

Clinical and pathological features and prevalence of gestational trophoblastic disease

1. Malika Rustamovna Mamatova, Assistant, The department of obstetrics-gynecology №1, Andijan State medical institute, Andijan, Uzbekistan.
e-mail: malika_mamatova@rambler.ru Born 1986
2. Nargiza Nematovna Zakhirova, DSc, The department of tumors of women's reproductive system, Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan.
e-mail: dr.zahirova@mail.ru, born 1971.
3. Nilufar Mahmudovna Akhmedova, Phd, The department of obstetrics-gynecology №1, Andijan State medical institute, Andijan, Uzbekistan.
4. Zilola Makhammadovna Nazirova, Assistant, The department of obstetrics-gynecology №1, Andijan State medical institute, Andijan, Uzbekistan.
e-mail: zilolanazirova81@gmail.com. Born 1981
5. Mehriyorbegim Mansurjonovna Mamadaliyeva, Assistant, The department of obstetrics-gynecology №1, Andijan State medical institute, Andijan, Uzbekistan. e-mail: mehriyorbegim@mail.ru, Born 1988.

Abstract:

The prevalence, clinical and pathological features of Gestational trophoblastic disease (GTD) was studied. GTD is a term that unites a group of pathological conditions associated with pregnancy that develop as a result of abnormal cell proliferation of the trophoblast after fertilization. The aim of the research was to study the clinical and pathological features and the prevalence of various forms of gestational trophoblastic disease in Uzbekistan. A retrospective analysis of the case histories of women with gestational

trophoblastic disease was carried out. As a result of the research, the following conclusions were made: there is a tendency to increase the incidence of gestational trophoblastic disease. Established the single center for monitoring, diagnostics and treatment of trophoblastic disease in the republic will improve the quality of diagnosis, treatment and rehabilitation of this category of patients. It is necessary to use markers to predict the malignant transformation of trophoblastic disease using modern diagnostic methods.

Key words: gestational trophoblastic disease, hydatidiform mole, choriocarcinoma.

Introduction

Gestational trophoblastic disease (GTD) is a term that unites a group of pathological conditions associated with pregnancy that develop as a result of abnormal cell proliferation of the trophoblast after fertilization [1,2, 3]. Includes benign forms: hydatidiform mole (HM, complete or partial) and malignant forms: invasive HM, placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor and choriocarcinoma (CC). [2,4,5]. The most common trophoblastic tumors in clinical practice are complete and partial HM. In modern classifications, these pathological processes are classified as benign. [2,3,6,7]. But the European Society for the Treatment of Trophoblastic Disease (EOTTD) and the International Society for the Study of Trophoblastic Disease (ISSTD) proposed to classify complete and partial HM as precancerous conditions and to register as 0 stage of malignant trophoblastic tumors. In the latest ESMO 2013 guidelines for the diagnosis, treatment and follow-up of patients with trophoblastic disease, complete and partial HM have already been classified as precancerous [8,9,10]. The reason for the increased attention of oncologists to HM is due to the fact that the HM can initiate all currently known malignant trophoblastic tumors:

choriocarcinoma(CC) associated with pregnancy, PSTT and epithelioid trophoblastic tumor [2,3,8,10].

There is a geographic diversity in the distribution of GTD. In the structure of oncogynecological pathology, the frequency of malignant neoplasms of the placenta ranges from 0.1 to 3.6%. The incidence rate varies widely - from 0.01% ooo in Africa, America, Europe, England, Canada and others to 2.2% ooo in Vietnam. In East Asian countries, trophoblastic tumors are found 30-40 times more often than in Europe, and CC is observed, respectively, in 42.0-70.0% of patients. According to the WHO, the number of annually registered cases of the disease is underestimated [1,6,10].

Human chorionic gonadotropin β (β -hCG) is currently used as a biomarker for GTD. Monitoring of β -hCG is the main method for assessing the transformation process from benign to malignant forms of the disease [11,12]. However, there is no diagnostic method to predict this transformation.

