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JMIG The Journal of Minimally Invasive Gynecology

Original Article

Hysteroscopic Endometrial Focal Resection followed by Levonorgestrel Intrauterine Device Insertion as a Fertility-Sparing Treatment of Atypical Endometrial Hyperplasia and Early Endometrial Cancer: A Retrospective Study

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ABSTRACT **Study Objective:** To evaluate safety and effectiveness of the combination of hysteroscopic endometrial focal resection with levonorgestrel-releasing intrauterine device (LNG-IUD) for International Federation of Gynecology and Obstetrics stage IA G1 early endometrial cancer (EEC) and atypical endometrial hyperplasia (AEH) in young women to preserve their fertility.
Design: Retrospective case series (Canadian Task Force classification II-3).
Setting: University Federico II, Naples, Italy.
Patients: The medical records of 69 consecutive patients treated from 2007 to 2017 with diagnosis of EEC (n = 14) or AEH (n = 55) meeting inclusion criteria were reviewed.
Interventions: Patients with focal EEC were treated by hysteroscopic resection of the lesion according to Mazzon's technique; patients with AEH were treated by superficial endometrial resection, preserving the basal layer of the endometrium. An LNG-IUD was inserted in all patients after surgery. Patients were followed for 24 months with serial hysteroscopic biopsies.
Measurements and Main Results: Rates of response, live birth, and recurrence were assessed. Of the 14 patients with EEC, 11 (78.6%) achieved a complete response, 2 (18.2%) of whom had subsequent relapse, 1 (7.1%) showed partial response, whereas 2 (14.3%) were nonresponders (1 stable disease and 1 progression). Of the 55 patients with AEH, 51 (92.7%) achieved a complete response, 2 (3.9%) of whom had subsequent relapse, 3 (5.5%) showed partial response, whereas only 1 (1.8%) was nonresponder with stable disease. Among 25 patients who had removed the LNG-IUD, 10 (40%) gave birth after natural conception in the last 12 months of follow-up.
Conclusion: The combination of hysteroscopic resection with an LNG-IUD as fertility-sparing treatment of EEC and AEH showed similar response and live birth rates compared with those reported in literature for progestins alone, but with considerably lower relapse rate. We advocate the use of this combined approach as an alternative fertility-sparing option in patients with ECC and AEH. Journal of Minimally Invasive Gynecology (2019) 26, 648−656. © 2018 AAGL. All rights reserved.

Keywords: Conservative; Endometrioid adenocarcinoma; Progestogen; Recurrence; Regression

Endometrial adenocarcinoma is the most common gynecologic tumor in developed countries [1]. Its precursor is endometrial hyperplasia, an irregular proliferative process of the endometrial glands that leads to an increase in the gland to stroma ratio. In the 2014 WHO Classification of Tumours of Female Reproductive Organs [2], endometrial hyperplasia has been separated into 2 groups based on the presence or absence of cytologic atypia to highlight the

Conflict of Interest: The authors declare that they have no conflict of interest.
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Submitted May 3, 2018, Accepted for publication July 2, 2018.
Available at www.sciencedirect.com and www.jmig.org

1553-4650/$ — see front matter
https://doi.org/10.1016/j.jmig.2018.07.001

prognostic impact of the presence of atypia on the potentially malignant transformation of the lesion.

Women with endometrial adenocarcinoma or atypical endometrial hyperplasia (AEH) should undergo a total hysterectomy with bilateral salpingo-oophorectomy. Although most endometrial cancer occurs after menopause, approximately 25% arise in premenopausal women, with 5% in women aged less than 40 years, of whom 70% are nulliparous at the time of diagnosis [3–5]. In young women most of cases are endometrioid type, focal, well-differentiated early endometrial cancer (EEC), limited to endometrium or superficial myometrium (International Federation of Gynecology and Obstetrics [FIGO] stage IA). Consequently, the 5-year disease-free survival rate of up to 99.2% in young women is higher than the 86% observed in women older than 45 [3–5]. Therefore, given the excellent oncologic outcomes associated with EEC in young women, the fertility-sparing is an important issue to consider when deciding the most proper management to be taken in women diagnosed with AEH and EEC limited to endometrium who desire pregnancy.

The conservative management of EEC and AEH is generally accepted in young women who desire to preserve their fertility or in women having serious surgical risk factors. This approach is usually based on progestins alone, with a levonorgestrel-releasing intrauterine device (LNG-IUD) considered as the first-line treatment [6,7]. However, uncertainty still exists in regard to patient selection criteria and optimal therapeutic and follow-up managements. The aim of this retrospective study was to assess safety and effectiveness of the combination of hysteroscopic resection with an LNG-IUD for the fertility-sparing treatment of EEC and AEH.

Methods

Study Design

The study was designed as a retrospective case series and followed the STROBE guidelines [8]. We reviewed the medical records of all patients aged 45 years or younger diagnosed with ECC or AEH who were treated with hysteroscopic resection followed by LNG-IUD insertion to preserve fertility from January 2007 to December 2017.

