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Efficacy and fertility outcomes of levonorgestrel-releasing intra-uterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: a retrospective study

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ABSTRACT

Objective: To investigate the efficacy of levonorgestrel-releasing intra-uterine system (LNG-IUS) treatment in patients affected by atypical complex hyperplasia/endometrial cancer (ACH/EC) wishing to preserve their fertility and to present fertility outcomes of those patients who actively tried to conceive.
Methods: Data of consecutive women with ACH/EC who underwent fertility-sparing treatment using LNG-IUS were retrospectively evaluated.
Results: Overall, 48 patients and the mean (±standard deviation) length of follow-up was 82.6±47.2 months. Among patients with ACH, 25/28 (89.3%) had a complete response (CR), 2/28 (7.1%) had a partial response (PR) and 1/28 (3.6%) had a progressive disease (PD). Mean (±standard deviation) time to CR was 6.7±4.0 months. Among patients with G1 EC, 13/16 (81.3%) had a CR, 1/16 (6.3%) had a PR and 2/16 (12.5%) had a PD. Mean (±standard deviation) time to CR was 5.0±2.9 months. Among patients with G2 EC, 3/4 (75.0%) had a CR and 1/4 (25.0%) had a PD. Mean (±standard deviation) time to CR was 4.0±0 months. Only 19 (39.6%) patients who had CR actually attempted to conceive. Eleven (57.9%) women tried to conceive naturally while 8 (42.1%) women underwent an in vitro fertilization (IVF). Fourteen (73.7%) patients wishing to conceive achieved a pregnancy (6 spontaneously and 8 through IVF).
Conclusions: Fertility-sparing treatment of patient with ACH/EC with LNG-IUS achieves high regression rates and good fertility outcomes. Future larger multi-institutional studies should be designed to confirm these preliminary findings.

Keywords: Endometrial Cancer; Fertility; Hyperplasia; Levonorgestrel; Pregnancy

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

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INTRODUCTION

Endometrial hyperplasia (EH) is the precursor of endometrial cancer (EC) [1]. When no treatment is performed, the risk of progression from EH to carcinoma is 1% for patients with simple hyperplasia, 3% for patients with non-atypical complex hyperplasia (non-ACH) and 15%–75% for patients with atypical complex hyperplasia (ACH) [2]. Invasive EC can already be found in approximately 30%–43% of patients initially diagnosed with ACH [3,4].

Worldwide in 2012, 527,600 women were diagnosed with EC, which is currently the most common malignancy of the female genital tract in developed countries [5]. In 2017, according to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, the USA estimated number of new cases of EC was 61,380 women while the estimated number of deaths was 10,920 women [6]. Although it is mainly a disease affecting postmenopausal women, 25% of them are premenopausal and 3%–5% are under the age of 40 years [7].

The current standard treatment of ACH and EC is hysterectomy with bilateral salpingo-oophorectomy and with or without peritoneal and retroperitoneal staging [8-10]. Although this approach offers a good 5-year oncologic survival outcome of 75%–90% in the overall population [11], it prevents prospects of future fertility. Furthermore, surgical treatment may be associated with intra- and postoperative complications, particularly in those populations of patients who are more frequently affected by ACH/EC such as obese women and conservative options may be chosen in this [12,13].

Given this background, the standard surgical option of hysterectomy and bilateral salpingo-oophorectomy may not be ideal for women interested in future fertility. Thus, conservative strategies should be discussed with patients affected by ACH/EC along with the associated outcomes of each approach. Different fertility-sparing options have been demonstrated safe and feasible such as oral hormonal therapy, hysteroscopic resection of focal lesions, and the use of medicated intra-uterine systems [14].

The primary outcome of the current study was to investigate the efficacy of the treatment with levonorgestrel-releasing intra-uterine system (LNG-IUS) in patients affected by ACH/EC who wish to preserve their fertility. Secondary outcomes of this study are to present the fertility outcomes of those patients who actively tried to conceive after the treatment.

MATERIALS AND METHODS

A large institutional prospectively collected database including patients between 2004 and 2017 was retrospectively reviewed, searching records of women with ACH/EC who underwent fertility-sparing treatment using LNG-IUS. All patients gave consent for the use of personal information for health research. The Institutional Review Board (IRB) of "Fondazione IRCCS Istituto Nazionale dei Tumori"– Milan approved the collection and use of patients' clinical data for this retrospective study (IRB approval number: INT/MI/006812).

