ANTICANCER RESEARCH *39*: 4897-4903 (2019)
doi:10.21873/anticanres.13676

Intrauterine Progestin Therapy as a New Approach to Premalignant Endometrial Polyps: A Prospective Observational Study

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Abstract. *Background/Aim: Endometrial hyperplastic polyps (EHP) may progress to endometrial carcinoma (EC) if left untreated. We aimed to prospectively investigate the efficacy of the low-dose levonorgestrel intrauterine system (LNG-IUS) as therapy for EHP with malignant potential. Patients and Methods: In total, 37 women with EHP underwent therapy with LNG-IUS containing 13.5 mg levonorgestrel for six months or 4-10 weeks depending on whether the EHP was characterized (by D-score analysis) as low- to medium-risk (n=33) or high-risk (n=4) of coexistent or future EC. Therapy response was defined as complete clearance of hyperplastic glands in post-therapy endometrial biopsy. Results: All women with low- to medium-risk EHP obtained therapy response, whereas only 1 out of 4 with high-risk EHP responded to therapy. None of the women were diagnosed with EC during the study and no serious adverse events occurred. Conclusion: Low-dose LNG-IUS represents a promising therapy for selected women with EHP.*

Endometrial polyps (EP) frequently occur in pre, peri and postmenopausal women and may be diagnosed in 20–30% of patients with abnormal uterine bleeding (1). Although most EP are benign, a systematic review has reported premalignant (hyperplastic) and malignant changes to be present in 0.2-23.8% and 0-12.9% of the cases, respectively (2).

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Key Words: Endometrial polyps, LNG-IUS, progestin therapy.

Previous research has mainly focused on the oncogenic potential of macroscopically visible polyps, related to clinical characteristics such as polyp size, symptoms, use of hormonal medication, patient's age, BMI and menopausal status, and whether such polyps should be hysteroscopically resected or not (3, 4). More recently, the coexistence of hyperplastic endometrial polyps (EHP) with endometrial hyperplasia (EH) and endometrial carcinoma (EC) in the surrounding non-polypoid endometrium, has gained increasing attention (5, 6).

Despite the fact that management of malignant EP now coincides with current therapy recommendations for EC, no therapy guidelines are available when EHP are detected in endometrial biopsies or polypectomy specimens. However, the described tendency of EHP to coexist with multifocal hyperplastic lesions in the non-polypoid endometrium and the suggested causal connection between polyp formation with and unopposed estrogen stimulation of the endometrium indicates a potential role for hormonal therapy with progestin in these women.

The pathogenesis of EP is not fully understood. In contrast, it is well established that non-polypoid EH is an estrogen-dependent precursor lesion to EC with up to 30% risk of malignant progression (7). Oral and intrauterine progestin has been routinely and successfully used as treatment for this condition since decades and randomized trials have shown higher regression rates for intrauterine compared to oral progestin therapy in patients with non-atypical EH (8-11).

So far, progestin therapy is poorly investigated in patients with EP and EHP although such studies have been requested (12, 13). A Cochrane review concluded that the LNG-IUS has a preventive effect and reduces the incidence of benign polyp formation in women undergoing tamoxifen therapy for breast cancer (14). A former retrospective observational study demonstrated that all women diagnosed with low- to medium-risk EHP were cured after six months treatment by the high-

dose LNG-IUS (Mirena®, 52 mg, Bayer Pharmaceuticals, Berlin, Germany), independent of diagnosis (simple, complex, or atypical hyperplasia), whereas only 25% of patients receiving oral progestin obtained response (15). Sustained regression of EHP for as long as the LNG-IUS (FibroPlant® APCOR Research, Ghent, Belgium) remained *in situ* was described in a single case report by Janssen *et al*. (16).

In a recent study, low-dose LNG-IUS (Jaydess®, Bayer Pharmaceuticals, Berlin, Germany), with a total content of 13.5 mg levonorgestrel, was successfully given as therapy for six months in women with low- and medium-risk EH (17). Compared to the high-dose LNG-IUS, the thinner insertion tube and smaller T-frame might prove beneficial for young nulliparous women and for elderly women with stenotic cervical channel simultaneously reducing systemic side-effects to a minimum. Thus, the main objective of the current pilot study was, as the first ever, to investigate if the low-dose LNG-IUS is sufficient therapy for EHP with various malignant potential.

