ORIGINAL RESEARCH

DOI: 10.5336/jcog.2024-107610

Gestational Trophoblastic Disease: Clinical Management and Outcomes: A Retrospective Study

Vildan NALBANT GÜRER[a], Mehmet KÜÇÜKBAŞ[a], Dilan ÜNSAL KAYA[a], Fatma Canan KARABAŞ[a], Ateş KARATEKE[a]

[a]Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye

ABSTRACT Objective: Evaluation of clinical management, pathological features and outcomes of patients diagnosed with gestational trophoblastic disease (GTD) in our clinic. **Material and Methods:** Thirty nine patients who were diagnosed with GTD in our clinic between October 2016 and June 2020 were included in this study. Demographic, clinical and pathological characteristics of the patients, treatment and follow-ups and outcomes were evaluated retrospectively. **Results:** In our study, a total of 39 GTD cases, including 35 cases reported as hydatiform mole (HM) (14 complete moles, 19 partial moles, 2 complete/partial moles cannot be differentiated) and 4 cases of gestational trophoblastic neoplasia (GTN) were included in the study. Post-molar GTN was diagnosed in 2 patients. Omentum biopsy was performed in a 41-year-old patient with a history of abdominal pain with elevated human chorionic gonadotropin levels and a history of total abdominal hysterectomy and bilateral salpingo-oophorectomy 8 months ago due to adnexal mass. Biopsy result revealed a malignant tumor with a trophoblastic reaction, the patient received 8 courses of actinomycin-D treatment, and deceased due to diffuse metastatic disease. **Conclusion:** Our first-line treatment in GTD is D&C. In cases diagnosed with GTN, hysterectomy was preferred in advanced age patients and the patients who completed their fertility. It has been observed that this application reduces the need for and the duration of subsequent chemotherapy.

Keywords: Gestational trophoblastic disease; gestational trophoblastic neoplasia

Gestational trophoblastic diseases (GTDs) are a heterogeneous group of diseases characterized by abnormal and excessive proliferation of trophoblasts that develop as a result of abnormal fertilization. They are characterized by high levels of human chorionic gonadotropin (β-hCG) and have a tendency to local invasion and spread.[1] According to the World Health Organization, GTDs are classified as hydatiform mole, complete mole, partial mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

Although the incidence of GTD varies according to ethnic groups, it is found in approximately 1-2/1000 births.[2] Risk factors include early menarche, parity, maternal 1st gestational age, previous molar pregnancy history, the time between previous pregnancies, genetic factors, environmental exposure, socio-economic level, and ethnicity. Although early pregnancy and advanced maternal age are associated with complete moles. The incidence of complete moles increases 1.9 times in pregnancies below the age of 21 and over the age of 35, while it increases 7.5 times over the age of 40.[3]

TO CITE THIS ARTICLE:
Nalbant Gürer V, Küçükbaş M, Ünsal Kaya D, Karabaş FC, Karateke A. Gestational trophoblastic disease: Clinical management and outcomes: A retrospective study. JCOG. 2025;35(1):25-31.

Correspondence: Vildan NALBANT GÜRER
Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye
E-mail: vnalbant3@gmail.com

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 16 Dec 2024 ***Accepted:*** 04 Feb 2025 ***Available online:*** 20 Feb 2025

Invasive mole, choriocarcinoma, PSTT, and ETT are subtypes of the gestational trophoblastic neoplasia (GTN) with malignant features. Diagnosis can usually be made by the increase in serial β-hCG levels after the evacuation of the molar pregnancy by vacuum aspiration curettage, but the pathological correlation is not always possible. It may occur in weeks or years following any pregnancy, but the most commonly it is encountered following molar pregnancy.[2,4]

International Federation of Gynecology and Obstetrics (FIGO) post-molar GTN diagnostic criteria:[5]

- A plateau of β-hCG levels in 4 measurements (days 0, 7, 14 and 21) in at least 3 weeks
- 10% or more elevation in β-hCG levels in 3 measurements (days 0, 7 and 14) in at least 2 weeks
- Persistency of elevated hCG levels for at least 6 months after molar pregnancy evacuation
- A histological diagnosis of choriocarcinoma

In this study, we aimed to determine demographic, clinical, pathological, and therapeutic characteristic findings of the patients who applied to our clinic in the last 4 years and to compare our findings with the literature.