Inclusion criteria were: fertile age, histologically proven ACH or well-differentiated (G1)/moderately-differentiated (G2) endometrioid EC, tumor that was presumed International Federation of Gynecology and Obstetrics (FIGO) stage IA limited to the endometrium at transvaginal ultrasound, desire to preserve their fertility.

Exclusion criteria were: incomplete medical records, age <18 years old, evidence of myometrial/cervical invasion, retroperitoneal lymph node involvement, suspicion of synchronous ovarian tumors at diagnosis, and/or distant metastasis at imaging assessment, women unwilling to undergo regular follow-up, use of additional systemic progesterone agents to treat ACH/EC during or after LNG-IUS placement. any condition precluding the acquisition of the informed written consent.

The primary outcome of this study was to estimate the proportion of women with ACH/EC showing histological regression after treatment with the LNG-IUS. The secondary outcome was to present the fertility outcomes of women wishing to conceive after that regression was achieved.

All patients were evaluated at baseline by pelvic examination, transvaginal ultrasound and abdominal magnetic resonance imaging (MRI). All imaging techniques were performed by expert physician specifically trained in gynecologic oncology. In particular, all ultrasonographic scans were performed by the same operator (Valentina Chiappa). In all the cases, the histologic diagnosis was performed by hysteroscopy; two expert pathologists specialized in gynecologic oncology examined all the slides and they always evaluate all the subsequent pathology slides from treatment and surveillance.

Once the diagnosis of ACH or EC was posed, all patients were thoroughly counseled on the merits, disadvantages, and risks of surgical and LNG-IUS treatments. Women accepting to receive conservative treatment were inserted an IUS releasing 20 μg of LNG daily (Mirena®; Bayer Schering Pharma AG, Berlin, Germany). Response to treatment was evaluated at endometrial biopsies obtained by hysteroscopy and classified as follows: complete response (CR) was defined as the lack of residual ACH or EC, partial response (PR) was defined if histological downgrade was diagnosed during follow-up, stable disease (SD) was defined as no evidence of disease regression/progression, progressive disease (PD) was defined if histological upgrade was diagnosed during follow-up. Time to CR was measured from the LNG-IUS insertion. Recurrence was defined as the presence of ACH or EC during follow-up after an endometrial sample that showed CR. Time to recurrence was measured since the date of CR.

At follow-up all patients were evaluated by hysteroscopy. LNG-IUS was left inside the uterus and 5 endometrial biopsies were always performed (at anterior, posterior, right, left uterine walls and fundus). In addition, all patients were assessed by abdominal MRI every 6 months to evaluate disease status. First follow-up was performed at 3 months and 6 months, then every 6 months until the end of treatment or until recurrence. Patients with PR or SD at 3- and 6-month follow-up continued LNG-IUS treatment until 9-month follow-up and then they were invited to undergo surgery, while those with PD were immediately proposed to undergo surgery. On the basis of ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer recommendation [15], women with CR who wanted to become pregnant, were removed LNG-IUS and were encouraged to conceive immediately or referred to in vitro fertilization (IVF) according to the clinical/gynecological history of themselves and of their partners. Women trying to conceive both naturally or by IVF were assessed through hysteroscopy every 3 months until they achieve pregnancy or decided to stop trying to conceive.

RESULTS

A total of 48 patients were included in the current study and complete data on their follow-up were available. The main characteristics of the study population are reported in **Tables 1** and **2**. The mean (±standard deviation) age of the patients included in the study was 34.5 (±5.0) years and a total of 10/48 (20.8%) women had previous live births.

The mean (±standard deviation) length of follow-up of the whole study population was 82.6±47.2 months. Overall, after conservative treatment with LNG-IUS, a total of 41/48 (85.4%) patients had a CR, 3/48 (6.3%) patients had a PR, 0/48 (0%) had a SD, and 4/48 (6.3%) had a PD. Mean (±standard deviation) time to CR was 7.6±4.0 months. Seventeen (41.5%) out of 41 women had a recurrence that occurred in 6/41 (14.6%) cases under LNG-IUS treatment (4 ACH and 2 EC grade 1). Mean (±standard deviation) time to recurrence in the study population was 28.6±20.1 months. Details about response to conservative treatment according to histological diagnosis at baseline are shown in **Table 3**. Noteworthy, 3/48 (6.3%) women, all with G1 EC, had a synchronous ovarian cancer.

