Gestational Trophoblastic Disease

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1 Introduction and Classification

Gestational trophoblastic disease (GTD) is a pregnancy-associated neoplastic condition [1]. It is uncommon but not a rare condition. The range of GTD includes hydatidiform mole, complete mole, partial mole, invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumours (ETT).

Persistent GTD refers to a condition that does not subside or become malignant after molar products evacuation and requires active treatment. All GTDs arise from extraembryonic structure tissue and are characterized by secretion of hCG.

Broadly GTD consists of a mixture of benign and malignant disorders and can be classified as follows.

Classification of GTD [2]:

1. Benign GTD—complete and partial hydatidiform mole.
2. Malignant GTD.
   (a) Non-metastatic—invasive mole and malignant choriocarcinoma.
   (b) Metastatic—malignant choriocarcinoma, placental site trophoblastic neoplasia (PSTT), and epithelioid trophoblastic tumours (ETT).In 2020 WHO has given a new classification of GTD [3]:

- *Tumour-Like Lesions*.
  - Exaggerated placental site reaction.
  - Placental site nodule and plaque.
- *Molar Pregnancies*.
  - Partial hydatidiform mole.
  - Complete hydatidiform mole.
  - Invasive and metastatic hydatidiform moles.
- *Gestational Trophoblastic Neoplasms*.
  - Epithelioid trophoblastic tumour (ETT).
  - Placental site trophoblastic tumour (PSTT).
  - Gestational choriocarcinoma.

Mixed trophoblastic tumour.GTD is one of the most curable gynaecologic malignancies because of the following reasons:

1. The proliferating trophoblast is extremely sensitive to certain chemotherapy drugs, such as methotrexate and actinomycin D.
2. The proliferation of various trophoblasts produces human chorionic gonadotropin (hCG). The concentration of hCG in urine or serum is directly related to the number of surviving tro-

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phoblasts. Therefore, hCG is a unique and sensitive marker for the treatment of GTD patients.

2 Epidemiology

The reported incidence of GTD in India is not consistent [4]. Some studies show significant differences in molar pregnancy rates worldwide [5]. The incidence in Indonesia, India, and Turkey is 12 per 1000 pregnancies. But in Japan and China it is 1–2 per 1000 pregnancies. In north America incidence is 0.5–1 per 1000 pregnancies. In Asia, the incidence of GTD is one in 250 pregnancies [6]. Although different studies showed different incidences across the world, but mostly the incidence is 1 in 1000 pregnancies [7].

Advanced maternal age more than 40 years and history of previous GTD are the most common risk factors [8]. The risk increases with the previous history of molar pregnancy. If a woman has been diagnosed with hydatidiform mole (HM) before, her risk of developing HM in a subsequent pregnancy is 1% and increases to 25% with more than one pregnancy with HM. The risk associated with maternal age is bimodal, and the risk increases for mothers under 20 and over 35 (especially mothers older than 45). More than 98% of women who fall pregnant after a molar conception will not develop another hydatidiform mole, and their pregnancies will not be at risk of other obstetric difficulties [9]. The association with the father's age is inconsistent. Numerous exposures for GTD have been studied, but no clear associations with smoking, drinking, diet, and oral contraceptives have been found [8].

3 Pathology

All GTDs arise from the placenta and it is a presentation of abnormal proliferation of villous and extravillous (interstitial) trophoblast counterparts.

3.1 Hydatidiform Mole (HM)

Hydatidiform mole is characterized by abnormal swelling and proliferation of placental cytotrophoblast and syncytiotrophoblast. There may be an abnormal foetus present or absent. A foetus is present in partial hydatidiform mole (PHM), and its absence denotes complete hydatidiform mole (CHM). Nonhydropic villi resemble 'cauliflower like' or 'club-shaped' vesicles, while complete hydatidiform moles resemble 'bunch of grapes' vesicles [10] (Fig. 1).

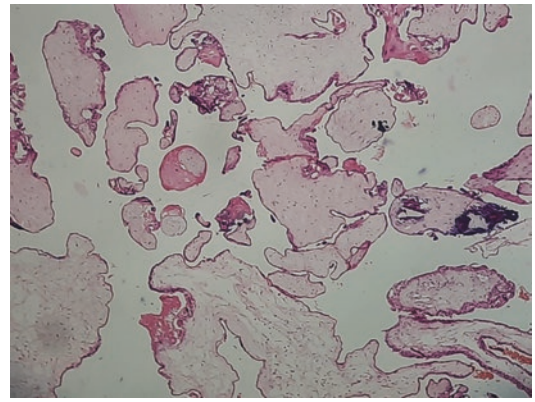

Fig. 1 Complete hydatidiform mole. (PC: Dr. Pakesh Baishya)

3.2 Invasive Moles (Chorioadenoma Destruens)

Invasive moles are malignant form of GTD, and they are defined when CHM infiltrates the myometrium and is associated with a continuous increase in human chorionic gonadotropin (hCG) after molar removal. Rarely PHM may also become an invasive mole. It can be distinguished from gestational choriocarcinoma by the presence of chorionic villi.

