workup given the limited sensitivity of imaging techniques and CA-125 to detect subclinical synchronous lesions [27]. Since it was negative in all patients, its usefulness seems to be questionable.

Of hormonal treatments in EC, oral progestin therapy is the most commonly used, and its efficacy is well-known compared with other treatment modalities. There is no consensus, however, regarding the ideal progestin agent, dose, or duration of treatment. The two most common regimens are MPA at 500 to 600 mg daily and MA at 160 mg daily. The potency of these two drugs has been reported to be similar [29], with complete response rates in the most contemporary studies on exclusive oral progestins ranging from 55% to 78% [29-31]. The 96.3% complete regression rate observed in our G1 patients suggests that the addition

Table 5. Most recent series of early, well-differentiated, endometrioid endometrial cancer conservatively treated by progestin alone

Study	No.	Progestin treatment (mg/day)	Oncologic outcome at 6 mo	Relapse	DFI (mo)	Pregnancy (no. of patients)	Live births	Follow-up (mo)	Current status
Cade et al. (2010) [32]	16	MPA (60–400), LNG-IUD, or both	7 CR, 9 PD	2	NR	3	4	3–134	NED
Koskas et al. (2012) [33]	8	MA (160), MPA (10), Ly (15), or NA (5)	5 CR, 1 P, 2 PD	2	12–34	2	3	17–86	NED
Kim et al. (2013) [34]	16	Combined MPA (500) and LNG-IUD	9 CR, 7 PD	2	6–7	3	2	16–50	NED
Park et al. (2013) [29]	148	MPA (30–1,500) or MA (40–240)	115 CR, 33 PD	35	4–61	44	NR	14–194	NED
Kudesia et al. (2014) [35]	10	MA (160–240), LNG-IUD, or both	7 CR, 3 PD	NR	NR	NR	2	3–74	NR
Ohyagi-Hara et al. (2015) [36]	16	MPA (400–600)	11 CR, 1 P, 4 PD	9	NR	1	2	4–154	NR

CR, complete regression; DFI, disease-free interval; LNG-IUD, levonorgestrel intrauterine device; Ly, lynestrenol; MA, megestrol acetate; MPA, medroxyprogesterone acetate; NA, nomegestrol acetate; NED, no evidence of disease; NR, not reported; P, progression; PD, persistent disease.

of a standardized three-step resectoscopy may improve the efficacy of progestin alone, maximizing the likelihood of a durable disease regression. The overall 93.3% (range, 78% to 100%) complete regression rate, observed in the studies on combined HR and progestin therapy (**Table 4**) [7-12], seems to be higher than that reported in the most recent series including progestin therapy alone (77% [range, 43% to 78%]) (**Table 5**) [29,32-36]. The potential late risks of additional HR may consist of intrauterine adhesions and uterine rupture during pregnancy. Nevertheless, such complications have been unfrequently described following hysteroscopic myomectomies. In our study, HR is a much less invasive procedure, and, with the limitation of the small number of patients, no complications occurred.

In the earlier cases of our series, we administered a MA-based adjuvant hormonal therapy, while more recently LNG-IUD was adopted. In general, high-dose progestins carry some risk of side effects and complications, with a high likelihood of non-compliance. The choice of progestin, dose, and route of administration should be individualized to minimize risks such as thrombophlebitis, weight gain, headaches, sleep disorders, mood and libido changes, and leg cramps. The LNG-IUD delivers progesterone locally at a much higher concentration than do oral formulations, avoiding the risks of side-effects and complications associated with high-dose oral progestins. Despite LNG-IUD has not been studied as oral progestins, preliminary reports have documented that the use of LNG-IUD is equally effective compared to oral progestins in terms of response in patients with early EC [37]. An important additional benefit of LNG-IUD includes the efficacious drug delivery for up to 5 years. This appears very useful for women not planning to attempt pregnancy immediately after achieving disease complete regression. In this setting, maintenance treatment with low-dose cyclic progestin or an LNG-IUD has been shown to lower the risk of recurrence [29].

BMI ≥25 kg/m^2 has been found to be significantly associated with a higher risk of failure in achieving complete response to progestin treatment [29]. In the present series, one of the two patients showing persistent disease had a BMI of 53.5 kg/m^2. Obesity which is part of the EC-1 related metabolic syndrome, remains a significant risk factor of endometrial transformation even after primary treatment. This evidence suggests that a programme of weight loss intervention in the obese patients should be included into fertility-sparing protocols. It is to mention that a randomised trial is currently running in Australia to detect the additional benefit from a weight loss programme associated with LNG-IUD in patients with early stage type 1 EC not suitable for surgery (feMMe Trial, ANZGOG 1301) [38].

