GESTATIONAL TROPHOBLASTIC DISEASES-DIAGNOSIS AND RISK FACTORS:A CASE SERIES

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ABSTRACT The aim of the study: Our study aims to investigate the role of the age, gravida, parity, blood group in the development of GTD also significance of the β-hCG levels and pelvic ultrasonography in the diagnosis and treatment of these patients. Comparisons of GTD incidence between Turkey and different regions of the world.
Materials and Methods: This retrospective study included 1813 patients who underwent vacuum aspiration from 2010 to 2018 years in Derince Training and Research Hospital, Kocaeli, Turkey. Files of 18 patients compatible with GTD in pathology were retrospectively scanned.
Result: As a result of the study, the average age of patients were 27.06, pathology results was found in 14 patients (77,7%) partial mol, in 2 patients (11,1%) complete mol, invasive mol in 1 patient (5,6%) and choriocarcinoma in 1 patient (5,6%). In these cases, 1 case of lung metastasis and three patients received chemotherapy treatment. There was no mortality associated with the disease during follow-up.
Conclusion: The calculated GTD incidence was 1,5 per 1000 births. Radiologist plays the primary role in the first diagnosis of GTD and basis disease management and early finding of its complications. Although serum β-hCG is a useful biochemical marker for GTD. Ultrasound is the initial line radiological examination in approving the diagnosis of GTD in a case suspected by clinical detections and β-hCG levels. We believe that diagnosis, adequate treatment and follow-up will make easy the cure of GTD and the incidence can be calculated more exactly by performing wide community-based studies.

KEYWORDS gestational trophoblastic disease, hydatidiform moles, molar pregnancy, gestational neoplasia

Introduction

Gestational trophoblastic disease (GTD)includes a heterogeneous group of disease that is defined by an abnormal proliferation of trophoblastic tissue. The modified World Health Organization (WHO) classification of GTD consists exaggerated placental site, placental site nodule, placental site trophoblastic tumour (PSTT), complete and partial hydatidiform mole, invasive mole, choriocarcinoma, and epithelioid trophoblastic tumour (ETT) [1,2]. Hydatidiform mole (HM) is the most common form of GTD[3]. PSTT is a rare form of GTD, with fewer than 250 cases noted in the literature [4]. Comparisons of GTD incidence ratios among different regions in the world are limited by the various methods used to determine ratios. The variation in worldwide incidence ratios results in part from inconsistency between population-based and hospital-based date [5,6]. Moreover, incidence ratios may be based on the total number of pregnancies, deliveries or live births [3,6].

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Though advanced maternal age is related to a higher risk for molar pregnancy, HM patients > 40 years represent 4,5–5% [7,9]. However, adolescents with HM account for 10–34% of the cases in large trophoblastic diseases referral centres [8.10.11].

Pelvic ultrasonography is the first investigation of choice, as it aids in excluding a normal pregnancy, identify the molar pregnancy and in some cases define the local tumour extent. The usual use of antenatal ultrasonography in early pregnancy has brought forth an essential change in the most often encountered findings of molar pregnancy from the classic "snowstorm" or "cluster of grapes" observe to that of missed abortion or failed pregnancy. The resent cure rate of GTD exceeds 90%, due to routine surveillance using highly sensitive β subunit of human chorionic gonadotropin (β-hCG) and high chemosensitivity of the tumour [12,13]. Even though surveillance with β-hCG can serve as a perfect surrogate tumour marker in an early finding of disease, it does not define the site of recurrence or metastases. Imaging with computed tomography (CT) of the chest, abdomen, and pelvis, and CT or MR imaging of the brain thus play an essential role in finding the site, and the number and extent of metastases, all of which are significant prognostic indicators in the management of GTD.

Trophoblast is contained cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. Cytotrophoblast shows high mitotic activity; however, it poor hormone synthesis. Syncytiotrophoblast forms the chorionic villi has poor mitotic activity, and produce beta-human chorionic gonadotropin (β-hCG), which is used as a tumour marker. Intermediate trophoblast has characteristic features of the other two components and is responsible for endometrial invasion and implantation. In the different forms of GTD, different components of trophoblast show unusual proliferation to a variable extent [14]. Although most GTNs synthesize β-hCG hormone with unusual elevation of β-hCG titers being one of their diagnostic features of GTD, the titers vary in different tumour types. Some choriocarcinomas and biomorphic tumour types synthesize only low levels of β-hCG [16]. PSTT demonstrates a neoplastic proliferation of intermediate trophoblasts [15]. Unlike other forms of GTD, it is described by low β-hCG levels because of the lack of syncytiotrophoblastic proliferation [15,17]. However, it shows raised expression of tissue as well as serum human placental lactogen (hPL) [17].

