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Reproductive outcomes after treatment of patients with gestational trophoblastic neoplasia

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Abstract

Objectives: To assess reproductive outcomes of gestational trophoblastic neoplasia (GTN) patients after treatment.

Methods: Patients with GTN who had treatment in our institution during January 2003 to December 2018 were identified. The patients must have had conservative treatment with intact uterus. Data collected were age at GTN diagnosis, menstrual and obstetrical history, characteristics of GTN, treatment, reproductive outcomes including menstrual and fertility function after treatment.

Results: From 80 GTN patients, 74 patients had available clinical data. Total of 50 patients met inclusion criteria. Their mean age was 30.8 ± 7.7 years old; 88.0% were 40 years or younger. Thirty-nine of 50 patients (78%) were in stage I and the other 11 patients (22%) were in stage III. Most patients were in low risk group with only 2 (4%) were high risk. All except one had chemotherapy. Methotrexate was the most common first line chemotherapy, 86.0%. Only 5 of 50 (10%) had abnormal menstruation: delayed menstrual resumption, abnormal pattern, or amenorrhea. The 41 patients who desired pregnancy had younger age and lower parity than the other nine who did not want further fertility: mean age of 28.7 years old and parity of 0.5 compared to 40.4 years and 2.1, respectively (P<0.001 both). Total of 22 patients of 41 patients who desired for pregnancy (53.6%) got pregnant. The median interval time after complete treatment to pregnancy was 2.7-97.2 months (median 43.6 months). Total of 33 pregnancies were achieved resulting in 28 live births (84.8%), 4 abortions (12.1%), and one repeated molar pregnancy (3.0%).

Conclusions: Almost all GTN patients (90%) could resume normal menstruation. Slightly more than half of the patients who desired for pregnancy could have at least 1 pregnancy after treatment with chemotherapy. Normal live births were achieved in 84.8% without perinatal adverse events.

Introduction

Gestational trophoblastic disease (GTD) is a wide spectrum of pregnancy-related disorders. It encompasses abnormal pregnancy including molar pregnancy, invasive mole, and neoplasms. The gestational trophoblastic neoplasm (GTN) is categorized as choriocarcinoma, placental site trophoblastic tumor and epithelioid gestational trophoblastic tumor. Diagnosis can be from histopathology or persistence or rising of serum human chorionic gonadotropin (hCG) after molar tissue evacuation even in an absence of tissue pathology.

The prognosis of patients with GTN is usually excellent because an availability of serum hCG to aid in diagnosis in a woman with abnormal uterine bleeding leading to a correct diagnosis. Furthermore, the tumor is very chemosensitive with high rate of response and survival after treatment [1,2]. The regimen of chemotherapy generally depends on the recommendation by International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO) which categorize GTN into low or high risk according to the prognostic score [3]. The scores of six or less is classified as low risk wherein the patients was treated with single agent chemotherapy, with methotrexate (MTX) or actinomycin-D as the two most common regimens. On the other hand, scores of seven or greater are classified as high risk which require multi-agent chemotherapy, with etoposidde, methotrexate, actinomycin, cyclophosphamide and vincristine (EMA-CO) as the most common regimen.

Being pregnancy-related disorders, most GTN patients are in reproductive age. With an excellent survival outcome after treatment, reproductive function is often the major concern for cancer survivors especially those who have not completed their conception plan. The reproductive function of the patients may be affected with an exposure to chemotherapy with or without surgical resection of the affected organs.

This was a parallel study with our previous work assessing clinical features, treatment and oncologic outcomes which would be presented elsewhere. This study focused on reproductive function including menstrual function and pregnancy outcomes among the GTN patients who had uterus and one or both ovaries remained in situ after treatment.

Materials and methods

An approval from the Ethics Committee for Research involving human subjects of the institution was obtained. A list of GTN patients who had diagnoses of GTN during January 2003 to December 2018 were searched from the hospital database using the following International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes: D39.2 and M9100/1 (invasive mole), 9100/3 (choriocarcinoma), 9104/1 (placental site trophoblastic tumor), and 9105/3 (epithelioid trophoblastic tumor). Additional numbers of patients were searched from the archives of the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology of our institution.

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Exclusion criteria were patients who had hysterectomy with or without oophorectomy before GTN diagnosis or at primary treatment (at diagnosis or during treatment) or had no available medical records. The patients who had hysterectomy during surveillance after GTN treatment were included if they were had reproductive function data after treatment.