All treatments had been performed or supervised by 2 authors (A.D.S.S. and A.M.) at the Department of Public Health or at the Department of Neuroscience, Reproductive Sciences and Dentistry of University Federico II, Naples, Italy, respectively. The histologic examination of all endometrial specimens had been performed or reviewed by the same expert gynecopathologist (L.I.) at the Department of Advanced Biomedical Sciences of University Federico II, Naples, Italy. Given the retrospective design of the study, the Institutional Review Board ruled that approval was not required.

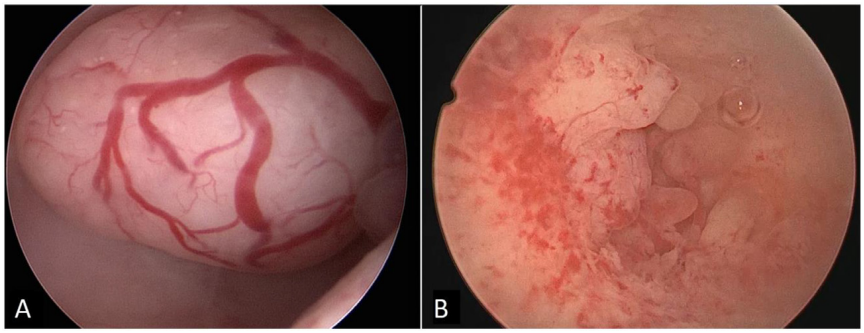
Data on Pretreatment Management

All patients had undergone gynecologic examination and transvaginal ultrasonography, and the initial diagnosis of EEC and AEH had been obtained by endometrial biopsy performed under direct visualization during in-office hysteroscopy, using miniaturizing instruments (grasping forceps). The most common hysteroscopic features of EEC are single or focally limited polypoid lesion with white or gray-greenish color, irregular margin, soft consistency, and atypical vascularization (i.e., branched, disordered aspect, with disagreement between the main vascular axis and the direction of growth) (Fig. 1A). The most common hysteroscopic features observed in AEH are endometrial thickening with irregular, papillary, or polypoid surface; interpapillary bridges and hemorrhagic background; white color; and glandular outlets with anomalous architecture that are difficult to view (Fig. 1B).

Women with EEC had been considered eligible for fertility-sparing treatment only in case of endometrioid type, focal development, tumor grade 1, absence of lymphovascular space invasion at the histologic examination on the target-eye biopsy and absence of myometrial or cervical invasion and extrauterine metastases at intravenous contrast-enhanced

Figure 1

(A) Hysteroscopic appearance of focal early endometrial cancer in a 34-year-old woman: a single polypoid lesion of soft consistency with exuberant and atypical vascularization can be noted. (B) Hysteroscopic appearance of atypical endometrial hyperplasia localized in the right cornual area of a 28-year-old woman: the endometrium appears thick, irregular, with polypoid surface, and hemorrhagic background.



abdomen and pelvis magnetic resonance [9,10]. CA-125 and CA 19.9 levels had also been obtained [11,12].

For patients older than age 40 years, before choosing a conservative treatment, a count of antral follicles to measure their ovarian reserve had been performed by transvaginal sonography in the early proliferative phase of the menstrual cycle. All patients had been informed that fertility-sparing treatment was not the standard treatment and that the gold standard for their condition was hysterectomy [6,7]. Patients had undergone fertility-sparing treatment only after providing written consent.

