

# A review on management of gestational trophoblastic neoplasia

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## ABSTRACT

**Background:** The rare presence of malignant cancerous cells after any type of pregnancy is known as gestational trophoblastic neoplasia (GTN). GTN are benign lesions which mostly happen due to the activity of extravillous trophoblast cells and the placental villous tree development. These kinds of diseases would be occurring mainly due to the following clinicopathologic conditions: (I) existence of epithelioid trophoblastic tumor (ETT), (II) rare type of choriocarcinoma cancer, (III) gestational trophoblastic tumor of mole, and (IV) the rare malignant tumor of placental site trophoblastic tumor. **Objective:** This comprehensive study is trying to review the most recent approaches in comprehension of pathogenesis, more precise diagnosis, and also the most effective therapeutic procedures for patients who suffer from GTN disorders. **Materials and Method:** A comprehensive research was carried out on scientific databases of Science Citation Index (SCI), MEDLINE, EMBASE, HMIC, PubMed, CINAHL, Google Scholar, Cochrane Database of Systematic Reviews (CDSR), and PsycINFO over the time period of 2005 to 2019. The keywords which applied for discovering more related records were including: Gestational trophoblastic diseases (GTD), Gestational trophoblastic neoplasia (GTN), molar pregnancy, choriocarcinoma, human chorionic gonadotropin (hCG), diagnosis, management and treatment. **Conclusion:** In spite of the fact that GTN patients are treated with conventional surgical therapies or/and chemotherapy, in some patients with resistant disease, these therapies may not be effective and patients may die. Some novel remedial agents are required for decreasing the level of toxicity caused through administering conventional chemotherapy and also treating the patients who suffer from refractory or resistant disease. The newest issues are related to GTN diagnosis, process of progression of hydatidiform mole (HM) to GTN, and the issue of GTN drug resistance. In this regard, we should have a comprehensive knowledge on GTN genetics for answering all the available questions about this disorder.

**Keywords:** Diagnosis, gestational trophoblastic neoplasia, management, treatment

## Introduction

One of the main group of diseases which occur as a pregnancy rare complication is gestational trophoblastic disease (GTD). GTDs are consist of a range of interdependant tumors which are happening due to abnormal reproduction of trophoblastic tissues such as invasive mole, HM, malignant tumors of

choriocarcinoma, epithelioid trophoblastic tumor (ETT), and placental site trophoblastic tumors (PSTT). GTD could happen after any kind of preceding pregnancy, mainly after molar pregnancy situations.<sup>[1,2]</sup> On the other hand, when the GTDs are persistent and the gestational trophoblastic tumors (GTT) are existing, they would be called gestational trophoblastic neoplasia (GTN). GTNs mainly consist of ETT, PSTT, malignant tumors of choriocarcinoma, and invasive mole tumors [Figure 1].

From pathobiological point of view, GTDs could be in general classified to three main groups which included: benignant

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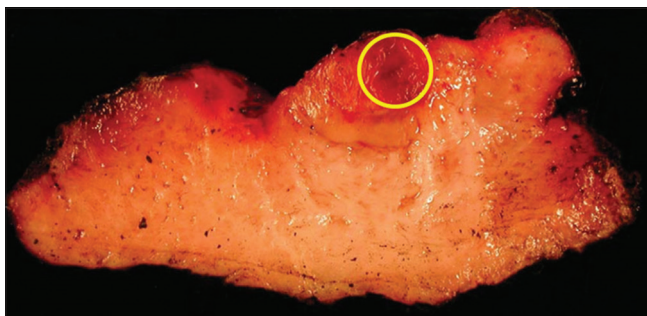
trophoblastic tumors, and tumor-like lesions, hydatidiform moles and true GTN.<sup>[3,4]</sup> In molar pregnancy situations, the malignant changes are consist of PSTT, choriocarcinoma cancer, and invasive mole. Partial hydatidiform molar (PHM) could transform to choriocarcinoma tumors or/and placental-site trophoblastic tumor (PSTT).<sup>[5]</sup> One of the main steps in the management of GTN is its diagnosis because these kinds of tumors could be treated nearly at all times and afterwards fertility could be maintained in the majority of cases.<sup>[5]</sup>

