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Levonorgestrel-Releasing Intrauterine Device Versus Dydrogesterone for Management of Endometrial Hyperplasia Without Atypia

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Abstract

Objective: To compare the efficacy and safety of the levonorgestrel-releasing intrauterine device (LNG-IUD) with dydrogesterone applied for the same duration in patients having endometrial hyperplasia (EH) without atypia. **Materials and Methods:** One hundred thirty eight women aged between 30 and 50 years with abnormal uterine bleeding and diagnosed as EH by transvaginal ultrasound were randomized to receive either LNG-IUD or dydrogesterone for 6 months. Primary outcome measures were regression of hyperplasia after 6 months of therapy. Secondary outcome measures were occurrence of side effects during treatment or recurrence of hyperplasia during follow-up period. **Results:** After 6 months of treatment, regression of EH occurs in 96% of women in the levonorgestrel-releasing intrauterine system (LNG-IUS) group versus 80% of women in the oral group ($P < .001$). Adverse effects were relatively common with minimal differences between the 2 groups. Intermenstrual vaginal spotting and amenorrhea were more common in the LNG-IUD group (P value .01 and .0001). Patient satisfaction was significantly higher in the LNG-IUS group (P value .0001). Hysterectomy rates were lower in the LNG-IUS group than in the oral group ($P = .001$). Recurrence rate was 0% in the LNG-IUD group compared to 12.5% in the oral group. **Conclusion:** In management of EH without atypia, LNG-IUS achieves a higher regression and a lower hysterectomy rate than oral progesterone and could be used as a first-line therapy.

Keywords

endometrial hyperplasia, progesterone, LNG-IUS, Mirena

Introduction

Endometrial cancer is the most common gynecologic cancer, and the incidence is still increasing. Endometrial cancer principally develops through preliminary stages called endometrial hyperplasia (EH) and 10% to 30% will develop into carcinoma when left untreated.[1] Thus, correct and optimal treatment of EH will prevent development of endometrial cancer and, also in the long term, reduce the incidence of endometrial cancer. Correct treatment of EH includes operative treatment with hysterectomy in the high-risk patients and conservative treatment and follow-up in patients with lower risk.[2]

Endometrial hyperplasia is classified according to increasingly abnormal architectural and cytologic criteria as simple, complex, and atypical hyperplasia. Cytological atypia is the most important prognostic factor with regard to progression to endometrial cancer. For nonatypical hyperplasia, there is a 1% to 3% chance of progression to cancer, with a 72% chance of regression after expectant management.

In contrast, for atypical hyperplasia, there is an 8% to 30% chance of progression to endometrial carcinoma, with only a 54% chance of spontaneous regression with expectant management.[3] In addition, endometrial cancer can coexist with atypical hyperplasia in up to 25% of patients. Because nonatypical hyperplasia is generally considered to be low risk for progression to cancer, many patients consider hysterectomy too invasive a treatment. Although there is no consensus on the best way to treat these women, they have often been treated with oral progestins.[4]

Progestin hormones are known to have a growth regulatory effect on the uterine mucosa. However, because of the systemic nature of the treatment, there can be significant side effects that limit compliance with treatment, and when the treatment is discontinued, the hyperplasia can recur. Systemic adverse effects such as headache, nausea, weight gain, and thromboembolic

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events may limit the overall efficacy of the drugs. Moreover, the type of progestin product, the optimal dose, and the duration of treatment are not clearly established.[5]

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an alternative to oral progesterone without its disadvantages. Locally acting progesterone has an effect on the endometrium several times stronger than that exerted by systemic products and with less systemic effect. Therefore, the dose of progesterone can be reduced and the adverse reactions minimized. So if the therapeutic efficacy of the LNG-IUS is similar to or greater than that of oral progesterone, the LNG-IUS could become the standard treatment for EH.[6]

The LNG-IUS (Mirena) is a T-shaped device, with a reservoir containing 52 mg of levonorgestrel. In vivo, the hormone is released at an initial rate of 20 μg daily, which progressively declines to half this rate by 5 years.[7] It exhibits a profound progestational effect on the endometrium. The endometrial lining becomes atrophic and inactive, and cervical mucus becomes thick and scant.[8]

The aim of this study is to compare the efficacy and safety of LNG-IUS to dydrogestrone (oral progesterone) applied for the same length of time in management of EH without atypia.

