Fertility sparing in young women with ovarian tumors

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Summary

Background: Surveys have shown that fertility sparing in patients with ovarian tumors has proven to be effective. Thus this approach in ovarian tumor cases has been carried out. The purpose of this study was to evaluate the clinical outcome and pregnancies in women who suffered from ovarian tumor and underwent conservative treatment. *Materials and Methods:* All cases who received conservative treatment and those who had recurrence of the disease during the follow-up period were evaluated at Vali-Asr Hospital from 2000-2004. *Results:* 60 of 410 patients with ovarian tumor (age range: 13-34) were treated conservatively. Three patients (5%) were infertile. Histology of tumors showed: 26 (43.3%) germ cell tumors, 15 (25%) borderline tumors, ten (16.7%) epithelial tumors and nine (15%) sex cord tumors. The cases were followed for 12-48 months. Seven term pregnancies occurred in six patients. Three in the borderline group, two in the germ cell group, one in the epithelial group and one in the sex-cord group. Nine recurrences were reported among our cases. Two of the patients (serous carcinoma and immature teratoma, both Stage IIIc) died during follow-up due to refusal to undergo radical surgery. *Conclusion:* Fertility preserving surgery in young women with epithelial ovarian tumors, borderline and sex-cord tumors Stage I, grade 1 and 2 is recommended.

Key words: Ovarian tumors; Young women; Desire of fertility; Fertility sparing; Epithelial ovarian tumor; Germ cell tumor; Borderline ovarian tumor.

Introduction

Although ovarian malignancy is predominantly a disease of aging, there is an increasing number of women that survive these malignancies before or during reproductive years. Eighty-nine percent of ovarian tumors occur after the age of 40 and the rest occur before this age [1].

The standard treatment for borderline and malignant ovarian tumors is cytoreductive surgery such as hysterectomy, oophorectomy, partial omentectomy and surgical staging. Surgical staging reveals the need for adjuvant chemotherapy to detect extension of the disease. Cytoreductive surgery causes infertility and, due to this, conservative surgery has been introduced [2, 3].

Conservative surgery consists of unilateral salpingo-oophorectomy, omentectomy, surgical staging, and debulking of metastases in germ cell tumors [4].

The 5-year survival of patients with Stage IA, grade 1, epithelial ovarian tumor who were treated conservatively is 90% [5, 6]. Germ cell tumors represent most (80%) of the pre-adolescent malignant ovarian neoplasms.The mean age at diagnosis is 16 to 20 years and the tumors may occasionally be diagnosed during pregnancy or puerpurium [7-10]. Sex cord-stromal tumors (SCSTs) are characterized by 85-100% long-term survival rates for Stage IA tumors, and they have a propensity for late recurrences [11]. Sertoli-Leydig cell tumors account for less than 0.5% of all ovarian tumors, and 75% of these neoplasms are diagnosed in women younger than 40 years of age [11].

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In Ayhan *et al.'s* study, it was noted that diagnosis of ovarian tumors in the premenopausal period has increased by improvement of diagnostic methods and regular gynecologic examination. Ovarian tumors that have been diagnosed in the premenopausal period are mostly in their early stage and lower grade and can be treated by a conservative surgery [4].

Although a variety of studies have tried to document the impact of conservative treatment aimed at preserving ovarian function and reproductive ability, little information is available regarding survivors [5, 12, 13].

Many studies have shown that conservative surgery in patients with germ cell ovarian tumors is successful in outcome and preservation of fertility [8-10].

In a series of borderline tumors (82 patients) with conservative management, fertility and survival have been acceptable after a 25-year follow-up [14].

In another study on 17 patients with Stage II and III borderline ovarian tumors, eight spontaneous pregnancies occurred. After conservative surgery, studies show the effect of conservation surgery on patients with an advanced stage of borderline ovarian tumors [15].