The aim of the study

Our study aims to investigate the role of the age, gravida, parity, blood group in the development of GTD also significance of the β-hCG levels and pelvic ultrasonography in the diagnosis and treatment of these patients. Comparisons of GTD incidence between Turkey and different regions of the world.

Materials and Methods

This retrospective study included 1813 patients who underwent vacuum aspiration from 2010 to 2018 years in Derince Training and Research Hospital, Kocaeli, Turkey. Files of 18 patients compatible with GTD in pelvic ultrasonography were retrospectively scanned. The pathology results of patients who had an abnormal pelvic ultrasound diagnosis were analyzed. The following data were collected by review of medical records: maternal age, gravidity, parity, gestational age at the diagnosis, uterine size, pre-evacuation beta-human chorionic gonadotrophin (β-hCG) level, anemia (haemoglobin <11 g/dL), vaginal bleeding,

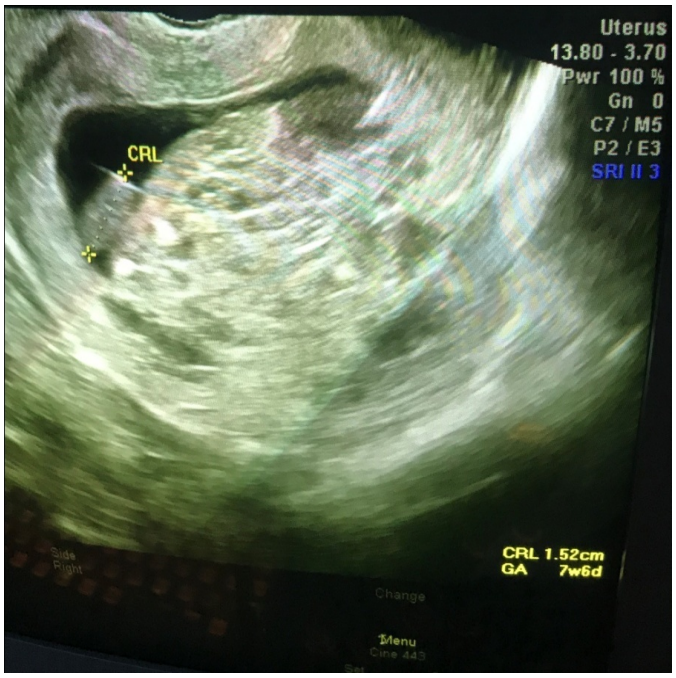

Fig.1. Transvaginal ultrasonography performed before vacuum aspiration.

ultrasonographic findings, laboratory results, histopathology findings, treatment modalities and beta-human chorionic gonadotropin (β-hCG) for following-up were record. Gestational age was calculated by the date of the last menstrual period. Subsequent observations of beta-human chorionic gonadotropin (β-hCG) and complete blood count values, the type of treatment administered, and pathology results were recorded. We used for vacuum aspiration paracervical block. The cervix dilated with the size of the pregnancy and for prevention of infection used Doxycycline 100mg, one hour before an abortion and 200 mg 30 minutes afterwards. Pelvic ultrasonography was performed with Voluson P6(GE Healthcare, USA). (Figure1)

Result

As a result of the study, the average age of patients were27.06, the smallest patient 17 and the oldest patient was 50 years old. One patient over 40 years old was diagnosed. Gravidity 1 in 8 (44.44%) patients and gravidity 2 in 6 (33.33%) patients were observed. Parity1was observed in 10 patients (55.55%). There was no significant difference between previous normal vaginal and cesarean delivery patients. Pathology results were found in 14 patients (77,7%) partial mol, in 2 patients (11,1%) complete mol, invasive mol in 1 patient (5,6%) and choriocarcinoma in 1 patient (5,6%).