The common forms of GTD like complete hydatidiform moles (CHM) and partial hydatidiform molar (PHM) could be presented in the first trimester with acute vaginal bleeding, that would lead patients to an initial ultrasound scan of pelvic. These are the most abnormal forms of internal uterus materials which enabling histopathological diagnosis for clinical specialists.<sup>[6]</sup> The precise diagnosis of hydatidiform mole masses is an important factor in instituting lifesaving chemotherapy for proper management of these malignant type of masses. As a fact it should be noted that, in women with GTN, the long-term survival rate after any type of pregnancy is almost lower than 80%.<sup>[7]</sup> This is because these patients would be affected with more advanced kind of disease later; therefore, some of them die before administering effective treatments and some other would be affected with other kinds of drug-resistant diseases.<sup>[8]</sup>

Recently, some advances in genetics and biological issues at a molecular level have provided some novel comprehension of GTN pathogenesis which could be applied for proper diagnosis, management, and treatment of such disorders. However, in spite of the fact that some challenges have been responded, proper management of patients with this kind of disorders is still challenging for clinicians. In addition, the main reason for HMs development is not still known well. On the other hand, the capability of clinicians in the prediction of malignancy of HMs is not expanded. In the present study, it is tried to review the most recent advances in diagnosis, management, and treatment of GTNs.<sup>[9,10]</sup>

### Materials and Method

General comprehensive searches were conducted on scientific databases of Science Citation Index (SCI), MEDLINE,

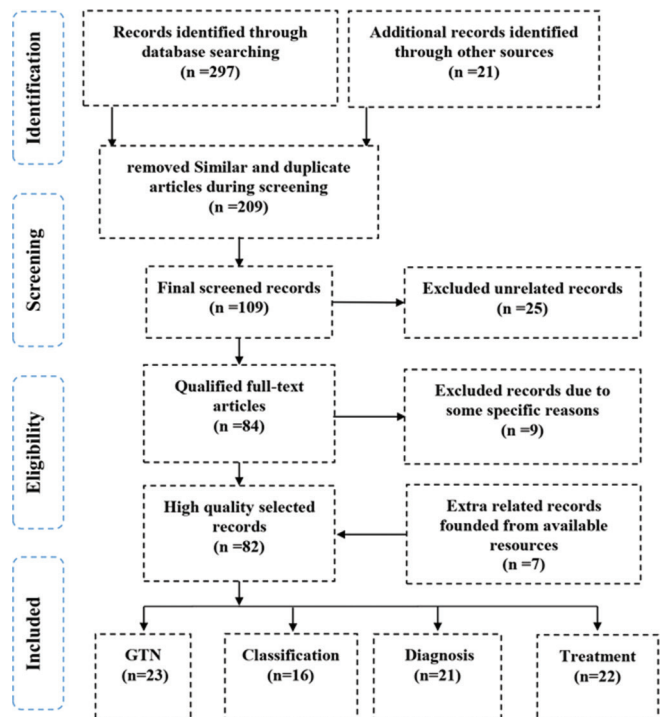


**Figure 1:** Yellow circle represents epithelioid trophoblastic tumor (ETT) appeared in surgical procedure of hysterectomy. Derived in accordance with<sup>[2]</sup>

EMBASE, HMIC, PubMed, CINAHL, Google Scholar, Cochrane Database of Systematic Reviews (CDSR), and PsycINFO over the time period of 2005 to 2019. The keywords which applied for discovering more related records were including: Gestational trophoblastic diseases (GTD), Gestational trophoblastic neoplasia (GTN), molar pregnancy, choriocarcinoma, human chorionic gonadotropin (hCG), diagnosis, management and treatment. In this regard, after completing the overall investigations, a total of 318 records were discovered, which after screening and excluding records with similar content and finally by adding few records searched through google search engine, the final number of reviewed articles reached to 81. The overall procedure of selecting articles based on the PRISMA method is demonstrated schematically in Figure 2.

### Epidemiology

The process of specifying etiological risk factors which could cause the GTN progression is not such easy. This is because gathering bias and dependable epidemiologic data and interpretation and various procedures of clarifying occurrence of these disorders are still a challenge. In spite of the existence of these challenges, a lot of information is available which could specify a broad range of alternation within the CHM incidence.<sup>[11]</sup> The prevalence rate of CHM is differing based on the various geographical location. As instance, the incidence rate of CHMs in Asia, Hispanics, American Indians, and African Americans is more than Europe, North America, and Australia.<sup>[12-15]</sup> However, there is not any decisive evidence that cultural factors or/and genetic characteristics could have a role in this rate differences.