Among those 41 women who achieved a CR, only 19 (39.6%) patients actually attempted to conceive. Eleven (57.9%) women tried to conceive naturally while 8 (42.1%) women underwent an IVF. Fourteen (73.7%) out of 19 patients wishing to conceive achieved a

Table 1. Main characteristics of the study population (n=48)

Characteristics	Value
Age (yr)	34.5±5.0
BMI (kg/m^2)	24.9±6.1
Level of education	
Primary	0 (0)
Secondary	30 (62.5)
University	18 (37.5)
Menarche age (yr)	12.5±1.6
Live births	0 (0–2)
Previous hormonal contraceptive	25 (52.1)
Previous IVF	5 (10.4)

Data are presented as mean±standard deviation, median (range), or number (%).
BMI, body mass index; IVF, in vitro fertilization.

Table 2. Main characteristics of the study population according to the disease

Characteristics	Cases (n=48)	Age (yr)	BMI (kg/m^2)	Smokers	Diabetes	PCOS	Synchronous ovarian cancer	HNPCC
ACH	28/48 (58.3)	35.1±5.3	25.0±4.3	7/28 (25.0)	1/28 (3.6)	3/28 (10.7)	0/28 (0)	0/28 (0)
EC G1	16/48 (33.4)	33.4±5.0	22.8±4.6	5/16 (31.3)	1/16 (6.3)	2/16 (12.5)	3/16 (18.8)	2/16 (12.5)
EC G2	4/48 (8.3)	34.5±3.3	31.3±14.5	3/4 (75)	0/4 (0)	3/4 (75.0)	0/4 (0)	0/4 (0)
Total	48 (100)	34.5±5.0	24.9±6.1	15/48 (31.3)	2/48 (4.2)	8/48 (16.7)	3/48 (6.3)	2/48 (4.2)

Data are presented as mean±standard deviation or number (%).
ACH, atypical complex hyperplasia; BMI, body mass index; EC, endometrial cancer; G, grade; HNPCC, hereditary non-polyposis colorectal cancer; PCOS, polycystic ovary syndrome.

Table 3. Therapeutic efficacy outcomes

Characteristics	CR	PR	PD	Time to CR (mo)	Relapse	Time to relapse (mo)	Follow-up (mo)
ACH	25/28 (89.3)	2/28 (7.1)	1/28 (3.6)	6.7±4.0	9/25 (36.0)	34.0±22.4	76.4±48.8
EC G1	13/16 (81.3)	1/16 (6.3)	2/16 (12.5)	5.0±2.9	5/13 (38.5)	25.0±12.9	85.3±48.3
EC G2	3/4 (75.0)	0/4 (0)	1/4 (25.0)	4.0±0	3/3 (100)	14.3±1.5	115.5±2.6
Total	41/48 (85.4)	3/48 (6.3)	4/48 (8.3)	7.6±4.0	17/41 (41.5)	28.6±20.1	82.6±47.2

Data are presented as mean±standard deviation or number (%).
ACH, atypical complex hyperplasia; CR, complete response; EC, endometrial cancer; G, grade; PD, progressive disease; PR, partial response.

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Table 4. Fertility outcomes over the study period

Characteristics	Patients attempting to conceive	Success in conceiving	ART	Single pregnancy	Twin pregnancy	Live birth rate	Spontaneous delivery	Caesarean section	Late miscarriage	Intrauterine fetal death
ACH	11/28 (39.3)	6/11 (54.5)	2/11 (18.2)	5/6 (83.3)	1/6 (16.7)	5/28 (17.9)	4/6 (66.6)	1/6 (16.7)	1/6 (16.7)	0/6 (0)
EC G1	8/16 (50.0)	8/8 (100)	6/8 (75.0)	6/8 (75.0)	2/8 (25.0)	7/16 (43.8)	5/8 (62.5)	2/8 (25.0)	0/8 (0)	1/8 (12.5)
EC G2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	19/44 (43.1)	14/19 (73.7)	8/19 (41.2)	11/14 (78.6)	3/14 (21.4)	12/44 (27.3)	9/14 (64.3)	3/14 (21.5)	1/14 (7.1)	1/14 (7.1)