Another study on borderline ovarian tumors shows that there is no significant difference regarding the survival of patients who are treated by conservative surgery or radical surgery, although there are more recurrences in patients with conservative surgery. They were treated by second-look surgery and there was no death reported to have occurred in these groups [16].

Recently, conservative surgery has been conducted on patients with epithelial ovarian tumors in early stage even with adjuvant chemotherapy in Stage IC and grade 3 [17]. In addition, in another study on ten patients with high-

stage and high-grade epithelial ovarian tumors, this modality for treatment has been performed [18].

The aim of the present study was to evaluate the outcome of patients who were treated conservatively for Stage I epithelial ovarian tumors, any stage borderline tumors, malignant ovarian germ cell tumors (MOGTs), and Stage I sex cord stromal tumors (SCSTs).

Materials and Methods

This was a retrospective study performed on patients with ovarian tumors who had been referred to the Gynecology-Oncology Department of Vali-Asr Hospital, Tehran, Iran in 2000-2004.

Among 410 patients with ovarian tumors who had been referred or were treated by different treatment modalities, 60 who had conservative ovarian surgery were evaluated for pregnancy and recurrence of the disease within 12 to 48 months of follow-up.

The selection criteria were diagnosis of Stage I epithelial ovarian tumors, any stage borderline ovarian tumors MOGCTs, Stage I SCSTs, primary conservative surgical treatment, and age under 40. One patient with a Stage IIIC epithelial ovarian tumor had refused to undergo a radical surgery in another hospital and was referred to our center with recurrence after five months.

Gynecologic pathologists of Vali-Asr Department of Pathology performed histology. Histopathology was classified according to the WHO criteria. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system. All the patients underwent surgery as the primary treatment. Conservative surgery comprised tumor excision with preservation of the uninvolved ovarian tissue or unilateral salpingo-oophorectomy (USO). In all cases, surgical staging was performed with peritoneal washing, omentectomy, multiple peritoneal biopsies, retroperitoneal sampling, lymphadenectomy, and debulking of metastasis implants for MOGCTs tumors.

No chemotherapy was given to the patients with Stage IA (G1) epithelial ovarian cancer, with borderline ovarian tumors unless invasive implants were present, with pure dysgerminoma Stage IA, with immature teratoma Stage IA grade 1, or with Stage IA sex cord stromal tumors. Only the patients with Stage I Sertoli-Leydig cell tumors that were poorly differentiated or contained heterologous elements were treated with chemotherapy.

The patients with stage > IA epithelial ovarian tumors received cisplatin in combination with cyclophosphamide or paclitaxel. Those with MOGCTs and Stage IA and grade 2, 3 were treated with BEP regimen (cisplatin, etoposide, bleomycin). This regimen was also administered to the patients with stage > IA SCSTs. The number of cycles depended on surgical staging, the patient's tolerance to chemotherapy and the objective response of any measurable disease. The different regimens were usually administered for four to six courses. After the primary surgery of chemotherapy in the case of adjuvant treatment, the patients were evaluated at regular intervals of three months in the first year and every six months thereafter. Follow-up examinations consisted of physical and gynecological examination, imaging of the abdomen and pelvis, and measurement of tumor markers.

Clinical data collected were age at diagnosis, desire of pregnancy, date of primary surgery, histology results, stage, grade, adjuvant treatment, second-look procedure, menstrual history, pregnancies and deliveries after treatment, diagnosis of relapse, and tumor status. Information was obtained from medical records and from a questionnaire mailed to all patients who were at least 13 years old at the time of the diagnosis. The project was approved by our Institutional Review Board, and a cover letter included the elements of informed consent, such as provision for confidentiality.