**Figure 2:** Schematic diagram of the method of article selection based on PRISMA technique applied in this study

On the other hand, the incidence rate of HM would be differing among various regions worldwide.<sup>[16]</sup>

Pregnancy at a progressive age (more than forty years) and abnormal form of hydatidiform mole are the main etiological risk factors of CHM progression.<sup>[17]</sup> Based on some proved nutritional studies, there is an inverse association among consumption of animal dietary fat and beta-carotene and the CHM incidence.<sup>[18]</sup> For example, with changing the Asian diet to the Western countries, the incidence rate of CHM could be decreased.<sup>[5]</sup> On the other hand, because the happening of choriocarcinoma is not much frequent and its clinical recognition from metastatic mole is difficult, specifying the incidence rate is still a big challenge.<sup>[19]</sup>

## Pathology

In a situation when molar villi exceed the uterine myocytes, the development process of an invasive mole would happen. The metastases process of molar villi which are invading could happen via direct development through different channels. Nearly about 15% of CHMs would cause local tumor invasion, and 5% will expand metastases commonly into vagina or lungs.<sup>[20]</sup> The progression of local tumor invasion after PHM would happen in about 5% of patients, while the occurrence rate of metastatic disease is more infrequent.<sup>[20]</sup> The diagnosis of postmolar GTN is based on the elevation of the levels of gonadotropin-releasing hormone (GnRH) after elimination of hydatidiform mole. Consequently, the process of chemotherapy would be conducted without any diagnostic histopathology except in the antecedent pregnancy.<sup>[21]</sup>

Choriocarcinoma is one of the most cancerous diseases which could be specified through tissue necrosis, the inner layer of the trophoblast, hyperplastic and anaplastic outer syncytioblast, chorionic villi absence, and acute bleeding. Choriocarcinoma could be spread through directly exceeding vascular channels and the middle layer of the uterine wall and would involve distant sites such as the vagina, adnexa, lungs, spleen, intestines, kidney, and liver. An extensive number of choriocarcinoma cases would happen after non-molar pregnancy instead of an invasive mole.<sup>[22]</sup>

PSTT is an extremely rare malignant tumor which could be resulted from the happening of the placenta implantation within the uterine fundus that includes non-villous, mononuclear intermediate trophoblastic cells without chorionic villi which could penetrate among myometrial fibers layers within chords or sheets. Placental site trophoblastic tumors could cause less blood or/and lymph vessel invasion, less amount of bleeding and necrosis in comparison with choriocarcinoma. The tendency of PSTT for lymphatic metastasis mechanism is higher than choriocarcinoma.<sup>[23]</sup>

Immunofluorescent staining manifests the spread of human chorionic somatomammotropin and cytokeratin (CKs), it is while the hormone of human chorionic gonadotropin (hCG)

would be just presented focally. Due to its slower rate of growth, lower production rate of human chorionic gonadotropin, and the absence of common symptoms, immediate diagnosis could not be carried out easily. In most of the cases, placental site trophoblastic tumors could happen after non-molar gestations.<sup>[24]</sup> Because placental site trophoblastic tumors are not much sensitive to chemotherapy, their mortality rate is higher than that of choriocarcinoma. One of the rare alternatives of placental site trophoblastic tumors is epithelioid trophoblastic tumor which could arise from neoplastic transformation of invasive extravillous trophoblasts.<sup>[25]</sup>

## GTN Clinical Presentation

Over the last half-century, the clinical presentation of hydatidiform mole (HM) has varied a lot. Formerly, the most prevalent presentations were the presence of metastatic diseases, early-onset preeclampsia (PE), thyrotoxicosis, anemia, excessive uterine enlargement, hyperemesis gravidarum, and enlargement of ovarian cysts.<sup>[26]</sup> However, these kinds of presentations are happening yet, especially in developing countries.<sup>[12]</sup> Approximately, in about 95% of patients, abnormal uterine bleeding is presenting within the initial period of pregnancy which sometimes could cause anemia. Unfortunately, the enlargement of the uterus to the extent that is not expected for gestational age could be seen yet in more than 25% of patients.<sup>[27,28]</sup>