3.3 Placental Site Trophoblastic Tumour (PSTT)/Epithelioid Trophoblastic Tumour (ETT)

Trophoblastic tumours originate from the implantation site of the placenta. It is characterized by a simple infiltrating nest and sheets of the mesenchymal trophoblast cell layer. It is associated with less vascular invasion, haemorrhage, necrosis, and lower levels of hCG. Compared with

choriocarcinoma, PSTT usually affects lymph nodes. On IHC it is positive for human placental lactogen.

A variant of PSTT is ETT, with similar clinical behaviour with a characteristic transparent hyaline-like matrix.

3.4 Choriocarcinoma

It is a malignant tumour that produces hCG. It may be gestational or non-gestation-related [11].

Choriocarcinomas are characterized by myometrial infiltration, specific trophoblastic proliferation and underdevelopment, unformed villi with haemorrhage and central necrosis (Fig. 2). Approximately 25% of cases occurs after miscarriages or ectopic pregnancies. Another 25% is related to the delivery term and preterm, and the remaining 50% are from HM. However, it is estimated that only 2–3% of HM will develop into CC.

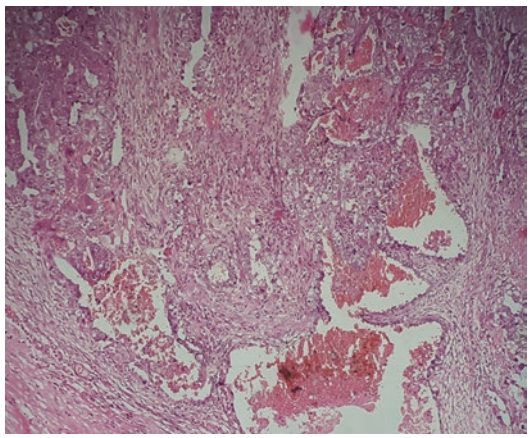

Fig. 2 Choriocarcinoma. (PC: Dr. Pakesh Baishya)

4 Molecular Biology

The chromosome composition of a complete mole is 46, XX. Both X chromosomes are paternal (double androgenic origin) [12].

The androgenic origin has been found to be the result of haploid paternal X sperm (23, X) replication and invasion of 'empty eggs' lacking functional maternal DNA which is shown in Fig. 3. However, the sperm mechanism (two haploid sperm passing through an 'empty egg cell') is also possible and may be the cause of 46, XX or 46, XY of paternal origin [13] (Fig. 4). Intact moles with single sperm are called 'homozygous' and the dispermic as 'heterozygous'. Complete and partial hydatidiform differ in pathogenesis and histologically which is shown in Table 1.

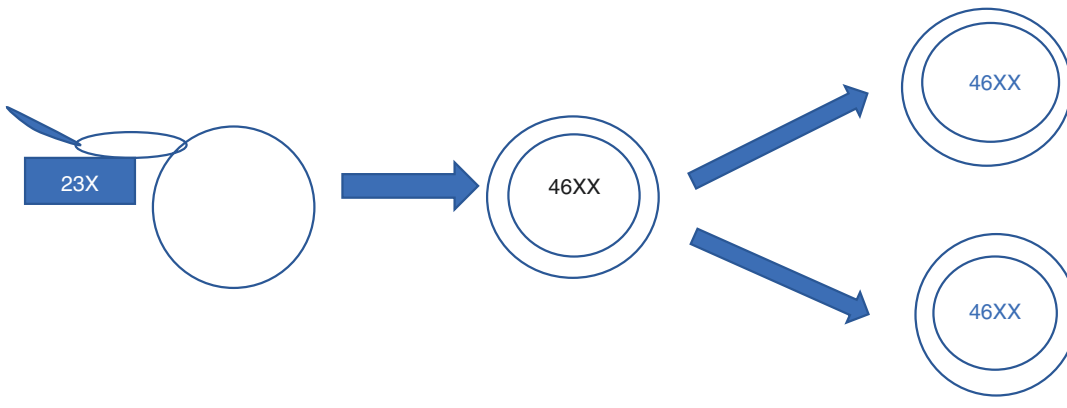

Fig. 3 Pathogenesis of complete mole by duplication of paternal chromosomal duplication after fertilizing inactivated gene containing ovum

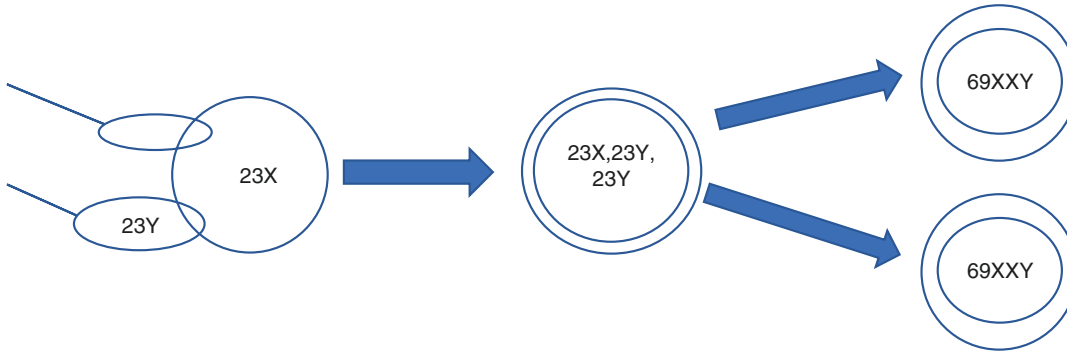

Fig. 4 Pathogenesis of partial mole by fertilization of normal ovum by two sperms either 23X or 23Y

