Frequency and characteristics of endometrial carcinoma and atypical hyperplasia detected on routine infertility investigations in young women: a report of six cases

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Infertility patients are known to be at increased risk of endometrial carcinoma (EC) and atypical hyperplasia (AH). However, the incidence and clinical features of EC and AH in these patients remain to be clarified. In this study, we examined the rate at which a routine infertility workup revealed EC/AH and investigated the clinicopathological features of EC/AH detected in this way. Among patients diagnosed with EC or AH at the Jichi Medical University Hospital between the 10-year period from 1997 to 2006, six patients were referred from Tochigi Central Clinic, a specialized infertility facility. We report the clinicopathological features of these patients and calculate the incidence of EC/AH detected from these investigations.

All six patients were younger than 40 and had early stage disease (final diagnosis: EC stage IA: 3, EC stage IB: 1, AH: 2). A total of 19,826 patients underwent routine infertility investigations at Tochigi Central Clinic during the same period. The incidence of EC/AH detected from these investigations was 0.03% (6/19,826) and that of EC was 0.02% (4/19,826): 5–10 times higher than the overall incidence in Japanese women of the same age. Routine infertility investigations may provide an opportunity to examine the corpus uteri of young women in whom examination is otherwise limited, contributing to the early detection of EC/AH.

Key words: endometrial carcinoma / routine infertility investigations / diagnosis / overall incidence

Introduction

In the USA and UK, endometrial carcinoma (EC) is the most frequent gynecological malignancy (Reeves et al., 2007; Sorosky, 2008). In Japan, the incidence of EC has recently increased, although it remains lower than in Europe and the USA (Parazzini et al., 1991a; Ajiki et al., 2000; Marugame et al., 2006). The reasons for the lower incidence of EC in Japan compared with Western countries are unknown. However, the incidence of EC has also recently been increasing in Japan, and this increase is attributed to factors related to changes in Westernization of the diet and lifestyle, such as an increasing obesity and tendency to marry later in life. EC is most frequent in peri- and post-menopausal women. However, women younger than 40 account for ~5% of EC patients, and the incidence has recently increased in this age group (Crissman et al., 1981; Gallup and Stock, 1984; Gitsch et al., 1995).

The infertility outpatient clinic represents one of the few opportunities for young women to undergo gynecological examination. Routine infertility investigations sometimes reveal abnormal pathological findings of the endometrium, such as EC or complex atypical hyperplasia (AH), despite the absence of symptoms (Roma Dalfo et al., 2004; Rackow and Arici, 2006). Transvaginal ultrasonography (TVU), hysterosalpingography (HSG) and hysteroscopy have been reported to be useful tests for detecting EC in high-risk patients such as those with post-menopausal bleeding. However, these tests are less useful in a population of young women because of the relatively low pretest odds for EC (Kim et al., 1998). Otherwise, they are effective for determining the morphology of the endometrium and the uterine cavity, and are widely used to investigate infertility (Brown et al., 2000; Clark, 2004; Kelekci et al., 2005; Eng et al., 2007). TVU is useful for evaluating the presence or absence of endometrial thickening and contrast abnormalities, HSG facilitates the...
detection of endometrial irregularity and hysterofiberscopy allows abnormalities to be detected under direct vision. In addition, with hysterofiberscopy, biopsy under direct vision facilitates the diagnosis of pathological abnormalities of the endometrium.

Patients undergoing infertility treatment are reported to be at increased risk of EC (Brinton et al., 1992; Lurain, 2007). These patients may have prolonged, unopposed estrogen stimulation related to an ovulation disorder, or progesterone deficiency, both of which are considered to increase the risk of EC. Infertility outpatient clinics manage these high-risk groups for EC/AH (Kurabayashi et al., 2003) and form the setting for various investigations that facilitate the screening of endometrial abnormalities. It is therefore conceivable that infertility patients will have a higher incidence of EC/AH compared with women with normal fertility. However, this incidence remains unclear.

This study was therefore conducted to investigate the incidence and clinicopathological features of EC/AH in infertility patients.

**Subjects and methods**

Among patients diagnosed with EC or AH at the Jichi Medical University Hospital between the 10-year period from 1997 to 2006, six patients were referred from Tochigi Central Clinic, a specialized infertility facility. We investigated the clinicopathological features of these six patients as well as the size of the population from which they were extracted.

At Tochigi Central Clinic, TVU and HSG are performed in all women presenting with infertility. When these investigations suggest endometrial abnormalities, hysterofiberscopy is immediately performed. When hysterofiberscopy reveals such abnormalities, hysterofiberscope-guided biopsy or endometrial curettage is performed to enable a pathological diagnosis.

We calculated the number of patients who initially consulted the clinic during the same period based on serial chart numbers. From this number, we subtracted the number of patients who consulted the clinic for reasons other than infertility or who underwent in vitro fertilization after having had routine infertility investigations at another hospital. This gave the number of patients who underwent routine infertility investigations at the clinic. Using this number as the denominator, we calculated the incidence of EC/AH detected at the time of routine infertility investigations.

