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Research Article

Role of transvaginal ultrasonography in the management of young patients affected by atypical endometrial hyperplasia and well-differentiated endometrial cancer undergoing hormonal fertility-sparing treatment

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ABSTRACT

Purpose: To evaluate the efficacy of transvaginal ultrasonography (TVUS) as a tool for selection and prospective surveillance of patients younger than 40 years undergoing hormonal uterus-sparing therapy for atypical endometrial hyperplasia (AEH) and endometrial cancer (EC).

Methods: From February 2006 to July 2014, patients younger than 40 with AEH and EC, referred to the European Institute of Oncology for conservative management, were enrolled in a prospective observational study, consisting of insertion of a levonorgestrel-releasing intrauterine device (LNG-IUD) for 1 year with GnRH analogue administration for 6 months. TVUS was performed every 3 months, to assess endometrial thickness, any signs of myometrial infiltration and ovarian morphology. Endometrial biopsy was performed at 6 and 12 months.

Results: 16 patients with AEH and 32 with well-differentiated EC were enrolled. Myometrial infiltration was correctly identified in 6 cases of EC at instrumental pre-treatment evaluation (66.7% at TVUS and 66.7% at MRI). Overall the reduction of endometrial thickness was of 6.0 ± 5.6 (52.6%) and 6.8 ± 6.2 (59.6%) millimeters at 6 and 12 months, respectively, compared to baseline ($P < 0.001$). Synchronous or metachronous early-stage ovarian cancer was observed in 10 patients (20.8%).

Conclusions: TVUS might be a helpful tool in the pre-treatment assessment of myometrial infiltration and synchronous ovarian disease, and in the prospective surveillance of patients undergoing hormonal fertility-sparing therapy, however endometrial biopsy still remains the gold standard for the evaluation of response to conservative treatment.

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Introduction

Less than 5% of cases of endometrial cancer (EC) occur in young women [1, 2]. However, a larger proportion of premenopausal patients are

diagnosed with atypical endometrial hyperplasia (AEH), that can progress to cancer in approximately 30% of cases [3]. In these patients AEH and EC are often associated with multiple risk factors such as long-lasting hyperestrogenism (polycystic ovarian syndrome, nulliparity,

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anovulation) and obesity; in such a scenario, EC is mostly an estrogen-dependent well-differentiated endometrioid adenocarcinoma diagnosed as FIGO stage IA, and therefore characterized by good prognosis [4, 5]. Standard treatment for EC consists of total hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic and paraaortic lymphadenectomy, depending on different risk factors [6, 7]. However young patients, who are nulliparous in over 70% of cases at the time of diagnosis [8, 9], may wish for a fertility-sparing approach, that however still represents a clinical challenge.

Given the demonstrated overexpression of estrogen, progesterone, and gonadotropin-releasing hormone (GnRH) receptors in AEH and EC cells, several fertility-preserving hormone therapies have been employed since the early 1980s, such as high dose oral progestins and in association with GnRH analogue (GnRHa) the levonorgestrel-releasing intrauterine device (LNG-IUD) that, providing very high hormone concentration at the disease site, avoids the possible adverse effects associated with oral administration [10-15]. Given the risks of disease progression or relapse, a thorough pre-treatment evaluation and a close follow-up during and after conservative treatment is mandatory in the management of young patients who desire uterine preservation.

The aim of our study was to investigate the role of transvaginal ultrasonography (TVUS) for pre-treatment evaluation and prospective surveillance of patients younger than 40 years diagnosed with AEH or presumed FIGO stage IA EC-G1, with a strong desire to preserve their fertility, treated with LNG-IUD in association with GnRHa.

Materials and Methods

All AEH or presumed FIGO stage IA EC-G1 women treated at the European Institute of Oncology, Milan, Italy, who were candidate for conservative management from February 2006 to July 2014, were enrolled in a prospective observational study to evaluate the role of TVUS in pre-treatment assessment and forthcoming surveillance of uterus-sparing treatment. These patients were offered conservative treatment if the following inclusion criteria were met: (i) age between 19 and 40 years; (ii) strong desire to preserve fertility; (iii) pathological confirmation by central review of AEH or well-differentiated (G1) EC, presumed FIGO stage IA limited to the endometrium. Patients were excluded in case of: (i) EC with suspicion of myometrial invasion on TVUS or magnetic resonance imaging (MRI); (ii) histological diagnosis of moderately- or poorly-differentiated EC; (iii) laparoscopic evidence of extrauterine disease.