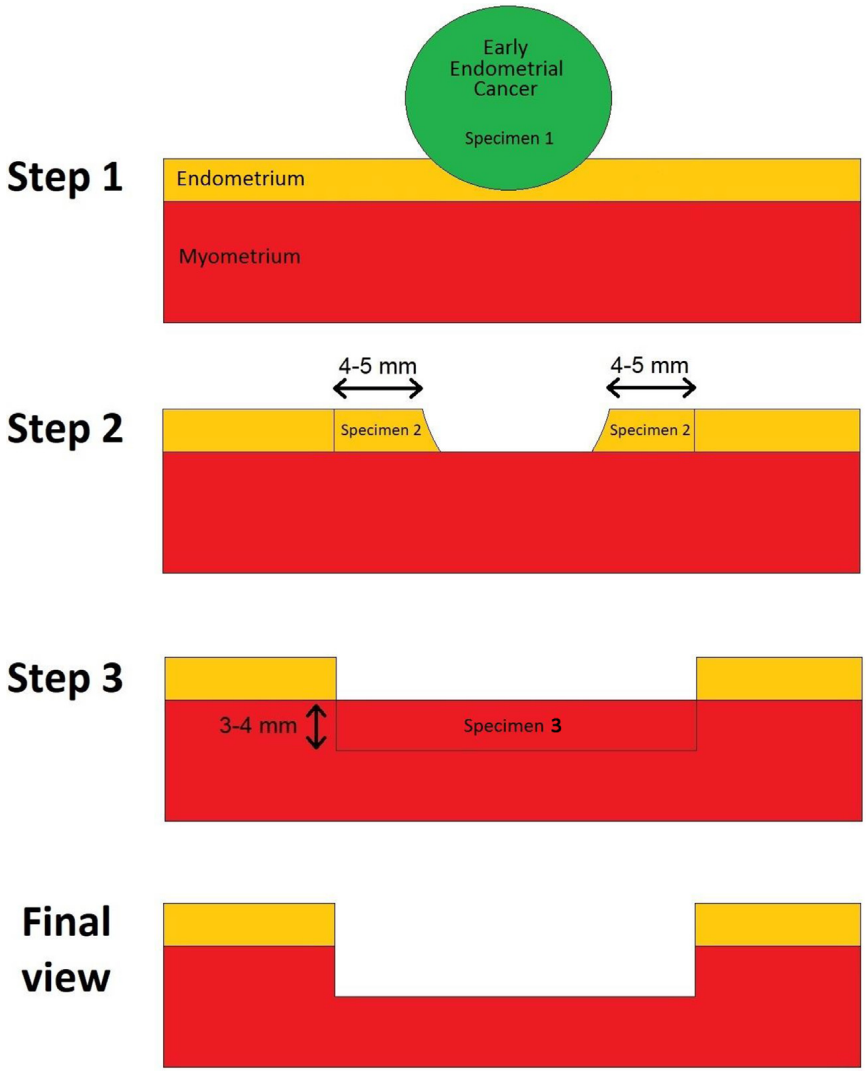
Combined Fertility-Sparing Treatment

Patients diagnosed with focal EEC had been treated by hysteroscopic resection following 3 steps: removal of the exophytic tumor lesion (specimen 1), removal of the endometrium adjacent (4−5 mm outside) to the lesion (specimen 2), and removal of the muscle layer beneath (3−4 mm) the lesion (specimen 3), according to the technique first described by Mazzon et al [13,14] (Fig. 2). Multiple random biopsies of endometrium had also been performed. In cases of histologic confirmation of EEC G1 on specimen 1 and if both specimens 2 and 3 were free of disease, the hysteroscopic treatment was definitive and an LNG-IUD (Mirena; Bayer Healthcare Pharmaceuticals, Pittsburgh, PA) was inserted.

The patients diagnosed with AEH had been treated by superficial endometrial resection (i.e., preserving the basal layer of the endometrium). The thickness of the hyperplastic endometrium was first tested using the loop in a cold way, like a curette, until the endometrium−myometrium junction was identified. This allowed modulating the depth of electrosurgical resection, preserving the basal

Figure 2

Schematic representation of hysteroscopic resection of focal early endometrial cancer following Mazzon's technique.



layer of endometrium, recognized by distinct signs of punctuation indicating the presence of glandular tissue. Immediately after the operative hysteroscopy, an LNG-IUD was inserted.

All operative hysteroscopic procedures were performed or supervised by expert surgeons (A.D.S.S and A.M.) under general or locoregional anesthesia. The cervix was dilated to 10 mm with Hegar's dilator, and a 26 to 27Fr bipolar resectoscope (Karl Storz, Tuttlingen, Germany; or Ethicon, Johnson & Johnson, Somerville, NY) with 0 to 12-degree lens was introduced. The uterus was distended with normal saline solution and a 4- to 5-mm cutting loop electrode used.

Therapy Outcomes

The oncologic outcomes at histologic examinations were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined as absence of any pretreatment lesions, PR as regression of EEC to AEH and regression of AEH to hyperplasia without atypia, SD as persistence of pretreatment lesions, and PD as progression of AEH to EEC or worsening of the histologic grade of EEC. Relapse was defined as the presence of EEC or AEH after CR had been previously achieved.

The reproductive outcome was assessed as achievement of successful pregnancy, and the results were subdivided by gestational age into full-term versus preterm. Moreover, we also reviewed the medical records about the occurrence of abnormal placentation in women who achieved pregnancy.

Follow-up

For every patient we collected the pathology reports of hysteroscopic biopsies at 3, 6, 12, and 24 months after treatment, as well as data on pregnancies. Because the time to response to conservative treatment reported in the international literature varies between 3 and 12 months [7], our internal protocol established that the LNG-IUD had to be maintained in situ for at least 12 months.

At this time, all women with CR on the last 2 biopsies had been proposed to remove the LNG-IUD and attempt to naturally conceive. On the other hand, all women showing no or PR to treatment during the 12 months had been informed at every follow-up visit about the risks of this conservative approach, and hysterectomy had been proposed as definitive treatment.

In case of recurrence between 12 and 24 months of follow-up, a hysterectomy had been recommended; in case of refusal, a second cycle of conservative treatment (second hysteroscopic resection followed by LNG-IUD insertion) had been performed after providing a new written consent. In case of second cycle treatment, pathology reports were collected every 3 to 6 months for another 24 months to assess the response to treatment.

