Case report

Pregnancy following intracytoplasmic sperm injection and preimplantation genetic diagnosis after the conservative management of endometrial cancer

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Abstract

A rare case of a patient with conservatively treated endometrial carcinoma who conceived and delivered a healthy baby after the transfer of embryos with intracytoplasmic sperm injection (ICSI) and preimplantation genetic diagnosis (PGD) is presented. A 41-year-old woman had an office hysteroscopy in the infertility work-up and stage I endometrial adenocarcinoma was diagnosed. After conservative treatment, the patient underwent ICSI and PGD. She achieved pregnancy with two normal embryos. Two gestational sacs were observed but one of them was blighted. The patient subsequently delivered a healthy female infant. Repeated office hysteroscopy and endometrial sampling was performed after delivery. The appearance of the endometrium was normal on hysteroscopy, and the histology report was normal. The principal concern with medical therapy is that the lesion cannot be fully evaluated until the hysterectomy is performed, the nodes palpated, and the uterus is sectioned. The patient was referred to a gynaecological oncologist for definitive surgery.

Keywords: *assisted reproduction, endometrial carcinoma, pregnancy, preimplantation genetic diagnosis*

Introduction

The standard therapy for endometrial cancer consists of staging laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Although most endometrial cancers occur around or after menopause (nearly 95%), other patients are affected during their child-bearing years (Crissman *et al*., 1981; Gallup and Stock, 1984).

In general, the prognosis in young women with endometrial carcinoma has been shown to be better than that in women older than 40 years because of high differentiation of the tumour and early stage disease (Gitsch *et al*., 1995). Therefore, conservative treatment such as hormonal therapy, chemotherapy or endometrial curettage may be recommended (Wentz, 1985). Successful pregnancies have been reported after conservative therapy (O'Neil 1970; Eddy 1978, Farhi *et al*., 1986; Lai *et al*., 1994; Kimming *et al*., 1995). After conservative treatment, assisted reproductive methods were applied in some cases and pregnancies were achieved (Paulson *et al*., 1990; Ogawa *et al*., 2001; Pinto *et al*., 2001; Lowe *et al*., 2002; Shibahara *et al*., 2002). Assisted reproduction is a good option to shorten the period to achievement of pregnancy.

This study presents the case report of a patient with conservatively treated endometrial carcinoma who conceived and delivered a healthy baby after the transfer of embryos by intracytoplasmic sperm injection (ICSI) and preimplantation

genetic diagnosis (PGD). As far as is known, this case report is the first to describe a successful pregnancy achieved by ICSI and PGD after conservative therapy of endometrial carcinoma.

Case report

A 41-year-old woman with a 2-year history of primary infertility was referred to the clinic for further investigation and treatment. She had been treated with three cycles of unsuccessful ovarian stimulation following intrauterine insemination (IUI) by another gynaecologist. Her menarche had been at the age of 16 years and her menstruation was regular. Her abdominopelvic examination was normal, as was a cervical smear test. She had no family history of diabetes, hypertension or cancer, and her body mass index was 22 kg/m^2.

Laboratory analysis at the early follicular phase yielded the following data: FSH 11.4 mIU/ml (normal, 2–13 mIU/ml), LH 6.3 mIU/ml (normal, 2–10 mIU/ml), oestradiol 91 pg/ml (normal 21–83 pg/ml). Semen analysis of the husband was normal according to the World Health Organization criteria (WHO, 1992). Hysterosalpingography (HSG) demonstrated bilateral normal patency, but there was an irregularity on the right corneal surface of the endometrial cavity. Transvaginal ultrasound showed normal looking ovaries, but there was a polyp-like appearance on the same area with HSG.