Results

Among 60 patients in this study, ten patients (16.6%) presented epithelial tumors (9 Stage I and 1 Stage IIIC who refused radical surgery), 15 (25%) borderline ovarian tumors (14 Stage I, 1 Stage III with no invasive implants), 26 (43.3%) MOGCTs tumors (13 Stage IA, 1 Stage IB, 1 Stage IC, 1 Stage IIA, 3 Stage IIIA and 6 IIIC), seven unknown stage endodermal sinus tumors (EST), and nine (15%) SCSTs (7 Stage IA, 2 Stage IC). (Table 1). The youngest patient was 13 and the oldest was 34 years old (mean age 23.2 years). The range of follow-up was 12 to 48 months.

Seven patients with epithelial ovarian tumors (7/10) undergoing conservative surgery received adjuvant chemotherapy (more than Stage IA or more than grade 1). Five received taxol + carboplatine (TC) and the other two received cyclophosphamide + cisplatinum (CP) courses. One of them had a successful pregnancy with a healthy child (she had a history of infertility).

Two cases had recurrence. One was in Stage IC and had recurrence after ten months. The recurrence was treated by omentectomy, appendectomy, and six courses of TC. She is in remission for the time being. The other patient was in Stage IIIC and had recurrence after five months. She was treated by a radical surgery (TAH + BSO + omentectomy) and six courses of TC, but she expired due to progression of the disease.

Eleven (11/15) ovarian borderline tumor patients desired pregnancy (including 2 cases with a history of infertility). The age range of these patients was 16 to 35.

Histologically, ten cases had serous and five cases had mucinous types. Primarily performed surgeries were 14 unilateral salpingo-oophorectomy and one cystectomy + cesarean section. Surgical staging was performed in ten

Table 1. — *Characteristics of patients with ovarian tumors undergoing conservative surgery.*

Histological type No. of patients	EOC 10 (16%)	BOT 15 (25%)	MOGCT 26 (43.3%)	SCST 9 (15%)
Stage I	Stage IA (7) Stage IC (2)	Stage IA (7) Stage IB (2)	Stage IA (13) Stage IB (1) Stage IC (1)	Stage IA (7) Stage IC (2)
Stage > I	Stage IIIC	Stage IIIA (1) UK (5)	Stage IIA (1) Stage IIIA (3) Stage IIIC (6) UK (EST)	
Adjuvant chemotherapy	5/10		13/26	2/9
Pregnancy	1	31 term 2 preterm	2	1
Recurrence	2	3	2	2
	DOD = 1 Stage IIIC		DOD = 1 Stage IIIC	

EOC: epithelial ovarian cancer; BOT: borderline ovarian tumor; MOGCT: malignant ovarian germ cell tumors; SCST: sex cord-stromal tumors; DOD: died of disease.

Table 2. — *Comparison of current series and other studies*.