In addition, we investigated the number of times each test was performed and determined the frequency of additional tests performed following routine infertility investigations at Tochigi Central Clinic, as well as the incidence of cases in which EC/AH was eventually detected.

**Results**

The patient profiles are shown in Table I. Ages ranged from 30 to 37 years. Pretreatment pathological findings suggested EC (G1) in three patients and AH in three. In all EC patients, stage was evaluated as IA.

Concerning risk factors for EC, ovulation disorder was noted in three patients. Two patients had a body mass index (BMI) of more than 25, suggesting obesity. Polycystic ovaries (PCO) were concomitantly observed in one patient. However, abnormal vaginal bleeding was noted in only one patient.
Table II  Treatment and clinical course of six patients with EC/AH detected on infertility investigations

<table>
<thead>
<tr>
<th>Case</th>
<th>Initial treatment</th>
<th>Effect</th>
<th>ART</th>
<th>Pregnancy after diagnosis</th>
<th>Recurrence</th>
<th>Clinical course</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MPA</td>
<td>CR</td>
<td>ICSI</td>
<td>G2P2</td>
<td>–</td>
<td>The patient has been recurrence-free on follow-up after delivery. The uterus has been preserved</td>
<td>AH</td>
</tr>
<tr>
<td>2</td>
<td>MPA</td>
<td>CR</td>
<td>—</td>
<td>G2P1</td>
<td>–</td>
<td>The patient has been recurrence-free on follow-up after delivery. The uterus has been preserved</td>
<td>AH</td>
</tr>
<tr>
<td>3</td>
<td>MPA</td>
<td>CR</td>
<td>—</td>
<td>G0P0</td>
<td>+</td>
<td>Recurrence was detected, and the MPA therapy was repeated. Thereafter, recurrence was again detected, and TAH was performed</td>
<td>EC(G1),IA</td>
</tr>
<tr>
<td>4</td>
<td>MPA</td>
<td>CR</td>
<td>ICSI</td>
<td>G1P1</td>
<td>+</td>
<td>After delivery, recurrence was detected, and TAH was performed</td>
<td>EC(G1),IA</td>
</tr>
<tr>
<td>5</td>
<td>MPA</td>
<td>CR</td>
<td>IVF</td>
<td>G1P0</td>
<td>–</td>
<td>The patient has been recurrence-free on follow-up. The uterus has been preserved</td>
<td>EC(G1),IA</td>
</tr>
<tr>
<td>6</td>
<td>MPA</td>
<td>No response</td>
<td>—</td>
<td>—</td>
<td>–</td>
<td>There was no response to initial MPA therapy, so TAH was performed</td>
<td>EC(G1),IB</td>
</tr>
</tbody>
</table>

MPA, medroxyprogesterone acetate; CR, complete response; ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; AH, complex atypical endometrial hyperplasia; EC, endometrial carcinoma; TAH, total abdominal hysterectomy.

Data on treatment course, final pathological diagnosis, pregnancy and clinical course are shown in Table II. All patients wished to undergo fertility-preserving therapy with medroxyprogesterone acetate (MPA); therefore, after informed consent was obtained, MPA (400–600 mg/day) was administered for 16 weeks. Concerning the primary effects of this treatment, complete response was achieved in five patients (83%); however, the remaining patient (Patient 6), who had a pretreatment diagnosis of EC, did not respond to MPA and therefore underwent total hysterectomy. However, contrary to the initial diagnosis for this patient, examination of the extirpated uterus suggested stage IB EC (G1).

Infertility treatment was started for the remaining five patients. A total of six pregnancies (intracytoplasmic sperm injection or in vitro fertilization: four, standard infertility treatment: two) were achieved in four of these women. Of these six pregnancies, three progressed, resulting in the birth of four neonates.

Recurrence was detected after 11 and 49 months, respectively, in two patients (40%) (Patients 3 and 4). These patients underwent total hysterectomy. In Patient 3, histological examination before MPA therapy suggested a diagnosis of AH; however, examination of the extirpated uterus suggested stage IA EC (G1). In Patient 4, the pathology of the extirpated uterus suggested stage IA EC (G1), which was consistent with the histology before MPA therapy. We proposed the option of preventive total hysterectomy to two patients (Patients 1 and 2) who had given birth and had achieved recurrent-free survival. However, they did not select this and are being followed up, with no recurrence so far (follow-up period: 59 and 65 months, respectively). Patient 5 did not give birth; however, complete response was achieved after initial treatment. This patient also elected to have her uterus preserved and has no recurrence during the 122-month follow-up period.

A total of 19 826 patients (range: 19–50 years, mean age: 32.5 years, median age: 32 years) underwent routine infertility investigations at Tochigi Central Clinic from 1997 to 2006 (Fig. 1). We also found out the number of times each test was performed at the clinic during the same period. Approximately 10% (1975/19 826) of all patients who underwent routine infertility investigations (TVU and/or HSG) showed abnormal findings and subsequently had hysterofiberscopy. Pathological tests were performed not for all, but for about 40% (731/1975) of patients undergoing hysterofiberscopy, and 0.8% (6/731) of the patients who had pathological tests showed EC/AH. The incidence of endometrial proliferative disease detected during these investigations was 0.02% (4/19 826) for EC and 0.03% (6/19 826) for EC/AH.