MATERIAL AND METHODS

Thirty nine cases who were treated and followed-up with the diagnosis of GTD between October 2016 and June 2020 in the Department of Obstetrics and Gynecology at Göztepe Prof. Dr. Süleyman Yalçın City Hospital were included in this study. Patient data were obtained retrospectively using patient files and computer records. Sociodemographic characteristics, clinical features, laboratory tests and pathology results of the patients were recorded. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (date: 24 March 2021; no: 2021/0233).

Descriptive statistical methods (mean, standard deviation) were used to evaluate the existing data. The Pearson chi-square test and the Fisher's exact test were used to compare qualitative data. Logistic regression analysis was also used to evaluate the relationship between parameters. Results are reported as adjusted risk ratios with 95% confidence intervals. p values of less than 0.05 were considered statistically significant. SPSS (version 20.0, IBM Corporation, New York) was used for statistical analysis.

RESULTS

Of the 39 patients included in this study during a 4-year period, 19 patients were diagnosed with partial moles, 14 complete moles, 2 hydatiform moles, 1 choriocarcinoma, 1 PSTT, 1 invasive mole, and 1 malignant tumor with trophoblastic reaction. Demographic data of the cases, consistency between preliminary diagnosis and final pathology results, comparison of symptoms and pathological diagnosis, the relation between age groups, the relation of blood groups were analyzed and the findings are presented in Table 1 and Table 2.

Logistic regression analysis was used to investigate the relationship between pathological diagnosis and maternal age, gravidity, parity, and baseline β-hCG levels. The results showed no statistically significant differences between the 2 groups, as all variables had p-values greater than 0.05 (Table 1).

The chi-square and Fisher's exact tests were employed to assess the relationship between clinical prediagnosis and final pathological outcomes. The analysis revealed a significant difference in the distribution of pathological results and clinical prediagnosis ($p=0.002$; $p<0.05$). Notably, a significantly higher frequency of missed abortion was observed in the diagnosis of partial mole, and a higher rate of prediagnosis of molar pregnancy was found in cases diagnosed with complete mole (Table 2).

TABLE 1: Demographic characteristics of the study population.

	Complete mole (n=14)	Partial mole (n=19)	p value
Maternal age	33.5±9.0333	32.05±8.801	0.383
Graviditiy	2.86±1.385	2.64±1.438	0.451
Parity	1.57±1.318	1.18±1.363	0.218
Baseline β-hCG levels	71038.9±50482.32	34230±47422.628	0.075

Logistic regression analysis; Significant level at p:0.05. β-hCG: human chorionic gonadotropin.

TABLE 2: Comparison of clinical prediagnosis and pathological final diagnosis.

		Complete mole		Partial mole		
		n	%	n	%	p value
Clinical Prediagnosis	Missed abort	6	18.2	18	54.5	p=0.002
	Molar pregnancy	8	24.2	1	3	
Total		14		19		

Fisher Exact test was used; Significant level at p:0.05; chi-square test was used.

Analysis of blood groups revealed that A Rh (+) was the most common blood type, accounting for 48.71% (n=19) of the patients, while AB Rh (-) was the least common, found in 2.56% (n=1) of the patients. In terms of age distribution, the youngest patient was 18 years old and the oldest was 52 years old, and the most cases were observed in individuals older than 30 years (56.41%).

Six of our patients were diagnosed with GTN or progressed to GTN during the follow-ups. These 6 GTN cases were furtherly analyzed in Table 3.

