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Retrospective evaluation of gestational trophoblastic disease – experience with ultrasounds

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Abstract. – OBJECTIVE: Our study aims to determine the frequency and types of GTD (Gestational Trophoblastic Disease) in our clinic, to evaluate its relationship with clinical parameters, and the consistency of clinical prediagnosis and pathological definitive diagnosis.

PATIENTS AND METHODS: In the present study, hospital records of 120 patients with gestational trophoblastic disease between January 2019 and August 2022 were obtained and evaluated retrospectively. Demographic, hematological, biochemical, and clinical data were collected in detail, and the data were analyzed statistically.

RESULTS: Our study included a total of 120 female patients, with an average age of 31.16±9.70. The average number of patients was 3. The average time for women to receive the diagnosis was 9.80±2.45 weeks, with the most frequent complaint on our part being bleeding (85.8%). When the pathology outcomes of the patients we included in our study were examined, it was found that the number of patients diagnosed with incomplete abortion was 34, the number of patients diagnosed with complete abortion was 82, the number of invasive moles diagnosed was 3, and the number of patient diagnosed with choriocarcinoma was 1. Kappa ratio was calculated as 0.419 (p<0.001) when the compliance of the clinical diagnosis was assessed. This value was consistent with median level alignment. In a study that examined the three years of our calism in our bulk, 1.8 per 1,000 births were followed frequently.

CONCLUSIONS: We should inform patients in detail about gestational trophoblastic diseases and warn patients not to delay their consequences. We should recommend that pregnancy be avoided for 12 months for low-risk patients and 18 months for high-risk patients after GTD.

Key Words:
Gestational trophoblastic diseases, Partial hydatidiform mole, Hydatidiform mole, Invasive mole, Choriocarcinoma.

Introduction

Gestational trophoblastic diseases (GTD) are a group of diseases that have not yet been established, with the etiology developed as a result of abnormal fertilization and characterized by an abnormal, excessive proliferation of trophoblasts. These masses, which are from the placenta and are likely to make metastases, are due to the placental structure rather than maternal tissue[1]. GTDs are a very large group of diseases that can be classified as pre-malignant [complete hydatidiform mole (CMH), partial hydatidiform mole (PMH)] and malignant (invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epitheloid trophoblastic tumor)[2].

Although epidemiological studies show a lot of variations, the incidence of GTD in many parts of the world is 1/1,000 of pregnancies[3]. While hydatidiform moles make up 80% of all GTDs, invasive moles make up 15%, and other types make up the remaining 5%[4]. One of the most important risk factors for developing GTD is the age of the pregnant woman (<15 years old, >45 years of age increased risk), while the other is the presence of a previous history of molar pregnancy, which increases the risk of GTD 10 times[5,6].

The predisposing factors considered to be influential in the development of gestational trophoblastic disease are parity, age of first pregnancy, early menarche, history of previous molar pregnancy, the period between pregnancies, genetic factors associated with the patient, socioeconomic level, malnutrition, viral infections, and Asian origin. Young and advanced mother age leads to complete hydatidiform mole associated with abnormal fertilization. In pregnancies under 21 and over 35 years of age, the incidence of complete mole increases

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1.9 times, and 7.5 times in pregnancies over 40 years of age. In pregnant women over 50 years of age, studies[7,8] have shown that one in three pregnancies results in a complete mole.

The karyotype of 90% of CMH is 46, XX, while the karyotype of 10% is 46, XY. It is formed by the duplication of anucleated ovum with two sperms or after fertilization with haploid sperm and thus has only paternal DNA.

In PMH, the karyotype is triploid, 69, XXX, or 69, XXY. Unlike complete moles, both paternal and maternal DNA is expressed in partial moles.

In partial hydatidiform mole (PMH), dyspermic fertilization of a normal ovum is present. Therefore, the biparental genome is included, and the triploid karyotype is observed. The most common is 69, XXX.

If the fetus is to be formed, fetal growth retardation and multiple congenital malformations occurs, and the fetus is not viable. These cases present with the clinic of incomplete abortion because they present with complaints of missed abortion or heavy bleeding and abortion. The uterus is usually normal in size, and classical molar pregnancy findings are rarer than those of a complete hydatidiform mole. β-HCG levels are lower than CMH, and ultrasound evaluation can even track a thick and hydropic placenta, fetal structures, and even fetal heartbeat[9,10].