Patients and Methods

The study was designed as a prospective, multicenter, pilot study to assess the efficacy of low-dose LNG-IUS as therapy for EHP. LNG-IUS 13.5 mg is approved as a contraceptive for up to three years use (18). The *in vivo* LNG-release rate declines progressively after insertion (19). After 24 days, 60 days and 3 years the LNG release rate was calculated to be 14 μg/24 h, 10 μg/24 h and 5 μg/24 h, respectively. Average LNG release rate over three years was 6 μg/24 h (19). Pre- and post-menopausal women with histologically confirmed EHP were eligible for study inclusion. Histopathological material (baseline biopsy) from the endometrium, obtained prior to study inclusion, was sampled by Pipelle (Pipelle, Laboratoire CCD, Paris, France) (n=22), D&C (dilatation and curettage) (n=10), or hysteroscopic transcervical resection (n=6). All women had consulted their gynecologists due to abnormal uterine bleeding, and were diagnosed with menometrorrhagia (n=20), menorrhagia (n=5), or postmenopausal bleeding (n=13). Endometrial thickness, measured by transvaginal ultrasound prior to therapy, varied from 3 to 30 mm.

Enrollment. The study was open for inclusion from August 1st, 2015 to August 1st, 2017. A total of 38 women were consecutively recruited to the study at six different gynecological outpatient clinics in northern Norway between December 8th, 2015 and July 17th, 2017. Written informed consent was obtained from all participants. The LNG-IUS was inserted by the responsible gynecologist in accordance to manufacturer's instructions. Blood samples were obtained at inclusion to measure s-estradiol and s-FSH. According to our laboratory practice, these values can be used to define menopausal status.

Study participants were assigned to two different therapy groups according to individual risk stratification, based on WHO94 classification and D-score (see Morphometric analysis (D-score)) in baseline biopsy, concerning the probability of coexistent or future EC. Women with low- to medium-risk hyperplastic polyps (simple hyperplasia (SH) or complex hyperplasia (CH) and a D-score ≥0) received conservative therapy with low-dose LNG-IUS for six months (therapy group A). Women with high-risk hyperplastic polyps (CH or atypical hyperplasia (AH) and a D-score <0) were scheduled for hysterectomy and underwent therapy with low-dose LNG-IUS for 4-10 weeks while awaiting surgery (therapy group B). CT scan of the chest, abdomen and pelvis and a pelvic MRI scan were performed in all women in therapy group B to exclude signs of EC (endometrial tumor, myometrial invasion, pathological lymph nodes, or presence of metastases).

Therapy was completed at 29th of November 2017. After completing the study, further therapy and surveillance were individualized and left to the patient's gynecologist to decide. Women in therapy group A were encouraged to keep the low-dose LNG-IUS *in situ* after the end of study period if side effects were acceptable, to provide long-term endometrial protection. No deviations from the study protocol occurred.

Outcome measures. The primary outcome of interest was endometrial tissue response assessed by light microscopy of repeat biopsy specimens. As quality evidence of different sampling methods during progestin therapy is lacking, feasibility in outpatient practice and consideration of cost perspective led to our choice of Pipelle as sampling method for obtaining post-therapy biopsy material in therapy group A. In group B, therapy response was evaluated by histopathological examination of the hysterectomy specimen.

For therapy group B, hysterectomy was performed after 4-10 weeks and post-therapy evaluation was based on standard histopathological examination of the hysterectomy specimen. Endometrium with progestin effect (atrophic glands and pseudodecidualized stroma) was defined as therapy response for both patient groups. Presence or absence of polyps or fragments of polyps were also evaluated. Secondary outcome was adverse events during therapy.