The study was approved by the hospital's institutional review board. At enrolment, after extensive counseling all patients signed an informed consent form. Data regarding principal demographic and clinical patients' characteristics were collected.

All patients underwent pre-treatment evaluation that consisted of: (i) hysteroscopy with curettage for histological diagnosis or pathology review of original slides if initial diagnosis was made at different institutions; (ii) TVUS and MRI to assess myometrial invasion; and (iii) diagnostic laparoscopy to rule out disease spread beyond the uterus or the presence of synchronous ovarian cancer.

All initial histological diagnosis and revisions of pathological slides from different institutions were performed by at least two independent dedicated gynecological pathologists working at the European Institute of Oncology. All ultrasound examinations were performed by two senior examiners, with 15-year experience in gynecological oncology ultrasound. High-end ultrasound equipment with a 5.0 to 9.0 MHz frequency vaginal probe, was employed for the examination of the pelvic cavity. At TVUS, the uterus was examined starting with a longitudinal median section, and the transvaginal probe was tilted from one uterine lateral border to the contralateral one, maintaining a longitudinal plane. Endometrial thickness was measured, perpendicular to the endometrial midline, where it appeared to be thickest, including both endometrial layers [16]. Any sign of myometrial infiltration and ovarian morphology were assessed at study entry and at any follow-up TVUS examinations during the study period. Myometrial infiltration was considered as any protrusion of the endometrium into the myometrium. The depth of myometrial invasion was subjectively evaluated and classified into two groups: no invasion or myometrial invasion [17, 18]. Thereafter, three-dimensional (3D) US, including virtual navigation through multiplanar display, was acquired to confirm the subjective impression of the regularity of the endometrial-myometrial junction (Figure 1) [19]. Conservative management consisted of insertion of an LNG-IUD system (Mirena®; Bayer Health Care Pharmaceutical Inc., Wayne, NY) in uterus for 12 months. The IUD is a T-shaped polyethylene device that releases 20 µg of LNG daily for up to 5 years [20]. All patients also received monthly depot injection of 3.75 ml of GnRHa for the first 6 months of therapy.

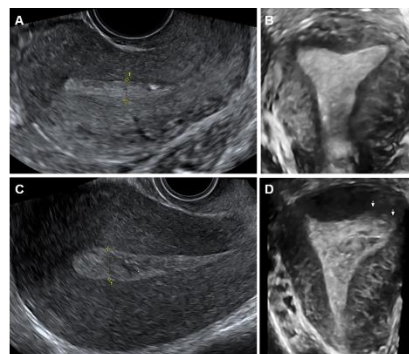


Figure 1: Pre-treatment TVUS evaluation of endometrial thickness in the longitudinal section and 3D mid coronal plane in Patient 1 (A-B), enrolled because of no evidence of myometrial infiltration (A-B), and in Patient 2 (C-D), excluded because of suspicion of infiltration (arrows).

Afterwards, patients underwent TVUS monitoring every 3 months; hysteroscopy and endometrial biopsy with cold non-crushing devices (pipelle or curettage) were performed at 6 and 12 months after LNG-IUD insertion. Endometrial thickness was evaluated as a potential target for ultrasonographic prospective surveillance of conservative management. At TVUS, in the longitudinal scan, the LNG-IUD stem produces a very strong distal acoustic shadow where endometrial thickness is not measurable. Hence, when endometrial thickness was uniform, measurement was usually performed in the longitudinal section, just aside the LNG-IUD stem, as soon as the endometrial double line was visible. Alternatively, we took the measurement where we observed the highest thickness (Figure 2). Response to treatment was evaluated by comparing the initial histological diagnosis with the histological findings of endometrial samples collected after 6 and 12

months of hormonal therapy. The final response was classified as: complete response (CR), if the final histological examination showed normal endometrial characteristics; partial response (PR) when AEH was diagnosed in patients with initial EC; stable disease (SD), in case of persistence of the same histological diagnosis at the beginning and at the end of the protocol; and progression of disease (PD), when women with initial AEH progressed to EC and/or women with initial well-differentiated (G1) EC developed moderately- (G2) or poorly-differentiated (G3) EC.

