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Original Article

Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GCIG) study

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ABSTRACT

Objective: 'The Endometrial Cancer Conservative Treatment (E.C.Co.). A multicentre archive' is a worldwide project endorsed by the Gynecologic Cancer Inter-Group, aimed at registering conservatively treated endometrial cancer (EC) patients. This paper reports the oncological and reproductive outcomes of intramucous, G2, endometrioid EC patients from this archive.
Methods: Twenty-three patients (Stage IA, G2, endometrioid EC) were enrolled between January 2004 and March 2019. Primary and secondary endpoints were, respectively, complete regression (CR) and recurrence rates, and pregnancy and live birth rates.
Results: A median follow-up of 35 months (9–148) was achieved. Hysteroscopic resection (HR) plus progestin was adopted in 74% (17/23) of cases. Seventeen patients showed CR (median time to CR, 6 months; 3-13). Among the 6 non-responders, one showed persistence and 5 progressed, all submitted to definitive surgery, with an unfavorauble outcome in one. The recurrence rate was 41.1%. Ten (58.8%) complete responders attempted to conceive, of whom 3 achieved at least one pregnancy with a live-birth. Two out of the 11 candidate patients underwent definitive surgery, while the remaining 9 have so far refused. To date, 22 patients show no evidence of disease, and one is still alive with disease.
Conclusions: Fertility-sparing treatment seems to be feasible even in G2 EC, although caution should be kept considering the potential pathological undergrading or non-endometrioid

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histology misdiagnosis. The low rate of attempt to conceive and of compliance to definitive surgery underline the need for a 'global' counselling extended to the follow-up period.

Keywords: Endometrial Neoplasm; Fertility Preservation; Hysteroscopy

INTRODUCTION

Although the primary treatment of endometrial cancer (EC) is usually hysterectomy, continuous progestin-based therapy may be offered as a temporizing measure for highly selected women wishing to preserve their fertility. To date, ideal candidates for conservative management are considered women of childbearing age with intramucous, well-differentiated (G1), endometrioid EC [1,2]. For moderately differentiated (G2) tumors, data concerning the efficacy and safety of fertility-sparing treatment are very limited and do not allow to draw definitive conclusions on the conservative approach in this setting of patients. These data are mostly based on case reports and small retrospective series generally in the absence of long-term treatment outcomes [3-17]. In general, G2 endometrioid ECs would seem less responsive to progestin therapy, with lower complete regression (CR) rates and longer times to CR than those observed in G1 cases [18,19].

First of all, the decision making process with respect to a fertility-sparing management must take into consideration the inherent oncologic risk of an inadequately categorized/treated disease. It is acknowledged that both tumor grade/histotype and stage definitions are affected by imperfect concordance between diagnostic and definitive pathology. It has been reported that higher the tumor grade, lower the accuracy of preoperative evaluation of grade and myometrial invasion [20,21]. Therefore, the risks potentially derivable from delaying definitive surgery to allow childbearing could be higher in women with early-stage G2 EC.

Since 2015, a project endorsed by the Gynecologic Cancer Inter-Group (GCIG) is ongoing aimed at registering conservatively treated EC patients in a centralized archive. The main purpose of this multicentre project is to collect a large series of cases allowing to learn more about the efficacy/safety of conservative treatment EC and subsequent fertility outcome.

The present paper shows the oncological and reproductive outcomes of women recorded into the aforementioned GCIG-endorsed archive and undergoing fertility-sparing treatment for intramucous, G2, endometrioid EC.

MATERIALS AND METHODS

The '*Endometrial Cancer Conservative Treatment (E.C.Co.). A multicentre archive*' (www.clinicaltrials.gov number: NCT04290299) is worldwide a project coordinated by the Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies group and endorsed by the GCIG, with the aim of systematically collecting data from consecutive EC patients managed according to established, not necessarily identical, fertility-sparing protocols. Patients are enrolled through the web (http:\\www.usc-intnapoli.net).

