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Research article

Fertility sparing surgery for stage Ic ovarian cancer: An eight case series

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Abstract

Introduction. One case out of 3 cases of primary ovarian cancer is diagnosed at an early stage. Almost 15% of ovarian cancers are diagnosed in women who are within the range of procreation age, raising the debate on the feasibility of fertility-sparing surgery (FSS) for those tumors. In the case the patient is admitted with stage 1A or 1B in most histologic types, it is still controversial in stage 1C.

Results and Discussions. This is an eight-patient-case series. The median age is 27 years old (ranging from 18 to 42). The main clinical manifestation was pelvic pain (87.5%). Four patients (50%) presented with tumor torsion. All patients underwent FSS; five of them (62.5%) had conservative staging, two (25%) underwent salpingo-oophorectomy and one (12.5%) ovariectomy, type histo + stade Figo. The chemotherapeutic treatment was administered to four patients (50%) following surgery without major side effects. One patient (12.5%) presented a loco regional recurrence that occurred 14 months later. She was treated with combined chemotherapy and radical surgery. One patient out of eight (12.5%) achieved a natural pregnancy after the treatment and another one (12.5%) was submitted to an assisted reproductive procedure which did not result in a viable pregnancy.

Conclusion. FSS seems to be a suitable approach for stage 1C ovarian cancer. However, more case series and meta-analyses should be conducted.

Keywords

: ovarian cancer, stage IC, surgery, fertility

Highlights

- ✓ Although radical surgery remains the gold standard in the treatment of ovarian cancer, the fertility sparing surgery can be an alternative for young patients with the desire of conceiving.
- ✓ For this approach cautious selection of patients is crucial depending on the tumor grade, disease stage, histologic subtypes and prognostic factors.

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Introduction

One case out of 3 cases of primary ovarian cancer is diagnosed at an early stage (1). The diagnosis of ovarian cancer in women of reproductive age has become more common, around 15% (2), since marriage was delayed until around the age of thirty (3). Therefore, fertility preservation is critical. Although radical surgery remains the gold standard in the treatment of this disease, fertility-sparing surgery (FSS) can be undergone by young patients with the desire of conceiving. FSS showed promising results in both oncologic safety and fertility preservation, however, there is a controversy over FSS in stage 1C of the disease. Therefore, a cautious selection of patients is crucial depending on many factors (4). Our aim is to report FSS trials in stage 1C of ovarian cancer and discuss their feasibility.

Materials and Methods

This retrospective case series involves 8 patients diagnosed with stage 1C ovarian cancer and treated at our Institute between January 2000 and May 2015. All the patients who had stage 1C ovarian cancer with desire of pregnancy were included. The FSS consisted in the preservation of the uterus and the healthy ovary with surgical staging. It comprised peritoneal cytology, omentectomy and multiple peritoneal biopsies. Lymphadenectomy was performed systematically for epithelial ovarian cancer, whereas for the other histological subtypes it was only performed if there were suspicious lymph nodes. The FIGO 2014 ovarian cancer staging classification was used in writing this manuscript. The pathological diagnosis was made according to the international histological classifications provided by the World Health Organization (WHO). According to the decision of a multidisciplinary meeting, chemotherapy was indicated to all patients with 1C tumors, with a tumor size >15 cm, poorly differentiated tumors and age inferior to 30 years.

Results

The median age was 25 years old (ranging from 18 to 42). Three patients were married and had already conceived. The median time for referral to the institute was 60 days (between 30 and 365). The main clinical manifestation was pelvic pain (87.5%). The abdominal examination revealed that two patients had palpable hypogastric mobile masses (25%). Four patients (50%) presented with acute abdominal pain due to tumor torsion. All patients underwent preoperative abdominopelvic sonography. The patients with tumor torsion underwent emergency surgery and the sonography was done by the gynecologist and for that reason a full report is not