Histological specimens. The histopathological material (baseline biopsies, post-therapy biopsies and hysterectomy specimens) was received at the Department of Pathology, University Hospital of North Norway for routine assessment. All biopsies were fixed in buffered formaldehyde and further processed in the laboratory to prepare standard histological sections. Microscopic assessment was performed by a trained gynecologic pathologist (AO) and one additional routine pathologist. EP diagnosis was made when microscopy revealed polyps or fragments of polyps, identified by the characteristic shape covered by surface epithelium, and/or by fibrous stroma with thick-walled or enlarged vessels (20). In the present study the diameter of polyps or fragments was >5 mm and <12 mm. Hyperplastic areas within the polyps were diagnosed according to WHO94 classification using one of the three terms: SH, CH, or AH, which was still considered the gold standard for evaluating EH when the study was planned and formally approved (7, 21). Ordinary light microscopy was always followed by D-score analysis (see Morphometric analysis (D-score)). Hysterectomy specimens from patients in therapy group B were also sent to the Department of Pathology, University Hospital of North Norway, for routine examination. The entire endometrium was embedded in paraffin blocks and evaluated for the presence of EH, EHP or EC.

Morphometric analysis (D-score). Because reproducibility of the different classification systems for the diagnosis of EH performed by light microscopy is still debated, the morphometric image analysis algorithm (D-score) has been introduced in the national routine recommendations in Norway to improve the selection of risk groups for hyperplastic lesions. Thus, hyperplastic lesions with D-score ≥0 are considered to be of low- to medium-risk and lesions

Table I. *Clinical and demographic patient characteristics of the study cohort, n=37.*

Characteristics	n	(%)
Age (years)		
<45	9	24.3
45-55	20	54.1
>55	8	21.6
BMI (kg/m^2)		
Normal Weight (<25)	8	21.6
Overweight (25-29.9)	16	43.2
Obese (≥30)	13	35.1
Estradiol level (nmol/l)		
<0.12	15	40.5
0.12-0.26	6	16.2
≥0.27	16	43.2
Menopausal status*		
Premenopausal	20	54.1
Perimenopausal	2	5.4
Postmenopausal	15	40.5
Vaginal bleeding		
Menometrorrhagia	20	54.1
Menorrhagia	4	10.8
Postmenopausal bleeding	13	35.1
Parity		
0	5	13.5
1-2	13	35.1
3-4	18	47.6
>4	1	2.7
Method of diagnosis		
Pipelle	22	59.5
D&C	9	24.3
Hysteroscopic resection	6	16.2
WHO94 diagnosis		
SH	14	37.8
CH	20	54.1
AH	3	8.1
D-score category		
<0	4	10.8
≥0	33	89.2

*Menopausal status was defined by serum levels of estradiol (nmol/l) and follicle stimulating hormone (FSH) (IU/l) according to our laboratory standard. Premenopausal, estradiol ≥0.12 FSH ≤30; Perimenopausal, estradiol ≥0.12 FSH >30; Postmenopausal, estradiol <0.12 FSH >20.

with D-score <0 are associated with a high risk of coexistent or future EC (22-24). In the original computerized morphometric analysis study on EH, a total of 10 nuclear features and 12 architectural features were analyzed (25). Using a linear stepwise regression analysis and discriminant analysis, three of these quantitative features were selected as having significant independent prognostic value and were combined into the formula called D-score, as follows: D-score=0.6229+0.0439x (volume percentage stroma) – 3.9934x Ln (standard deviation of shortest nuclear axis) – 0.1592x (outer surface density glands), where Ln stands for natural logarithm (25). The measurements were performed with a Q-PRODIT image analysis system (version 6.1; Leica, Cambridge, UK). The method of the D-score analysis has been described in detail in former studies (22-24).

Table II. *Distribution of histological WHO94 diagnosis and D-score categories in baseline biopsies.*

WHO94 diagnosis/ therapy group	n=33 D-score ≥0	n=4 D-score <0	Total
SH	14	0	14
CH	19	1	20
AH	0	3	3
	33	4	37

Patients with D-score ≥0 were included in therapy group A and patients with D-score <0 were included in therapy group B. SH: Simple hyperplasia; CH: complex hyperplasia; AH: atypical hyperplasia.