Bias Evaluation

In the evaluation of potential sources of bias, we referred to methodologic items for nonrandomized study [15]. In particular, we tried to ensure clearly stated aims, inclusion of consecutive patients, endpoints appropriate to the aim of the study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, and a loss to follow-up less than 5%.

Results

Characteristics of the Included Patients

A total of 69 patients meeting the inclusion criteria were included in this retrospective study: 14 had been diagnosed with EEC and 55 with AEH. The mean age was 35.1 ± 4.8 years (range, 20−44), and the mean body mass index was 25.9 ± 5.3 kg/m^2 (range, 20.2−44.8). Twenty-nine patients (42%) were nulliparous. No women were using hormonal therapy at the time of the initial diagnosis. The main characteristics of the patients are shown in Table 1.

Histologic analysis of surgical specimens obtained by operative hysteroscopy confirmed in all patients pretreatment diagnosis on hysteroscopic biopsy and in patients who had been diagnosed with EEC the absence of myometrial infiltration. None of the enrolled patients had any complications or adverse effects related to the hysteroscopic surgery or hormonal therapy.

Table 1

Characteristics of patients

Characteristics		No. of Patients (%)
Age, yr	<35	36 (52.2)
	>35	33 (47.8)
Body mass index, kg/m^2	<30	45 (65.2)
	>30	24 (34.8)
Parity	0 para	29 (42)
	≥1 para	40 (58)
Smoke	No	52 (75.4)
	Current smoker	10 (14.5)
	Ex-smoker	7 (10.1)
Familiarity for endometrial cancer	Yes	7 (10.1)
	No	62 (89.9)
Current diseases	Hypertension	4 (5.8)
	Thyroid disease	18 (26.1)
	Endometriosis	8 (11.6)
	Polycystic ovarian syndrome	11 (15.9)
Previous diseases	Endometrial polyps	21 (30.4)
	Ovarian cysts	6 (8.7)
Symptoms	Pelvic pain	7 (10.1)
	Abnormal uterine bleeding	28 (40.6)
	None	34 (49.3)
History of infertility	Yes	21 (30.4)
	No	48 (69.6)

Oncologic Outcomes

Three-Month Follow-Up

In the EEC group (n = 14) 11 patients obtained a CR, 1 obtained PR, 1 showed SD, and 1 showed PD and underwent total hysterectomy: the pathology report of the surgery specimen indicated FIGO stage IA G3 (cancer invading less than half of myometrium). In the AEH group (n = 55) 50 patients obtained a CR, 2 obtained PR, and 3 showed SD.

Six-Month Follow-Up

In the EEC group (n = 13) histologic examination confirmed the report of the 3-month follow-up (11 CR, 1 PR, 1 SD). In the AEH group (n = 55) 51 patients showed CR, 2 had PR, and 2 had SD, because 1 patient with previous SD achieved a CR.

Twelve-Month Follow-Up

In the EEC group (n = 13) 2 of 11 patients with CR relapsed. Given their strong wish to preserve fertility, after refusal of demolitive treatment, they were retreated with a second-cycle hysteroscopic resection and insertion of an LNG-IUD. The other 11 patients were found unchanged (9 CR, 1 PR, 1 SD). No patient with CR or PR wanted to have the LNG-IUD removed. The reasons are explained below (see Reproductive Outcomes). The patient with SD underwent total hysterectomy, and the pathology report of the surgery specimen confirmed a FIGO stage IA G1 endometrioid carcinoma without myometrial infiltration.

In the AEH group (n = 55), 4 of 51 patients with CR at 6 months were lost to follow-up. The other outcomes were 47 CR, 3 PR, and 1 SD, because 1 patient with previous SD achieved a PR. Of the 47 patients with CR, 25 decided to have the LNG-IUD removed to attempt to conceive.

Twenty-Four–Month Follow-Up

In the EEC group (n = 12) 1 patient with previous CR was lost to follow-up. One of the 2 EEC patients who relapsed underwent total hysterectomy, because she had shown SD at 3, 6, and 12 months after second-cycle treatment: Biopsy diagnosis was confirmed at histologic examination of the surgery specimen. The other EEC relapser had achieved and maintained a CR at 3, 6, and 12 months after retreatment. The other outcomes were 8 CR and 1 PR.

In the AEH group (n = 51) 4 patients (of whom 2 had shown CR, 1 PR, and 1 SD at 12 months) were lost to follow-up. Two patients with previous CR relapsed: 1 had opted for total hysterectomy, and the pathology report of the surgery specimen confirmed AEH diagnosis. The other patient who relapsed had a strong wish to preserve fertility and thus underwent a second cycle of endometrial resection and LNG-IUD insertion; she achieved and maintained CR at 3 and 6 months after retreatment. The remaining outcomes were 43 CR (of whom 25 had the LNG-IUD removed) and 2 PR.

