Fertility Preserved Hysteroscopic Approach for the Treatment of Stage Ia Endometrioid Carcinoma

Fangfang Wang, MD,* Aijun Yu, MD,* Haichao Xu, MD, PhD,† Xiaojing Zhang, MD,* Li Li, MD, PhD,* Hanmei Lou, MD,* Hua Yu, MD,* and Jun Lin, MD, PhD‡

Objective: This study aims to explore the feasibility of a hysteroscopic procedure combined with progestin therapy in young patients with stage Ia endometrioid carcinoma (EC) to avoid sterilization.

Materials and Methods: Eleven young women with stage Ia EC (International Federation of Gynecology and Obstetrics grade 1) who were treated with a hysteroscopic approach combined with progestin from July 2004 to June 2016 were retrospectively analyzed and followed up to monitor their general recovery and pregnancy outcome.

Results: The patients' median age was 27.3 years (range, 25–39 years). Comorbidities consisted of primary infertility in 8 patients, polycystic ovary syndrome in 4, uterine fibroids in 2, and diabetes in 1. The results of immunohistochemical analysis were positive for all estrogen and progestin receptors. After treatment, 9 patients attained complete remission, and 2 patients achieved partial remission. The results of peritoneal cytology in 4 patients were negative. As of this writing, 6 of the 11 patients have given birth to 7 infants, and 1 patient had an ectopic pregnancy. Two patients ultimately underwent radical resection. The average follow-up time was 82.3 months (range, 15 to 152 months), and all patients remain disease-free.

Conclusions: Hysteroscopic surgery combined with progestin treatment for stage Ia EC in young patients to avoid sterilization was practical and may represent a new option for patients with stage Ia EC who wish to preserve their fertility.

Key Words: Endometrioid carcinoma, Fertility preservation, Hysteroscopy, Progestin

Endometrioid carcinoma (EC) is one of the most common malignant tumors, accounting for about 8% of cancers in women.[1,2] Although EC is more common in perimenopausal women, 5% to 7% of cases occur in women younger than 40 years of age.[3–6]

Total hysterectomy with bilateral salpingo-oophorectomy and lymph node assessment is the standard treatment for early EC, leaving patients sterile after this almost curable disease.[7,8] Therefore, for patients with stage Ia EC who wish to remain fertile, progestin seems to be a good alternative therapy in that some young patients test positive for the progestin receptor on immunochemical analysis and have a good prognosis.[9] Even though few relative reports exist, hysteroscopy might be a good approach to fertility-sparing management of EC because it offers

Departments of *Gynecologic Oncology, †Musculoskeletal Oncology, Zhejiang Cancer Hospital, and ‡Obstetrics and Gynecology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China.

Address correspondence and reprint requests to Fangfang Wang, MD, Department of Gynecologic Oncology, Zhejiang Cancer Hospital, No 1 Banshan East Rd, Gongshu District, Hangzhou 310000, People's Republic of China. E-mail: wangfangf@zju.edu.cn.

The authors declare no conflicts of interest.

an obvious advantage over dilatation and curettage (D&C) in localizing lesions in the uterus, avoiding endometrial damage and minimizing disturbance to implantation.[10–13] We investigated the effect of hysteroscopic resection combined with progestin therapy in a series of young women with early-stage EC who wished to preserve their fertility.

MATERIALS AND METHODS

Research Subjects

The study was approved by the institutional review board of Zhejiang University Women's Hospital and Zhejiang Cancer Hospital. All participants signed an informed-consent form after thorough counseling. The clinical information was collected in these hospitals from July 2004 to June 2016 including patient presentation, diagnostic method, pathological results, peritoneal cytology (PC), treatment, and follow-up results for survival rate and pregnancy outcome. These data were then analyzed retrospectively.

The inclusion criteria were as follows. (1) Patients had undergone hysteroscopic resection for lesion biopsy as the initial treatment. (2) Patients met the following conditions for the treatment of fertility preservation[3,4,14]: (a) nulliparity, age less than 40 years, and a desire to retain fertility; (b) histologic classification of cancerous tissue as well-differentiated endometrioid adenocarcinoma (International Federation of Gynecology and Obstetrics [FIGO] grade 1) and confirmation of progestin receptor positivity; (c) an absence of myometrium invasion, cervical involvement, or extrauterine lesions on transvaginal ultrasound and magnetic resonance imaging (MRI) studies, in accordance with FIGO stage Ia; and (d) normal liver and kidney function. (3) Patients had undergone regular hysteroscopic examination and electrosurgery, combined with conservative treatment with progestin.

