

# Germinal Ovarian Tumors In Reproductive Age Women: Fertility-Sparing And Outcome

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## Abstract

### Purpose

MOGCTs (malignant ovarian germ cell tumours) is a rare tumour, which mainly affects patients in reproductive age. The aim of this study is evaluate the fertility and survival outcomes in young women with MOCGTs treated with fertility-sparing surgery (FFS).

### Methods

From 2000 to 2018 twenty-eight patients with diagnosis of MOGCTs in reproductive age at the University of Bari were collected. Most received FFS and in patients treated conservatively, the reproductive outcome and survival were investigated. Data of patient demographics, clinical presentation, oncology markers dosage, staging, type of surgery histological examination, survival and reproductive outcome were collected from hospital and office charts. All informed consent was obtained from all patients

### Results

Twenty-eight patients with diagnosis of MOGCTs were collected. The median age was 24 (range: 9-45). The majority of the patients had stage IIIC. Twenty-four woman received fertility-sparing surgery consisting in unilateral ovariectomy and omentectomy whereas only 4 women based on their stage (IIIC) received a radical surgery (hysterectomy with bilateral adnexectomy, lymphadenectomy and omentectomy). Our study shows that FFS in MOGCTs can produce good results both on reproductive outcomes and on survival. Indeed, in our group there was only one case of exitus as result of recurrence. On the other side, patients after FFS maintained normal ovarian function and 5/5 women who have looked for pregnancy, obtained it spontaneously. The median follow-up was 90 moth (range 3-159).

### Conclusion

Conservative surgery for MOGCTs should be considered for women in the reproductive age group who desire preservation of fertility.

### Introduction

Germ cell tumors (OGCTs) represent the 20–25% of all ovarian neoplasms, whereas malignant ovarian

germ cell tumors (MOGCTs) comprise only 5% of all ovarian cancers [1, 2].

MOGCTs show a peak prevalence in young women and adolescents. Approximately 60% of ovarian tumours are germ cell tumors in patients younger than 20 years and one third of these cases are malignant [3].

The MOGCTs include several histotypes, all deriving from primordial germ cells of the ovary and represent a heterogeneous group of tumours with variable biological behavior, clinical presentation and prognosis [4].

There is a variety of histologic types: dysgerminoma, immature teratoma, endodermal sinus tumor, choriocarcinoma, polyembryoma, and mixed MOGCTs [5].

These tumors differ from epithelial ovarian cancer (EOC) by incidence at an earlier age, for localization, almost unilateral (95% of cases), for the high rate of growth, rare tendency to spread and finally for their good prognosis [6, 7]. This is explained by the numerous of diagnoses at early stages and their high chemosensitivity [8].

Therefore, the treatment of this pathology in early stages requires only surgery while in presence of high-risk factors or advanced disease, after surgical treatment chemotherapy is highly recommended [9, 10].

The most used chemotherapeutic protocol is the combination of Bleomycin, Etoposide and Cisplatin (BEP) or Bleomycin, Vinblastine, Cisplatin (PVB) for 4-6 cycles and this is based on histotype and stage [11].

Patients are followed up with abdominal-pelvic examination and ultrasound, complete blood count, and biochemistry profile every 2-3 months for the first 2 years, at semi-annual intervals up to year 5 and annual intervals thereafter. Chest X-ray is ordered at annual intervals or in case of clinical suspicion. Computed tomography of thorax and abdomen is performed every 6 months for the first 2 years and at annual intervals up to year 5 [12].

A variable long-term survival rate of 82%-100% is reported in the literature in the early stages and 75% in the advanced stages [12]. Considering the frequent incidence of MOGCTs in young women and the high survival rate clinician should consider fertility-sparing surgery (FSS) [13]. The correct

information about the risks of iatrogenic infertility and the strategies available to reduce the incidence of this effect (reproductive counselling) should be offered to young cancer patients immediately after diagnosis, subsequent stage of the disease and before the start of treatment [14]. The main techniques of fertility preservation in patients who need to undergo cancer treatments are: cryopreservation of embryos or eggs, cryopreservation of ovarian tissue, gonadic suppression with similar LHRH and conservative surgery. FFS is identified as the cornerstone of early-stage MOGCTs treatment. On the other hand, for the advanced stages, the possibility of performing an FFS in young patients who desire a pregnancy should be assessed in a personalized manner and after counselling with the patient [10]. Indeed, current literature presents reassuring data relating to favorable overall survival and reproductive outcome after FFS [11]. In this study we analyzed survival outcomes in women of childbearing age diagnosed with MOGCTs and treated with FFS. We also evaluated changes in the menstrual cycle and post-treatment pregnancies.

## Material And Methods

From 2000 to 2018 all women in reproductive age with diagnosis of MOGCTs at the University of Bari were collected.

