The efficacy of intrauterine versus oral progestin for the treatment of endometrial hyperplasia. A prospective randomized comparative study

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Summary

Objectives: This study compared the efficacy of the levonorgestrel-releasing intrauterine device (LNG-IUD) to oral medroxyprogesterone acetate (MPA) applied for the same length of time for the management of endometrial hyperplasia without atypia. *Study Design:* This was single-center, open, randomized, and clinical trial. One hundred four patients aged between 30-50 years and diagnosed with endometrial hyperplasia without atypia by endometrial biopsy, were randomized to receive LNG-IUD or MPA. Both groups were further divided into two groups as three-month and six-month treatment subgroups. The primary objective was to compare the complete regression rates of hyperplasia, and the secondary objective was to determine the minimum duration of time required for the achievement of regression. *Results:* At two-year follow-up, the success rates of LNG-IUD treatment and oral MPA for three months therapy were 84% and 50%, respectively. While the regression rate was 100% in the six-month LNG-IUD group, it was 64% in the oral MPA group. LNG-IUD appeared to have a significantly higher success rate ($p = 0.0001$). *Conclusion:* It is believed that by this study LNG-IUD applications may be a reliable preference for younger patients who wish to preserve their uterus and especially for non-atypical cases, and if the patient demands fertility, even a six-month application will provide effective treatment.

Key words: Endometrial hyperplasia; Non-atypical; Theraphy; Levonorgestrel-releasing intrauterine system; Oral progestin.

Introduction

Endometrial hyperplasia is thought to occur as the result of endometrial suffering due to a relatively strong estrogenic influence in the absence of adequate progesterone secretion. Aside from causing abnormal uterine bleeding, endometrial hyperplasia is an important clinical entity, since it may accompany estrogen-secreting tumors, and occur prior to endometrial cancers [1]. It has an increased prevalence between 40-55 years of age. In developed countries, approximately 200,000 new cases are estimated to occur each year [2].

The histologic changes in hyperplasias may vary from a mildly excessive appearance of endometrial proliferation to a complex structure including severe changes that can be hardly distinguished from a carcinoma [3]. As reported by the study of Kurman *et al*., the rate of progression to cancer is 1% for simple hyperplasia, 3% for complex hyperplasia, 8% for simple atypical hyperplasia, and 29% for complex atypical hyperplasia [4]. The appropriate treatment is decided by considering various characteristics of the patients such as age, hyperplasia type, and wish for future childbearing [5]. Most commonly preferred treatment methods include the administration of progesterone at varying doses and via diverse routes, or surgical intervention. Several recent studies have shown that intrauterine devices (IUDs) with the ability of releasing levonorgestrel (LNG) and other similar gestagens can be used in the treatment of hyperplasia without inducing a systemic side-effect that may be observed in oral progesterone administration [6, 7]. In the present study, in order to evaluate the efficacy of levonorgestrel-releasing intrauterine device (LNG-IUD) in a comparative fashion, the authors preferred medroxyprogesterone acetate (MPA) as the oral progesterone.

The first objective of this study was to compare the long-term outcomes of endometrial hyperplasia cases treated either with LNG-IUD or oral progesterone for the same length of time. Since patients of hyperplasia without atypia may have a wish for childbearing, the authors aimed to compare the long-term outcomes of short-term treatments by a prospective study including similar groups receiving the related therapy for same length of time. Therefore, the second objective was to determine the minimum duration of successful treatment in 30-50 age group with a wish for childbearing. The increasing fertility age of women in developed countries has contributed to the importance of this problem. The treatment success was defined as regression of endometrial hyperplasia. To the authors' knowledge, this study is the first investigation to evaluate and compare the long-term outcomes of oral progesterone and LNG-IUD therapies applied for the same length of time against hyperplasia without atypia in the published literature.

