Main Research Article

Young girls with malignant ovarian germ cell tumors can undergo normal menarche and menstruation after fertility-preserving surgery and adjuvant chemotherapy

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Abstract

Objective. To evaluate the long-term outcome and ovarian function in premenarcheal and adolescent patients with malignant ovarian germ cell tumors after fertility-preserving surgery and adjuvant chemotherapy. Design. Retrospective review of medical records. Setting. Ajou University Hospital, a tertiary care hospital in South Korea. Population. Forty-five patients with malignant ovarian germ cell tumors. Methods. A retrospective analysis of patients with malignant ovarian germ cell tumors was conducted and a statistical analysis was performed. Main outcome measures. There were 9 premenarcheal and 16 adolescent patients; the median ages at diagnosis were 7 and 18 years, respectively. All patients were treated with fertility-preserving surgery. Seventeen of the patients received adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (68.0%). There were no disease recurrences or deaths. Of the nine premenarcheal patients, eight (88.9%) subsequently had normal menarche. Among the 16 adolescent patients, 15 (93.8%) resumed normal menstruation and 1 had premature ovarian failure. Conclusion. Premenarcheal and adolescent patients with malignant ovarian germ cell tumors have excellent survival with fertility-preserving surgery and adjuvant chemotherapy. The majority of these patients can have normal menarche and menstruation.

Key words: Malignant ovarian germ cell tumor, premenarche, fertility-preserving surgery

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare gynecologic malignancies and account for approximately 5% of all ovarian malignancies in Western countries (1). These tumors occur mainly in children and young women, have high chemosensitivity, and are predominantly unilateral (2,3). Therefore, most young patients with MOGCTs undergo fertility-preserving surgery, followed by platinum-based chemotherapy, and have an excellent prognosis (2,4–8).

There have been a number of studies with a focus on reproductive function after conservative surgery and chemotherapy in young women with MOGCTs. Most investigators have reported that fertility-preserving surgery with adjuvant chemotherapy is associated with a favorable prognosis and preserves ovarian function (8–16). Recently, Gershenson et al. reported a large prospective, matched case-control study involving 132 MOGCT survivors and 137 controls with respect to menstrual and reproductive outcomes (17). Of the 71 survivors who had fertility-sparing surgery, 62 (87.3%) had normal menstrual periods, and 24 (33.8%) delivered 37 infants. The authors concluded that women who underwent fertility-sparing surgery were very likely to retain menstrual function and fertility after chemotherapy.

Up to 20% of MOGCTs occur in premenarchal girls (8). However, the reproductive function of these patients has received relatively little attention. Although some investigators have reported that normal menarche occurs in most premenarchal MOGCT patients treated by fertility-sparing surgery and...
adjacent chemotherapy (14–16), these results do not provide adequate information on the feasibility and safety of conservative surgery and chemotherapy.

The purpose of this study was to investigate whether fertility-preserving surgery and adjuvant chemotherapy influences the clinical outcome and menstrual function in premenarchal and adolescent patients with MOGCTs.

Material and methods

This retrospective study included all patients with a pathologic diagnosis of a MOGCT who were evaluated and treated at the Ajou University Hospital between June 1994 and December 2008. The study was conducted in accordance with local regulations and with the approval of the local Institutional Review Board. A total of 45 MOGCT patients underwent primary surgery in our institution. The patients who were >25 years of age were excluded and a total of 25 patients with MOGCTs were identified and analyzed. The medical records were reviewed to obtain details regarding patient age, gravidity, parity, personal medical-surgical history, preoperative serum levels of tumor markers (α-fetoprotein, β-human chorionic gonadotropin, CA-125, and lactate dehydrogenase), type of primary surgery, stage, histology, grade, tumor size, adjuvant chemotherapy, duration of follow-up, disease recurrence, and deaths.

