Successful fertility-sparing surgery and chemotherapy for stage IC3 ovarian cancer with the postoperative use of the traditional Japanese herbal formulation hachimijiogan: A case report

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ABSTRACT

Case: A 32-year old, unmarried, nulligravida woman was diagnosed as having ovarian cancer stage IC3. The patient received six cycles of carboplatin and paclitaxel every 4 weeks after surgery. She was given a gonadotropin-releasing hormone agonist as an ovarian safeguard while receiving treatment with anticancer agents.

Outcome: After treatment with the traditional Japanese herbal formulation hachimijiogan and oral contraceptives, the patient spontaneously became pregnant and gave birth to a healthy baby at 40 gestational weeks.

Conclusion: A hachimijiogan treatment may be effective for treating decreased ovarian function following chemotherapy.

KEY WORDS: hachimijiogan, infertility, ovarian neoplasms, pregnancy

INTRODUCTION

The number of ovarian cancer patients hoping to get pregnant is expected to increase in proportion with the trend pertaining to late marriage. According to the International Federation of Gynecologists and Obstetricians (FIGO), fertility-sparing surgery in early epithelial ovarian cancer (stage IA) has been widely accepted although there is no consensus regarding conservative treatment for ovarian cancer at FIGO stage IC3 (stage IC ovarian cancer with malignant cells in ascites). It is well known that chemotherapy leads to infertility and premature ovarian failure, decreases the number of follicles, and leads to follicular maturation failure [1]. Carboplatin and paclitaxel are now frequently used in the treatment of epithelial ovarian cancer. Carboplatin confers an intermediate risk in relation to cytotoxic agents according to the degree of gonadotoxicity [2] and the adverse effects of taxanes have not been fully evaluated. Gonadotropin-releasing hormone (GnRH) agonists are useful in providing protection against ovarian toxicity and have been used to treat Hodgkin’s disease and breast cancer [3]. The traditional Japanese herbal formulation hachimijiogan, also known as hachimigan and Bā Wèi Di Huáng Wán in Chinese, was first described in classic Chinese medical publications. Hachimijiogan is comprised of eight types of herbs: rehmannia root, cornus fruit, dioscorea rhizome, alisma rhizome, hoelen, moutan bark, cinnamon bark, and aconite tuber. Hachimijiogan translates as an ‘8-ingredient pill with rehmannia’ with the following concentrations: rehmannia root (shu di huang, 5.0 g), cornus fruit (shan zhu yu, 3.0 g), dioscorea rhizome (shan yao, 3.0 g), alisma rhizome (ze xie, 3.0 g), moutan bark (mu dan pi, 3.0 g), cinnamon bark (gui pi, 1.0 g), hoelen (fu ling, 3.0 g), and processed lateral root of aconite (fu zi, 1.0 g). Hachimijiogan have been used to ameliorate low sexual energy. In most cases, symptoms that require a hachimijiogan treatment are observed in the elderly. Such symptoms include emaciation, skin dryness, weakening of the lower body, urinary problems, diabetes, benign prostatic hypertrophy, lower back pain, general arthrosis causing pain in the knee joint, hypertension, atherosclerosis, and a cold state. Hachimijiogan also changes the serum hormone levels and improves spermatogenesis in oligozoospermic men [4] and it may be effective in infertility treatments in women aged over 40 years because of its use to ameliorate low sexual
energy. However, to date, no English language reports of female infertility and treatment with hachimijiogan have been reported. Our presentation of this case represents an effort to answer the following questions: First, is fertility-sparing surgery in ovarian cancer at FIGO stage IC3 even reasonable? Second, is hachimijiogan an effective formula for protecting ovarian function during chemotherapy? We experienced a patient who spontaneously became pregnant after surgery and chemotherapy using hachimijiogan and a GnRH agonist for FIGO stage IC3 and who gave birth to a healthy baby at 40 gestational weeks.