Materials and Methods

Trial design

The authors designed an open-label, prospective, and randomized single-center trial for comparison of LNG-IUD and oral progesterone efficacies in the treatment of hyperplasia without atypia. The patients who presented to the Outpatient's Clinic between January 2, 2005 – December 31, 2009 due to abnormal uterine bleeding and who were diagnosed with endometrial hyperplasia, were included in the study. Since most of the hyperplasia with atypia cases were generally above 40

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years of age, had no childbearing, and with a tendency to prefer hysterectomy due to cancer risk, the authors constituted the study population from cases of hyperplasia without atypia. Prior to the study, approval from the local ethics committee and informed consents from each patient were obtained.

This manuscript is reported according to the revised recommendations of the Consolidated Standards of Reporting Trials statement for improving the quality of reports of parallel group randomized trials [8].

Participants

The authors aimed to study patients below 50 years of age who were diagnosed with endometrial hyperplasia without atypia. Since one of the study objectives was to determine the minimum treatment duration in patients that might have a wish to remain fertile, the patients aged above 50 years, were excluded from the study. Among the individuals who presented abnormal uterine bleeding, 84 patients aged between 30-50 years and diagnosed as endometrial hyperplasia without atypia by endometrial biopsy, were included in the study. The patients with atypia, as well as those with submucous myoma, ovarian tumor, and a uterine myomatosis greater than 12 cm, were excluded from the study.

Symptoms, histopathologic results, and socio-demographic data (age, body mass index (BMI), parity, presence of diabetes or hypertension) of all the patients were recorded.

Interventions

Endometrial biopsy with a suction catheter was performed by a single investigator (KD) in patients that presented with abnormal uterine hemorrhage, and curettage was always recommended when the biopsy specimens were insufficient for diagnosis. The acquired histologic materials were evaluated by the gynecologic pathology department. Endometrial diagnosis was achieved by an experienced gynecologic pathologist (AB) based on the criteria defined by Kurman *et al*. [3]. Hyperplasia was categorized in two groups: hyperplasia with and without atypia. Each of the 16 patients with atypical hyperplasia who were aged above 40 years and had no concern about fertility, preferred to undergo hysterectomy.

In this study, two different treatment models, LNG-IUD and oral MPA, were investigated. Both of these two groups were further divided into two groups as three- and six-month treatment subgroups. LNG-IUD was left in the uterine cavity for three-months in Group 1 (n = 26) and six months in Group 3 (n = 26). Oral MPA treatment was applied for three months in Group 2 (n = 26) and six months in Group 4 (n = 26), with a dose of ten mg/day given ten days per month. Control biopsy for histologic assessment was performed four times in Groups 1 and 2: right after the treatment and at six, 12, and 24 months; whereas it was performed three times in Groups 3 and 4: right after the treatment and at 12 and 24 months. The histopathologic results of the control biopsies were assessed in three groups: persisting hyperplasia, regression of hyperplasia (an endometrium under the influence of gestagen or proliferative endometrium), and reversion of hyperplasia where the hyperplasia recurs shortly after achievement of regression. In cases where hyperplasia regression could not be achieved, the patients were recommended to undergo continuous LNG-IUD replacement or hysterectomy.

Sample size

A power analysis was performed to determine the number of subjects required for the study. The primary objective was to compare the regression rates of endometrial hyperplasia without atypia. The previous studies have shown that oral MPA success in three to six month treatment is 48%-60%, whereas the success of long-term LNG-IUD therapy is known to be 63%-100% [2, 9]. Based upon those data, when the power of a test and level is recognized as 90% and 0.05 by the help of two-sided Chi-squared (χ^2) test, the required sample size can be found as 96 patients (24 patients in each group).

Table 1. — *Baseline characteristics*.