When we look at the patients diagnosed with CMH, they usually present with the complaint of menstrual delay or abnormal vaginal bleeding. Due to trophoblast proliferation, β-HCG levels are quite high compared to the gestational week, significantly increased according to the gestational week determined by the uterine size and the last menstrual period, and excessive subjective pregnancy symptoms can be seen. While fetal structures are not monitored in ultrasound, the intracavitary mass structure is monitored, called "irregular snowstorm appearance", with thick and anecogenic focuses. With the increased opportunities for patients to consult a doctor, the development of high-resolution ultrasound devices, the entry into use, and the increase in the use of transvaginal ultrasound (TVS), the diagnosis of GTD can be made even in the first trimester and even during the asymptomatic period from the second trimester of pregnancy[11,12].

Ultrasonic findings of gestational trophoblastic diseases are typical of the cavity appearance of the uterus filled with a large number of sonolucent cysts in different sizes and shapes, often described as the appearances of the grape cluster ("cluster of grapes") and the snow storm ("snowstorm"). Magnetic resonance imaging (MRI) can be used to determine the depth of invasion and extent of disease in premalignant and malignant cases such as invasive moles and choriocarcinoma[13].

As soon as a molar pregnancy is diagnosed, the uterine cavity should be emptied by dilatation and curettage. After the necessary blood preparation, the procedure should be performed under operating room conditions. Oxytocin infusion can be administered before and during the procedure to reduce bleeding. Since the risk of uterine perforation is high, it is appropriate to perform curettage with ultrasonography. Anti-D prophylaxis should be applied to Rh-negative cases. In addition, the risk of developing pulmonary embolism should be kept in mind. It is a suitable practice to offer hysterectomy to patients who do not have a desire for fertility.

Invasive mole, a subtype of gestational trophoblastic neoplasia (GTN), poses a clinical challenge in its management. A recent study conducted at Tu Du Hospital in Southern Vietnam by Vo et al[14] delves into the efficacy of hysterectomy as a primary or delayed intervention for invasive mole. The research, spanning from January 2016 to December 2020 and involving 189 patients, reveals that while hysterectomy proves to be a safe and effective treatment, a noteworthy 24.87% of patients necessitated salvage chemotherapy within a 12-month follow-up period. Prophylactic chemotherapy and elevated postoperative hCG levels emerged as factors associated with an increased risk of requiring salvage chemotherapy, emphasizing the intricacies in determining optimal therapeutic approaches for invasive mole. Furthermore, the study underscores the crucial role of postoperative chemotherapy in mitigating the risk of relapse, shedding light on the malignant nature of invasive mole beyond its local invasion characteristics[14].

It should be explained in detail that low-risk patients with GTD should be protected from pregnancy for 12 months and high-risk patients for 18 months and that pregnancy should be avoided. Our study aims to determine the frequency and types of GTD in our clinic, to evaluate its relationship with clinical parameters, and to determine the consistency of clinical prediagnosis and pathological definitive diagnosis.

Patients and Methods

A total of 120 patients who applied to the Konya City Hospital Gynecology and Obstetrics Clinic between January 2019 and August 2022 and who were diagnosed with GTD pathological-

ly were included in our study. Patient information and file records were obtained retrospectively from the hospital system. This study has been approved by the Ethics Committee for Non-Drug and Non-Medical Device Research of KTO Konya Karatay University with document date and number 26.09.2023-69155.

Age, gravida, parity, the number of previous abortions, number of living children, blood group, pre-op and post-op complete blood hematocrit, platelet, AST, ALT, urea, creatinine, serum thyroid stimulating hormone (TSH), free thyroxine (T4), free triiodothyronine (T3), β-HCG values, the pregnancy in which these patients were diagnosed were recorded. The data on the preoperative diagnosis and the final diagnosis after the pathology of the patients, according to the week of pregnancy, previous molar pregnancy history, the treatments applied, the presence of complications, the need for chemotherapy or oncology follow-up, the need for blood transfusion, the complaints of the patients, the histological subtype of GTD were also recorded.

Statistical Analysis

Data input and analysis were carried out using SPSS 20 software (IBM Corp., Armonk, NY, USA). Mean, standard deviation, average (minimum-maximum), numbers, and percentages were used in summarizing categorical data. The suitability of numerical variables to normal distribution was evaluated by visual (histogram and q-q plot) and statistical Kolmogorov-Smirnov/Shapiro-Wilk tests, and it was determined that the variables were not normally distributed. Relationships between variables were investigated using Friedman's variance analysis, Wilcoxon test, and Kappa test. The coefficient obtained in the Kappa test was interpreted as <0.00 lower than chance-related match, 0.01-0.20 insignificant level of matching, 0.21-0.40 weak match, 0.41-0.60 medium match, 0.061-0.80 good match, and 0.81-1.00 very good match[15,16]. Values of $p<0.05$ were considered statistically significant.

