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ORIGINAL ARTICLE

Curative effects of hysteroscopic resection combined with progesterone on early-stage endometrial cancer and its prognosis

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Summary

Purpose: *To explore the clinical efficacy of hysteroscopic resection combined with megestrol acetate in the treatment of patients with early-stage endometrial cancer (EC) and its prognosis.*

Methods: *130 patients with early-stage EC were divided into two groups: MA group (hysteroscopic resection combined with megestrol acetate, n=65) and Control group (hysteroscopic resection alone, n=65). The clinical efficacy, serum carbohydrate antigen 125 (CA125) level and incidence of adverse reactions were compared between the two groups, and the patients' pregnancy status, pregnancy outcome, survival status and tumor recurrence were recorded through follow-up.*

Results: *The curative effect was assessed in all patients after treatment. The overall response rate was 83.1% (54/65) and 65.2% (43/65), respectively, in MA group and Control group, which was significant better in MA group than that in Control group. After treatment, the serum CA125 levels markedly declined in both groups. The pregnancy rate in MA group was obviously higher than in Control group. The follow-up results revealed that the 5-year overall survival (OS) was 83.1% (54/65) and 81.5% (53/65) and the progression-free survival (PFS) was 76.9% (50/65) and 73.8% (48/65), respectively, in MA group and Control group.*

Conclusion: *Hysteroscopic resection combined with megestrol acetate has superior clinical efficacy to hysteroscopic resection alone in the treatment of patients with early-stage EC, which can greatly increase the success rate of pregnancy and reduce the serum CA125 level. However, thelong-term survival and PFS of patients had no significant differencesbetween the two treatment methods.*

Key words: *hysteroscopic resection, megestrol acetate, endometrial cancer, early stage, curative effect*

Introduction

Endometrial cancer (EC) is a clinically common malignant tumor of the female reproductive system, which accounts for about 20-30% of all types of malignant tumors in females [1]. In recent years, its incidence rate has gradually increased showing a younger trend, and more than 70% of patients even have no childbearing history. Therefore, preservation of fertility has become a clinical problem urgently to be solved [2,3]. The clinical treatment of early-stage EC is dominated by operation, and hysteroscopic resection is characterized by small trauma and little bleeding, which has been widely applied in clinical practice. However, there are deficiencies such as a high postoperative recurrence rate and a high metastasis rate of cancer cells [4,5]. Megestrol acetate can directly act on the endometrium to promote the apoptosis of cancer cells [6]. It has been found that hysteroscopic resection com-

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bined with progesterone therapy can preserve the fertility of patients with EC, with a good effect, but EC is prone to recurrence after operation [7,8].

In the present study, the clinical data of 130 patients with early-stage EC were retrospectively analyzed, so as to explore the efficacy and safety of hysteroscopic resection combined with megestrol acetate, and analyze the influencing factors for the prognosis of patients.

Methods

General data

The clinical data of 130 patients with early-stage EC were collected. Inclusion criteria: 1) patients diagnosed with well-differentiated endometrioid adenocarcinoma through postoperative histopathological examination, 2) those with no cervical involvement and myometrial invasion of lesions shown in MRI, and no extrauterine lesions (FIGO stage IA), 3) those aged <40 years old, without childbearing history or still with childbearing intention, and 4) those positive for progesterone receptor (PR). Exclusion criteria: 1) patients in FIGO stage IB or above, 2) those treated with hormone therapy, neoadjuvant chemotherapy or radiotherapy before operation, 3) those complicated with severe dysfunction of the heart, lung, liver or kidney, coagulation dysfunction, immune system disorder or infectious disease, 4) those complicated with other tumors, or 5) those with neurological dysfunction. All patients were divided into MA group (hysteroscopic resection combined with megestrol acetate, n=65) and Control group (hysteroscopic resection alone, n=65) according to different therapeutic regimens. The patients were aged 25-39 years (mean 30.29±7.17). Clinical baseline data had no statistically significant differences between the two groups (p>0.05), and they were comparable at the baseline (Table 1). All patients enrolled were informed in accordance with the *Declaration of Helsinki*, and signed the informed consent form. This study was approved by the ethics committee of our hospital.

