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Fertility-sparing treatment in stage IA grade 2 endometrioid endometrial cancer: Outcomes of a standardized approach

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HIGHLIGHTS

- Standardized hysteroscopic resection plus progestins achieved 100% complete response.
- Recurrences were successfully managed with repeat conservative treatment.
- No disease progression occurred, with 96% disease-free at follow-up.
- More than half of patients attempting conception achieved pregnancy.
- This cohort showed a high prevalence of β-catenin mutations.

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ABSTRACT

Objective. To evaluate oncologic and reproductive outcomes of fertility-sparing treatment in women with stage IA grade 2 endometrioid endometrial cancer (EEC) without myometrial invasion treated with a standardized protocol.

Methods. Consecutive women diagnosed with stage IA grade 2 EEC without myometrial invasion between June 2019 and August 2024 at a single tertiary center were treated with hysteroscopic resection followed by combined progestin therapy with oral megestrol acetate (MA) 160 mg/day and a levonorgestrel intrauterine device (LNG-IUD).

Results. Twenty-five patients were included; median follow-up was 33 (IQR 12–90) months and median age 34 years (IQR 20–41). Complete response (CR) was achieved in 100% (25/25), with 84% at 6 months. Median time to CR was 6 months (range 6–12). Fifteen patients (60%) attempted conception, and 8 (53.3%) achieved pregnancy. Three delivered at term, three pregnancies are ongoing, and two resulted in miscarriage. Recurrence occurred in 56.0% (14/25) with a median time of 16.6 months. Six patients underwent definitive surgery, while eight were successfully retreated conservatively and are disease-free. Overall, 24/25 (96%) showed no evidence of disease at last follow-up. Most tumors were mismatch repair proficient (95.4%), none p53-mutated, with high ER/PR expression. All tested cases harbored β-catenin mutations. No treatment-related complications were observed.

Conclusions. A standardized fertility-sparing approach combining hysteroscopic resection and progestins achieved effective and safe management in stage IA grade 2 EEC without myometrial invasion, with favorable reproductive outcomes. These findings support its use in carefully selected patients, although longer follow-up is needed.

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1. Introduction

Endometrial cancer is the 6th most common cancer in women and the 15th most commonly occurring cancer overall [1]. The incidence of endometrial cancer has been steadily increasing worldwide [2]. Although most cases of endometrial cancer are diagnosed after menopause, approximately 25% occur in premenopausal women, and 5–7% are diagnosed in women younger than 40 years [3,4]. The standard treatment consists in total hysterectomy, bilateral salpingo-oophorectomy, with or without lymph node assessment (sentinel lymph node biopsy and/or pelvic and aortic lymphadenectomy) [5].

However, in the last two decades, the mean age of women at childbirth and at first childbirth progressively increased [6]. Consequently, the demand for fertility-preserving treatment is steadily increasing.

Until recently, candidates for fertility-sparing treatment were generally limited to women younger than 40 years with diagnosis of complex atypical endometrial hyperplasia or well-differentiated endometrioid endometrial cancer, without myometrial invasion, with no evidence of extrauterine disease at pre-operative work up, highly motivated to preserve their reproductive function after an adequate counselling. The preferred treatment consisted in hysteroscopic resection followed by progestin therapy [5,7]. On the other hand, very limited evidence was available regarding patients with stage IA grade 2 endometrioid endometrial cancer without myometrial invasion [8].

Recently, an international multidisciplinary panel convened by ESGO/ESHRE/ESGE developed updated guidelines for fertility-sparing management. According to these recommendations, the combined treatment consisting of endometrial hysteroscopic resection followed by either oral and intra-uterine released progestins in patients stage IA grade 2 endometrioid endometrial carcinoma appear feasible and safe [9].

In this study, we aimed to evaluate the oncological and reproductive outcomes of fertility-sparing treatment in early-stage grade 2 endometrioid endometrial cancer without myometrial invasion.

2. Materials and methods

2.1. Study population

This retrospective observational cohort study was conducted from June 2019 to August 2024 at the Fondazione Policlinico A. Gemelli IRCCS in Rome.