The diagnosis and treatment of GTN patients in our institution generally followed the standard guidelines for diagnosis and management of GTD recommended by FIGO/WHO which have been serially released [3,4]. A diagnosis was made when there was a plateau of serum hCG levels for 3 consecutive weeks or longer, a 10% rise in 2 consecutive weeks, or a histologic diagnosis of choriocarcinoma. After diagnosis, a thorough physical examination, laboratory investigations including serum hCG, biochemical study, urinalysis, and imaging studies were performed. The patient was staged and categorized into low risk (LR) or high risk (HR) including ultra-HR groups according to FIGO stage and WHO classification respectively. Chemotherapy regimen given based on the risk score group was given until remission or a decline of serum hCG level to normal (< 5 mIU/ml) plus additional courses according to their risk. Surveillance after completion of treatment included physical examination and serum hCG determination every month along with a recommendation for oral contraception for at least 12 months. The patients were counseled to have early visit for antenatal care once pregnancy commencement.

Data collected were: age, date at GTN diagnosis, index pregnancies, interval from index pregnancy, FIGO stage of disease and risk score group, date and type of treatment including chemotherapeutic regimen, histopathology if available, response, dates of last treatment and follow-up, and living status. Reproductive function included menstrual pattern before, during, and after treatment, contraception, desire of pregnancy, use of fertility assisting techniques, number of pregnancy and outcomes.

Data were analyzed using SPSS statistical software, version 22 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to analyze demographic data and were summarized as numbers with percentage, mean with standard deviation (SD) or median with range. Data were compared using chi-Square or Fisher Exact tests as appropriate. A p-value <0.05 was considered significant.

Results

During the study period, 80 patients were identified having the diagnosis of GTN by the ICD-10 codes in the electronic database. From 74 patients who had available data, the oncologic outcomes after treatment were reported separately elsewhere. Fifteen patients were excluded because they had hysterectomy either 10 years prior to GTN diagnosis (for abortion in 1 patient) or during the course of primary treatment for GTN (14 patients). The other 9 patients who had no data of menstrual and reproductive function were also excluded. Total of 50 patients who met inclusion criteria were included in the study.

The mean age was 30.8 ± 7.7 years old, 44 patients (88.0%) were 40 years or younger. The most common preceding pregnancy prior to GTN was molar pregnancy, 45 patients (90.0%). Data of age and type of index pregnancy prior to GTN are shown in Table 1. Median time from index pregnancy to GTN was 1.4 months (range 0.3-403.5 months). All had abnormal serum hCG levels (persistent or elevated) after index pregnancy. Of note, 5 patients also had pathology of choriocarcinoma revealed from the uterine content. Thirty-nine of 50 patients (78%) were in stage I and the other 11 patients (22%) were stage III. Most patients were in low risk group with only 2 (4%) were high risk. All except one had chemotherapy. Methotrexate was the most common first line chemotherapy, 86.0%.

Table 1. Characteristic features of the patients with gestational trophoblastic neoplasia who had uterus remained and available data (N=50)

Characteristic features	N	%
Age at GTN diagnosis ± SD (years)	30.8 ±7.7	
≤ 30 years	25	50.0
≤ 40 years	44	88.0
Type of antecedent pregnancy prior to GTN		
Molar pregnancy	45	90.0
Abortion	3	6.0
Ectopic pregnancy	1	2.0
Term pregnancy	1	2.0

Among 47 patients with available past obstetrical history, 17 (36.2%) had index pregnancy prior to GTN as their first pregnancy. The other 30 patients had 49 episodes of pregnancy prior to the index pregnancy of GTN: 38 live births (77.6%), 8 abortions (17.0%), 1 molar pregnancy (2.0%), 1 blighted ovum (2.0%), and 1 ectopic pregnancy (2.0%).

Four patients (all had stage I and LR with scores of 0-2) experienced recurrence after remission from primary treatment. One had surgical resection of lung lesion without adjuvant chemotherapy whereas three had switched chemotherapy from first-line MTX to actinomycin-D or EMA-CO. All achieved remission. After a median follow-up of 23.0 months (range 0.37-211.0 months), all were doing well without evidence of diseases.

Among 50 patients who had data of menstruation after treatment, 45 resumed menstruation in a regular pattern as pre-GTN diagnosis (90.0%). Five patients (10.0%), who had normal menstrual pattern prior to GTN, reported abnormal menstruation after chemotherapy. Menstruation function after GTN treatment according to age of the women and characteristic features of GTN are shown in Table 2. The 5 women who had abnormal menstruation after GTN treatment were in their 30's (3 women) or 20's (2 women). The abnormal menstruation was delayed menstrual resumption of 6-17 months before menstrual resumption (n=2), amenorrhea of unknown cause until last follow-up (n=1) or temporary amenorrhea due to uterine synechiae (n=1), and abnormal pattern of menstruation (n=1). No differences of clinical features of GTN of the women including treatment and their menstruation after treatment (Table 3).

