Reproductive Function after Treatment of Ovarian Germ Cell Malignancy

A N Anita, MMED (O&G), M N Rushdan, MMED (O&G)

Gynaecology Oncology Unit, Obstetric & Gynaecology Department, Sultanah Bahiyah Hospital, Malaysia

SUMMARY

Objective: This study was undertaken to evaluate the reproductive and oncologic outcomes of patients diagnosed with Ovarian Germ Cell Malignancy (OGCM) who underwent fertility preserving surgery and adjuvant chemotherapy treated in Gynaecology Oncology Unit, Sultanah Bahiyah Hospital, Kedah, Malaysia.

Methods: We retrospectively reviewed 33 patients who had fertility preserving surgery and adjuvant chemotherapy in our center from 2000 – 2010. Gynaecology oncology record and histopathology database were reviewed. Patients were contacted, assessed and interviewed via telephone using standardized questionnaire to assess their menstrual, reproductive function and disease status after treatment, post therapeutic status of pregnancy or delivery and overall survival.

Result: Thirty three patients diagnosed with OGCM underwent unilateral salphingo oophorectomy and staging surgery followed by adjuvant chemotherapy (BEP regimen). The mean age at presentation was 19.8 years (range, 9 – 34years). Histological subtypes were 21.2% dysgerminoma, 21.2% immature teratoma, 42.4% yolk sac tumour and 15.2% mixed germ cell tumour. After treatment, 71.4% resumed their menstrual cycles within 6 months. During follow up, 5 patients conceived with 5 live birth deliveries and 3 miscarriages (3 patients had two pregnancies). The overall survival rate was 87.9% with median follow up of 45.2 months. 30.3% of patient had disease recurrence with median disease free interval of 5 months while 6.0% had disease progression despite of adjuvant chemotherapy. One of the most important adverse prognostic factors for recurrence and disease progression is Yolk sac tumour (non DSG/IMT) histotype.

Conclusion: Fertility preserving surgery and adjuvant chemotherapy appear to have little effect on fertility and menstrual cycle with a good overall survival. Patients diagnosed with histopathological yolk sac tumour element had poor outcome and perhaps need more aggressive and longer adjuvant therapy.

KEY WORDS:
Germ cell ovarian malignancy, Fertility preserving surgery, Reproductive function

INTRODUCTION

Ovarian germ cell malignancy (OGCM) is a rare malignancy, representing approximately less than 5% of all ovarian neoplasms. It generally affects children and young women, grow rapidly, usually involves one ovary (unilateral) and is highly chemosensitive [1, 2]. Because of these malignancies affected women of reproductive age groups, preservation of fertility is an important consideration during surgical treatment.

More than 40 years ago, the prognosis of OGCM was poor however currently with an effective chemotherapeutic agents, the outcome of this cancer is very much improved. With advances of chemotherapy, the prognosis of OGCM had changed from deadly disease to highly curable cancer. If correctly managed, the 5 years survival rate were nearly 100% for dysgerminomas and more than 85% for non dysgerminoma [3]. The management evolved and currently the increase cure rate shifted the focus of initial management to fertility preserving surgery i.e. preservation of uterus and unaffected ovary then followed by administration of post operative adjuvant chemotherapy i.e. BEP regimens which consists combination of Belomycin, Etoposide and Cisplatin in high risk early disease and advanced disease [2, 3, 4].

The majority of patients with OGCM received multidrug combination chemotherapy post or pre operatively. In these patients, a decrease number of primordial follicles and an increase in stromal fibrosis in atrophied cortices are present after chemotherapy thus resulting in elevated serum gonadotrophin levels with declined serum oestrodial levels [5, 6, 7]. These factors combined with type, dose of cytotoxic drugs and the duration of chemotherapy commenced are associated with an increase incidence of ovarian dysfunction. It has now became a major concern as there is an increasing trend where females associated with OGCM are generally young adults within the reproductive age, and fertility is a main issue for this group. The two main questions at the moment are how much of the ovarian function we can preserve after the series of chemotherapy, and how severe would the effect be.