Treatment options were discussed with the couple. Assisted reproduction was recommended because of the advanced maternal age, elevated FSH concentrations and three previous failed stimulated IUI cycles. In order to confirm diagnosis and treatment, office hysteroscopy was performed under sedation with intravenous midozolam 1 mg/kg before the treatment cycle. The hysteroscopy was performed in the early proliferative phase using saline distension medium and a 5-mm continuous flow office hysteroscope (Bettocchi Office Hysteroscope, size 5; Karl Storz GmbH and Co., Tuttlingen, Germany). The scope was based on a rod lens system with a diameter of 2.9 mm and 30º view. The continuous flow sheath had an oval profile and maximum 5-mm diameter with an incorporated 5-Fr working channel; the mechanical instruments used were grasping forceps with teeth and scissors (Karl Storz). Intrauterine pressure was maintained at a constant 25/235 mmHg, using an electronic pump for irrigation and aspiration (Endomat; Karl Storz). Hysteroscopic examination showed an endometrial polyp around 1.5 cm on the right corneal area of the endometrial cavity, as suspected with HSG and transvaginal ultrasound. There were two other polyps <0.5 cm diameter in the same area. The polyps were excised with a forceps adapted to the hysteroscope and at the end of the procedure, endometrial biopsy was performed with aspiration. Histopathology identified endometrial adenocarcinoma, endometrioid type, grade I (polyp) and atypical endometrial hyperplasia (endometrial aspiration).

Pelvic and abdominal computerized tomography (CT) scan showed normal lymph nodes and normal intra-abdominal and pelvic organs. Magnetic resonance imaging (MRI) revealed a normal junctional zone. Chest X-ray was normal.

After consultation, the patient and her husband strongly requested conservative treatment for preservation of fertility. A gynaecological oncologist evaluated the patient and discussed the risks of conservative management. High dose progestin therapy was recommended, with megestrol acetate (Megace; Bristol Myers, Evensville, IN, USA) at a dose of 160 mg/day for 6 months. After the medical treatment, a repeat office hysteroscopy and dilatation and curettage was arranged. Histopathological examination did not show any residual malignancy. A repeat transvaginal ultrasound and MRI were also normal.

ICSI was performed as soon as possible after the treatment. The patient was placed on a ovarian stimulation protocol that began with daily subcutaneous injections of leuprolide acetate (Lucrin; Abbott, Rungis cedex, France) 0.5 mg on day 21 of that cycle and continued until day 3 of the next menstrual cycle. Ovarian suppression was achieved (oestradiol <40 pg/ml) with 600 IU/day of gonadotrophin (recombinant FSH, Gonal-F; Serono Laboratories, Geneva, Switzerland) started on day 3 or 4 and the dose was formulated on the basis of individual response. An ovulatory dose of 10,000 IU human chorionic gonadotrophin (HCG, Profasi; Serono Laboratories) was given when one follicle was 18 mm diameter and the other four follicles each had a diameter of ≥15 mm. Transvaginal ultrasound-guided oocyte retrieval was performed. Six oocytes were retrieved, of which all were metaphase II. ICSI was performed in all metaphase II oocytes as described previously (Van Steirteghem *et al*., 1993). Fertilization was observed 16–18 h after the injection. All the injected oocytes were fertilized and four of them cleaved. PGD was performed on day 3 because of advanced maternal age. Embryo biopsy was performed in Ca- and Mg-free medium (embryo biopsy medium; Vitrolife, Gothenburg, Sweden). Embryos were positioned and held such that a nucleated cell was placed adjacent to the intended biopsy site, and a 30- to 40-µm hole was opened in the zona pellucida (ZP) with a series of single pulses using a laser beam (Saturn 2 Laser System; Research Instruments, Falmouth, Cornwall, UK). Blastomeres were fixed separately with methanol:acetic acid (3:1) under an inverted microscope and fluorescence in-situ hybridization (FISH) was performed for chromosomes 13, 16, 18, 21, 22, X and Y. After PGD, two embryos had trisomy for chromosomes 21 and monozomy for 16 respectively. Two of the four embryos were diagnosed as normal and they were transferred on day 4. Luteal support was given by progesterone vaginal suppositories (Progestan; Koçak, Istanbul, Turkey). Two gestational sacs were seen by transvaginal ultrasound 4 weeks after embryo transfer. Two weeks later, ultrasound was repeated and there was fetal cardiac activity in one of the gestational sacs and crown–rump length was normal for the date of embryo transfer; the other sac was blighted. Pregnancy follow-up was performed with periodical examinations and amniocentesis was performed in the 17th gestational week. The result of the amniocentesis was normal with 46XX karyotype. There was no obstetric complication during pregnancy related to the advanced maternal age. All screening tests related to the pregnancy, including induced hypertension and gestational diabetes, were normal and periodical check-up tests were performed when necessary. Caesarean section was performed in the 39th gestational week, and a healthy, female infant weighing 3200 g was born.