Women were eligible for inclusion if they had a histologically confirmed diagnosis of stage IA (International Federation of Obstetrics and Gynecology, FIGO 2009, stage IA1 FIGO 2023) grade 2 endometrioid endometrial cancer without myometrial invasion and underwent a conservative treatment with hysteroscopic resection followed by a combined progestin therapy with oral megestrole acetate 160 mg/die (Megace®) and levonorgestrel intrauterine device (LNG-IUD, Mirena®, Bayer Healthcare Pharmaceuticals, Pittsburgh, PA, USA). Clinical data were prospectively collected from patients' medical records. The study was approved by the Ethics Committee of the "Comitato Etico Territoriale Lazio Area 3" with ID N. 7309 and registered on ClinicalTrials.gov (ID NCT07077876).

All procedures were performed by an experienced surgeon (UC). The histological slides have been evaluated by dedicated pathologists' expert in the gynecologic oncology field (ND). These patients were offered a tumor-only targeted next-generation sequencing panel as part of an institutional comprehensive cancer genome profiling (CGP) program (ClinicalTrials.gov identifier NCT06020625; protocol FPG500).

Patients were selected according to the following inclusion criteria: age ≤ 41 years old; pathological diagnosis of grade 2 endometrioid endometrial cancer; no radiologic evidence of deep myometrial invasion, retroperitoneal lymph node involvement, suspicious of synchronous or metachronous ovarian cancer or distant metastasis; strong desire to preserve fertility; no contraindication for progestin treatment; provision of written informed consent. Patients were excluded if any of the inclusion criteria were not met; non-endometroid histology; any reasons preventing adequate follow-up.

2.2. Diagnosis and pre-operative management

In all cases, the diagnosis was established by endometrial biopsy under direct hysteroscopic visualization in an office-setting, without anesthesia or sedation unless indicated for specific reasons (i.e., patient's request), with a vaginoscopy "no touch" approach [10]. Endometrial biopsy was performed with a 5-mm rigid continuous flow operative hysteroscope, using saline solution as the distention medium, and a 5 Fr grasping forceps [11,12].

All patients underwent gynecological examination, transvaginal-ultrasonography, magnetic resonance imaging (MRI) and oncofertility counselling. Overweight and obese patients were routinely counselled regarding lifestyle modifications and referred to the Clinical Nutrition Service as part of the multidisciplinary management pathway; however, adherence to nutritional interventions and subsequent weight-loss outcomes were not systematically recorded in the study database. Patients were informed that the fertility-sparing treatment is not considered the standard of care for endometrial cancer, and that definitive surgery with hysterectomy, salpingo-oophorectomy and lymph node assessment would be strongly recommended after completing childbearing, or in case of treatment failure, recurrence, or disease progression.

2.3. Treatment

All the operative procedures were performed according to an ambulatory model of care [13,14] in the Digital Hysteroscopic Clinic (DHC) CLASS Hysteroscopy in Fondazione Policlinico Gemelli IRCCS of Rome - Italy, under general anesthesia (laryngeal mask).

In case of a focal disease patients underwent hysteroscopic resection with the three-steps technique described by Mazzon [15], that includes: 1) the removal of the lesion itself; 2) the removal of the endometrium adjacent (4–5 mm outside) to the lesion; 3) the removal of the myometrium beneath (3–4 mm) the lesion. Random biopsies of the contralateral uterine walls were then performed. All the samples have been sent separately for pathological review. In all these procedures, a 15 Fr bipolar miniresectoscope or a 26 Fr bipolar resectoscope were used.

In case of a diffuse lesion, patients were treated with a combined approach using a 15 Fr bipolar miniresectoscope and a 6 mm Tissue Removal Device (TRD) [16]. The 15 Fr miniresectoscope was used to remove the main lesions [15]. The TRD was then used to complete the resection of the pathological tissue in difficult-to-access areas, such as the tubal ostia.

In all cases, hysteroscopic resection was followed by LNG-IUD insertion and oral megestrol acetate at a dose of 160 mg/day.

Specimens have been analyzed by expert pathologists and immunohistochemical analysis has been performed: estrogen receptors (ER),

progestin receptors (PR), p53, Mismatch Repair (MMR) proteins (MSH2, MSH6, MLH1, PMS2). According to MMR status, in case of instable phenotype (i.e. absence of one of the tested proteins, MLH1, MSH2, MSH6 or PMS2 at IHC), patients underwent evalutation for Lynch syndrome [17]. Patients with MMR deficiency were referred for genetic counselling and underwent germline testing according to institutional recommendations. Moreover, a molecular analysis has been performed: Next-generation sequencing (NGS) was performed to assess POLE and CTNNB1 (β-catenin) mutations.