A 2018 study in Poland used clinical proteomics [12]. Clinical proteomics is the identification and quantification of all individual proteins that are contained in a biological sample (serum, cerebrospinal fluid, urine, tissue) and monitoring changes in their concentrations. This study included the identification of 17 altered expression proteins, 11 of which (including septin 1, choriomammotropin, cytokeratin 8, and peroxiredoxin-2) were potential biomarkers of malignant transformation. In 2011, another study was carried out aimed at identifying prognostic biomarkers that indicate malignant transformation of the HM. The authors compared the protein profiles of HM with the profiles of malignant-transformed HM. 18 altered proteins were found in the malignant-transformed group. Among them, chloride intracellular channel protein 1 (CLIC1) was selected by the authors of the 2011 study for further study, the expression levels of CLIC1 in the choriocarcinoma tissue were higher than in the tissue of complete HM. The

study showed that CLIC1 is a potential new prognostic biomarker that may indicate a high risk of malignant transformation of the HM [13]. Based on this, we can conclude that proteomics is a promising method for detecting protein profiles and increasing the sensitivity and specificity of currently used biomarkers [12, 13,14,15].

At present, the epidemiology of GTD in Uzbekistan has been insufficiently studied, statistics only take into account its malignant forms, and there are no single centers for monitoring this disease. Absence of methodological principles for monitoring women after evacuation of the HM often leads to late detection of the disease, inadequate chemotherapy carried out in clinics that have no experience in treatment, with the subsequent development of resistant tumors and a worsening prognosis. To improve the quality of medical care for this category of patients in 2011, the European Society for the Treatment of Trophoblastic Disease (EOTTD) initiated the creation of a unified European "Protocol for the diagnosis and treatment of gestational trophoblastic disease (hydatiform mole and malignant trophoblastic tumors)" [10]. The paper analyzes the current state of the problem.

The relevance of the problem of GTD is quite high, since women, predominantly of young reproductive age, sometimes under 20 years old, are susceptible to this disease. In studies conducted in 2018, clinically significant increases in the level of anxiety, depression, sexual dysfunction and stress were found in women who underwent GTD [16]. The issues of prevention and successful treatment are closely related to the medical and social problems of maternity protection, intra-family relationships, and medical rehabilitation.

The purpose of the research.

To study the clinical and pathological features and prevalence of various forms of GTD in Uzbekistan.

Materials and methods.

To achieve this goal, information was collected from the statistical department of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology on the number of cases of GTD registered in this center for the period 2011-2019. A retrospective analysis of the case histories of women with GTD was carried out. 150 cases of GTD were analyzed. The age of patients ranged from 17 to 77 years; the average age was 30 ± 3.5 years.

Results.

According to the statistical data for the period 2011-2019, 150 cases of GTD were registered. Of these, 102 (68%) were HM, 9 (6%) were placental site trophoblastic tumors, 12 (8%) were invasive HM, and 27 (18%) were CC. Among the cases of HM, 70 (68.6%) were complete HM, 32 (31.3%) were partial HM (table 1).

Table 1.Characteristics of the surveyed group.

Type of GTD	Incidence, n=150
Hydatidiform mole:	102 (68%)
complete	70 (68,6%)
partial	32 (31,3%)
Invasive HM	12 (8%)
PSTT	9 (6%)
Choriocarcinoma	27 (18%)

As seen from Fig. 1, the largest number of patients were from the Tashkent city (n = 28, 18.6%), the least number of patients were from

Namangan region (n=3, 2%), probably this is due to the problem of diagnosis and insufficient histological examination of the abortion material.

There were 91 women living in rural areas (60, 6%), which confirms the authors' opinion about the correlation between trophoblastic disease and nutritional deficiency of mothers during the conception of their daughters and the development of HM during pregnancy of these daughters in the future. This is mainly a deficiency of vitamin A and / or B9 (folate) during the first week of development of the female fetus, which can disrupt the normal differentiation of their oocytes [17].