Treatment methods

The patients in the Control group were treated with hysteroscopic resection: After subarachnoid anesthesia, the cervix was gradually expanded with a #6-10 expanding-uterus stick. The instruments, reagents and parameters used were as follows: a 8.5 mm bipolar hysteroscope (purchased from Olympus, Japan), 0.9% sodium chloride solution as uterine distention media, uterine distention pressure at 70-110 mmHg (1 mmHg=0.133 kPa), uterine distention flow rate of 200-250 mL/min, resection power of 260-320 W, and electrocoagulation power of 200 W. The endometrial lesions and superficial muscular layer 3 mm under the lesion were excised with the resection loop perpendicularly, and the excised tissues were taken out under the hysteroscope, followed by pathological examination. After it was confirmed that there were no residual lesions, uterine distention pressure was reduced, whether there was active bleeding was checked, hysteroscope was withdrawn, and uterine distention fluid was released.

In MA group, megestrol acetate (Qingdao GuoHai Biological Pharmaceutical Co., Ltd., NMPN H20073612, 80 mg) was given combined with hysteroscopic resection. The procedure of hysteroscopic resection was the same as that in Control group. After operation, megestrol acetate was orally taken at 80mg/time, twice a day for 6 months.

Observation indexes

The clinical efficacy after treatment was evaluated in the two groups. Complete response (CR): Tumor disappeared without new lesions. Partial response (PR): Tumor regression >50% compared with that before treatment. Stable disease (SD): Tumor regression ≤50% compared with that before treatment, or tumor expansion ≤25%. Progressive disease (PD): Tumor expansion >25% compared with that before treatment or appearance of new lesion(s). Total response rate=(CR+PR)/total cases×100%.

Before and after operation, 3 mL of venous blood was drawn and centrifuged in the two groups, and the serum was collected. Then carbohydrate antigen 125 (CA125) was detected by Bayer 180 chemiluminescence

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*MA group (n=65)* n (%)	*Control group (n=65)* n (%)	*p value*
Age, years	31.13±7.47	29.72±6.61	0.257
BMI (kg/m^2)	26.63±4.84	27.37±4.49	0.368
Irregular menstruation	44 (67.7)	48 (73.8)	0.563
Infertility	16 (24.6)	21 (32.3)	0.437
PCOS	20 (30.8)	24 (36.9)	0.578
Insulin resistance	22 (33.8)	17 (26.2)	0.444
Systemic disease			
Hypertension	10 (15.4)	7 (10.8)	0.604
Diabetes mellitus	12 (18.5)	9 (13.8)	0.534
Family history of cancer	6 (9.2)	11 (16.9)	0.298

MA: megestrole acetate, BMI: body mass index; PCOS: polycystic ovary syndrome.

method using the kit purchased from Beijing Jingmei Bioengineering Co., Ltd (Beijing, China). The incidence of treatment-related adverse reactions was compared between the two groups.

EC patients achieving response at 3 months after treatment were followed up continuously for 5 years. In the first 1-2 years after treatment, the patients were subjected to pelvic CT or MRI once every 3 months and B-ultrasound every 6 months. After 2 years, vaginal cytological examination was performed every 6-12 months and pelvic CT or MRI once a year. The pregnancy status and pregnancy outcome were compared between the two groups. During the follow-up period, patients achieving CR at 1 year after operation were encouraged to actively prepare for pregnancy or adopt assisted reproductive technology, and the patients' pregnancy status and pregnancy outcome were recorded. The postoperative survival status and tumor recurrence were recorded. Progression-free survival (PFS) refers to the duration from the start of treatment to the first PD or death of any cause, and overall survival (OS) refers to the duration from the start of chemotherapy to death or the last follow-up. Appearance of cancer cells or atypical cells or distant metastasis found in pathological examination within 6 months after operation indicated recurrence [10].

Statistics

SPSS 22.0 software was used for statistical analyses. Measurement data were expressed as mean±standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was performed to detect whether the difference in survival rate was statistically significant between the two groups. P<0.05 suggested statistically significant difference.