Table 1 Differences between complete and partial mole

Features	Complete mole	Partial mole
Pathogenesis	Paternal origin	Have genetic material from both paternal and maternal side
Karyotype	46XX/46XY	69XXX/69XXY/69XYY
Embryonic material	Absent	Present
Trophoblastic proliferation	Diffuse	Focal
Villous scalloping	Absent	Present

5 Diagnosis

Symptoms and signs:

1. History of amenorrhea followed by vaginal bleeding is the most common presenting symptom in GTD.
2. Uterine size is usually more than gestational age. The molar tissues may separate from decidua and disrupt the maternal blood vessels, and collected blood distends the uterine cavity. This blood may undergo oxidation and liquefication, causing 'prune juice' like discharge per vaginum.
3. Patients may also present with hyperemesis gravidarum and toxaemia early in pregnancy.
4. Patients may also have complaints related to hyperthyroidism, e.g. tachycardia, weight loss, irritability, and tremor. Diagnosing and treating hyperthyroidism with a beta-adrenergic blocker is essential to prevent thyroid storm, which may occur during molar evacuation.
5. Respiratory distress—this may occur due to trophoblastic pulmonary embolization and patients may present with chest pain, dyspnoea, tachypnoea, tachycardia, and severe respiratory distress. These symptoms usually resolve 72 h after evacuation and proper supportive measure.
6. Theca lutein cyst >6 cm in diameter occurs due to excessive ovarian stimulation by β-hCG.
7. Persistence of lochia longer than usual.

5.1 Measurement of Serum hCG

hCG is a glycoprotein and has two non-covalently bound subunits, alpha and beta.

hCG has many forms: (1) intact heterodimeric hCG (hCG), (2) nicked hCG (hCG), (3) free beta subunit of hCG, (4) nicked free beta subunit of hCG (hCGbn), (5) hCG beta subunit core fragment (hCGbcf), (6) hyperglycosylated hCG (hCGH), and (7) sulphated hCG. Non-trophoblastic malignancies produce solely the free hCG subunit, which is a monomeric glycosylated version of hCG released by trophoblast neoplasms. In a variety of ways, GTD can create hCG molecules [14].

GTD patients are primarily monitored using assays that measure both hCG and β-hCG. The

use of independent hCG and β-hCG assays makes it easier to distinguish between benign and malignant trophoblastic disorders. Relapse is diagnosed when there is a rise of hCH level after it has become undetectable whereas resistant disease is diagnosed when hCG levels remain elevated in spite of treatment.

Treatment failure or drug resistance is said to develop when three consecutive serum hCG values fall by less than 10% over 2 weeks or by one log hCG level over 2 weeks, or two consecutive hCG values rise, or if new metastases arise [15–17].

The phrase 'phantom hCG' is frequently misused to refer to any situation in which hCG is found in a non-pregnant person. The term implies the occurrence of a false positive hCG immunoassay caused by the presence of cross-reactive antibodies. Even when no actual hCG or trophoblastic tissue is present, patients with phantom hCG sometimes have a persistent mildly positive quantitative hCG test result. The most common cross-reactive substances that lead to 'ghost hCG' are heterophile antibodies. A negative urine hCG result at the same time as a positive serum hCG result from the same patient would be the most sensitive differentiating method to detect the condition.

5.2 FIGO criteria for diagnosing GTN after molar pregnancy are [18]:

1. hCG values of four or more that plateaued for at least 3 weeks (days 1, 7, 14, and 21),
2. hCG values that increased at least by 10% in 3 or more occasions over 2 weeks (days 1, 7, and 14),
3. Detection of features of choriocarcinoma histologically.

6 Role of Imaging

Diagnosis of GTN after molar pregnancy is done by measuring hCG titres and by use of FIGO diagnostic criteria [18]. Radiological imaging is used to assess the local extent of disease and monitor the patient's overall health. Imaging is also essential for detecting and treating problems, including uterine and pulmonary arteriovenous fistulas.

Ultrasonography: On ultrasonography complete hydatidiform mole has a 'snowstorm' appearance due to heterogeneous echogenic mass with several hypoechoic foci seen (Fig. 5). Theca lutein cyst may also be seen. The USG finding in invasive mole and choriocarcinoma is shown below (Figs. 6 and 7).

In the case of partial mole, USG findings are:

1. An empty gestational sac or one with amorphous echoes representing foetal parts.
2. Foetal demise, anomalies, or growth restriction.
3. Oligohydramnios.
4. An enlarged placenta size with 'Swiss cheese' appearance.

