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Conservative management in young patients with borderline and malignant ovarian tumors: outcomes and pregnancies

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Abstract

Background: Recent studies have showed conservative management in selective patients with borderline and malignant ovarian tumors is safe; therefore this management is considered in patients with ovarian tumor who desire to preserve fertility.

Objective: This study has been performed to evaluate the clinical outcome and fertility in patients with ovarian tumors who were treated conservatively.

Materials and Methods: All patients who were treated conservatively (preservation of uterus and at least one ovary) or were on follow-up and had recurrence were evaluated in Vali-e-Asr Hospital during 2000-2004.

Results: Among 410 patients with ovarian tumors, 60 were treated conservatively. Age range was 13-34 years. Twenty-six of patients (43.3%) were desired pregnancy and 34 (56%) patients did not. Three (5%) patients had history of infertility. Histological types of tumors were as follows; 15(25%) borderline tumors, 10(16.7%) epithelial tumors, 26(43.3%) germ cell tumors, and 9(15%) sex cord tumors. Range of follow-up time was 12-48 months. Seven term pregnancies in 6 patients had been occurred, 1 in epithelial group, 2 in germ cell group, 1 in sex cord group and 3 in borderline group. Nine patients had recurrence and 2 patients expired, including one patient with serous cyst carcinoma (Stage IIIC).This patient had refused radical surgery and referred to our center with recurrence. Another patient had immature teratoma (Stage IIIC).

Conclusion: Conservative surgical management in young patients with stage I (grade 1, 2) of epithelial ovarian tumor and sex cord-stromal tumor and in patients with borderline and germ cell ovarian tumors could be performed in order to preserve fertility.

Key words: *Ovarian cancer, Conservative management, Fertility sparing surgery.*

Introduction

Although ovarian malignancy is predominantly a disease of aging, an increasing number of women suffer from these malignancies before or during reproductive years. Eighty nine percent of ovarian tumors occur after the age of 40 years and the reminders occur before this age (1). Standard treatment for borderline and malignant ovarian tumors is cytoreductive surgery as hysterectomy and oopherectomy, partial omentectomy and surgical staging. Surgical staging reveals the need of adjuvant chemotherapy to detect extension of the disease. Cytoreductive surgery will cause infertility and due to this problem, conservative surgery has

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been introduced (2, 3).

Conservative surgery consists of unilateral salpingo-oopherectomy, 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 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 16–20 years and they may occasionally be diagnosed during pregnancy or the 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). In Ayhan *et al*. study, it has been mentioned that diagnosis of ovarian tumors in pre-menopausal period is increased by improvement of diagnostic methods and regular gynecologic examination. Ovarian tumors that have been diagnosed in premenopausal period are mostly in early stage and lower grade and could be treated by 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 has been available regarding survivors (5, 12, 13). By many studies had showed 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 were acceptable after 25 years follow-up (14). In other study on 17 patients with stage II and III, borderline ovarian tumors after conservative surgery, 8 spontaneous pregnancies had been occurred. These studies could show the ability of conservation surgery in patients with advanced stage of borderline ovarian tumors (15).

Another study on borderline ovarian tumors showed that there was no significant difference in survival of the patients who was treated by conservative surgery or radical surgery, although there were more recurrences in patients with conservative surgery but they were treated by second look surgery and there was no death in these groups (16). Recently, conservative surgery had been performed on patients with epithelial ovarian tumors in early stage even with adjuvant chemotherapy in stage IC and grade 3 (17). Also in another study on 10 patients with high stage and high grade epithelial ovarian tumors, this modality for treatment had been performed (18).

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

Materials and methods

This study designed as a retrospective study and performed on patients with ovarian tumor who were referred to Gynecology Oncology Department of Vali-e-Asr Hospital, Tehran, Iran in 2000-2004. Among 410 patients with ovarian tumors who referred or treated by different treatment modalities, 60 who had conservative ovarian surgery have been evaluated for pregnancy and recurrence of the disease between 12-48 months range follow-up. The selection criteria were: diagnosis of Stage I epithelial ovarian tumor, any stage borderline ovarian tumors MOGCTs, or Stage I SCSTs; primary conservative surgical treatment; and age less than 40. One patient with epithelial ovarian tumor stage IIIC had refused radical surgery in other hospital and refereed to our center with recurrence after 5 months.

Histology reviews were performed by gynecologic pathologists of Vali-e-Asr Department of Pathology. Histopathology was classified according to the WHO criteria. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system. All patients underwent surgery as primary treatment. Conservative surgery comprises 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 patients with Stage IA (G1) epithelial ovarian cancer, borderline ovarian tumors unless invasive implants were present, pure dysgerminoma Stage IA, immature teratoma Stage IA grade 1, or Stage IA sex cord stromal tumors. Only patients with Stage I Sertoli-Leydig cell tumors that were poorly differentiated or that contain heterologous elements were treated with chemotherapy.

