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Conservative treatment of ovarian cancer

Safety, ovarian function preservation, reproductive ability, and emotional attitude of the patients in Saudi Arabia

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ABSTRACT

الأهداف: تقييم سلامة العملية الجراحية التقليدية لدى المريضات المصابات بسرطان المبايض، بالإضافة إلى تقييم سلامة الحفاظ على وظائف المبايض، والقدرة على الإنجاب، وسلوك المريضات العاطفي بعد إجراء مثل هذه العملية.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في مستشفى الملك عبدالعزيز الجامعي، جدة، المملكة العربية السعودية، حيث قمنا بمراجعة سجلات المريضات اللاتي خضعن للعلاج التقليدي جراء الإصابة بسرطان المبايض الأولي خلال الفترة من يناير 2000م إلى ديسمبر 2010م. لقد قمنا بمراجعة جداول المرضى من أجل التقصي عن أسباب المرض، ومرحلته، ومدى الحاجة للعلاج الكيميائي المساعد، ونسبة رجوعه، بالإضافة إلى تاريخ الدورة الشهرية واحتمال الحمل بعد العلاج. وقمنا خلال المتابعة بطرح 3 أسئلة على المريضات وذلك من أجل الكشف عن سلوكهن العاطفي بعد الإصابة بالمرض.

النتائج: شملت الدراسة 39 مريضة (متوسط العمر: 22 عاماً)، وكانت 31 مريضة (80%) مصابة بسرطان المبايض في مرحلته الأولى، فيما كانت 20 مريضة (52%) مصابة بورم الخلية الجرثومية. ولقد تلقت 15 مريضة (39%) العلاج الكيميائي الأساسي بعد إجراء العملية الجراحية، وظهر المرض مرة أخرى في 3 مريضات (8%)، وقد انتظمت الدورة الشهرية بعد العلاج في 38 مريضة (98%)، وكان الحمل طبيعياً بعد العلاج في 8 مريضات (20%). أما بالنسبة للأسئلة الثلاث التي طرحت على المريضات فقد أجابت 10 مريضات (44%) بأن المرض لم يكن له أي تأثير على رغبتهم في الإنجاب، فيما تخوفت 12 مريضة (52%) من تأثير المرض على قدرتهن على الإنجاب، ولم تُبدي 9 مريضات (39%) أي قلق حيال تأثير العلاج على أطفالهن في المستقبل.

خاتمة: أثبتت هذه الدراسة مدى سلامة العملية التقليدية التي تحافظ على الخصاب لدى المريضات المصابات بسرطان المبايض، كما أنها تعد علاجاً عملياً لدى بعض الحالات المختارة. ولهذا فإن بإمكان غالبية المريضات المصابات بهذا الورم الاحتفاظ بوظائف المبايض، كما ينبغي تشجيعهن لمعاودة الحمل مرة أخرى.

Objectives: To evaluate the safety, ovarian function preservation, reproductive ability, and the emotional attitude after a conservative surgery for ovarian cancer.

Methods: This is a retrospective study of women conservatively treated for primary ovarian cancer between January 2000 and December 2010 at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Patient's charts were reviewed for pathology, stage, requirement of adjuvant chemotherapy, and recurrent, as well as menstrual history, and pregnancy after treatment. During follow up the patients were asked 3 questions about their emotional attitude toward their disease.

Results: There were 39 patients identified (mean age 22 years). Thirty-one (80%) patients were presented with stage I and 20 (52%) were Germ cell tumor. Fifteen (39%) patients received initial chemotherapy after primary surgery. Three (8%) patients had recurrent. Thirty-eight (98%) patients returned to a regular menstruation after treatment. Eight patients (20%) had a normal pregnancy. Of the respondents to the given questions, 10 (44%) patients claimed that their disease did not have any impact on their desire to have children and 12 patients (52%) feared that their ovarian disease could have damage in their reproductive potential. Only 9 patients (39%) had no concern about the effect of the treatment they received on the offspring.

Conclusion: Fertility sparing surgery in ovarian cancer appears to be safe, and a practical treatment option in selected cases with ovarian cancer diagnosis. Most patients can have ovarian preservation after treatment and should not be discouraged from getting pregnant.