Data are presented as number (%).
ACH, atypical complex hyperplasia; ART, assisted reproductive techniques; EC, endometrial cancer; G, grade.

pregnancy (6 spontaneously and 8 through IVF); among these patients 11/14 (78.6%) had a single pregnancy, whereas 3/14 (21.4%) women had a twin pregnancy. One (7.1%) pregnancy terminated in late miscarriage at the 20th week, one (7.1%) intrauterine fetal death at 37th week was reported, while 11 (78.7%) women delivered at full term and one woman (7.1%) delivered beyond at late term. Spontaneous delivery occurred in 9/12 (75.0%) patients while caesarean section was performed in 3/12 (25.0%) cases. **Table 4** summarizes detailed information on fertility outcomes in the study population.

All patients with PD and recurrence received conventional surgery.

DISCUSSION

This study investigated the efficacy and fertility outcomes of the treatment with LNG-IUS in patients of reproductive age affected by ACH/EC, reporting three main messages. Firstly, the conservative strategy with LNG-IUS was demonstrated efficacious in 41/48 (85.4%) patients. Secondly, 17/41 (41.5%) women had a recurrence and, in most of the cases (11/17, 64.7%), recurrence was reported among women who removed the LNG-IUS. Thirdly, in our study population, about 40% of the patients who achieved a CR attempted to conceive and pregnancy occurred in the majority of the cases (14/19, 73.7%).

The relationship between epidemiological risk factors and the progression to EC can be explained by the unopposed estrogen hypothesis [16]. Progesterone, by antagonizing the effect of estrogen on the endometrium, may reverse this neoplastic process. In particular, treatment with progesterone/progestin works as in inhibition of the estrogen receptor, leading to a decrease in endometrial cell mitosis, promotion of apoptosis, and production of secretory endometrium. The use of progesterone/progestins in human EH and cancer has been described since the sixties [17-20]. Available evidence showed a variable range of risks for persistence or progression of EH in women treated with progestin, 1% for patients with simple hyperplasia, 3% for patients with non-ACH and 15%–75% for patients with ACH [2]. Both oral and local progestins have been investigated for conservative treatment of patients with ACH/EC [21,22]. In the current study, all women were treated with the same progestin treatment using the LNG-IUS. In 2012, a systematic review and meta-analysis was performed to compare the therapeutic efficacy of LNG-IUS with oral progestins for treatment of patients with ACH or early EC. The Authors concluded that there was a lack of high quality evidence for the efficacy of progestin in ACH or EC. However, available evidence suggested that treatment with oral or intrauterine progestin were similarly effective. Furthermore, it was pointed out that the risk of progression during treatment was small but longer follow-up was required [22]. In 2013, an English comparative cohort study addressed the issue of long-term efficacy in patients with EH and ACH; this study included women with complex non-atypical

