Case report

ICSI outcome following conservative fertility sparing management of endometrial cancer

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Abstract

Approximately 5% of cases of endometrial cancer occur in women aged 40 years or younger. In the presence of early staged endometrial cancer, fertility sparing management may be considered in selected patients. Following high dose progestin therapy and confirmation of the regression of cancer, the patient might attempt to conceive spontaneously. However, assisted reproduction techniques might increase the likelihood of pregnancy and decrease the time interval to conception. In this report, the authors present four patients with endometrial cancer who were treated conservatively with high dose progestin. In all of the cases, the endo-myometrial junctional zone was intact with no evidence of extra-uterine spread on pelvic imaging. A total of seven intracytoplasmic sperm injection and embryo transfer cycles were performed in four patients; five healthy infants were delivered. Two additional spontaneous pregnancies occurred in two patients. During the follow-up period, no recurrence was noted. Although there are limited data, fertility sparing with high dose progestin therapy may be offered to patients with early stage disease and subsequently assisted reproductive techniques may be employed to achieve immediate pregnancy.

Keywords: assisted reproduction technologies, endometrial cancer, fertility sparing, ICSI, infertility, pregnancy

Introduction

Endometrial adenocarcinoma is the most common cancer of the female genitalia (Wang et al., 2002). The traditional method of treatment is surgical staging including hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic/para-aortic lymphadenectomy and omentectomy when indicated (Mariani et al., 2001). Patients less than 40 years of age account for 5% of the cases, in these patients fertility preservation should be considered in selected patients (Benshushan, 2004). In such cases, polycystic ovary syndrome (PCOS) is an established risk factor for endometrial hyperplasia and/or adenocarcinoma, probably due to the unopposed exposure of the oestrogen to the endometrium (Meizow and Schenker, 1996).

Following fertility preserving treatment with high dose progestin and documentation of the regression of endometrial cancer, the patient might attempt to conceive spontaneously. However, assisted reproduction techniques may be considered to increase the likelihood of pregnancy and decrease the time interval to conception (Rackow and Arici, 2006).

There is a limited number of reports of pregnancies achieved with IVF following fertility preserving treatment for endometrial cancer (Paulson et al., 1990; Kimmig et al., 1995; Sardi et al., 1998; Shibahara et al., 1999; Ogawa et al., 2001; Pinto et al., 2001; Lowe et al., 2002; Nakao et al., 2004; Yarali et al., 2004; Demirok et al., 2005; Park et al., 2006; Piura, 2006; Elizur et al., 2007) excluding pregnancies achieved with uterine surrogacy. In this case report, the authors present the outcome of intracytoplasmic sperm injection (ICSI) and embryo transfer in four patients (six cycles) after conservative treatment of endometrial adenocarcinoma.
Cases

Case A

A 32-year-old woman, suffering from PCOS was diagnosed with a well-differentiated endometrial carcinoma. Her body mass index was 38 kg/m². Magnetic resonance imaging (MRI) of the uterus showed an intact endo-myometrial junctional zone and no evidence of extra-uterine spread. Fertility preserving surgical staging including peritoneal cytology, complete pelvic–para-aortic lymphadenectomy and omentectomy were performed. No extra-uterine tumour spread was noted at pathology. Megestrol acetate (Megace; Bristol-Myers Squibb, Istanbul, Turkey) at a dose of 160 mg/day was prescribed for 6 months; a repeat endometrial biopsy revealed persistent adenocarcinoma. Repeat MRI of the uterus and abdominopelvic computerized tomography (CT) at 6 months after diagnosis were normal. Progesterone treatment was switched to continuous medroxyprogesterone acetate (MPA; Farlutal; Deva, Istanbul, Turkey) at a dose of 160 mg/day. After 6 months of treatment with MPA, a repeat endometrial biopsy revealed complex atypical hyperplasia with no persistent cancer. The patient was referred for IVF for immediate achievement of pregnancy. An office hysteroscopy using a 2.9 mm diameter rigid scope (Karl Storz, Tuttlingen, Germany) was performed after progestrogend withdrawal bleeding. Of interest, a diffuse cauliflower appearance was noted in the uterine cavity. There was no intrauterine synchieae. An ICSI cycle was performed; the outcome is given in Table 1. A healthy, normal female infant with a birth weight of 1740 g was born by Caesarean section due to preterm labour and breech presentation at 30 weeks. No tumour could be identified in the placenta. The first pregnancy of this case was reported previously (Yarali et al., 2004).

After the first delivery, regular menstrual cycles were restored probably due to a weight loss of 7 kg. Therefore, every 3–6 months, endometrial biopsies using Karman aspiration with a cannula, 4 mm in diameter, were performed all of which were tumour negative without progestin treatment. A repeat ICSI cycle was scheduled 2 years after the delivery (Table 1). The patient delivered two healthy male infants at 33 weeks gestation, 1600 and 2500 g healthy infants were delivered by Caesarean section owing to preterm labour. No tumour could be identified in the placenta.