**CASE PRESENTATION**

A 32-year old, unmarried, nulligravida woman was referred to our outpatient clinic for the chief complaint of abdominal discomfort over the previous month. Ultrasonography demonstrated a solid ovarian tumor with lobular components. Magnetic resonance imaging showed a cystic solid mass measuring 6 × 5 cm with a small solid portion in the right adnexa. No ascites were observed. The CA125 level was 90 U/mL and the CA19-9 level was 214 U/mL. She strongly preferred fertility-sparing surgery. After an extensive discussion, written consent was obtained and she underwent a right salpingo-oophorectomy. The final histopathological diagnosis was endometrial adenocarcinoma grade 2 and peritoneal cytology was positive. She was diagnosed as having ovarian cancer at FIGO stage IC3. The patient received six cycles of carboplatin and paclitaxel every 4 weeks after surgery. She was given a GnRH agonist as an ovarian safeguard while receiving treatment with anticancer agents. She experienced an absence of menses for 6 months after completion of GnRH agonist administration and anticancer drug treatment. Following chemotherapy, amenorrhea persisted for approximately 6 months. Irregular menses spontaneously resumed 6 months after the last chemotherapy cycle. We initiated oral contraceptives to regulate the menstrual cycle. Three courses of oral contraceptives were initiated but her menses period did not spontaneously start. Therefore, we administered hachimijiogan. Three months after the administration of the last oral contraceptive, she successfully menstruated. Her follicle-stimulating hormone (FSH) level decreased from 64 mIU/mL to 12 mIU/mL after the last chemotherapy cycle before pregnancy (Fig. 1). Her antimüllerian hormone (AMH) levels were <1 ng/mL during chemotherapy and before the last chemotherapy cycle 2 months later. The AMH levels increased to 1.6 ng/mL after resumption of menses and subsequently decreased to <1 ng/mL after the final administration of oral contraceptives. — AMH; — FSH.

**DISCUSSION**

The clinical course of this patient raised two important clinical issues. At present, 5 years after the surgery, there are no signs of recurrence. While there is no true consensus regarding fertility-sparing surgery for ovarian cancer at FIGO stage IC with malignant cells in ascites (FIGO stage IC3), a report has stated that this surgery is feasible, even with malignant cells in ascites, if the patient receives follow up with adjuvant chemotherapy [5]. There were no significant differences in 5 year overall survival and disease-free survival rates between patients treated with fertility-sparing surgery and those who underwent radical surgery for ovarian cancer at FIGO stage IC with malignant cells in ascites [6]. On the other hand, fertility-sparing surgery for patients with epithelial ovarian cancer (Stage IA, Grade 1 disease) is a reasonable consideration in young patients who wish to preserve their fertility [7]. Consequently, we must take into account the individual circumstances of our patients, despite the lack of consensus regarding fertility-sparing surgery for ovarian cancer at FIGO stage IC3.

Carboplatin is said to confer an intermediate risk in relation to cytotoxic agents according to the degree of gonadotoxicity, whereas there are currently no data on paclitaxel [2]. Therefore, we consider protection of the ovaries to be necessary and one treatment option is ovarian suppression. Currently available options for fertility preservation in women treated for breast cancer include embryo cryopreservation, oocyte cryopreservation, ovarian tissue freezing, and ovarian suppression [8]. Embryo cryopreservation,
oocyte cryopreservation, and ovarian tissue freezing involve the risk of a possible recurrence of ovarian cancer because of damage to the ovaries. Thus, ovarian suppression is controversial. The efficacy of the GnRH-agonist in providing protection against ovarian toxicity has been reported [3]. However, GnRH-agonist co-treatment does not provide a significant protective effect for ovarian function in patients receiving cyclophosphamide-based chemotherapy [9]. Whether the effects of a GnRH-agonist are adequate for patients with ovarian cancer remains to be evaluated. In Japan, infertility is on the rise because of the trend pertaining to late marriage coupled with the age-related decline in oocyte quality. Hachimijiogan is considered effective in improving the age-related decrease in reproductive function. Although hachimijiogan has been sporadically prescribed in daily clinical practice to women aged over 40 years who have undergone in vitro fertilization (IVF), there is no clear evidence that shows its effectiveness. Here, we report our experience with a patient who wished to bear a child, despite her decreased ovarian function following postoperative chemotherapy for ovarian cancer, and who successfully gave birth after treatment with hachimijiogan. Dehydroepiandrosterone (DHEA), a well-known nutrient found in the South American wild yam, significantly increases the number of developing follicles in women undergoing IVF, decreases the abortion rate, and increases AMH levels [10]. In this case, the patients’ AMH levels did not change. On the other hand, improvement in hormone level reportedly associated with hachimijiogan [4] might decrease the FSH level. The Radix Dioscoreae Oppositae contained in hachimijiogan may also have a DHEA-like action. The DHEA-like action raises the possibility that hachimijiogan contributes to ovarian function. In addition, the bloodstream-improving effects of dried aconite root and Chinese cinnamon, which are constituents of hachimijiogan, may help to improve uterine function.

A hachimijiogan treatment may be effective for treating decreased ovarian function following chemotherapy. Our experience with this case contributes to the management of ovarian cancer patients hoping to preserve their fertility and later become pregnant.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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