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MENSTRUAL AND REPRODUCTIVE FUNCTION FOLLOWING TREATMENT OF MALIGNANT GERM CELL TUMORS OF THE OVARY AND HIGH RISK GESTATIONAL TROPHOBLASTIC NEOPLASM OF UTERUS

Oncology

KEYWORDS: malignant ovarian germ cell tumors, high risk gestational trophoblastic neoplasm, menstrual and reproductive function, fertility preservation

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ABSTRACT

Introduction: Malignant ovarian germ cell tumours (MOGCT) and gestational trophoblastic neoplasms (GTN) of uterus are diseases affecting females during their reproductive age. With the advent of combination chemotherapy there has been higher cure rates in these diseases and thus there is a shift in the focus to study the quality of life of these females in terms of their menstrual and reproductive health following their treatment. The aim of our study is to investigate menstrual and reproductive functions of the females who attained remission following treatment of MOGCT with conservative surgeries and adjuvant combination chemotherapy and in females with high risk GTN treated with combination chemotherapy with or without fertility preserving surgeries.

Methods: Between January 2000 to December 2015, a total of 227 MOGCT and approximately 71 patients with high risk GTN who underwent treatment at our institute were included in this study. The current study was retrospective analysis of menstrual health and reproductive function of these patients following their remission which were prospectively collected during their follow up visits.

Results: Among the 227 MOGCT patients, 188 underwent fertility preserving surgery which was followed by adjuvant chemotherapy with 3 to 4 cycles of BEP (Bleomycin, Etoposide, Cisplatin). Among the 54 pre-menarchal patients, 35 (64.8%) attained menarche and the cycles were regular and normal and among 173 post menarchal patients 166(95%) resumed their cycles within 6months of their remission. Among the patients on follow-up, 16 patients desired to conceive, of which 14(87.5%) patients conceived and 7 (58%) had achieved at least one pregnancy. Five (41%) had achieved at least two pregnancy. Nine (64.5%) delivered healthy term baby and 2 patients had spontaneous abortion and 3 were lost to follow up after conception. Average time interval between completion of chemotherapy and conception was 24 months (ranging from 5 months to 60 months). Among the patients who conceived, 9 were International Federation of Gynaecology and Obstetrics (FIGO) stage I, none were stage II, and 3 were stage III. Average dosage of chemotherapy received by these patients were 210U for Bleomysin (120 to 300U), 2600mg for Etoposide (2000-3200mg) and 520mg for cisplatin (400 to 640mg).

Among the high risk GTN who attained remission and were on follow-up, 21 patients desired conception, of which 14(66.6%) patients conceived, 8(57.1%) had received EMACO as the first line chemotherapy and had remission, 6(42.8%) had to receive in addition 2nd line chemotherapy EMAEP to attain remission. Three patients underwent conservative resection of the uterine tumor in addition to chemotherapy to attain remission. Four patients had more than one subsequent pregnancy. Of the patients who conceived average cycles of EMACO was 6. During the follow up period 4 conceived within 1yr(in spite of contraception being advised), 10 conceived within 2-5yrs of remission. During chemotherapy, 97% of patients developed amenorrhea but 94% of these women resumed normal menstrual function within 6 months of completion of chemotherapy. Six (2.6%) had premature ovarian failure.

Conclusion: Fertility sparing treatments are safe in patients with MOGCT and in high risk GTN. Among the patients who attempted conception, most of them conceived and had healthy children. Combination chemotherapy has dramatically improved the prognosis in both these group of patients. Treating surgeons should have a comprehensive approach in counselling the patients regarding fertility sparing procedures and positively assure them regarding future reproductive function.

INTRODUCTION:

Cancer can affect all ages including children, adolescent girls and females of reproductive age group. With the advances in recent years, treating cancer has become less destructive and more specific and effective without compromising on survival rates and quality of life [(1)]. Malignant ovarian germ cell tumours (MOGCT) are highly malignant and rapidly growing tumours with a peak incidence occurring in adolescent and young women [(2)]. Gestational trophoblastic neoplasm(GTN) also occur in females of reproductive age group, most of whom desire for future normal conception after their treatment [(3).]

Combination chemotherapy has effectively improved the prognosis of MOGCT and high risk GTN to have higher cure rates. Fertility preservation is effectively achieved with conservative surgery and adjuvant chemotherapy, even in patients with advanced disease. With better cure rates, now the treatment focus is shifted towards quality of life like menstrual health and reproductive functions in these cured females.