One year after the second delivery, the patient conceived spontaneously and a singleton infant with a birth weight of 3250 g was delivered. No tumour could be identified in the placenta.

Case B

A 31-year-old woman presented with primary infertility of 10 years’ duration. Her body mass index was 28 kg/m². The couple had not been investigated for infertility and ovulation induction had never been performed. Owing to suspicion of endometrial polyp at transvaginal ultrasonography, a diagnostic endometrial biopsy had been performed and a well-differentiated adenocarcinoma had been diagnosed. MRI of the uterus showed an intact endo-myometrial junctional zone and no evidence of extra-uterine spread. Megestrol acetate (Megace) at a dose of 160 mg/day was prescribed for 3 months; a repeat endometrial biopsy using Karman aspiration with a cannula, 4 mm in diameter, revealed an iatrogenic endometrium due to the impact of progestins without any foci of adenocarcinoma. The patient was referred for assisted reproductive treatment (Table 1). Owing to a low total antral follicle count of four, micro dose flare up protocol and recombinant FSH (Gonal-F) with a starting dose of 450IU/day were employed. She failed to conceive.

Micro dose flare-up protocol was employed for the second cycle (Table 1). A biochemical pregnancy was achieved. The patient conceived spontaneously thereafter. Currently, the gestational age is 24 weeks with no obstetric problem.

Case D

A 31-year-old woman presented with primary infertility of 10 years’ duration. Her body mass index was 28 kg/m². The couple had not been investigated for infertility and ovulation induction had not been performed. Owing to thickened endometrium, a diagnostic endometrial biopsy had been performed and a well-differentiated adenocarcinoma had been diagnosed. MRI of the uterus showed an intact endo-myometrial junctional zone and no evidence of extra-uterine spread. Megestrol acetate (Megace) at a dose of 160 mg/day was prescribed for 3 months; a repeat endometrial biopsy using Karman aspiration with a cannula, 4 mm in diameter, did not reveal any persistent cancer. The patient was referred for assisted reproductive treatment. A total of 15 antral follicles were observed at transvaginal ultrasonography. Luteal-long leuprolide acetate (Lucrin; Abbott, Istanbul, Turkey) with oral contraceptive pre-treatment and recombinant FSH (Gonal-F) were employed (Table 1). The patient failed to conceive.

The patient conceived at the second ICSI cycle employing the same protocol for ovarian stimulation as in the first ICSI cycle (Table 1). During the antenatal period, one of the twins was diagnosed as intrauterine growth retarded. At 37 weeks gestation, 1600 and 2500 g healthy infants were delivered by Caesarean section owing to preterm labour. No tumour could be identified in the placenta.
Discussion

Five percent of cases of endometrial cancer are encountered in patients less than 40 years of age in whom fertility preservation should be considered in selected patients (Benshushan, 2004). Young women with endometrial carcinoma are generally reported to have a more favourable prognosis due to early stage and good differentiation (Rackow and Arici, 2006). In patients wanting to preserve their fertility, conservative management with high dose progestin treatment may be considered after detailed counselling. However, the time taken to conceive spontaneously may be discouraging for the patient and the physician. Therefore, assisted reproductive technology may be a feasible option in order to increase the likelihood of immediate conception.

Appropriate patient selection for fertility sparing in patients with endometrial cancer is essential to avoid under-treatment and recurrence of cancer. Early stage disease with well-differentiated adenocarcinoma without myometrial invasion and extra-uterine spread at pelvic imaging is generally considered to be a prerequisite for conservative management (Yarali et al., 2004; Azim and Oktay, 2007). In such patients, high dose progestin treatment should be prescribed following detailed counselling on the experimental nature of this treatment option. The role of surgical staging to evaluate extra-uterine spread is highly controversial; although it was employed before the first ICSI cycle in the first patient, it was not performed in the remaining three patients once the pelvic imaging was negative. Megestrol acetate is the most commonly used progestin (Paulson et al., 1990; Pinto et al., 2001; Lowe et al., 2002; Yarali et al., 2004; Demiroi et al., 2005; Park et al., 2006; Piura, 2006). Although 160 mg/day for 3–6 months is the most reported regimen, 80–600 mg/day up to 24 months has been employed before an assisted reproduction cycle (Rackow and Arici, 2006). However, if megestrol acetate fails to regress cancer, medroxyprogesterone acetate might be employed (Yarali et al., 2004) at a dose of 60–500 mg/day for 3–12 months (Salha et al., 1997; Ogawa et al., 2001; Nakao et al., 2004; Piura, 2006). A progestin-releasing intrauterine device may be an alternative option for systemic progestin treatment (Montz et al., 2002).

Table 1. Intracytoplasmic sperm injection cycle outcome of patients with endometrial cancer.

