

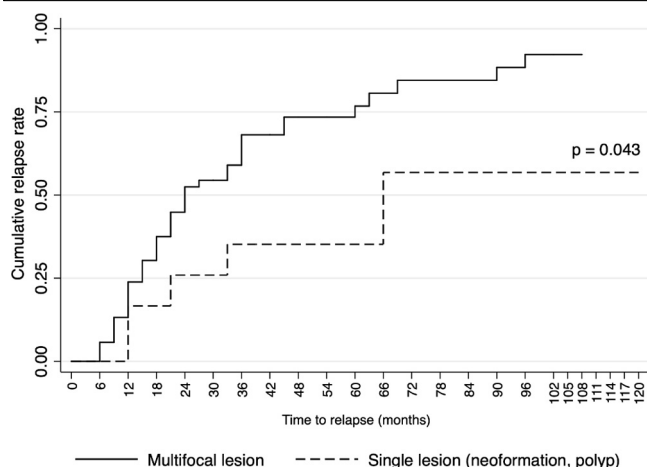
Prognostic impact of hysteroscopic resection of endometrial atypical hyperplasia-endometrioid intraepithelial neoplasia and early-stage cancer in combination with megestrol acetate

OBJECTIVE: In 5% to 30% of cases, endometrial cancer occurs in women aged 45 years or younger. A valid option for women desiring fertility is primary hormonal treatment, such as oral megestrol acetate (MA), alone or combined with hysteroscopic resection,¹ or a levonorgestrel-releasing intrauterine system; however, 20% to 30% and 41% of patients undergoing progestin-based treatments alone failed to achieve complete response (CR) and recurred.² The current knowledge is drawn from observational cohort studies on small series of patients for which long follow-up is rare.³ Moreover, the worldwide data on hysteroscopic treatment are still limited.⁴ Here, we evaluated the prognostic outcome of a large, single-institution series of young women diagnosed with endometrial atypical hyperplasia (EAH)/endometrioid intraepithelial neoplasia (EIN) and early-stage endometrial cancer (EEC) who were selected for fertility preservation and treated with oral MA combined with hysteroscopic resection in the subgroup of patients carrying a single lesion.

STUDY DESIGN: Patients with EAH/EIN (n=49) or well-differentiated EEC (n=36), International Federation of Gynecology and Obstetrics stage IA (no myometrial invasion at magnetic resonance imaging), were prospectively included from June 2007 to December 2019. The inclusion criteria for conservative treatment followed National Comprehensive Cancer Network guidelines 2018.⁵ All patients received a dose of MA 160 mg daily for a minimum of 6 months and were evaluated by hysteroscopy-guided biopsy and ultrasounds every 3 months until achieving CR. Next, follow-up was performed every 3 months until pregnancy was obtained. Only suspected single lesions (cancerous polyp or neof ormation) were hysteroscopically removed before progestin treatment with the Neoplasia Endometrium Myometrium organized sections (NEMos) technique.^{1,6} Multifocal lesions were treated with MA alone.

RESULTS: The median follow-up time was 36 months (range, 6–150 months). A total of 82 patients (96.5%) achieved CR. The mean treatment duration for achieving CR was 4.51 months (range, 3–18 months). Hysteroscopic removal of EAH/EIN or EEC before therapy was the only factor significantly associated with shorter treatment duration to achieve CR ($P=.001$). Patients who underwent hysteroscopic resection plus MA (n=15) or MA therapy alone (n=67) achieved CR in 3.4 months (range, 3–18 months) and 4.75 months (range, 3–18 months),

FIGURE
Cumulative relapse rate according to hysteroscopic resection plus MA vs MA alone



Patients with a single endometrial lesion removed by hysteroscopy with the NEMos technique before progestin therapy had a longer time to relapse than patients treated with progestin therapy alone. Single lesion: 15 entered, 5 relapsed; multifocal lesion: 65 entered, 46 relapsed. Patients who were treated with hysteroscopic resection plus MA had a median relapse of 33 months (range, 6–150 months) vs patients treated with MA alone who had a median relapse of 18 months (range, 6–108 months) ($P=.043$). The relative risk of relapse was estimated by Cox univariate analysis; however, statistical significance was not reached ($P=.054$). Univariate Cox regression analysis showed that the surgical removal of EAH/EIN or EEC as a single lesion (neof ormation or cancerous polyp) before therapy was the only factor significantly associated with shorter treatment duration to achieve CR (OR, 1.36; 95% CI, 1.13–1.65; $P=.001$). Patients who underwent hysteroscopic resection plus MA or MA therapy alone achieved CR in 3.4 months (range, 3–18 months) and 4.75 months (range, 3–18 months), respectively.

CI, confidence interval; CR, complete response; EAH, endometrial atypical hyperplasia; EEC, early-stage endometrial cancer; EIN, endometrioid intraepithelial neoplasia; MA, megestrol acetate; NEMos, Neoplasia Endometrium Myometrium organized sections; OR, odds ratio.

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respectively. The cumulative relapse rate was 62% (51/82) and the median time to relapse was 21 months (28 months for EAH/EIN and 21 months for EEC). Patients with lesions removed by hysteroscopy plus MA relapsed later (average, 38 months; median, 33 months; range, 6–150

months) than patients who were treated with MA alone (average, 27 months; median, 18 months; range, 6–108 months) ($P=.043$) (Figure). Among the 82 patients who achieved CR, 52 patients planned for parenthood, and 26 patients (50%) achieved at least 1 pregnancy. Only 4 patients received in vitro fertilization. Spontaneous miscarriage rate was 17% (9 out of 52 cases) and live birth rate was 32.7% (17 out of 52 cases), respectively.

CONCLUSION: In this study, we report our institutional experience with a large series of patients with EAH/EIN ($n=49$) and EEC ($n=36$) eligible for fertility-sparing treatment with MA alone or combined with NEMOs hysteroscopic resection.^{1,5} We found that hysteroscopic resection of EAH/EIN or EEC in combination with oral progestin therapy was significantly associated with shorter treatment duration to achieve CR and longer time to relapse than treatment with progestin therapy alone. This large, single-institution study provides convincing data on the efficacy of MA plus hysteroscopic resection in conservative treatment of both patients with EAH/EIN and EEC, which will have to be confirmed in a prospective multi-institutional trial.

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REFERENCES

- Mazzon I, Corrado G, Masciullo V, Morricone D, Ferrandina G, Scambia G. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. *Fertil Steril* 2010;93:1286–9.
- Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2012;207:266.e1–12.
- Fan Z, Li H, Hu R, Liu Y, Liu X, Gu L. Fertility-preserving treatment in young women with grade 1 presumed stage IA endometrial adenocarcinoma: a meta-analysis. *Int J Gynecol Cancer* 2018;28:385–93.
- Falcone F, Laurelli G, Losito S, Di Napoli M, Granata V, Greggi S. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. *J Gynecol Oncol* 2017;28:e2.
- Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine neoplasms, version 1. 2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16:170–99.
- Mazzon I, Masciullo V, Scambia G, Ferrandina G, Corrado G. Long term survival of young endometrial cancer patients desiring fertility preservation and treated with hysteroscopic resection followed by hormone therapy (NEMO technique). *Int J Gynaecol Obstet* 2020;151:305–7.

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