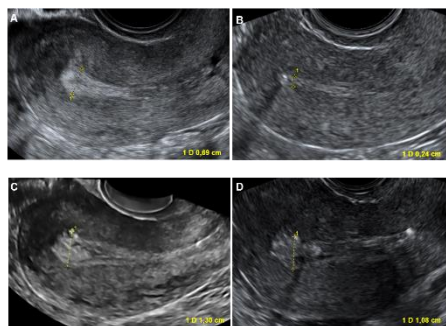


Figure 2: TVUS evaluation of response to hormonal treatment of two patients affected by EC-G1 at baseline and after 6 months-therapy with the LNG-IUD in situ (arms visible as cone shadows): Patient 1, responder (A: baseline, B: 6 months), and Patient 2, not-responder (C: baseline, D: 6 months).

According to protocol, conservatively treated patients who developed EC after AEH at 6 or 12 months, and patients with EC, showing SD at 6 months received standard definitive surgical treatment. The final histological diagnosis was made at the time of hysterectomy.

Statistical analysis

Patient's characteristics and the endometrial thickness evolution were summarized and tabulated by count, mean, Standard Deviation (SD), median, min, max or percentage as appropriate. A linear mixed model for longitudinal data with random intercepts has been used to analyze the endometrial thickness from baseline to 6 and 12 months after log-normal transformation to normality. Covariables were age, BMI, follow-up time, histology and the endometrial thickness at baseline. Post-hoc between group comparisons for endometrial thickness at baseline, 6 and 12 months and for changes with respect to baseline was tested by the two-sample Wilcoxon and the paired t-test respectively as appropriate. All tests were two-sided and considered statistically significant at the 5 % level. All analyses were done using SAS 9.3 (N.C., Cary USA).

Results

49 patients with AEH and well-differentiated EC with a strong desire of fertility-sparing treatment were enrolled. One patient with an initial diagnosis of EC-G1 was upgraded to EC-G3 according to the pathology review, and therefore excluded from the analysis, leaving 48 patients. The initial diagnosis was obtained by cold and non-crushing devices (pipelle or curettage) in 9 patients at our institute, whereas in 39 cases, the original pathology slides from different institutions were reviewed by our dedicated pathologists. Most significant patients' characteristics are shown in Table 1. The mean age was 33 years. Among all patients, 10 (20.8%) subjects had a BMI ≥ 30 kg/m² and 14 (32.6%) were

diagnosed with polycystic ovarian syndrome. After pathology review 3 patients with initial diagnosis of AEH were upgraded to EC-G1, 3 patients with a presumed EC-G1 were downgraded to AEH and 6 patients diagnosed with EC-G2 were downgraded to EC-G1. Sixteen patients (33.3%) with AEH and 32 (66.7%) with EC-G1 met the criteria to undergo hormonal uterus-sparing treatment and therefore were enrolled in our prospective study.

Table 1. Patient's and endometrial disease's characteristics at entry study (N = 48).

| Patient | | Mean (SD) |
|---------------------------|------|------------|
| Age, years | | 33.0 (5.7) |
| Age of menarche, years | | 12.1 (3.5) |
| BMI (kg/m ²) | | 25.7 (7.8) |
| | | N (%) |
| PCOS | | 14 (32.6) |
| Smoking | | 13 (27.1) |
| Diabetes | | 1 (2.1) |
| Hypertension | | 1 (2.1) |
| Endometrial disease | | Mean (SD) |
| Endometrial Thickness, mm | TVUS | 11.4 (7.1) |
| | | N (%) |
| Histology | EC | 32 (66.7) |
| | AEH | 16 (33.3) |
| Myometrial Invasion | TVUS | 4 (8.3) |
| | MRI | 4 (8.3) |

SD=standard deviation

BMI=body mass index

PCOS=polycystic ovarian syndrome

TVUS=transvaginal ultrasonography

EC=endometrial cancer

AEH=atypical endometrial hyperplasia

MRI=magnetic resonance imaging

Pre-treatment instrumental evaluation of myometrial infiltration was performed in all cases. No suspicion of infiltration was reported for all patients affected by AEH. MRI showed suspicion of infiltration in 4 out of 32 (12.5%) cases of EC, also TVUS described myometrial infiltration in 4 out of 31 (12.9%) patients with EC. The uterus of 1 patient was not evaluable for infiltration at TVUS but described as not-infiltrated at MRI. Due to the evidence of myometrial infiltration 3 patients with EC-G1 underwent standard surgical treatment: in 1 case MRI and TVUS were concordant, while they were discordant in the other 2 patients. However, initial infiltration was confirmed at the final pathology examination in all 3 cases. Moreover, other 3 patients with suspected infiltration, declined definitive treatment against clinical advice from their referring doctors, and received hormonal therapy, thus leaving 29 patients with EC evaluable at 6 months; again, MRI and TVUS were concordant in 1 patient only. Biopsies performed at 6 months showed CR and SD in 93.8%, (15/16) and in 6.2% (1/16) patients with initial diagnosis of AEH, respectively. Whereas, patients initially diagnosed with EC experienced CR in 51.8% (15/29), PR in 24.1% (7/29), and SD in 24.1% (7/29) of cases. In the latter group, 4 patients underwent definitive surgery, including those who had initially declined surgical treatment, due to suspicion of myometrial infiltration at baseline, eventually confirmed at final histology in all cases. One patient with SD

