Conservative management of a patient with endometrial carcinoma desiring fertility: how to inform?

S. Topuz, *M.D.*; **I. Kalelioğlu,** *M.D.*; **C. Iyibozkurt,** *M.D.*; **B. Ergun,** *M.D.*

Department of Obstetrics and Gynecology, Istanbul University, School of Medicine (Turkey)

Summary

Conservative management of patients with endometrial cancer who desire fertility is becoming widespread in certain circumstances. A 36-year-old women desiring fertility with early-stage endometroid type adenocarcinoma of the endometrium was treated with 160 mg/d megestrol acetate for six months. After confirmation of a normal endometrial biopsy she became pregnant spontaneously. Following an uneventful pregnancy a healthy baby at term was delivered by cesarean section. Definitive surgery was performed. The risks and benefits of this thereupeutic approach are discussed and informing style of the patients emphasized.

Key words: Endometrial carcinoma, Conservative management, Patient information.

Introduction

Carcinoma of the endometrium is the most common female pelvic malignancy worldwide. Although primarily seen in postmenopausal women, disease may occur in childbearing age. It is well known that 3-5% of affected women are 40 years old or younger [1]. Another fact is that age at first pregnancy, especially in developing countries, is increasing due to the lifestyle of modern women. Thus the number of younger women with endometrial carcinoma desiring fertility preservation may be expected to increase. As a consequence, conservative management of endometrial cancer for a selected group of young women desiring fertility will be a challenging alternative to traditional surgical management in the future. However the optimal conservative management methodology has not been well formed by evidence in medicine yet. Many case reports and reviews addressing the subject comprise the indications for management. Although the medical treatment approach for young patients is very appealing, it should be remembered that the data are from small series or case reports, with short follow-up.

We present a case managed conservatively following the choice of an appropriately informed patient.

Case Report

A 36-year-old patient (gravida 1, para 1) was referred to our clinic following abnormal dilatation and curretage (D&C) with abnormal pathology. She was examined due to amenorrhea following regular menses. Gynecological examination revealed normal genital findings and transvaginal ultrasonography (U5) demonstrated normal genital sonography except for endometrial fluid accumulation with a small echogenic mass inside. The endometrium was also noted as normal and regular in the sonographic documentation. Minimal endometrial tissue was obtained during the D&C procedure. Pathology, which was reviewed and confirmed by an expert gynecologic-pathologist, demonstrated endometroid-type adenocarcinoma or polyps showing atypical adenomatous hyperplasia. The woman was referred to us due to her desire to preserve further fertility.

She had an unremarkable medical and family history. On physical exam, the patient weighed 75 kg, and had a body mass index (BMI) of 26 kg/m2. Her general physical examination was unremarkable. No remarkable finding was observed on genital examination or transvaginal US during the initial evaluation. A Pap smear was within normal limits. Abdominopelvic magnetic resonance imaging (MRI) showed normal findings except for a minimally irregular endometrium with no signs of myometrial invasion. No cervical involvement was detected at MRI. CA-125 level were in normal range. Hysteroscopic endometrial evaluation and sampling were performed. Treatment options, risks, and success rates were explained and the patient preferred conservative management.

She was treated with megestrol acetate (Megace) with a daily dose of 160 mg for six months. The endometrial cavity was serially controlled by sonography during each visit. Two control hysteroscopies with endometrial sampling were performed after three and six months following initialization of medication. The endometrial cavity was observed to be regular during the controls. Hysteroscopy and pathologic results of endometrial samples were within normal ranges.

Ovulation induction was offered to the patient to obtain a pregnancy but she preferred spontaneous follow-up. She got pregnant after six months following cessation of medication. Following an uneventful pregnancy, a healthy baby at term was delivered by cesarean section. At the fourth postpartum month, the patient was examined and informed about risks and possible management options for the subsequent period. She opted for surgery at this point and total abdominal hysterectomy and bilateral salpingo-oophorectomy with bilateral pelvic lymph node sampling and partial omentectomy were performed. Pathologic examination of specimens showed proliferative endometrium and normal omentum, and seven lymph nodes obtained during sampling were normal.

Revised manuscript accepted for publication January 7, 2008

Discussion

Conservative treatment has been increasingly chosen by most premenopausal women with endometrial carcinoma who have a strong desire to bear a child. This tendency is probably caused by a lack of nondirectional approaches of physicians under the guidance of successful consequences of several case reports and by patients' irresistible desire to have a baby. The question is whether the patients are sufficiently and correctly informed. While informing a woman with endometrial carcinoma who has a strong desire for pregnancy, all clinical data must be sufficiently and correctly stressed in a way the patient can understand clearly.

Cell type, myometrial invasion and histologic grade are the main prognostic factors for patients who choose conservative fertility-preserving treatment. We offered conservative management to our patient because of the fact she was in early-stage and well differentiated endometroid cells were observed in the pathologic specimens.

Risk of pelvic and paraaortic lymph nodes and ovarian involvement and a consequence of such involvement in grade 1 tumors must be explained in detailed fashion. Creasman *et al.* showed that 2.8% of all grade 1 lesions have pelvic node involvement and 1.7% paraaortic node involvement [2]. Moreover, they showed 6% adnexal spread of tumors in clinical Stage I and occult in Stage II patients. It should be kept in mind that endometrial cancer is a surgically staged disease because only cell type and grade can be determined before hysterectomy. In a comparision of preoperative findings with surgical pathology, tumor histology was changed in 27% of patients, tumor grade was changed in 34% of patients, and the stage was changed in 51% of patients. Patients must be informed about possible errors in preoperative clinical staging.