Results Summary

Of the 14 patients diagnosed with EEC, 11 (78.6%) achieved a CR, 2 (18.2%) of whom had subsequent relapse, 1 (7.1%) showed PR, and 2 (14.3%) were nonresponders (1 SD and 1 PR). Of the 55 patients diagnosed with AEH, 51 (92.7%) achieved a CR, 2 (3.9%) of whom had subsequent relapse, 3 (5.5%) showed PR, and only 1 (1.8%) was a nonresponder with SD. Oncologic outcomes are reported in Table 2 for patients with EEC and in Table 3 for patients with AEH.

Reproductive Outcome

Of the 56 patients who had achieved and maintained a CR, 25 (44.6%; all first diagnosed with AEH) had the

Table 2

Oncologic outcomes in patients with EEC

Follow-up	Patients assessed	Pathologic reports					Patients addressed to hysterectomy	Patients lost to follow-up	Changes compared with previous follow-up
		CR	PR	SD	PD	Recurrence of disease			
3 months	14	11 (78.6)	1 (7.1)	1 (7.1)	1 (7.1)	—	1 (7.1)	0 (0)	—
6 months	13	11 (84.6)	1 (7.7)	1 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 PD had undergone hysterectomy
12 months	13	9 (69.2)	1 (7.7)	1 (7.7)	0 (0)	2 (15.4)	1 (7.7)	0 (0)	2 CR had relpase
24 months	11	9 (81.8)	1 (9.1)	1 (9.1)	0 (0)	0 (0)	1 (9.1)	1 (9.1)	1 CR was loss to follow-up 1 SD had undergone hysterectomy 1 relapser achieved CR; 1 relapser had SD
Total	14	11 (78.6)	1 (7.1)	2 (14.3)	1 (7.1)	2 (14.3)	3 (21.4)	1 (7.1)	1 SD had undergone hysterectomy

Values are n (%).

Table 3

Oncologic outcomes in patients with AEH

Follow-up	Patients assessed	Pathologic reports					Patients addressed to hysterectomy	Patients lost to follow-up	Changes compared with previous follow-up
		CR	PR	SD	PD	Recurrence of disease			
3 months	55	50 (90.1)	2 (3.6)	3 (5.5)	0 (0)	—	0 (0)	0 (0)	—
6 months	55	51 (92.7)	2 (3.6)	2 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)	1 SD achieved CR
12 months	51	47 (92.2)	3 (5.9)	1 (2)	0 (0)	0 (0)	0 (0)	4 (7.8)	4 CR were lost to follow-up 1 SD achieved PR
24 months	47	43 (91.5)	2 (4.3)	0 (0)	0 (0)	2 (4.3)	1 (2.1)	4 (8.5)	2 CR, 1 PR, 1 SD were lost to follow-up 2 CR relapsed
Total	55	51 (92.7)	3 (5.5)	1 (1.8)	0 (0)	2 (3.6)	1 (1.8)	8 (14.5)	1 relapser had undergone hysterectomy

Values are n (%).

LNG-IUD removed. The remaining 31 patients (55.4%), although motivated to preserve their fertility, did not wish or could not get pregnant at the time of survey because of several reasons (e.g., economic problems, male infertility, family or work issues). Therefore, they decided to leave the LNG-IUD in situ as a contraceptive device. Among the 25 patients who had removed the LNG-IUD, 10 patients (40%) became pregnant after natural conception in the following 12 months.

Three infants were born by cesarean section at 39 weeks of gestation, and 7 were born at term spontaneously. No abnormality of placentation or complications during pregnancy and delivery occurred. The treatment did not cause complications affecting fertility (e.g., Asherman's syndrome). Reproductive outcomes are reported in Table 4.

Discussion

According to our results, the combined treatment with hysteroscopic endometrial focal resection followed by LNG-IUD insertion appears as an effective and safe fertility-sparing approach in young women with EEC and AEH. Presenting 1 of the largest patient series in this field, our study strengthens evidence that such combined treatment may achieve rates of response and live birth rates at least similar to progestins alone, with considerably lower relapse rate.

Response to Therapy

The efficacy of oral and intrauterine-released progestins as fertility-sparing treatments in patients with EEC and AEH has been evaluated in many studies [15−28]. A recent meta-analysis demonstrated that women managed with progestins had a pooled CR rate of 71%, although the separate CR rates for EEC and AEH were not reported [29]. A previous meta-analysis reported a pooled regression rate of 76.2% for EEC and 85.6% for AEH [30], although the authors did not perform a subgroup analysis for each of several treatments included (oral progestins, LNG-IUD, hysteroscopic resection). However, in women with AEH a major effectiveness of LNG-IUD compared with oral progestins was observed in a meta-analysis [31] and in a comparative cohort study [32] by the same author. By contrast, in women with EEC the use of an LNG-IUD was found to be similarly effective compared with oral progestins [33], although the use of an LNG-IUD alone in EEC patients has not been extensively reviewed as oral progestins. More recently, hysteroscopic resection of EEC and AEH followed by oral or intrauterine-released progestins has been demonstrated to be an effective fertility-sparing treatment [14,34−37].