Hysteroscopy Procedure

After epidural anesthesia and cervical dilatation, the uterus was distended with 5% glucose solution or mannitol solution, at 80 to 100 mm Hg perfusion pressure. The patient first underwent hysteroscopy (Richard Wolf GmbH, Germany) to observe the cervical canal, uterine cavity, and endometrial tissue and to localize lesions. Using the loop electrode, the lesions and the endomyometrium underlying the lesion were completely resected and sent for pathological assessment. The operation time was controlled at about 30 min.

Evaluation Criteria

The evaluation criteria of this study were as follows[15]: (1) complete remission (CR): complete removal of lesions, no cancerous tissues or atypical hyperplasia tissue discernible by hysteroscopy and biopsy; (2) partial remission (PR): pathological classification downgraded from cancer to atypical hyperplasia; (3) no change: lesion remained stable; (4) progression: results of pathology trending toward a higher histological grade, or myometrium and a wider range of invasion, cervical involvement, and extrauterine lesions newly identified; and (5) relapse: emergence of cancer tissue after CR.

Drug Therapy

Five patients were treated with medroxyprogesterone acetate (MPA) of 250 to 500 mg and 4 with megestrol acetate (MGA) of 160 to 320 mg regularly after diagnosis. One patient received MPA of 500 mg (intramuscular) twice weekly, and 1 developed abnormal liver function and was switched to a different regimen after 3 months (see Results section). If patients had not attained CR or PR after progestin treatment for 3 months, they were asked to undergo traditional surgery and were excluded from the study. Indications for withdrawal were either (1) no sign of relapse 3 months after the patient had reached CR or (2) pathological findings that had not worsened after at least 1 year of continuous medication and the desire to become pregnant.

Follow-Up and Surveillance

Follow-up began in the first discharge month, as of March 2017. Observed for surveillance were symptoms, gynecological examination, fertility, pelvic imaging (ultrasound or MRI), and the blood tumor markers (carbohydrate antigen-125 and -199). Hysteroscopy or hysteroscopic electrosurgery were assessed every 3 months until CR. After progestin treatment, all patients were referred to a reproductive specialist. The patients were surveilled every 3 months during the first 2 years after CR and every 6 months thereafter for the next 3 years; all received the medical tests mentioned above, except hysteroscopy. Once tumor relapse was verified, patients underwent surgical resection and were excluded from the study.

RESULTS

General Clinical Features

The median age of the 11 patients was 27.3 years (range, 25–39 years). Irregular menses were the initial complaint in 7 patients; the other 4 had no symptoms and were diagnosed by an incidental imaging examination. Concomitant diseases were primary infertility (PI) in 8 patients, polycystic ovary syndrome (PCOS) in 4, uterine fibroids in 2, and diabetes in 1. No other patients had any history of diabetes or hypertension. All patients were married and had no previous successful delivery. One patient had 2 miscarriages; the others had no pregnancy history. The median body mass index was 23.6 kg/m^2 (range, 18.1–28.6 kg/m^2).

Uterine enlargement was found by pelvic examination in 1 patient; there were no remarkable findings in the other patients. Transvaginal ultrasound examination revealed 1.0 to 2.5 cm endometrial polyps in 8 patients, 5 of whom had increased vascularity within the endometrium; echo guidance found heterogeneous endometrial tissue in 3 patients (Table 1). No myometrial invasion, cervical or lymph node involvement, or extrauterine infiltration were revealed on MRI scans. Also, serum tumor marker levels of all patients were under the limit.

