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Gestational trophoblastic disease a contemporary review of diagnostic and pathology. Current challenge and future directions for gynecologists and obstetricians

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Abstract

Purpose

The aim of this review is to provide an overview of existing literature and current knowledge on fertility rates and reproductive outcomes after gestational trophoblastic disease.

Gestational trophoblastic disease (GTD) is a heterogeneous group of disorders associated with abnormal proliferation of trophoblast and their course is characterized by varying degrees of malignancy. WHO classified GTD into three categories: tumor-like lesions, molar pregnancies and gestational trophoblastic neoplasms. HM is characterized by abnormal proliferation of both syncytiotrophoblast and cytotrophoblast, edema of placental villi, with or without the presence of a fetus. Complete and partial moles have been classified as two separate disease entities, and their division depends on the genetic material they contain. The complete mole has a complete set of chromosomes coming only from the paternal genome, while the partial mole is triploid and the genetic material transferred comes from the father and mother. Post-molar gestational trophoblast neoplasia (GTN) is a clinical diagnosis based on the observation of a persistent increase or persistently high hCG concentration after evacuation of the mole, requiring evaluation and treatment. Invasive hydatidiform mole, together with choriocarcinoma and placental tumor, belong to gestational trophoblast neoplasia. Currently, research has shown that short tandem repeat (STR) genotyping is the gold standard for making the correct diagnosis and this test should be performed if possible. Ultrasound examination has replaced all other non-invasive methods of diagnosing gestational trophoblastic disease. Imaging tests can show: an empty fetal egg, a "blizzard" image, and fetal death around the 8th-10th week of pregnancy. After the end of a mole pregnancy, patients must have the hCG (chorionic gonadotropin) level in the blood serum checked on days 1, 7, 14, 21, etc. To talk about a favorable prognosis after the treatment is to achieve normal hCG level within 18 weeks. It is also extremely important to determine the stage of advancement of cancer lesions in order to implement appropriate treatment. To determine the invasiveness of GTN several laboratory and imaging tests must be performed which will enable us to determine cancer progression with the greatest possible accuracy. GTD diseases originate from both syncytiotrophoblast and cytotrophoblast tissues and as a result of which they produce an extremely sensitive marker - human chorionic gonadotropin. The facts stated above and significant sensitivity to chemotherapy mean that the average cure rate for this disease currently exceeds 90%. Although the main treatment of gestational trophoblast neoplasia involves the use of cytostatics, in cases with worse prognosis, i.e. those with a higher risk, surgery turns out to be an invaluable treatment method.

Key Words: Gestational trophoblastic disease; gestational trophoblastic neoplasia; syncytiotrophoblast; invasive hydatidiform mole; choriocarcinoma.

Introduction

Gestational trophoblastic disease (GTD) is a heterogeneous group of disorders associated with abnormal proliferation of trophoblast and their course is characterized by varying degrees of malignancy. The moles were first described by Hippocrates (470–410 BC) who explained their formation through the consumption of dirty water by the pregnant women, where the water originates from the marshes. GTD was classified into three categories: tumor-like lesions, molar pregnancies and gestational trophoblastic neoplasms. Molar pregnancies usually occur as hydatidiform mole (complete or partial). Hydatidiform is a benign placental tumor with malignant potential and it is considered as a pre-cancerous condition. HM may also present as invasive and metastatic type. [1–4] Gestational trophoblastic tumors have been categorized as epithelial trophoblastic tumor (ETT), placental site trophoblastic tumor (PSTT), gestational choriocarcinoma and mixed trophoblastic tumor. However, tumor-like lesions manifest as exaggerated placental site reaction and placental site nodule and plaque. [1] The above-mentioned entities are characterized by different histopathological features. Benign tumors include hydatidiform mole, while the remaining tumors are malignant. [5] A common feature of all pathological entities belonging to gestational trophoblastic disease is the secretion of chorionic gonadotropin into the blood and chemosensitivity (except for placental tumor). In order to quickly diagnose and implement appropriate treatment it is extremely important to understand the pathophysiology of this disease. In the era of ultrasound, it is possible to identify mole pregnancies very early, even before the manifestation of clinical symptoms. [4,6] Modern methods of chemotherapy have made it possible to use cytostatics as a therapy with the prospect of complete recovery; in the past the diagnosis of gestational trophoblastic disease often resulted in the patient's death. [6,7] However, the importance of surgical treatment cannot be forgotten, as it is extremely useful in clinical cases with poor prognosis. Hydatidiform mole is a benign placental tumor with malignant potential. [2,8,9] It is characterized by abnormal proliferation of both syncytiotrophoblast and cytotrophoblast, edema of placental villi, with or without the presence of a fetus. Currently available data