Early Endometrial Cancer

In our series, all women with EEC had undergone hysteroscopic resection of the lesion in 3 steps followed by insertion of an LNG-IUD. This approach resulted in an overall response rate of 85.7% (12/14) and a CR rate of 78.6% (11/14). Our results essentially confirmed the major effectiveness of such combined approach, as reported by other authors [14,34−37]. In fact, the CR rate achieved in our series (78.6%) was within the range of 78% to 100% CR reported by Falcone et al [37] in their literature review of the studies on combined therapy and was slightly higher than those reported in recent studies and meta-analyses on progestin therapies alone [19,29,30,38].

Atypical Endometrial Hyperplasia

In contrast with EEC, limited data are available in literature on the combined surgical and medical treatment of AEH [35,39]. Shan et al [39] reported a CR rate of 83.3% in patients with AEH treated by extensive endometrial hysteroscopic curettage followed by megestrol acetate. More recently, De Marzi et al [35] reported a CR rate of 100% in

Table 4

Reproductive outcomes

Item		No. of Patients (%)
Women who maintained CR at 12 months (n = 56)	Histologic diagnosis	EEC = 9 (16.1%) AEH = 47 (83.9%)
	Mirena removed to attempt to conceive	Removed = 25 (44.6%) Not removed = 31 (55.4%)
Women who attempted to conceive during follow-up (n = 25)	Histologic diagnosis	EEC = 0 (0%) AEH = 25 (100%)
	Conception achieved	Yes = 10 (40%) No = 0 80%)
Pregnancies (n = 10)	Conception method	Natural = 10 (100%) Assisted = 0 (0%)
	Live birth achieved	Yes = 10 (100%) No = 0 (0%)
	Complications	Yes = 0 (0%) No = 10 (100%)
	Abnormal placentation	Yes = 0 (0%) No = 10 (100%)
Deliveries (n = 10)	Delivery method	Spontaneous vaginal delivery = 7 (70%) Cesarean section = 3 (30%)
	Delivery time	Full term = 10 (100%) Preterm = 0 (0%)
	Complications	Yes = 0 (0%) No = 10 (100%)

patients with AEH treated by hysteroscopic resection of hyperplastic areas and subsequent hormonal therapy.

In our series all patients diagnosed with AEH underwent superficial endometrial resection followed by insertion of an LNG-IUD. As already described by Shan et al [39], this technique allows the removal of most, if not all, pathologic tissue, thus probably increasing the responsiveness to progestin treatments. Furthermore, the preservation of the basal layer of the endometrium allows the complete regeneration of endometrium after the end of the medical treatment, thus preserving women's childbearing potential. Our combined approach resulted in an overall response rate of 98.2% (54/55) and a CR rate of 92.7% (51/55). Our CR rate achieved was higher than those reported in recent studies on women with AEH treated by oral progestins alone (range, 46.2%−81.8%) [16,17,32], but it was in the range observed for LNG-IUD alone (range, 67%−100%) [20,32,40−42]. This would indicate the need for further comparative cohort studies.

Relapse

A recent meta-analysis [29] showed an overall relapse rate of 20% in women with EEC or AEH successfully treated by progestins, over a median follow-up time ranging from .3 to 98 months, and the relapse rate was higher in women treated by oral progestins than those treated by intrauterine-released progestins. This relapse rate appears to be considerably higher than the 6.5% (4/62) observed in our series of patients with EEC or AEH.

Early Endometrial Cancer

Considering only EEC, in our series 2 patients who had previously achieved CR (2/11, 18.2%) were found to have a relapse of the lesions at 12 months. A meta-analysis of 7 studies [33] reported a 24.6% relapse rate in women with EEC treated by progestins alone during a mean follow-up of 27 months. Another contemporary meta-analysis [30] on women with EEC showed a pooled relapse rate of 40.6% after successful fertility-sparing therapy, although the median follow-up time of the studies included ranged from 11 to 76.5 months and thus was longer than ours. Our findings suggest that the combined treatment might be safer than progestin therapies alone, in agreement with results reported by other authors. In fact, Falcone et al [37] had already observed that the pooled relapse rate of EEC in studies on women treated by combined therapy (16%) was lower than that reported in most recent studies on progestin therapies alone (32%).

Atypical Endometrial Hyperplasia

Concerning only AEH, in our series 2 patients who previously achieved CR (2/51, 3.9%) were found to have a relapse of the lesion at 24 months. In a cohort study, relapse of AEH occurred in 27.3% of women treated by an LNG-IUD and 50% of women treated by oral progestins [32], and a consistent number of patients relapsed during the first 24 months. Moreover, the risk of relapse of AEH is especially high in the first 2 years from diagnosis [14]. In the most recent study on women with AEH treated by combined approach, De Marzi et al [36] reported a relapse rate

of 0% (0/20) after a mean follow-up time of 25 months. Taking into account all previous observations, our results might confirm the major safety of the combined treatment for AEH compared with the progestin therapies alone.