In the present article, data are presented on intramucous, G2, endometrioid EC women registered into the *E.C.Co. archive* and treated between January 2004 and March 2019. All

retrieved cases were from Cancer Centres or University Hospitals where pathologic revision was performed according to WHO criteria by institutionally dedicated pathologists [22].

The primary and secondary endpoints for this study were, respectively, to evaluate the CR and recurrence rates, and pregnancy and live birth rates.

The Institutional Review Boards (IRB) of participating centres approved the study, except for those where analyses of existing data were exempt from formal IRB approval. All patients included in the present analysis gave written consent to data collection and to the use of personal records for health research, in the absence of any identifiers linking individuals to the data.

All data were collected through the above reported website with dedicated electronic Case Report Forms (eCRFs), and checked for plausibility and completeness by two authors (FF, SG).

In particular, data were retrieved on: patient- (age; body mass index), disease- (tumor diameter), and treatment-related characteristics (type and duration of hormonal therapy).

Patients were considered non-eligible if: i) myometrial/cervical invasion and/or extrauterine disease were not assessed at pre-treatment imaging (transvaginal ultrasound [TVS] plus abdomen-pelvis magnetic resonance [MR] or computed tomography [CT]); ii) infertility/sterility diagnosed at the routine pre-treatment reproductive counselling. All patients were counselled about the oncologic risks associated with deviation from the standard of care. Baseline diagnostic laparoscopy and psychological support were not routinely provided.

Follow-up schedule was the same in all participating centres starting 3 months after beginning of hormonal therapy, and based on: 3-monthly general and gynecological examinations, TVS, and office hysteroscopic biopsies; an abdomen-pelvis CT/MR was performed at 6 months and 6-monthly thereafter. After 2 years, patients still in CR and wishing to maintain their reproductive potential were followed through 6-monthly general and gynecological examinations, TVS, and office hysteroscopic biopsies.

Patients in CR after hormone treatment were encouraged to conceive with or without assisted reproduction technology (ART). Definitive surgery was recommended following childbearing completion. Patients showing persistent, progressive, or recurrent disease were invited to immediate definitive surgery.

Response criteria were defined as follows: i) CR, no evidence of residual EC or hyperplasia at follow-up endometrial sampling (time until CR was measured from the progestin start date); ii) partial regression, presence of G1 EC or hyperplasia (with or without atypia) during follow-up endometrial sampling; iii) persistent disease, no evidence of disease regression within 6 months from progestin initiation; iv) progressive disease, EC invading the myometrium (>stage IA, according to 1988 FIGO staging system) and/or poorly differentiated (G3) EC during follow-up. Recurrence was defined as the presence of EC or hyperplasia during follow-up after an endometrial sample showing disease CR. Time to recurrence was measured from the date of CR first assessment. Patient follow-up data were gathered until the end of February 2020.

RESULTS

A total of 23 patients with intramucous, G2, endometrioid EC, undergoing fertility-sparing treatment in 10 Centres, were registered into the *E.C.Co. archive* and included in the present analysis. Patient, tumor- and treatment-related characteristics at the time of conservative management are detailed in **Table 1**.

Seventeen patients (17/23, 74%) were conservatively treated by combined hysteroscopic resection (HR) and progestin therapy, the latter consisting of levonorgestrel intrauterine device (LNG-IUD) (12 cases), megestrol acetate (MA) at 160 mg daily (4 cases), or norethisterone acetate at 10 mg daily (1 case). Four patients (4/23, 17.4%) received LNG-IUD alone, and one (1/23, 4.3%) was treated by combined LNG-IUD and oral MA (160 mg daily). The remaining patient (1/23, 4.3%) received oral MA alone (160 mg daily).

All HR were performed according to a standardized three-step technique first described by Mazzon et al. [23], consisting of the resection of i) the tumor lesion, ii) the endometrium adjacent to the tumor, and iii) the myometrium underlying the tumor. A LNG-IUD, releasing 20 mg of levonorgestrel daily (Mirena®; Bayer Schering Pharma AG, Berlin, Germany), was used in all cases who had been treated with intrauterine device-delivered progestin (alone or in combination).

