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Original Article

The effectiveness of levonorgestrel releasing intrauterine system in the treatment of endometrial hyperplasia in Korean women

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Objective: Levonorgestrel releasing intrauterine system (LNG-IUS) has been shown to treat patients with non-atypical & atypical endometrial hyperplasia (EH) successfully in many western studies. Our purpose was to examine the effectiveness of LNG-IUS in the treatment of Korean women with EH.

Methods: We conducted a prospective observational study of 12 women diagnosed with EH and treated with LNG-IUS insertion between February 2007 and August 2009 at the Department of Gynecology of Gangnam CHA Hospital, CHA University School of Medicine. Baseline endometrial biopsies were done before insertion of LNG-IUS, and outpatient follow-up endometrial biopsies were undertaken at 3-month intervals after insertion of LNG-IUS. We investigated the regression rate and the time to regression.

Results: Four patients had simple hyperplasia without atypia, 7 patients complex hyperplasia without atypia, and just 1 patient complex atypical hyperplasia. Complete regression of EH was achieved in all cases (100%, 12/12), with the significant proportion (66%, 8/12) achieving it within 3 months. The mean duration to regression was 4.5 months. All cases had regression within 9 months. In the case of complex atypical hyperplasia, the regression was attained at the 9th month after insertion of LNG-IUS. The mean follow-up duration was 12 months (range, 3 to 27 months). As long as LNG-IUS was maintained, the EH did not recur.

Conclusion: LNG-IUS appears to be as highly effective in treating Korean women with EH.

Key Words: Endometrial hyperplasia, LNG-IUS, Korean women, Progestin, Mirena

INTRODUCTION

Endometrial hyperplasia (EH) is defined as a morphologic and biologic alteration of endometrium as a result of protracted estrogen stimulation in the absence of progestin influence. EH has been regarded as a premalignant lesion. Cytologic atypia is the most important factor for progression to carcinoma.[1-3] About 1-3% of hyperplasia without atypia were observed to progress to carcinoma over 10 years' follow-up. On the contrary, 8-29% of atypical hyperplasia progress to carcinoma over 4 years' follow up.[1]

The goals of treating women with EH include not only relieving the symptoms of abnormal uterine bleeding but also preventing progression to carcinoma.[4,5] From the viewpoint of oncogenic potential of EH, hysterectomy has been generally recommended for the treatment of atypical EH except when the women have strong desire for fertility or have serious surgical risk factors.[4,6,7] Oral progesterone has been used to treat women with EH who want to the conserve uterus. But some systemic side effects and poor compliance have been reported to be associated with oral progesterone. Compared with oral progesterone, LNG-IUS has been reported to have less systemic side effects and higher efficacy for the treatment of EH in many studies targeting the women of western countries.[8-12]

To our knowledge, there has been no study reporting the effectiveness of LNG-IUS in treating Korean women with EH. Considering the variation of treatment responses among the variable ethnicity, we investigated the effectiveness of LNG-IUS in treating non-atypical and atypical EH in Korean women.

MATERIALS AND METHODS

Twelve patients participating in this study had presented

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with abnormal uterine bleeding to the Gynecologic Department, Gangnam CHA Hospital. All women were diagnosed with EH and treated with LNG-IUS (Mirena®) from February 2007 to August 2009.

For diagnosis and assessment of treatment responses, we performed transvaginal sonography (TVS) and outpatient endometrial biopsy. The methods of endometrial biopsy were endometrial sampling with a catheter (8 women, 66.6%), D&C (3 women, 25%), and hysterscopic biopsy (1 woman, 8.3%). One patient who had been suspected of an endometrial polyp on TVS was eventually diagnosed with EH after hysteroscopic polypectomy, and she entered the study.

EH was divided into 4 categories by the Kurman criteria: simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia, and complex hyperplasia with atypia.[13] In assessing the histological treatment response, complete regression was defined as endometrial atrophy, pseudodecidualization of stroma without evidence of hyperplasia. Complete regression could be accompanied by secretory change of glandular tissue or metaplasia.[4,14]

We collected the demographic data including age and risk factors for EH, such as parity, weight, height, diabetes, and hypertension. The method of initial diagnosis and the type of EH were recorded. During follow-up at scheduled intervals, we conducted TVS and endometrial biopsy using a Walleth catheter with IUD in situ. The first two follow-ups were scheduled at the 3rd month and 6th month after insertion. If complete regression was achieved within 6 months, the follow-up interval was extended to 6 months thereafter. The primary outcome was the proportion of women with complete regression of EH. The secondary outcome was the time to complete regression.

Table 1. Baseline characteristics

Characteristics	Mean values
Age (yr)	39.1 (25-46)
Body weight (kg)	53.5 (46-62)
Body mass index (kg/m^2)	21.40 (17.47-25.51)
Parity	
0	6 (50)
1	2 (16.7)
2	4 (33.3)
Menopause premenopausal	12 (100)
Diabetes mellitus	1 (10)
Hypertension	1 (10)

Values are presented as mean (range) or number (%).