Ethical considerations. The current study was approved by the Regional Committees for Medical and Health Research Ethics (2015/381) and by the Norwegian Medicines Agency (EUDRACT number 2015-000612-17). All participants gave written informed consent. Insurance for the coverage of pharmaceutical injuries was signed for all study participants.

Statistics. Descriptive statistics was performed using IMB SPSS Statistics version 24 (IMB, Armonk, NY, USA).

Results

Patients. A total of 38 women were consecutively assigned to therapy group A (n=34) and therapy group B (n=4). One patient in therapy group A experienced expulsion of low-dose LNG-IUS after 13 weeks of therapy owing to excessive vaginal bleeding (Figure 1). Clinical and demographic data of the women completing the study (n=37) are summarized in Table I. Median age at diagnosis was 51 years (range=30-84 years). Median BMI (body mass index, kg/m^2) was 27.7 (range=20.1-40.6). Altogether, 78.3% of the women were overweight (BMI 25-29.9) or obese (BMI ≥30). Classification of hyperplastic areas (within endometrial polyps or fragments of polyps), according to WHO94 and D-score, in baseline biopsies are presented in Table II. Among women with D-score ≥0, none was diagnosed with AH. However, three out of four women with D-score <0 were diagnosed with AH and none had SH.

Response to therapy. All women (n=33) in therapy group A obtained complete response after six months of therapy with the LNG-IUS Jaydess. Thus, post-therapy biopsies displayed no sign of hyperplastic areas, and only inactive or sparse atrophic endometrial glands as well as pseudodecidualized endometrial stroma were observed by light microscopy (Figure 2A-B). Nevertheless, small fragments of endometrial polyps were evident in the post-therapy biopsy of five women. The majority of women in therapy group A (n=31) preferred to keep the LNG-IUS *in situ* after completing the study. Only one out of four women in therapy group B responded to therapy according to histopathological investigation of the hysterectomy specimen. The baseline biopsy diagnosis of the responding woman was