showed in situ EC at final histology. Overall, the 6 cases of EC with histological confirmed myometrial infiltration were correctly identified at pre-treatment evaluation (4/6, 66.7%, at TVUS, and 4/6, 66.7%, at MRI), with a 33.3% (2/6) agreement between the two methods. The remaining 3 women with SD were allowed to continue with the study treatment, since there was only a focal area of EC-G1 in the sample biopsy; this left 25 patients with EC who were evaluable for response at 12 months.

After 12 months of hormonal treatment, 2/25 (8.0%) and 4/25 (16.0%) patients with EC presented PD and SD, respectively; hence standard treatment was ensued. Whereas women displaying CR (16/16, 100% of AEH and 17/25, 68.0% of EC) or PR (2/25, 8.0% of EC) pursued further follow-up by TVUS and endometrial biopsy every 6 months. Furthermore, in case of CR, IUD was removed, and reproductive attempts were subsequently allowed.

The mean TVUS endometrial thickness was 11.4±7.1 mm at baseline, 5.1±3.4 mm after 6 months and 4.4±2.6 mm after 12 months. Endometrial thickness detailed by histology and follow-up time is shown in Table 2. Overall reduction of endometrial thickness was of 6.0±5.6 (52.6%) and 6.8±6.2 (59.6%) millimeters at 6 and 12 months,

respectively, compared to baseline values (P<0.001) (Table 3). Even though patients undergoing surgery were selected on the basis of the histological response and not on endometrial thickness, a correlation between trend of reduction of the latter and pathology response was certainly observed. In details patients with an initial diagnosis of EC who showed SD at 6 and 12 months had a greater endometrial thickness at TVUS (7.0±2.4 mm and 6.9±3.8 mm, respectively) than subjects who displayed CR, whose endometrial thickness was 4.2±2.2 mm and 3.4±1.1 mm at 6 months and 12 months, respectively (Figure 2). However, there was an overlapping of endometrial thickness measurements correlated to either SD/PD or PR/CR. Indeed, considering a cut-off of endometrial thickness of 3 mm at 12 months, a thinner endometrium was observed only in 3 (18.7%) patients with CR after AEH, in 7 patients (28.0%) with CR and 1 (4.0%) with PR after initial diagnosis of EC. If we consider a cut-off of 4 mm at 12 months, a thinner endometrial thickness was recorded in 9 (56.2%) AEH with CR, in 14 (56.0%) EC with CR/PR, but also in 2 (8.0%) patients with SD/PD. Furthermore, increasing the 12 months' cut-off level to 5 mm, endometrial thickness was thinner in 14 (87.5%) women with AEH showing CR, and in 20 (80.0%) with EC, showing CR/PR and SD/PD in 68.0% and 12.0% of cases, respectively.

Table 2. Endometrial thickness (mm) by time and histology.

| Follow-up Time | Histology | N | Mean (SD) | Median | Min,Max | P-Value |
|----------------|-----------|----|------------|--------|----------|---------|
| Baseline | EC | 32 | 12.1 (7.4) | 10.9 | 2.4,30.0 | 0.246 |
| | AEH | 16 | 10.1 (6.5) | 7.3 | 5.0,28.0 | |
| | Overall | 48 | 11.4 (7.1) | 9.1 | 2.4,30.0 | |
| 6 months | EC | 29 | 4.7 (2.4) | 3.8 | 1.2,11.2 | 0.569 |
| | AEH | 16 | 5.8 (4.8) | 4.4 | 2.0,22.4 | |
| | Overall | 45 | 5.1 (3.4) | 4.2 | 1.2,22.4 | |
| 12 months | EC | 25 | 4.3 (2.6) | 3.7 | 1.8,11.0 | 0.543 |
| | AEH | 16 | 4.5 (2.7) | 3.9 | 2.0,14.0 | |
| | Overall | 41 | 4.4 (2.6) | 3.8 | 1.8,14.0 | |