As seen in Table 3; three cases (Case 1, Case 2, Case 3) were diagnosed with post-molar GTN. Hysterectomy was performed in 3 of 6 cases due to bleeding and in 1 case due to PSTT. Case 6 was already hysterectomized when admitted to our clinic.

Data on age groups of GTN and GTD cases are shown in Table 4 and Table 5.

The t-test was used to determine the difference between GTN and GTD cases in terms of mean age, and the Kolmogorov-Smirnov test was used to determine whether or not the continuous variables are normally distributed. Since the data set comes from a normal distribution and the t-test is 0.012, it is seen that there is a statistically significant difference between the development of GTD and GTN in terms of age (Table 4).

The ROC curve was used to determine the critical age value. The age of 40 was found significantly important between GTN and GTD cases according to the ROC curve. With a sensitivity of 87.5%, being over the age of 40 was found to be significant for the development of GTN (Table 5).

TABLE 3: Descriptive features, treatment modalities and outcomes of 6 cases diagnosed with gestational trophoblastic neoplasia.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	46	42	52	22	47	41
Gravidity	3	6	5	2	2	2
Parity	2	5	4	1	1	2
Pre-diagnosis	Molar pregnancy	Molar pregnancy	Molar pregnancy	Molar pregnancy	Molar pregnancy	Peritonitis carcinomatosis
Complaint	Vaginal bleeding	Vaginal bleeding	Vaginal bleeding	Vaginal bleeding	Vaginal bleeding	Abdominal pain
Clinico-pathology	Postmolar GTN (after complete mole)	Invasive mole	Choriocarcinoma (after complete mole)	PSTT	Choriocarcinoma	Malignant tumor with trophoblastic reaction
Treatment	1 cure Mtx	TAH	TAH+BSO 7 cures Mtx	TAH	TAH 11 cures EMA/CO	8 cures Actinomycin-D (hysterectomize)
Treatment outcomes	Remission	Remission	Remission	Remission	Remission	Exitus (After 4 months)
Blood type	0+	0+	0+	A+	A-	B+
Follow-up time (month)	24	15	35	34	30	4
GTN risk score	5	8	9	-	9	-

GTN: Gestational trophoblastic neoplasia; PSTT: Placental site trophoblastic tumor; TAH: Total abdominal hysterectomy; BSO: Bilateral Salpingo-Oophorectomy; Mtx: Methotrexate; EMA/CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine

TABLE 4: Statistical comparison of mean ages of gestational trophoblastic neoplasia and gestational trophoblastic disease cases.

		n	Minimum	Maximum	$\bar{X}$	SD	p value
Age	GTN	6	22	52	41.67	10.4	**0.012**
	GTD	33	18	49	32.08	7.94	

Student t test was used; Significant level at p:0.05; Kolmogorov-Smirnov test was used. SD: Standard deviation; GTN: Gestational trophoblastic neoplasia; GTD: Gestational trophoblastic disease.

TABLE 5: Comparison of gestational trophoblastic neoplasia and gestational trophoblastic disease cases by age groups.

		GTN		GTD		Total		p value
		n=6	15.3%	n=33	84.7%	n=39	100%	
Age	<40[a]	1	3.5%	28	96.5%	29	74.3%	**0.011**
	>40[a]	5	50%	5	50%	10	25.7%	

[a]ROC curve was used; Logistic regression analysis; Significant level at p:0.05. GTN: Gestational trophoblastic neoplasia; GTD: Gestational trophoblastic disease.

DISCUSSION

The incidence of gestational trophoblastic diseases shows regional differences in epidemiological studies. It varies between 0.57-1.1 per 1,000 pregnancies in North America, Australia, and Europe, while this rate is 2 per 1,000 pregnancies in Southeast Asia and Japan.[6] In our clinic, the total number of births in a 4-year period (October 2016-June 2020) was 7,012, and the incidence of GTD was calculated as 0.45/1,000 births. The ratio of deaths due to GTD was calculated as 2.56%.