hyperplasia or ACH who were treated with the LNG-IUS (n=250) or oral progestogens (n=94). The mean (±standard deviation) length of follow-up in the two groups was 66.9±35.1 months for the LNG-IUS and 87.2±45.5 months for the oral progestin group. Regression of hyperplasia was achieved in 94.8% (237/250) of patients with the LNG-IUS compared with 84.0% (79/94) of patients treated with oral progestogens (p=0.001). Regression rate was significantly higher for complex non-atypical hyperplasia in patients with LNG-IUS (221/229, 96.5%) versus those with oral progestogens (73/81, 90.1%; p=0.032). However, no difference was reported between the two treatment groups since regression of ACH was reported in 76.2% (16/21) of patients with the LNG-IUS compared with 46.2% (6/13) of patients treated with oral progestogens (p=0.082) [23]. Only scanty evidence is available on the use of only LNG-IUS in patients with EC and no direct comparison with oral progestins have been performed [22,24]. Montz and colleagues [24] reported data on the use of local progestins in patients with EC. They conducted a study to assess the feasibility of using a progesterone-containing intrauterine device to treat presumed FIGO stage IA, grade 1 endometrioid cancer in women at high risk for perioperative complications (American Society of Anesthesiologists class III or IV). Out of sixteen eligible patients, 12 women with a mean (±standard deviation) age of 60±16 years, were finally included in the study. Histologic studies identified no residual carcinoma in 6/12 (50%) women at 3 months, 7/11 (63.6%) women at 6 months, 7/9 (77.8%) women at 9 months, and 6/8 (75.0%) women at 12 months. Recently, Pal et al. [25] conducted a study to assess the efficacy of the LNG-IUS for treatment of 46 patients ACH or low-grade EC. At 6-month follow-up, out of 32 evaluable patients, 15 (47%) had ACH, 9 (28%) had G1 EC (28%), and 8 (25%) had grade 2 EC. Overall response rate was 75% (95% confidence interval [CI]=57–89) at 6 months; 80% (95% CI=52–96) in ACH, 67% (95% CI=30–93) in grade 1 EC, and 75% (95% CI=35–97) in grade 2 EC. However, among patients with G1 EC only 22.2% achieved CR at 6-month follow-up versus the CR rate of 81.3% reported in our study. It should be underlined that patients included in the two studies are completely different. In our study only fertile patients were included and the mean (±standard deviation) body mass index (BMI) was 24.9±6.1. In the study by Pal et al. [25] a mixed population of fertile and postmenopausal women were included with a significantly higher median (range) BMI of 45.45 (19–74). Thus, it cannot be excluded that these baseline characteristics may have influenced response to treatment.

Some important issues about conservative treatment of patients with ACH/EC wishing to conceive should be addressed. A first critical issue in endometrial tissue studies is diagnostic reproducibility. The lack of standardized pathology review by pathologists in most studies may contribute to the observed variability in outcomes. For this reason, we deem that, when conservative treatment is chosen for patients with ACH/EC, it is recommendable that follow-up consultations are performed in the same institution and that specimens are examined by an expert pathologists in gynaecologic diseases to increase histological assessment (ACH or EC) and the reliability of tumor grading [15]. Secondly, robust evidence on the optimal dosage of progestins and, in particular, on the best formulation (oral versus local) is still almost completely lacking and the regimens advocated are essentially arbitrary [26]. In our opinion, the use of LNG-IUS may represent an excellent choice for the conservative management of ACH/EC due to its good safety and tolerability profile [27,28]. A third relevant point is the potential coexistence of other tumors, in particular of ovarian cancer. In our study population, three (6.3%) women with EC G1 had a synchronous ovarian cancer. This result is in line with the prevalence reported in previous publications that is between 5% and 6.5% [29,30]. For this reason, when the fertility sparing management is adopted it may be recommendable to perform regularly a transvaginal ultrasound evaluation during the follow-

up of the patient. A fourth point that deserves attention is the limited number of patients that actually attempted to conceive. Thus, clinicians should thoroughly inform the patients on which is the standard management (hysterectomy and bilateral salpingo-oophorectomy) of ACH/EC and on the potential risks of a fertility-sparing treatment. Furthermore, patients should be clearly informed that the use of a conservative treatment only aims to create a time window to allow achieving a pregnancy and should not be considered as a long-term solution for their disease.

The current study is mainly limited by the inherent biases of the retrospective study design. In addition, the findings of this study should be considered carefully, because high response rates may be related to careful selection of patients for conservative therapy. However, although the overall number of participants reported in this study was small, this report is the largest case series investigating the efficacy and fertility outcomes of the treatment with LNG-IUS in patients of reproductive age affected by ACH/EC. In addition, it reports 4 cases of patients affected by EC G2 treated conservatively, showing a very promising rate of CR (75%). However, it should be pointed out that all these 3 patients relapsed in about 14 months and, despite our strong recommendations, they did not attempt to conceive. Therefore, these preliminary data suggests the possibility of a fertility-sparing option in patients with EC G2, opening the way for applying this treatment modality in a larger number of fertile women. However, these findings should be confirmed in larger population of patients to be considered reliable.

In conclusion, fertility-sparing treatment of patient with ACH/EC with LNG-IUS achieves high regression rates and good fertility outcomes. Future larger multi-institutional studies should be designed to confirm these preliminary findings and to draw any definitive conclusion on this issue.

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