Psychological support was institutionally provided in 4 out of 10 (40%) participating Centres.

Table 1. Patient-, tumor- and treatment-related characteristics

Case #	Age (yr)	BMI (kg/m²)	Previous pregnancy	Diagnostic method	Tumor diameter (cm)	Diagnostic laparoscopy	Fertility-sparing treatment modalities	Progestin therapy (mo)
1	39	24.3	-	Office HSC with EB	>2	Yes	HR + LNG-IUD	3
2	32	36.5	-	Office HSC with EB	>2	No	HR + LNG-IUD	9
3	31	21.4	-	D&C	≤2	Yes	HR + MA (160 mg/d)	11
4	33	29.3	-	HSC followed by D&C	≤2	Yes	HR + MA (160 mg/d)	3
5	31	24	-	HSC followed by D&C	≤2	Yes	HR + MA (160 mg/d)	22
6	28	42	1 NFTD; 1 SFTM	HSC followed by D&C	≤2	No	HR + LNG-IUD	24
7	32	30	-	HSC followed by D&C	≤2	No	HR + LNG-IUD	6
8	37	24	-	Office HSC with EB	≤2	No	MA (160 mg/d)	13
9	34	23.5	-	HSC followed by D&C	≤2	No	HR + LNG-IUD	12
10	37	24	-	Office HSC with EB	n/a	Yes	LNG-IUD	14
11	43	21	-	Office HSC with EB	n/a	Yes	LNG-IUD	32
12	28	31	-	Office HSC with EB	n/a	Yes	LNG-IUD	36
13	31	29	-	Office HSC with EB	n/a	Yes	LNG-IUD	46
14	36	26	2 NFTDs	Office HSC with EB	≤2	No	HR + MA (160 mg/d)	12
15	37	24.1	-	Office HSC with EB	n/a	No	HR + LNG-IUD	6
16	31	19.8	-	Office HSC with EB	n/a	No	HR + LNG-IUD	6
17	28	38.3	-	Office HSC with EB	n/a	No	HR + LNG-IUD	26
18	40	21.3	1 NFTD	Office HSC with EB	>2	No	HR + LNG-IUD	10
19	44	28.9	1 NFTD; 2 SFTMs; 1 EA	Office HSC with EB	>2	No	HR + LNG-IUD	6
20	42	34.1	-	Office HSC with EB	≤2	No	HR + NET (10 mg/d)	9
21	32	31.6	-	Office HSC with EB	≤2	No	LNG-IUD + MA (160 mg/d)	6
22	34	31.2	1 SFTM	Office HSC with EB	n/a	No	HR + LNG-IUD	8
23	37	34.9	-	Office HSC with EB	n/a	No	HR + LNG-IUD	77

BMI, body mass index; D&C, dilation and curettage; EA, elective abortion; EB, endometrial biopsy; HR, hysteroscopic resection; HSC, hysteroscopy; LNG-IUD, levonorgestrel intrauterine device; MA, megestrol acetate; n/a, not available; NET, norethisterone acetate; NFTD, normal full-term delivery; SFTM, spontaneous first-trimester miscarriage.

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The median follow-up time from the progestin start date was 35 months (range, 9 to 148 months). CR was achieved in 43.4%, 56.5% and 65.2% of the patients after 6, 9 and 12 months from the progestin start date, respectively. A complete response was observed in 2 further patients (no. 8 and no. 23) after 13 months from progestin initiation, with an overall CR rate of 73.9%. Among complete responders, the median duration of progestin therapy was 13 months (range, 6 to 77 months).

Among the 6 patients who did not show complete response, one showed persistent disease at 6 months and underwent hysterectomy with a final pathology of stage IA (intramucous) G2 endometrioid EC. The remaining 5 patients experienced progressive disease and were submitted to definitive surgery (**Table 2**). In particular, patients no. 1 and no. 4 progressed at 3 months. Both these patients underwent definitive surgery and the final pathology showed a $FIGO_{2009}$ stage IA (with myometrial invasion) G3 endometrioid EC for the former, and a $FIGO_{2009}$ stage IA (with myometrial invasion) G1 endometrioid EC for the latter.