Discussion

This report showed that the detection rates of EC/AH and EC on routine infertility investigations were 0.03 and 0.02%, respectively. In Japan, the incidence of EC has increased but remains lower than in Europe or the USA. In Japan, the incidence of EC is reported to be 0.0019% in females aged 30–34 years and 0.0037% in those aged 35–39 years (Ajiki et al., 2000; Marugame et al., 2006). Therefore, we found that the detection rate of EC on routine infertility investigations was 5–10 times higher than the overall incidence in Japan. Although we cannot conclude that the detection of EC is increased by 5–10 times based on the present study alone due to its small sample size, it is clear that EC/AH is detected at a higher rate among infertility patients. This finding should be borne in mind when performing routine infertility investigations in females, especially those aged over 30.

This elevated incidence of EC in infertility patients might result from these patients being more likely than the general population to be exposed to unopposed E2 because of conditions such as ovulation disorder, obesity or PCO (Parazzini et al., 1991b; Brinton et al., 1992; Lurain, 2007). In the present study, ovulation disorder was observed in three of the six patients in whom EC/AH was detected on infertility investigations.

Another reason for the elevated incidence might be that EC is incidentally detected at an early stage as a result of various infertility investigations.
investigations (investigational bias). Of the present patients in whom EC/AH was detected on infertility investigations, two had AH and three had stage IA EC. This suggests the usefulness of routine infertility investigations in the early detection of EC/AH. Of six patients in whom EC/AH was detected on infertility investigations, two had no risk factors for EC such as obesity, ovulation disorder or PCO. Furthermore, vaginal bleeding was not noted in five of these patients.

The proportion of young women undergoing cancer screening in the absence of symptoms is extremely low. Health professionals also rarely perform endometrial investigations in such low-risk patients. Therefore, if these patients had not undergone infertility investigations, EC/AH detection would have been delayed. Hence infertility investigations may contribute to the early detection of EC/AH. The literature contains case reports in which HSG has revealed EC (Menczer et al., 1980), and many studies have reported the usefulness of TVU and hysterofiberscopy in EC diagnosis (Clark et al., 2002; Sawicki et al., 2003; Williams et al., 2003). However, it is not efficient to employ procedures such as TVU, HSG and hysterofiberscopy for EC screening. On the other hand, at infertility outpatient clinics, these diagnostic procedures are routinely performed as part of the infertility workup to evaluate endometrial features. This may be advantageous for the early detection of EC/AH. In other words, this study suggests that clinicians working at infertility outpatient clinics should also bear in mind the role of the infertility workup in EC screening.

In this report, EC or AH was detected at the stage for which MPA therapy is indicated (EC, G1 and stage IA). Such early diagnosis of EC/AH is important for young nulliparous women with EC who wish to maintain fertility. Infertility treatment was administered in the five patients in whom MPA therapy achieved complete response; a total of six pregnancies were achieved and four neonates were born. Infertility investigations, in contributing to early detection, may therefore be useful for saving patients’ lives and maintaining their fertility.

The response rates of fertility-preserving therapy with MPA are ~60–70% in EC and 80–90% in AH. In patients wishing to bear a child, this therapeutic strategy may be acceptable. However, relapse is detected in 11–50% of patients (Kim et al., 1997; Randall and

Figure 1 A flow-chart of routine infertility investigations of the uterine cavity at Tochigi central clinic. The numbers in each box indicate the number of patients during this period (1997–2006). Hysterosalpingography (HSG) and transvaginal ultrasonography (TVU) are initially performed to examine the uterine cavity in all women with infertility. Next, hysterofiberscopy (HFS) is performed if HSG and/or HFS findings are abnormal. If HFS shows abnormal intrauterine findings such as polypoid lesions, HFS-guided biopsy or the curettage is performed and the material is examined histopathologically.
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Kurman, 1997; Imai et al., 2001; Kaku et al., 2001; Gotlieb et al., 2003; Ushijima et al., 2007). Therefore, close patient selection and follow-up are essential. Of our series, in one patient who did not respond to MPA therapy, pathological examination following total hysterectomy suggested stage IB G1EC. Moreover, recurrence was detected in two of five patients achieving complete response. Physicians should explain to patients that fertility-preserving therapy with MPA for EC/AH is not standard therapy but an option worthy of consideration. Moreover, patients should be fully informed about the risks and benefits of this therapy.

This report demonstrated that routine infertility investigations facilitated the detection of EC patients. These investigations provided an opportunity to examine the corpus uteri of young women, for whom examination is usually limited, contributing to the early detection of EC/AH. We must recognize that, when investigating the cause of infertility, EC/AH is more frequently detected than in the general population.

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**References**


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