Materials and Methods

A total 280 women attended to the outpatient clinic in Zagazig University Hospital and were complaining of abnormal uterine bleeding (AUB) in the period from May 2011 to November 2012 and were screened to select eligible women for inclusion into the study. All these women underwent a detailed history, clinical examination, Papanicolaou test, a transvaginal ultrasound (TVUS), and for selected patients an endometrial biopsy by dilatation and curettage (D&C) was taken following inpatient admission. A written informed consent was obtained from all participants of the study after proper counseling and explanation of steps of the study. The study protocol was approved by the local research and ethics committee of Zagazig University Hospital. Inclusion criteria were age between 30 and 50 years old, those with histologically confirmed nonatypical simple or complex EH, a desire to avoid hysterectomy, and no contraindications against progestin hormones. Exclusion criteria include uterine anomaly, women with fibroids (more than 12 weeks size or distorting the uterine cavity), malignancy, genital infection, liver disease or liver tumor (benign or malignant), thromboembolic disease, deep vein thrombosis, hypercoagulable state, a history of coronary artery disease, or myocardial infarction. After randomization using computer-generated random numbers, the treatment according to assigned treatment arm was started.

The patients were randomly assigned into 2 groups, A and B. The levonorgestrel-releasing intrauterine device (LNG-IUD) group (group A) had 60 patients and the oral progesterone group (group B) had 78 patients.

In group A patients, the LNG-IUD (Mirena; Bayer Schering Oy, Turku, Finland) was inserted in the uterine cavity in the postmenstrual phase in the outpatient department and kept in situ for 6 months, while patients in group B were counseled to take dydrogesterone (duphaston; Solvay pharmaceuticals B V, the Netherlands) 10 mg, 2 tablets twice daily from fifth day of menstruation for 21 days for 6 months. Patients in the both the groups were followed up at 3, 6, 9 months, and at the end of 1 year. At each follow-up visit, TVUS was used to assess endometrial thickness, occurrence of side related to treatment. Endometrial histological assessment was done by biopsy with D&C at the end of treatment (after 6 months from starting which line) and 6 months later on. Primary outcome measures include regression of hyperplasia after 6 months of therapy. Secondary outcome measures include occurrence of side effects related to any line of treatment and recurrence of hyperplasia during the follow-up period.

SPSS software (SPSS Inc, Chicago, Illinois) Version 16 for windows was used, and the results were considered statistically significant at $P < .05$. Qualitative data were expressed as number and percentage and compared using chi-square test. Quantitative data were either parametric or nonparametric. Parametric data, mean $\pm$ standard deviation (SD), were compared using unpaired Student *t* tests on comparison between the groups and paired *t* test in the same group. Nonparametric data were compared between each sampling point (first, third, or sixth menstrual cycles). Differences were evaluated using **Mann-Whitney *U* test** on comparison between the groups and Wilcoxon signed-rank test in the same group.

Results

A total of 280 women attended the outpatient clinic during the study period from May 2011 to November 2012 complaining of AUB. In all, 123 women were excluded (68 had uterine myoma, 17 had corporeal or cervical polyp, 21 had other ovulatory dysfunction, and 17 had general causes) .Thus, 157 women met the inclusion criteria and were invited to participate; of them 19 declined to participate and 138 were initially included in this study. Of them, 78 were assigned to receive oral progesterone and 60 were assigned to insert LNG-IUD after appropriate counseling. In all, 18 women withdrew from the oral group before completion of the study because of noncompliance to progesterone side effects, and another 2 women withdrew from the LNG-IUD group because of noncompliance to menstrual spotting. Thus, the final studied group included 118 women (60 in the oral group and 58 in the LNG-IUD group). Eighteen women (10 from the oral group and 8 from the LNG-IUD group) were lost to follow-up and thus were excluded. Finally, 100 women completed the study, 50 in each group, and were included in final analysis. A flowchart of women included in the study is depicted in Figure 1. All patients had EH diagnosed by TVUS. The mean age of the patients was 41 $\pm$ 2.3 years in group A and was 42 $\pm$ 1.6 years in group B. Table 1 summarizes the demographic characteristics of patients of both the groups. There were no significant differences between both the groups with regard to age, parity, body weight, body mass index, or medical disorders like diabetes mellitus or hypertension.