There is no doubt that at the early stage of OGCM, a patient has an excellent prognosis as compared to the advanced stage whereby the treatment remains a great challenge as treatment modalities may jeopardize the patient's fertility. As this tumor is a relatively rare ovarian cancer, the information about it in terms of prognostic factors, tumour biology is still lacking.

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Corresponding Author: Nor'Anita Abdullah, Gynae Oncology Unit, Department of Obstetric & Gynaecology, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia Email: nbdullah73@yahoo.com

OBJECTIVE OF STUDY

The aims of this study were:

a. To evaluate the reproductive outcome of patients with Ovarian Germ Cell Malignant tumour who underwent primary fertility preserving surgery followed by adjuvant chemotherapy in our center since 2000.
b. To evaluate the overall survival and recurrence rate in patients with OGCM
c. To determine the prognostic factors associated with OGCM

MATERIALS AND METHODS

We conducted a retrospective study from January 2000 to December 2010 on patients with ovarian germ cell malignancy treated in Gynaecology Oncology Unit, Sultanah Bahiyah Hospital, Kedah, Malaysia. Forty-four patients were identified during this period and their age ranged between 8 to 49 years old at the date of primary surgery or diagnosis. During this period, 33 patients underwent fertility preserving surgery and post operative adjuvant chemotherapy. Eleven patients diagnosed with OGCM were excluded as they were in early stage, low risk group and did not require any adjuvant chemotherapy post fertility preserving surgery.

Those diagnosed with OGCM and underwent fertility preserving surgery either in our center or were referrals from other centers where they were operated by other gynaecologists followed by adjuvant chemotherapy were included. Patients with Grade 1, stage 1A Immature Teratoma and patients with stage 1A/ 1B Dysgerminoma were excluded in this study since they did not require adjuvant chemotherapy.

Data were retrieved from histopathology records/ database and gynaecology oncology records, and were available for all patients. Tumours were staged according to Federation of Gynaecology and Obstetrics (FIGO) 1987 staging system for ovarian cancer. Data included: age of diagnosis, FIGO stage, histopathological type of tumour, type of surgery, numbers of chemotherapy cycle received, marital status before and after treatment, menstrual history, current status, disease recurrence and length of survival. The information on oncologic and reproductive outcome was obtained from patients either during cancer clinic follow-up or by telephone conversation by single operator.

The study was reviewed and approved by Ministry of Health Medical Research Ethics Committee (MREC) and Clinical Research Committee (CRC) Malaysia.

Primary surgery

Tumour markers (AFP, Beta-hCG, CEA and CA 125) and CT scan were performed on all patients. Exploratory laparotomy and staging surgery including unilateral salphingo-oophorectomy, selective systematic pelvic (up to level of common iliac nodes) lymphadenectomy in apparent early staged disease as well as peritoneal cytology and omentectomy were performed. Cytoreductive surgery to an optimal residual tumour was attempted in advanced disease.

Chemotherapy

Chemotherapy was administered according to department protocol and the standard first line regimen was BEP (Bleomycin, Etoposide and Cisplatin). Patient received Bleomycin (15 u on day 1 and 2 then 30 u at day 6), Etoposide (100mg/m2 on day 1-5) and Cisplatin (20mg/m2 on day 1 -5) for every 3 weeks. Total cumulative doses of Bleomycin were kept less than 300mg as unacceptable toxicity such as pulmonary fibrosis is increasing if exceeding this limits. The toxicity evaluations were conducted by performing full blood counts, renal and liver function tests prior to each cycle. The lung function test was performed before commencing chemotherapy followed by serial testing accordingly. The toxicity and respond to treatment were defined according to EORTC (European Organization for Research and Treatment of Cancer) criteria.