Data of patient demographics, clinical presentation, oncology markers dosage, staging, type of surgery histological examination, survival and reproductive outcome were collected from hospital and office charts. All informed consent was obtained from all patients.

The evaluation of the disease stage has been performed using the FIGO classification [14] whereas the histopathological definition has been evaluated according to the classification of germ cell tumors of the ovary World Health Organization (WHO). [15].

A cytological analysis of the ascitic fluid or the peritoneal washing and an intra-operative histological examination was performed in all cases. In addition, all patients presented an extemporaneous of germ cell tumour subsequently confirmed at the definitive histological examination.

The "maximum" debulking was defined as a tumour residue = 0 after primary or recurrent surgery, "optimal" in the case of a 1 cm tumour residue and "not optimal" > 1 cm.

Disease-free survival (DFS) was defined as the period between diagnosis and recurrence, whereas overall survival, (OS) was identified as the period between diagnosis and the time of death or last follow up [16].

Adjuvant BEP or PVB (average of 4 cycles every 3 weeks) was indicated for patients with IC or higher disease, immature teratoma or high-grade tumors, residual disease after cytoreductive surgery. Patient are followed up with abdominal and pelvic examination and ultrasound, blood count and tumor marker dosage every 2–3 months, for the first 2 years, at semi-annual intervals up to year 5 and at annual intervals thereafter. Computed tomography of thorax and abdomen is performed every year for the first 5 years. Chest X-ray was indicated at annual intervals for the first two years.

## Results

Twenty-eight patients with diagnosis of MOGCTs were collected. The median age was 24 (range: 9–45). The majority of the patients had stage IIIC. Most received fertility-sparing surgery consisting in unilateral ovariectomy and omentectomy whereas only 4 women based on their stage (IIIC) received a radical surgery (hysterectomy with bilateral adnexectomy, lymphadenectomy and omentectomy) The median follow-up was 90 moth (range 3-159).(Table I). The onset of the disease was pain in 18 (64%), abdominal distension in 26 (26%), ascites in 2 (7%), dyspareunia in 3 (10%), weight gain 2 (7%), vaginal bleeding 1 (3,5%) and symptomless in 3 women (10%). The average diameter of the neoplasms was 9.2 cm (range 5–20). It was also recorded an increase in the following tumor markers CA-125 in 3 (10,7%),  $\beta$ -hcg in 6 (21,4%) a-feto-protein (AFP) in 11 (39%), CA 19.9 in 2 (7%) and CA-15.3 in 1 patient (3%). None of our patients showed an increase of the CEA. Tumor histology included 4 (14%) teratomas, 11dysgerminomas (39%), 3 (10%) endodermal sinus tumor, mixed MOCGTs 10 tumors (35%). Ten women had I A (35%), 5 presented stage I C (32%), 5 stage II A (18%) and 4 IIIC (14%) stage disease. Therefore, a total of 18 patients were treated with adjuvant therapy: 16 with BEP and 2 with PVC. The chemotherapeutic regimen was administered for 4 cycles every 3 weeks (Table 1). Three women (12%) treated with FFS with an histology different from dysgerminoma had a recurrence 6 years after treatment, therefore a completion of surgery was performed. Of the 28 women, two women expired: one with a diagnosis of endodermal sinus tumor dead for her disease

progression despite radical surgery and chemotherapy and another dead for her severe fatal toxicity after the first cycle of PVB chemotherapy. Fertility preservation techniques were used in 8 patients by performing GnRH analogues during chemotherapy and in two cases through cryopreservation of ovarian tissue and cryopreservation of oocytes upon commencement of treatment, respectively. Later in these last two cases both patients had spontaneous pregnancy without having to resort to thawing. Of the 28 patients of child-bearing age diagnosed with MOCGTs excluding the 4 patients who had performed hysterectomy after diagnosis, 3 after recurrence, 1 patient with pure gonadal dysgenesis (Swyer syndrome -karyotype 46 XY) and 1 death after chemotoxicity, we investigated on the regularity of the post-treatment menstrual cycle and reproductive status. Among these nineteen women, 15 (78%) reported regular menstrual cycles during and after chemotherapy; on the other hand the remaining 4 (21%) presented amenorrhea during chemotherapy but referred regular cycles after the end of treatment. Regarding the reproductive outcome, 4 patients had a pregnancy before the disease without attempting further conception, 11 patients (average age 32 years) declared that they were not currently interested in childbearing, 1 women had a spontaneous abortion (SAB) at 7 weeks, 1 had a voluntary pregnancy interruption (IVP) at 22 weeks following a diagnosis of multiple fetal malformations and the remaining 5 reported having achieved pregnancy through spontaneous conception and with vaginal delivery. Of these 5 women the median time to achieve a pregnancy was 8 years from surgery (range 3-15 years) and 4 of them had a combination of BEP + GnRH analogue whereas 1 only chemotherapy after surgery. (Table 2).