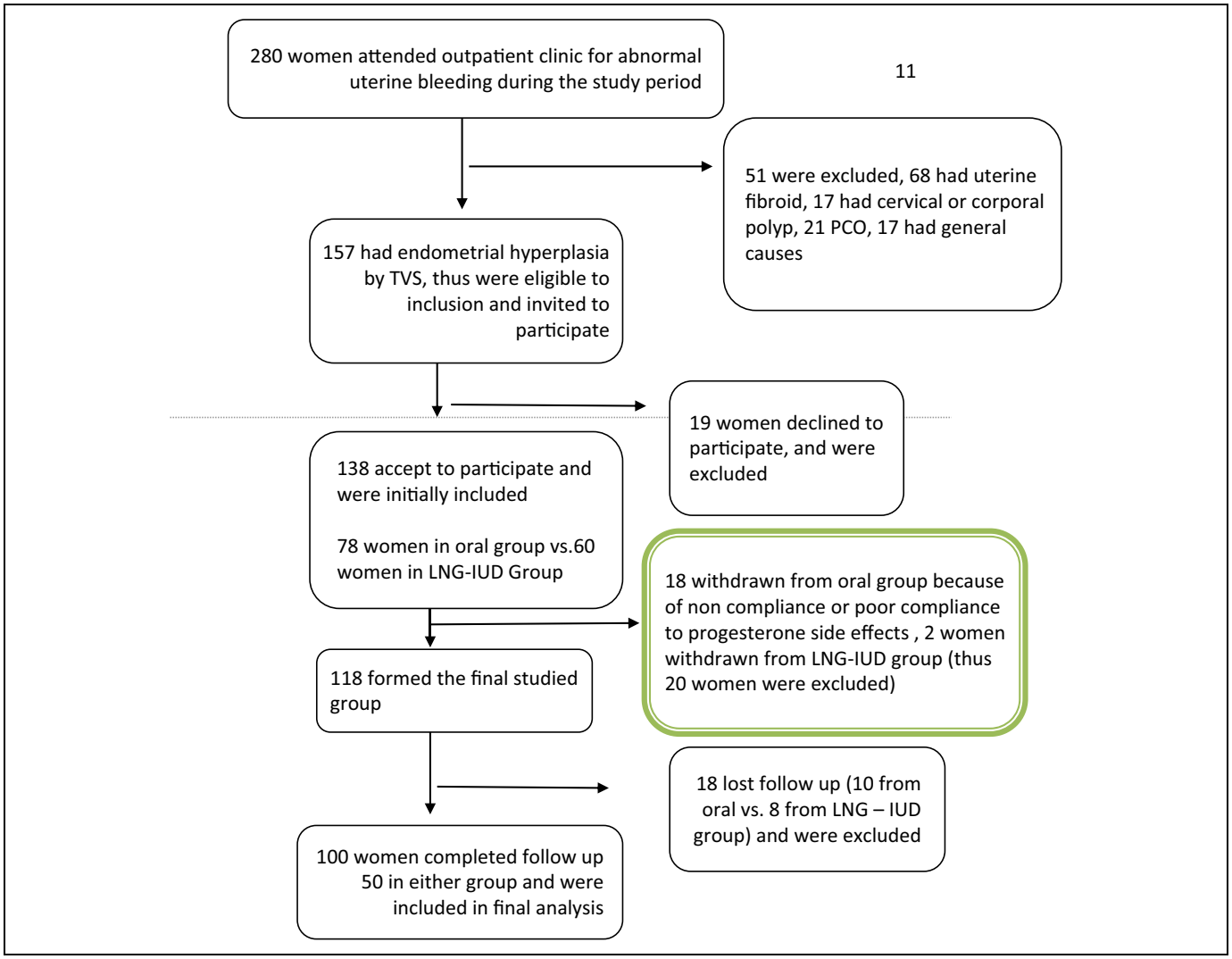

Figure 1. A flowchart of women included in the study.