MOGCTs were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (18). Surgery was the initial treatment for all patients. The goals of surgery were to achieve complete resection or optimal tumor debulking with removal of as much gross tumor as could be done safely while preserving fertility. The surgery followed institutional guidelines, which recommend an open laparotomy, washing cytology, surgical staging, a fertility-conserving procedure with removal of the affected ovary and other gross tumor manifestations, an omental biopsy, and biopsy of the contralateral ovary if dysgerminoma is suspected in the primary site. After the surgical specimen was analyzed by frozen-section histopathology and the surgical exploration was performed with thorough inspection and palpation, the decision about further surgical procedures was made. Systemic pelvic and/or para-aortic lymphadenectomy was performed in patients who had tumors with ruptured capsules or capsular invasion identified on frozen-section, enlarged lymph nodes, or gross lesions on abdomino-pelvic cavity.

Histologic diagnosis was established after surgical resection. The pathologic specimens were reviewed in detail, and the histologic type was defined according to the World Health Organization classification (19).

Chemotherapy was administered according to the bleomycin, etoposide, and cisplatin (BEP) regimen (bleomycin [10–15 mg daily on days 1–3], etoposide [100 mg/m² daily on days 1–3], and cisplatin [100 mg/ m²/day on day 1]). Four courses of BEP were administered to patients with advanced MOGCT or high grade tumors (Grade 2 or more). Before each course of chemotherapy, patients had a complete blood count, platelet count, chemical survey, and serum tumor marker studies, as indicated. Pulmonary and renal function tests were monitored closely in all patients. Chest radiographs were obtained as indicated.

Follow-up information was abstracted from the medical records for all patients after completion of chemotherapy. Patients were evaluated at 3-monthly intervals during the first year and at gradually increasing intervals thereafter. In addition, follow-up information regarding each patient’s tumor status, last physician visit, menstrual history, and use of hormones was obtained on all patients by telephone. Normal menstruation was defined as regular menstruation within a range of approximately 21–42 days established by the 7th cycle.

All patients were grouped by menstrual status into the following two groups: (1) the premenarchal group who had not commenced menstruation and (2) the menstruating adolescent group.

Results

Twenty-five young patients with MOGCTs had been evaluated at Ajou University Hospital since 1994. There were 9 premenarchal and 16 adolescent patients; the median patient age was 7 years (range 4–12 years) and 18 years (range 14–23 years), respectively. The most common histologic type was an immature teratoma (n = 12; 48.0%). Twenty-one tumors were FIGO stage I, and four were of advanced stage. Mean tumor size was 14 cm (range 4–24 cm). All patients underwent fertility-preserving surgery; 16 patients had a unilateral salpingo-oophorectomy (USO) or cystectomy only and 9 patients a USO or cystectomy with surgical staging procedures, including peritoneal washing, omentectomy, pelvic and/or para-aortic lymphadenectomy, and resection of any grossly visible masses. Adjuvant chemotherapy was administered to 17 (68%), and all received four courses of BEP. After a median follow-up of 66 months (range 8–162 months), all patients were alive and disease-free (Table I).
Table I. Characteristics of patients with malignant ovarian germ cell tumors.

<table>
<thead>
<tr>
<th>Type of surgery (n)</th>
<th>Mean tumor size (cm, range)</th>
<th>FIGO stage (n and %)</th>
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<tbody>
<tr>
<td></td>
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<td>Ia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>14 (8–20)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td></td>
<td>17 (4–24)</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>USO or cystectomy</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>only</td>
<td></td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>USO or cystectomy</td>
<td>6</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>+ staging procedure</td>
<td>10</td>
<td>6 (31.3)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>12 (75.0)</td>
<td>5 (55.6)</td>
</tr>
</tbody>
</table>

Median follow-up (months) 66 (8–162)
Histologic type (n and %)

| Dyserginoma | 1 (11.1) |
| Yolk sac tumor | 1 (11.1) |
| Immature teratoma | 5 (55.6) |
| Mixed germ cell tumor | 2 (22.2) |

Staging procedures include peritoneal washings for cytology, omentectomy, pelvic and/or para-aortic lymphadenectomy, and resection of grossly visible masses.