Results

The mean age of 120 women in the study was 31.16±9.70. The obstetric characteristics of the participants are shown in Table I. The mean duration of diagnosis for women was 9.80±2.45 weeks, and the median was 9 (6-17) weeks. The most common complaint at admission was bleeding, with a frequency of 85.8%. The characteristics of the patients with molar pregnancy are presented in Table II.

When the compatibility of clinical diagnosis and pathological diagnosis was evaluated, the Kappa coefficient was calculated as 0.419 ($p<0.001$). This value was consistent with the moderate agreement. The cross-table in which the clinical diagnosis and the pathological diagnosis were evaluated, and the Kappa test results are shown in Table III.

Table I. Characteristics of patients' obstetric history.

Age	Mean±sd	31.16±9.70
	Median (Min-Max)	29 (16-57)
Number of pregnancies	Mean±sd	3.21±2.15
	Median (Min-Max)	3 (1-9)
Parity	Mean±sd	1.69±1.78
	Median (Min-Max)	1 (0-7)
Abortion	Mean±sd	0.58±0.95
	Median (Min-Max)	0 (0-4)
Blood group n (%)	0 rh negative	1 (0.8)
	0 rh positive	32 (26.7)
	A rh negative	4 (3.3)
	A rh positive	49 (40.8)
	AB rh negative	1 (0.8)
	AB rh positive	5 (4.2)
	B rh positive	28 (23.3)
Mole history in previous pregnancies n (%)	Absent	118 (98.3)
	Present	2 (1.7)

Table II. Characteristics of patients with molar pregnancy.

		n	%
Application complaint	Bleeding	103	85.8
	Abdominal pain	3	2.5
	Control	8	6.7
	Referral from the external center	6	5.0
Procedure	R/C	115	97.5
	TAH-BSO	1	0.8
	TAH-BSO after R/C	2	1.7
Complication	Present	120	100
	Absent	0	0
Transfusion need	Present	109	90.8
	Absent	11	9.2
Chemotherapy need	Absent	113	94.2
	Present	7	5.8
Clinical diagnosis	Incomplete mole	42	35.0
	Invasive mole	2	1.7
	Complete mole	75	62.5
	Choriocarcinoma	1	0.8
Pathological diagnosis	Incomplete mole	34	28.3
	Invasive mole	3	2.5
	Complete mole	82	68.3
	Choriocarcinoma	1	0.8

R/C: revision-curretage; TAH- BSO: total abdominal hysterectomy.

Table III. Evaluation of the consistency between clinical diagnosis and pathological diagnosis.

			Pathological diagnosis			
			Incomplete mole	Invasive mole	Complete mole	Chorio-carcinoma
Clinical diagnosis	**Incomplete mole**	n	24	0	18	0
		Line %	57.1	0.0	42.9	0.0
		Column %	70.6	0.0	22.0	0.0
	Invasive mole	n	0	0	2	0
		Line %	0.0	0.0	100.0	0.0
		Column %	0.0	0.0	2.4	0.0
	Complete mole	n	10	3	62	0
		Line %	13.3	4.0	82.7	0.0
		Column %	29.4	100.0	75.6	0.0
	Chorio-carcinoma	n	0	0	0	1
		Line %	0.0	0.0	0.0	100.0
		Column %	0.0	0.0	0.0	100.0

Kappa=0.419; $p<0.001$.

When we looked at the outcomes of the pathology results of the patients we included in our study, the number of patients with the diagnosis of incomplete abortion was 34, the number of patients with complete diagnosis was 82, the area of invasive mole diagnosis was 3, the number of patients diagnosed with choriocarcinoma was 1.

The difference between the three measurements of β-HCG was determined by variance

Table IV. Patient blood values before and after the procedure and comparisons of these values.