2.4. Endpoints

The primary endpoint was the complete response rate (CR) to treatment. The secondary endpoints included a) to evaluate the stability of disease (SD) versus CR, the median time to response to treatment after 6 months, recurrence or progression of disease (PD) after initial response, median time to recurrence, pregnancy and live birth rates. Moreover, we aimed to evaluate progression-free survival (PFS) and overall survival (OS) after conservative treatment at 24 months, when assessable.

The immunohistochemical and molecular profile of the specimen of patients at diagnosis and at recurrence have been evaluated, comparing the profile between responders and non-responders.

2.5. Follow-up

All patients included in the study underwent hysteroscopic endometrial biopsies every 3 months (until 15 months at most) in an office setting, as described before for the initial diagnosis. Women with at least two negative consecutive biopsies were encouraged to discontinue progestin therapy and attempt to conceive [18]. On the other hand, in case of SD or PD after 9 months of follow-up, if the desire to preserve fertility was still strong after an accurate counselling, a second conservative approach could be proposed on a case-by-case basis [9]. In case of recurrence between 12 and 24 months of follow-up, a radical treatment was recommended.

Data were prospectively collected on REDCap by a data manager and revised by a co-investigator (GD).

2.6. Measurement of outcomes and statistical analysis

CR is defined as the achievement of two consecutive negative biopsies with an interval of 3 months; SD a positive histology at the biopsy after 6 months of progestin therapy with the same grading as at diagnosis; and PD a positive histology at the biopsy after 6 months of progestin therapy with higher grading than at diagnosis. Recurrence was defined as the reappearance of either endometrial intraepithelial neoplasia (EIN)/atypical hyperplasia or endometrioid endometrial carcinoma following a previous complete response. The time from the end of treatment to recurrence or to the last observation has been defined as DFS, and the time from the end of treatment to death or to the last observation will be defined as OS.

3. Results

3.1. Baseline patient characteristics

A total of 25 consecutive patients diagnosed with endometrioid endometrial cancer, stage IA, grade 2, without myometrial invasion undergoing fertility-sparing treatment were recruited. One patient had synchronous ovarian and endometrial cancer. The median age at surgery was 34 years (range 20–41), while median BMI was 23,40 kg/m^2 (range 19,5-46,7), with two-thirds of patients overweight or obese. Overall, one third of patients had bleeding at diagnosis. All patients, except one with a previous pregnancy, were nulliparous. Patient characteristics are summarized in Table 1.

All patients were conservatively treated by combined hysteroscopic resection and progestin therapy consisting of Megestrole acetate at a dose of 160 mg/daily combined with levonorgestrel intrauterine device (LNG-IUD, Mirena®; Bayer Schering Pharma AG, Berlin, Germany). The hysteroscopic resection has been performed as described in Methods.

3.2. Oncological outcomes

The median follow-up time was 33 months (range, 12–90 months). Complete response was achieved in all patients (25/25), with 21

Table 1
Patients' characteristics and treatment.

Cases	Age (yr)	BMI (kg/m^2)	Previous pregnancies	Surgical treatment	Tumor type	Megestrol Acetate (160 mg/d)	MA duration (months)	IUD	IUD duration (months)
1	41	29.70		HSC resection	diffuse	Yes	10	Yes	35
2	34	26.90		HSC resection	diffuse	Yes	12	Yes	12
3	30	20.43		HSC resection	diffuse	Yes	8	Yes	7
4	28	39.30		HSC resection	diffuse	Yes	40	Yes	35
5	40	25.60	Yes	HSC resection	diffuse	Yes	14	Yes	7
6	25	19.8		HSC resection	diffuse	Yes	24	Yes	24
7	38	20.93		HSC resection	diffuse	Yes	14	Yes	15
8	36	46.70		HSC resection	diffuse	Yes	14	Yes	11
9	33	23.60		HSC resection	diffuse	Yes	21	Yes	9
10	35	25.20		HSC resection	focal	Yes	9	Yes	9
11	20	33.30		HSC resection	diffuse	Yes	10	Yes	10
12	27	21.50		HSC resection	diffuse	Yes	6	Yes	6
13	36	23.40		HSC resection	diffuse	Yes	8	Yes	8
14	40	20.00		HSC resection	focal	Yes	6	Yes	6
15	41	23.44		HSC resection	diffuse	Yes	18	Yes	18
16	30	20.2		HSC resection	focal			Yes	12
17	38	23.4		HSC resection	diffuse	Yes	15	Yes	20
18	33	43.3		HSC resection	diffuse	Yes	20	Yes	19
19	41	37.3		HSC resection	diffuse	Yes	17	Yes	17
20	26	30.1		HSC resection	focal	Yes	59	Yes	44
21	26	20.4		HSC resection	diffuse			Yes	25
22	34	22.2		HSC resection	diffuse	Yes	18	Yes	17
23	29	20.2		HSC resection	focal	Yes	21	Yes	21
24	36	19.5	Yes	HSC resection	focal	Yes	15	Yes	15
25	37	33.2	1 abs	HSC resection	diffuse	Yes	25	Yes	16