The median follow-up time in our study is the longest so far reported (92 months), confirming a very long median duration of response (94.5 months [range, 8 to 175 months]) allowing a sufficient time interval for childbearing before definitive surgery.

The risk of recurrence reported after completion of treatment is relatively high. The most contemporary meta-analysis showed a pooled recurrence rate of 40.6% after successful fertility-sparing therapy [5].

Overall, the recurrence rate observed in our study (7.7%) as well as in the studies of combined HR and progestins (16%) seems to be lower (**Table 4**) [7-12] than that reported after progestin therapy alone (32%) (**Table 5**) [29,32-36]. Although such comparisons are not methodologically correct, it may be argued that the hysteroscopic tumor resection gives some additional benefit. Such a potential benefit could be explained by the fact that an earlier complete regression can allow a more precocious attempt to conceive, with the pregnancy itself having a therapeutic effect.

Close surveillance is mandatory after achieving a complete response and should include a 3 to 6 monthly general and pelvic examination, endometrial sampling, serum CA-125, and TVS or CT to obtain a thorough evaluation of the adnexa. It is to note that the two recurrences in our series occurred in patients developing a concurrent OC. At the time of present publication, the mutational status of these patients is still unknown due to a delayed genetic testing. These cases showed both negative ovarian surface biopsies and peritoneal cytology at pre-treatment laparoscopy. Diagnosis of ovarian second neoplasm, however, occurred 18 and 44 months after staging laparoscopy, an interval time compatible with such negative findings.

It is important to recognize that conservative treatment is a temporizing measure. Recurrence rates after fertility-sparing therapy justify the main goal of conservative treatment: delaying any definitive surgery to allow childbearing. In this respect, the importance of counseling is to be emphasized. In our series, an adequate pre- and post-treatment counseling approach allowed us to perform definitive surgery in all but five patients.

Data on the pregnancy outcome after fertility-sparing therapy in EC are much less known than those on the oncologic safety. In a meta-analysis including 325 women from 26 studies, a pooled live birth rate of 28% is reported [5]. This rate, however, would be higher if only women who tried to conceive are considered. Park et al. [39] reported the largest series (141 patients) evaluated in terms of pregnancy outcome after progestin therapy in women with intramucous G1 EC. The overall live birth rate was 26%, but it was 66% when considering only women who tried to conceive [39]. Although all women included in our series wished to preserve their reproductive potential, only 57.7% of complete responders attempted to conceive during the study period. Among them, pregnancy and live birth rates were 93.3% and 86.6%, respectively. Overall, considering also women who did not attempt to conceive, pregnancy and live birth rates were 53.8% and 50%, respectively, which appear higher than those usually reported. These findings suggest that the addition of HR does not affect reproductive outcomes, if performed with a standardized technique and in selected patients with unifocal EC.

It was reported that use of ART is associated with higher pregnancy and live birth rates compared with spontaneous conception in young women with EC, because of the possible presence of risk factors of infertility [5,39]. In our series, 11 out of 15 patients attempting

to conceive underwent ART. To date, only few investigators have assessed the association between the use of fertility drugs and the risk of recurrence after successful conservative EC management, and they did not find any association. In contrast, it was found that patients who achieved at least one pregnancy had a lower risk of disease recurrence regardless of the use of fertility drugs [39]. The limited data available do not allow to draw definitive conclusions on the safety of ART in these patients. In the light of the considerations above, however, we believe that early referral to reproductive endocrinologist should be mandatory in order to maximize the likelihood of a live birth and minimize the time between diagnosis and definitive EC treatment.

The limited sample size and format of our study represent the main limitations; moreover, two different hormonal therapies have been adopted over a long period of patient recruitment.

In conclusion, although fertility-sparing management is not the current standard of care for young women with EC, it may be considered for those patients with early-stage G1 disease wishing to preserve their reproductive potential. To date, such an approach is still experimental and should be offered only in the framework of scientific protocols conducted in cancer centers. The gynecological oncologist and gynecological pathologist expertise is crucial to ensure the correct decision making process within a complex algorithm for fertility preservation. Candidates should be carefully selected and counseled about the oncologic risks associated with deviation from the standard of care. Early reproductive and genetic counseling also should be considered as mandatory. Although the ideal fertility-sparing management of EC is yet to be defined, data presented are very promising. Larger series are needed to further assess benefits potentially derivable from the addition of a standardized three-step resectoscopy to progestin alone.

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