Repeated office hysteroscopy and endometrial sampling was performed 10 weeks after delivery. The appearance of the

endometrium was normal in hysteroscopy and the histology report was normal. Conservative treatment permitted postponement of the definitive surgery to achieve pregnancy, but it could not replace surgery. With respect to this subject, the patient was referred to a gynaecological oncologist for definitive surgery.

Discussion

The standard treatment of stage 1 endometrial carcinoma consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy. In general, the prognosis in young women with endometrial carcinoma has been shown to be better than that in women older than 40 years because of high differentiation of tumour and early stage disease. In addition to this, progestagen therapy alone for early-stage, low-grade endometrial carcinoma arising in young women has been shown to reverse and regress the lesion to preserve fertility (John *et al*., 1974; Bochman *et al*., 1985; Farhi *et al*., 1986; Randall and Kurman, 1997). Moreover, a few cases of successful pregnancy have been reported after conservative therapies (O'Neil, 1970; Eddy, 1978; Farhi *et al*., 1986; Muechler, 1986; Lai *et al*., 1994; Niwa *et al*., 1994; Kimming *et al*., 1995; Kowalczyk *et al*., 1999)

With the development of more efficient fertility treatments, successful conception in women who respond to progestagen therapy has become possible. After conservative treatment, assisted reproductive techniques were applied in some cases and pregnancies were achieved (Paulson *et al*., 1990; Ogawa *et al*., 2001; Pinto *et al*., 2001; Lowe *et al*., 2002; Shibahara *et al*., 2002). In some of these cases, assisted reproduction was performed for immediate treatment to avoid the risk of recurrence of neoplastic endometrial lesions by oestrogens. In the present case, advanced maternal age, high FSH concentrations and previous failed stimulated IUI cycles were the other reasons for assisted reproduction treatment.

Conservative treatment with progestagens often fails to eradicate the carcinoma. In the literature, there are reports on patients who did not respond to conservative treatment and who therefore needed a hysterectomy (Kempson *et al*., 1968; Fechner *et al*., 1974; Greenblatt *et al*., 1982; Lee and Scully, 1989; Kim *et al*., 1997; Schammel *et al*., 1998; Mitsushita *et al*., 2000). The principal concern with medical therapy is that the lesion cannot be fully evaluated until the hysterectomy is performed, the nodes palpated, and the uterus is sectioned (Kurman *et al*., 1994). In this case, the patient was extensively counselled concerning the progression and recurrence of the disease, especially in advanced age. In this report, the patient and her husband declined standard surgical management and requested conservative treatment in an attempt to preserve her fertility. After delivery, the couple were counselled again and repeated hysteroscopy and endometrial sampling was performed. The histopathology was normal, but she was referred for definitive surgery to the oncology unit.

In conclusion, at the beginning of a treatment cycle, complete evaluation of the patient is very important. Office hysteroscopy is a well-established procedure for investigating endometrial pathology (Demirol and Gurgan, 2004). In this report, an endometrial polyp was recognized and removed by office hysteroscopy and endometrial carcinoma was diagnosed at the base of the polyp. A comprehensive guideline for selection, treatment and follow-up is not available for early-stage endometrial adenocarcinoma, but based on the review of the literature and on the data presented in this report, medical therapy may permit deferral of definitive surgery to achieve child-bearing. Assisted reproduction is an important option for giving a reasonable chance of pregnancy, and PGD is a valid technique for selected couples.

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