Abbreviations: BMI, Body Mass Index; HSC, hysteroscopic; IUD, intrauterine device.

patients (84%) achieving CR within 6 months. Fourteen (56.0%) patients experienced disease recurrance. Seven patients (28%) underwent radical surgical treatment, six of them for recurrence, but one immediately after delivery. Only one patient had residual node-negative, non-myoinvasive grade 2 endometrioid adenocarcinoma at final histology with no lymphovascular space invasion as final histology; two patients experienced recurrence with grade 1 disease, and two patients with atypical hyperplasia, after discontinuation of progestin therapy in order to attempt conception. Final histopathological analysis in two cases confirmed the histology; while one patient confirmed atypical hyperplasia but with an initial transformation in grade 1 endometrioid adenocarcinoma, the remaining had a negative histology (although the biopsy was positive for grade 1 endometrioid adenocarcinoma). Only one patient (19) (4% of total cohort), experienced a recurrence at 9 months after achieving an initial complete response at 6 months. She attempted to continue conservative management up to a total of 15 months; however, due to lack of response (stable disease, SD), radical surgical treatment was ultimately undertaken. Her final histological examination showed endometrium with extensive stromal pseudodecidualization associated with foci of atypical hyperplasia. Following appropriate counselling, the remaining eight patients (32% of total cohort; 57.1% of recurrent patients) with recurrence strongly wished to preserve fertility and therefore underwent a second conservative treatment consisting of operative hysteroscopy combined with the same medical therapy using oral and intrauterine progestins. All achieved a complete response and were disease-free at the time of the study. Three patients (12%) continued treatment without interruption, while five (20%) temporarily discontinued therapy to attempt conception, whom three achieved pregnancy; however, none of these pregnancies resulted in a live birth.

The median duration of complete response was 18 months (range, 9 +; 90+). The overall recurrence rate after initial response was 56.0% (14/25). The median time to recurrence was 16.5 months (range 6–36 months). No patient experienced disease progression.

The overall complete response rate was 100%. Among complete responders, the median duration of progestin therapy was 17 months (range, 6–59 months). The median time to response to treatment was 6 months (range 6–12).

At the latest follow-up, 24/25 (96%) patients had no evidence of disease, except one patient with SD, who is continuing progestin therapy (Table 2).

None of the patients presented with a family history suggesting a hereditary cancer syndrome or known genetic mutations. All patients underwent molecular analyses. Twenty-one (95.4%) were found mismatch repair (MMR) proficient, in the remaining patient hypermethylation of the MLH1 promoter was detected in the tumor, consistent with loss of MLH1/PMS2 expression. Three were not tested for MMR. Germline testing was negative, except for a variant of uncertain significance (VUS) in ATM, and the patient was referred for genetic counselling. No patient was p53-mutated, and all of them had high expression of ER and PR receptor, with a median of 72% and 90%, respectively. More than one-third of the cohort underwent multigene panel test finding that the 100% of tested patients had beta-catenin mutation, none was POLE-ultramutated (Table 3).

3.3. Reproductive outcomes

After complete response, 15 (60%) patients attempted to conceive, of whom 8 (53.3% of them) achieved one pregnancy. Three of them (37.5%) delivered healthy term infants (one delivered with a cesarean section and two with vaginal delivery at full-term), of whom two were afterwards undergo definitive surgery. Three patients are currently pregnant, two in the first and second trimester respectively (one of them experienced a previous therapeutic abortion), and one

Table 2
Patients' clinical outcomes.