Patient no. 9, after 12 months from progestin initiation, was suspected for cervical involvement and treated by definitive surgery with a diagnosis of $FIGO_{2009}$ stage II G2 endometrioid EC.

Patient no. 19, 6 months from the progestin start date, was found to have an ovarian mass and treated by definitive surgery, showing a $FIGO_{2009}$ stage IA (with myometrial invasion) G1 endometrioid EC and a synchronous $FIGO_{2014}$ stage IC2 G2 endometrioid ovarian cancer (OC).

Patient no. 22 was diagnosed with G3 histology and myometrial invasion at the 9-month follow-up and underwent definitive surgery with a diagnosis of $FIGO_{2009}$ stage IIIC1 G3

Table 2. Oncologic and reproductive outcomes

Case #	Oncologic outcome at			Relapse (mo)	Second cancer (mo*)	Attempting to conceive	Pregnancy	Follow-up (mo)	Current status
	6 mo	9 mo	12 mo						
1	Progression†	-	-	-	-	-	-	119	NED‡
2	Persistence	CR	CR	Endometrial (4)	-	Yes	-	29	NED
3	Persistence	Persistence	CR	-	-	Yes	1 NFTD	139	NED‡
4	Progression†	-	-	-	-	-	-	106	NED‡
5	CR	CR	CR	Endometrial (28)	-	Yes	-	93	NED‡
6	CR	CR	CR	-	-	Yes	-	24	NED‡
7	CR	CR	CR	Endometrial (6)	-	-	-	48	NED‡
8	Persistence	Persistence	CR§	-	-	Yes (ART)	-	19	NED
9	Persistence	Persistence	Progression	-	-	-	-	21	NED‡
10	CR	CR	CR	Endometrial (21)	-	-	-	119	NED‡
11	CR	CR	CR	Endometrial (32)	Ovarian (37)	-	-	80	NED‡
12	Persistence	CR	CR	Endometrial (17)	-	-	-	131	NED‡
13	CR	CR	CR	Endometrial (142)	-	-	-	148	NED‡
14	CR	CR	CR	-	-	Yes	1 NFTD	30	NED
15	CR	CR	CR	-	-	Yes	1 NFTD; 2 SFTM	35	NED
16	CR	CR	CR	-	-	Yes (ART)	-	44	NED
17	CR	CR	CR	-	-	-	-	18	NED
18	Persistence	Persistence	CR	-	-	Yes	-	26	NED
19	Progression	-	-	-	Ovarian (6)	-	-	15	NED‡
20	Persistence	CR	CR	-	-	Yes	-	23	NED
21	Persistence‖	-	-	-	-	-	-	9	NED‡
22	Persistence	Progression	-	Retroperitoneal (12)	-	-	-	31	AWD‡
23	Persistence	Persistence	CR§	-	-	-	-	64	NED

ART, assisted reproduction technology; AWD, alive with disease; CR, complete regression; NED, no evidence of disease; NFTD, normal full-term delivery; SFTM, spontaneous first-trimester miscarriage.
*After endometrial cancer diagnosis; †Definitive surgery at 3 months; ‡Submitted to definitive surgery; §CR at 13 months; ‖Definitive surgery at 6 months.

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endometrioid EC. Twelve months from surgery and after completion of the planned adjuvant sequential chemoradiation, this patient showed para-aortic nodal relapse; she underwent para-aortic lymphadenectomy achieving complete removal of the recurrence and received post-operative chemotherapy.

Details regarding pathological evaluation, treatment and follow-up of women showing progressive disease are summarized in **Tables 2** and **3**.

The overall recurrence rate was 41.1% (7/17). The median duration of complete response was 21 months (range, 4 to 142 months). All recurrent patients but one (patient no. 2) underwent definitive surgery. Final pathology showed superficial myo-invasion due to a G2 endometrioid histotype and to a G1 endometrioid in 5 and one patient, respectively. A synchronous stage IA G1 endometrioid OC was detected in one case (patient no. 11). Patient no. 2, although fully informed about her high oncologic risk, refused the proposed definitive surgery and was conservatively re-treated by combined LNG-IUD and MA (160 mg daily), achieving a complete response 6 months after re-treatment.