	Number of patients with value	Mean	SD	Median	Min	Max	p
PRE β-HCG	107	251,115.98	262,495.87	140,729.00	924.00	1,322,174.00	<0.001*
β-HCG (in the first 48 hours of POST)	65	129,933.86	149,943.98	74,404.00	2,211.00	596,387.00	
β-HCG (after the first 48 hours of POST)	74	12,195.64	33,175.27	1,869.00	29.60	242,011.00	
PRE HGB	101	11.82	1.72	12.20	7.00	15.10	<0.001*
POST HGB	69	10.29	1.53	10.60	5.60	13.50	
PRE WBC	91	21.00	111.12	8.77	4.49	1.069,00	0.193
POST WBC	66	7.81	2.34	7.48	3.32	15.00	
PRE PLT	101	251.90	68.29	261.00	9.24	424.00	<0.001*
POST PLT	66	221.86	56.08	224.50	19.00	328.00	
PRE AST	100	23.33	11.74	20.00	11.00	83.00	0.894
POST AST	14	26.86	20.03	19.50	7.00	75.00	
PRE ALT	99	18.89	15.75	14.00	3.00	110.00	0.507
POST ALT	13	29.15	23.39	20.00	13.00	93.00	
PRE UREA	62	11.69	28.76	3.50	1.09	222.00	0.123
POST UREA	10	4.183	6.860	1.890	1.160	23.500	
PRE Creatinine	82	0.58	0.11	0.58	0.27	1.07	1.000
POST Creatinine	9	0.58	0.19	0.60	0.22	0.82	
PRE TSH	60	1.46	4.13	0.46	0.01	29.84	–
POST TSH	0	–	–	–	–	–	
PRE T3	55	12.39	48.03	3.88	1.24	360.00	0.655
POST T3	10	4.88	2.99	4.11	1.44	12.27	
PRE T4	62	11.69	28.76	3.50	1.09	222.00	0.075
POST T4	10	4.183	6.860	1.890	1.160	23.500	

PRE: pre-process; POST: shows post-process values; *indicates values with $p<0.05$.

analysis ($p<0.001$). Pre- and post-operative blood values for patients and comparisons of these values are shown in Table IV.

Discussion

In our study, we performed detailed analyses such as clinical approach, detailed biochemical parameters, post-disease follow-up, and estimation of pathological diagnosis in GTD.

In the literature[17-19], GTDs have been found to occur in all pregnancies, both planned and unplanned, and are most commonly seen in the early stages of reproductive age.

Although the risk of GTD increases in women over the age of 35 and under the age of 20, it is more common in reproductive period women in this age range. The disease is less common in those who become pregnant at an advanced age, but it has been reported that postmolar GTD formation is more common in pregnancies occurring after the third decade[20,21].

Worldwide epidemiological studies have shown that the incidence of gestational trophoblastic disease differs between national and ethnic groups, with an approximate incidence of 1/1,500 reported in the United States.

The incidence of hydatidiform mole was found to be 1.1, per 1,000 births over 11 years, and 3.5 per 1,000 births in a study conducted in Izmir over four years[22,23]. As can be seen from these figures, there is an almost ten-fold variation in the incidence of hydatidiform moles between geographic regions. This difference may be due to changes in socioeconomic conditions of geographic regions and sensitivity in recording data on early pregnancy loss. Gestational trophoblastic diseases are thought to be more common in regions where families migrated from rural areas live, belong to large and crowded families, have a low sociocultural and economic level, and where

contraception methods are not used adequately and effectively. In another study examining the three years in our study in our region, it was observed with a frequency of 1.8 per 1,000 births. In a study conducted by Gül et al[24] in Van, in which hydatidiform mole cases were discussed, the mean age was found to be 28.5. In the study by Çetin et al[28], the average age range was found to be the highest in the age range of 20-25, and the rate was determined to be 37.03%. In our study, the average age of our pregnant women was 31.16, the minimum age was 16 years, and the maximum age was 57.

In previous studies, it was observed that the development of GTD was higher in patients with an A blood group. Kurdoğlu et al[25] detected an A blood group in 46.9% of GTD patients. Our study was also compatible with the literature, and the blood group of 40.8% of our patients was ARh positive, followed by a 0 Rh positive blood group at a rate of 32%.

Having a previous molar pregnancy is a risk factor for GTD, and in the study conducted by Sand et al[26] it was observed that the recurrence rate of the disease increased 10 times in women who had a molar pregnancy once. Kars et al[27] found the rate of patients who had a previous molar pregnancy to be 3.3%. In our study, 2 of the patients (1.7%) had a history of previous molar pregnancy.