Cases	Oncological outcome								Obstetrics outcome			
	3 months	6 months	9 months	12 months	Time to CR	Relapse (months)	Definitive surgery	Last hysteroscopy (months) and status	Attempting to conceive (modality)	Pregnancy	Obstetrics Outcome (N)	Follow-up (months)
1	CR	CR	CR	CR	6	Yes (21)	Yes		Yes (ART)			71
2	SD	CR	CR		9	Yes (18)		32 (CR)	Yes (ART)	Yes	Abortion (23w)	35
3	CR	CR			6		Yes		Yes (spontaneous)	Yes	CT (1)	43
4	SD	SD	CR	CR	12			54 (CR)				54
5	CR	CR		relapse	6	Yes (12)	Yes		Yes			41
6	CR	CR	CR	CR	6			46 (CR)				46
7	CR	CR		CR	6	Yes (30)	Yes		Yes			42
8	SD	SD	CR	CR	12	Yes (21)		40 (CR)	Yes			40
9	CR	CR	CR		6	Yes (15)	Yes		Yes (ART)			69
10	SD	CR	CR	CR	9	Yes (36)	Yes	15 (CR)	Yes (spontaneous)	Yes	VB (1)	45
11	CR	CR	CR		6	Yes (21)		37 (CR)	Yes (ART)	Yes	Ongoing at 6w GA	37
12	CR	CR	CR	CR	6			17 (CR)				28
13	CR	CR	CR		6	Yes (23)		28 (SD)	Yes (spontaneous)	Yes	Abortion (6w)	33
14	CR	CR	CR	CR	6			14(CR)	Yes (ART)	Yes	VB (1)	20
15	SD	CR	CR		9			9 (CR)				14
16	CR	CR		CR	6			27 (CR)	Yes	Yes	Ongoing at 33 w GA (1) + CT (1)	27
17	CR	CR		CR	6			17 (CR)	Yes (ART)			17
18	CR			relapse	6	Yes (12)		12 (relapse)				12
19	SD	CR	relapse		6	Yes (9)	Yes	15 (SD)				28
20						Yes (15)		90 (CR)	Yes (ART)	Yes	ongoing at 16w GA (1); abortion (2)	90
21	CR	CR		relapse	6	Yes (12)		18 (CR)				27
22	SD	CR	SD	CR	6			23 (CR)	Yes (ART)			23
23	CR	CR	CR	CR	6			15 (CR)				22
24	PR	PR	CR	CR	9			16 (CR)				16
25	PR	relapse	PR	CR	12	Yes (6)		17 (CR)				26

Abbreviations: ART, assisted reproductive technology; CR, complete response; CT, cesarean T-section; GA, gestational age; VB, vaginal birth; w, weeks.

Table 3
Population's molecular characteristics.

Molecular characteristics	N (%)
MLH1	
Negative	1 (4.54)
Positive	21 (95.45)
PMS2	
Negative	1 (4.54)
Positive	21 (95.45)
MSH2	
Negative	0
Positive	22 (100)
MSH6	
Negative	0
Positive	22 (100)
MMR status	
Proficient	21 (95.4)
Deficient	1 (4.5)
PR	
1+	2 (11.1)
2+	1 (5.6)
3+	14 (77.8)
Median (range)	90% (0–98)
NA	7
ER	
1+	2 (11.1)
2+	9 (50)
3+	7 (38.9)
Median (range)	72,5% (40–90)
NA	7
p53	
Wt	20 (100)
Mutated	0
NA	5
BETA-CATENIN mutation	
Yes	11 (100)
No	0
NA	14

Abbreviations: ER, estrogen receptor, PR, progesterone receptor; MMR mismatch repair; NA, not available; wt, wild type.

in the third trimester (who is experiencing her second pregnancy after conservative treatment and has a history of cesarean section for breech presentation). Lastly, two pregnancies ended in miscarriage, one of which was a late abortion at 23 weeks of gestation with no apparent cause, and she is still attempting to conceive at the time of the study.

Five (33.3%) patients underwent assisted reproductive technology without success and two of them had to undergo definitive surgery for disease recurrence during therapy discontinuation. The remaining 3 patients are still attempting to conceive and are free of disease (Table 2).

