Editorial

J Gynecol Oncol Vol. 25, No. 3:164-165
http://dx.doi.org/10.3802/jgo.2014.25.3.164
pISSN 2005-0380 · eISSN 2005-0399

Journal of Gynecologic Oncology
jgo

Conservative treatment for atypical endometrial hyperplasia: what is the most effective therapeutic method?

Mi Kyoung Kim, Seok Ju Seong
Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul, Korea

See accompanying article by Shan and colleagues on page 214.

Endometrial hyperplasia (EH), especially in the presence of atypia, has a strong tendency to the development of endometrial carcinoma. In this respect, hysterectomy is a preferred treatment for atypical EH. However, for young patient who desire to preserve their fertility or for patients not selected for surgery, conservative treatments using progestin are widely accepted as a treatment option [1].

Oral use of progestin, such as megestrol acetate (MA), and medroxyprogesterone acetate (MPA) is the most commonly used method with various regimens available for treatment of EH. Nonetheless, the response rate is unsatisfactory, especially in atypical EH (approximately 70%). Moreover, oral progestins are associated with poor compliance and systemic side effects that may limit overall efficacy [2]. Therefore, to find a more effective therapeutic method, variable studies are conducted. Currently, the most notable studies of that are the treatment of EH using levonorgestrel-releasing intrauterine system (LNG-IUS) or metformin [3-13].

The LNG-IUS has already been used successfully to treat EH. Several observational studies have shown higher regression rates for LNG-IUS than for the oral progestin [4-7]. Meta-analysis of 190 observational studies including 1,001 women showed that a significantly higher regression rate was achieved with LNG-IUS than with oral progestins in treatment of atypical EH (90% vs. 69%) [2]. Recently, randomized trial comparing LNG-IUS and oral progestin as treatments for endometrial hyperplasia proved the effectiveness of LNG-IUS [8,9]. Orbo et al. [9] showed that after 6 months, all the patients in the LNG-IUS group (53/53) including 6 atypical hyperplasia were obtained complete remission. The response rate of continuous oral progestin was 96% (46/48) and cyclic oral progestin was only 69% (36/52).

In this issue of the *Journal of Gynecologic Oncology*, Shan et al. [10] reports a pilot study that compared the efficacy of metformin plus MA with MA alone in treating endometrial atypical EH patients. To date, only a few case report about combined metformin with high dose progestin or oral contraceptives therapy for progestin resistant atypical EH have been reported [11,12]. Even though 75% of response rate in metformin plus oral progestin group is relatively unsatisfactory compared to reported result in treatment of atypical EH with LNG-IUS, the present study is meaningful for being the first clinical trial that has evaluated the efficacy of metformin plus oral progestin for treatment of atypical EH.

Obesity, metabolic syndrome, polycystic ovarian syndrome (PCOS), insulin resistance and type II diabetes are significant risk factors of EH. Furthermore, chronic hyperinsulinemia may have a direct mitogenic effect on the endometrium and may inhibit progestogen therapy [14]. Metformin, insulin sensitizer, decreases insulin resistance by the inhibition of hepatic gluconeogenesis. Metformin not only lowers insulin levels and can also provide benefits by decreasing body weight, which diminishes the peripheral conversion of androgen. In addition, a low body index is related to a high resolution rate in EH patients with progestin treatment [15]. Therefore, metformin may be proposed as an alternative agent for treatment of EH, especially for patients who have progestin resistance or other metabolic disorders. Then, what is the best way to treat atypical EH to alternate oral progestin or in case of treatment failure in oral progestin therapy- LNG-IUS or oral progestin

Correspondence to Seok Ju Seong
Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, 566 Nonhyeon-ro, Gangnam-gu, Seoul 135-913, Korea.
E-mail: sjseongcheil@naver.com

with metformin?