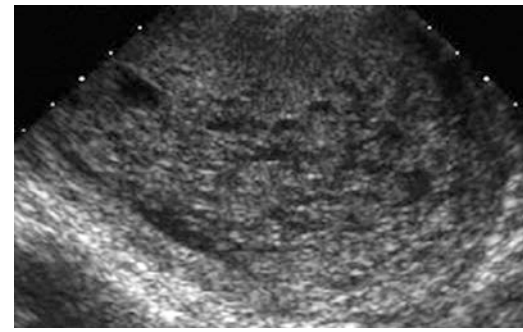

Fig. 5 USG finding of choriocarcinoma. (PC: Dr. Pavel Barmon)

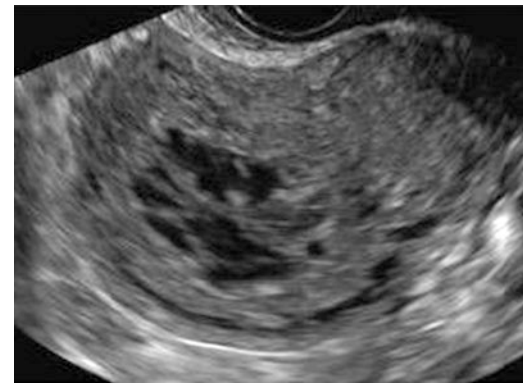

Fig. 6 TVS image of invasive mole. (PC: Dr. Pavel Barmon)

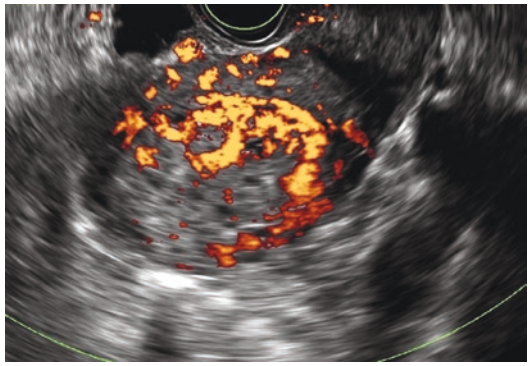

Fig. 7 Sagittal TVS image of increased vascularity in myometrium in a case of choriocarcinoma. (PC: Dr. Pavel Barmon)

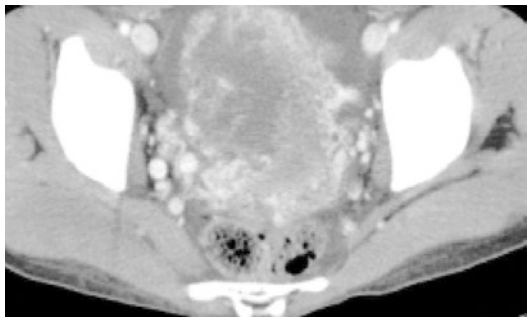

Fig. 8 Axial CT image of invasive choriocarcinoma extended to parametrium. (PC: Dr. Pavel Barmon)

Because of the increased incidence of postmolar GTN in CHM (18–29%) compared to PHM (5%), distinguishing between PHM and CHM has prognostic importance [19].

Computed tomography—It has limited use except in staging of GTN (Figs. 8 and 9). For detecting pulmonary metastasis chest CT scan is more sensitive than a chest X-ray. CT scan abdomen can also be done for a metastatic lesion in abdomen.

MRI—In GTN incidence of brain metastasis ranges from 3.4 to 8.8% [20].

In the case of pulmonary metastasis, brain MRI is done to look for brain metastasis.

PET-CT- (PET)/CT—In PET scan the metastatic sites appear as sites of increased metabolic activity. Its role in GTD is not well established as it does not have any advantage in tumour staging compared with conventional imaging [21].

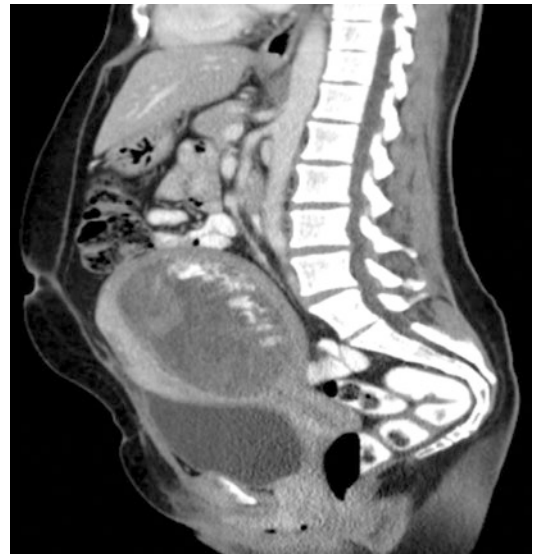

Fig. 9 Sagittal CT image of molar pregnancy. (PC: Dr. Pavel Barmon)

7 Metastasis in GTN

Four percent of patients after molar evacuation develop metastasis [22].

Metastasis is more common in GTN developing after non-molar pregnancy.

Pulmonary metastasis—At the presentation, 80% of patients of metastatic GTN present with lung metastasis. The usual presentation is cough, dyspnoea, chest pain, or haemoptysis. Typical radiological findings are alveolar snowstorm pattern, discrete rounded opacities, pleural effusion, or embolic pattern due to pulmonary artery occlusion.