Clinical Observation of Hysteroscopy

We performed cavitary exploration in hysteroscopic surgery in all patients. Nine patients had a uterine cavity length of 8.0 cm or less (6.5 to 8.0 cm), and 2 patients, between 8.5 and 9.0 cm. On hysteroscopy, we observed smooth endometrial polypoid lesions that were soft in texture and locally

TABLE 1. General clinical features of all cases

Number	Age, y	BMI	Menarche, y	PI	PCOS	Myoma	Symptom	Transvaginal Ultrasound
1	27	19.6	12	Yes	Yes	No	Irregular menses	Uterine neoplasm
2	30	19.6	15	Yes	Yes	No	Irregular menses	Uterine neoplasm
3	31	24	16	Yes	No	Yes	No	Uterine neoplasm
4	39	22.7	11	No	No	Yes	Irregular menses	Uterine neoplasm
5	31	23.7	12	Yes	Yes	No	Irregular menses	Heterogeneous
6	28	25.6	13	No	No	No	Irregular menses	Uterine neoplasm
7	25	20.5	13	Yes	No	No	Irregular menses	Hyperplasia
8	26	24.6	15	Yes	No	No	No	Uterine neoplasm
9	26	24.7	12	Yes	No	No	Irregular menses	Uterine neoplasm
10	26	18.1	13	No	No	No	No	Hyperplasia
11	27	28.6	12	Yes	Yes	No	No	Uterine neoplasm

BMI, body mass index.

hypervascular in 8 patients; 1 patient showed small, white, brittle cauliflower excrescences, and the other 2 patients had floating pink endometrioid tissue.

Pathological Results

Well-differentiated endometrioid adenocarcinoma (FIGO grade 1) was diagnosed in all patients. Nine patients had complex endometrial hyperplasia with atypia and local carcinogenesis, 1 had malignant transformation of endometrial polyps, and 1 had endometrial adenocarcinoma with squamous differentiation (Table 2). All resected tissue below the lesion showed no tumor. Immunohistochemical analysis confirmed that both estrogen and progestin receptors were positive.

PC Examination

Four of the 11 patients underwent PC by combined laparoscopy and hysteroscopy (3) or posterior fornix aspiration (1). The former procedure included collection of a 20- to 30-mL peritoneal washing sample after irrigation of the peritoneal and pelvic cavities with 200 mL of normal saline solution. The latter

procedure consisted of collection of 20 mL of peritoneal washing liquid via posterior fornix aspiration after percutaneous peritoneal injection of 50 mL of normal saline solution. No tumor cells were found in the peritoneal lavage fluid (Table 3).

Treatment Outcome and Pregnancy

Five patients received MPA 250 to 500 mg daily, 4 patients received MGA 160 to 320 mg daily, and one patient received MPA 500 mg twice per week by intramuscular injection. One patient developed abnormal liver function after receiving MPA 500 mg/d for 3 months and instead began receiving MGA 320 mg/d and never had any complications. Nine patients had achieved CR after 3 to 12 months of fertility-sparing treatment, and all patients had achieved at least PR within 3 months (Table 2). The average response time was 6 months.

At the end of follow-up, 6 patients had successful pregnancies with 7 infants, and 1 patient had an ectopic pregnancy after ovulation induction. The other 4 patients failed to become pregnant after 1 to 4 attempts at in vitro fertilization and embryo

TABLE 2. Pathological diagnosis by hysteroscopy

Number	Initial Tumor Differentiation	3 mo Later	6 mo Later	9 mo Later	12 mo Later	15 mo Later
1	Well differentiated	CR				
2	Well differentiated	PR	PR	PR	CR	
3	Well differentiated	CR				
4	Well differentiated	PR	PR	CR		
5	Well differentiated	CR				
6	Well differentiated	PR	PR	CR		
7	Well differentiated	PR	PR	PR	PR	PR
8	Well differentiated	PR	PR	PR	PR	PR
9	Well differentiated	CR				
10	Well differentiated	PR	PR	CR		
11	Well differentiated	CR				