Successful Pregnancies

A meta-analysis of women with EEC and AEH, managed with fertility-sparing treatments, found pooled live birth rates of 28% and 26.3%, respectively [30]. In recent studies on women treated by hysteroscopic and medical treatment, De Marzi et al [36] and Falcone et al [37] reported a pooled live birth rate of 21.7% and 50% respectively, not assessing separately EEC and AEH rates. In our series the pooled live birth rate was 14.5% (10/69), because no patient with EEC achieved pregnancy, whereas 18.2% (10/55) of patients with AEH achieved pregnancy and gave birth; nonetheless, this rate would have been higher (21.3%) if we had considered only the patients who had reached the 24-month follow-up (10/47). These slightly lower rates could be explained by the more restrictive follow-up time retrospectively analyzed in our series compared with the mean follow-up times of other authors [14,37]. However, excluding the 31 CRs who decided to leave the LNG-IUD in situ as contraceptive device, not wishing to get pregnant in the short term, the live birth rate rises up to 26.3% (10/38), which is in the range reported in literature.

Strength and Limitations

To our knowledge, in regard to the fertility-sparing combined hysteroscopic and medical treatment, our study is the largest series of patients with AEH in literature and the second largest with EEC after Falcone et al [37]. Our findings strongly suggest that this combined approach might have a lower relapse rate than progestin therapies alone, with similar response and pregnancy rates. These results should be considered carefully, because of the retrospective design of our study and the lack of a control group. Nonetheless, we included consecutive patients opting for fertility-sparing treatment, limiting selection bias. Furthermore, our results were in agreement with those reported in other studies.

Given the correlation between obesity and risk of endometrial hyperplasia and cancer [43], our results might not be generalizable to patients with higher body mass indices than our study population (25.9 $\pm$ 5.3 kg/m^2). However, a meta-analysis showed no association between obesity and response to fertility-sparing treatment of AEH and EEC [44].

Another limitation of our study may be the follow-up time restricted to 24 months, which did not allow us to assess the live birth rate in patients with EEC, because none of them had wish to get pregnant in the short term. Moreover, this follow-up time may have led to lower pooled live birth and relapse rates compared with other studies considering a longer follow-up. However, as discussed above, this effect may be limited because most pregnancies and relapses occur in the first 2 years.

Regarding patients lost to follow-up, our rate was 0% at 6 months of follow-up (which is the minimum time recommended to evaluate the response to treatment [6]) but was higher than 5% (13%) at 12 months. The reason probably was that our institution is a referral center in a large macroregion of southern Italy for the fertility-sparing treatment of AEH and EEC. These patients were lost only to our follow-up, whereas they continued to be followed at other centers closer to home.

Conclusion

Taking into account the oncologic and reproductive outcomes, we believe the combined treatment with hysteroscopic endometrial focal resection followed by LNG-IUD insertion for 12 months could be considered an effective and safe approach in the management of EEC and AEH in young women who desire to preserve fertility, because it showed similar response and live birth rates but considerably lower relapse rate when compared with progestins alone. However, larger series and randomized clinical trials are needed to further assess the effectiveness and safety of such combined treatments.

References

1. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet*. 2016;387:1094–1108.
2. Kurman RJ, Carcangiu ML, Herrington CS, Young RHE, editors. *WHO Classification of Tumours of Female Reproductive Organs*. Lyon, France: IARC; 2014.
3. Kalogera E, Dowdy SC, Bakkum-Gamez JN. Preserving fertility in young patients with endometrial cancer: current perspectives. *Int J Womens Health*. 2014;6:691–701.
4. Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. *Gynecol Oncol*. 2001;83:388–393.
5. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. *Obstet Gynecol*. 2007;109:655–662.
6. Royal College of Obstetricians and Gynaecologists (RCOG) with the British Society for Gynaecological Endoscopy (BSGE). *Management of Endometrial Hyperplasia. Green-top Guideline No. 67. RCOG/BSGE Joint Guideline*. London, UK; 2016 Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg67/. Accessed August 7, 2018
7. Royal College of Obstetricians and Gynaecologists (RCOG). *Fertility Sparing Treatment in Gynaecological Treatment. Scientific Impact Paper No. 35*. RCOG. London, UK; 2013. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip35/. Accessed August 7, 2018.
8. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.
9. Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16:170−199

10. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:16–41.
11. Yildiz A, Yetimalar H, Kasap B, et al. Preoperative serum CA 125 level in the prediction of the stage of disease in endometrial carcinoma. *Eur J Obstet Gynaecol Reprod Biol*. 2012;164:191–195.
12. Antonsen SL, Høgdall E, Christensen IJ, et al. HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: a prospective multicenter study (ENDOMET). *Acta Obstet Gynaecol Scand*. 2013;92:1313–1322.
13. Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. *Int J Gynecol Cancer*. 2005;15:974–978.
14. Mazzon I, Corrado G, Masciullo V, Morricone D, Ferrandina G, Scambia G. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. *Fertil Steril*. 2010;93:1286–1289.
15. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *Austr N Z J Surg*. 2003;73:712–716.
16. Ohyagi-Hara C, Sawada K, Aki I, et al. Efficacies and pregnant outcomes of fertility-sparing treatment with medroxyprogesterone acetate for endometrioid adenocarcinoma and complex atypical hyperplasia: our experience and a review of the literature. *Arch Gynecol Obste*. 2015;291:151–157.
17. Simpson AN, Feigenberg T, Clarke BA, et al. Fertility sparing treatment of complex atypical hyperplasia and low grade endometrial cancer using oral progestin. *Gynecol Oncol*. 2014;133:229–233.
18. Kudesia R, Singer T, Caputo TA, et al. Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma. *Am J Obstet Gynecol*. 2014;210:255.
19. Chen M, Jin Y, Li Y, Bi Y, Shan Y, Pan L. 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;132:34–38.
20. Varma R, Soneja H, Bhatia K, et al. The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia—a long-term follow-up study. *Eur J Obstet Gynaecol Reprod Biol*. 2008;139:169–175.
21. Dursun P, Erkanli S, Güzel AB, et al. A Turkish Gynecologic Oncology Group study of fertility-sparing treatment for early-stage endometrial cancer. *Int J Gynaecol Obstet*. 2012;119:270–273.
22. Hahn HS, Yoon SG, Hong JS, et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. *Int J Gynecol Cancer*. 2009;19:1068–1073.
23. Pronin SM, Novikova OV, Andreeva JY, Novikova EG. Fertility-sparing treatment of early endometrial cancer and complex atypical hyperplasia in young women of childbearing potential. *Int J Gynecol Cancer*. 2015;25:1010–1014.
24. Koskas M, Azria E, Walker F, Luton D, Madelenat P, Yazbeck C. Progestin treatment of atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium to preserve fertility. *Anticancer Res*. 2012;32:1037–1043.
25. 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;25:2798–2803.
26. Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. *Ann Oncol*. 2011;22:643–649.
27. Minaguchi T, Nakagawa S, Takazawa Y, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. *Cancer Lett*. 2007;248:112–122.
28. Laurelli G, Di Vagno G, Scaffa C, Losito S, Del Giudice M, Greggi S. Conservative treatment of early endometrial cancer: preliminary results of a pilot study. *Gynecol Oncol*. 2011;120:43–46.
29. Wei J, Zhang W, Feng L, Gao W. Comparison of fertility-sparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: a meta-analysis and systematic review. *Medicine (Baltimore)*. 2017;96:e8034.
30. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. 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*. 2012;207:266.
31. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2010;203:547.
32. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. LNG-IUS versus oral progestogen treatment for endometrial hyperplasia: a long-term comparative cohort study. *Hum Reprod*. 2013;28:2966–2971.
33. Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. *Gynecol Oncol*. 2012;125:263–270.
34. Arendas K, Aldossary M, Cipolla A, Leader A, Leyland NA. Hysteroscopic resection in the management of early-stage endometrial cancer: report of 2 cases and review of the literature. *J Minim Invasive Gynecol*. 2015;22:34–39.
35. De Marzi P, Bergamini A, Luchini S, et al. Hysteroscopic resection in fertility-sparing surgery for atypical hyperplasia and endometrial cancer: safety and efficacy. *J Minim Invasive Gynecol*. 2015;22:1178–1182.
36. Wang Q, Guo Q, Gao S, et al. Fertility-conservation combined therapy with hysteroscopic resection and oral progesterone for local early stage endometrial carcinoma in young women. *Int J Clin Exp Med*. 2015;8:13804–13810.
37. Falcone F, Laurelli G, Losito S, Di Napoli M, Granata V, Greggi S. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. *J Gynecol Oncol*. 2017;28:e2.
38. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). *Eur J Cancer*. 2013;49:868–874.
39. Shan BE, Ren YL, Sun JM, et al. A prospective study of fertility-sparing treatment with megestrol acetate following hysteroscopic curettage for well-differentiated endometrioid carcinoma and atypical hyperplasia in young women. *Arch Gynecol Obstet*. 2013;288:1115–1123.
40. Orbo A, Vereide A, Arnes M, Pettersen I, Straume B. Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. *BJOG*. 2014;121:477–486.
41. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. *Am J Surg Pathol*. 2007;31:988–998.
42. Vereide AB, Kaino T, Sager G, Arnes M, Ørbo A. Effect of levonorgestrel IUD and oral medroxyprogesterone acetate on glandular and stromal progesterone receptors (PRA and PRB), and estrogen receptors (ER-alpha and ER-beta) in human endometrial hyperplasia. *Gynecol Oncol*. 2006;101:214–223.
43. Wise MR, Jordan V, Lagas A. Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review. *Am J Obstet Gynecol*. 2016;214:689.e1–689.e17.
44. Koskas M, Uzan J, Luton D, Rouzier R, Daraï E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. *Fertil Steril*. 2014;101:785–794.