In the studies conducted by Altman et al. and also in many similar studies, it has been reported that GTDs are more common in the group above the age of 30 and under the age of 20.[7] In our study, it was observed that the cases were clustered at the age of 30 and above, predominantly in the group above 20 years of age. This difference was thought to be due to the low number of cases. The fact that GTD was generally seen in the reproductive age group, was considered as the common feature of the present studies.

In our study, the patients most frequently applied to the hospital with no symptoms, and the second most common complaint was vaginal bleeding. In the study conducted by Sun et al., it was reported that patients applied to the hospital with similar symptoms as in our study.[8]

β-hCG is the most important parameter used in the diagnosis and during the follow-ups. In the study of Hou et al., β-hCG levels were found to be higher in complete molar pregnancies than partial molar pregnancies.[9] In our study, β-hCG levels showed no significant difference between the partial molar and complete molar pregnancies. In another study involving GTN cases, baseline β-hCG levels were mostly above 10.000 IU/mL, and β-hCG levels clustered between 10,000-100,000 IU/mL.[10] It was observed to be similar in our study as well.

Determination of blood group is necessary to compensate blood loss before curettage or surgical procedure and to determine the need for anti-D immunoglobulin in Rh (D) negative patients. In a study by Jagtap et al. it was reported that maternal A blood group was more common in GTD cases.[11] Similarly, in our study, the most common blood group was A Rh (+) (48.71%).

Depending on the type and the stage of the disease, the treatment approach for GTD can be dilatation and vacuum aspiration curettage (D&C) or hysterectomy, chemotherapy, or a combination of these methods. The first-line treatment approach is uterine evacuation and the recommended procedure is D&C.[1,12] We also preferred D&C as the first-line treatment approach in GTD cases. A single session of D&C was performed on 12 patients diagnosed

with complete moles, 19 patients with partial moles, and 2 patients with hydatiform moles (without discrimination of complete or partial moles), no further treatment was required.

Six patients who developed post-molar GTN or were pathologically diagnosed with GTN were analyzed separately (Table 3).

Case 1; A 46-year-old patient diagnosed with complete mole; due to β-hCG progression at the 3rd week of the weekly follow-ups after D&C, the patient diagnosed with postmolar GTN. One course of mtx treatment was administered, and complete remission was achieved.

Case 2; A 42-year-old patient who was diagnosed with partial mole after curettage, was diagnosed with postmolar GTN at the follow-ups and 13 courses of mtx treatment was applied. After 13 courses of mtx treatment, she applied to our clinic with the complaint of vaginal bleeding and hysterectomy was performed. No additional treatment was required in the patient with the pathological diagnosis of invasive mole after the operation.

Case 3; A 52-year-old patient with pre-diagnosis of complete mole underwent TAH+BSO due to bleeding. Complete mole was diagnosed pathologically after the operation. Due to β-hCG progression in weekly follow-ups, our patient was diagnosed clinically with post-molar GTN (choriocarcinoma). Complete remission was achieved after 7 courses of mtx treatment.

Case 4; A 22-year-old patient who completed her fertility, was diagnosed with PSTT, underwent hysterectomy due to the chemoresistance of the neoplasia, and complete remission was achieved. According to the literature, hysterectomy is important in the management of this pathology, especially in advanced cases. Chemotherapy can be combined with hysterectomy, and in our case, chemotherapy was not needed due to the achievement of complete remission with hysterectomy.[13]

Case 5; Hysterectomy was performed on a 47-year-old patient, who completed her fertility and applied with the complaint of vaginal bleeding after 16 weeks of amenorrhea. Hysterectomy was performed due to bleeding and for reducing the tumor burden. She was diagnosed with high-risk metastatic choriocarcinoma due to the FIGO staging system (stage: 3, score: 9). After the hysterectomy, 11 courses of EMA/CO protocol were administered. Complete remission was achieved.