OBJECTIVES:

To investigate menstrual and reproductive functions of the females who attained remission following treatment of MOGCT with conservative surgeries and adjuvant chemotherapy and in females with high risk GTN treated with combination chemotherapy with or without fertility preserving surgeries.

MATERIAL AND METHODS:

The current study was a retrospective review of 227 patients with MOGCT treated with surgery and adjuvant chemotherapy and 71 patients with high risk GTN who were treated with combination chemotherapy with or without resection of uterine tumour at Kidwai Memorial Institute of Oncology between January 2000 to December 2015. Menstrual and reproductive function after conservative surgery were analysed which was obtained prospectively during follow up visits of the patients. Histopathology of the tumor was confirmed by onco- pathologists at our institute, and was classified according to WHO classification. Tumors were staged according to International Federation of Gynaecology and obstetrics(FIGO) staging system. Patient details like age at presentation, menstrual and obstetric history, surgery performed, chemotherapy details, stage of the disease and histological type, and post remission menstrual and reproductive health which were noted down during the patient follow-up were compiled from case files.

RESULTS:

Between January 2000 and December 2015, a total of 227 patients with MOGCT and 121 patients with GTT (Gestational Trophoblastic Tumor) were treated at our Institute.

Among the MOGCT, 188 patients underwent fertility preserving surgery followed by adjuvant combination chemotherapy. According to FIGO, the histological subtypes were 93(41%) dysgerminoma, 25(11%) immature teratoma, 63(27%) endodermal sinus tumor, 44 (19%) mixed germ cell tumor, 1(0.4%) embryonic cell tumor and 1 (0.4%) choriocarcinoma. Age of patients ranged from 10 to 35yrs with a mean age of 20.9yrs. (Table 1)

TABLE 1: Histological type of MOGCT (Total 227)

Histological type	Number(%)
Dysgerminoma	93(41%)
Endodermal Sinus Tumor	63(27%)
Mixed Germ Cell Tumor	44(19%)
Immature Teratoma	25(11%)
Embryonic Cell Tumor	1(0.4%)
Choriocarcinoma	1(0.4%)

Of the 227 patients, 54 (23.7%) patients were premenarchal (4 patient had primary amenorrhoea) and 173 (76.2%) were post menarchal.

Among the 54 premenarchal patients, 35 (64.8%) attained menarche post remission and there cycles were regular and normal. In 10 (18.5%) patients menstrual history was unknown as there was no documentation of the same. One (1.8%) patient had hypoplastic uterus hence menstruated only to withdrawal bleeding. Four (7.4%) patients had primary amenorrhoea (2 had karyotype of 46XY, 1was 46XX and 1 was 46XXX). Four patients died, 2 due to post chemotherapy septicaemia and 2 due to progressive disease. (Table 2)

TABLE 2: Menstrual outcome in premenarchal patients (total-54)

During follow up	Number (%)
Attained menarche	35 (64.8%)
Unknown	10(18.5%)
Hypoplastic uterus	1(1.8%)
Primary amenorrhoea	4(7.4%)
Dead	4(7.4%)

Among 173 post-menarchal patients, 166(95%) resumed their cycles within 6 months of their remission.

Among 227 MOGCT patients with 54 (23.7%) being premenarchal and among 173 post menarchal, 83 (47.9%) patients were without a partner. At presentation, 65 (37.5%) patients were parous and 16(9.2%) were nulliparous. Nine (5.2%) patients had hysterectomy done elsewhere and were treated with adjuvant chemotherapy at our hospital.

TABLE 3: Reproductive demography of post menarchal patients (Total-173)

	Number of
Parous	65 (37.5%)
Nulliparous	16 (9.2%)
Post menarchal without partners(Unmarried)	83 (47.9%)
Post Hysterectomy	9 (5.2%)

During follow up after remission, nearly 16 patients desired to conceive of which 14 (87.5%) patients conceived spontaneously. Seven patients had achieved at least one pregnancy. Five patients had achieved at least 2 pregnancies. Nine patients delivered healthy term baby and there was no documented birth defects. Two patients had spontaneous abortion. Rest of the 3 patients, lost follow up after conception. Average time interval between completion of chemotherapy and conception was 32.5 months (5 to 60 months)

Among the 14 patients who conceived, 9(64.5%) were FIGO stage IC, none were stage II, and 5(35.7%) were stage III. All 14 patients received combination chemotherapy regimen- BEP(Bleomysin, Etoposide, Cisplatin). Average dosage of chemotherapy 210U for Bleomysin (120 to 300U), 2600mg Etoposide (2000-3200mg) and 520mg for cisplatin (400 to 640mg). (Table 4)

