Chapter 6 ■Fertility-Preserving Treatment

Overview

Conservative treatment for fertility preservation is considered a possibility for well-differentiated (G1) endometrioid adenocarcinoma at stage Ia and confined to the endometrium. According to the report of the Gynecologic Tumor Committee of the Japan Society of Obstetrics and Gynecology (registered 2001), 6.2% of uterine body cancer occurs in patients younger than 40 years old.[1] Thirty-three percent of young women with uterine body cancer are at stage Ia. According to the results of the National Uterine Body Cancer Survey (4th report), 79% of uterine body cancer patients younger than 40 years old had G1 endometrioid adenocarcinoma.[2] We must acknowledge that not all uterine body cancer cases in younger patients are G1 endometrioid adenocarcinoma confined to the endometrium, for which conservative treatment can be considered. If patients strongly desire to preserve their fertility regardless of their age, the indications for fertility preservation should be examined carefully based on accurate tissue diagnosis and clinical diagnosis.

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CQ36

Is progesterone therapy useful for a patient with well-differentiated endometrioid adenocarcinoma who desires fertility preservation?

Recommendations

Fertility-preserving treatment is sometimes useful for a patient with well-differentiated endometrioid adenocarcinoma thought to be confined to the endometrium (Grade C).

Complete endometrial curettage must be performed repeatedly, and elimination of cancer must be confirmed histologically to assess the effect of progesterone therapy during treatment. Even if progesterone therapy is apparently effective, recurrences are common after completion of therapy. Therefore, progesterone therapy should only be performed at institutions with staff thoroughly experienced its practice.

Background and Objectives

We examined the benefits of progesterone therapy as conservative treatment for patients with well-differentiated uterine body cancer desiring to preserve their fertility.

Explanations

Indications for this treatment are a tissue diagnosis of well-differentiated endometrioid adenocarcinoma (endometrioid adenocarcinoma G1) obtained from complete endometrial curettage, at stage Ia, and no myometrial invasion or extrauterine spread. For preoperative assessment of myometrial invasion, MRI is considered to be significantly more accurate than CT scanning or ultrasonography.[1] Significantly more synchronous ovarian cancer and uterine body cancer metastases to the ovaries are seen in younger patients, indicating that caution is necessary with this age group.[2,3]

A small number of studies have reported that progesterone therapy was useful in patients with well-differentiated uterine body cancer. Although all these studies have reported good response rates, most have been case reports with small subject numbers.[4-14] After a central pathological review, Kaku et al. derived a response rate of 75% (9/12 patients) using MPA 200-800 mg/day. The mean time until the initial response was 3 months (1-12 months), and recurrence was seen in 2 patients (22%) after completion of treatment. There were 2 patients who later became pregnant.[5] Wang et al. administered megestrol acetate 160 mg/day + tamoxifen 30 mg/day for 6 months. They achieved a complete response in 89% of patients (8/9). Two patients had a normal pregnancy after *in vitro* fertilization, and another 2 patients had ectopic pregnances. Recurrence was observed in 4 of 8 patients with complete response.[12] This was the only published prospective study.

A recently completed prospective study investigated the use of high dose MPA in the treatment of uterine body cancer and atypical endometrial hyperplasia. This was a phase II multicenter trial of fertility-preserving treatment by the Planning Research Group supported

by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare. The standard treatment was MPA 600 mg/day for 26 weeks and complete endometrial curettage every 8-9 weeks. If no response was evident from the curettings, the treatment was terminated. According to the interim report, 52% of subjects (11/21) showed complete response.[6] Of the 11 subjects with complete response, recurrence was detected in 3 subjects at 13, 15, and 19 months after treatment, respectively.

The indication for this treatment is limited to patients who desire uterine preservation. An upper limit of patient age should be established, and informed consent obtained, before commencing this treatment. The recommended dosages and duration of treatment have not been established.

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CQ37

What treatments are recommended for recurrent cases of well-differentiated endometrioid adenocarcinoma after fertility preservation therapy?

Recommendations

(1) The effectiveness of retreatment with progesterone has not been established in patients with recurrent disease (Grade D).
(2) Total hysterectomy is recommended for patients with recurrent disease, who are not disease-free, or who have extrauterine disease (Grade A').

Background and Objectives

We examined treatments for cases of recurrence after fertility preservation.

Explanations

The effectiveness of progesterone retreatment has yet to be elucidated in cases of recurrence. In a prospective study, Wang et al. reported that 4 of 8 patients with complete response later developed recurrent disease. The interval between initial diagnosis and recurrence was 20-23 months. One patient promptly underwent surgery, and the other 3 underwent progesterone retreatment. Two of these 3 patients had complete response, and the remaining one patient underwent surgery for persistent recurrent disease.[1] In phase II trials of MPA, if complete or partial response was not obtained and hormone therapy was discontinued, total hysterectomy was considered the treatment of choice.[2,3] In 2 other studies, two patients developed recurrences after an initial complete response, falling pregnant, and giving birth.[4,5] Recurrence in 1 of these patients occurred 87 months after initial diagnosis and 22 months after giving birth.[4] The effectiveness of progesterone retreatment for recurrent cases has not been established, and total hysterectomy should be considered for recurrent and non-responsive cases.