Field	Authors	Year	Patient number	Histologic type	Mean age	Follow-up	Recurrence	Preg.
Non-epithelial cell tumors	Koji Kanazawa *et al*. 2000 [8]	1981-96	31	Dys (7) Yolk sac (10) Immature (7) Chorio (1) Mixed (6)	18.6	–	–	8 (6)
	EI-Lamie *et al*. (2000) [9]	1994-99	16	Dys (6) Immature (6) Endodermal (4)	20.5 (13-40)	30.5 mo.	1 immature Tratoma (Stage IIIC)	3
	Zanagnolo *et al*. (2004) [10]	20 yrs	36	Dys (12) Immature (6) Yolk sac (4) Endodermal (6) Mixed (8)	20.5 (13-22yr40)	129 mo.	–	11 (9)
	Current series (2005)	2000-2004 (5 yrs)	26	Dys (13) Immature (4) Embryomal (4) Mixed (2)	20.3 (13-33)	30 mo.	1 dysgerminoma (Stage IIA)	2 (1)
				Yolk sac (1) Granulosa (8) Androblastoma (I)	22		Granulosa (2 Stage IA)	1
Borderline tumors	Gotlieb *et al*. (1998) [14]	25 yrs	39	Serous (22) muc (17)	–	69 mo.	–	22 (15)
	Camatte *et al*. (2002) [15]	10 yrs	17	–	–	50 mo.	–	8 (7)
	Donnez *et al*. (2003) [16]	1989-2001	16	–	–	–	–	12 (7)
	Current series (2005)	2000-2004 (5 yrs)	15	Serous (8) muc (7)	24 yr (16-35)	30 mo.	Ser (Stage IB) Ser (IIC) Muc (Stage IIIA)	3
Epithelial ovarian tumors	Zanetta *et al*. (1996) [17]	10 yrs	99	–	–	30 mo.	–	25 (17)
	Raspagliesi *et al*. (1997) [18]	1980-94	10	22.7 yrs	Ser (5) MUC (4) Undiff (1)	70 mo.	–	3
	Morice *et al*. (2001) [19]	1982-99	25	24 yrs	Ser (16) MUC (19) Muc (21) Ser (3)	42 mo.	7	4
	Morice *et al*. (2005) [20]	1987-2004	34	27 yrs (14-36)	Endometrial (5) Small cell (2) Mixed (3)	60 mo.	10	10 (9)
	Current series (2005)	2000-2004 (5 yrs)	10	26.2 yrs (19-32)	Ser (5) Muc (4) Brenner (1)	30 mo.	2 serous Stage IC, Stage IIIC	1
	Zanetta *et al*. (1996) [17]	10 yrs	99	–	–	30 mo.	–	25 (17)
	Raspagliesi *et al*. (1997) [18]	1980-94	10	22.7 yrs	Ser (5) MUC (4) Undiff (1)	70 mo.	–	3
	Morice *et al*. (2001) [19]	1982-99	25	24 yrs	Ser (16) MUC (19)	42 mo.	7	4
		1987-2004	34	27 yrs (14-36)	Muc (21)			
	Morice *et al*. (2005) [20]				Ser (3) Endometrial (5) Small cell (2) Mixed (3)	60 mo.	10	10 (9)
	Current series (2005)	2000-2004 (5 yrs)	10	26.2 yrs (19-32)	Ser (5) Muc (4) Brenner (1)	30 mo.	2 serous Stage IC, Stage IIIC	1

Dys: dysgerminoma; Muc: mucinous; Chorio: choriocarcinoma; Ser: serous.

patients and the other patients without surgical staging were in Stage I formally at the suggestion of surgeons. Three of these cases had successful pregnancies (1 term + 2 preterm but all of them were healthy). Three cases had recurrence, one after five months and the other two after seven months from the primary treatment. All are in remission for the time being.

Eight (8/26) germ cell tumor patients desired pregnancy (age range; 13-33 years). Thirteen patients had dysgerminoma, four immature teratoma, four embryonal tumors, three mixed germ cell tumors, and two had yolk sac tumors. Primarily performed surgeries included 24 unilateral salpingo-oophorectomies and one bilateral salpingo-oophorectomy with preservation of the uterus

and one case of cystectomy + cesarean section (in yolk sac tumor patients). Surgical staging was performed in 25 (25/26) cases.

Thirteen cases who had dysgerminoma or immature teratoma with stage > IA, grade 3 and EST treated by BEP (bleomycin, etoposide, and cisplatinum). Two pregnancies had occurred in a patient. One patient 14 years old, had immature teratoma and died in Stage IIIC after three courses of BEP and one course of VAC (vincristine, actinomycine, cyclophosphamide) without any response to the treatment ten months after diagnosis.

Four (4/9) sex cord tumor patients desired pregnancy. Eight (8/9) patients had granulosa cell tumors and the other one androblastoma.

Primarily performed surgeries in these groups included one salpingo-oophorectomy+cesarean section and eight unilateral salpingo-oophorectomies. Surgical staging was performed in all the cases. Seven were in Stage IA and two in Stage IC. Two cases with Stage IC were treated by BEP chemotherapy, but they had recurrences. The first recurrence occurred after 24 months and was treated by debulking surgery followed by four BEP courses. The second one occurred after five months and was treated by TC chemotherapy. Both of these patients are in remission for the time being.