TABLE 4: Profile of patients with MOGCT who conceived (Total-14)

	Number (%)
Number of patients conceived	14/16 (87.5%) (16 desiring pregnancy)
Stage I II III	 9(64.2%) 0(0) 5 (35.7%)
Surgery performed • Cystectomy • Unilateral salphingoophorectomy (USO) • USO + infra colic omentectomy (ICO) • USO+ICO + pelvic lymph node dissection • USO + contralateral cystectomy + ICO + appendectomy	1 5 4 3 1
Chemotherapy received Yes No	 14(87.5%) 0
Regimen-BEP dosage- average(Range) • Bleomycin • Etoposide • Cisplatin	210U(120 to 300) 2600mg (2000-3200) 520mg (400 to 640)
No of patients with documented healthy normal delivery	9(64.2%)

Among the 121 patients with gestational trophoblastic tumors (GTT) treated, 71 were high risk GTN, 48 were low risk GTN and 2 were Placental site trophoblastic tumor. Patient's age ranged from 18 to 24 years, with median age of 21 years. Of the 71 high risk GTN in remission 48 (67.6%) patients were parous with atleast 1 live child, 21 (29.5%) were nulliparous and 2 patients were without a partner (unmarried). Among 21 patients desiring fertility, 14 (66.6%) patients conceived spontaneously. 8(57.1%) patients had received EMACO as the first line chemotherapy and have had complete remission. Six (42.8%) patients had to receive in addition 2nd line chemotherapy EMAEP to attain remission. Of these 3 underwent conservative resection of the uterine tumor in addition to chemotherapy to attain remission. Four patients had more than one subsequent pregnancy. There were 18 conceptions with documented 16 term healthy offspring. Of the patients who conceived average cycles of EMACO were 6. (Table 5) During the follow up period 4 conceived within 1yr (in spite of advising contraception), 10 conceived within 2-5yrs.

TABLE 5 : Profile of high risk GTN patients who conceived after remission

	Number (%)
Total number of patient's conceived	14/21(66.6%) (21 patients desiring pregnancy)

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Median age (years)	21(18-24yrs)
Chemotherapy received EMACO EMACO followed by EMAEP(II LINE)	 8(57.1%) 6(42.8%)
Conservative surgery in resistant cases (in addition to chemotherapy)	3(21%)
Average number of chemotherapy cycles EMACO EMAEP	 6(5-7) 5(4-5)

During chemotherapy 97% of patients developed amenorrhea but 94 % of these women resumed normal menstrual function within 6 months of completion of chemotherapy. 6(2.6%) had premature ovarian failure. The overall mean follow up period was 42 months.

DISCUSSION:

Since 1970s the treatment of MOGCT has seen improved success with favourable outcome due to the change from cyclophosphamide based chemotherapy to platinum based chemotherapy[4].

Several case series reviews have examined the question of menstrual and reproductive function after treatment of MOGCT with combination chemotherapy, primarily BEP regime[5]. Many studies have shown documented successful pregnancies in these patients following fertility preserving surgery and combination chemotherapy [7,8,9]. The majority of the patients treated with surgery and chemotherapy resumed normal menstrual cycles within 6 months of completion of the treatment [4,6].Consistent with our study, where 95% patients resumed normal menstrual function within 6 months after completing chemotherapy and 14 patients spontaneously conceived. (Table 6)

Jacob Tangir et al found that women with stage III MOGCT successfully treated with fertility preserving surgery were able to conceive [4]. In our study 3 (25%) patients who conceived spontaneously after fertility preserving surgery and adjuvant chemotherapy were with stage III diseases.

TABLE 6 : Menstrual and reproductive outcome of MOGCT

Author (ref)	No. patients	No. normal menses	No. Pregnancies
Low 2000 (6)	74	43/47 (92%)	14 in 19
Zanetta 2001 (10)	138	80/81 (99%)	41 in 16
Tangir 2003 (4)	64	28/40 (69%)	47 in 29
Gershenson 2002 (11)	133	59/77 (77%)	37 in 35
Gershenson2007(5)	132	62/132 (87.3%)	37 in 24
Gershenson2011(12)	22		11 in 8 (1- IVF, 1 Donor egg)
Our study	227	166/173(95%) (post menarchal group)	14 in 16

GTT occur in women during their reproductive age. Since the discovery of effective combination chemotherapy, most patients even in the setting of widespread metastasis attain remission while preserving fertility [13].

More than 70% of survivors express a wish to conceive again [14]. Data from several centres similarly show that the subsequent pregnancy experience in patients treated for GTN is similar to that of general population and have reported that chemotherapy does not harm the outcome of subsequent pregnancies[15,16].