SD=standard deviation
 EC=endometrial cancer
 AEH=atypical endometrial hyperplasia

Table 3. Endometrial thickness (mm) changes with respect to baseline by follow-up time and histology.

| Follow-up Time | Histology | N | Mean (SD) | Median | Min,Max | P-Value |
|----------------|-----------|----|------------|--------|------------|---------|
| 6 months | EC | 29 | -7.0 (6.4) | -4.8 | -26.2, 0.6 | 0.275* |
| | AEH | 16 | -4.3 (3.3) | -3.1 | -13.8,-1.0 | |
| | Overall | 45 | -6.0 (5.6) | -4.5 | -26.2,0.6 | |
| 12 months | EC | 25 | -7.6 (6.9) | -6.1 | -27.4,0.6 | 0.355* |
| | AEH | 16 | -5.6 (5.1) | -4.0 | -18.0,1.7 | |
| | Overall | 41 | -6.8 (6.2) | -5.1 | -27.4,1.7 | |

Overall comparison 12 to 6 months: P-Value = 0.186

SD=standard deviation
 AEH=atypical endometrial hyperplasia
 † Compared to baseline

EC=endometrial cancer
 * Between histology comparison

Concomitant early-stage ovarian cancer was diagnosed in 10 patients (20.8%). Synchronous early-stage ovarian cancer, suspected at pre-operative TVUS, was confirmed in 6 women (12.5%) at laparoscopy. All these patients received conservative treatment for both EC/AEH and for ovarian cancer. Five (10.4%) were diagnosed as ovarian cancer FIGO

stage IA (4 G1 and 1 G2), whereas 1 (2.1%) was staged as IC G2 and received adjuvant chemotherapy after fertility-sparing surgery. Although with a previous history of ovarian cancer stage IA G2, another subject was allowed to be enrolled in the study protocol. During prospective ultrasonographic surveillance, metachronous early-stage ovarian cancer

was diagnosed at TVUS in 3 women (6.3%). Two were stage IA G1 and were diagnosed respectively 14 and 29 months after the diagnosis of endometrial disease. The third one was diagnosed with ovarian cancer at the 6-month TVUS follow-up and then underwent definitive surgery, followed by adjuvant chemotherapy, with final pathology findings confirming ovarian endometrioid adenocarcinoma IB G2 (Figure 3).

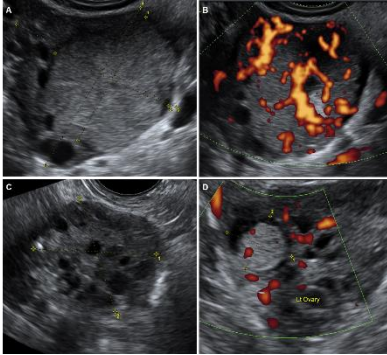


Figure 3: TVUS evaluation of ovarian involvement. Patient 1 with synchronous early-stage ovarian cancer of 23 mm at baseline (A-B). Patient 2 with PCO at baseline (C), who developed a metachronous early-stage ovarian cancer of 10 mm after 12 months (D).

Discussion

This study shows that TVUS could be helpful in the management of young patients with AEH or presumed FIGO stage IA EC-G1 treated by uterus-sparing hormonal treatment with LNG-IUD and GnRH analogue. In our study, in contrast to what described in younger age population, a higher number of young patients presented with EC than with AEH, most likely due to the fact that most of the patients were referred to our tertiary care cancer center because of their cancer diagnosis [2]. To the best of our knowledge, this is the first prospective clinical trial using TVUS for pre-treatment selection and forthcoming surveillance of young patients treated conservatively for AEH or well-differentiated EC.

The main weakness of the study is the small sample size, partly related to the strict inclusion criteria and to the uncommon diagnosis in young women. The main strengths of the study consist of its prospective nature, the novelty of the aim pursued by the authors and the homogeneity of the study population and the treatment. Accurate patient evaluation before conservative treatment is mandatory, therefore a pre-treatment assessment both by TVUS and MRI was performed in all cases to exclude myometrial infiltration. As a matter of fact, the two cases in which myometrial infiltration was suspected at MRI and not at TVUS were both enrolled in 2006. At that time our TVUS examiners were not adequately experienced yet in pre-operative evaluation of myometrial invasion, thereafter, there were no more discordant findings between MRI and TVUS. Savelli et al. showed that the sensitivity and specificity in the evaluation of myometrial infiltration were 84% and 83% for TVUS and 84% and 81% for MRI, respectively [17]. However, although pelvic ultrasound is less expensive, MRI is still considered the gold standard due to the fact that TVUS is more experienced operator-dependent than MRI to achieve similar accuracy [17, 21].