The average gestational age for these patients was 7.89 week. The smallest gestational age is 4, and the highest gestational age is 14 weeks in the patient with choriocarcinoma.

Blood type A was observed in 10 patients (55,6%), 4 patients (22,2%) in type O and 4 patients (22,2%) in blood type B.

The average value of β-hCG is 179018,72. The lowest β-hCG 26459 and highest 396400 were observed. Anaemia was detected in 3 patients (16,7%).

In these cases, 1 case of lung metastasis and three patients received chemotherapy treatment.

Patient characteristics for the eighteen women.									
No	Age	Parity	NVD	CS	Pathology	Gestational week	Blood group	b-HCG	Haemoglobin
1	26	G2P1	1	0	PARTIAL MOLE	10	ORH +	171212	12
2	23	G1P0	0	0	CORIOCARSINOMA	14	ORH+	267000	12
3	18	G1P0	0	0	PARTIAL MOLE	6	ARH +	189176	10
4	31	G3P2	2	0	INVAZIV MOLE	8	ORH+	378459	11
5	28	G1P0	0	0	PARTIAL MOLE	7	ARH +	356041	13
6	50	G4P3	3	0	PARTIAL MOLE	8	ARH +	396400	8
7	26	G1P0	0	0	PARTIAL MOLE	5	ARH +	87710	12
8	26	G2P1	1	0	PARTIAL MOLE	6	BRH-	66624	12
9	26	G1P0	0	0	PARTIAL MOLE	9	ARH +	26459	13
10	32	G2P0	0	0	PARTIAL MOLE	7	BRH-	56075	8
11	26	G2P0	0	0	PARTIAL MOLE	10	BRH+	27000	15
12	17	G1P0	0	0	COMPLETE MOLE	9	ARH +	93001	12
13	40	G4P2	2	0	PARSIEL MOLE	8	BRH+	75704	13
14	28	G2P1	0	1	COMPLETE MOLE	8	ARH +	160000	12
15	21	G1P0	0	0	PARTIAL MOLE	6	BRH+	259000	12
16	24	G1P0	0	0	PARTIAL MOLE	9	ARH +	182476	12
17	25	G2P1	1	0	PARTIAL MOLE	4	ARH +	150000	11
18	20	G3P2	0	2	PARTIAL MOLE	8	ARH +	280000	11

Discussion

The reported rate varies widely in different areas of the world. In North America and Europe, rates of HM are about 0,5 to 1 per 1000 pregnancies. Higher frequencies have been announced for different regions of Asia and the Middle East, with rates ranging from 1 to 12 per 1000 pregnancies [18,20]. As has been announced for HM, incidence ratios for choriocarcinoma also differ markedly throughout the world. In Europe and North America, ratios of 2 to 7 per 100,000 pregnancies have been noted, whereas in Asia ratios have been as reported high as 5 to 200 per 100,000 pregnancies [18.19.21.22].

While the incidence of GTD in our country (Turkey) is reported as 0,6 / 1000, in our study, it is 1,5 / 1000. The reason for the high incidence of GTD in our study is the fact that our hospital is the centre of reference and that the city has a cosmopolitan structure.

Maternal age has been noted as a significant risk factor for molar pregnancy across many countries including the United States, Asia, Europe and the Middle East [23,24]. Women <16 or >40 years of age have a 4–10 times higher risk of appearing a hydatidiform mole (HM) than those aged 20–30 [25,26]. In the U. K, the overall risk for women of reproductive age is <1: 500 [23]. However, risks are lightly higher for younger women (1:378–563 for teenagers aged 14–17), and remarkably increased for those aged >40 (1:423 at 40, 1:101 at 45). At the extremity of the reproductive age range, the risk of HM for girls pregnant at the age of 13 is 1:208, and 1:8 for women aged $\geq$ 50 [23]. As a result of our study, the average age of patients was 27.06, the smallest patient 17 and the oldest patient was 50 years old. One patient over 40 years old was diagnosed.

ABO blood groups were associated with the risk of gestational trophoblastic disease. Compared to women of group O or B, women of group A and AB had an elevated relative risk. The risk estimates were higher for the persistent trophoblastic disease. The tests for linear trend in risk from benign to persistent disease were statistically significant in both A and AB groups. There was a significant interaction between blood group and age since the ABO-related risk was elevated only for women over the age of 35. [27,28].In our study also blood type A was observed in 10 patients (55,6%).