As we know, LNG-IUS have high intrauterine, but low systemic levels of progestin. Therefore, it can be more effective in endometrium without incurring side effects such as breast tenderness, mood changes and weight gain. Moreover, it is convenient compared to daily dosing with oral progestin. Meanwhile, as mentioned above, insulin resistance and metabolic syndrome can be related with progestin resistance. In the present study, patients who met at least on metabolic syndrome criterion were enrolled. Relatively low response rate could be explained in this way. In these patients with progestin resistant or metabolic disorder such as PCOS, obesity, adding metformin can be helpful. Recently, as a conservative treatment of EH, the study about LNG-IUS with metformin is ongoing along with LNG-IUS or oral progestin plus metformin [16].

Although this study is a pilot study and has limitations to conclude effectiveness and safety of medical treatment using metformin for atypical EH, the significance of metformin can be suggested as combined therapy with progesterone in patients with expected progestin resistance. Further investigation and large prospective clinical trial in this area is needed.

CONFLICT OF INTEREST

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

REFERENCES

1. Anastasiadis PG, Skaphida PG, Koutlaki NG, Galazios GC, Tsikouras PN, Liberis VA. Descriptive epidemiology of endometrial hyperplasia in patients with abnormal uterine bleeding. Eur J Gynaecol Oncol 2000;21:131-4.
2. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2010;203:547.e1-10.
3. Lee TS, Seong SJ, Kim JW, Ryu HS, Song ES, Nam BH. Management of endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: single arm, prospective multicenter study: Korean gynecologic oncology group study (KGOG2006). Jpn J Clin Oncol 2011;41:817-9.
4. Lee SY, Kim MK, Park H, Yoon BS, Seong SJ, Kang JH, et al. The effectiveness of levonorgestrel releasing intrauterine system in the treatment of endometrial hyperplasia in Korean women. J Gynecol Oncol 2010;21:102-5.
5. Varma R, Soneja H, Bhatia K, Ganesan R, Rollason T, Clark TJ, et al. The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia: a long-term follow-up study. Eur J Obstet Gynecol Reprod Biol 2008;139:169-75.
6. Wildemeersch D, Janssens D, Pylyser K, De Wever N, Verbeeck G, Dhont M, et al. Management of patients with non-atypical and atypical endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: long-term follow-up. Maturitas 2007;57:210-3.
7. Orbo A, Arnes M, Hancke C, Vereide AB, Pettersen I, Larsen K. Treatment results of endometrial hyperplasia after prospective D-score classification: a follow-up study comparing effect of LNG-IUD and oral progestins versus observation only. Gynecol Oncol 2008;111:68-73.
8. Abu Hashim H, Zayed A, Ghayaty E, El Rakhawy M. LNG-IUS treatment of non-atypical endometrial hyperplasia in perimenopausal women: a randomized controlled trial. J Gynecol Oncol 2013;24:128-34.
9. Orbo A, Vereide A, Arnes M, Pettersen I, Straume B. Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. BJOG 2014;121:477-86.
10. Shan W, Wang C, Zhang Z, Gu C, Ning C, Luo X, et al. Conservative therapy with metformin plus megestrol acetate for endometrial atypical hyperplasia. J Gynecol Oncol 2014;25:214-20.
11. Session DR, Kalli KR, Tummon IS, Damario MA, Dumesic DA. Treatment of atypical endometrial hyperplasia with an insulin-sensitizing agent. Gynecol Endocrinol 2003;17:405-7.
12. Shen ZQ, Zhu HT, Lin JF. Reverse of progestin-resistant atypical endometrial hyperplasia by metformin and oral contraceptives. Obstet Gynecol 2008;112(2 Pt 2):465-7.
13. Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007;25:2798-803.
14. Lin J, Li R, Zhou J. The influence of insulin on secretion of IGF-I and IGFBP-I in cultures of human endometrial stromal cells. Chin Med J (Engl) 2003;116:301-4.
15. Penner KR, Dorigo O, Aoyama C, Ostrzega N, Balzer BL, Rao J, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. Gynecol Oncol 2012;124:542-8.
16. UNC Lineberger Comprehensive Cancer Center. Metformin with the levonorgestrel-releasing intrauterine device for the treatment of complex atypical hyperplasia (CAH) and endometrial cancer (EC) in non-surgical patients (clinical trial.gov identifier: NCT 02035787) [Internet]. 2014 [cited 2014 Jun 18]. Available from: http://clinicaltrials.gov/show/NCT02035787.