According to a study by Çetin et al[28], approximately 30% of the cases were partial mole, and 65% were complete mole. According to another study conducted by Kars et al[23], 25% of the cases were diagnosed as partial moles, and 68% as complete moles. The trophoblastic disease was complete mole in 82 (68.3%) patients, 34 patients were diagnosed as incomplete mole with a frequency of 28.3%, invasive mole in 2.5% and 3 patients, and choriocarcinoma in 1 patient with a frequency of 0.8%.

With the widespread use of ultrasound, GTD can often be diagnosed even in the first trimester while pregnancy is still asymptomatic[29]. The average pregnancy week was 10 weeks at the time of diagnosis in Karateke et al[30] study. Neelakanthi et al[19] stated the average diagnosed pregnancy age of patients was 12.4±4.1 weeks. In our study, the average time for women to receive the diagnosis was 9.80±2.45 weeks, and the average was 9 (6-17) weeks; according to the literature, our week of diagnosis was quite early, and this can be seen as the success of our clinic.

In the study by Karateke et al[30], the majority of cases referring to the clinic were due to vaginal bleeding, as well as cases of secondary amenorrhea and abdominal pain. Neelakanthi et al[19] reported that 34 patients (65.4%) were initially referred due to only vaginal bleeding with abdominal pain, almost all (98%) had amenorrhea except one, and most patients (61.5%) were referred in the first trimester. In our study, the most frequent complaint of our patients was bleeding in 85% of cases.

115 (97.5%) of the patients who applied to us were subjected to revision curettage and 3 patients were tested for non-fertility desire after revision curettage. The average β-hCG value was 251,115.98 when routine-watched pre-procedure-behavior values were scanned for patients and after 48 hours, the average beta-hcg value was found as 129,933.86.

Serum β-HCG levels are a measure of trophoblastic activity, which plays an important role in the diagnosis and treatment of gestational trophoblastic diseases. Serum β-HCG levels after curettage are monitored, and persistent hydatidiform mole phenomena can be detected at an early stage[23,31].

Vacuum curettage is a treatment that is considered in the treatment of GTD patients and should be used in all cases. In our study, vacuum curettage was applied to all cases, and no complications were found during the procedure.

In our study, two patients with diagnosed invasive mole and choriocarcinoma were followed up and treated by medical oncology after a hysterectomy was applied. Patients receiving chemotherapy, other than those with a diagnosis of GTD, were subsequently receiving chemotherapy due to β-hCG persistence. Seven of our patients involved in the study needed follow-up chemotherapy and oncology.

The pre-op Hgb values of the patients we included in our study were 11.8 on average, a minimum value of 7, a maximum value of 15, a post-op average Hgb value of 10.29, a minimum value of 5.6, a maximum value of 13.5, and 11 patients (9.2%) were found to require a blood transfusion.

There was no significant difference between HGB, PLT, WBC, TSH, urea, creatinine T3, and T4 levels and the other parameters.

Strengths and Limitations

The strength of our work is that our patients are in a regional hospital with a high rate of transfer and actively working and receiving patients during the pandemic period. The weakness of our study is that some of our patients are foreign patients, and some do not have prospective values because they are subject to follow-ups with these patients.

Conclusions

We should inform patients in detail about gestational trophoblastic diseases and warn patients not to delay their consequences. We should recommend that pregnancy be avoided for 12 months for low-risk patients and 18 months for high-risk patients after GTD.

Conflict of Interest
The authors declare no conflicts of interest.

Ethics Approval
The study was reviewed and approved by the ethics committee of KTO Konya Karatay University with document date and number 26.09.2023-69155. All procedures were performed according to the Declaration of Helsinki and its latest amendments.

Informed Consent
All participants signed informed written consent before being enrolled in the study.

Availability of Data and Materials
The data supporting this study is available from the corresponding author upon reasonable request. The datasets and code used and/or analyzed during the current study are also available from the corresponding author upon reasonable request.

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None.

Authors' Contributions
Oğuzhan Günenc: protocol/project development, data collection, data analysis, manuscript writing/editing. Melike Geyik Bayman: data collection, data analysis, manuscript writing/editing. Ethem Ömeroğlu: data collection, data analysis, manuscript writing/editing. Nur Gözde Kulhan: protocol/project development, data collection, data analysis, manuscript writing/editing. Mete Can Ateş: data analysis, manuscript writing/editing. Ayşe Nur Uğur Kılınç: data analysis, manuscript writing/editing. Elif Nur Yıldırım Öztürk: data analysis, manuscript writing/editing. All authors read and approved the final version of the manuscript.

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