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Ten to twenty percent of ovarian cancers occur before the age of 40 years.¹ The 5-year survival of patients with Stage IA, grade 1, epithelial ovarian cancer treated conservatively is 90%.² Malignant ovarian germ cell tumors (MOGCTs) represent approximately 5% of all ovarian neoplasms observed in Europe and North America.³ 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 puerperium.⁴ In the literature, a 5-year survival rate of 90-100% has been reported with the use of the new combination chemotherapy regimens.¹ Sex cord-stromal tumors (SCSTs) are rare neoplasms that account for approximately 3-5% of ovarian malignancies and the majority of them are functioning tumors with clinical manifestations.⁵ These are characterized by 85-100% long-term survival rates for Stage IA tumors, and a propensity for late recurrences.⁶ The juvenile form of granulosa cell tumors occurs before the age of 30 in 97% of cases, and is often associated with precocious puberty. Almost all tumors are present at Stage I.^{7,8} 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.¹ Preservation of reproductive ability has become an important issue in the treatment of young patients with malignant ovarian tumors, that may be cured and lead normal lives. A variety of studies⁹⁻¹² have tried to document the impact of conservative treatment aimed at preserving ovarian function and reproductive ability, little information has been available regarding survivors' attitudes and emotions, and their choice to have children. The aim of this study is to evaluate the safety, ovarian function preservation, reproductive ability, and emotional attitude after conservative surgery for ovarian cancer.

Methods. This is a retrospective study of women conservatively treated for primary ovarian cancer between January 2000 and December 2010 at King Abdulaziz University Hospital (KAUH), Gynecology Oncology Unit, Jeddah, Saudi Arabia. Patients were identified using the KAUH database. All stages and all histopathological type of ovarian cancer conservative surgery comprised of tumor excision with preservation of the uninvolved ovarian tissue or unilateral salpingo-oophorectomy (USO) were included. Low malignant

potential (LMP) were excluded. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system.¹³

All patients underwent conservative surgery for primary treatment. Preoperative informed consent were obtained from the patient or patient's parents if she was under 18. Surgical staging was performed with peritoneal washing, omentectomy, multiple peritoneal biopsies, retroperitoneal lymphadnectomy and debulking if required with conservation of the uterus and the other ovary. Patients' charts were reviewed for histopathological type and type of surgery requirement of adjuvant chemotherapy and recurrent as well as menstrual history, pregnancy, and deliveries after treatment. Information was obtained from the patient directly by inquiring 3 questions about their emotional attitude toward their disease. These questions were extrapolated from the questionnaire sent to the patients belonging to the Cleveland Clinic foundation tumor registry, and presented in the paper by Shover et al¹⁴ to evaluate survivors, attitude, and emotional choices with regards to having children.

All participants were verbally informed by the interviewers that the information obtained by them were kept confidential and will be further collected and analyzed by the research team. Respondents were ensured about the confidentiality, they were briefed that their participation is voluntary and they have full right to withdraw from the study at any point. This procedure were approved by the Unit of Biomedical Ethics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Data were entered and analyzed using SPSS version 17.0. We used simple percentage for the analysis.

Results. Of the 39 patients in the study, 16 were married and 23 were single with a mean age of 22 years (range 4-35). Only 4 patients had 1 and/or 2 children, with a mean follow up of 51 months and range of 12-90 (Table 1). Thirty-one (80%) patients were presented with

Table 1 - Characteristics of who had undergone conservative surgery for ovarian cancer (N=39).

Characteristics	N
<i>Age (years)</i>	
Mean	22
Range	4-35
<i>Marital status</i>	
Married	16
Single	23
<i>Parity</i>	
1	2
>1	2
<i>Follow up (months)</i>	
Median	51
Range	12-90

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stage I and 8 (20%) patients with more than stage I. Germ cell tumor was the most common histopathology in the study populations (20 [52%]), 15 (39%) patients received initial chemotherapy after primary surgery, and 5 of them had an advanced epithelial ovarian cancer that treated conservatively. They received taxotair and carboplatin for 6 cycles after an informed consent and for patient who refuse complete surgery, no patient with high risk stage I in the study group. Nine patients received chemotherapy in form of Bleomycine, Etoposide, Cisplatin (BEP) for 4 cycles, 4 with stage III MOGCTs and 5 with high risk MOGCTs stage I, one with stage Ic dysgerminoma, one with Ia mixed germ cell tumor and 3 were stage Ia endodermal sinus tumor. One patient with stage Ic and Sertoli-Leydig cell tumor received chemotherapy (Table 2). Three patients had conservative ovarian surgery, recurred with a recurrence rate of 8%.