TABLE 3. Follow-up of 12 cases

Number	Treatment Time, mo	PR, mo	CR, mo	PC	Method of Pregnancy	Pregnancy Outcome
1	6	3	3	Negative	COH + IUI	1 Term infant by C-sect
2	12	3	12	Negative	IVF-ET	1 Term infant by C-sect
					Spontaneous	1 Term infant by C-sect
3	3	3	3	Negative	IVF-ET	1 Term infant by eutocia
4	9	3	9	N/A	IVF-ET	Not conceived
5	3	3	3	Negative	Spontaneous	1 Term infant by C-sect
6	9	3	9	N/A	COH + IUI	Ectopic pregnancy
7	15	3	N/A	N/A	IVF-ET	Not conceived
8	15	3	N/A	N/A	COH	1 Term infant by eutocia
9	6	3	3	N/A	COH	1 Term infant by C-sect
10	12	3	9	N/A	COH	Not conceived
11	6	3	3	N/A	COH	Not conceived

COH, controlled ovarian hyperstimulation; IUI, intrauterine insemination; C-sect, Caesarean section; IVF-ET, in vitro fertilization and embryo transfer; N/A, not applicable.

transfer or controlled ovarian hyperstimulation and intrauterine insemination (Table 3).

Prognosis

The average follow-up was 82.3 months (range, 15–152 months), and no patients were lost to follow-up. Two patients underwent radical hysterectomy after successful delivery, and the postoperative pathological examination showed no recurrence of the disease. As of March 2017, all 11 patients were disease-free survivors (Table 3).

DISCUSSION

The estrogen dependency of most ECs in young patients may be owing to the long-term lack of counteracting progestin. The pathology of this type of tumor is mainly endometrioid adenocarcinoma with a high expression rate of both estrogen and progestin receptors. The general prognosis of this disease is good, even though many patients have concomitant PI, irregular menstruation, polycystic ovaries, and endometrial hyperplasia.[16] The 11 patients in this study were younger than 40 years of age and had well-differentiated endometrioid adenocarcinomas. Also, immunohistochemical analysis confirmed positivity for both estrogen and progestin receptors. Among the patients studied, 7 had a history of irregular vaginal bleeding, 8 had PI, and 4 had PCOS.

Soliman et al[17] reported that 70% of young patients with EC were childless at their initial diagnosis. The European Society of Gynecological Oncology has published a clinical recommendation for a conservative approach to EC, considering that progestins can offer very good results in treating early-stage EC in nulliparous women who have a strong desire to maintain their fertility.[9,18] However, repeated D&C to obtain histology and monitor the disease may cause endometrial impairment and failure of implantation. Hysteroscopy is a means to view directly the cervical canal and uterine cavity and the extent of tumor invasion, thus greatly improving the accuracy of preoperative staging. Some large-sample and multicenter

clinical research studies have shown the sensitivity of EC diagnosed by hysteroscopy to be 60.9% to 72.4%; the specificity was 94.7% to 99.9%, and the accuracy was 97.1%. In addition, excision of focus by hysteroscopy can reduce tumor load and improve the treatment effect. These studies have led to the acceptance of hysteroscopy as the criterion standard for the diagnosis of endometrial lesions.[19–23] All patients in our study underwent hysteroscopy, and all received treatment with progestins after EC was confirmed. We found that 81.8% patients achieved CR after 3 to 12 months of treatment.

Pregnancy is the ultimate goal of fertility-sparing treatment. Gunderson et al[24] reported that the pregnancy rate in the group receiving progestins was 35.7% (78/218). In this study, 6 patients had successful delivery of seven infants, with a pregnancy rate of 54.5%, consistent with the result of a prospective study reported by Mazzon et al.[18] However, because our sample size was too small to provide valid evidence for evidence-based medicine, we still need more multicenter, large population studies to evaluate the advantages of combined hysteroscopy and progestin in stage Ia EC over progestin treatment alone.

Because the uterus must be filled with fluid to maintain intrauterine pressure in the procedure of hysteroscopy, whether it would increase the PC positive rate and thus affect prognosis is controversial.[25–33] Zerbe et al[26] and Bradley et al[28] performed retrospective analysis on the PC-positive rate of EC patients with a history of preoperative hysteroscopy and compared with the patients without preoperative hysteroscopy, and they found that the hysteroscopy group had a higher PC-positive rate than the control group. Arikan et al[34] used surgical specimens from EC patients to simulate the process of hysteroscopy in vitro and observed that perfusate leaked from tubes in 83% of the uterine specimens. They found tumor cells in 71% of the leakage fluid samples, and 42% of the cells showed viability. In contrast, some reports have stated that hysteroscopy does not increase the PC-positive rate or affect the prognosis. Obermair et al[27,31,35,36] conducted a multicenter study to compare the PC results of patients with and without hysteroscopy;