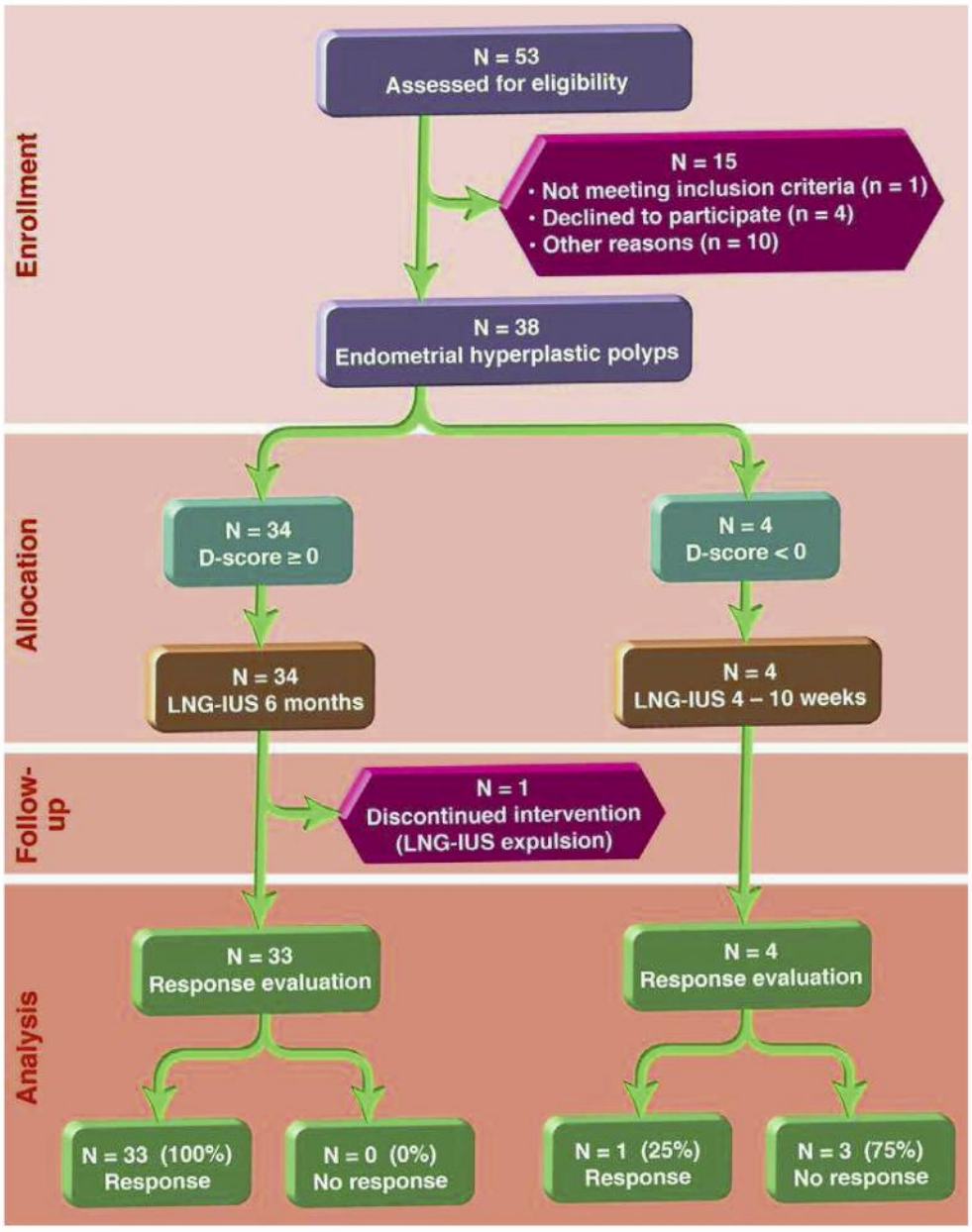

Figure 1. *Flow chart showing enrollment, allocation, follow-up and analysis. Therapy response was defined as endometrium with progestin effect (atrophic glands and pseudodecidualized stroma).*

CH/D-score –0.4, and therapy duration for LNG-IUS Jaydess prior to hysterectomy was seven weeks. The other three women (who did not respond to therapy) were diagnosed with AH according to baseline biopsy, and therapy duration was four, five and 10 weeks, respectively. Although hyperplastic changes were still evident in the hysterectomy specimens of these three women, microscopy revealed typical progestin-induced changes with stromal pseudodecidualization and no sign of cytological atypia after 10 weeks of therapy (Figure 2C-D). Endometrial polyps were seen in the hysterectomy specimen of the women treated for five weeks. None of the included women were diagnosed with EC during the study.

Adverse events. No serious adverse events occurred during the study period. Adverse events reported were vaginal bleeding, headache, and mild abdominal pain (Table III). Bleeding disturbances were most prominent during the first three months of therapy, and it persisted in only two women after six months of therapy. The two women reporting headache had sparse and short-lived symptoms. Two women decided to