Case 6; A 41-year-old patient, who had undergone TAH+BSO operation for benign reasons 8 months ago at another center, applied with the complaint of abdominal pain, and a diagnostic laparotomy was performed due to peritonitis carcinomatosis clinic and elevated β-hCG levels. Omental biopsy and abdominal fluid sampling were taken from the patient who had diffuse ascites in the abdomen, unresectable diffuse tumor implants in the liver surface, parietal peritoneum, omentum, intestinal serosa, and mesentery. The pathological diagnosis was reported as a malignant tumor with a trophoblastic reaction. The patient was evaluated as stage: 4 (high risk) disease according to the FIGO staging system and was given 8 courses of actinomycin-D treatment. The patient deceased 4 months later due to extensive metastatic disease.

One of our GTN cases was hysterectomized already when admitted to our clinic. Hysterectomy operation was performed in four of other five cases with GTN due to vaginal bleeding, persistent β-hCG levels or unresponsiveness to treatment. Three of four patients who underwent hysterectomy had a high-risk score (≥7) for GTN, while the other patient underwent hysterectomy due to PSTT. The mean age of GTD cases was 32.08, and the mean age of GTN cases was 41.67 (Table 4). While the rate of development of GTN in the group below the age of 40 was 3.5% in our GTD cases, the rate of development of GTN in the group over the age of 40 was 50% (Table 5). GTN cases could be followed-up for maximum of 35 months and no recurrence was detected during the follow-up periods.

According to the literature, the risk of developing GTN after D&C in patients with complete hydatiform mole aged >40 and >50 is 54% and 60%, respectively; it has been reported that hysterectomy reduces this risk and subsequently the need for chemotherapy. Therefore, hysterectomy may be con-

sidered in complete hydatiform mole patients over 40 years.[14,15] Zhao et al. reported that performing hysterectomy over the age of 40 was decreasing the risk of developing GTN from 41.7% to 11.4%.[16] Although a study conducted by Giorgione V. et al. reported that hysterectomy did not change the risk of developing GTN in patients over 40 years of age diagnosed with hydatiform mole, many studies show the opposite.[17]

Some types of GTN respond well to single or combined chemotherapy; however, chemotherapy is not effective for all types of the disease. Due to the high risk of metastatic spread of GTN, it has been emphasized by some authorities that hysterectomy and chemotherapy can be combined in the treatment of patients who have completed their fertility.[18]

In our series, we observed that GTN developed 50 percent in GTD cases over the age of 40. GTN cases requiring hysterectomy are mostly the cases with high-risk scores (≥7) and age over 40. Our requirement for hysterectomy in GTN cases was 66 percent.

CONCLUSION

When we examine our cases that developed GTN, we may state that hysterectomy will be required in cases of molar pregnancy who have completed their fertility, have a high-risk FIGO score, over 40 years of age and have severe or prolonged vaginal bleeding, as well as in cases of chemotherapy resistant and advanced GTN. We observed that hysterectomy can be a good option that increases the success of treatment and shortens the treatment period. The limitation of our study is the insufficiency of the number of patients. Results of large series are needed in this regard.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ateş Karateke;* ***Design:*** *Mehmet Küçükbaş, Ateş Karateke;* ***Control/Supervision:*** *Mehmet Küçükbaş;* ***Data Collection and/or Processing:*** *Vildan Nalbant Gürer, Fatma Canan Karabaş;* ***Analysis and/or Interpretation:*** *Vildan Nalbant Gürer, Mehmet Küçükbaş;* ***Literature Review:*** *Vildan Nalbant Gürer;* ***Writing the Article:*** *Vildan Nalbant Gürer;* ***Critical Review:*** *Mehmet Küçükbaş, Dilan Ünsal Kaya.*

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