<table>
<thead>
<tr>
<th>Patient Cycle</th>
<th>Case A</th>
<th>Case B</th>
<th>Case C</th>
<th>Case D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>32</td>
<td>36</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Duration of infertility (months)</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>120</td>
</tr>
<tr>
<td>Presence of PCOS</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Protocol of ovarian stimulation with oral contraceptive pretreatment</td>
<td>LL-LA</td>
<td>Micro dose flare-up</td>
<td>Micro dose flare-up</td>
<td>LL-LA</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Oestradiol concentration on day of HCG (pg/ml)</td>
<td>697</td>
<td>4372</td>
<td>748</td>
<td>1117</td>
</tr>
<tr>
<td>No. of oocytes</td>
<td>9</td>
<td>19</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Endometrial thickness on day of HCG (mm)</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Trilaminal appearance on day of HCG</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Outcome</td>
<td>Delivery of a healthy infant of 1740 g at 30 weeks</td>
<td>Delivery of two infants of 2430 g and 2480 g at 33 weeks</td>
<td>Not pregnant</td>
<td>Not pregnant</td>
</tr>
<tr>
<td></td>
<td>Biochemical pregnancy</td>
<td>Not pregnant</td>
<td>Delivery of two infants of 1600 g and 2500 g at 37 weeks</td>
<td></td>
</tr>
</tbody>
</table>

HCG = human chorionic gonadotrophin; LL-LA = luteal-long leuprolide acetate; PCOS = polycystic ovarian syndrome.
Even in early stage cases, achieving remission and preserving the reproductive capability may not always be possible (Gurgan et al., 2007). Therefore, following progestin treatment, one should document the regression of cancer with repeat endometrial biopsy before an attempt to conceive either spontaneously or with assisted reproduction treatment. Since the routine use of office hysteroscopy before IVF to improve implantation is controversial (Bozdag et al., 2008), the authors did not perform it for cases B, C and D. Female age, history and duration of infertility, ovarian reserve, presence of anovulation or male-factor infertility are the determinants for the management strategy of such patients. For younger patients, with a shorter duration of infertility and reassuring ovarian reserve without anovulation or severe male-factor infertility, spontaneous conception may be attempted for a limited time period (Rackow and Arici, 2006). With a similar patient profile but with anovulation, ovulation induction with clomiphene citrate or exogenous gonadotrophin treatment with low-dose protocols may be undertaken (Rackow and Arici, 2006). If spontaneous or non-IVF ovulation induction fails in favourable patients, or immediate achievement of pregnancy is desired, IVF should be considered. Although few data are available after conservative management of endometrial carcinoma, assisted reproduction treatment does not seem to worsen the prognosis, and probably increases the chances of successful conception and decreases the interval to conception (Lowe et al., 2003).

There are little data on the optimal protocol for ovarian stimulation in patients with endometrial adenocarcinoma undergoing an assisted reproduction cycle. It may be postulated that high oestradiol concentrations during ovarian stimulation may exaggerate the progression of endometrial cancer, which is usually oestrogen dependent in young affected patients (Azim and Oktay, 2007). In a recent study, Azim and Oktay (2007) reported the use of a combined letrozole-FSH protocol for ovarian stimulation to diminish peak oestradiol concentrations in four patients (five cycles) with endometroid carcinoma undergoing IVF.

There is limited reported data on IVF outcome in patients with endometrial cancer following progestin treatment. Paulson et al. (1990) first presented a successful IVF pregnancy following treatment with daily 160 mg megestrol acetate for 6 months in 1990. Since then, as far as is known, there have been 12 reports of 24 infants conceived and delivered following IVF or ICSI without surrogacy (Paulson et al., 1990; Sardi et al., 1998; Shibahara et al., 1999; Ogawa et al., 2001; Pinto et al., 2001; Lowe et al., 2002; Nakao et al., 2004; Yarali et al., 2004; Demiroi et al., 2005; Park et al., 2006; Piau, 2006; Elizur et al., 2007). In this case report, clinical pregnancy was achieved in three of the seven ICSI cycles. The authors present four patients with a total of five pregnancies and six healthy infants. Three of the five pregnancies were achieved with an ICSI and the remaining two were spontaneous. In all patients, male-factor infertility necessitated ICSI.

The necessity of complementary surgery after the delivery of a healthy infant is not clear. Following complementary surgery with hysterectomy and bilateral salpingoophorectomy, only one case with a well-differentiated endometrial cancer has been reported to have a residual malignancy of the left ovary (Pinto et al., 2001). In all of the authors’ four patients, no residual cancer was noted during the pathological examination of the placenta or during repeat endometrial biopsy after delivery. Therefore, none of the patients wanted to undergo hysterectomy and bilateral salpingoopherectomy. However, great caution should be exercised during the follow-up of such patients. The recurrence of cancer following progestin treatment was evaluated in 13 patients with a mean follow-up of 82 months (Gotlieb et al., 2003). Despite regression of the endometrial cancer in all of the 13 patient with progestins, six had recurrence with a period extending between 19 and 358 months (median 40 months) (Gotlieb et al., 2003). These data indicate that such cases should be closely followed-up if hysterectomy is not performed.

It is concluded that fertility sparing may be considered in selected patients with early stage endometrial cancer. Assisted reproduction technology is a viable option to achieve immediate conception in such patients.

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