After the completion of treatment, all patients were assessed by imaging studies (CT scan) 4 weeks post adjuvant chemotherapy for any residual disease. Patients who had completed the treatment were followed up every 3 months for the first year, 4 monthly on the second year and 6 months thereafter. Their health status and progress of the disease were monitored by clinical, biochemical (tumour markers i.e. AFP, Beta-hCG and CA 125) and radiological assessment during follow up. Complete remission was defined as normalization of the relevant tumour marker (e.g. AFP and bhCG levels) and resolution of all residual masses, assessed by clinically or imaging studies. Survival was considered from the date of initial surgery to the time of death or to the date of last contact. The patients who succumbed from the disease were confirmed their date of death with their relatives. Recurrence was considered if new evidence of cancer (proven histologically) after initial complete resection or complete regression of all measurable disease with tumour marker normalized at least for one month.

Statistical analysis

Data are presented as counts and percentages. Fisher's exact test and independent paired t test were used for univariate analysis. P values less than 0.05 were considered statistically significant. Multivariate analysis was not carried out because of the small number of patients. Overall survival and recurrence rate were compared using Kaplan-Meier method.

RESULTS

A total of 44 patients diagnosed with ovarian germ cell malignancy (OGCM) were treated in our center during this study. Thirty three patients had undergone primary fertility preserving surgery and adjuvant chemotherapy while the remaining were not included in this study as they only had fertility sparing surgery without any adjuvant chemotherapy. Due to comprehensive record keeping, we managed to trace and contact all those diagnosed with OGCM.

Characteristics of these 33 patients with OCGM is presented in Table I. The median age at presentation was 19.8 years (ranged, 9 – 34 years). The mean follow up was 42.5 months. The mean age for each OGCM were 16.4 years, 22.2 years, 20.4 years and 19.8 years for Immature teratoma (IMT), Dysgerminoma (DSG), Yolk sac tumour (YST) and mixed germ

Table I: Characteristic of patients with Ovarian Germ Cell Malignancy (n = 33)

Parameter	Number(n)	%
Median age, year (range)	19.8 (9- 34)	
Marital status (at diagnosis)		
- Single	28	84.8
- Married	5	15.2
Marital status (after treatment)		
- Single	22	66.7
- Married	11	33.3
Histological type		
- Dysgerminoma	7	21.2
- Immature Teratoma	7	21.2
- Yolk Sac Tumour	14	42.4
- Mixed Germ Cell Tumour	5	15.2
Stage (FIGO 2000)		
- Stage I	19	57.6
- Stage II	2	6.1
- Stage III	2	33.3
- Stage IV	1	3

Table II: Outcome of reproductive function

Characteristics	Number of patients (%)
Recovery of menstruation	
- 0 – 6 months	20 (71.4%)
- 6 – 12 months	6 (21.4%)
- Amenorrhea	1(3.5%)
- Not applicable	5
Marital status after treatment	
- Single	22 (66.7%)
- Married	11(33.3%)
Conception after treatment (out of 11 married patients)	8 conceptions in 5/9 married patients
- Miscarriage	3
- Term pregnancy	5

Table III: Survival and recurrence rate in relation to patients' age

Parameter	Age < 18 years	Age > 18 years	p value
Recurrence/ progression	6/15 (40%)	6/18(33.3%)	p = 0.6992
Median recurrence (SD)	8.20 mths (12.23)	12.67 mths (12.62)	p=0.568
Status on follow up			
- Alive	12(80%)	17(94.4%)	p=0.206
- Death	3(20%)	1(5.6%)	
Median survival (SD)	41.53 mths (32.40)	48.33 mths(28.94)	p=0.529

Table IV: Survival and recurrence rate in relation to stages of disease

Parameter	Early stages (stage I/II)	Advanced stages (stage III/ IV)	p value
Recurrence/ progression	6/15 (40%)	6/18(33.3%)	p = 0.6992
Median recurrence (SD)	10.17 mths (11.21)	11.20 mths (14.30)	p=0.896
Status on follow up			
- Alive	12(80%)	17(94.4%)	p=0.206
- Death	3(20%)	1(5.6%)	
Median survival (SD)	51.57 mths (32.41)	34.17 mths(23.34)	p=0.113