Table 2 shows clinical presentation and histological classification of patients of both the groups. Patients of both the groups presented with abnormal vaginal bleeding, and their EH was either simple hyperplasia or complex hyperplasia without atypia. No significant difference was observed between the 2 groups ($P > .5$).

After 6 months of management, there was good clinical response in both the groups with no complaint of abnormal vaginal bleeding. Using TVUS, it was found that all apart from 2 patients in group A (one had endometrial thickness of 8 mm and the second had endometrial thickness of 10 mm) and 10 patients in group B (with endometrial thickness >5 mm with range from 7- to 15-mm thick) were still complaining of abnormal vaginal bleeding. All other asymptomatic patients in either groups had a thin endometrium <5 mm on TVUS.

After comprehensive counseling, 12 patients with persistence of abnormal vaginal bleeding decided to undergo hysterectomy. Their histopathology report revealed persistence of EH without atypia. At 6-month follow-up, histopathology of D&C biopsy revealed no recurrence rate ($0 / 50 - 2 = 0\%$) in group A compared to 5 patients in group B ($5 / 5 - 10 = 12.5\%$; 0% vs. 12.5%; P value .001). Also, there was lower hysterectomy rate in group A than in group B (16% vs 38%) with a P value of .001.

Follow-up of those patients for 6 months revealed no recurrence of EH in group A even after removal of LNG-IUS, but there was recurrence in 5 patients in group B with recurrence of symptoms and rethickening of endometrium seen by TVUS (Table 3). Those patients were counseled for hysterectomy. Histological reports of their hysterectomy specimens showed persistent nonatypical complex EH.

Table 4 indicates the side effects in both groups; amenorrhea occurred in 26% in group A, and no patient had amenorrhea in group B with P value of .0001. Also, vaginal spotting mainly in the first 3 months was higher in group A (3 patients) than in group B with P value of .01, and vaginal spotting mainly in the first 3 months of medications was higher in group A than in group B (P value .01). In group A, 3 patients could not tolerate

Table 1. Characteristics of Patients.[a]

Characteristics	Group A LNG-IUS, N = 50	Group B Dydrogesterone, N = 50	*P* Value
Age, years	41 ± 2.3	42 ± 1.6	.18
Body weight, kg	75.2 ± .1	77.8 ± 1.4	.31
Body mass index, kg/m^2	30.06 ± 1.8	31.03 ± 3.4	.15
Parity			.61
0	10 (20%)	8 (16%)	
<3	25 (50%)	27 (54%)	
>3	15 (30%)	15 (30%)	
Diabetes mellitus	8 (16%)	6 (12%)	.71
Hypertension	7 (14%)	9 (18%)	.71

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; SD, standard deviation.
[a] Values are presented as n (%) or mean ± SD.

Table 2. Clinical and Histological Presentations.[a]

Item	Group A IUD, N = 50	Group B Oral Progesterone, N = 50	*P* value
Irregular vaginal bleeding	35 (70%)	33 (66%)	.70
Prolonged or heavy menstruation	15 (30%)	17 (34%)	.61
Histological pattern of endometrial hyperplasia			.82
Simple without atypia	32 (64%)	30 (60%)	
Complex without atypia	18 (36%)	20 (40%)	

Abbreviation: IUD, intrauterine device.
[a] Values are presented as n (%).

Table 3. Outcomes in LNG-IUS and Oral Progesterone Groups.[a]

Item	Group A IUD, N = 50	Group B oral Progesterone, N = 50	*P* Value
Regression rate after 6 months of treatment	N 48 (96%)	N 40 (80%)	.001
For simple endometrial hyperplasia	N 31 (62%)	N 26 (52%)	
For complex hyperplasia	N 17 (34%)	N 14 (28%)	
Recurrence rate at 12 months	N 0 0%	N 5 (12.5%)	.001
Hysterectomy rate	N 8 (16%)	N 19 (38%)	.001

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a] Values are presented as n (%). *P* value < .05 is significant.

Table 4. Side Effects of Both Regimens.