4. Discussion

4.1. Summary of main results

The present study represents the largest series of patients with non-myoinvasive stage IA, grade 2, endometrioid endometrial cancer who underwent a standardized fertility-sparing management. All patients were treated with hysteroscopic resection followed by combined progestin therapy (oral and intrauterine) as per current guidelines. Available evidence remains limited because this condition is rare among women of reproductive age and due to the broad variability in the management of these patients. Complete response was achieved in all patients (100%) within 12 months. Recurrence occurred in approximately half of the cohort, mainly when the combined progestin therapy was discontinued for pregnancy attempts. More than half of the 15 patients who attempted to conceive after treatment, achieved pregnancy. No patient experienced disease progression, and all patients were alive at the last follow-up, and all but one were free of disease.

Most patients were MMR proficient. All patients had high expression of estrogen and progesterone receptors, with no POLE-ultramutated or p53 aberrant cases. Importantly, 100% carried a beta-catenin mutation among the tested ones.

4.2. Results in the context of published literature

Among the few reported cases, the one with the biggest sample size was a multicenter study including 23 patients with grade 2 Stage IA endometrioid endometrial carcinoma, which reported a complete response rate of 73.9% with all patients undergoing hysteroscopic resection plus progestin, although the medical regimen (oral or IUD) was not standardized [19]. Similarly, Bogani et al. reported on 23 patients treated with heterogeneous strategies (resection in 39% and combined oral and intrauterine progestins in 30%), achieving a 68.8% complete response at 12 months and a live birth rate of 8.7% [20] In contrast, our monocentric cohort, uniformly managed with hysteroscopic resection followed by combined oral and intrauterine progestins, showed 100% complete response and higher reproductive outcomes. Interestingly, the numerically higher recurrence rate observed among women aged ≥40 years deserves attention, although our study was not powered to evaluate age-specific outcomes. Advanced reproductive age may identify a subgroup of patients with a less favorable overall prognosis, warranting further investigation in larger prospective studies.

Notably, we observed a high prevalence of CTNNB1 (β-catenin) mutations, detected in 100% of patients, which aligns with previously published data on the molecular characteristics of early-stage EC.

Recent literature has increasingly highlighted the prognostic relevance of CTNNB1 (β-catenin) mutations in early-stage, low-grade endometrioid endometrial cancer. A pivotal meta-analysis reported that CTNNB1 exon 3 mutations are significantly associated with increased risk of recurrence, particularly in tumors lacking other defining molecular alterations (NSMP group), with odds ratios rising from 3.0 to 5.95 after excluding non-NSMP cases, and a hazard ratio for disease-free survival of 2.83 in NSMP tumors ($p = 0.026$) [21]. Similarly, Kurnit et al. found that CTNNB1 mutation is a strong independent predictor of decreased recurrence-free survival in low-grade, early-stage EC, with a hazard ratio of 5.97 in multivariate analysis—outperforming traditional clinicopathologic risk factors [22]. Notably, although β-catenin expression is often linked with favorable histologic features (low grade, endometrioid histotype), its nuclear localization, as a surrogate for mutation, identifies patients at higher risk of recurrence within the NSMP group [23]. In our cohort, despite a high prevalence of CTNNB1 mutations, no disease progression was observed. These favorable outcomes may be explained by our patient selection criteria and follow-up duration. These findings emphasize the need for larger studies to further clarify the prognostic role of CTNNB1 mutations in this setting and support its integration into molecular risk stratification models for tailoring fertility-sparing strategies in endometrial cancer.

On the same line, building on the groundbreaking study introducing the molecular classification of endometrial cancer [24], and the subsequent Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) study providing a clinically applicable molecular-based prognostic tool [25], the latest fertility sparing ESGO guidelines [9], emphasizes as the molecular analysis is particularly crucial in these patients. A more accurate assessment of oncologic risk helps tailoring personalized therapeutic approaches, such as patients with p53-abnormal tumors should generally not be considered candidates for fertility-sparing treatment.

Notably, in our study two thirds of patients attempted conception, which appears substantially higher than rates reported in previous studies [19]. Overall, considering women who attempted to conceive, more than the half successfully achieved pregnancy, with a live birth rate of 37.5%, which may increase to 62.5% if the ongoing pregnancy results in a live birth. In this setting, fertility preservation strategies with the LNG-IUD in situ may represent an attractive strategy to shorten the interval between complete response and conception, potentially

limiting the duration of treatment interruption and reducing the risk of recurrence while attempting pregnancy.