Table V: Survival and recurrence rate in relation to histology

Parameter	DSG/ IMT	Non DSG/ IMT	p value
Recurrence/ progression	4/14 (28.6%)	8/19 (42.1%)	p = 0.335
Median recurrence (SD)	21.5 mths (14.66)	4.43 mths (3.25)	p =0.013*
Status on follow up			
- Alive	14 (100%)	15/19 (78.9%)	P = 0.095
- Death	0	4/19 (21.05%)	
Median survival(SD)	54.57 mths (27.40)	38.37 mths (31.12)	P = 0.131

DSG, dysgerminomas; IMT, Immature Teratoma; Non DSG, non dysgerminomas

Table VI: Characteristic of patients with relapse/recurrence

Age	Histology	Stage	Primary surgery	Primary chemotherapy (cycle)	Recurrence (months)	Secondary surgery: chemotherapy	Overall survival (months)
17	IMT	1	SO	BEP (4)	30	BEP	84(L)
21	IMT	3	SO	BEP(4)	36	BEP	66(L)
28	MGT	3	SO	BEP(6)	2	TAHLSO: BEP	56(L)
34	YST	3	SO	BEP(6)	11	TAHRSO: POMB/ACE	52(L)
17	YST	3	SO	BEP(4)	4	TAHLSO: BEP	17(L)
12	MGT	3	SO	BEP(4)	-	Non	4(D)
12	YST	1	SO	BEP(6)	1	Non	7(D)
19	MGT	1	SO	BEP(6)	5	LSO: BEP	40(L)
12	YST	1	SO	BEP(6)	3	TAHRSO: VIP	13(D)
25	YST	1	SO	BEP(6)	5	TAHLSO: POMB/ACE	26(D)
12	IMT	3	SO	BEP(4)	3	Non	48(L)
24	DSG	1	SO	BEP(4)	17	RSO: BEP	84(L)

YST, yolk sac tumour; MGCT, mixed germ cell tumour; IMT, immature teratoma; DSG, dysgerminoma; L, live; D, dead; BEP, Bleomycin/ Etoposide/ Cisplatin; SO, Salphingo oophorectomy; TAHLSO, Total Abdominal Hysterectomy + Left Salphingo Ophoretomy; TAHRSO, Total Abdominal Hysterectomy Right Salphingo Ophorectomy; POMB/ACE, Cisplatin/ Vincristine/ Methotraxate/ Bleomycin – Actinomycin/ Cyclophosphamide/ Etoposide; VIP, Vinblastine/ Ifosfamide/ Cisplatin, LSO, Left Salphingo-ophorectomy; RSO, Right Salphingo-ophorectomy;

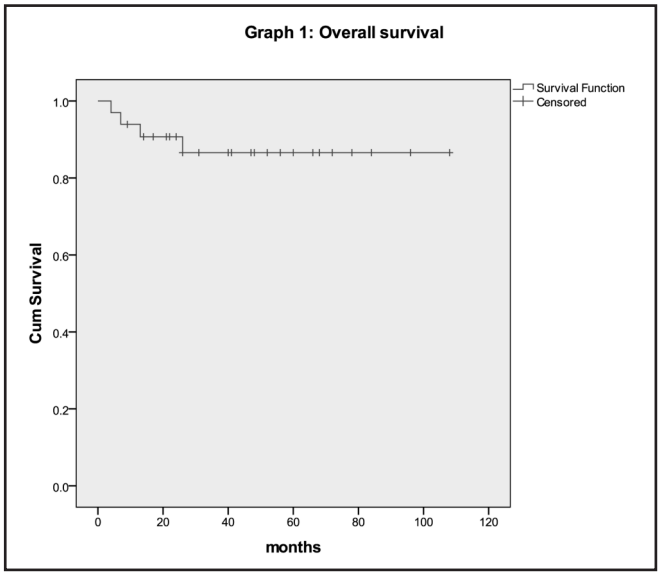

Fig. 1: Overall survival.