The patients with stage> IA epithelial ovarian tumor received cisplatin in combination with cyclophosphamide or paclitaxel; those with

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MOGCTs and stage IA and grade 2, 3 were treated with BEP regimen (cisplatin, etoposide, bleomycin). This regimen was also administered to patients with stage >IA SCSTs. The number of cycles depended on the surgical staging, the patient's tolerance to chemotherapy and the objective response of any measurable disease. The different regimens were usually administered for 4-6 courses. After primary surgery or chemotherapy in the case of adjuvant treatment, patients were evaluated at regular intervals of 3 months for the first year and every 6 months thereafter. Follow-up examinations consisted of physical and gynecological examination, imaging of the abdomen and the pelvis, and measurement of tumor markers.

Statistical analysis

The 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, 10 patients (16.6%) presented with epithelial tumor (9 stage I and one stage IIIC who refused radical surgery), 15 (25%) with borderline ovarian tumor (14 Stage I, one Stage III with no invasive implants), 26 (43.3%) with MOGCTs tumors (13 Stage IA, 1 Stage IB, 1 Stage IC, 1 Stage IIA, 3 Stage IIIA and 6 IIIC) and 7 unknown stage with endodermal sinus tumor (EST) , and 9 (15%) with SCSTs (7 Stage IA, 2 Stage IC) (Table I). The youngest patient was 13 years old and the oldest patient was 34 years old (mean age 23.2 years) and range of follow-up was 12-48 month. Seven patients with epithelial ovarian tumor (7/10) with conservative surgery received adjuvant chemotherapy (more than Stage IA or more than grade 1).

Five received TC (taxol + carboplatine) and other two got CP (cyclophosphamide + cisplatinum) courses, and 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 10 months and recurrence was treated by omentectomy, appendectomy, and 6 courses of taxol + carboplatine. She is in remission for the time being. The other one was in stage IIIC and had recurrence after 5 months. She was being treated by radical surgery (TAH + BSO + Omentectomy) and 6 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 history of infertility). Age range of these patients was 16-35. Histologically, 10 cases had serous and 5 cases had mucinous types. Primary performed surgeries were; 14 unilateral salpingo-oophecrectomy and one cystectomy + caesarean section.

Surgical staging had been performed in 10 patients and other patients without surgical staging were in stage I formally with suggestion of surgeons. Three cases of them had successful pregnancy (1 term + 2 preterm but all of them were healthy). Three cases had recurrence, 1 after 5 months and the other 2 cases after 7 months from primary treatment, but all of them 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, 4 immature teratoma, 4 embryonal tumors, 3 mixed germ cell tumor, and 2 yolk sac tumor. Primary performed surgeries were; 24 unilateral salpingo-oophecrectomy and one bilateral salpingo-oophecrectomy with preservation of uterus and one case of cystectomy + caesarean section (in yolk sac tumor patient). Surgical staging had been 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 been occurred in a patient. One patient was 14 years old, had immature teratoma and deceased in stage IIIC, after 3 courses of BEP and one course of VAC (Vincristine, Actinomycine, Cyclophosphamide) without response to treatment 10 months after diagnosis. Four (4/9) sex cord tumor patients desired pregnancy. Eight (8/9) patients had granulosa cell tumor and the other one had androblastoma. Primary performed surgery in these group were; 1 salpingo-oophecrectomy + caesarean section and 8 unilateral salpingo-oophecrectomy. Surgical staging had been performed in all cases. Seven of them were in stage IA and 2 were in stage IC. Two cases with stage IC were treated by BEP chemotherapy and they had recurrences. First

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recurrence had been occurred after 24 months and was treated by debulking surgery followed by 4 BEP courses and second one occurred after 5 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 have been evaluated in 60 patients less than 40 years of age, considering this fact that there are only 26 patients (26/60) who desired pregnancy and there was a history of infertility in 3 patients.

Seven pregnancies occurred (in 6 patients) during follow-up period. Two pregnancies were preterm in patients with borderline ovarian tumors but all of them were healthy. Nine patients had recurrence and 7 are in remission after secondary treatment.

Table I. Characteristics of patients with ovarian tumors and conservative surgery.

Histological type	EOC	BOT	MOGCT	SCST
No. of patients	10 (16%)	15 (25%)	26 (43.3%)	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 DOD=1 Stage IIIC	3	2 DOD=1 Stage IIIC	2

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

Table II. Comparison of current series and other studies in non-epithelial cell tumors.

Authors	Year	No of patients	Histologic type	Mean age	Follow up	Recurrence	Preg.
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)	30.5M	1 immature Tratoma (stage IIIC)	3
Zanagnolo *et al* (2004) (10)	20yr	36	Dys(12) Immature(6) Yolk sac(4) Endodermal(6) Mixed(8)	20.5(13-22yr40)	129 M	-	11(9)
Current series (2005)	2000-2004 (5yr)	26	Dys(13) Immature(4) Embryomal(4) Mixed(2)	20.3(13-33)	30 M	1 Dysgerminoma (stage IIA)	2(1)
			Yolk sac(1) Granulosa(8) Androblastoma(I)	22		Granulosa (2 stage IA)	1

Table III. Comparison of current series and other studies in borderline tumors.