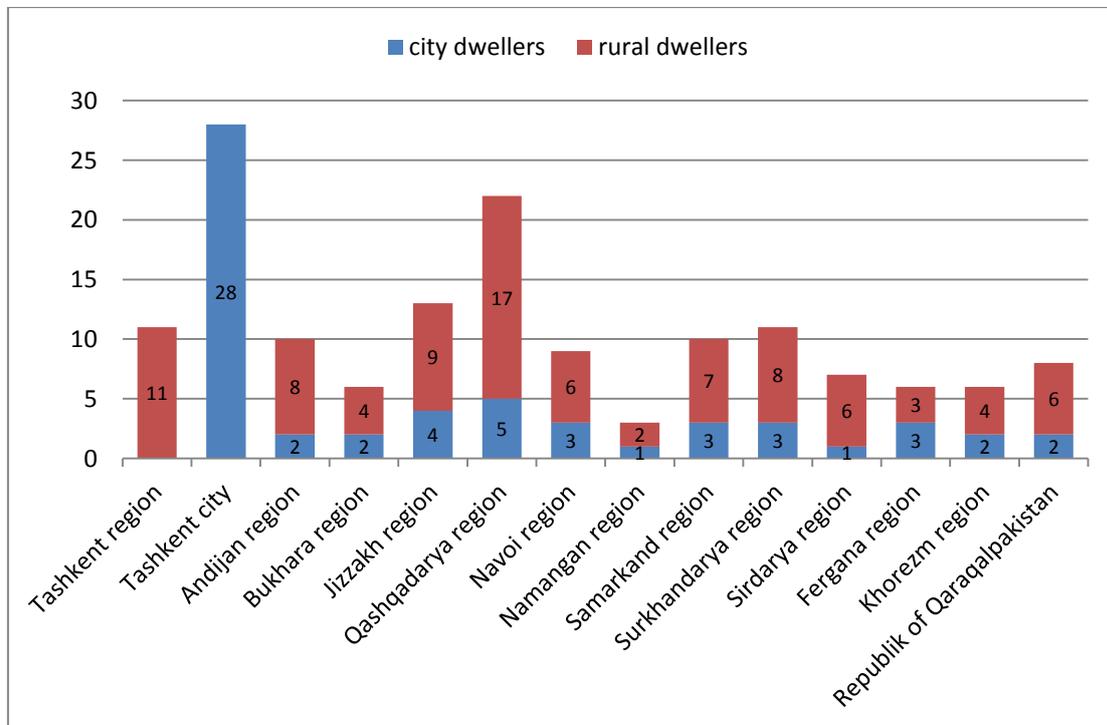


Figure 1. The incidence of GTD disease by regions of Uzbekistan (2011-2019)

The distribution of women by age is shown in Fig. 2, most of all GTD was diagnosed in women aged 20-34 years.

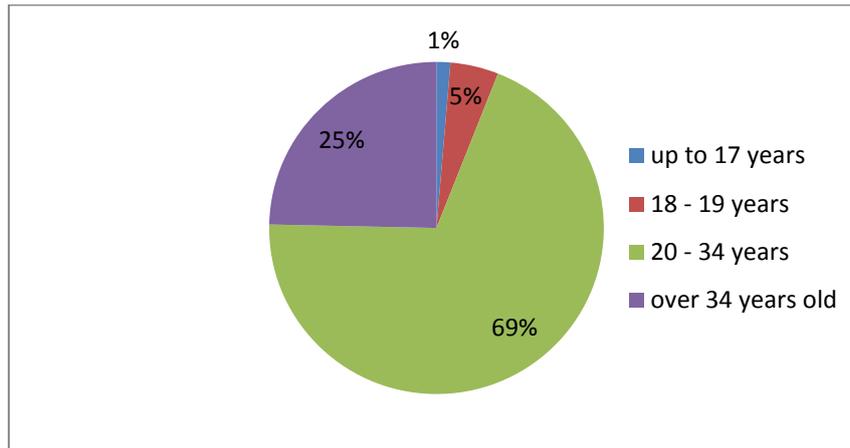


Figure 2. Distribution of patients by age

The average age of women with malignant forms of GTD was: invasive HM - 26.6 years, CC - 30.8 years. These results indicate that malignant forms occur at a young reproductive age and in most cases lead to loss of fertility due to hysterectomy.

Most women (45%) had a history of spontaneous abortions and non-developing pregnancies. Comorbidities: iron deficiency anemia occurred in 90% of cases, urinary tract infection - 65% of women, colpitis and other inflammatory diseases of the genital organs - 75%.

A common clinical symptom in women with complete HM was uterine bleeding, signs of early pregnancy toxemia. There was an excessive increase in the size of the uterus relative to the gestational age. In 50% of women, ultrasound examination revealed thecalutein cysts larger than 6 cm, with bilateral localization. In most cases, beta-hCG levels were between 50,000 - 100,000 mIU/ ml.

In women with partial HM, 23 (71.8%) had uterine bleeding. Fetal heartbeat was absent in 12 (37.5%) patients. No uterine enlargement and no thecalutein cysts were detected. The level of beta-hCG before removal of molar tissues was measured in all patients and was more than 100,000 mIU / ml in only 2 patients (6.25%).