Characteristic	Group 1 (n = 26)	Group 2 (n = 26)	Group 3 (n = 26)	Group 4 (n = 26)	Total (n = 104)	*p* value
Age (years)	45.2	43.4	41.8	43.8	*	0.711
Weight (kg)	69.0	72.2	73.5	71.2	**	0.602
BMI (kg/m^2)	30.0	32.2	29.0	31.2	***	0.506
Parity						
Parity 0	5	6	3	5	19 (18%)	0.111
Parity 1-2	12	9	14	11	46 (44%)	0.274
Parity ≥ 3	9	11	9	10	39 (38%)	0.232
Menopausal status						
Premenopausal	22	20	23	22	87 (84%)	0.732
Postmenopausal	4	6	3	4	17 (16%)	0.401
Diabetes	4	6	4	3	17 (16%)	0.361
Hypertension	3	8	5	4	20 (19%)	0.112
Types of Hyperplasia						
Simple	14	15	17	15	61 (59%)	0.328
Complex	12	11	9	11	43 (41%)	0.304

* Mean 43.5 (standard deviation 7.2, range 34 - 49).
** Mean 71.5 (standard deviation 22.4, range 56 - 111).
*** Mean 30.6 (standard deviation 7.4, range 21 - 42).

Randomization

Eight of 112 patients who fulfilled the inclusion criteria, rejected to participate in the study after being informed about its design, and they preferred hysterectomy. The remaining 104 patients that provided an informed consent, were randomized. Randomization was conducted by using a computer-generated table of random numbers with allocation concealment.

Statistical analysis

Demographic and baseline data such as age, parity, BMI, diabetes, and hypertension, were compared. The data with normal distribution were expressed as mean and standard deviation values, whereas interquartile range was used for skewed data. The groups were analyzed by intention to treat. Accordingly, Wilcoxon (rank sums), χ^2, and Fisher's Exact tests were applied. As the changes in continuous variables were evaluated by paired t-test, categorical variables were evaluated by McNemar test. Kaplan-Meier survival curves were performed to calculate time to treatment failure and log-rank test was used to compare time to treatment failure between the groups. All statistical analyses were performed using SPSS version 15.0 software.

Results

Recruitment

Among 112 patients fulfilling the study inclusion criteria who presented between January 2, 2005 – December 31, 2009, 104 endometrial hyperplasia patients that provided an informed consent (61 simple and 43 complex), were included in the study and randomized into LNG-IUD and MPA groups, while eight patients rejected to participate in the study. As 102 of 104 patients completed the two-year follow-up period, one patient from Group 1 and another from Group 4 could not be reached and were both excluded from the study. The follow-up completion rate was 96.1% in Groups 1 and 4, whereas it was 100% in Groups 2 and 3; there was no statistically significant difference between the groups according to completion rate (χ^2 test, p = 0.834).