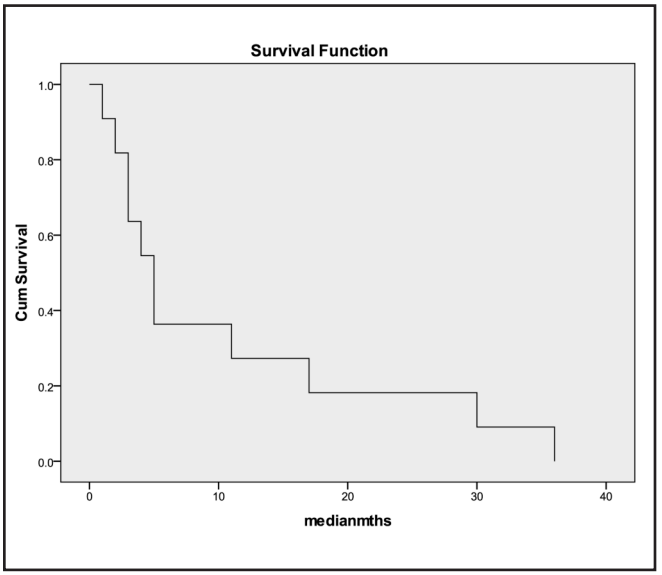

Fig. 2: Recurrence/ relapse disease.

cell tumour (MGCT), respectively. Histological evaluation revealed 42.2% of patients had yolk sac tumours, followed by dysgerminoma (21.2%), immature teratoma (21.2%) and mixed germ cell tumour (15.2%). The distributions by FIGO staging at time of diagnosis were as followed: stage I in 57.6%, stage II in 6.1%, stage III in 33.3% and stage IV in 3%.

When treatment commenced and at diagnosis, there were 28 patients who were single and only 5 patients were married. By the time this study was completed, 22 patients were still single and 11 patients were married.

Reproductive function

After adjuvant chemotherapy, menstruation had resumed in 20 (71.4%) patients within six months, 6(21.4%) within twelve months and one patient did not recover their menses. 5 patients were pre menarchal prior fertility preserving surgery and adjuvant chemotherapy. Two attained menarche at 2 and 10 months after completed their treatments. In five patients who had recurrence or persistence disease, laparotomy and extrafasial hysterectomy and bilateral salpingoophorectomy (EFHBSO) were performed.

Eleven out of 33 patients contacted who underwent fertility sparing surgery followed by adjuvant chemotherapy are married at end of this study. Two of the married patients had recurrence and underwent EFHBSO. Conception during follow up occurred in five patients (45.5%), four out of eleven patients had term pregnancies while two ended with miscarriages. One of the patients required in vitro fertilization (IVF) after failed three cycles of in utero insemination and had delivered term normal baby by caesarean section. One of the patients had two full term normal deliveries and a miscarriage after completed treatment.

Clinicopathological prognostic factors associated with recurrence and survival are shown in following tables (Table III, IV and V)

The median duration of recurrence in relation to patients' age at diagnosis was 8.20mths (less than 18 years) vs. 12.7 mths (more than 18 years) (p = 0.568) and in relation to stages of disease were 10.17 mths (early stage) vs. 11.20mths (advanced stage) (p = 0.896). Prognostic factors for median duration of recurrence and survival associated with age at diagnosis and stages at diagnosis were not statistically significant.

Patients diagnosed with non DSG/IMT was associated with significantly increased risk of early recurrence (4.4 mths vs 21.5mths, p = 0.013). Out of 8 patients in non DSG/IMT group who had recurrence or progression of disease, four died due to disease progression.

After the initial surgery, post operative systemic chemotherapy i.e. BEP regimens were administered to all these patients. Twelve out of thirty three (12/33) patients relapsed during the study period. Their characteristics were shown as table above (Table 6). Three patients diagnosed with Immature Teratoma, (Grade III), 5 diagnosed with Yolk sac tumour, 3 had mixed germ cell tumour while only one diagnosed with Dysgerminoma. Two had disease progression while on treatment while the rest relapse at median of 5 months and received second line treatment either POMB/ACE (Cisplatin/ Vincristine/ Methotraxate/ Bleomycin – Actinomycin/ Cyclophosphamide/ Etoposide) or VIP (Vinblastine/ Ifosfamide/ Cisplatin) regimens. Eight patients underwent secondary debulking and five had TAHBSO. Three patient presented with recurrent YST succumbed to the disease.