their results showed no statistical difference between the 2 groups. Moreover, throughout the follow-up, they also found no significant difference in the mortality rate from EC. Some scholars considered that the prognosis was unaffected by PC positivity if the patient had no other metastases.[37,38] Revel et al[29] reviewed the literature on Medline about the risk of hysteroscopy in EC patients from 1980 to 2001 and concluded that there was as yet no confirmation that the endometrial cells in the peritoneum are washed by the uterine lavage fluid, and no prospective randomized trial has confirmed that hysteroscopy causes cancer spread. In addition, Revel et al[29] found it difficult to determine any difference in EC patients' prognosis between those who underwent hysteroscopy and those who underwent other traditional examinations such as D&C. We summarized recent studies on the abdominal dissemination of EC that might be caused by hysteroscopy and found that, in general, PC positivity had a prognostic significance only in EC patients with extrauterine metastases; otherwise, it would not affect patient survival.[25,35–39]

Because of the potential risk of tumor spread, the surgeon should not only be gentle and quick in the process of hysteroscopy for EC patients but also should attempt as much as possible to reduce intrauterine pressure without affecting the operative field. Evidence-based medicine has provided no data to recommend that intrauterine pressure should be lower than a certain value to avoid the spread of endometrial cells. Chang et al[40] concluded from a meta-analysis that, at intrauterine pressures of 100 mm Hg or lower, there would be no increase in the risk of cancer cells spreading into the abdominal cavity. Bacskó et al[41] reported that, at intrauterine pressures of greater than 80 mm Hg, the perfusion fluid would flow through the fallopian tubes into the abdominopelvic cavity. In our study, all patients underwent successful hysteroscopy when the intrauterine pressure was maintained at 80 to 100 mm Hg, the procedure time was controlled in 30 minutes, and the PC results were negative for the 4 patients who underwent the procedure.

The ideal result of fertility preservation in EC patients should be both a successful pregnancy and a good outcome. However, whether conservative treatment would worsen the prognosis is dubious. Because young women's ECs are well differentiated and restricted to the uterus, the disease progresses slowly. Hence, we emphasize the importance of monitoring the process of treatment. Patients whose endometrial biopsy reveals a poor response to conservative treatment should expeditiously undergo hysterectomy. Indeed, most reports have discovered that patients with a poor response to conservative treatment or with relapse after treatment rarely had extrauterine metastases.[12,42] Other studies reported on patients with well-differentiated EC for whom conservative treatment had been unsuccessful and who had promptly undergone hysterectomy; on long-term follow-up, none of these patients had died from tumor.[5,43,44] Nevertheless, because of the small sample sizes of these studies, some researchers have also advanced the objection that the risk of disease progression is as high as 5% to 6% over the course of conservative treatment.[3,10] Furthermore, some studies reported that one third of patients who underwent conservative treatment ultimately had disease recurrence,

which is a significantly higher proportion than that in patients who underwent radical surgery.[15,17,24,45–49] Consequently, we recommend that all patients who receive conservative treatment be followed closely and undergo radical surgery immediately after giving birth.

CONCLUSION

Because of the advantages of performing uterine biopsy under dynamic and direct vision, we believe that hysteroscopy is one of the most accurate and reliable methods to diagnose intrauterine lesions, especially for early EC. Combined hysteroscopic resection and progestin therapy is an innovative and feasible treatment for young women with stage Ia EC who wish to preserve their fertility, with regard to improving the pregnancy rate under close follow-up. Overall, hysteroscopy is a safe, reliable, and effective procedure for patients with early EC, but its efficacy requires further confirmation by multicenter studies.