4.3. Strengths and Weaknesses

This study includes strengths to acknowledge. All treatments were performed at a single high-volume referral center by an experienced surgeon and dedicated pathologists. This consistency of care, coupled with the use of an established data collection system, reflects a robust real-world scenario of fertility-sparing treatment. Despite the rarity of non-myoinvasive grade 2 endometrioid endometrial cancer in reproductive-age women, this study prospectively collected data on a well-defined cohort. The standardization of our surgical and medical protocol minimizes variability in treatment, enhancing the internal validity of the study.

By evaluating both oncological and reproductive outcomes the study offers a holistic view of the feasibility and safety of fertility-sparing management in this specific patient population, together with valuable insights into the biological profile of these tumors. These data may guide future personalized treatment strategies and risk stratification.

Besides this, our study had some limitations. Although data collection was prospective, the study design itself was retrospective. Given the low incidence of non-myoinvasive grade 2 endometrial cancer in young women, the cohort included only 25 patients, and one had synchronous endometrial and ovarian cancer. However, the ovarian disease had been definitively treated surgically before initiation of fertility-sparing management for endometrial cancer, and the patients was in follow-up. Therefore, the inclusion of this patient is unlikely to have affected the interpretation of our findings, as fertility-sparing management was directed exclusively toward the endometrial carcinoma after definitive treatment of the ovarian disease. These factors further restrict the generalizability of the results. Longer follow-up is needed to confirm the durability of complete response and the long-term safety of fertility preservation.

4.4. Implications for practice and future research

A tailored treatment plan with the standardization of treatment protocols, incorporating regular monitoring through imaging and biopsy, is essential to manage the risk of progression.

Our study emphasizes the importance of a multidisciplinary approach involving gynecologists, reproductive specialists, oncologists and geneticists. An oncofertility counselling is mandatory either before treatment to consider the feasibility to pursue a conservative management, or for patients achieving remission to encourage prompt childbearing after the fertility-sparing treatment. In this regard, ART plays a critical role in shortening the interval between complete response and conception, thereby limiting the duration of progestin therapy discontinuation; fertility preservation strategies with the LNG-IUD in situ may further support this strategy in selected patients. According to the ESGO/ESHRE/ESGE guidelines, ART should be actively considered to enhance the success rate and reduce the time to conception, thereby limiting unopposed estrogen exposure and potentially reducing the risk of recurrence in this high-risk patient population [9].

Longitudinal studies with larger cohorts are necessary to establish the long-term safety and efficacy of fertility-sparing treatments in grade 2 endometrial cancer, so as obstetrics outcomes.

Additionally, better refine the molecular characterization of these patients may help exploring the role of novel therapeutics, such as immune checkpoint inhibitors, in combination with fertility-sparing strategies.

5. Conclusions

A significant proportion of patients are diagnosed with endometrial cancer during their reproductive years, which poses a challenge for fertility preservation, particularly in light of the progressive increase in maternal age at first childbirth. Moreover, the increased risk of recurrence in stage IA grade 2 lesions compared to grade 1 underscores the need for careful patient selection, multidisciplinary managment and rigorous follow-up program to ensure patient safety and optimal outcomes. Overall, the study showed favorable oncologic outcomes with a high complete response rate and no disease progression, when treated by hysteroscopic resection and combined oral and intrauterine progestin therapy, while also providing encouraging reproductive outcomes.

CRediT authorship contribution statement

Ursula Catena: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Giorgia Dinoi:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Valeria Masciullo:** Writing – review & editing, Data curation. **Nicoletta D'Alessandris:** Writing – review & editing, Data curation. **Angelo Minucci:** Writing – review & editing, Methodology, Data curation. **Fossatelli Alessia:** Writing – review & editing, Data curation. **Alessia Fossatelli:** Writing – review & editing, Data curation. **Eleonora La Fera:** Methodology, Formal analysis, Data curation. **Emma Bonetti Palermo:** Writing – review & editing. **Emanuele Perrone:** Writing – review & editing. **Maria De Bonis:** Writing – review & editing, Methodology, Data curation. **Diana Giannarelli:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Giacomo Corrado:** Writing – review & editing. **Gian Franco Zannoni:** Writing – review & editing. **Anna Fagotti:** Writing – review & editing, Conceptualization. **Francesco Fanfani:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will not be shared publicly but are available from the corresponding author upon reasonable request.

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