Table 1  
Patient Characteristics and Treatment Data

a. Characteristic	Data
No. of patients	28
Median age (yr) (range)	24 (9-45)
Median gravidity (range)	1 (0-6)
Median age at menarche (yr) (range)	14 (11-17)
Median follow-up	90 (3-159)
b. Clinical presentation	Data (%)
Pain or pressure	18 (64%)
Symptomless	3 (10,7%)
Abdominal distention	26 (92%)
Ascites	2 (7,1%)
Mass diameter (range)	9,2 cm (5-20)
Dyspareunia	3 (10%)
Weight gain	2 (7, 1%)
Vaginal bleeding	1 (3,5%)
c. Surgical procedure	Data (%)
Unilateral oophorectomy	9(32%)
Unilateral oophorectomy, omentectomy, lymphadenectomy	13 (46,4 )
Bilateral oophorectomy	1(3, 5%)
Hysterectomy with unilateral oophorectomy, lymphadenectomy, omentectomy	1(3, 5%)
Hysterectomy with bilateral oophorectomy,lymphadenectomy, omentectomy	3 (10, 7%)
d. Stage	Data(%)
IA	10 (35%)
IC	9 (32,1%)
IIA	5 (17,8%)
IIIC	4(14,2%)
e. Cell Type	Data (%)
Teratomas	4 (14,2%)
Dysgerminomas	11 (39%)
Endodermal sinus tumor	3 (10,7%)
Mixed MOGCTs	10 (35%)
f. Markers	Data
CA-125	3 (10,7%)
CA 19.9	2 (7,1%)
CA 15.3	1 (3,5%)
α-FP	11 (39,2%)
β-hcg	6 (21,4%)
CEA	0
β-hcg + α-FP	3 (10,7%)
Ca-125 + α-FP	2 (7,14%)

Table 2  
Pregnancy Outcome

Case no.	Stage	Histology	Procedure	CHT	Pregnancy event	status
1	IA	Mixed MOGCTs	U.A.+Omentectomy	NO	2 Term SVD	NED
2	IC	Endodermal sinus tumour	U.A.+Omentectomy	BEPx5	1 Term SVD	NED *
3	IC	Teratomas	U.A.+Omentectomy	BEPx 5	2 Term SVD	NED
4	III C	Mixed MOGCTs	U.A.+Omentectomy + multiple biopsies	BEP X 5	1 Term SVD	NED
5	III C	Dysgerminomas	U.A.+Omentectomy + multiple biopsies	BEP X 5	2 Term SVD	NED
6	IIIC	Dysgerminomas	U.A.+Omentectomy + multiple biopsies	BEP X 5	1 SAB	NED
7	IIIC	Mixed MOGCTs	U.A.+Omentectomy + multiple biopsies	BEP X 5	1 IVP	NED

UA = unilateral adnexectomy, SAB = spontaneous abortion, SVD = spontaneous vaginal delivery, NED = no evidence of disease, BEP = Bleomycin, Etoposide and Cisplatin, IVP: voluntary interruption of pregnancy  
\*DDI: patient NED deceased regardless of illness (suicide)

## Discussion

About 60% of OGCTs are diagnosed in patients under the age of 20 and one third of these are malignant [16]. Most of these tumors present a favorable prognosis due to early diagnosis, unilateral localization, rare metastatization [17] and high chemo-sensitivity [18].

Therefore, FSS in MOCGT in the early stages is considered the therapeutic standard in women who want to maintain their reproductive function [19, 20].

Several studies report reassuring data even in advanced MOGCTs, both on overall survival (87.9% at 5 years) and on the absence of alterations of the menstrual cycle and reproductive function [21].

In literature, the increase in AFP levels and a different histology from the dysgerminoma has been correlated to a greater incidence of recurrences. Therefore, in these cases a more extensive surgical treatment and a greater number of chemotherapy cycles could be indicated, after individualized evaluation of the risk factors[22-24] This is also reflected in terms of OS which in the literature is reported to be equal to 97% in cases of dysgerminoma while in non-germinomas is 60% ( $p < 0.001$ ) [25].