Only 41 out of 50 patients in this study desired to conceive. Total of 22 patients (53.6%) had 1 to 3 episodes of pregnancy. These included the 35 years old patient who had menstruation only once after GTN treatment and the 20 years old patient with uterine synechiae who got pregnant spontaneously or after surgical/ hormonal correction. Younger age was the only significant factor associated with pregnancy: median age of 27.1 years (range 17-35 years) compared to 32.9 years (range 21-38 years) in the women without pregnancy, p=0.043. We did not find any association of pregnancy and other features of stage, risk group, and total chemotherapy cycles with the pregnancy achievement (Table 4).

Except one patient who conceived during the last cycles of chemotherapy (6th cycle of methotrexate), the interval from last treatment to conception in the others ranged from 2.7-97.2 months (median 43.6 months).The pregnancy outcomes included 28 live births, 4 abortions, and 1 molar pregnancy. The patient who had

Table 2. Characteristic features of gestational trophoblastic neoplasia patients and their menstrual function after treatment (N=50)

Characteristic features	Menstrual function after treatment (%)		
	Normal n=45	Abnormal n=4	No menstruation n=1
Median age (range)	30.98 (17-50)	28.25 (20-36)	33 (NA)
Stage			
I (n=39)	36 (92.3)	2 (5.1)	1 (2.6)
III (n=11)	9 (81.8)	2 (18.2)	-
Risk group			
LR (n=48)	44 (91.7)	3 (6.3)	1 (2.1)
HR/ Ultra-HR (n=2)	1 (50.0)	1 (50.0)	-
Chemotherapy cycles	6 (1-14)	6 (1-6)	5 (NA)

Abbreviations: HR, high-risk; LR, low-risk

Table 3. Details of women who had abnormal menstruation after treatment for gestational trophoblastic neoplasia (N=5)

Clinical features	# 1	# 2	# 3	# 4	# 5
Age (year)	36	35	33	22	20
FIGO stage	3	3	1	1	1
WHO score	6	7	2	6	5
Treatment	MTX * 6	EP * 6	MTX * 5	Uterine fundal wedge resection then EP * 1 then EMA-CO * 3	MTX * 6
Menstruation post treatment	Delayed	Delayed --- amenorrhea until pregnant---amenorrhea again	Amenorrhea until last follow-up	Longer interval but normal period and amount	Amenorrhea, and resumed normal pattern after treatment

Abbreviation: EP, etoposide, cisplatin; EMA-CO, etoposide, methotrexate, actinomycin, cyclophosphamide, vincristine; MTX, methotrexate

Note:
1 had delayed menstruation 16 months after last treatment before resumption to normal pattern
2 had menstruation only once 7 months after completion of treatment (1 episode only), got pregnant without any assisted reproductive technique 58.3 months after treatment, then amenorrhea postpartum (without breastfeeding or contraception) until an age of 54 years.
3 never had menstrual resumption without any recognized pathology until the time of her last follow-up visit 9 months after GTN treatment.
4 had menstrual resumption few months after treatment but with longer interval of 45-60 days between menstrual cycles despite normal amount and period (days) of each episode.
#5 had no withdrawal bleeding or menstruation during oral contraceptive pills. Cervical dilatation was performed for a clinical diagnosis of cervical stenosis without success. Subsequent hysteroscopy revealed uterine synechiae which was managed by lysis of fibrotic band followed by estrogen and progesterone therapy, her menstruation was restored.

Table 4. Pregnancy outcomes after treatment for gestational trophoblastic neoplasia among women who desired pregnancy (N=41)

Characteristic features	Pregnancy after treatment (%)	
	Pregnant n=22	Not pregnant n=19
Median age (range)	27.1 (17-35)	32.9 (21-38)
Parity		
0 (n=26)	14 (53.8)	12 (46.2)
1-2 (n=15)	8 (53.3)	7 (46.7)
Stage		
I (n=32)	17 (53.1)	15 (46.9)
III (n=9)	5 (55.6)	4 (44.4)
Risk group		
Low risk (n=48)	21 (52.5)	19 (47.5)
High and ultra-high risk (n=2)	1 (100.0)	-
Total chemotherapy cycles	5.5 (2-14)	6 (1-14)

another episode of molar pregnancy after GTN was able to get another pregnancy with one full term baby. Of note, examination of the placenta from one 18-year old patient of the 3rd normal pregnancy after GTN treatment showed benign chorioangiosis. Data of other obstetrical and fetal outcomes were unremarkable.