ACKNOWLEDGMENTS

REFERENCES

1. Chen W, Zheng R, Baade PD, et al. Cancer Statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115–132.
2. Kurman RJ, Carcangiu ML, Herrington CS. *WHO Classification of Tumours of Female Reproductive Organs. 4.* Lyon: IARC; 2014:125–135.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
4. Howlader N, Noone AM, Krapcho M. 1975–2012, National Cancer Institute. Available at: http://seer.cancer.gov/archive/csr/1975_2012/. Accessed November 18, 2015.
5. Qi J, Gao GX. The changes of incidence age of patients with cervical and endometrial cancers in the period of 22 years. *Chin J Clin Oncol*. 2001;28:519–521.
6. Kataoka H, Mori T, Yamamoto T, et al. Outcome of fertility-sparing treatment with medroxyprogesterone acetate for atypical hyperplasia and endometrial carcinoma in young Japanese women. *Eur J Gynaecol Oncol*. 2014;35:11–15.
7. Colombo N, Preti E, Landoni F, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2011;22 :vi35–vi39.
8. NCCN Guidelines. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Version 3.2012.
9. Jongen V, Briët J, de Jong R, et al. Expression of estrogen receptor-alpha and -beta and progestin receptor-A and -B in a large cohort of patients with endometrioid endometrial cancer. *Gynecol Oncol*. 2009;112:537–542.
10. Kim YB, Holschneider CH, Ghosh K, et al. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. *Cancer*. 1997;79:320–327.
11. Pinto AB, Gopal M, Herzog TJ, et al. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. *Fertil Steril*. 2001;76:826–829.

12. Ramirez PT, Frumovitz M, Bodurka DC, et al. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. *Gynecol Oncol.* 2004;95:133–138.

13. Yang YC, Wu CC, Chen CP, et al. Reevaluating the safety of fertility-sparing hormonal therapy for early endometrial cancer. *Gynecol Oncol.* 2005;99:287–293.

14. Wang CB, Wang CJ, Huang HJ, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. *Cancer.* 2002;94:2192–2198.

15. Ushijima K, Yahata H, Yoshikawa H, 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;25:2798–2803.

16. Gao JS, Shen K, Lang JH, et al. [Clinical analysis of endometrial carcinoma patients aged 45 years and younger]. *Zhonghua Fu Chan Ke Za Zhi.* 2004;39:159–161.

17. Soliman PT, Oh JG, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. *Obstet Gynecol.* 2005;105:575–580.

18. Mazzon I, Corrado G, Masciullo V, et al. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. *Fertil Steril.* 2010;93:1286–1289.

19. Deckardt R, Lueken RP, Gallinat A, et al. Comparison of transvaginal ultrasound, hysteroscopy, and dilatation and curettage in the diagnosis of abnormal vaginal bleeding and intrauterine pathology in perimenopausal and postmenopausal women. *J Am Assoc Gynecol Laparosc.* 2002;9:277–282.

20. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. *Fertil Steril.* 2003;80: 1315–1324.

21. de Wit AC, Vleugels MP, de Kruif JH. Diagnostic hysteroscopy: a valuable diagnostic tool in the diagnosis of structural intra-cavital pathology and endometrial hyperplasia or carcinoma? Six years of experience with non-clinical diagnostic hysteroscopy. *Eur J Obstet Gynecol Reprod Biol.* 2003; 110:79–82.

22. Cutillo G, Cignini P, Visca P, et al. Endometrial biopsy by means of the hysteroscopic resectoscope for the evaluation of tumor differentiation in endometrial cancer: a pilot study. *Eur J Surg Oncol.* 2007;33:907–910.

23. Siristatidis C, Chrelias C, Salamalekis G, et al. Office hysteroscopy: current trends and potential applications: a critical review. *Arch Gynecol Obstet.* 2010;282:383–388.

24. Gunderson CC, Fader AN, Carson KA, et al. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a system review. *Gynecol Oncol.* 2012;125:477–482.

25. Lo KW, Cheung TH, Yim SF, et al. Hysteroscopic dissemination of endometrial carcinoma using carbon dioxide and normal saline: a retrospective study. *Gynecol Oncol.* 2002; 84:394–398.

26. Zerbe MJ, Zhang J, Bristow RE, et al. Retrograde seeding of malignant cells during hysteroscopy in presumed early endometrial cancer. *Gynecol Oncol.* 2000;79:55–58.