Results

Comparison of clinical efficacy

The curative effect was assessed in all patients after treatment. In the MA group there were 29 cases (44.6%) of CR, 25 cases (38.5%) of PR, 8 cases (12.3%) of SD, and 3 cases (4.6%) of PD, with an overall response rate of 83.1% (54/65). In the Control group, there were 23 cases (35.4%) of CR, 20 cases (30.8%) of PR, 16 cases (24.6%) of SD, and 6 cases (9.2%) of PD, with an overall response rate of 65.2% (43/65). It can be seen that the total response rate was significant better in the MA group than that in the Control group, showing a statistically significant difference (p=0.043) (Table 2).

Comparison of adverse reactions between the two groups

The main adverse reactions of patients treated with MA included skin rash, mild liver function damage, elevation in fasting blood glucose, weight gain and gastrointestinal reactions, all of which were in grade I-II and improved after symptomatic treatment. There was no statistically significant difference in the incidence rate of adverse reactions between the two groups (p>0.05).

Comparison of serum CA125 level before and after treatment between the two groups

No statistically significant difference was found in the serum CA125 level between the two groups before treatment (p>0.05). After treatment, the serum CA125 level declined from 40.24±5.87 U/mL

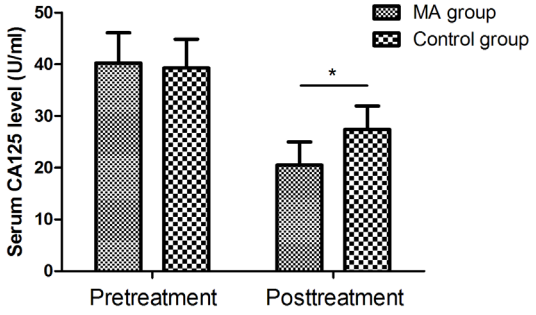

Figure 1. Comparison of pretreatment and posttreatment serum CA125 level of the studied patients. The difference between pretreatment serum CA125 level of patients in MA group and Control group had no statistical significance. Serum CA125 level of patients were significantly decreased after treatment. Posttreatment serum CA125 level of patients in MA group was significantly lower than that of Control group. *p<0.05.

Table 2. Comparison of tumor response of patients in the two studied groups

Parameters	*MA group (n=65)* *n(%)*	*Control group (n=65)* *n(%)*	*p value*
CR	29 (44.6)	23 (35.4)	
PR	25 (38.5)	20 (30.8)	
SD	8 (12.3)	16 (24.6)	
PD	3 (4.6)	6 (9.2)	
ORR (CR + PR)	54 (83.1)	43 (65.2)	0.043

MA: megestrole acetate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate.

Table 3. Comparison of pregnancy rate and pregnancy outcome of patients in the two studied groups

Parameters	*MA group (n=65)* *n(%)*	*Control group (n=65)* *n(%)*	*p value*
Pregnancy rate	57 (87.7)	44 (67.7)	0.011
Natural pregnancy	39 (68.4)	28 (63.6)	
ART pregnancy	18 (31.6)	16 (36.4)	
Pregnancy outcome			0.473
Abortion	4 (7.0)	4 (9.1)	
Premature delivery	3 (5.3)	5 (11.4)	
Full-term delivery	50 (87.7)	35 (79.5)	

MA: megestrole acetate, ART: assisted reproductive technology.