indicate that the main role in the development of a mole is played by angiogenic factors: vascular endothelial growth factor (VEGF) and epithelial growth factor receptor (EGFR). Hydatidiform mole is most often diagnosed in the first half of pregnancy. The most important and common symptom is vaginal bleeding, with possible excretion of swollen villi. Invasive mole is a hydatidiform mole in which villous trophoblasts invade the myometrium or blood vessels or even metastasize to extrauterine sites.[[10–12]] Invasive hydatidiform mole, together with choriocarcinoma and placental tumor, belong to gestational trophoblast neoplasia. It infiltrates surrounding tissues and may cause metastases, which are most often located in the lungs and vagina. Invasive mole may develop on the basis of a mole, usually complete, or may be invasive from the beginning. [[13]] The risk factors include the mother's age under 16 or over 35, smoking, previous miscarriages, previous molal pregnancy and a lack of carotene in diet during pregnancy. The symptoms are similar or the same as in the case of mild gestational trophoblastic disease. [[14]]

Clinical observation may reveal larger uterine dimensions than expected for a given gestational age, thecalutein cysts, lack of fetal heart activity, hypervomiting leading to early gestosis, pregnancy-induced arterial hypertension in the first trimester, and abnormally high hCG levels in relation to the gestational age. [[5]] The chromosome constitution of complete moles is usually 46,XX A partial mole manifests itself as a missed miscarriage. Thanks to the widespread use of ultrasound in the diagnosis of pregnant women, the incidence of symptoms has significantly decreased. [[12,15,16]] Epidemiological studies have observed high regional variability in the incidence of the above pathology. Based on statistics from Europe, New Zealand, Australia and North America, the estimated incidence was 0.57-1.1 cases per 1000 pregnancies, while in Japan and Southeast Asia these values ranged around 2 cases per 1000 pregnancies. The age of the patient seems make the highest risk factor of hydatidiform mole occurrence. Studies have shown that the incidence of this disease increases in patients under 20 years of age and in patients over 40 years of age. Statistically, 20% of GTN’s are teenage pregnancies. Another risk factor was identified as a previously occurring hydatidiform mole. However, the occurrence of the disease does not affect the reproductive capacity of female patients. [[17–19]]

Complete and partial moles have been classified as two separate disease entities, and their division depends on the genetic material they contain. The complete mole has a complete set of chromosomes coming only from the paternal genome, while the partial mole is triploid and the genetic material transferred comes from the father and mother. [[5]] From a clinical point of view, such reproduction of genetic material may lead to the development of gestational

trophoblast neoplasia, which, without proper treatment, may result in the woman's death. [20] The differentiation table is presented below.

Table 1. Features of complete and partial mole

Characteristic	**Complete mole**	**Partial mole**
karyotype	46,XX or 46,XY paternal origin	69,XXX or 69,XXY 2/3 paternal origin, 1/3 maternal origin
histopathology		
signs of fetal presence	do not occur	may occur
amnion, fetal red blood cells	do not occur	occur
swelling of the villi	scattered	changeable
trophoblast proliferation	scattered	focal changes
p57 protein (in staining)	occurs	current
clinical form	molal pregnancy or incomplete spontaneous miscarriage	
clinical diagnosis	up to 50% of cases exceed the	incomplete spontaneous miscarriage
size of the uterus	size appropriate for gestational age	small in relation to gestational age
thecalutein cysts	9–25%	rare
complications	6–20%	rare
Postmolar gestational trophoblastic neoplasia	7–30%	2,5–7,5%