Discussion

Our study demonstrated 90% of our GTN patients had normal menstruation after treatment. This high percentage of normal menstrual resumption in our patients might lie on their young age at diagnosis (approximately half aged < 30 years). Without any pathology, ovarian function of any young individuals should still be good and represents a favorable prognostic factor [5,6]. Aside from age, other factors which may influence the recovery of ovarian/ menstrual function is the type of treatment particularly the chemotherapy regimen. Single agent of MTX or actinomycin-D (for LR GTN) did not have much detrimental effects on the ovaries whereas combined chemotherapy regimen (for HR GTN) which usually contained alkylating agent is notorious in causing ovarian dysfunction [7,8]. Previous study which found higher rate of abnormal menstrual function in HR than LR GTN patients after treatment: 2 folds higher rate of temporary amenorrhea (67% vs 33%) and longer duration (6.8 months vs 1.3 months) [9]. Furthermore, premature menopause was experienced in 9% among HR but none in LR patients [9]. A high rate of menstrual function recovery in our study may, aside from young age, lie on finding that majority of our patients were in low risk group and had only single chemotherapy treatment. We could not demonstrate other factors as important affecting menstruation. This may partly lie on a small number of HR GTN in our study.

Aside from the factors of disease and treatment themselves, other problems may also contribute to return of menstruation e.g. stress from illness, underlying gynecologic problems, etc. Among the 5 patients who had abnormal menstruation or menopause, two were in their 20's and three in 30's. No obvious detrimental factors or causes of abnormal menstruation were identified in all except one who had uterine synechiae from uterine surgical procedure (molar suction and curettage). Fortunately, she was able to conceive after surgical correction followed by hormonal support. With an unusually long period of amenorrhea after treatment for GTN especially in young age and with low risk disease, mechanical obstruction/ uterine synechiae should be kept in mind.

Regarding the fertility function, only 80% of our patients expressed their desire to conceive by the time of their last follow-up visit or contact. This group of women were younger compared to the others. The 53.6% rate of successful pregnancy in our study was comparable to 57% pregnancy rate in LR patients in one previous study [9]. However, these was much lower than data from one systematic review, including 27 studies reporting reproductive function after GTN, which demonstrated pregnancy rate as high as 87% [10]. These various rates of pregnancy may lie on several factors e.g. age, characteristic features of GTN (LR *vs* HR) and treatment, desire to conceive, the use of assisted reproductive techniques, inherent reproductive function including gynecopathologic conditions of individuals, etc. One study reported age and desire to conceive as independent factors for pregnancy [9]. The rate of pregnancy was nearly 2 folds higher among LR than HR patients were found in their study: 57% vs 36% [9].

The optimal interval to have another pregnancy has not been well defined. Although a standard recommendation was the patient should have contraception for 12 months after disease remission [3], few

patients may get pregnant sooner. Data of early pregnancy outcomes from previous studies or systematic review were inconsistent. One systematic review by Tranoulis et al. also found that conception within 12 months post-chemotherapy did not appear to increase the risk of adverse sequelae [10]. However, another systematic review including 18 studies reported higher abortion rates in patients who conceived within 6 months after chemotherapy compared to those who waited longer [11]. Early and successful pregnancies with normal live births within 6 months were found in two of our patients (one conceived 2 weeks after the last cycle or 4.5 months after the last cycle of MTX). Few authors also reported no adverse obstetrics outcome in their patient who got pregnant as soon as 1 month after EMA-CO treatment [12]. This incidental pregnancy should be caveat for both parties (patient and physician) because there had been no solid evidence to confirm the safety of prompt pregnancy after treatment especially with MTX which is well known to have teratogenic effect [13]. In pregnant women who were exposed to MTX, the risks of spontaneous abortions and major birth defects in the offspring increased [14].

Our study did not find any increased rates of abortion, stillbirth or congenital malformations in our patients who conceived. The 12% abortion rate of our patients was rather comparable to the rate reported in general population. However, limited number of patients precluded a definite conclusion. Previous studies reported inconsistent findings on adverse perinatal outcomes. Some found higher stillbirth rate [15-18], abortion, or congenital anomalies especially after combination chemotherapy [19,20]. However, other reports did not find such unfavorable findings [9,21]. One systematic review reported only 5% preterm and as high as 76% term live births. Fetal malformation was only 1.8% which was not higher than other pregnancies without history of GTN [10]. These different outcomes might lie on the different characteristic features of the population studied especially risk group with type of chemotherapy regimens as well as number of cycles.

One unique pregnancy complication which should be kept in mind among the GTN patients was repeated molar pregnancy. This was demonstrated in one of our patients (3%); however, she was able to get pregnant again after repeated molar pregnancy evacuation. Previous studies reported 1.3% to 4.5% of molar pregnancy which was higher than that found in general population [10,22].

In conclusion, the reproductive outcomes after treatment of GTN patients were good. Details of pre-treatment reproductive function, the patients' desire, and plan of child bearing are important. Effective contraception should be emphasized especially after completion of treatment. Contraception during chemotherapy treatment may be considered in some patients who had persist or rapid resumption of menstrual function in order to prevent detrimental effect of chemotherapy on fetus.

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