Overall survival and recurrence rate

The median follow up was 45.2 months (range: 4 - 108 months). Overall, 21 patients diagnosed with OGCM who underwent fertility preserving surgery and adjuvant chemotherapy were alive without evidence of disease at a median follow up of 40 months (range: 9 – 108 months). The 5 years actuarial survival rate was 87.9% (Figure 1)

Progression disease or recurrence/ relapse were diagnosed in 12 patients with the median of 5 months (range: 1 – 36 months). Ten patients who had recurrence received second line treatment either repeat BEP regimens, POMB ACE regimens or VIP regimen while two patients had disease progression while on treatment. 50% of those with recurrence or relapse were diagnosed at 5 months after completed conservative treatment (fertility sparing surgery and adjuvant chemotherapy i.e. BEP regimen), Figure 2

Complete remission (CR) was achieved in 8 out of 12 patients with relapse. A total of 4 patients died due to progression of the disease.

DISCUSSION

Ovarian cancer can occur at any age, including childhood and adolescence. In contrast to epithelial ovarian cancer (EOC), OGCM is largely detected in patients at a younger age of the reproductive age group. In view of this, it is noted that one of the biggest challenges is to preserve the patients' fertility throughout the treatment. Patients that were diagnosed at the early stage of OGCM have the benefit of undergoing conservative surgical treatment, which is easily understood and managed by the clinician. However, for those that were diagnosed in advanced stages, the residual tumour presented in peritoneal cavity is causing conflict within clinicians on whether the preservation of patients' fertility should still be the main goal. With advances in chemotherapy, patients with OGCM are now better managed and have an excellent prognosis and survival. However, these chemotherapeutic agents are also inducing ovarian toxicities which could impair the future reproductive functions.

In this study, the median age of patients diagnosed with OGCM at presentation was 19.8 years (ranged: 9 – 34). The most common histological types was yolk sac tumour (42.2%), immature teratoma (21.2%), Dysgerminoma (21.1%). More than half (33/44) of OGCM patients treated with fertility sparing/preserving surgery in our center required adjuvant chemotherapy. Surveillance, Epidemiology and Result (SEER) between 1973 – 2002, identified 1262 cases of OGCM. Of these cases, 414(32.8%) are Dysgerminoma, 449 (35.6%) are immature teratoma and 362 (28.7%) are mixed germ cell.10 57.6% of patients in our study were diagnosed at early stage at time of presentation and 51.5% (17/33) of patients were in the first two decade of life, thus conservative management was the preferred treatment's option. In other studies, the most common histology types was immature teratoma and mixed germ cell tumour (1/3 patients each) and more than 50% was in advanced stage [11]. In contrast with longer doubling time of epithelial ovarian tumour, germ cell malignancies tend to grow rapidly and often are characterized by sub acute pelvic pain related to capsular distension, haemorrhage or necrosis. They are more likely to present with disease beyond the affected ovaries.

In term of reproductive function, majority of our patients maintained their ovarian function. Our data showed that the recovery of menses among our OGCM patients who had fertility sparing surgery and adjuvant chemotherapy were 71.4% within 0 – 6 months and 21.4% within 12 months. Only one patient had premature ovarian failure and required hormone replacement therapy. Post operative adjuvant chemotherapy (BEP regimen) was given for 4 – 6 cycles and the decision of cycles for each patient was based on the histotype and the advanced of the disease. These regimens are the most sensitive chemotherapy for OGCM and data showed that there was no so significant adverse effect to the ovarian function and menstrual cycles [12, 13, 14]. Sagae *et al* showed that recovery of menstruation after completed chemotherapy was 74% within 0 – 6 months and 11.5 % within 12 months.15 Other authors also reported an excellent recovery result rate of menstruation of 80 -99% after completed chemotherapy for malignant germ cell ovarian tumour [14, 16, 17].