currently available. The four remaining patients had the sonography done by a radiologist. All four tumors had both solid and cystic components. Two of the tumors were located in the right ovary, one in the left one, while for the last patient it could not be associated to any of the ovaries. The median size was 150 mm (between 140 to 170). Tumor markers such as: alpha fetoprotein (AFP), beta-chorionic gonadotropic hormone, CA125 were measured in three patients and presented high values in one patient. The eight patients underwent FSS; five of them had conservative staging (62.5%), three salpingo-oophorectomy (25%), two had germ cell tumors and one patient who had epithelial cancer refused further surgery. Four patients out of eight underwent unilateral pelvic lymphadenectomy. Four patients (50%) underwent para-aortic lymphadenectomy (Table 1). The median size in the histological examination was 100 mm (between 60 to 220). The other two patients had a different regimen of chemotherapy. One patient had four courses of EC (Etoposide and Cisplatin), since there was a shortage of Bleomycin at the time. The last one with epithelial ovarian cancer had four courses of Carboplatin-Taxol. No major side effects were reported for the four patients (Table 2). The median follow-up period was 55 months (between 13 and 199). One patient with epithelial ovarian cancer and who only underwent salpingo-oophorectomy, refusing further therapy, suffered a loco-regional relapse after 14 months (Table 2). The treatment combined the completion of surgery including hysterectomy, contralateral salpingo-oophorectomy, peritoneal cytology, omentectomy, multiple peritoneal biopsies and pelvic and para-aortic lymphadenectomy with chemotherapy. Two patients out of eight succeeded to conceive. One patient achieved a full term viable natural pregnancy (Table 2). The second one (12.5%) used assisted reproductive technology to get pregnant, but she had a miscarriage after 16 weeks of amenorrhea.

Discussions

Radical surgery consisting in total hysterectomy plus bilateral salpingo-oophorectomy associated with peritoneal staging and lymph-node sampling remains the gold standard in the treatment of early stage ovarian cancer. However, fertility-sparing surgery (FSS) can be proposed to selected patients who want to get pregnant (5). FSS is defined as unilateral salpingo-oophorectomy and the optimal surgical staging depends on the histologic type: peritoneal cytology, omentectomy, multiple peritoneal biopsies and lymph node sampling (6). This conservative management can be suggested to selected women depending on tumor grade, disease stage, histologic subtypes and prognostic factors (6).

Table 1. Patients' characteristics

Patients	Age	Tumor Morphology	Frozen section	Surgery	Contro-lateral ovary	Pelvic lymph-adenectomy	Para-aortic lymphade-nectomy	Final histology	FIGO
1	24	Solido-cystic	Malignant	Conservative staging	Wedge biopsy	Left	Yes	Immature teratoma grade 1	I C1
2	28	Cystic	-	USO	No	No	No	Immature teratoma grade 1	I C2
3	29	Solido-cystic	-	Conservative staging	Wedge biopsy	Right	Yes	Immature teratoma grade 3	I C2
4	25	Solid	-	Conservative staging	Wedge biopsy	Right	Yes	Serous cystadenocarcinoma grade 3	I C2
5	42	Solido-cystic	-	USO	No	No	No	Papillary serous cystadenocarcinoma	I C1
6	35	Cystic	-	Conservative staging	Wedge biopsy	Bilateral	Yes	Papillary serous cysradenocarcinoma	IC2
7	20	Solido-cystic	Malignant	Conservative staging	No	Right	No	Sertoli-Leydig tumor	I C1
8	18	Cystic	-	USO	No	No	No	Immature Teratoma grade 3	IC2

*USO: Unilateral Salpingeco- Oophorectomy * - : Not mentioned*conservative staging: USO + Staging surgery (peritoneal cytology, omentectomy and multiple peritoneal biopsies)

1. Oncologic safety

FSS is suggested to women with fertility desire who were diagnosed with FIGO stage 1A grade 1 tumors (7). For stage 1C ovarian cancer, the use of FSS remains controversial (5). The analysis of the SEER (Surveillance Epidemiology and End Results) database showed the absence of influence on survival of ovarian preservation in stage 1A or 1C disease (8).