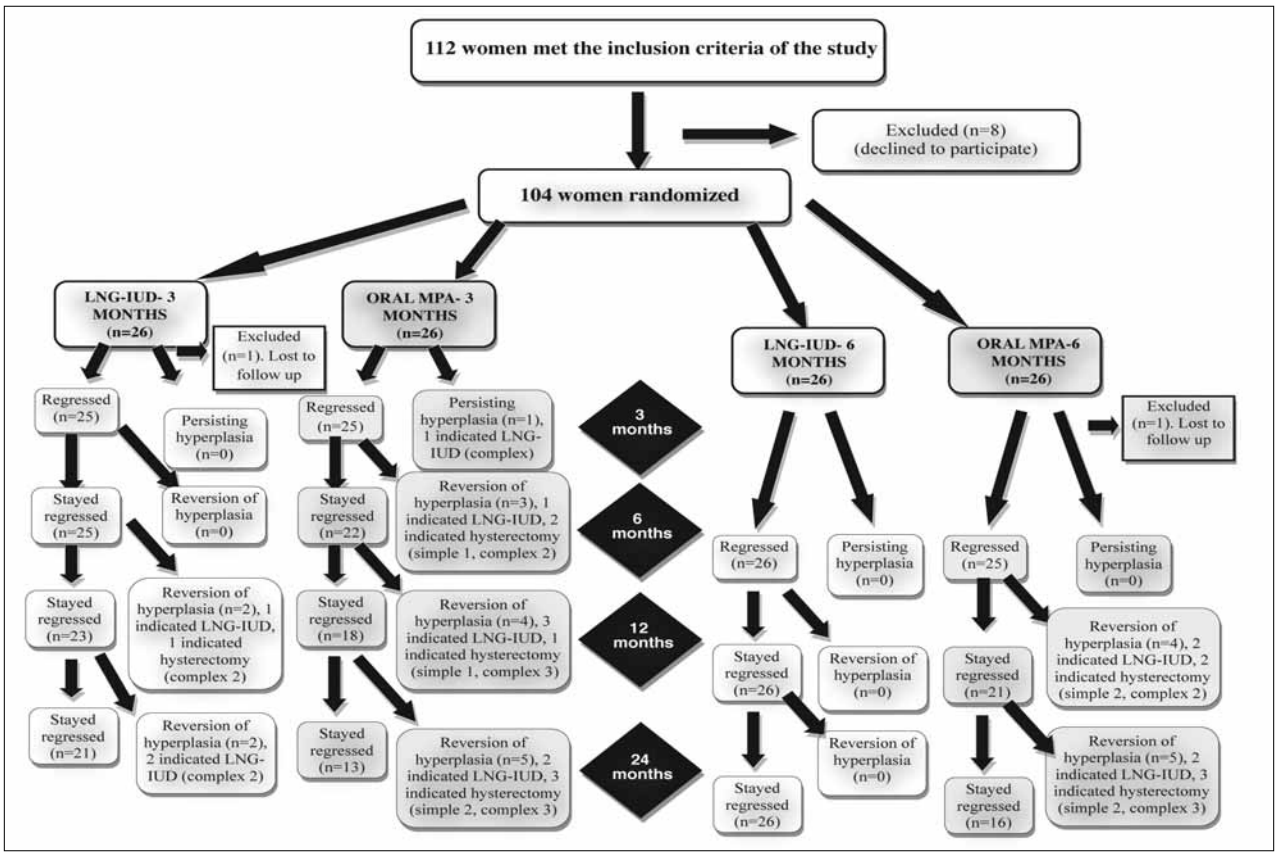

Figure 1. — Flow chart of the study population.

Baseline data

The mean age of the patients was 43.5 years. There was no difference between the groups in terms of age, weight, BMI, parity, and menopausal status. As 87 (83.7%) of the patients were premenopausal, 17 (16.3%) were postmenopausal, and none of them had received tamoxifen or hormone replacement therapy prior to the study. The postmenopausal patients were not excluded from the study, since they had a chance of pregnancy with help of donor oocyte programs. Baseline characteristics are shown in Table 1.

Outcomes

The outcomes obtained throughout a two-year follow-up period are shown in Figure 1. At two-years follow-up, the success rates for the three-month LNG-IUD treatment in Group 1 and three-month oral MPA therapy in Group 2 were 84% (21 regression in 25 patients) and 50% (13 regression in 26 patients), respectively. The LNG-IUD treatment showed a statistically significantly higher success rate ($p = 0.001$). While the regression rate was 100% (26/26) in the six-month LNG-IUD group, it was 64% (16/25) in the oral MPA group. LNG-IUD appears to have a significantly higher success rate ($p = 0.0001$).

Treatment failure

Treatment failure was observed in 28 of 102 patients followed-up for two years. The failures were significantly less in the LNG-IUD compared to the MPA groups, with four out of 51 (7.8%) in the LNG-IUD compared to 22 out of 51 (43.1%) in the MPA group, with a hazard ratio of 0.45 (95% CI, 0.21-0.93, log-rank test $p = 0.002$) (Figure 2). Among four cases of failure in Group 1, one patient preferred hysterectomy and three patients opted for the reapplication of LNG-IUD. Among 12 cases of failure in Group 2, six preferred LNG-IUD and the other six preferred hysterectomy. Among eight cases of failure in Group 4, three preferred LNG-IUD and five preferred hysterectomy. Histopathologic examinations of the preoperative biopsy and postoperative hysterectomy materials were consistent in all 12 patients who preferred to undergo hysterectomy.