Outcome	Group A LNG-IUD	Group B Oral Progesterone	*P* Value
Amenorrhea	13 (26%)	0 (0%)	.0001
headache	29 (59%)	26 (52%)	.0781
Mood swing	8 (16%)	10 (19%)	.853
Weight gain	6 (12%)	7 (14%)	1.000
Intermenstrual spotting	25 (50%)	13 (25%)	.01
Nausea	3 (5%)	10 (24%)	.04
Breast tenderness	10 (20%)	11 (22%)	.734
Proportion of women satisfied with treatment and willing to continue the treatment	38 (75%)	13 (25%)	.0001

Abbreviations: LNG-IUD, levonorgestrel-releasing intrauterine device.
[a] Values are presented as n (%). *P* value < .05 is significant.

such vaginal spotting and decided to undergo hysterectomy. Histopathological assessment of their hysterectomy specimens confirmed regression of EH. Another 3 patients complained of recurrent attacks of vaginal bleeding, and by TVUS assessment it was found that there was a thin endometrium <5 mm. Despite appropriate counseling and reassurance, they were unsatisfied to continue the treatment and underwent hysterectomy. The histopathology assessment of their hysterectomy specimens confirmed regression of EH. No significant difference was noted between both the groups with regard to breast pain, headache, or weight gain. Still nausea in group B was significantly higher than that in group A.

Regarding patient satisfaction to continue the treatment, it was higher in group A than in group B with a *P* value of .0001. Additionally, 4 patients in group B couldn't tolerate headache or nausea and underwent hysterectomy. Histopathological assessment of their hysterectomy specimens confirmed regression of EH.

Discussion

Endometrial hyperplasia is a common disease affecting women of all ages. Endometrial hyperplasia represents a spectrum from an exaggerated physiologic state to carcinoma in situ as a result of unopposed estrogen stimulation in the absence of progestin influence. Endometrial hyperplasia is clinically important because they may cause AUB and precede or occur concurrently with endometrial carcinoma. Cytological atypia is the most important risk factor for progression to carcinoma.[9]

Although many gynecologists proceed to hysterectomy when hyperplasia with cellular atypia is found on an endometrial biopsy or curettage specimen, a number of conservative therapies are particularly useful for younger patients who wish to preserve fertility and for women who do not desire or can't undergo hysterectomy.[10]

Because EH is estrogen dependent, progestins are often used to induce regression. Progestin appears to decrease glandular cellularity in these lesions by triggering apoptosis. Progestin is most commonly used as a safe, uterus-preserving alternative to hysterectomy. Nonatypical (simple) hyperplasia is usually treated by oral administration of progestogens in sufficient dose and duration. However, if the treatment is discontinued, recurrence may occur.[11]

Several retrospective studies demonstrated a beneficial effect of progestin treatment of EH either with or without atypia. In a trial by Randall and Kurman, the authors showed that oral megestrol 80 to 120 mg daily or oral medroxy progesterone acetate (MPA) 10 to 30 mg daily for approximately

6 months has been shown to cause regression to loss of atypia in 94% of patients with complex atypical hyperplasia and finally to normal endometrium in 81% of patients.[12] Nonetheless, systemic side effects and poor compliance were often associated with oral progesterone; clinical trials of progestin therapies for atypical EH, furthermore, have not yet established a standard regimen.[13] Compared with oral progestin, LNG-IUS in many studies has been found to have less severe systemic side effects and higher efficacy as a treatment for EH.[14] Wildemeersch and Dhont[6] reported on women with AUB and nonatypical and atypical EH who were treated with a ''frameless'' LNG-IUS, which releases 14 μg/d of levonorgestrel. The cure rate was 100% as confirmed by repeat endometrial biopsy at 12 months and concluded this is an effective method for suppression of the endometrium and may be considered as an alternative to hysterectomy.[6] Vereide et al worked on EH and compared treatment with LNG-IUS and oral gestagen. After 3 months of treatment, all the LNG-IUS patients showed regression of hyperplasia, whereas 45% of the peroral gestagen patients still had the disease. The authors concluded that LNG-IUS was a superior treatment for EH.[14]

Gallos et al[15] recently published a systematic review and meta-analysis that had compared regression rates of EH between oral progestin and LNG-IUS. In cases of simple hyperplasia, treatment with oral progestin showed a pooled regression rate of 89% versus the 96% rate for LNG-IUS patients. In cases of complex hyperplasia, oral progestin patients showed a pooled regression rate of 66% versus the 92% rate for LNG-IUS patients. Overall, the treatment outcomes for LNG-IUS were statistically more significant than those for oral progestin ($P < .01$).