In term of reproductive function, our series showed that 5/9 of patients who are married have conception after completed treatment (fertility sparing surgery and chemotherapy). Five full term normal deliveries and three miscarriages occurred in these patients. One patient had a full term infant after in vitro fertilization and another one had two full term babies after completed the treatment. Thus, the fertility rate was 55.5% in our study. Recent study showed that spontaneous pregnancies with fertility rate of 80% was achieved in patients who were diagnosed with malignant ovarian germ cell tumour and trying to get pregnant [18]. Other studies have reported the fertility rates from 50% up to 95% [12, 14, 16, 17, 19]. These showed that fertility is not seriously affected by the fertility-preserving surgery and chemotherapy used to treat OGCM even in advanced stages.

In this study, 12 (36.3%) of 33 patients who received platinum based chemotherapy (apart of BEP regimen) had relapsed with median duration of recurrence of 5 months. Histopathological type of OGCM was a significant adverse prognostic factor for relapse. Those diagnosed with yolk sac tumour and mixed germ cell tumour (with YST elements) were noted to have a high risk of relapse and poor outcome. 42.1% of our patients diagnosed with non DSG/IMT relapsed after the end of chemotherapy or developed progression of disease. Other studies reported that the recurrence rate of YST following surgery and adjuvant platinum- based chemotherapy was 14% up to 39% [20, 21, 22]. Our data showed higher rate of relapsed in non DSG/IMT tumour as most of these patients underwent surgery performed by general gynaecologist, outside an oncology setting and considerable delayed in starting chemotherapy. Some GOG studies suggest that patients with advanced disease who undergo surgical resection plus adjuvant chemotherapy have higher complete remission rate than patients who are not debulked [23]. Apart from delay in commencing the chemotherapy, studies showed that YST histology and high level of alpha fetoprotein (AFP) level were associated with poor prognosis [22, 24]. Due to rapid growth of a tumour in some patients, especially yolk sac tumour, treatment should be initiated as soon as possible after surgery, preferable 7-10 days [25]. No prognostic differences were found between age at diagnosis and staging at presentation in those with or without relapse/ progression. The presence of YST component in histopathology partly contributed to poor prognosis in OGCM.

We showed that the 5 years overall survival rate for our patients who had fertility preserving surgery and

chemotherapy was 87.9%. This was most likely related to the usage of BEP chemotherapy regimen as the first line treatment after the surgery, supported by other previous studies that showed BEP regimens are highly active agents against malignant germ cell tumor [26, 27]. Our findings are consistent with other studies where the long term survival rate for patients with OGCM after completed chemotherapy (BEP regimen) ranged from 82% to 100% for early stage and 75% for advance stage [2, 18, 27]. Despite disease spread beyond the ovaries in 42.6% of cases, the survival rate was still good. Of 33 patients who underwent fertility sparing/preserving surgery and chemotherapy, 12(36.3%) of the patients had disease progression and relapsed with the median duration of relapse of 5 months. Repeat surgery was performed in 8 patients, 5 had TAHBSO and all of them had second line chemotherapies commenced after the surgery either repeat BEP regimens for those platinum sensitive, POMB/ ACE or VIP regimens. Two of these patients had disease progression during the treatment. These findings support the notion that fertility preserving surgery does not have worse outcomes in terms of survival or recurrence even though in advanced stage as compared to epithelial ovarian cancer. As most of the patients are young and nulliparous, fertility preservation is advocated as the most important secondary objective without compromising long term survival.

In summary, our study showed that fertility preserving surgery and adjuvant chemotherapy appears to have little effect on fertility and the menstrual cycle with a good overall 5 years survival of 87.9%. Patients diagnosed with histopathological yolk sac tumour elements had poor prognosis for early recurrence, thus aggressive treatment should be initiated earlier with a higher number of cycles. Due to the bad prognosis of YST as compared to the other histological types, it is strongly suggested that further prospective trials be conducted. Risk-adapting approach should be used in order to increase the survival and cure rate for this rare disease.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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