All patients underwent uterine cavity curettage and vacuum aspiration. Repeated curettage was performed in 15 women: 3 patients were curettaged 2

times, 5 patients -3 times, 2 patients -4 times, 2 patients -5 times, 2 patients -6 times, in 1 case, curettage was performed 11 times. In the future, these women were monitored at their place of residence, and no increase in beta-hCG levels was observed.

Characteristics of malignant forms of GTD.

According to the FIGO classification (2000), the distribution of CC by stage was as follows: stage I – 9 (33.3%) patients, stage II – 6 (22.2%), stage III – 7 (26%), stage IV – 5 (18.5%). The outcome of previous pregnancy was HM in 16 (59.2 %) patients, abortion – in 9 (33.3 %), and childbirth – in 2 (7.4 %). The interval from the end of the last pregnancy to the manifestation of the disease varied from 1 month to 5 years.

Morphological verification of the tumor was obtained in all cases. Tumor samples were examined only by classical microscopic analysis without the use of modern additional techniques (immunohistochemistry).

In 30 (62.5%) of 48 women with trophoblastic neoplasms, treatment was initiated with surgery, and patients were operated without prior chemotherapy. Total surgical activity was in 36 (75%) cases. The main indication was bleeding and perforation of the uterus with a tumor. The tendency to profuse bleeding in GTD, especially in CC, is a life-threatening complication of the patient. The cause of this complication was studied by American researchers. They explained massive bleeding and necrosis in CC by vasculogenic mimicry, which is less effective than true tumor angiogenesis [17].

In 7 (19.4%) patients, the volume of treatment was extirpation of the uterus with ovaries, in 10 (27.7%) – supravaginal amputation of the uterus with ovaries, in 12 (33.3%) – supravaginal amputation of the uterus without ovaries.

In no case has an organ-preserving operation been performed.

Standard chemotherapy of the 1st line was performed for all patients. The development of resistance was observed in 8 women, which was expressed by an increase in the hGC titer after chemotherapy in 3 subsequent measurements during 3 months. These patients were assigned 2nd-line chemotherapy. Remission of the disease was observed in 27 (75%) cases, and 5 (18.5%) cases were fatal (Table 2).

Table 2. Characteristics of patients with choriocarcinoma (n=27)

Characteristics	Rate, n (%)
I stage	9 (33,3%)
II stage	6 (22,2%)
III stage	7 (26%)
IV stage	5 (18,5%)
Frequency of resistance development	8 (29,6%)
The frequency of hysterectomies	15 (55,5%)
Died	5 (18,5%)
Unknown outcome	4 (14,8%)

Discussion. It is difficult to judge the true incidence of the disease, because not all cases of abortion are registered and the materials of curettage are not subjected to histological examination [2,18]. This leads to a complicated course of pathology due to the lack of specific treatment and monitoring of patients. As a result, it is not rare to develop a malignant process, followed by hysterectomy in women of reproductive age [9,15]. It is important to note the need for a required histological examination of the material obtained by the scraping of uterine cavity during a missed miscarriage and abortion. The necessity of these studies

stems from the fact that there is an increasing number of cases when, in the absence of any clinical symptoms (due to early ultrasound examination), a complete HM is misdiagnosed as a missed miscarriage[19]. The importance of registration of all cases of HM is evidenced by the fact that in recent years the issue of the need for staging HM as stage 0 of GTD with subsequent restaging in the case of the development of a malignant trophoblastic tumor initiated by HM has been actively discussed [14].

The study has shown that GTD is not a rare disease [20], as previously thought, especially its malignant forms.

Conclusions. Pregnant women with clinical presentation of abnormal vaginal bleeding should be evaluated for GTD. Histopathological examination is required to confirm the diagnosis. Thorough examination and observation of these patients is important for the early diagnosis of malignant forms of GTD. Established the single center for monitoring, diagnostics and treatment of trophoblastic disease in the republic will improve the quality of diagnosis, treatment and rehabilitation of this category of patients.

It is very difficult to diagnose HM in the early stages, when the increase in villus size and trophoblastic proliferation are less pronounced. In such situations, morphological examination of the cystic tissue should be supplemented by immunohistochemical studies [6,18,19]. The study of protein profiles by mass spectrometry will also help in predicting and early diagnosis of malignant forms. Thus, according to the authors, CLIC 1 is a potential new prognostic biomarker that may indicate risk of malignant transformation at patients with HM [12,13,14,15].

All of the above requires further study of the GTB problem, especially the way of early diagnosis and prognosis of malignant forms.

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