The increment of application of ultrasonography diagnostic imaging technique during the pregnancy period of time makes the immediate diagnosis of molar pregnancies possible.<sup>[29]</sup> In situations when the CHM are existing, their commonest growth pattern includes multiple cluster of sonolucent, which represents the multiple hydropic chorionic villi. On the other hand, in PHM situations, sonographic findings are not much exuberant and the diagnostic procedure is mostly conducted after the review of histology. Anyway, fetal parts and a major combination of sonolucent clusters are two of the most frequent PHM sonographic finding.<sup>[30]</sup> The application of endovaginal ultrasound provides the initial and immediate diagnosis of hydatidiform mole in some special cases.<sup>[31]</sup>

Based on Braga *et al.*<sup>[5]</sup> suggestions, standardized guidelines for the diagnosis for more accurate diagnosis of postmolar GTN are including:

- I: The choriocarcinoma histologic diagnosis
- II: Persistence of human chorionic gonadotropin 6 months after molar pregnancy
- III. Various values of human chorionic gonadotropin plateaued during about 21 days
- IV: The increment of human chorionic gonadotropin level about 10% or more for at least three values during 14 days.

The most frequent GTN seen during the microscopic examination of histopathology is malignant, trophoblastic cancer of choriocarcinoma which mostly arises from spontaneous abortion or term pregnancies. On the other hand, choriocarcinoma may be

presented without any special symptoms and signs that makes the precise diagnosis challenging and would make a delay in diagnosis. Accordingly, GTN must be considered precisely and human chorionic gonadotropin examination should be performed in all women during their reproductive years mainly who suffer from abnormal bleeding of uterus or any related unknown metastatic disease.<sup>[32,33]</sup>

Gestational trophoblastic neoplasia diseases would be mostly happening after premature birth and commonly present with bleeding of uterus because of the presence of tumor invasion or growth of special metastatic tumors. Acute bleeding due to metastatic lesions or/and perforation of the uterus would cause melena, hemoptysis, and abdominal pain.<sup>[34]</sup>

### GTN risk Evaluation and Staging

Based on the risk factor scoring and staging system for GTN adopted by the international cancer committee of federation of gynecologists and obstetricians (FIGO), an anatomic staging for GTN is presented in Table 1.<sup>[35]</sup> Epithelioid trophoblastic tumor and placental site trophoblastic tumors are classified separately. The treatment procedure could be carried out based on the total FIGO score, which expresses the possibility of expanding the risk of drug resistance among patients.<sup>[36]</sup>

The therapeutic procedure of patients who suffer from stage I GTN disease (non-metastatic) and also stages II and III GTN diseases (low-risk metastatic) could be carried out initially through single agent chemotherapy with the remedial success rate up to 85%. Moreover, patients with stage IV GTN diseases (high-risk metastatic) must undergo multi-agent chemotherapy or maybe with adjuvant surgery or/and radiation for gaining higher cure rates.<sup>[37,38]</sup> The application of FIGO system for scoring and staging GTN diseases becomes an essential tool for specifying the most appropriate initial therapy which could provide the best outcomes with the lowest rate of morbidity for patients.<sup>[39]</sup>

### GTN Management

The diagnosis procedure of GTN mainly carried out based on the persistent increment of the levels of hCG exactly after a molar pregnancy. While, the choriocarcinoma presentation could be extremely variable, and about 33% of these patients are presenting with symptoms resulting from distant cancers.<sup>[5]</sup> However, the responsible clinicians must consider malignant GTN nearly in all patients who are in childbearing age with a metastatic tumor, because a simple evaluation of hCG in urine or

serum would be lifesaving. Patients who suffer from post-molar GTN need a history, clinical examination, urine or/and serum hCG testing, ultrasonography of chest, and also pelvic Doppler ultrasonography.<sup>[40]</sup>

The routine scanning of the chest with computed tomography (CT) could not be applied for remedial management of GTN patients and also in the field of scoring system of FIGO.<sup>[41]</sup> The imaging techniques of ultrasonography and pelvic color Doppler imaging could be applied not only for general diagnosis but also in cases of persistent GTN or molar pregnancy, especially when the hCG level is increased and a mass of vascular uterine is existing without any fetus.<sup>[42]</sup> The volume of uterine is associated with the burden of tumor. Both pulsatility index and the volume of uterine could provide the independent medical predictive information which can provide resistance mechanisms to methotrexate in tumors.<sup>[43]</sup>