In summary, conservative surgery and fertility outcomes were evaluated in 60 patients less than 40 years of age, considering the fact that there were only 26 patients (26/60) who desired pregnancy and there was a history of infertility in three patients. Seven pregnancies occurred (in 6 patients) during the follow-up period. Two pregnancies were preterm in patients with borderline ovarian tumors but all of them were healthy. Nine patients had recurrence and seven are in remission after the secondary treatment.

Discussion

This study may emphasize the point that conservative surgery can be performed on premenopausal patients with a selective histological type of ovarian tumors, who desire to preserve fertility, even in a higher stage or grade. However, in epithelial ovarian tumors, it can be done just in early stages (up to Stage IC).

Thus the type of surgery should be decided depending mainly on age of the patient and her desire for fertility preservation. Surgical staging should be performed in all cases to evaluate the extent of the disease, to determine prognosis, and to guide postoperative management. Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is now considered an appropriate surgical treatment for patients with Stage IA, grade 1 epithelial ovarian cancer, any stage borderline ovarian tumors with no invasive implants, SCSTs and MOGCTs, and even an advanced germ cell disease, particularly if the contralateral ovary is normal. Removal of the preserved ovary should be considered after completion of pregnancy (ies) in order to reduce the risk of ovarian tumor recurrence [1].

In a current study on 26 patients with a germ cell ovarian tumor, two pregnancies occurred in eight patients who desired pregnancy during the follow-up. One of these cases had recurrence which is comparable to other studies (Table 2).

In Kanazawa *et al.'s* study on 31 germ cell tumors (during 15 years), eight pregnancies occurred in six patients [8]. In El-Lamie *et al.'s* study on 16 patients (over 5 years, with a 30.5 month follow-up), two patients had three pregnancies and there was one case of recurrence [9].

In the study by Zanagnolo *et al*. on 36 germ cell tumors (with a 10-year follow-up), nine patients had 11 pregnancies with no report of recurrence [10]. In sex cord tumor patients, four desired pregnancy and one pregnancy occurred. These data could show the possibility of conservative surgery on the patients as well.

In 15 patients with borderline tumors in our study, three pregnancies occurred (only 11 were desired pregnancies and there was a history of infertility in 2 of them).

Table 3 shows different studies in which borderline tumors were treated by conservative surgery. In Gotlieb *et al.'s* study on 39 patients (with 69 months of follow-up), there were 22 pregnancies in 15 patients (there were 3 abortions, 1 early pregnancy, and 1 twin pregnancy) [14].

In Camatte's study on 17 patients (with 50 months of follow-up), eight pregnancies occurred in seven patients [15]. In Donnez *et al.'s* study on 16 patients (during 12 years), 12 pregnancies occurred in seven patients [16].

Conservative surgery can be performed on patients with early-stage epithelial tumors, but it is necessary to have adjuvant chemotherapy in high-grade cases. Table 4 compares different studies on epithelial ovarian tumors.

Zanetta *et al.'s* study (with 30 months of follow-up) on 99 Stage IA epithelial ovarian tumor patients showed 25 pregnancies in 17 patients [17]. Thus conservative therapy can be performed on Stage IA epithelial tumor patients.

In another study by Raspagliesi *et al*. on ten epithelial tumor patients with a higher grade or stage undergoing conservative surgery (with 70 months of follow-up), three pregnancies occurred and there was no recurrence [18].

In two other studies, one in 2001 and another of multicentral type in 2005, Morice et al showed that conservative surgery should be performed on patients with Stage IA, grade 1 and it can also be considered for grade 2 [19, 20] (Table 4).

The results from our study confirm that management of Stage I (grade 1, grade 2) epithelial ovarian cancer, any stage borderline ovarian tumors with no invasive implants, MOGCTs and SCSTs with fertility-sparing surgery is a safe, practicable treatment option. Of course, further studies are recommended to evaluate this important issue.

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