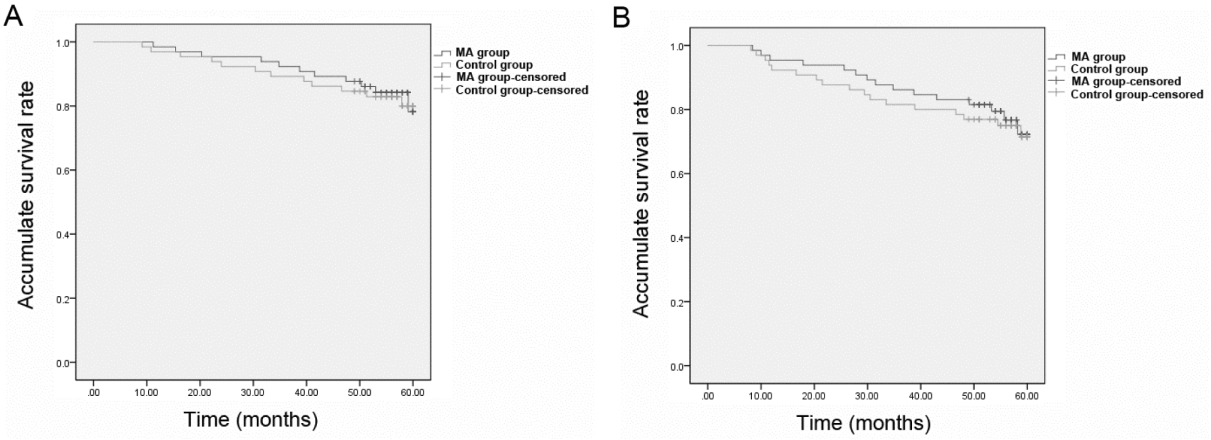

Figure 2. Kaplan-Meier survival curves of patients in MA group and Control group. The difference between overall survival rate **(A)** and progression free survival rate **(B)** of patients in MA group and Control group had no statistical significance (p=0.614,p=0.509).

and 39.31±5.56 U/mL to 20.48±4.49 U/mL and 27.38±4.54 U/mL, respectively, in the MA group and Control group (p<0.05), which was significantly lower in the MA group than in the Control group, showing a statistically significant difference (p<0.001) (Figure 1).

Comparison of pregnancy status and pregnancy outcome between the two groups

During the follow-up period, the pregnancy rate in the MA group [87.7% (57/65)] was obviously higher than in the Control group [67.7% (44/65)] (p=0.011). Natural pregnancy and assisted pregnancy accounted for 68.4% (39/65) and 63.6% (28/65), 31.6% (18/65) and 36.4% (16/65) in the total, respectively, in the MA group and Control group. Among pregnant patients, the abortion, premature delivery and full-term delivery accounted for 7.0% and 9.1%, 5.3% and 11.4%, 87.7% and 79.5%, respectively, in the MA group and Control group, displaying no statistically significant differences in pregnancy outcomes between the two groups (p=0.473) (Table 3).

Follow-up results of survival status

All patients were followed up for 8-60 months until May 2020. In the MA group and Control group, the 1-year, 3-year and 5-yearOS was 98.5% (64/65) and 96.9% (63/65), 92.3% (60/65) and 89.2% (58/65), 83.1% (54/65) and 81.5% (53/65), and PFS was 95.4% (62/65) and 92.3% (60/65), 86.2% (56/65) and 81.5% (53/65), 76.9% (50/65) and 73.8% (48/65), respectively. The survival curves of the two groups were plotted using the Kaplan-Meier method. The results of log-rank test showed no statistically significant differences in OS and PFS between the two groups (p=0.614, p=0.509) (Figure 2).

Discussion

EC frequently occurs in postmenopausal women. However, with changes in social rhythms and lifestyles, the incidence rate of the disease has shown an increasingly younger trend in the clinic, and patients aged below 40 years old account for 3-14 %, most of whom have the desire

to preserve the fertility, bringing new requirements to hysteroscopic surgery [9,10]. Traditional total hysterectomy combined with bilateral adnexectomy, pelvic and peritoneal lavage cytology and retroperitoneal lymphadenectomy can minimize recurrence and remove the lesions, but the fertility of patients is also deprived, causing pain to patients and affecting the quality of life after operation. The uterus of early-stage EC patients with a strong fertility desire can be retained under strict indications. However, there has been no unified standard regimen of conservative treatment yet in China and beyond. At present, high-dose progesterone is mostly used in conservative treatment, which meets the desire of patients to preserve the fertility, but it has a long treatment cycle, a low effective rate and a high recurrence rate [11]. Some authors proposed hysteroscopic resection performed before the application of progesterone [12].Although the current viewpoint on the treatment of early-stage EC with resection combined with progesterone is not uniform, it has been found in clinical exploration that its clinical effect on early patients is more obvious, without leading to poor prognosis. Based on the pathological characteristics of patients with early-stage EC (stage Ia, well-differentiated, ER^+ and PR^+), hysteroscopic resection combined with progesterone is more advisable, especially for young women with childbearing demand [13].