None of our patients presented with a family history suggesting a hereditary cancer syndrome. Only a minority (26%) of patients underwent genetic analyses (IHC with or without germline Lynch syndrome [LS] testing) with a positive rate for MMR IHC abnormal in 2/6 (MSH2 and MSH6 in both), and germline mutations in 1/5 (one patient refused the germline testing). The germline test was negative for BRCA mutations in the two patients (no. 11 and 19) developing an ovarian second neoplasm. Patient no. 11 resulted to be a carrier of MSH2 germline mutation, whereas case no. 19 had germline LS genetic testing negative.

Ten complete responders (58.8%) attempted to conceive, of whom 3 (30%) achieved at least one pregnancy giving birth to a healthy child. Only 2 patients (20%) underwent ART, both without achieving pregnancy (**Table 2**).

Of the 11 women candidates for definitive surgery, hysterectomy was performed in one at the time of caesarean section, and in another before the completion of the 5-year follow-up, while the remaining 9 have so far refused.

At the end of the observation period, 22 patients (95.7%) show no evidence of disease, and one (4.3%) is still alive with disease (**Table 2**).

Table 3. Pathologic characteristics and treatment at the time of endometrial cancer progression

Characteristics	Patient No. 1	Patient No. 4	Patient No. 9	Patient No. 19	Patient No. 22
Tumor grade	3	1	2	1	3
Myometrial invasion	<50%	<50%	<50%	<50%	>50%
Lymph vascular space invasion	Absent	Absent	Absent	Absent	Present
Tumor size (cm)	>2	<2	<2	<2	>2
Cervical involvement	Absent	Absent	Present	Absent	Absent
Adnexal involvement	Absent	Absent	Absent	Synchronous OC	Present
Lymphadenectomy	Pelvic	n/p	n/p	Pelvic and para-aortic	Pelvic
Lymph node involvement	Absent	n/a	n/a	Absent	Present
No. of positive nodes/total no. of lymph nodes removed	0/21			0/19	1/17
Metastatic pattern (mm)	n/a			n/a	>2
Adjuvant therapy after definitive surgery	n/p	n/p	n/p	Yes	Yes

n/a, not applicable; n/p, not performed; OC, ovarian cancer.

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DISCUSSION

Even though fertility-sparing options for EC have increasingly been investigated during the last decade, there is still lack of defined consensus both in terms of patient eligibility and treatment approach. In particular, experience with conservative treatment of early-stage G2 EC is very limited, partly due to the rarity of such a diagnosis in the reproductive age, partly due to the *a priori* exclusion of these cases from conservative management.

The present study, conducted among referral centres collaborating in the GCIG, reports the largest series of intramucous, G2, endometrioid EC patients who were selected for fertility preservation and treated by progestin therapy (with or without HR). After a median follow-up of about 3 years, 73.9% of patients achieved a complete response with a recurrence rate of 41.1%. These figures do not appear substantially different from those obtained in G1 patients, leaving room for consideration of fertility-sparing treatment in selected G2 EC.

To date, only 49 early-stage G2 endometrioid EC patients have been reported in the literature as having received fertility-sparing treatment, mostly from small institutional series except for one multicentric study (**Table 4**) [3-17]. Five of these patients [4,13] have been also included in the present study.

The CR rate observed in our patients (73.9%) is very consistent with that extrapolated from the studies published so far (71.4%) (**Table 4**) [3-17]. Again, the median time to CR (6 months), the duration of CR (21 months), and the recurrence rate (41.1%) do not substantially differ from those reported for G2 EC so far (**Table 4**). The multicentric study by Park et al. [15] is the only series reporting a lower (27.2%) rate of recurrence. This could be explained by the different follow-up modalities: the endometrial biopsy was not included among the first level procedures, as routinely done in our study. Moreover, an accurate meta-analysis on a large patient sample (n=408) including also >G1 cases showed a pooled recurrence rate of 40.6% [24], thus confirming that our findings can be considered representative of conservative treatment outcomes in G2 EC.