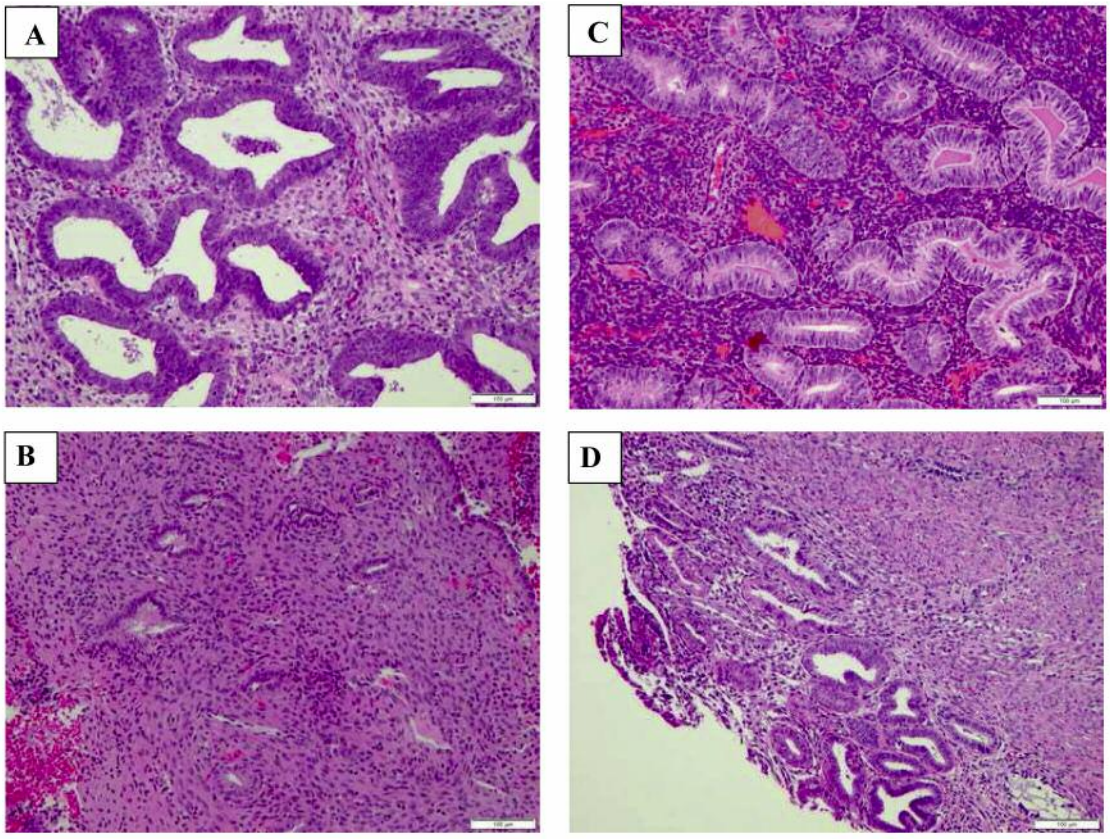

Figure 2. *Microphotographs of histological specimens from endometrial biopsies taken before (baseline biopsy) and after (post-therapy biopsy) therapy with the LNG-IUS Jaydess (hematoxylin and eosin, 20× magnification). (A) Baseline biopsy. Fragments of an endometrial polyp containing hyperplastic areas classified as complex hyperplasia. The Dscore value was 1.4. (B) Post-therapy biopsy after six months treatment showed complete therapy response characterized by extensive glandular atrophy and pseudodecidualized stroma. No endometrial polyps or fragments of polyps were seen. (C) Baseline biopsy. An area with tightly packed glands within a hyperplastic endometrial polyp is seen. The hyperplastic areas were classified as atypical and the D-score value was –0.5. (D) Post-therapy biopsy (hysterectomy specimen) after 10 weeks treatment. Only one single superficial focus of complex hyperplasia was found in the endometrium of the hysterectomy specimen. The remaining endometrium revealed complete therapy response. No endometrial polyps or fragments of polyps were seen.*

remove the LNG-IUS after six months therapy due to vaginal bleeding (n=1) and recurrent urinary infections (n=1).

Discussion

Our pilot study is, to our knowledge, the first ever to investigate the efficacy of low-dose LNG-IUS 13.5 mg as a therapeutic option for EHP. The demonstrated therapy response for all the women with low- to medium-risk EHP in our study corresponds to the results described by Arnes *et al*. reporting 100% regression for high-dose LNG-IUS 52 mg in women with EHP, independent of risk group, after six months of therapy (15).

In contrast, only one among four women with EHP showing high-risk hyperplasia responded to therapy after 4-10 weeks in the current study. A higher dose requirement for atypical lesions may be of importance although the shorter treatment time offered to these women may also be a crucial point. Ideally, the women with high-risk EHP should have received LNG- IUS therapy for a longer period of time to allow adequate evaluation of therapy response.

However, ethical considerations prevented conservative management for these women as low- dose LNG-IUS had never before been explored as therapy for EHP.

Table III. *Adverse events during therapy with LNG-IUS Jaydess.*

Symptoms/Grading of adverse effects	Grade 1	Grade 2
Vaginal bleeding	6	10
Headache	2	0
Abdominal pain	0	1

Grade 1 means adverse event ≤10 days/month, grade 2 means adverse event >10 days/month.