It is reported that after 14 years of follow-up, laparoscopic surgery has no adverse effects on the 5-year survival rate and prognosis of patients with EC [14]. Progesterone can directly produce a pharmacological effect on the endometrium to promote changes in the growth process of the endometrium, and accelerate the apoptosis of cancer cells, thereby inhibiting the growth and proliferation of cancer cells, and exerting an effective anti-tumor effect [15]. Compared with traditional total resection, progesterone combined with hysteroscopic resection is able to not only preserve the integrity of uterine tissues and reduce the risk of loss of fertility, but also inhibit the tissue hyperplasia around the focus, lesions and recurrence, exerting a therapeutic effect. The main progestogens used in the conservative treatment of EC in China and beyond are MPA and MA [16]. The daily doses of MA and MPA are 40-240 mg and 100-800 mg, respectively, in China, while they are 80-160 mg and 200-800 mg, respectively, in foreign countries. In a large number of studies, 160 mg/d MA or 250 mg/d MPA is adopted. In this study, all patients underwent hysteroscopic resection. In MA group, the patients received MA at 160 mg/d for 6 months after operation, and the total response rate was 83.1% (54/65), which was greatly higher than that in Control group [65.2% (43/65)] (p=0.043), basically consistent with the research results of Zhou et al [17] and Ohyagi-Hara et al [18], indicating that hysteroscopic resection combined with high-dose progesterone is effective for patients with early-stage EC.

During the follow-up period, the pregnancy rate in MA group was far higher than that in Control group [87.7% (57/65) *vs.* 67.7% (44/65)] (p=0.011), and the natural pregnancy rate was also higher than that in Control group, but the difference was not statistically significant. There was no statistically significant difference in pregnancy outcomes between the two groups (p=0.473) and it can be concluded that hysteroscopic resection combined with progesterone can protect the patient's fertility to the greatest extent. Under direct vision, the conditions of the cervical canal and uterine cavity can be observed more intuitively in hysteroscopic surgery, which is characterized by less trauma, less bleeding and quicker postoperative recovery. Moreover, hysteroscopic surgery is minimally invasive and visible, so it can effectively reduce the damage to the body, and the entry depth and cutting direction can be adjusted to reduce the damage to the patient's fertility, there by raising the re-pregnancy rate of patients.

CA125 produced by the coelomic epithelium during embryonic development is widely present on the surface of tumor cells in patients with EC, which can be used for disease detection and prognostic evaluation [19]. The results of this study manifested that the serum CA125 level in the MA group was far lower than in the Control group after treatment. The 5-year follow-up results showed that there were no statistically significant differences in OS and PFS between the two groups (p=0.614, p=0.509).

Garg et al [20] found that higher age, longer maximum diameter of tumor, lower uterine infiltration, low grade of cell differentiation, myometrial infiltration, lymphovascular space invasion and non-endometrioid adenocarcinoma are risk factors for poor prognosis or recurrence. At the same time, Park et al [21] argued that obese patients with a body mass index≥ 25 kg/m^2 have a higher risk of recurrence, and obesity is often associated with EC-induced metabolic syndrome. Therefore, hysteroscopic resection is not recommended for patients with the above risk factors. If the patients do have a strong fertility desire, experimental hysteroscopy can be conducted under the following indications: age ≤40 years old, endometrioid adenocarcinoma or adenosquamous, no

extrauterine lesions, no myometrial infiltration or cervical involvement, moderately or highly differentiated, PR+, a normal level of serum CA125, and normal function of other organs. In addition, Laurelli et al [22] found that EC may recur in some patients within a short period of time after hysteroscopic resection and delivery. In the present study, the sample size was limited, and the follow-up content was not comprehensive enough, so the conclusions made may be biased.In the future, it is necessary to design rigorous, highly-reliable and large-sample prospective clinical research to support the conclusions of this study.