Table 3 summarize the patients with recurrences after conservative surgery for ovarian cancer. One

patient recurred after completing chemotherapy for Stage III with an ovarian epithelial carcinoma, treated with complete surgery followed by a second line chemotherapy; hence, she is alive and doing well.

Two patients recurred with MOGCTs. One recurred in the upper abdominal after unilateral salpingo-oophorectomy for immature teratoma. Four years after the initial surgery, the tumor was excised with no residual disease taken from the remaining ovary, and the uterus were free of tumor. The other one was advanced mixed germ cell tumor treated conservatively with de-bulking, received 4 cycles of BEP, had tumor recurrence within <6 months and after the second line chemotherapy the patient died from intracranial hemorrhage as a result of thrombocytopenia, a complication of chemotherapy.

Table 4 shows the reproductive ability after conservative surgery in patient with ovarian cancer. Patients who received chemotherapy or not as an initial

Table 2 - Recurrences after conservative surgery for ovarian cancer.

Histopathology types	Stage			Initially required chemotherapy	Recurrence
	I	> I	All		
EOC	9 (23)	5 (13)	14 (36)	5 (13)*	1 (3)
GCT	17 (44)	3 (7)	20 (51)	9 (23)†	2 (5)
SSCT	5 (13)	0 (0)	5 (13)	1 (3)‡	0 (0)
Total	31 (80)	8 (20)	39 (100)	15 (39)	3 (8)

EOC - epithelial ovarian cancer, GCT - germ cell tumor,
 SSCT - stromal-sex cord tumor. *More than stage I, †Five cases with stage I and 4 cases with more than stage I,
 ‡Case with stage I c (Sertoli-Leydig cell tumor)

Table 3 - Summary of patients with recurrences after conservative surgery for ovarian cancer.

Case	Age	Pathology	Initial Surgery	Stage	Initial chemotherapy	Treatment of recurrence	Alive
1	22	EOC	USO and Debulking	IIIC	Yes	TAH BSO and chemotherapy	Yes
2	18	MGCT	USO and Debulking	III	Yes	chemotherapy	Died
3	35	Immature teratoma	USO	? I	No	Removal of abdominal tumor and chemotherapy	Yes

EOC - epithelial ovarian cancer, MGCT - mixed germ cell tumor, USO - unilateral salping-oophorectomy,
 TAH - Total abdominal hysterectomy, BSO - Bilateral salping-oophorectomy

Table 4 - Ovarian preservation - reproductive ability after conservative surgery for ovarian cancer.

Treatment types	N (%)	Return normal menstruation	Attempt pregnancy	Pregnancy	Pregnancy outcome
Conservative surgery plus chemotherapy	15 (38)	14 (36)*	4 (10)	2 (5)	Term normal baby
Conservative surgery alone	24 (62)	24 (62)	5 (13)	6 (15)	Term normal baby
Total	39 (100)	38 (98)	9 (23)	8 (20)	

*One patient recur before get normal period. Actual pregnancy rate 89%

Table 5 - Emotional attitude on patient undergone conservative surgery for ovarian cancer (23 patients responded).

Questions	Yes	No	I don't know
Do you think the treatment will have impact of your desire to have children in future?	10 (44)	10 (44)	3 (12)
Are you afraid that the treatment could damage your reproductive potential?	12 (52)	5 (22)	6 (26)
Are you concern that the treatment will affect on your offspring?	2 (9)	9 (39)	12 (52)

Data are expressed as number and percentage (%)

treatment result in return of normal menstrual cycles. Twenty percent had an attempted pregnancy.

Table 5 shows the emotional attitude of patients who undergone conservative surgery for ovarian cancer. Of the 39 patients, 23 responded to the direct questions during the follow up either in the clinic or by phone conversation. Ten patients (44%) responded that their disease did not have any impact on their desire to have children. Whereas, 12 (52%) patients fear that their ovarian disease could have damage on their reproductive potential. Only 9 (39%) patients were not concerned about the effect of the treatment they received on the offspring.

Discussion. Too often in the past, children and young women affected by ovarian tumors have been unnecessarily treated with radical surgery due to the suspected risk of microscopic involvement of a seemingly normal contra-lateral ovary and uterus.⁸ Most Stage I epithelial ovarian cancer, Stage I SCSTs and MOGCTs are unilateral, with the exception of pure dysgerminomas, which are bilateral in 10-15% of cases.^{3,15-17} Bilateral involvement with tumors may also occur in cases of advanced-stage MOGCTs tumors, in which there is metastasis from one ovary to the other.¹⁸ For the latter, the availability of effective chemotherapy that may sterilize microscopic or macroscopic foci of a tumor in the residual gonad, without the need to remove the contra-lateral ovary, has changed the surgical approach toward this disease.