The magnetic resonance imaging (MRI) of pelvis and brain and abdomen and chest computed tomography are commonly administered in patients who suffer from drug-resistant or recur disease, PSTT, and choriocarcinoma. In addition, precise localization of tumor could assist in specifying the determination of the possibility of utilizing therapeutic resection.<sup>[44]</sup> However, fludeoxyglucose positron emission tomography (FDG-PET) imaging technique would be beneficial in positioning relapsed or residual disease.<sup>[44]</sup> The imaging techniques of MRI and CT scan could be utilized for evaluation of the human chorionic gonadotropin levels of cerebrospinal fluid for discovering occult diseases in the central nervous system (CNS).<sup>[5]</sup>

### GTN Patient's Treatment

#### Low-risk GTN

Based on the level of GTN disease, it could be classified to low and high-risk GTN. The treatment procedure for low-risk GTN has not been changed a lot over recent years. The most common remedies which are utilized within this category of diseases are dactinomycin and amethopterin. Amethopterin is safer and has less side effects with or without the release of leucovorin. Moreover, daily or every other day dosing of amethopterin for treatment during a week is more effective than weekly or its irregular pulse administrations.<sup>[19]</sup> In situations when the serum hormone of human chorionic gonadotropin has normalized, the treatment with amethopterin would be conducted within consolidated treatment systems which could be tolerated well without any spot baldness.<sup>[45]</sup>

Some other side effects which are less frequent are such as inflammation of a serous membrane and derangement within the renal and liver function. In addition, one other rare side effect is the suppression of bone marrow, which known as myelosuppression.<sup>[19]</sup> The most appropriate schedules for dactinomycin is daily intravenous administration regimens with a dosage of 0.5 mg.<sup>[46]</sup> The dactinomycin short-term toxicity is more than that of amethopterin. Nevertheless, the more common side effects of dactinomycin are including myelosuppression,

**Table 1: GTN FIGO staging. Derived in accordance with<sup>[37]</sup>**

Stage	Description
I	GTNs are completely restricted to the corpus of uterus
II	GTNs developing to the vagina or adnexa but are restricted to the genital structures
III	GTNs developing to the lungs may involve genital tract
IV	All other metastatic sites

the stomach discomfort of nausea, hair loss, and the painful inflammation of mucositis.<sup>[45]</sup> It's while, compared with amethopterin, dactinomycin does not have potential long-term sequelae.

**Low-risk persistent GTN**

The most delicate index of resistance mechanism to amethopterin in tumors is the increment of levels of serum hormone of human chorionic gonadotropin in about more than three serial values. However, the level of hormone of human chorionic gonadotropin at which the persistence condition progresses would help the selection of salvage chemotherapy.<sup>[47]</sup> Patients, whose treatment with dactinomycin failed or their developed amethopterin resistance with a hCG hormone over than 100 IU/l, were treated through chemotherapy enriched with amethopterin, etopophos, and dactinomycin. It's while, in some cases, the patients who are resistant to amethopterin could be treated without considering their levels of hCG hormone through combining chemotherapy with amethopterin, etopophos, and dactinomycin or dactinomycin and etopophos.<sup>[48,49]</sup>

In spite of the fact that these therapeutic schedules could certify a quicker treatment, a large number of patient would expose to more toxic drugs while the risk of tumor recurrence will be increased.<sup>[50]</sup> In this regard, the cutoff values for human chorionic gonadotropin could be increased from <100 to <300 IU/l for dactinomycin therapy in patients who are resistant to amethopterin. On the other hand, the pulsed dactinomycin could be applied as a rescue therapy for low-risk GTN patients whose treatment with amethopterin failed. However, approximately all patients could be healed in higher rates with combination chemotherapy.<sup>[51,52]</sup>

**High-risk GTN**

In situation when the patients are at higher risks, the most appropriate treatment option is combination chemotherapy. In this regard, the most frequent applied therapeutic regimen is the combination of chemotherapy with etopophos, amethopterin, and dactinomycin alternating with vincristine and cytophosphane [Table 2].

