

Embryo cryopreservation after diagnosis of stage IIB endometrial cancer and subsequent pregnancy in a gestational carrier

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Objective: To describe a case of embryo cryopreservation before hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer.

Design: Case report.

Setting: University and community service.

Patient(s): An infertile woman with endometrial biopsy demonstrating grade II/III moderately differentiated endometrial adenocarcinoma.

Intervention(s): A Progestasert intrauterine device (IUD) was inserted into the uterine cavity to potentially reduce tumor proliferation during the stimulation cycle followed by oocyte retrieval and cryopreservation of 14 embryos.

Main Outcome Measure(s): Pregnancy.

Result(s): Successful pregnancy in a gestational carrier.

Conclusion(s): Embryo cryopreservation and use of a gestational carrier may offer a fertility option for patients with endometrial malignancies without substantially delaying treatment. (Fertil Steril® 2005;83:1041.e5–e7. © 2005 by American Society for Reproductive Medicine.)

Key Words: Endometrial cancer, gestational carrier, embryo cryopreservation

Endometrial cancer is the most common malignancy of the female reproductive tract and the fourth most common malignancy in women overall, with 40,320 new cases estimated for 2004. However, endometrial cancer accounts for only 3% of cancer deaths in women, reflecting the often curable nature of this disease (1). The vast majority of patients present with early stage disease limited to the uterine corpus (2). Five-year overall survival rates range from 76.3% for stage I disease and 59.2% for stage II disease, to 29.4% and 10.3% for stage III and IV, respectively (3).

Risk factors for endometrial cancer include those that lead to unopposed estrogen, such as anovulatory cycles, obesity, and nulliparity. Although the vast majority of cases of endometrial carcinoma involve postreproductive women, still about 5% of cases involve women under 50 years of age, who may not have completed their procreative plans. As women are delaying childbearing for personal and professional reasons, more women are faced with the dilemma of weighing treatments for endometrial cancer against the desire for future fertility. Several investigators have described conservative treatment for endometrial hyperplasia and cancers with use of progestins (4, 5). In vitro fertilization (IVF)

has been described in several case reports for patients treated conservatively, generally with stage IA disease (6–8). We are not aware of any reports in the literature of embryo cryopreservation with subsequent pregnancy in a gestational carrier for patients with more advanced endometrial cancer.

CASE REPORT

A 37-year-old woman with a long history of oligomenorrhea and infertility developed increasing dysmenorrhea and irregular bleeding. After 6 months, she presented to her gynecologist, who performed an endometrial biopsy that showed grade II/III endometrial adenocarcinoma. The patient had no family history of breast, colon, or ovarian cancer. As part of her evaluation, a pelvic ultrasound was performed that showed an endometrial stripe of 11 to 12 mm with regular texture.

Because the patient wished to remain fertile, she elected to delay definitive surgical staging and treatment to pursue options for assisted reproductive technology. Given the moderate grade and clinical stage of tumor, the patient was advised against using her own uterus for the gestation. Rather, care was promptly coordinated with the Reproductive Endocrinology Service so that the patient could undergo ovum retrieval. Before starting ovarian stimulation with gonadotropins, a Progestasert intrauterine device (IUD) was inserted into the uterine cavity to potentially reduce growth of the tumor during the cycle.

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After maturation of the follicles was sonographically documented, 21 oocytes were retrieved, and 14 were fertilized and cryopreserved at the pronuclear stage. Sixteen days after retrieval, the patient underwent a laparoscopic hysterectomy, bilateral salpingo-oophorectomy, appendectomy, and lymphadenectomy. Pathology showed moderately differentiated endometrioid adenocarcinoma with superficial myometrial invasion and endocervical stromal invasion. Given her stage IIB disease, she received whole pelvic four-field external beam radiotherapy postoperatively, receiving 5,040 cGy.

Two years after her treatment, with no evidence of recurrent disease by clinical and radiographic examination and serum tumor markers, the patient elected to proceed with transfer of her cryopreserved embryos to a gestational carrier. The patient had decided to wait the first 2 years when her risk of recurrence was highest. The gestational carrier, the patient's niece, was a 24 year-old gravida 3, para 1 woman with no notable past medical history. She underwent an extensive medical and psychological screening before proceeding as a gestational carrier for her aunt.

After all legal documents had been completed among the family members, the gestational carrier underwent a standard protocol for endometrial preparation. On the 11th day of estradiol valerate, transvaginal ultrasound was performed and an endometrial lining of 10 mm with a triple-line pattern was seen. Four days later, 25 mg of progesterone in sesame oil was given IM. Each morning thereafter 50 mg of IM progesterone was given.

Embryos were thawed 2 days after the progesterone was initiated. Two days after that, three 6-cell to 8-cell embryos were selected for transfer. Ten days after embryo transfer, her β human chorionic gonadotropin (β -hCG) level was 52 mIU/mL, which rose to 181 mIU/mL 2 days later. Her first vaginal ultrasound at 7 weeks' gestational age revealed a crown rump length of 13 mm with cardiac activity. She tapered her estrogen and progesterone injections and was off all hormone therapy by 10 weeks of gestation. The remainder of her prenatal course was uneventful, and she delivered a healthy baby boy, 8 lbs 1 oz, at term.