The type of surgery is presently decided depending mainly on the age of the patient and the desire for 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 most appropriate surgical treatment for patients with Stage IA grade 1 epithelial ovarian cancer, Stage I SCSTs, and MOGCTs, even in the case of advanced

germ cell disease, particularly, if the contra-lateral ovary is normal.^{9,19-21} There is evidence that showed an equivalent cure rate after fertility-sparing surgery compared with a non-conservative procedure.^{9-11,17-21} In this study, 3 of our patient recur with over all recurrence rate of 8%, and one patient died from the disease, the pathology was mixed germ cell tumor, which was chemotherapy resistance. The availability of effective chemotherapy and the improvement of surgical technique allow the survival of the majority of patients with recurrence of MOGCTs, irrespective of primary conservative or radical surgery. Because of the increasing frequency of long-term survivors, attention has focused on a variety of late sequelae of surgery and chemotherapy. One aspect of quality of life for cancer survivors is the preservation of reproductive-endocrine function and fertility. The specific effects of cancer therapy on reproductive function are not as well understood, and there is no test for fertility except for a resulting pregnancy proving that fertility is maintained. Morice et al² reported on 25 patients treated conservatively for epithelial ovarian cancer, Among the 18 patients who were alive without recurrent disease, one developed early menopause and another one had irregular menses. Only 4 pregnancies in 4 patients were obtained and 3 normal infants were born. Zanetta et al²² reported on 56 women treated conservatively for Stage I ovarian carcinoma; of the 51 women who had their fertility preserved, 20 (39%) conceived, with 17 normal pregnancies. Perrin et al²³ reported on 45 patients with MOGCTs treated conservatively. Adjuvant chemotherapy was administered in 29 patients. Ninety-six percent resumed normal menstrual function on completion of treatment. Seven healthy babies were recorded in the chemotherapy group and no birth defect occurred in any of these. There were 4 recurrences and 2 deaths. In the present study, in agreement with these data, most (98%) of the patients had regular menses at the time of interview; one patient recurred before getting the menstrual period. In addition, we found that 9 patients attempted pregnancies, 8 of them had successful pregnancy with healthy babies (pregnancy rate of 20% and actual pregnancy rate of 89%). The reason given of not having children for the rest of the patients were 9, still not married 2, for personal choices and the rest, no information was received. Our questionnaire returned rate was 23 (59%) in agreement with the response rates reported in the literature.^{12,14,24-27} The fact that only 23% of patients attempted pregnancy and 44% patients think that the treatment has an impact on their desire to have children, and 52% had fear that treatment could damage their reproductive potential, these rise the question whether they had been educated about the

reproductive impact of cancer treatment. Therefore, this observation underlines the need for health care providers to educate the patient about their disease and the impact that cancer treatment may have on reproduction.

Given the small sample size and various diagnoses, the comparison between different cancers or types of treatment is not feasible. However, based on the distribution by histology, it seems that the worse diagnosis had any impact on our patients' desire to have children. Our results on patients' attitude and knowledge about their cancer treatment is way behind and is in disagreement with the finding reported by Schover et al¹⁴ as 80% of the sample viewed themselves very positively as potential parents. Another major finding is that our survivor (39%) do not seem to be concerned about the potential risks to their children having birth defects as related to the mother's cancer treatment. However, this has great limitation for this survey because 52% answered that they "do not know". This has some agreement with the survey results published by Schover et al¹⁴ which showed that cancer survivor were quite concern and uncertain about healthy risks to the offspring. This result disagreed with the recently published study¹² in which 76% were not concern.

In summary, fertility sparing surgery in ovarian cancer appears to be safe and a practical treatment option in selected cases with ovarian cancer diagnosis. Most patients can have ovarian preservation after treatment and they should not be discouraged from getting pregnant. Though, preliminary survey provides insight into the attitudes and experiences of young women of ovarian cancer survivors regarding fertility. Future studies need to examine attitudes and choices with regard to having children prospectively; beginning at the time of the initial treatment, and in trying to assess the influence of particular diagnoses or treatment protocols. Most importantly, health care provider need to work together to spent more time to educate patients about their disease and encourage a positive attitude.

As our study represents a single institution's study and survey, it remains to be validated through a prospective multi-institutional or national Saudi registry.

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