Conclusions

Hysteroscopic resection combined with megestrol acetate has superior clinical efficacy to hysteroscopic resection alone in the treatment of patients with early-stage EC, which can greatly increase the success rate of pregnancy and reduce the serum CA125 level. However, the long-term survival and PFS of patients have no significant differences between the two treatment methods.

Conflict of interests

The authors declare no conflict of interests.

References

1. Moore K, Brewer MA. Endometrial Cancer: Is This a New Disease? Am Soc Clin Oncol Educ Book 2017;37:435-42.
2. Chen L, Xiang Q. Effect of postoperative sequential chemoradiotherapy and concurrent chemoradiotherapy in treating advanced endometrial cancer. JBUON 2020;25:2271-8.
3. Lee YC, Lheureux S, Oza AM. Treatment strategies for endometrial cancer: current practice and perspective. Curr Opin Obstet Gynecol 2017;29:47-58.
4. Suri V, Arora A. Management of Endometrial Cancer: A Review. Rev Recent Clin Trials 2015;10:309-16.
5. Passarello K, Kurian S, Villanueva V. Endometrial Cancer: An Overview of Pathophysiology, Management, and Care. Semin Oncol Nurs 2019;35:157-65.
6. Wen W, Lowe G, Roberts CM et al. Pterostilbene, a natural phenolic compound, synergizes the antineoplastic effects of megestrol acetate in endometrial cancer. Sci Rep 2017;7:12754.
7. De Marzi P, Bergamini A, Luchini S et al. Hysteroscopic Resection in Fertility-Sparing Surgery for Atypical Hyperplasia and Endometrial Cancer: Safety and Efficacy. J Minim Invasive Gynecol 2015;22:1178-82.
8. Yang HC, Liu JC, Liu FS. Fertility-preserving treatment of stage IA, well-differentiated endometrial carcinoma in young women with hysteroscopic resection and high-dose progesterone therapy. Taiwan J Obstet Gynecol 2019;58:90-3.
9. Won S, Kim MK, Seong SJ. Fertility-sparing treatment in women with endometrial cancer. Clin Exp Reprod Med 2020;47:237-44.
10. 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.
11. Yamagami W, Susumu N, Makabe T et al. Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility? J Gynecol Oncol 2018;29:e21.
12. Fan Z, Li H, Hu R et al. 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.
13. Wang CJ, Chao A, Yang LY et al. Fertility-preserving treatment in young women with endometrial adenocarcinoma: a long-term cohort study. Int J Gynecol Cancer 2014;24:718-28.
14. Vilos GA, Edris F, Al-Mubarak A et al.. Hysteroscopic surgery does not adversely affect the long-term prognosis of women with endometrial adenocarcinoma. J Minim Invasive Gynecol 2007;14:205-10.
15. Yang B, Xu Y, Zhu Q et al. Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrial cancer. Gynecol Oncol 2019;153:55-62.
16. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol 2004;95:133-8.
17. Zhou R, Yang Y, Lu Q et al. Prognostic factors of oncological and reproductive outcomes in fertility-sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin in Chinese patients. Gynecol Oncol 2015;139:424-8.
18. Ohyagi-Hara C, Sawada K, Aki I et al. Efficacies and pregnant outcomes of fertility-sparing treatment with medroxyprogesterone acetate for endometrioid adenocarcinoma and complex atypical hyperplasia: our experience and a review of the literature. Arch Gynecol Obstet 2015;291:151-7.
19. Jiang T, Huang L, Zhang S. Preoperative serum CA125: a useful marker for surgical management of endometrial cancer. BMC Cancer 2015;15:396.

20. Garg K, Soslow RA. Endometrial carcinoma in women aged 40 years and younger. Arch Pathol Lab Med 2014;138:335-42.
21. Park JY, Kim DY, Kim JH et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer 2013;49:868-74.
22. Laurelli G, Di Vagno G, Scaffa C et al Conservative treatment of early endometrial cancer: preliminary results of a pilot study. Gynecol Oncol 2011;120:43-6.