**Table 2: Combination chemotherapy regimen applied for patients with high-risk GTN. Derived in accordance with<sup>[53]</sup>**

Treatment schedule		
	Week one	Week two
Day one	Day two	Day one
I: Dactinomycin 0.5 mg intravenous bolus injection	I: Dactinomycin 0.5 mg intravenous bolus injection	I: Leurocristine 1.4 mg/m <sup>2</sup> intravenous bolus injection
II: Etopophos 100 mg/m <sup>2</sup> intravenous during half hour	II: Etopophos 100 mg/m <sup>2</sup> intravenous during half hour	II: cytophosphane 600 mg/m <sup>2</sup> intravenous during half hour
III: Amethopterin 300 mg/m <sup>2</sup> intravenous during 12 h	III: Oral leucovorin 15 mg for 12 h during 2 days and 24 h after the onset of amethopterin	

The rate of healing by means of these kind of regimen is reported to be about 90%.<sup>[7,54]</sup> The combination chemotherapy with etopophos, amethopterin, and dactinomycin alternating with vincristine and cytophosphane is more toxic and has short-term side effects such as reversible hair loss, bone marrow suppression, the painful inflammation of the mucous membranes, and the peripheral neuropathy disorder resulted from leurocristine. Moreover, the potential for a tiny second tumors is available mainly as a result of the etopophos agents.<sup>[50]</sup>

In this regard, the most frequent tumors are breast cancer, colorectal cancer (CRC), and acute myeloid leukaemia (AML) and their relative risks are 5.8, 4.6, and 17, respectively.<sup>[50]</sup> The normal menstrual cycle would be renovated about 5 months after accomplishing the treatment. It's while in older women this cycle may not come back since etopophos, amethopterin, and dactinomycin or vincristine and cytophosphane could hasten the menopause menopause by 3 years.<sup>[55]</sup> A comprehensive chemotherapy drug regimen such as amethopterin, etopophos, and dactinomycin is administered for proper management of patients with higher risks of GTN, which in about 70% of cases would be effective. On the other hand, any individual regimen effectiveness in the management of both low and high risk GTN diseases remains to be appointed.<sup>[56,57]</sup>

**Mediastinal Tumors Growth Management**

Residual brain damages after applying chemotherapy must either be removed through surgical therapy or should be remedied by advanced radiation treatment of gamma knife or/and stereotactic radiation therapy. This experimental approach points out the fact that the management of tumor recurrence within the brain would not be such easy and also chemotherapy may not easily interpenetrate to the central nervous system (CNS) in addition to other tissues. The comparison of recurrence risk in this patients with minimal residual disease (MRD) and without any kind of residual abnormalities demonstrated there is no need to invasive pulmonary resection among these patients.<sup>[58,59]</sup>

**Management of Resistant GTN Patients**

One of the main abnormal specifications of resistant GTN patients is the possibility of their treatment even after the failure of primary treatment. This objective could be achieved through a combination of chemotherapy and surgical therapy for removing resistant disease. In situations when the residual disease site could not be diagnosed via functional and anatomical imaging techniques, the surgical operation of hysterectomy would be considered in the primary step. However, when the application of surgical options is not possible, a weekly regimen of etopophos, amethopterin, and dactinomycin alternating with vincristine and cytophosphane could be applicable. In spite of its toxicity, it is an effective regimen with salvage rates even more than 80%.<sup>[60,61]</sup>

This regimen is the most appropriate one which has the higher salvage rate in comparison with the treatment

combination remedies of velban-platinum-etopophos and cisplatin-bleomycin-etopophos.<sup>[62]</sup> On the other hand, the application of paclitaxel among resistant GTN patients alone or in combination with cisplatin could be effective.<sup>[61]</sup> Moreover, it should be noted that, in spite of its effectiveness, the administering chemotherapy in higher dosage peripheral blood stem cell in these patients has not been assessed correctly. On the other hand, there are two case reports of assisted remission within patients who received remedies in higher dosage which include:<sup>[60,63]</sup>

- A:) treatment with the combination of cytophosphane, melphalan, and etopophos
- B:) treatment with the combination of etopophos, paraplatin, and ifosfamide (IFO).