Lee et al[16] reported on the effectiveness of LNG-IUS in management of EH. In all of the patients, complete regression of EH was achieved.

Orbo et al[17] in a multicenter, randomized trial comparing low-dose oral progestin therapy with LNG-IUS, reported that at 6 months of follow-up, patients in the LNG-IUS arm had significantly higher rates of regression, 100%, versus 96% for the women in the continuous oral progesterone group.

So most of the results of those studies were similar to the results of the current study. We found no case of recurrence in group A compared to 5 cases of recurrence in the oral progesterone group B (0% vs 12.5%) with *P* value of .001.

Regarding the type of oral progesterone that we used in our study, many studies used MPA, megestrol acetate, gestagen, or norethisterone acetate, with different doses and schedules, as the most commonly used progestin therapies. Reed et al found that there are no differences in regression of EH between the various oral progestogens.[18] But, in our study, we tried to use a new type of progesterone, dydrogesterone, as it is a potent, relatively safe, and well tolerated orally, active progestogen indicated in a wide variety of gynecological conditions related to progesterone deficiency. Its freedom from estrogenic, androgenic, anabolic, corticoid, and other undesirable hormonal effects gives it additional benefits over most of other synthetic progestogens like medroxyprogesterone. So, it has selective progestogenic properties although its progestogenic potency is 20 times higher than that of progesterone. Furthermore, it has anti-estrogenic activity.[19] It is a potent one so it is recommended for postmenopausal patients under hormone replacement therapy at a dose of at least 10 mg for 14 days which is acceptable for endometrial protection.[20]

Actually, we lack sufficient evidence to give a firm recommendation for using dydrogesterone for treating EH in premenopausal women. However, the main reason to choose dydrogesterone in this study is to select a potent oral progesterone with least systemic side effects. However, still with this choice, 18 women from the total of 118 women who were finally included withdrew before the study completed due to either noncompliance or poor compliance with side effects such as nausea or headache compared to 2 women in those treated by LNG-IUD (*P* value .04). Alternatively, the progesterone concentrations in the uterine mucosa when delivered through an IUD directly into the cavity were reported to exceed that of the oral treatment by several fold. Also, it is associated with higher patient satisfaction, and therefore, patients are more likely to continue the treatment. This higher chance of patients continuing the LNG-IUD treatment resulted in higher compliance and better efficacy in treating EH compared to oral progestogens.

Regarding patient preference, we found that after randomized treatment assignment (78 oral and 60 IUD), 20 women withdrew (18 oral vs 2 IUD) and 18 were lost to follow-up (10 oral vs 8 IUD; Figure 1) which translates to 36% ([18 + 10] / 78) attrition rate for the oral group and 17% ([2 + 8] / 60) attrition rate for the IUD group. Thus, in our study we found that patient's satisfaction to complete their line of management was significantly lower in the oral group than in the LNG-IUD with a *P* value of .0001.

Endometrial aspiration biopsy with LNG-IUD in place is less accurate than D&C after removal of LNG-IUD where there is insufficient tissue for pathologic evaluation due to endometrial atrophy, and it might not be reliable for follow-up and evaluation of management of EH.[21] In the current study, we depended on D&C biopsy to decrease the percentage of errors in results of histopathology. In disagreement of our claim, Demirkiran et al[21] showed that the rate of insufficient tissue sample in general was 3% with pipelle and 2% with D&C and that the concordance rate was 67% between pipelle and hysterectomy and 70% between D&C and hysterectomy (almost equal success rate in the diagnosis of endometrial pathologies) and concluded that neither pipelle nor D&C is an adequate method for focal endometrial pathologies.

Conclusion

In management EH without atypia, LNG-IUD achieves a higher regression rate and lower hysterectomy rate than oral progesterone and could be the first-line therapy. Thus, in selected women treatment with LNG-IUD could be beneficial to preserve the uterus and decrease the need for hysterectomy.

However, a continuous observation is necessary. Patients who showed a positive response could remain protected for years with a long-acting, hormone-releasing IUD.

Declaration of Conflicting Interests

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