Actually, in our experience all cases of recurrence recorded showed a histology different from the

dysgerminoma and high dosage of AFP in the only case evolved in exitus for her disease. Surgical treatment of advanced states must be supplemented with chemotherapy whose effects on fertility have been widely discussed in literature. Solheim et al. compared patients who received 3 cycles of platinum-based chemotherapy with those who received more than three cycles. In the latter group the rate of infertility was significantly higher ( $p = 0.040$ )[26–28]. Some authors found a reduction of primordial follicles, stromal fibrosis following chemotherapy, with a parallel increase in gonadotropins and reduced levels of estrogen. [29, 30]. These effects seem to be closely related to the type of drugs, dose and chemotherapy duration. [31]

In our study there is no evidence on any reproductive outcome reduction following multiple chemotherapy cycles. Similar data are reported in several papers that showed that PEB versus PVC chemotherapy for MOCGTs does not appear to affect reproduction or menstrual cycle which normalized within 6 months in 90% of cases [32–34]. Similarly, we reported that 78% of the patients had regular menstrual cycles during and after chemotherapy, on the other side 22% patients presented amenorrhea during chemotherapy but had regular cycles 5 months after treatment. As regards of fertility preservation techniques, treatment with GNRH analogues concomitant with adjuvant chemotherapy was proposed in 8 of the 18 patients and 4 of these had spontaneous pregnancies. In one case the chemotherapy was performed alone. Indeed, recent studies support that chemotherapy regimens used for these neoplasms do not show particular toxicity, therefore the association with GNRH analogues would not change the effects on fertility compared to the execution of the isolated therapy [35, 36].

Although in subjects with ovarian dysfunction at the starting stage, the association of the GnRH analogue may be indicated. Pre-treatment anti-Mullerian-hormone (AMH) serum levels and age of each patient, appear to be reliable predictive factors of ovarian activity recovery after treatment [13, 36].

Similarly, literature reports that AMH dosage and the fertility evaluation pre-treatment can help in the identification of patients with deficient ovarian reserve and who could benefit from a fertility preservation technique [37].

In this study, there were a very small percentage of pregnancy failure: 1 had SAB and 1 had IVP; these percentages are typically reported in a general population [38], therefore it is difficult to demonstrate a relationship [39]. The literature on the possible dangerous effects of cancer treatments on pregnancy did not show an increased risk of genetic or other defects in births of women previously receiving treatment antineoplastic [40]. Nevertheless, in these women, considering limited cases studied, it would be advisable monitoring pregnancy more strictly [14]. Indeed, the limitations of this study are represented by the limited number of cases, and retrospective analysis

## Conclusions

MOGCTs are rare tumors, which mainly affects patients in reproductive age [13]. The increase of therapeutic rates has moved the attention of recent studies on variations of the menstrual cycle and reproductive outcome in patients after cure. Several studies report reassuring data relating to FFS treatment of MOCGTs in early stages, therefore in these cases conservative surgery is now consolidated as a safe procedure. Moreover, for MOGCTs in advanced stages treated conservatively, literature reports a non-compromised DFS and OS [7]. In this case personalized follow-up should be proposed in order to consider the risk factors, timing and nature of the relapse [4]. Furthermore, our study shows that FFS in advanced stages can produce good results both on reproductive outcomes and on survival. Indeed, in our group there was only one case of exitus as result of recurrence. On the other side, patients after FFS maintained normal ovarian function and 5/5 women who have looked for pregnancy, obtained it spontaneously. Also literature studies performed on a larger population report that patients with MOGCTs undergoing FST had reassuringly high conception rates and low premature ovarian failure rates; however, in pre-treatment counselling, the risks of this approach in such young population should be discussed[41]. Nevertheless, considering the rarity of advanced stage MOGCTs (20-30%) [17] and the few cases treated conservatively, safety of FFS is accepted but not fully clinically supported yet [42]. Therefore, conservative surgery for MOGCTs in advanced stages needs greater number of cases and meta-analysis in order to obtain a higher grade of recommendation [21] but currently may represent a therapeutic option in patients available for extended follow-up and after subscribing to informing consent [43].

## Declarations

### **Ethical Approval and consent to participate**

There is no formal approval of the Ethics Committee, but the procedures were carried out in accordance with the Helsinki Declaration, as revised in 2013.

Informed consent was obtained for the patient through a dedicated form containing study design.

### **Consent For Publication**

Written informed consent for the anonymous publication of information relating to the disease is regularly obtained, from all individual participants included in the study, during the medical interview with the patient prior to the surgical or chemotherapy treatment.

### **Availability of data and materials**

The datasets used during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests

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### **Authors Contribution**

**MD: (Corresponding authors)** She has made substantial contributions to the conception of the work and she approved the submitted version and she agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which she was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

**ES:** She has made substantial contributions to design of the work and approved the submitted version and is agreed both to be personally accountable for the author's own contributions and to ensure that

questions related to the accuracy or integrity of any part of the work, even ones in which she was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

**VL:** She has made substantial contributions to the acquisition, analysis of data and she approved the submitted version and she agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

**AP:** He has made substantial contributions to draft the work and substantively revise it. He has also approved the submitted version and he agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which he was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature

**GC:** He has made substantial contributions to draft the work and substantively revise it. He has also approved the submitted version and he agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which he was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature

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