Pulmonary artery hypertension may develop due to pulmonary artery occlusion.

Vaginal metastasis—It is seen in 30% of metastatic GTN. They are highly vascular and should not be biopsied. Sites are fornixes or suburethral area.

7.1 Hepatic Metastasis

Ten percent cases of metastatic GTN present with hepatic metastasis. Epigastric or right upper abdominal pain may be a presenting feature. They are friable and may rupture and cause bleeding.

7.2 Brain Metastasis

Ten percent of metastatic GTN present with brain and spinal cord metastasis. Almost all patients have pulmonary or vaginal metastasis. Neurological symptoms like nausea, vomiting, blurring of vision, and hemiparesis are presenting symptoms.

8 Staging and Risk Categorization

To date various scoring system for risk categorization has been developed for GTN [23–25].

In 1982 FIGO started staging based on spread into anatomical location. In 1983 a working group from WHO adopted 9 prognostic factors from Bagshawe's [23] scoring system. In 1992 the FIGO committee simplified 9 factors into 2. But in 2000 the FIGO committee changed the WHO score from 9 to 8 by removing the blood group, and they also changed the liver metastasis score from score 2 to 4.

In 2000 FIGO and WHO combined anatomic and WHO prognostic score for GTD staging which is described below [18]:

Stage I—When gestational trophoblastic tumours strictly confined to the uterus.
Stage II—Gestational trophoblastic tumours extending and involving adnexa or vagina but limited to the genital structures.
Stage III—Gestational trophoblastic tumours extending to the lungs, with or without genital tract involvement.
Stage IV—All other metastatic sites.

Before scoring a metastasis workup to be done as follows [18]:

1. Chest X-rays are appropriate for diagnosing lung metastases. It is used to count the number of metastases during the scoring of prognostic scoring.
2. Ultrasound/computed tomography scanning can be used for detecting liver metastasis.
3. MRI or CT scanning can be used for detection of brain metastasis.

8.1 Prognostic Scoring

Traditionally WHO divided GTN into low, medium, and high-risk groups, which was modified and divided into low-risk and high-risk group later on. Risk is defined as the risk of developing drug resistance and is determined by the WHO prognostic scoring system (Table 2).

Low-risk disease is diagnosed when score is less than or equal to 6 (≤6) and high-risk disease when score is more than 6 (>6).

While giving patient's diagnosis both staging and scoring are done and after denoting stage in Roman numerals score is given in Arabic numerals, which is separated by colon, i.e. stage I: 2, Stage III: 6.

9 Pretreatment Evaluation of GTN

1. Complete history taking is essential and it should include history of pregnancies, menstrual history including the last date of men-

Table 2 FIGO modified WHO prognostic scoring system [18]

	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 tumour size including uterus, cm	–	3–4	≥5	–
Site of metastases including uterus	Lung	Spleen, kidney	GIT	Brain, liver
Number of metastases identified	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single dose	Two or more drugs

struation, and use of oral contraceptive pills. If history of molar evacuation is present then date of evacuation, presence of bleeding, and any respiratory or central nervous system-related symptoms should be enquired.
2. Measurement of serum hCG levels.
3. Hepatic, renal thyroid function test.
4. Baseline peripheral WBC, CBC, and platelet counts.
5. Stool guaiac testing.
6. Chest X-ray pelvic USG—to confirm the absence of pregnancy, detect pelvic disease, retained products, and myometrial invasion.

Metastatic workup:

1. Chest CT, if chest X-ray is positive. If a chest X-ray is negative, it is not needed as micrometastasis does not affect the outcome.
2. USG/CT abdomen and pelvis.
3. MRI/CT brain.
4. CSF hCG level measurement.
5. Pathology review—histological confirmation of the diagnosis of GTN is not required for treatment. However, a biopsy of the metastatic site may be done if in doubt.

10 Treatment of Benign GTD

Suction and evacuation are the primary treatment of complete and partial moles.

Prophylactic Chemotherapy After Suction and Evacuation of Molar Pregnancy.

A Cochrane data review has done for prophylactic chemotherapy after suction and evacuation of molar pregnancy. They concluded that benefits from use of prophylactic chemotherapy is limited as all studies showing benefits either of low methodological values or has smaller sample size. In complete molar pregnancy where risk of malignant transformation to GTN is more, prophylactic chemotherapy may minimize the risk to progression. This method cannot currently be recommended because prophylactic chemotherapy may enhance medication resistance, delay GTN treatment, and expose women to hazardous adverse effects [26].

11 Treatment of Malignant GTN

Before starting treatment, proper workup and risk categorization of the disease is to be done. The primary management is chemotherapy which is different for low-risk and high-risk groups which are discussed below.

11.1 Low Risk

A simple evacuation of the uterus with judicious use of single-agent chemotherapy can cure low-risk GTN. Worldwide different chemotherapy regimen is followed, but the risk and benefits of each regimen are unclear.

Commonly Used Single Drug Regimens:

Methotrexate and actinomycin D are two drugs used commonly for single-drug regimens. The various regimens are shown in Table 3.