Vajinal bleeding is the most common reason for patients with GTD to refer to the clinic.

Pelvic sonography is performed as a routine investigation during early pregnancy to accurately date the gestation and determine any abnormalities [29,30]. Therefore, hyperthyroidism, preeclampsia and anaemia are less common nowadays. In our study, the average gestational week of patients with GTD was 8. It has been determined that the majority of our cases refer to the clinic with vaginal bleeding. It has also been seen in cases with secondary amenorrhea and abdominal pain.

Hydatidiform mole (HM) is the most common form of GTD[3].PSTT is a rare form of GTD, with fewer than 250 cases noted in the literature [4].Our study showed 16 patient(%88,8) with diagnosis of Hydatidiform mole (HM) ,which is 14 patients (77,7%) partial mole and 2 patients (11.1%) complete mole.

β-hCG levels show large variation in normal, multiple, and abnormal gestations and when considered in isolation may be incorrect for diagnosis of the hydatiform mole. Therefore, early first-trimester sonography data the investigation of choice for initial diagnosis of hydatiform mole [31,32].

Table 1
FIGO staging of trophoblastic tumors.

FIGO Stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus
II	Gestational trophoblastic tumors extending to the adnexae or to the vagina, but limited to the genital structures
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement
IV	All other metastatic sites

β-hCG is the most important test used in the follow-up of GTD diagnosis and treatment. The average value of β-hCG is 179018,72 in our study. The lowest β-hCG 26459 and highest 396400 were observed.

Conclusion:

This retrospective study included 1813 patients who underwent vacuum aspiration from 2010 to 2018 years in Derince Training and Research Hospital, Kocaeli, Turkey. During this period, 18 cases were diagnosed as GTD histopathologically. The calculated GTD incidence was 1,5 per 1000 births.

As a result, the etiopathogenesis unexplained GTD can be diagnosed early by the ultrasound, so early treatment is possible. Radiologist plays the primary role in the first diagnosis of GTD and basis disease management and early finding of its complications. Although serum β-hCG is a useful biochemical marker for GTD. Ultrasound is the initial line radiological examination in approving the diagnosis of GTD in a case suspected by clinical detections and β-hCG levels.

We believe that diagnosis, adequate treatment and follow-up will make easy the cure of GTD and the incidence can be calculated more exactly by performing wide community-based studies.

In 2000, FIGO suggested a clinical staging of gestational trophoblastic tumours and requested that such cases be noted in the Annual Report on the Results of Treatment of Gynecological Cancers. The descriptions of the clinical stages of gestational trophoblastic tumours are shown in Table 1.

In 2000, FIGO accepted the WHO scoring system based on prognostic factors [33] (Table 2). Score values for risk factors are 1, 2, and 4. Blood groups are not used in this system. Liver metastases are given 4 points. Cut-off scores for low-risk and high-risk neoplasia were approved by the FIGO's Gynecological Oncology Committee in June 2002. A score of 6 or less is a low-risk disease that can be treated alone agent chemotherapy. A score of 7 or higher is a high-risk disease that requires combination chemotherapy.

The FIGO Committee accepted this combining of the modified WHO risk factor scoring system with the FIGO staging on Gynecologic Oncology in September 2000 and ratified in June 2002 with the FIGO announcement [34]. It is now part of the FIGO staging and scoring system for GTN.

Table 2
FIGO/WHO scoring system based on prognostic factors.

FIGO/WHO risk factor scoring with FIGO staging	0	1	2	4
Age	<40	>40	-	-
Antecedent pregnancy	Mole	Abortion	Term	
Interval from index pregnancy, months	<4	4–6	7–12	>12
Pretreatment hCG mIU/mL	$<10^3$	$>10^3$–10^4	$>10^4$–10^5	$>10^5$
Largest tumor size including uterus, cm	-	3–4	≥5	-
Site of metastases including uterus	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	-	1–4	5–8	>8
Previous failed chemotherapy	-	-	Single drug	Two or more drugs

Table.2.

Ethics approval and consent to participate

The study protocol for the reported case was approved by Derince Training and Research Hospital.

Competing interests

The author declares that he has no competing interests.

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Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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