The patient is doing well, without evidence of disease, 5 years after treatment for endometrial cancer.

DISCUSSION

Endometrial cancer is surgically staged according to International Federation of Gynecology and Obstetrics (FIGO) criteria. Recommended surgical treatment for a well-differentiated stage IA tumor includes a hysterectomy and bilateral salpingo-oophorectomy. However, for patients desiring fertility and/or conservative management, the treatment of both endometrial hyperplasia and well-differentiated early adenocarcinomas using progestins has been described.

In 12 patients with well-differentiated adenocarcinoma, Randall and Kurman (9) found a 75% rate of initial regres-

sion with progestin therapy; no recurrence was noted at a mean follow-up of 40 months. In a case series and review of the literature, Kim et al. (5) noted that 13 of 21 patients (62%) with endometrial carcinoma had an initial response to progestin treatment. Only 3 of these patients became pregnant after treatment, and 3 other patients later developed a recurrence. Kaku et al. (4) reported that 75% of women (9 out of 12) with endometrial adenocarcinoma had an initial response to progestin therapy but 2 of these women developed a recurrence. Patients had been screened to rule out myometrial invasion using transvaginal ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI).

The use of a progestin IUD as a form of localized treatment has also been examined. Montz et al. (10) studied 13 patients with high perioperative risk (Society of Anesthesiologists, class III or IV) who had grade I endometrial adenocarcinoma with no myometrial invasion detected by imaging. Patients had a progesterone-containing IUD placed with subsequent endometrial biopsy sampling every 3 months over a period of 1 year. Negative biopsy samples were seen in 7 of 11 patients at 6 months, and 6 of 8 patients at 12 months.

These studies suggest that patients with well-differentiated stage IA adenocarcinomas may benefit from conservative treatment with high-dose oral as well as local progestin treatment. However, there still is a notable possibility of recurrence within the preserved uterus, and fertility plans should be pursued in an expeditious manner when possible. This can be particularly problematic for patients whose risk factors for endometrial cancer may also be associated with infertility, such as advanced maternal age, polycystic ovarian syndrome, anovulation, and obesity. In this setting, reproductive technologies seem potentially promising as a means both to treat infertility and to allow for more timely completion of child-bearing.

Several investigators have described successful pregnancies following assisted reproductive technologies in women with low-grade tumors. Shibahara et al. (7) report a case of IVF/intracytoplasmic sperm injection (ICSI) in a woman with a well-differentiated adenocarcinoma who had undergone multiple endometrial curettages before her pregnancy. Two months after delivery, she was found to be free of disease by transvaginal ultrasound and endometrial biopsy sampling. Pinto et al. (6) reported the case of a patient with a grade 1 carcinoma diagnosed at hysteroscopy who was treated with high-dose progesterone, followed by an IVF cycle. Following a cesarean section for triplets, a subsequent hysterectomy and bilateral salpingo-oophorectomy demonstrated no residual endometrial cancer, although a mixed endometrioid and clear-cell adenocarcinoma of the left ovary was found. Lowe (8) noted a patient with grade 1 endometrial cancer who was treated with progesterone and subsequently underwent an IVF cycle; 2 years after delivering twins, a frozen IVF cycle led to a second twin gestation.

In these cases, all of the patients were thought to have well-differentiated stage I endometrial adenocarcinomas based on histologic sampling and imaging studies. Outside of the well-differentiated stage IA adenocarcinoma, conservative medical treatment has not generally been advocated. Although there is some debate regarding low and intermediate grade tumors, generally full surgical staging including lymph node dissection has been advocated for stage I tumors (limited to the uterine corpus) with risk factors including high and moderate grade, invasion into the myometrium, and high-risk histologies such as clear-cell and uterine papillary serous carcinomas. In a patient with such factors, a delay in treatment of up to a year to achieve pregnancy and delivery, even with the aid of reproductive technologies such as IVF, may be detrimental to overall prognosis. In patients with more advanced stage disease or high risk factors who still desire fertility, the use of embryo cryopreservation with transfer to a gestational carrier offers a potentially useful alternative.

Moreover, as our case illustrates, it is often difficult to predict extent of disease based on endometrial sampling and imaging alone. Creasman et al. (11) found that 22% of 621 patients with clinical stage I endometrial carcinoma had disease outside of the uterus at the time of surgical staging. Even in patients with preoperative grade 1, stage I disease, Ben-Shachar (12) reported that 19% of patients were up-graded, 4.4% had positive lymph nodes, and 7.7% had other extrauterine sites of disease-spread. A delay in treatment may be detrimental in treating a patient who, in actuality, has higher stage or more aggressive disease histology. In this patient, surgical staging revealed invasion into the endocervical stroma consistent with stage IIB disease with grade 2 histology.

Certainly, further studies as well as case individualization are warranted. However, in highly motivated patients desiring fertility options in the setting of early endometrial cancers, the retrieval of oocytes and subsequent pregnancy in a gestational carrier may offer a means to achieve fertility

goals while minimizing delay of definitive treatment. Collaboration between the gynecologic oncologist and reproductive endocrinologist enabled this patient to safely maximize her reproductive desires.

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