Post-molar gestational trophoblast neoplasia (GTN) is a clinical diagnosis based on the observation of a constant increase or persistently high hCG concentration after evacuation of the mole, requiring evaluation and treatment. [5] Complete hydatidiform mole was identified as a high-risk factor for development of GTN and it is more likely for this condition to occur

in cases of heterozygous HM rather than in cases of monospermic moles. [21] In addition, a previous cesarean section is considered as one of the risk factors for GTN and invasive mole. [22] It is still unknown why some HM regress spontaneously after treatment while others progress to GTN. [23] GTN is most often a consequence of a molar pregnancy in the history of the disease, but it can also occur after any other pregnancy. The symptoms of GTN are non-specific and may ever appear as asymptomatic. Imaging shows an enlarged and irregular uterus as well as enlargement of both ovaries. Patients often report irregular vaginal bleeding. [24]

Diagnostics

If a molal pregnancy is suspected, chorionic gonadotropin (characterized by very rapid and uncontrolled increase in blood serum level) should be tested. The patient's blood group should be determined as well. Ultrasound examination has replaced all other non-invasive methods of diagnosing gestational trophoblastic disease. [25] Thanks to ultrasound, the initial diagnosis of molal pregnancy is most often possible at its early stage between the 8th and 10th week of pregnancy before the appearance of clinical symptoms. Imaging tests may show: an empty fetal egg, a "blizzard" image and fetal death around 8-10 weeks. week of pregnancy. [3,5,26]
Currently, research has shown that short tandem repeat (STR) genotyping is the gold standard for making the correct diagnosis and this test should be performed if possible. [1] Currently, p57 immunostaining and genotyping are used as important additional methods for the differential diagnosis and treatment of GTD. [27]
After the end of the mole pregnancy, patients must have the level of hCG (chorionic gonadotropin) in the blood serum checked on days 1, 7, 14, 21, etc. To talk about a favorable prognosis after the treatment, the hCG level should return to normal. The diagnosis of gestational trophoblastic neoplasia should be clinically suspected when the hormone concentration increases. In 2000, FIGO standardized the hCG concentration values as criteria for diagnosing extramacular GTN. [25,28]
Conducting rapid diagnostics using various imaging tools allows for early detection of the disease. Given the availability of sensitive hCG tests and the introduction of effective chemotherapy, this once fatal cancer is now curable. [25,29]

Criteria for the diagnosis of GTN

1. hCG concentration after mole evacuation
- maintained constant (±10%) concentration in 4 determinations over 3 weeks
- persistent increase in concentration by >10% in 3 determinations over 2 weeks
- persistent detectable concentration >6 months after mole evacuation
2. Presence of metastases
3. Histological diagnosis of GTN
- invasive mole
- choriocarcinoma
- tumor of the placental site
- epithelial trophoblastic tumor. [5,7,30]

It is also extremely important to determine the stage of advancement of cancer lesions in oqrder to implement appropriate treatment. To determine the invasiveness of GTN, several laboratory and imaging tests must be performed, which will enable us to determine cancer progression with the greatest possible accuracy.

Determining the stage of clinical advancement is based WHO score system for accessing risk groups (Table 2) FIGO 2000 anatomical classification system (Table 3). Depending on the number of points, patients were divided into two groups: low risk and high risk. The table below shows how the risk rating is determined. Each prognostic factor was assigned a score. All scores for each predictor are then summed to calculate the WHO risk score.

Low risk is less than or equal to 6. The prognosis for people with low-risk cancer is good, even if the cancer has spread, treatment is usually very effective.

High risk is a score of 7 and above. People with high-risk cancer may require more intensive treatment despite local tumor growth and the absence of metastases.

Table 2. WHO risk score.

Prognostic Factor	0	1	2	4
Ag				
Pr				
Mo pregnancy	Less than 4	4 to 6	7 to 12	More than 12
Pretreatment hCG (IU/mL)	Less than 10^3	10^3 to 10^4	Greater than 10^4 to 10^5	10^5 or more
Largest tumor size, including uterus	Less than 3 centimeters (cm)	3 to less than 5 cm	5 cm or more	—
Site of spread	lung	spleen or kidney	gastrointestinal tract	brain, liver
Number of tumors that have spread*	Zero	1 to 4	5 to 8	More than 8
Number of drugs used to treat the tumor that have not worked	None	None	1 drug	2 or more drugs

Stage I	Disease is only in uterus.
Stage II	GTD extends outside the uterus but is limited to the genital structures.
Stage III	GTD extends to the lungs and may or may not involve the genital tract.
Stage IV	GTD has extended to other distant sites, called metastasis.