There is a body of opinion that total hysterectomy should be performed after pregnancy and childbirth, even if there are no signs of recurrence.[1,5,6]

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CQ38

What are the adverse effects of progesterone therapy and their associated risk factors?

Recommendations

Thrombosis is a serious adverse reaction associated with progesterone therapy. Use of progesterone should be avoided in patients at high risk of thromboembolic events (Grade A').

Background and Objectives

We examined adverse events associated with progesterone therapy and their risk factors.

Explanations

The package inserts for medroxyprogesterone acetate (MPA) warn of possible serious thromboembolic events including cerebral infarction, myocardial infarction, and pulmonary embolism. MPA is contraindicated in patients at high risk of thromboembolic events, such as the following groups:

- Patients who have had surgery within the previous week
- Patients with a history of thrombotic disorders such as cerebral infarction, myocardial infarction or thrombophlebitis
- Patients with arteriosclerosis
- Patients with cardiac conditions such as valvular heart disease, atrial fibrillation, endocarditis or severe heart failure
- Patients on hormone therapy
- Patients with severe hepatic disease

The GOG conducted a thorough study of adverse events with MPA therapy in patients with recurrent and advanced uterine body cancer.[1] In this comparative controlled study, a low incidence of adverse events were recorded in both the 200 mg MPA group (145 subjects) and 1,000 mg MPA group (154 subjects), with no difference seen between groups. The most frequently seen adverse event was thrombophlebitis, seen in 5% of subjects, 2% experiencing adverse reactions of grade 3 or 4. Pulmonary embolism occurred in 1% of subjects. Other adverse events were mild. As part of diagnosis and treatment, it is necessary to perform complete endometrial curettage in patients who will undergo fertility-preserving treatment. Since risk factors such as obesity due to concurrent polycystic ovary syndrome can be present in these patients, all care must be taken to prevent thromboembolic events. In phase II trials using MPA, low dose aspirin has been used in combination with MPA as a preventative measure.[2,3] The risk of thrombosis increases with concurrent use of progesterone, estrogen, and corticosteroids.

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CQ39

Is the induction of ovulation safe for fertility-preserved patients?

Recommendations

It is highly likely that induction of ovulation is safe, although the evidence is insufficient (Grade C).

Background and Objectives

We examined problems with, and the safety of, induction of ovulation in fertility-preserved patients.

Explanations

Jadoul et al. reviewed the literature on conservative treatments for young women with atypical endometrial hyperplasia and endometrial adenocarcinoma. They reviewed papers published over the past 30 years, and found a total of 26 pregnancies, 24 following progesterone therapy, reported in 20 articles.[1] The duration of progesterone therapy ranged from 2 to 6 months. The mean follow-up period was 39 months (2-90 months). The majority was treated for 3-6 months before the treating physician approved their patient becoming pregnant. At least 15 patients (17 pregnancies) or 55% of the conceptions were by in vitro fertilization. Planned total hysterectomy was performed postpartum in 5 patients, with no residual disease found. An ovarian cancer (mixed endometrioid and clear cell-type) was found in 1 patient, however.

Recurrent disease was detected during postpartum follow-up in 3 patients. Of these, recurrence was found 6 months postpartum in 1 patient who had used clomiphene to induce ovulation.[2] Another patient who had used hMG-hCG to induce ovulation experienced recurrence 22 months postpartum.[3] Some are of the opinion that infertility treatment should be offered to patients following conservative treatment, not only to increase the chance of pregnancy, but also to decrease the risk of recurrence.[4]

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CQ40

What intervals are recommended for follow-up after fertility-preserving treatment? What examinations and investigations should be performed?

Recommendations

Following medroxyprogesterone acetate (MPA) therapy, follow-up should include complete endometrial curettage and transvaginal ultrasonography every 3 months (Grade E).

Background and Objectives

We examined the appropriate examinations and investigations to be performed after fertility-preserving treatment, and the optimum duration of progesterone therapy for these patients.

Explanations

There is insufficient evidence on which to base a recommendation, as there have been no studies conducted with sufficient subject numbers. In a prospective study, Wang et al. followed up patients assessed as complete response, using transvaginal ultrasonography every 2 months, and hysteroscopy and complete endometrial curettage every 6 months. Complete response was defined as a tumor-free state as assessed by post-treatment hysteroscopy and complete curettage. Oral contraceptives were administered for 3 months after treatment, although reproduction assistance was given if patients desired to become pregnant urgently.[1]

A phase II prospective study was recently conducted using MPA. Subjects were administered a combination of estrogen and progesterone (Duoluton or Sophia A) after MPA therapy. One estrogen-progesterone tablet was administered daily for 21 days for 6 weeks. A complete response was reconfirmed by histological examination of uterine curettings after completion of combination therapy. Patients were followed up by endometrial biopsy every 3 months for 2 years after treatment.[2,3]

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