In our study a decrease of the mean endometrial thickness was observed, that was consistent with histological response to treatment at 6 and 12 months. Indeed, patients with an initial diagnosis of EC who displayed

CR showed a TVUS mean endometrial thickness of 4.2 ± 2.2 mm and 3.4 ± 1.1 mm at 6 and 12 months, respectively, as opposed to 7.0 ± 2.4 mm and 6.9 ± 3.8 mm at 6 and 12 months in case of SD or PD. There are no available data in the literature regarding endometrial thickness at TVUS evaluation during extended use of LNG-IUD in patients with AEH or presumed FIGO stage IA EC-G1. Pakarinen et al. have already described the morphologic changes of the endometrium, monitored by TVUS, induced by intracervical or fundal administration of levonorgestrel for contraception [22]. After 3 months, the endometrium was significantly thinner compared with the measurement at insertion, even though the insertion was performed at the early follicular phase; in both groups, there was no further significant decrease in endometrial thickness. Another study reported, during extended use of the LNG-IUD system for contraception, a mean endometrial thickness of 2.79 ± 0.1 mm at 84 months, increasing to 3.75 ± 0.3 and 3.76 ± 0.5 mm at 96 and 102 months of use, respectively [23]. Locally released levonorgestrel is known to cause suppression of the endometrium; the glands are scarce, and the stroma shows pseudodecidual morphology [24]. Furthermore, it is well-known that progestin acts directly on endometrial cancer by inducing endometrial cell apoptosis and indirectly on withdrawal by physical shedding of neoplasia [25]. Our prospective analysis represents the first study to show a statistically significant reduction in the mean endometrial thickness, monitored by means of TVUS, in patients diagnosed with AEH and EC-G1 and managed with hormonal fertility-sparing treatment. However, a meaningful cut-off for endometrial thickness in these patients treated with LNG-IUD and GnRHa was not identified, since an overlapping of endometrial thickness measurements correlated to either SD or CR was observed, suggesting that histology still remains the gold standard for the evaluation of treatment-response. Risk of concomitant ovarian cancer in young patients with early-stage EC has been reported in up to 25% of the cases [26,27], thus pre-treatment laparoscopic evaluation has been recommended by several authors [28, 29]. Moreover, the risk of ovarian involvement can persist over time, therefore a thorough sonographic evaluation is crucial in the detection of synchronous or metachronous early-stage ovarian cancer [30].

Given the lack of definitive data about conservative treatment for patients with AEH or EC who wish to preserve their fertility, they should be extensively counseled regarding the risk of treatment failures due to possible pre-existing invasive or poorly responding disease and the risk of concomitant ovarian cancer [31]. Finally, our data suggest that the duration of hormonal therapy required to maximize therapeutic response is at least 6 months, when patients with AEH and EC-G1 had the greatest rate of disease regression. Overall, endometrial thickness decreased of 6.0 and 6.8 millimeters at 6 and 12 months, respectively, compared to baseline ($P < 0.001$), and accordingly the reduction in the mean endometrial thickness was of 52.6% and 59.6% at the same time intervals. However, a clinical benefit of LNG-IUD is maintained during the second 6-month period of treatment as shown at histological evaluation after 12 months, although there was no greater difference in the sonographic measurements of endometrial thickness. Data from the literature suggest that longer treatment should be considered for obese and anovulatory patients that usually tend to be more resistant to therapy [31-33].

In conclusion, based on our results, TVUS seems to be an effective imaging tool for pre-treatment assessment of myometrial infiltration and synchronous ovarian disease, and for prospective surveillance of young

patients affected by endometrial pre-cancerous lesions and EC-G1 undergoing hormonal uterus-sparing treatment to preserve their fertility.

Although a significant correlation has been observed between the degree of reduction in endometrial thickness and histologically confirmed clinical response at 6 and 12 months, an overlapping of endometrial thickness measurements correlated to either SD/PD or PR/CR, was observed, therefore histology obtained through hysteroscopy and endometrial biopsy still remains the gold standard for the follow-up of young patients undergoing conservative management. However, the results of the present study need to be confirmed with larger number of patients and longer follow-up.

Compliance with ethical standards

Funding

None

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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