Note: USO, unilateral salpingo-oophorectomy; BEP, bleomycin, etoposide, and cisplatin; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Menstrual function of malignant ovarian germ cell tumors patients after adjuvant chemotherapy (n = 17).

<table>
<thead>
<tr>
<th>Menstrual status</th>
<th>Prepubertal</th>
<th>Menstruation</th>
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<tbody>
<tr>
<td>(n = 5)</td>
<td>(n = 12)</td>
<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Menstruation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular*</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Irregular</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Secondary amenorrhea</td>
<td>0</td>
<td>1</td>
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*Regular cycles within a range of approximately 21–42 days.

Discussion

We investigated whether fertility-preserving surgery and adjuvant chemotherapy influenced the clinical outcome and menstrual function in premenarchal and adolescent patients with MOGCTs. Our findings indicate that fertility-preserving treatment for MOGCTs, perhaps even in advanced stages, can provide these young patients with good survival and normal menstrual cycles, which corresponds with the findings of an earlier study which reported that children with MOGCTs have an excellent prognosis (20).

Of the nine premenarchal patients, eight (88.9%) subsequently underwent normal menarche. Among the 16 adolescent patients, 15 (93.8%) resumed normal menstruation and 1 had premature ovarian failure. The two patients who did not menstruate were from among those who were treated with adjuvant chemotherapy (Table II). There were no attempts to conceive or pregnancies during the follow-up period.

Of the 17 patients who underwent fertility-sparing surgery and platinum-based chemotherapy, there were 2 who did not have menstrual cycles (11.7%). One was a 21-year-old woman with a Grade 2 immature teratoma. Her menstruation ceased after three cycles of adjuvant chemotherapy and never resumed; an elevated follicle-stimulating hormone level confirmed menopause (secondary amenorrhea). The other patient was nine years of age and prepubertal at the time of the study.

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It is well-known that a proportion of women may experience premature menopause following chemotherapy (23). Chemotherapy, especially alkylating agents, can cause DNA-directed lesions of the ovary, and induce impairment of ovarian function (24). The most toxic of the alkylating agents are chlorambucil, cyclophosphamide, ifosfamide, melphalan, busulfan, and procarbazine (25).

The precise mechanism for the high sensitivity of ovarian tissue to the effects of chemotherapy is unclear. Blumenfeld and Eckman reported that ovarian function is preserved in most long-term survivors who are treated prepubertally for lymphomas, but only in about a half of similarly treated adult patients (26). It has been hypothesized that chemotherapy-induced injury to ovarian tissue may result in a feedback loop with follicular loss, placing additional germ cell tissue at risk for damage (27). We postulate that because premenarchal girls have relatively quiescent ovarian tissue, the risk for loss of ovarian follicles may be reduced.

After the BEP regimen was shown to yield successful treatment results for MOGCTs, it became the new standard treatment for MOGCTs, replacing the VAC regimen (28–30). The BEP regimen of current study is similar to that of Brewer et al. (9). They changed the planned number of cycles depending on the response, the patient’s tolerance, and the preferences of the attending physicians. We unified the number of cycles. The dose of platinum may be too much for Stage I patients, but there were no serious problems.

Because of the rarity of these tumors, it is difficult to gather large numbers of patients. Therefore, achieving significant differences in statistical analyses is unlikely. We had clinical data to estimate ovarian function, but no objective data, such as hormonal profiles, were available. The follow-up period was also too short to demonstrate the reproductive outcome or long-term effects of treatment. The median age of adolescent group at the time of this report was 23 years, which is a relatively low age to have a baby. Actually, there were no attempts to conceive. The data presented here do, however, suggest that fertility-preserving surgery followed by combination chemotherapy may yield excellent survival and will not affect normal menstrual function in premenarchal and adolescent girls. Fertility-preserving surgery with or without chemotherapy should remain the standard of care for patients with MOGCTs.

References

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