In order to determine the advancement of the disease it is critical to use FIGO staging is also presented below. [8,31]

Treatment

Treatment of a hydatidiform mole involves procedure called vacuum removal of the mole under ultrasound guidance, which is the preferred method in patients who want to preserve fertility. The procedure should be performed immediately due to the risk of complications, which increases with gestational age. The procedure is usually performed under general anesthesia but in a cooperative patient with a small uterus local or regional anesthesia may be used. After emptying the uterus, anti-D immunoglobulin should be administered in RhD-negative women. It is also necessary to monitor the oxygen saturation of arterial hemoglobin in women with a uterine size exceeding that typical for 14 weeks of gestation, as well as to measure the hCG level. Complications depend on the initial size of the uterus, if it is larger than the appropriate one according to the gestational age corresponding to 14-16 weeks, their frequency is 25%, but less common in patients with a smaller uterus. [32,33] The prognosis in women after mole evacuation is very good, the main risk is incomplete removal, therefore ultrasound control is required up to 15 days after the procedure. [2,3,5,7,34]

GTD diseases originate from both syncytiotrophoblast and cytotrophoblast tissues, because of which they produce an extremely sensitive marker - human chorionic gonadotropin. The above fact and significant sensitivity to chemotherapy mean that the average cure rate for this disease currently exceeds 90%. Although the main treatment of gestational trophoblast neoplasia involves the use of cytostatics, in cases with worse prognosis, i.e. those with a higher risk, surgery turns out to be an invaluable treatment method. Chemotherapy still remains as the standard treatment for GTN and is based on FIGO staging. Single agent chemotherapy is administered to patient with I stage or stage II/III, if the WHO score is <7. Patient with stage IV or WHO score ≥ 7 are considered as a high-risk group and should be given multi-agent chemotherapy. [35] However, recent studies have shown that treatment with anti-PD1/PD-L1 immune checkpoint inhibitors holds great promise with relapse cases. [35,36] Approximately half of the cases of patients from high-risk groups (FIGO stage IV) and those receiving 7 or more points on the modified WHO point scale require therapeutic surgical procedures, despite the introduction of basic pharmacotherapy. [36]

The treatment of low-risk patients involves chemotherapy, as the cure rate is estimated to be approximately 100%. The cytostatics used include methotrexate and dactinomycin. Clinical trials of their therapeutic effectiveness showed a significantly higher percentage of complete response to treatment achieved during treatment with dactinomycin at a lower dose. Gentle induction chemotherapy helps reduce early deaths in patients with extensive tumor burden,

but late mortality still occurs from recurrent resistant tumors. [[37]] However, the significant toxicity of dactinomycin compared to methotrexate should be emphasized. Recent studies have shown that treatment consisting of methotrexate and folic acid, aministered for 8 days, remains the best option for patients presenting with low-risk postmolar GTN. [[38]]

The use of adjuvant surgical procedures in patients from higher risk groups is primarily aimed at reducing the tumor mass, removing resistant disease in the uterus or at the site of metastasis, stopping hemorrhage caused by the tumor or its metastasis, as well as treating infected tumors. [[39,40]] The most common and preferred procedure is hysterectomy performed in patients with persistent or chemoresistant focal lesions as well as to stop hemorrhages. In the case of an isolated lung metastasis, we perform resection of a part of the lung using thoracoscopy or thoracotomy. Less frequently used procedures that are used to stop hemorrhage include embolization of the uterine arteries, ligation of the internal iliac arteries, or embolization of the uterine arteries in the case of more profuse hemorrhage in patients who want to preserve fertility. [[2,3,7,8]].

Conclusions

Available diagnostic and therapeutic measures enable early and quick diagnosis and implementation of treatment. This procedure ensures a high percentage of complete cures for patients suffering from mole acinar. It is important to choose targeted therapies individually, depending on the criteria met by the patient and her needs.

Authors Contribution:

Conceptualization,HS, AM, AS; methodology, PB; check, AN and ZM; formal analysis, PG; writing - rough preparation, HS, PB and AS; writing - review and editing, AM, PG; supervision, ZM, AN, ; project administration, HS; receiving funding, AS,PG. All authors have read and agreed with the published version of the manuscript.

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