The risk of tumor progression is the most important concern among these patients. In our series, 5 women experienced progressive disease and were submitted to definitive surgery (**Tables 2** and **3**). Four of them had uterine-confined EC at final pathology, and did not experience subsequent disease relapse. In the remaining patient (no. 22), final pathology showed extrauterine spread with both ovarian and nodal metastases. She recurred 7 months after completion of the planned adjuvant chemoradiation and, at the time of present publication, is alive with peritoneal carcinosis. Such a negative oncologic outcome is, however, anecdotal. In fact, this is the only one (1.5%) poor outcome out of the 5 (7.4%) progressions observed among a total of 67 G2 ECs reported so far, including the present study. This case of unfavourable outcome may be explained by the presence of occult extrauterine disease and/or by tumor undergrading at the time of conservative treatment.

A diagnostic laparoscopy is included in some studies workup, given the limited sensitivity of imaging techniques and CA-125 to detect subclinical extrauterine lesions [4,25,26]. This was due to the overestimated risk of synchronous OC which likely accounts for only 3% to 4.5% [27,28]. In our previous series of G1 EC conservatively treated, about 80% of the patients were submitted to laparoscopy which was negative in all cases, in spite of the occurrence of two subsequent OCs [4]. In the present series, only 21.7% of patients underwent pre-treatment laparoscopy all

Table 4. Literature review of intramucous, moderately differentiated, endometrioid endometrial cancers conservatively treated

Author (yr), [Reference]	Study design	No. of cases	BMI (kg/m^2)	Treatment	Oncologic outcomes	Time to CR (mo)	Relapse	DFI (mo)	Pregnancy (No. of patients)	Live births	Follow-up (mo)	Current status
Brown et al. (2012), [3]	R	1	47.7	LNG-IUD (20 μg/d)	CR	3	0	n/a	0	0	13	NED
Falcone et al. (2017), [4]	P	1	24.3	HR + LNG-IUD (20 μg/d)	Prog	n/a	n/a	n/a	n/a	n/a	78	NED
Gotlieb et al. (2003), [5]	R	2	n/r	MPA (200–600 mg/d)	CR	3–5	1	40	1	3	18–94	NED
Han et al. (2009), [6]	R	2	n/r	MA (80 mg/d) or MPA (500 mg/d)	CR	3	0	n/a	2	0	42–52	NED
Hwang et al. (2017), [7]	R	5	18.5–30.5	MPA (500 mg/d) + LNG-IUD (20 μg/d)	3 CR; 2 PR	6–18	1	14	1	0	12–71	NED
Imai et al. (2001), [8]	R	2	n/r	MPA (600 mg/d)	1 CR; 1 PD	9	1	7	0	0	7–47	1 NED; 1 LTFU
Kaku et al. (2001), [9]	R	2	<27.3	MPA (600–800 mg/d)	1 CR; 1 PD	4	0	n/a	1	1	19–22	NED
Kim et al. (2016), [10]	R	1	24.8	MA (160 mg/d)	CR	8	0	n/a	0	0	8	NED
Koskas et al. (2011), [11]	R	3	n/r	MA (160 mg/d), NG (5 mg/d) or NET (20 mg/d)	CR	3–6	2	3–36	1	2	6–60	1 AWD; 2 NED
Le Digabel et al. (2006), [12]	R	1	n/r	Repetitive D&C	CR	n/r	0	n/a	0	0	39	NED
Leone Roberti Maggiore et al. (2019), [13]	R	4	16.8–45.8	LNG-IUD (20 μg/d)	3 CR; 1 Prog	4	3	12–16	0	0	112–118	NED
Pal et al. (2018), [14]	R	8	20–74	LNG-IUD (20 μg/d)	3 CR; 2 PD; 3 PR	3–9	n/r	n/r	n/r	n/r	n/r	n/r
Park et al. (2013), [15]	R, M	14	18.5–38.2	MA (40–240 mg/d) or MPA (80–1,000 mg/d)	11 CR; 3 PD	3–12	3	8–20	3	n/r	7–136	NED
Rossetti et al. (2014), [16]	R	2	20–23	MA (160 mg/d)	CR	6	2	13–18	2	2	14–52	NED
Zuckerman et al. (1998), [17]	R	1	n/r	MPA (600 mg/d)	CR	3	0	n/a	1	2	n/r	NED
Total	-	49	-	-	35 CR; 7 PD; 5 PR; 2 Prog	3–18	13	3–40	12	10	6–136	39 NED; 1 AWD; 9 LTFU / n/r