Risk of probable coexisting ovarian and colorectal cancer and difficulties in early detection of such tumors should also be stressed. Crissman *et al.* [3] reported six of 32 (19%) patients had coexisting ovarian neoplasms. Mutations in the MSH2 and MLH1 genes increase the risk of endometrial carcinoma. These mutations are also associated with an increased risk of colorectal cancer [4]. Patients must be informed that for early detection of these tumors rigorous and expensive evaluations are required and diagnoses of these tumors may be delayed until symptoms appear.

Patients also need to be informed about evaluation methods in the pretreatment period and the period of treatment or follow-up such as CA-125 values, endometrial sampling, D&C, HS, US, CT and MRI, and the accuracy of these methods before conservative therapy. No study has addressed the role of CA-125 in conservative management. Powell *et al.* reported that sensitivity and specificity of a preoperative CA-125 cutoff level of 35 U/ml were 63% and 88%, respectively, with a positive predictive value of 61% and negative predictive value of 89% [5]. A steady correlation between an endometrial biopsy and D&C in the diagnosis of endometrial cancer has not been shown in the literature. Office endometrial biopsy may be unable to diagnose the disease. Even D&C may miss the focal endometrial carcinoma located at the tubal cornua. Bettocchi *et al.* [6] report that five of 15 cases of focal endometrial carcinoma located at the tubal cornua and four of 20 cases of complex hyperplasia were missed by curettage, and were subsequently found at hysterectomy. In another study, Stock *et al.* [7] found that less than one-half of the uterine cavity was curetted in 60% of cases and less than one-fourth in 16%. A recently published meta-analysis on radiologic staging in patients with endometrial cancer reported no significant difference in the overall performance of CT, US and MRI. However, contrast-enhanced MRI performed significantly better in the evaluation of myometrial invasion than non-enhanced MRI or US [8]. Endometrial carcinoma, especially in early stages, may be missed in diagnostic imaging studies and this probability must also be explained to the patient.

Choices of drugs that can be used in treatment, probable side-effects of these drugs, and lack of the data comparing dosages and the effects of drugs on disease and subsequent fertility need to be stressed. Medroxyprogesterone acetate (MPA) at a dose of 100-800 mg/day and Megace at a dose of 40-160 mg/day are the most commonly used regimens in treatment. An alternative and uncommonly used method is a combination of tamoxifen and progestin to promote induction of progesterone receptors, and thus overcome the possible down-regulation of progesterone receptors, by continuous administration of progesterone alone. Although there is currently no consensus as to which progesterone to use, nor to the dose and length of treatment, it appears that 62-75% of women with clinical Stage I, well differentiated adenocarcinoma will respond well to progestational therapy within three to nine months of initiation of treatment [9]. Patients also should be informed about the possible cost and need for ovulation induction with drugs after regressions and lack of data about the effect of these drugs on the disease. Although the risks of ovulation induction drugs are unknown at this point, Benshushan *et al.* found no evidence that the use of ovulation induction agents, including clomiphene citrate, were associated with a higher risk of endometrial carcinoma [10].

In conclusion, the most important step after initial evaluation in the management of women with endometrial carcinoma who have a strong desire for pregnancy is giving the correct and enough information about the disease. Directional, insufficient, and incorrect counseling may often lead to medicolegal situations.

Although there are no standard recommendations for the selection of appropriate women, treatment protocols, or long-term surveillance for the conservative management of clinical Stage I endometrial adenocarcinoma endometroid-type histology, well differentiated tumor and strong patient motivation are clearly necessary.

References

[1] Hoskins W.J., Perez C.A., Young R.C.: "Principals and Practice of Gynecologic Oncology". 3rd edition, Philadelphia, PA, Lippincott Williams and Wilkins, 2000, 981.

[2] Creasman W.T., Morrow C.P., Bundy B.N., Homesley H.D., Graham J.E., Heller P.B.: "Surgical pathologic spread patterns of endometrial cancer (a Gynecologic Oncology Group study)". *Cancer* 1987, *60*, 2035.

[3] Crissman J.D., Azoury R.S., Barnes A.E., Schellhas H.F.: "Endometrial cancer in women 40 years of age or younger". *Obstet. Gynecol*., 1981, *57*, 699.

[4] Vasen H.F.A., Wijnen J.T., Menko F.H., Kleibeuker J.H., Taal B.G., Griffioen G. *et al*.: "Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis". *Gastroenterol.*, 1996, *110*, 1020.

[5] Powell J.L., Hill K.A., Shiro B.C., Diehl S.J., Gajewski W.H.: "Preoperative serum CA-125 levels in treating endometrial cancer". *J. Reprod. Med.,* 2005, *50*, 585.

[6] Bettocchi S., Ceci O., Vicino M., Marello F., Impedovo L., Selvaggi L.: "Diagnostic inadequacy of dilatation and curettage". *Fertil. Steril.,* 2001, *75*, 803.

[7] Stock R.G., Kanbour A.: "Prehysterectomy curettage". *Obstet. Gynecol.,* 1975, *45*, 537.

[8] Saez F., Urresola A., Larena J.A., Martin J.I., Pijuan J.I., Schneider J., Ibanez E.: "Endometrial carcinoma: assessment of myometrial invasion with plain and gadolinum-enhanced MR imaging". *J. Magn. Reson. Imaging.,* 2000, *12*, 460.

[9] Benshushan A.: "Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2004, *117*, 132.

[10] Benshushan A., Paltiel O., Brzezinski A., Tanos V., Barchana, Shoshani O. *et al.*: "Ovulation induction and risk of endometrial cancer: a pilot study". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2001, *9*, 53.

Address reprint requests to:
S. TOPUZ, M.D.
Erzurum Sitesi, Palandoken Sk.
Yazici apt. no: 14/1 Daire 4
Altunizade - Istanbul (Turkey)
e-mail: samettopuz@yahoo.com