RESULTS

1. Baseline characteristics

Twelve women with EH (simple hyperplasia without atypia 4, complex hyperplasia without atypia 7, complex hyperplasia with atypia 1) were included in this study. The summary of the baseline characteristics are shown in Table 1. The mean age was 39.1 years (range, 25 to 46 years). All women included were premenopausal. Six among the twelve women were nulliparous.

2. Endometrial regression after LNG-IUS insertion

The outcomes of the study is summarized in Table 2. All women developed a thin endometrium (≤4 mm) on TVS examination. All women achieved endometrial regression within 9 months after LNG-IUS insertion. In eight women out of twelve (66%), the regression was achieved at the 3rd month. The mean time to regression was 4.5 months. EH recurred in 1 patient whose LNG-IUS had been removed because of breast pains associated with LNG-IUS. Except for

Table 2. Levonorgestrel releasing intrauterine system (LNG-IUS) insertion and follow-up of regression of endometrial hyperplasia

Case no.	Age	Parity	Type	Time to regression (mo)*	Biopsy result	Follow-up (mo)
1†	44	2	SH	6	SD, AG, PE	30
2	25	0	CHA	9	SD, AG, PE	27
3	29	0	SH	6	SD, AG, PE	24
4	40	2	SH	9	SD, PE	9
5	46	2	CH	3	SD, IG, PE	12
6	41	1	CH	3	SD, AG	11
7	37	0	CH	3	SD, IG, PE	6
8	32	0	CH	3	SD, IG, PE	6
9	43	0	CH	3	SD, IG, PE	6
10	34	0	CH	3	SD, IG, PE	3
11	45	2	SH	3	SD, IG, PE	3
12	44	1	CH	3	SD, IG, PE	3

SH: simple hyperplasia without atypia, CHA: atypical complex hyperplasia, CH: complex hyperplasia without atypia, SD: stromal pseudodecidualization, AG: atrophic glands, IG: inactive glands, PE: consistent with Progeterone effect.
*Complete regression was defined as endometrial atrophy, pseudodecidualization of stroma without evidence of hyperplasia. It could be accompanied by secretory change of glandular tissue or metaplasia.[4,14] †This patient got the regression after LNG-IUS insertion, but she wanted to remove her LNG-IUS because of breast pain. It was removed at 24th month later.

this case, there has been no other recurrence to date.

In the patient with CAH, complete regression was achieved at the 9th month, and has sustained until now for 21 months.

DISCUSSION

EH 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. EH are important clinically because they may cause abnormal uterine bleeding, and precede or occur concurrently with endometrial carcinoma. Cytologic atypia is the most important risk factor for progression to carcinoma.

When it comes to EH without atypia, the malignant potential is low, the rate of spontaneous resolution is high[1-3] and the therapeutic response to oral progesterone is also high. Therefore, hysterectomy for EH without atypia may be regarded as an over-treatment.[4-8] According to three observational studies, the rate of spontaneous resolution for EH without atypia was 72% which was higher than 54% of atypical hyperplasias.[2-4] Recently, conservative treatment has been considered to be acceptable when the strict follow-up is possible to detect cases of persistence, recurrence, and progress to carcinoma.[15]

Oral progesterone has been used to treat women with EH who wish to conserve the uterus. But some systemic side effects and poor compliance have been reported to be associated with oral progesterone. Compared with oral progesterone, LNG-IUS has been reported to have less systemic side effects and higher efficacy for the treatment of EH in many studies targeting the women of western countries.[6-12] LNG-IUS has been regarded as a beneficial conservative treatment modality for non-atypical and atypical EH.[8-12] But none of these studies have targeted Korean women. Thus, we do not have any reliable data for Korean women with EH. Besides, we had to consider the variation of treatment responses and the side effects of LNG-IUS according to Korean ethnicity. The results of this study support that LNG-IUS may also be a highly effective method for suppressing non-atypical and atypical EH in Korean women. The regression rate was 100%. The advantageous effects were observed within 9 months in all cases.

A significant proportion of the patients with non-atypical hyperplasia achieved regression at the 3rd month after LNG-IUS insertion. This success can be compared with the results of a recent long-term follow-up large observational European study, in which the regression rates of non-atypical hyperplasia and atypical hyperplasia were 90% and 54%, respectively.[10] In this study, one patient with atypical hyperplasia achieved complete regression with LNG-IUS insertion at the 9th month. The results of our study targeting Korean women were in agreement with the beneficial effects of LNG-IUS on non-atypical and atypical EH observed in many other studies targeting western women.

There are weaknesses in this study. The first one is the small sample size of this study. Especially, there was only one case of atypical hyperplasia included in this study. The second one is that we conducted follow-up endometrial biopsies with the LNG-IUS in situ. The presence of the LNG-IUS in the uterine cavity may affect the accuracy of the endometrial biopsy. A large, long-term follow-up study may overcome these weaknesses. Nevertheless, this is the first study to evaluate the effectiveness of LNG-IUS for treatment of EH in Korean women, and the result was successful.

CONFLICT OF INTEREST

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

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