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Editorial

The current situation of the levonorgestrel intrauterine system (LNG-IUS) in conservative treatment for patients with early-stage endometrial cancer and atypical hyperplasia

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Conflict of Interest
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With an increasing incidence of endometrial cancer worldwide, fertility-sparing management for young patients with early-stage endometrioid endometrial cancer (EEC) and atypical hyperplasia (EAH) has turned into an important issue.

Conservative treatments for this population are mainly based on progestin therapies, of which medroxyprogesterone acetate (MPA) and megestrol acetate (MA) systematic therapy are the classic regimens [1]. However, the therapeutic effects of MPA or MA are not yet optimal [2,3]. The complete response (CR) rate is 70%–80% in EEC and EAH patients after a median treatment period of 6–9 months using MPA or MA. The most common side effects are weight gain, headache, and vaginal spotting. Thrombosis also occurs in some patients using high dose progestins, which could be serious and life-threatening.

In this circumstance, levonorgestrel intrauterine system (LNG-IUS) has been drawing more attention as an alternatively conservative option for EEC/EAH patients [4]. As an intrauterine progestin releasing system, the advantages of LNG-IUS are obvious. Compared with the oral use of hormone, levonorgestrel is released inside uterine cavity, leading to a lower serum level of progestin, therefore reducing the risk of most side effects as weight gain and thrombosis. Also, the patient's compliance is better due to this "one-time insertion and long-term protection" device frees these patients from taking pills every day. Particularly, the persistent release of progestin to endometrium might be promising to prevent disease recurrence after CR.

However, clinical evidences to prove LNG-IUS as an effectively and safely conservative treatment are still lacking, especially for EEC patients, despite many studies supporting its effect on non-atypical endometrial hyperplasia [5]. All reported effects of LNG-IUS on EEC/EAH patients are from retrospective or observational studies, with a limited case number less

than 100 for EEC patients. In a systemic analysis of 189 EAH patients from 14 studies, LNG-IUS achieved a higher pooled regression rate compared with oral progestogens (pooled rate, 90% vs. 69%; p=0.03) [6]. Another retrospective study [7] on LNG-IUS showed response rates of 80% (95% confidence interval [CI]=52–96) in EAH patients (n=15), 67% (95% CI=30–93) in EEC G1 (n=9) and 75% (95% CI=35–97) in EEC G2 patients (n=8). Median uterine diameter was 1.3 cm larger in women who did not respond to LNG-IUS (p=0.04). The RCOG guideline recommend LNG-IUS as the first-line conservative treatment for endometrial hyperplasia and EAH [8]. National Comprehensive Cancer Network added LNG-IUS as one of the options for fertility preserving treatment for EEC G1 patients since 2014.

In this issue of the *Journal of Gynecologic Oncology*, Leone Roberti Maggiore et al. [9] reported the effect of LNG-IUS on conservative treatment on 28 EAH, 16 EEC G1 and 4 EEC G2 patients with a relatively long follow-up period (82.6±47.2 months). In their study, LNG-IUS alone achieved a CR rate of 89.3% (25/28) in EAH patients, 81.3% (13/16) in EEC G1 patients, and 75% (3/4) in EEC G2 patients. Despite the retrospective nature, this is to date the largest case series investigating the efficacy and fertility outcomes of LNG-IUS in patients of reproductive age affected by EEC/EAH, which provides evidence to the further use of LNG-IUS in EAH/EEC patients.

Several aspects should be paid attention regarding the use of LNG-IUS in conservative treatment of EAH and EEC patients:

Firstly, LNG-IUS alone should be used carefully in patients with enlarged uterine cavity [7]. The local releasing levonorgestrel can only reach the endometrium near the device, therefore, may fail to treat the endometrial lesion beyond LNG-IUS reachable range in an enlarged uterine cavity. In such case, systemic therapies such as oral progestins or GnRH-a combined with LNG-IUS should be suggested [10,11].

Secondly, although the effect of LNG-IUS on EAH is promising, the effect of LNG-IUS alone on EEC G1 still warrants further investigation. The reported CR rate using LNG-IUS alone in EEC varied from 22% [12] to 81.3% in the present study. Given the retrospective nature of the studies, we cannot yet tell which EEC G1 patients are most appropriate for LNG-IUS treatment.

Thirdly, due to the modest effect of progestin on EEC G2 patients, cautions should be made when LNG-IUS is used as fertility-sparing regimen for this advanced subtype.

There are several clinical trials carried on investigating the effect of LNG-IUS alone or in combination with oral progestins on EEC/EAH patients (NCT03241914, NCT03463252, and NCT03241888). The results of these trials might provide us further information regarding the use of LNG-IUS in EEC/EAH patients.

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