Authors	Years	P. no	Histologic type	Mean age	Follow up	Recurrence	Preg.
Gotlieb *et al* (1998) (14)	25yr	39	Serous(22) MUC(17)	-	69M	-	22(15)
Camatte *et al* (2002) (15)	10yr	17	-	-	50 M	-	8(7)
Donnez *et al* (2003) (16)	1989-2001	16	-	-	-	-	12(7)
Current series (2005)	2000-2004(5yr)	15	Serous(8) MUC(7)	24 yr (16-35)	30 M	Ser (IB) Ser (IIC) MUC(IIIA)	3

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Table IV. Comparison of current series and other studies in epithelial ovarian tumors.

Authors	Years	P. no	Mean age	Histologic Type	Staging	Follow up	Recurrence	Preg.
Zanetta *et al* (1996) (17)	10yr	99	-	-	Stage IA	30 M	-	25(17)
Raspagliesi *et al* (1997) (18)	1980-94	10	22.7yr	Ser(5) MUC(4) Undiff(1)	Stage IA(2) (G3) Stage IC(2) Stage III(2) Stage IIIC(4)	70 M	-	3
Morice *et al* (2001) (5)	1982-99	25	24yr	Ser(16) MUC(19)	Stage IA (19) GI=9 G2=10 Stage IC=2 Stage II=2 Unknown=2	42M	7	4
Morice *et al* (2005) (19)	1987-2004	34	27yr (14-36)	Muc (21) Ser(3) Endometrial (5) Small cell(2) Mixed(3)	Stage IA(30) G1=13, G3=3 Stage IC=(3) Stage IIC(1)	60 M	10	10(9)
Current series (2005)	2000-2004 (5yr)	10	26.2 (19-32)	Ser(5) MUC(4) Brenner(1)	Stage I(6) G1=3 G1=2 G3=1 Stage IC(3) Stage IIIC(1)	30 M	2 serous stage IC, stage IIIC	1

Discussion

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

Therefore the type of surgery should be decided depending mainly on age of the patient and desire to fertility preservation. Surgical staging should be performed in all cases to evaluate the extent of disease, to determine prognosis, and to guide postoperative management. Unilateral salpingo-oophorectomy with preservation of the contra lateral ovary and the uterus is now considered the 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, even in the case of advanced germ cell disease, particularly if the contra lateral 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 current study on 26 patients with germ cell ovarian tumor, 2 pregnancies were occurred in 8 patients who desired pregnancy during follow up. One of these cases had recurrence which is comparable to other studies (Table II). In Koji Kanazawa study on 31 germ cell tumors (during 15 years), 8 pregnancies had been occurred in 6 patients (8). In El-Lamie study on 16 patients (during 5 years, with a 30.5 months follow-up), 2 patients had 3 pregnancies and there was a case of recurrence (9).

In Zanagnolo study on 36 germ cell tumors (with a 10 year follow-up), 9 patients had 11 pregnancies with no recurrence report (10). In sex cord tumor patients, 4 desired pregnancy and one pregnancy occurred. These data could show probability of conservative surgery in these patients as well. In 15 patients with borderline tumor of this study 3 pregnancies had been occurred (only 11 desired pregnancy and there was a history of infertility in 2 of them).Table III shows different studies on borderline tumors, treated by conservative surgery. In Gotlieb study on 39 patients (with 69 months of follow-up), they had 22 pregnancies in 15 patients (there was 3 abortions, 1 EP and 1 twin pregnancy) (14).

In Camatte study on 17 patients (with 50 months follow-up), 8 pregnancies had been occurred in 7 patients (10). In Donnez study on 16 patients (during 12 years), 12 pregnancies had been occurred in 7 patients (15). Conservative surgery could be performed in patients with early stage epithelial tumors, but adjuvant chemotherapy is necessary in high grade cases. Table IV compares different studies on epithelial ovarian tumors.

Zanetta study (with 30 months follow-up) on 99 stage IA epithelial ovarian tumor patients showed

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25 pregnancies in 17 patients. Therefore conservative therapy could be performed on stage IA epithelial tumor patients (17).

In another study by Raspagliesi *et al* on 10 epithelial tumor patients with higher grade or stage which had conservative surgery (with 70 months follow-up), 3 pregnancy had been occurred and without any recurrence (18).

But two other series by Morice *et al* showed that conservative surgery should be performed just on patients with stage IA and grade 1 and it could be considered for grade 2 (5,19) (Table IV) .

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 and practicable treatment option. Therefore further studies should be recommended to evaluate this important issue.

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