27. Obermair A, Geramou M, Gucer F, et al. Does hysteroscopy facilitate tumor cell dissemination? Incidence of peritoneal cytology from patients with early stage endometrial carcinoma following dilatation and curettage (D & C) versus hysteroscopy and D & C. *Cancer.* 2000;88:139–143.

28. Bradley WH, Boente MP, Brooker D, et al. Hysteroscopy and cytology in endometrial cancer. *Obstet Gynecol.* 2004;104:1030–1033.

29. Revel A, Tsafrir A, Anteby SO, et al. Does hysteroscopy produce intraperitoneal spread of endometrial cancer cells? *Obstet Gynecol survey.* 2004;59:280–284.

30. Selvaggi L, Cormio G, Ceci O, et al. Hysteroscopy does not increase the risk of microscopic extrauterine spread in endometrial carcinoma. *Int J Gynecol Cancer.* 2003;13:223–227.

31. Kudela M, Pilka R, Dzvincuk P, et al. [Risks in hysteroscopy in patients with endometrial carcinoma—a prospective clinical study]. *Ceska Gynekol.* 2002;67:74–78.

32. Yazbeck C, Dhainaut C, Batallan A, et al. [Diagnostic hysteroscopy and risk of peritoneal dissemination of tumor cells]. *Gynecol Obstet Fertil.* 2005;33:247–252.

33. Gu M, Shi W, Huang J, et al. Association between initial diagnostic procedure and hysteroscopy and abnormal peritoneal washings in patients with endometrial carcinoma. *Cancer.* 2000;90:143–147.

34. Arikan G, Reich O, Weiss U, et al. Are endometrial carcinoma cells disseminated at hysteroscopy functionally viable. *Gynecol Oncol.* 2001;83:221–226.

35. Biewenga P, Blok S, Bimie E. Does diagnostic hysteroscopy in patients with stage I endometrial carcinoma cause positive peritoneal washings? *Gynecol Oncol.* 2004;93: 194–198.

36. Soucie JE, Chu PA, Ross S, et al. The risk of diagnostic hysteroscopy in women with endometrial cancer. *Am J Obstet Gynecol.* 2012;207:71.e1–71.e5.

37. Sáinz de la Cuesta R, Espinosa JA, Crespo E, et al. Does fluid hysteroscopy increase the stage or worsen the prognosis in patients with endometrial cancer? A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol.* 2004; 115:211–215.

38. Tebeu PM, Popowski Y, Verkooijen HM, et al. Positive peritoneal cytology in early-stage endometrial cancer does not influence prognosis. *Br J Cancer.* 2004;91:720–724.

39. Cicinelli E, Tinelli R, Colafiglio G, et al. Risk of long-term pelvic recurrences after fluid minihysteroscopy in women with endometrial carcinoma: a controlled randomized study. *Menopause.* 2010;17:511.

40. Chang YN, Zhang Y, Wang YJ, et al. Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis. *Fertil Steril.* 2011;96:957–961.

41. Bacskó G, Csiszár P, Csécsei K. Determination of the functional state of the uterine tube by hysteroscopy. *Orv Hetil.* 1993;134:625–627.

42. Nakao Y, Nomiyama M, Kojima K, et al. Successful pregnancies in 2 infertile patients with endometrial adenocarcinoma. *Gynecol Obstet Invest.* 2004;58:68–71.

43. Gotlieb WH, Beiner ME, Shalmon B, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. *Obstet Gynecol.* 2003;102:718–725.

44. Kaku T, Yoshikawa H, Tsuda H, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. *Cancer Lett.* 2001; 167:39–48.

45. Chiva L, Lapuente F, González-Cortijo L, et al. Sparing fertility in young patients with endometrial cancer. *Gynecol Oncol.* 2008;111():S101–S104.

46. Signorelli M, Caspani G, Bonazzi C, et al. Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. *BJOG.* 2009;116:114–118.

47. Laurelli G, Di Vagno G, Scaffa C, et al. Conservative treatment of early endometrial cancer: preliminary results of a polit study. *Gynecol Oncol.* 2011;120:43–46.

48. Varma R, Soneja H, Bhatia K, 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: 169–175.

49. Minaguchi T, Nakagama S, Takazawa Y, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. *Cancer Lett.* 2007;248:112–122.