Kajiyama et al. demonstrated that no significant difference in disease free survival (DFS) or overall survival (OS) was found between the young patients with stage 1C1 and those with stage 1A who underwent FSS. However, they found a difference in DFS and OS between 1C2/3 and 1A (9). The study conducted by Park *et al.* in 2008 concluded that FSS could be undergone by young patients with 1A-C grade 1-2 (10). A Japanese multicenter study

recommended conservative management in stage 1C only with favorable histological subtype including serous, mucinous and endometrioid subtypes in epithelial ovarian cancer (5). The recommendations of the Fertility Task Force of the European Society of Gynecologic Oncology (3) concluded that FSS is safe in epithelial ovarian cancer for stage 1C grade 1 and it presented an option for stage 1C grade 2. However, it is contraindicated for grade 3 tumors, stage >1 and histologically aggressive tumors (11). In a recent study, Kashima et al. mentioned that the recurrence rate for FIGO stage 1C was 16.4%. They also showed that a 46.8% recurrence rate was described in the residual ovary (8). In our study, one patient (12.5%) who only underwent unilateral salpingo-oophorectomy and refused further treatment experienced recurrence in the contralateral ovary. Satoh et al. (5) suggested that FSS followed by chemotherapy might be suggested to FIGO stage 1C patients with favorable histology (5).

There is a lack of information about chemotherapy schemes, however a platinum-based regimen is frequently used. At least four or six courses of platinum-based adjuvant chemotherapy improve survival and delay recurrence in the early stage of ovarian cancer (12, 13). The use of completion surgery after pregnancy, or after the age of 40 years is still under debate, but it could be considered in order to reduce the risk of recurrence on the spared ovary (6).

2. Fertility outcome

The diagnosis of ovarian cancer in women of reproductive age has become more common, since marriage was delayed until around the age of thirty (3).

FSS can be therefore undergone by early-stage ovarian cancer patients who want to retain fertility. In some studies, the biopsy of the contralateral ovary was not regularly done because of the risk of postoperative adhesions which can induce infertility (6, 14). In previous studies (3), we noticed cases in which pregnancy was achieved naturally or by means of assisted reproductive technology. Two patients out of eight succeeded to conceive. One patient achieved a full-term viable natural pregnancy (Table 2). The second one (12.5%) used assisted reproductive technology to get pregnant but she had a miscarriage after 16 weeks of amenorrhea. Although information about the effect of chemotherapy on the ovarian function is still subject to debate, the existing studies in the literature did not succeed in determining the exact consequences of chemotherapy on the ovarian function. It is known that systemic treatment will reduce the ovarian reserve, but it does not necessarily mean infertility (9). Chemotherapy and fertility are difficult topics to study for two reasons: first, the scarcity of published cases in the literature and second, the absence of a key determinant of fertility (15, 16). The best time for pregnancy after undergoing a conservative treatment has not been established. Since the time period of follicle development is six months, it is safe not to conceive in the first six months after chemotherapy (6).

Table 2. Patients Outcomes

Patients	Chemo-Therapy	Type of CT	Loco-regional recurrence	Time to recurrence	Localisation of recurrence	Treatment	Pregnancy	Type of pregnancy	Follow-up period in months	Death
1	No		No				No		144	No
2	No		No				No		13	No
3	Yes	Cisplatin-Etoposide	No				Yes	Natural	199	No
4	Yes	Taxol-carboplatinum	No				Yes	Assisted reproductive procedure	48	No
5	No		Yes	14 months	Contra-lateral ovary	Radical surgery + CT	No		24	No
6	No		No				No		82	No
7	Yes	BEP	No				No		55	No
8	Yes	BEP	No				No		120	No

Conclusions

One case out of three cases of primary ovarian cancer is diagnosed at an early stage. Moreover, the diagnosis of ovarian cancer in young women has become more frequent since the age of marriage tends to be postponed. Although radical surgery remains the gold standard in the treatment of this disease, fertility-sparing surgery (FSS) can be undergone by young patients with the desire of conceiving. The cautious selection of patients is crucial depending on the tumor grade, disease stage, histologic subtypes and prognostic factors. This retrospective case series, with one case of recurrence and two patients getting pregnant, showed that conservative management was a suitable option. However, the controversy over stage 1C disease still remains unsolved and more case series and meta-analyses are required to support our conclusion and then provide a higher grade of recommendation to FSS in stage 1C ovarian cancer.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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