Alazzam et al. conducted a metaanalysis to analyse available data on the different treatment regimens of low-risk GTN and found six commonly used regimens. These were either single or combined regimens using methotrexate and dactinomycin. Methotrexate was used weekly, in a 5-day regimen, with folinic acid in an 8-day methotrexate-folinic acid regimen. Dactinomycin was used as in 'pulsed' dactinomycin, 5-day dactinomycin, and the combination therapy included use of both methotrexate and dactinomycin. They concluded that dactinomycin pulse therapy was superior to weekly methotrexate in terms of obtaining primary cure while posing a lower risk of toxicity [27, 28].

Another meta-analysis was performed to compare the regimen concluded that in low-risk GTN, Actinomycin D has a higher chance of achieving a primary cure rate with fewer chances of treatment failure than a methotrexate regimen. While comparing side effects between actinomycin D and methotrexate, there is no difference. But actinomycin D may have a higher

Table 3 Single-agent drug regimens

Regimen	Drug schedule	Response rate [27]
Methotrexate 5 day	MTX 0.4 mg/kg/day IV or IM for 5 days, not to exceed 25 mg/day Repeat cycle every 14 days	87–93%
Methotrexate 8-day alternate	MTX 1 mg/kg IM days 1, 3, 5, and 7 plus folinic acid 15 mg PO 30 h after each MTX dose on days 2, 4, 6, and 8 Repeat cycle every 14 days	74–90%
	MTX 100 mg/m^2 IVP, then 200 mg/m^2 in 500 mL D5W infused over 12 h on day 1 plus folinic acid 15 mg IM/PO q12h for 4 doses Initiate folinic acid 24 h after start of MTX Repeat cycle every 18 days or as needed	69–90%
Methotrexate weekly	MTX 30–50 mg/m^2 IM weekly	49–74
Actinomycin regimen 5-day act-D regimen	Act-D 10–13 μg/kg or 0.5-mg flat dose IV qd for 5 days Repeat cycle every 14 days	77–94
Actinomycin D pulsed	Actinomycin 1.25 mg/m^2 IV every 2 weeks	100

risk of severe adverse events than a methotrexate regimen [29].

Primary resistance develops in 10–30% of patients with low-risk GTN and is defined as either increase or plateau in two serial hCG values following single-agent treatment. hCG syndrome must be ruled out if hCG levels are low [30].

11.2 High-Risk Regimens

11.2.1 EMACO

EMACO chemotherapy, when used as primary treatment for metastatic high-risk GTN, has a remission rate of 72%, sustained remission rate of 80%, and survival rate of 86% [31, 32]. However, roughly 30–40% of women may develop resistance or recurrence following remission, necessitating salvage chemotherapy [33].

Day 1—Etoposide 100 mg/m^2 intravenous infusion over 30 min.

Actinomycin D 0.5 mg intravenous bolus.
Methotrexate 100 mg/m^2 intravenous bolus 200 mg/m^2 intravenous infusion over 12 h.

Day 2—Etoposide 100 mg/m^2 intravenous infusion over 30 min.

Actinomycin D 0.5 mg intravenous bolus.
Folinic acid rescue 15 mg intramuscularly or orally every 12 h for four doses (starting 24 h after beginning the methotrexate infusion).

Day 8—Vincristine 1 mg/m^2 intravenous bolus (maximum 2 mg).

Cyclophosphamide 600 mg/m^2 intravenous infusion over 30 min.

11.2.2 EMA-EP

Patients with high-risk GTN can achieve complete remission with the EMA/EP treatment in 88% of cases. In patients who have failed single-agent chemotherapy, EMA/EP is suggested as a first-line therapy. However, sufficient precautions should be taken to avoid and minimize EMA/EP haematological effects [32].

OTHER AGENTS are bleomycin, etoposide, cisplatin (BEP), Ifosfamide, carboplatin, etoposide (IEP), Etoposide, ifosfamide, cisplatin (VEP).

11.3 Ultra-High Risk

Patients having a FIGO score ≥12 are categorized as ultra-high-risk GTN. The 5-year overall survival (OS) of ultra-high-risk is around 67.9%. They have a poor prognosis compared to low-risk and high-risk GTN. Ultra-high-risk GTN following non-molar antecedent pregnancy, brain metastases, and previous multiagent chemotherapy failure needs more emphasis. Moreover, salvage surgery may improve the prognosis. Floxuridine-based multiagent chemotherapy is

an effective regimen whose toxicities are manageable for ultra-high-risk GTN patients [16].

When normal chemotherapy is started in a patient with a large tumour, it can result in abrupt tumour collapse, severe bleeding, metabolic acidosis, myelosuppression, septicaemia, and multiple organ failure, all of which can lead to death. For this reason, the initial gentle use of chemotherapy as induction is an option. In induction chemotherapy etoposide and cisplatin are used. Dose of etoposide is 100 mg/m^2 on day 1 and day 2. Dose of cisplatin is 20 mg/m^2 on days 1 and 2. This regimen is repeated weekly for 1–3 weeks, before starting standard chemotherapy. In one study induction chemotherapy has shown to eliminate early deaths and in other studies showed promising results [34].