AWD, alive with disease; BMI, body mass index; CR, complete regression; D&C, dilation and curettage; DFI, disease-free interval; HR, hysteroscopic resection; LNG-IUD, levonorgestrel intrauterine device; LTFU, lost to follow-up; M, multicentric; MA, megestrol acetate; MPA, medroxyprogesterone acetate; n/a, not applicable; NED, no evidence of disease; NET, norethisterone; NG, nomegestrol; n/r, not reported; P, prospective; PD, persistent disease; PR, partial regression; Prog, progression; R, retrospective.

with negative findings, including one out of the three showing subsequent ovarian involvement. Based on the above, the usefulness of laparoscopy seems to be questionable. Nevertheless, it has to be considered that laparoscopy was not included in the pre-treatment workup of both cases showing progressive disease with ovarian involvement within the first year. Although is difficult to draw any recommendation with respect to diagnostic laparoscopy in conservatively treated EC patients, its use may be advisable in >G1 EC.

Grade and histotype assignment is subject to imperfect concordance between diagnostic and hysterectomy specimens [1,29-31]. In particular, up to 26% of ECs defined as G2 endometrioid on biopsy are upgraded or read as high-risk histologies on final pathology [30]. Office hysteroscopic biopsy is increasingly used for the diagnosis of EC. The dilation and curettage/HR show a significantly lower rate of histological undergrading if compared with office hysteroscopy/pipelle biopsy, and they are considered by some authors as the optimal diagnostic method in a fertility-sparing setting [2,32-34]. Moreover, young EC women usually present with low-volume disease, while adequate tissue sampling is of utmost importance to accurately assign tumor histotype and grade. Therefore, additional HR to progestin seems to offer an advantage in terms of pathologic assessment, maximizing the chance of optimal

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tissue sampling and minimizing the risk of erroneous histotype and grade assignment. In the present study, two-third of patients (74%) underwent HR, thus providing a likely good pathological accuracy.

In the present series, all recurrent patients (7/17, 41.1%) are still alive and well at the time of the present analysis. The safety of fertility-sparing therapy is further supported by the overall data available on G2 EC showing that all reported recurrences (17) are curable with definitive surgery. Standard treatment for recurrent disease after fertility-preserving treatment is total hysterectomy and bilateral salpingo-oophorectomy. Some women still wish to maintain their reproductive potential and continuing/repeat fertility-sparing treatment may be considered. In these circumstances, however, data are even more limited than in the primary setting, and for G2 than G1 EC. In G1 EC, the CR (70%–85%) and recurrence (42%) rates after second-round treatment are similar to those reported after primary conservative approach [33,35,36]. In the present series, one recurrent patient refused definitive surgery and was successfully re-treated with combined LNG-IUD and MA (160 mg daily). Fertility-sparing re-treatment, although still feasible in G2 patients declining definitive surgery at the time of uterine recurrence, should be considered with caution.