Survival analyses based on Kaplan-Meier and Cox proportional hazards model revealed shorter time to regression in the LNG-IUD group. There was no statistically significant relation between the regression rates and baseline covariates of survival analyses.

Discussion

After the fact that unopposed estrogen causing hyperplasia of the endometrium was discovered, oral proges-

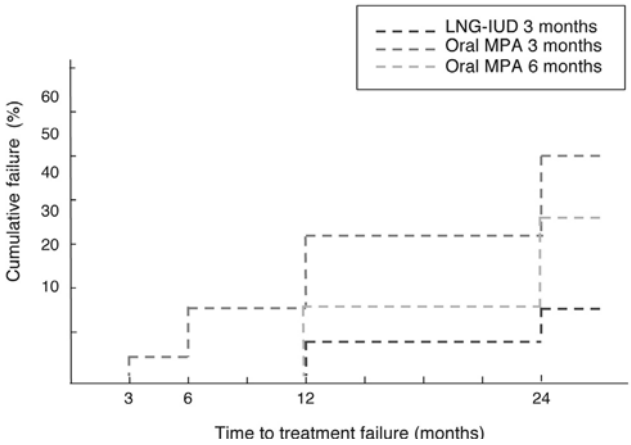

Figure 2. — Kaplan-Meier plot for treatment failure in the LNG groups compared to MPA groups. LNG-IUD: levonorgestrel intrauterine device; MPA: medroxyprogesterone acetate; Log-rank test p = 0.003.

terone supplementation became the mainstay for treatment. Without clear-cut consensus on the length and how much progesterone would suffice, hysterectomy remained a more reliable and definitive mode of treatment. After the advent of gestagen-releasing IUDs, it was readily foreseen that local delivery of high concentrations of progesterone for a local disease, such as endometrial hyperplasia, would be more logical. The success of LNG-IUD treatment in endometrial hyperplasia cases with or without atypia has been shown by various studies. Wildemeersch and Scarselli obtained successful results in all types of hyperplasias by inducing levonorgestrel release into the uterine cavity at a dose of 20 µg/day [10-12]. Compared with the systemic delivery option, using an IUD device for administration of progesterone has been shown to help attain higher concentrations in the endometrial tissue [13]. Although there are three previous studies comparing the efficacies of oral progesterone and LNG-IUD in endometrial hyperplasia treatment, this study is the first prospective study comparing the long-term outcomes of different treatments applied for the same length of time [2, 9, 14]. Orbo *et al*. [14] conducted a multicenter study in which the patients were divided into three groups and 85 patients received oral MPA ten mg/day for ten days per month (continued for three to six months), 66 received LNG-IUD depending on the patient satisfaction for three to 108 months, and 107 patients were followed-up but received no treatment. In conclusion, regression was achieved in 54% of the oral MPA group, 100% of the LNG-IUD group, and 50% of the non-treatment group. However, the objectivity of the study was compromised due to application of oral treatment in one group for only six months at most, while using LNG-IUD, known to reach markedly higher intrauterine concentrations, for a much longer time [14]. The success rate of 100% after the removal of the LNG-IUD at the end of the two years does not seem to match the data of Orbo *et al*. [14]. They have reported a response as low as 63% following the removal of the LNG-IUD in 22 of the 66 patients. In this study, the authors have preferred to use the WHO criteria for the classification of hyperplasia, and a homogeneous group of cases with hyperplasia without atypia was selected. Orbo *et al*. [14], however, have made a D-score-based classification. It is noteworthy in terms of the reliability of the classification that, in their study, there were 15 cases without atypia in the D score < 0 group which expresses a high malignant potential, and 33 cases with atypia in the D score > 1 group, which expresses a low malignant potential [14]. In addition, Wheeler has stated the cytologic atypia to be the most important prognostic factor in endometrial hyperplasia [15]. The treatment groups are highly variable and multicentered in Orbo's study. The intrauterine release of LNG-IUD is very variable, changing from 3 to 108 months, with a very broad scale of follow-up, varying from 58 to 106 months [14]. On the other hand, the present study was more homogenous being performed in a single-center with a standard duration of application of LNG-IUD, and a 24-month follow-up for all patients. Vereide *et al*. applied oral MPA ten mg/day in 29 patients and LNG-IUD in 21 patients for three months; the biopsies obtained from the patients at three months follow-up displayed a success rate of 51.7% for the oral MPA group and 100% for the LNG-IUD group. In their study, although the treatment durations were the same, the follow-up period appears to be brief [9]. In the retrospective study of Buttini *et al*. [16], in a group of patients with hyperplasia without atypia, 22 cases were treated with LNG-IUD, and ten cases with oral progestin. A success rate of 100% was reported in the group with LNG-IUD in situ, whereas the group with oral progestin had a success rate of 70% [16]. In their retrospective study, Clark *et al*. [17] have reported that the cases with atypical hyperplasia were often treated by hysterectomy, and there was no consensus on how to approach patients without atypia. Although there was no clear data about the duration of the progesterone therapy, Randall *et al*. reported that minimum time span was nine months [7]. Wheeler has noted that, in the presence of atypia, there is a lower rate of regression and higher recurrence rates after discontinuation of the treatment [15].