EP (etoposide and platinum)/EMA or another more intensive chemotherapy regimen than EMACO may provide a better response and outcome for patients with liver metastases, with or without brain metastases, or having a very high-risk score. A lengthier consolidation with four cycles of chemotherapy might be considered for such high-risk individuals [35].

Other salvage regimen are [18]:

- Etoposide, cisplatin, etoposide, methotrexate, and actinomycin D (EP-EMA).
- Paclitaxel, cisplatin/paclitaxel, etoposide (TP/TE).
- Methotrexate, bleomycin, etoposide (MBE).
- Etoposide, ifosfamide, and cisplatin or carboplatin (VIP/ICE).
- Bleomycin, etoposide, cisplatin (BEP).
- 5-fluorouracil, actinomycin D (FA)
- Floxuridine, actinomycin D, etoposide, vincristine (FAEV).
- Use of high-dose chemotherapy in association with autologous bone marrow or stem cell transplant.
- Use of immunotherapeutic agents like pembrolizumab.

Managing brain metastasis:

1. IV Methotrexate as methotrexate infusion to 1 g/m^2.
2. Intrathecal methotrexate dose is 12.5 mg.
3. Both IV and intrathecal methotrexate can be given during EMA-CO and EMA-EP regimen. They are administered during CO or EP phase of regimen.
4. Radiotherapy: whole brain RT or stereotactic RT.
5. Decompression surgery may sometimes be lifesaving when intracranial pressure is raised due to intracranial bleed.

12 Role of Surgery

1. Dilatation and evacuation is the mainstay of the evacuation of molar pregnancy in a patient desiring fertility. However, hysterectomy is another option for patients non-desirous of future fertility.

Hysterectomy may be used as primary treatment of unevacuated mole and management of GTD [36]. Hysterectomy reduces the number of cycles of chemotherapy needed in low-risk non-metastatic GTN patients [37]. However, acute blood loss is more than suction and evacuation.

Induction of labour and abdominal hysterotomy are rarely employed for the primary evacuation of hydatidiform moles due to higher morbidity and a high incidence of post-molar GTN [38].

In PSTT with non-metastatic disease, hysterectomy is curative in two-thirds of patients [39].

After a hysterectomy, the total risk of post-molar GTD drops to about 3.5%, compared to the expected 20% after a suction D&C [36].

Surgical intervention may be needed to control intractable bleeding or for stabilization of the patient for receiving chemotherapy in localized chemo-resistant disease. Secondary hysterectomy is indicated in localized drug-resistant cases.

Hysterectomy is also an indication for intractable bleeding p/v.

Theca lutein cyst—They may require several months to resolve. Surgical intervention is needed only in 3% of cases when there is torsion or rupture [40].

Other Surgeries- Thoracotomy is indicated when resistant pulmonary metastases are present. A craniotomy is indiacted for intracranial haemorrhagic and persistent drug-resistant metastasis.

13 Role of Radiotherapy

It has a limited role in the management of GTD. Brain RT and liver RT can be given to prevent haemorrhagic complications to this organ, 2000–4000 cGy in 10–20 equal fractions. Whole-brain radiation is given concurrently with combination chemotherapy, with reduced-field boosts given in selected patients.

The concurrent Chemotherapy-radiation therapy (CTRT) act as tumouricidal and haemostatic [41].

14 PSTT

PSTTs are a relatively rare GTD. They arise from the intermediate trophoblastic cell layer. Molecularly this tumour occurs due to alteration in intracellular signalling pathways, intercellular information transmission, and extracellular matrix. It is found that ERK, MAPK, mTOR signalling pathway, transcription factor NF-kB, Kiss-1, and GATA3 may play critical roles in the invasion and metastasis of PSTT [42].

PSTT is a disorder that affects women of childbearing age, who are on average 32 years old. PSTT can occur as a consequence of a full-term pregnancy, a premature birth, a hydatidiform mole, or choriocarcinoma. Duration of development from previous pregnancy may range from several months to several years.

But the most common time of occurrence is 1 year after the previous pregnancy. The main symptoms of PSTT include vaginal bleeding and amenorrhea. PSTT has an unusual clinical picture, which makes diagnosis difficult. After an interval of amenorrhea, patients frequently report with irregular vaginal bleeding or menorrhagia, as well as an enlarged uterus. Blood β-hCG usually normal or may be slightly increased and are not proportional to the tumour burden. This is in contrast to many GTDs, which contain a high level of β-hCG. Other forms of GTDs with low serum β-hCG levels, on the other hand, have been reported. Ultrasound findings are frequently unspecific. A mix of histology and IHC examinations is required for a clear diagnosis. Histologically PSTT is constituted of intermediate trophoblasts; cytotrophoblasts or chorionic villi are absent. The tumour cells show hPL strong positivity with weak positivity for hCG [43].

β-hCG is usually not raised in these tumours, and metastasis is usually late, but when metastasis occurs, the lung and brain are the commonest sites.

PSTT does not have a prognostic index score like GzTN.

The different poor prognosis factors of PSTT are:

The interval between antecedent pregnancy >2 years, deep infiltration, necrosis, mitotic index >5/10 under a microscope.