### Further Investigations on hCG Hormone

The main impressive factor for achieving the most effective management of GTD is the measurement of the amount of beta-human chorionic gonadotropin in the blood among GTN patients. Among cancer patient's various beta-hCG forms could be created which are including nicked free-beta, beta-core, beta-carboxyl terminal fragment and free beta in addition with regular and hyperglycosylated hCG forms.<sup>[64]</sup> This issue is in conflict with pregnancy, where beta-hCG is fixed and during the initial 3 months of pregnancy is presented only as hyperglycosylated. As a result, the process of investigation of hCG applied in evaluation of cancer patients should be capable of detecting all hCG forms.<sup>[65]</sup>

The false positive error of examinations could be solved through the conducting urine hCG measurement. It's while the false negative error could not be overcoming easily. However, because it could stop the chemotherapy as fast as possible and also the potential of yielding higher recurrence rates, it considered to be an important issue.<sup>[64]</sup> A novel investigation of hyperglycosylated hCG have been reported for more accurate detection GTD malignant forms which need chemotherapy.<sup>[66]</sup> Based on these investigations, hyperglycosylated hCG contains an invasive phenotype within the choriocarcinoma and trophoblast cells.<sup>[67]</sup> It should be noted that more accurate investigations should be carried out for assessment of hyperglycosylated hCG values in GTD. However, two major notifications which should be pointed out are: the possibility of existence of cancers which do not yield hyperglycosylated hCG, and the fact that this investigation method could not be applied any more commercially.<sup>[29,68]</sup>

### Follow-up GTN Patients after Treatment

In situation when the hCG levels were not diagnosed correctly after three weekly sequential examinations and chemotherapy, quantitative hCG levels of the serum must be obtained during one year at monthly intervals mainly for GTN patient who are at stages I and III and also during two years at monthly intervals for GTN patients who are at stage IV, exactly before entering the pregnancy period.<sup>[69]</sup> Generally, during the first

year after conducting related therapy on GTN patients, the recurrence risk is at the range of 4% to 10%. However, accurate medical examinations must be carried out every 3 months during the time when hCG level is examined. Moreover, radiographic imaging techniques should be applied only in specific situation.<sup>[70]</sup>

The procedure of fertility control mainly during treatment and 1 or 2 years follow-up after conducting chemotherapy should be carried out mainly through administering combined oral contraceptive pills. In situation when, the level of hCG could not be detectable, the application of intrauterine contraceptive devices could have adverse side effects. On the other hand, due to the possibility of further GTD events within the potential following pregnancy, conducting ultrasonography scan of pelvic is recommended in later gestations after about 10 weeks for satisfying the development of normal fetal. Moreover, an examination of level of hCG hormone must be carried out 6 weeks after the time when all of future gestations completed.<sup>[71,72]</sup>

In situation when a patient has experienced a kind of molar pregnancy or GTN diseases before, with abnormal uterine bleeding or metastatic disease signs after a miscarriage or pregnancy, postabortal or postterm choriocarcinoma must be considered. Based on the previous studies, the application of drug combinations which contain etopophos could increase the risk of secondary malignances such as breast cancer, malignant melanoma, CRC, and the blood and bone marrow cancer.<sup>[73]</sup> This mainly could be happening due to the inappropriate drug combination dosage, which have adverse effects on the patients whose overall etopophos dosage exceeds 2 g. Improving the patient's and clinician's knowledge on these kind of happenings must be one the main parts of clinical health surveillance mainly in patients who are more sensitive.<sup>[74]</sup>

### GTN Psychosocial Sequels

The GTN expansion among women would cause considerable mood affective, sexual, and marital disorders as well as creating extra concerns around the possibility of future fertility issue.<sup>[75]</sup> Because GTN is could be induced from pregnancy mainly, anti-disease activities against the pregnancy loss and malignancy threat should be carried out at the same time. However, notable levels of anger, sexual problems, exhaustion, confusion, anxiety and concerns about future fertility would last over long periods of time.<sup>[76]</sup>

Moreover, patients who suffer from active and metastatic disease and relatively would face with acute psychosocial reactions must receive swift psychosocial interventions and evaluations. Immediately after the time when patients visit the related clinics, appropriate psychosocial counseling services should be delivered to the patients. However, the social and psychological stresses induced from persistent GTN would be existing for long periods of time even after treatment of patients.<sup>[75,76]</sup>

## Conclusion

The GTN prognoses after conducting therapeutic management are very vital, and most of the available knowledge in this regard has been achieved during the past half century mainly through considering natural and biological history of GTN malignant disorders. The survival rate among patients who suffer from low and high risk GTN disease is over than 95% and 80%, respectively. One of the main future challenges in this regard is the capability of optimizing strategies of treatment for those patients who are drug-resistant. The progression of anti-angiogenesis therapy and also molecular targeted cancer therapies would be capable of improving the therapeutic perspective among these patients.

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## Conflicts of interest

There are no conflicts of interest.

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