In order to have an objective comparison, the oral MPA therapy was intended to be given for three or six months without interruption in beginning of the study. However, due to the risk of the side-effects of MPA and the absence of previously issued studies in which MPA was given in a similar way, this proposal was not approved by the Ethics Committee, and eventually the classical MPA treatment of ten days per month was given.

In the present study, except comparing the success of oral and intrauterine progesterone therapies, the authors aimed to determine the minimum duration of LNG-IUD treatment for successful outcomes, which appears to be a popular option in women with a wish for childbearing. Thus, each patient was followed-up for a period of two years. In relatively young patients who might have a wish

for childbearing, the minimum duration of therapy that would be successful has not been studied by other authors. Therefore, one of the two objectives in this study was to determine the minimum amount of time required to achieve successful outcomes by LNG-IUD treatment.

Baseline and postoperative histopathologic evaluations on pipelle samples of 12 patients who underwent hysterectomy were performed by a single physician (KD) and evaluated by another single experienced cytopathologist (AB). Baseline and postoperative histopathologic evaluations of these 12 patients were found to be completely consistent. Since some cases of hyperplasia without atypia can resolve without any treatment, the absence of a third group receiving no therapy which would allow to investigate the spontaneous regression rates in people undergoing no treatment, can be recognized as a limitation of this study. Bearing this weakness in mind, the authors decided to avoid such a non-treatment group due to ethical concerns. Nevertheless, Orbo *et al*. observed that the regression rates of the non-treatment group and the standard low-dose (ten days a month, ten mg/day) MPA group were similar [14].

The success rates at two-years follow-up were 84% in the three-month LNG-IUD group and 50% in the three-month oral MPA group, whereas 100% in the six-month LNG-IUD group and 64% in the six-month oral MPA group. Regression rates were found to be statistically significantly higher in the LNG-IUD groups than in the oral MPA groups. Two recent studies have reported the regression rates of LNG-IUD therapy in hyperplasia without atypia as 92% (88/96) and 100% (12/12), which are consistent with the results of the present study [18, 19].

Since this study group consisted of patients that could have a wish for childbearing, they were aged below 50 years. One patient in Group 3 became pregnant 27 months after the removal of LNG-IUD and successfully gave birth with cesarean section four months prior. Moreover, one patient from Group 1 and another from Group 2 became pregnant two and three years after the treatment, respectively; the first patient ended her pregnancy by her own will and the latter experienced an abortion during the third trimester.

Conclusion

Previous oral progesterone and hysterectomy were the most common treatment modalities of endometrial hyperplasia, then LNG-IUD replaced the oral progesterone therapy and has become the most preferred alternative management to hysterectomy. The authors believe that LNG-IUD can be preferred as a safe and effective treatment of women for childbearing, particularly in cases without atypia, and that pregnancy can be planned after a six-month period of treatment.

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