It has to be noted that the CR rate (73.9%) observed in our G2 EC study seems to be similar to that reported in the largest series of G1 patients conservatively treated with high-dose progestins (77.7%) [37]. Interestingly, the time to achieving a CR seems to be slightly longer (6 vs. 4.5 months), and, on the contrary, the duration of response shorter (21 vs. 58 months) in G2 cases, although the median follow-up is different in favour of the G1 group (35 vs. 66 months). It is reasonable to think that higher the grade, longer the time to response to progestins, in the presence of approximately the same (or slightly lower) rate of regression. It has been reported that the HR of the tumor before high-dose progestin therapy could shorten the time between diagnosis and complete response [4]. In our study, patients receiving progestin alone and those undergoing HR plus progestin therapy showed superimposable times to CR, thus not providing further evidence of an additional benefit from HR.

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 [24]. Similarly, the overall live birth rate was 28.5% (10/35) from studies on early-stage G2 ECs (**Table 4**) [3-17]. Although all women included in our series wished to preserve their reproductive potential, only 58.8% of complete responders attempted to conceive during the study period. Overall, considering also women who did not attempt to conceive, live birth rate was 17.6%, which appear even lower than that reported in the literature. This difference could be explained by the significantly higher mean age in our study compared to those included in previous series (mean±standard deviation: 34.6 years±4.73 vs. 29.8 years±4.76, $p<0.001$), with the age having a crucial role in influencing reproductive capacity.

It is acknowledged that women who are diagnosed with EC before age 50 years have a heightened risk for hereditary cancer syndrome. In particular, young EC patients are potentially (5% to 10%) harbouring a germ-line mutation in DNA mismatch repair (MMR) genes (LS/hereditary nonpolyposis colorectal cancer), characterized by increased lifetime risk for EC and OC (up to 60% and 24%, respectively) [38]. International guidelines have introduced the microsatellite instability and/or MMR immunohistochemistry (IHC) screening in all patients with EC, especially in those younger than 50 years of age, with

approximately 90% concordance between germline analysis and IHC [1]. Moreover, it has been reported that these molecular analyses work successfully also on resectoscopic specimens of EC patients candidate for conservative treatment, allowing a reliable and early hereditary cancer risk assessment [39]. In spite of the considerations above, genetic analyses (MMR IHC with or without germline LS testing) were performed in only one-fourth of our patients, with a positive rate for germline mutations in one out of five. This is a study limitation and is mostly due to the relatively long time of enrolment. The *Proactive Molecular Risk Classifier for Endometrial Cancer* (ProMisE) has been recently reported in a small series of G1 EC conservatively treated suggesting a potential role for a more reliable prognostic information [39]. The application of ProMisE could be even more appropriate in G2 EC.

To date, it is debatable whether an EC young patient with an MMR or a BRCA1/2 mutation should not be offered a conservative management. In fact, this should be considered as a limited time window for conception, followed by definitive surgery. In this perspective, fertility-sparing treatment may be offered also to patients at genetic high risk after appropriate counselling included in the pre-treatment workup.

Definitive surgery, however, still represents a problem. Despite adequate pre-treatment counselling, the patient compliance to definitive surgery is very poor, with high rate of repetitive refusals. Definitive surgery is likely lived as definitive loss of womanhood, in patients harboring a strong desire of preserving their fertility regardless of childbearing. This aspect underlines the need for appropriate psychological support to be routinely provided not only in the pre-treatment counselling but also in the follow-up period.

The small sample size, the retrospective setting, the long study period, and the use of different therapies represent the main limitations of our study. Moreover, although pathological diagnosis was reviewed by institutionally dedicated pathologists, there was not a central review. Nevertheless, the present study reports on the largest series of intramucous, G2, endometrioid EC selected for fertility preservation with a long median follow-up time.

In conclusion, fertility-sparing treatment seems to be feasible even in a higher than G1 risk category of EC patients. Although the population sample is very limited, the rates of CR, recurrence, and duration of response are similar to those observed in G1 patients, with less than 2% risk of unfavourable outcome. Caregivers, however, should apply caution with the potential pathological undergrading or non-endometrioid histology misdiagnosis. The low rate of attempt to conceive and the disappointing compliance to definitive surgery underline the role for a 'global' counselling including psychological support extended to the follow-up period. Routine MMR IHC analyses should be recommended while ProMisE application may be adopted for a better risk stratification.

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