Wooles et al reported no difference in conception rate or pregnancy outcome between low risk GTN and high risk GTN treated with single agent methotrexate and multiagent chemotherapy respectively [18]. The multidrug regimens used for GTN has demonstrated subsequent successful term deliveries in our study as seen in other studies. (Table 7) It could be concluded that patient treated for high risk GTN can anticipate normal future reproductive outcome.

TABLE 7: Reproductive outcome of high risk GTN

Author (ref)	No. patients cured	No. of patients conceived	Total pregnancies	Term deliveries
Woolas(14)	336	315	315	280(83%)
Mousavi (13)	23	13	13	8(40%)
Our study	71	14(of 21 who desi red conception)	18	16(88%)

Patients with MOGCT and high risk GTN and their family members should be reassured about the high chance of retaining the patient's ability to conceive and have normal children after conservative surgery and combination chemotherapy.

Limitations:

The study is retrospective analysis of the data entered in the past and hence suffered few missing details.

CONCLUSION:

Fertility sparing treatments are safe in patients with MOGCT and in high risk GTN. Among the patients who attempted conception, most of them conceived and had healthy children. Combination chemotherapy has dramatically improved the prognosis in both these group of patients. Treating surgeons should have a comprehensive approach in counselling the patients regarding fertility sparing procedures and assure them of having a good chance of resuming normal menstrual health and reproductive function in future.

REFERENCES

1) Kovacs P. Fertility Preservation in Reproductive Age Women with Cancer. J Obstet Gynaecol India. 2014 Dec; 64(6) : 381–7.
2) Parkinson CA, Hatcher HM, Earl HM, Ajithkumar TV. Multi-Disciplinary Management of Malignant Ovarian Germs and Tumours. Gynecol Oncol. 2011 Jun 1; 121(3): 625-36.
3) H Matsui, Y Iitsuka, K Suzuka, K Yamazawa, K Seki, S Sekiya. Outcome of Subsequent Pregnancy After Treatment for Persistant Gestational Trophoblastic Tumour. Hum Reprod. 2002 Feb; 17 (2): 469-472
4) Tangir J, Zelterman D, Ma W, Schwaertz PE : Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. Obstet Gynecol. 2003; 101:251-257.
5) Gershenson DM, Miller AM, Champion VL, Monahan PO, Zhao Q, Cella D, et al. Reproductive and sexual function after platinum-based chemotherapy in longterm ovarian germ cell tumor survivors: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:2792–7.
6) Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. Cancer 2000;89:391–8.
7) Williams S, Blessing JA, Liao SY, Ball H, Hanjani P. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. J Clin Oncol 1994;12:701–6.
8) Segelov E, Campbell J, Ng M, et al: Cisplatin based chemotherapy for ovarian germ cell malignancies: The Australian experience. J Clin Oncol1994; 12: 378-384.
9) Brewer M, Gershenson DM, Herzog CE, Mitchell MF, Silva EG, Wharton JT. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. J Clin Oncol 1999;17:2670–5.
10) Zanetta G, Bonazzi C, Cantu MG, Bini S, Locatelli A, Bratina G, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. J Clin Oncol 2001; 19 : 1015 – 20.
11) Gershenson DM, Miller A, Champion VL, Johnson CS, Cella D, Williams SD. Reproductive function after chemotherapy for malignant ovarian germ cell tumors. Proc ASCO 2002 ; 21 :373a: 1491 .
12) Lori E. Weinberg, John R. Lurain, Diljeet K. Singh, Julian C. Schink. Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumors. Gynecologic oncology 2011;121:285-9.
13) Azam SM, Afsaneh T, Nadereh B, Fatemeh G, Mitra M, Roudabeh P, et al. Outcome of subsequent pregnancy in patients with gestational trophoblastic disease. Cancer Therapy 2005; 3: 227-230.
14) Woolas, R. P., Bower, M., Newlands, E. S., Seckl, M., Short, D. and Holden, L. Influence of chemotherapy for gestational trophoblastic disease on subsequent pregnancy outcome. BJOG: An International Journal of Obstetrics & Gynaecology, 1998; 105: 1032–1035.
15) Kim JH, Park DC, Bae SN, Namkoong SE, Kim SJ Subsequent reproductive experience after treatment for gestational trophoblastic disease. Gynecol Oncol. 1998; 71, 108-12.
16) Khoo SK . Clinical aspects of gestational trophoblastic disease: A review based partly on 25-year experience of a statewide registry. Aust N Z J Obstet Gynaecol. 2007; 43, 280-9.