Chapter 7 ■Atypical Endometrial Hyperplasia

Overview

Endometrial hyperplasia with cellular atypia (nuclear atypia) is more likely to progress to cancer than hyperplasia without atypia, and endometrial hyperplasia is in general classified into lesions with and without pathological atypia. It is further subdivided into simple and complex types from its structural features. The rates of progression to cancer are 1-3% for endometrial hyperplasia without atypia, 8% for simple atypical endometrial hyperplasia, and 29% for complex atypical endometrial hyperplasia.[1] Similar results have been obtained with Japanese subjects.[2] Treatment strategies should be formulated with consideration of the precancerous characteristics of atypical endometrial hyperplasia and the frequent occurrence of synchronous endometrial hyperplasia and endometrial cancer. Studies have examined the comorbidity of atypical endometrial hyperplasia and cancer. In subjects first diagnosed with hyperplasia at endometrial biopsy, the rate of cancer comorbidity was 17-50% in the final diagnosis after total hysterectomy.[1,2] Total hysterectomy is therefore recommended in patients who do not desire fertility preservation. If conservative treatment is to be performed in patients with atypical endometrial hyperplasia, complete endometrial curettage needs to be performed to avoid missing coexistent cancer.

Note: Some studies have advocates the name endometrial intraepithelial neoplasia (EIN) for early-stage endometrial cancer and atypical endometrial hyperplasia.[3,4] However, it is probably more practical to distinguish clinically between hyperplasia and endometrial cancer and classify them separately. A p53 suppressor oncogene mutation has been found in endometrial intraepithelial carcinoma, considered to be a precursor of serous adenocarcinoma, that should be clearly differentiated from endometrial hyperplasia.[5,6]

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If fertility-preserving treatment is to be performed for atypical endometrial hyperplasia:

(1) Is progesterone therapy useful?

(2) What intervals are recommended for follow-up, and what examinations and investigations should be performed?

Recommendations

(1) Progesterone therapy is useful in some cases as fertility-preserving treatment (Grade C).
(2) Follow-up, including complete endometrial curettage and transvaginal ultrasonography, should be performed at intervals of 3-6 months, or greater (Grade E).

Background and Objectives

We examined the usefulness of progesterone therapy as conservative treatment for atypical endometrial hyperplasia. Atypical endometrial hyperplasia has a high risk of coexistence with cancer, and for progression to cancer during follow-up. We examined the examinations and investigations that should be performed as part of the management of atypical endometrial hyperplasia, and follow-up intervals.

Explanations

Some studies have shown progesterone therapy to be useful in the treatment of atypical endometrial hyperplasia, with good response rates, although subject numbers were small.[1-4] Randall et al. used megestrol acetate or medroxyprogesterone acetate (MPA) in 19 subjects, obtaining a response rate of 94%.[1] Kaku et al. achieved a response rate of 83% (15/18) using MPA 100-800 mg/day in a study following central pathological review. The mean time until initial response was 2 months (1-4 months), and recurrent disease was detected in 2 patients after completion of treatment. Uterine cancer was present at the time of hysterectomy in 1 out of 3 refractory patients.[2]

A study comparing 12 patients administered low dose MPA (10 mg for 14 days, rest period from drug for 14 days; 6 cycles) and 8 patients administered high dose MPA (400 mg/day) yielded a response rate of 75% in both groups. However, 2 patients in the low-dose MPA group progressed to uterine body cancer during the treatment period, 1 with G1 stage Ia disease (73 months after diagnosis) and the other with G2, stage Ib disease (32 months after diagnosis).[3] A recently completed phase II study examined high dose MPA as fertility-preserving treatment in patients with uterine body cancer and atypical endometrial hyperplasia. This is the only multicenter prospective study that has examined high dose MPA as fertility-

preserving treatment. According to the interim report, complete response was seen in 81% (13/16) of patients administered the standard treatment of 600 mg/day MPA for 26 weeks, with complete endometrial curettage every 8-9 weeks.[4] No deaths were reported in any of these studies.

All the above studies reported good response rates using progesterone therapy in atypical endometrial hyperplasia, suggesting that it is highly likely to be useful. Until the final results are available from the multicenter prospective study, however, progesterone therapy should be administered with caution.

Progesterone therapy is only indicated for patients with atypical endometrial hyperplasia who strongly desire uterine preservation, after informed consent has been obtained.

A number of studies have reported that the rate of progression of atypical endometrial hyperplasia to cancer is approximately 20% (16-29%).[5-8] Kurman et al. stated that the mean time of atypical endometrial hyperplasia progressing to cancer was 4.1 years (1-11 years). Of the cases which progressed to cancer, they found that 91% (10/11) were G1 disease, and 91% stage I, although 1 case was already stage IV disease when detected.[5] Baak et al. stated that of 11 cases that progressed to cancer, 6 were G1 disease, 4 G2, and 1 G3, with 7 at stage Ia, 3 stage Ib, and 1 stage Ic.[6] MRI and CT scanning should be performed to rule out myometrial invasion or metastatic spread.

Many studies excluded patients with atypical endometrial hyperplasia who were diagnosed with uterine body cancer within 1 year of fertility-preserving treatment. It is therefore difficult to obtain evidence to support recommendations for follow-up intervals. In general, follow-up should be performed at intervals of no greater than 1 year, but more typically 3-6 months.[4,7,8]

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