In the present study we hypothesized that hyperplastic foci within EP had the same risk of malignant progression as EH and that these hyperplastic foci would respond to progestin therapy in a similar manner as observed for nonpolypoid EH (10, 17, 26). Risk-stratification of EH by D-score analysis have been successfully used for years in our clinic and in a recent retrospective study with long-term follow-up, these methods were reported to be applicable as predictors of malignant transformation in EHP as well (15).

As hyperplasia within an EP has been demonstrated to be a strong marker of wider endometrial pathology, our results support the rationale behind intrauterine progestin therapy for these women. Kelly *et al*. have found hyperplasia in the surrounding endometrium in more than half of the women with EHP (5). Another study reported that over 90% of women demonstrated residual hyperplasia in the hysterectomy specimen, despite normal hysteroscopic view, after removal of EP containing complex atypical hyperplasia (6). The authors concluded that hysteroscopic evaluation of the uterine cavity and polyp resection are insufficient for eradication of premalignant and malignant endometrial lesions (6). On this background, the ability of intrauterine progestin therapy to induce strong antiproliferative effect throughout the entire endometrial mucosa is considered advantageous over hysteroscopic resection of such lesions alone.

Previous research on EP has mainly focused on the malignant potential in macroscopically visible polyps available for resection by hysteroscopy. In contrast, the present study was designed to assess if progestin therapy is effective treatment in women with EHP diagnosed by microscopy. Small EP have shown to be frequently overlooked by vaginal ultrasonography and hysteroscopy, and incidental discovery of EP, with and without hyperplastic areas during routine histopathological examination of endometrial biopsy specimens, is common (15, 27). Correspondingly, EP was suspected by vaginal ultrasonography in only nine out of 37 women in the present study population.

In the current study we defined therapy response as complete clearance of hyperplastic glands, but presence or absence of polyp tissue in post-therapy biopsies was also of interest. In therapy group A, only five women had fragments of polyps in post-therapy biopsies but no evidence of hyperplastic areas. These women kept the low-dose LNG-IUS *in situ* and underwent additional endometrial sampling outside the study protocol 12 months after LNG-IUS insertion. The following microscopical investigation of biopsy material demonstrated sustained progestin effect and no signs of EP or fragments of polyps. Thus, low-dose LNG-IUS seems capable to induce regression of both hyperplastic areas within EP, and EP without hyperplasia.

None of our study participants reported persisting systemic side-effects, and the therapy was generally well tolerated throughout the treatment period, making the low-dose LNG-IUS optimal for long-term use. Recurrence rate after hysteroscopic resection of EP is high (13.3%) and hyperplastic EP recurs more frequently than benign ones (43.6%) (28). Even though relapse during long-term follow up was not investigated in the current study, favorable clinical effect to prevent recurrence of EH by long-term LNG-IUS therapy has been observed by others (29).

To conclude, we demonstrated encouraging therapy responses for low- to medium-risk EHP after six months therapy with low-dose LNG-IUS. Whether or not the progestin dose provided by this IUS is too low to induce regression of high-risk EHP, or if therapy response could have been achieved by extending therapy duration, still remains unclear. Such studies should be addressed by future research with larger study populations.

Conflicts of Interest

There are no conflicts of interest regarding this study.

Authors' Contributions

Elise Thoresen Sletten is the main author of the manuscript, performed the clinical patient work and statistical analysis of patient data. Marit Arnes contributed to the microscopical work and data analyses. Anne Beate Vereide facilitated recruitment of patients. Anne Ørbo is the project leader and supervisor and performed all the microscopical work.

Acknowledgements

The Authors would like to thank participating gynecological outpatient clinics in northern Norway (Tromsø, Harstad, Stomarknes, Kirkenes, Finnsnes, Alta, Hammerfest), Lena M. M. Lyså, B.Sc., and Bjørn T.G. Moe, M.Sc., for skilled image analyses performed on endometrial biopsy material, and Roy A. Lyså, Ph.d. for figure artwork.

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Received June 27, 2019
Revised July 20, 2019
Accepted July 22, 2019