Patients with high risk are recommended to use multi-drug combined chemotherapy.

Patients in stage I can be treated with a straightforward hysterectomy, which can include or exclude pelvic nodal biopsy.

Hysterectomy with adjuvant chemotherapy is an ideal approach for FIGO stage II-IV patients [44].

If fertility preservation is necessary, conservative treatments such as uterine curettage, hysteroscopic resection, and chemotherapy may be considered, especially in a limited local lesion [45].

15 ETT

It is an unusual trophoblastic tumour. Usually, they are reported in the age group of 15–48 years. Abnormal vaginal bleeding is the most common presenting symptom.

The tumour often comprises a population of mononuclear cells that form nests and solid masses that mimic cells of the intermediate trophoblast of chorionic leaf. ETTs are well-demarcated, with a surrounding lymphocytic infiltrate. The tumour may also have typical

extensive necrosis that creates a geographic pattern. This pattern is sometimes accompanied by dystrophic calcification [46].

The tumours are IHC positive for cytokeratin, epithelial membrane antigen, and inhibin. P63 is positive in the majority of ETTs and can be especially helpful when the differential diagnosis includes a placental trophoblastic tumour [47]. p63 expression is useful in the distinction of epithelioid trophoblastic and placental site trophoblastic tumours by profiling trophoblastic subpopulations [47].

hCG levels are usually raised.

ETTs do not respond to chemotherapy drugs used to treat other types of GTD.

Any GTD not responding to chemotherapy ETT must be ruled out first.

Hysterectomy is the treatment of choice. ETT is more aggressive in nature than PSTT.

16 Follow-Up

The normal follow-up routine for low-risk and high-risk GTN is as follows:

1. Molar pregnancy—after surgical treatment β-hCG is monitored weekly until 3 consecutive values are normal and then monthly for 6 months.
2. In GTN—during treatment β-hCG is monitored until 3 consecutive weekly values are normal. After that low-risk GTNs are followed with monthly β-hCG monitoring for 12 months, then 6 monthly for 1 year, and annually till 5 years.

   High-risk GTNs are followed with monthly β-hCG levels for 18 months, then 6 monthly for 2 years, and then annually till 5 years.

In case of complete molar pregnancy, if hCG level is normalized in 56 days of the pregnancy event, follow-up is indicated for 6 months from the date of suction and evacuation. But if β-hCG has failed to normalize within 56 days then follow-up is done for 6 months after the date of normalization of values.

Follow-up for partial molar pregnancy is till the hCG becomes normal on two samples, taken 4 weeks apart.

There is still a lack of consensus in the literature on how to follow up on PSST/ETT patients. PSTT/ETT patients should be observed for at least 5 years since they produce little hCG, grow slowly, and have late metastases [30].

17 Recurrent GTN

GTN is a highly chemo-sensitive tumour. But around 25% of tumours are resistant, relapse, or recur after initial treatment. As per FIGO 2020, re-staging is done for relapse, and a complete reassessment of spread and previous chemotherapy response is used [18].

Second-line chemotherapy, with or without surgery, can be used to achieve remission after first-line treatment fails in low-risk GTN. Several secondary treatment regimens have been described, with varying success rates and toxicity profiles, including single-agent pulsed dactinomycin (where methotrexate has been used as first-line therapy); five-day dactinomycin etoposide and dactinomycin (EA); methotrexate, dactinomycin, and cyclophosphamide (MAC); and etoposide, methotrexate, and dactinomycin [48].

The most often utilized first-line therapy for high-risk GTN is EMA/CO, with platinum-etoposide combinations, particularly EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin), being preferred as salvage therapy. This resulted in a response rate of 75–80%. EMA/EP regimen is associated with significant hepatotoxicity and myelosuppression. According to some research, TE/TP (paclitaxel and etoposide alternated twice weekly with paclitaxel and cisplatin) is as effective as EMA-EP while being less hazardous [49].

Alternatives include BEP (bleomycin, etoposide, cisplatin), FAEV (floxuridine, dactinomycin, etoposide, vincristine), and FA (5-fluorouracil, dactinomycin).

However, it is unclear whether fluorouracil (5-FU), dactinomycin is as effective as EMA/EP and has fewer side effects [48].

Other regimens that can be used are MEA (methotrexate, etoposide, dactinomycin), MAC or methotrexate, dactinomycin, chlorambucil, FA (5-FU, dactinomycin) or FAV (5-FU, dactinomycin, vincristine), MEF (methotrexate, etoposide, 5-FU), EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin) whereby EMA and EP are alternated weekly, and CHAMOCA (methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, vincristine).

The identification of isolated active disease areas susceptible to surgical excision benefits these individuals. Secondary hysterectomy and metastasectomy (pulmonary resection, craniotomy, and liver lobe resection) are important in chemo-resistant cases [50].

18 Contraception and Fertility Preservation

Patients are counselled not to conceive until all of their follow-up appointments have been completed. Contraception is correlated to hCG monitoring throughout follow-up, not to the chance of recurrence. For mole, oral contraceptive is recommended for 6 months. In low-risk cases advise is given to avoid pregnancy for 12 months, and in high-risk cases pregnancy is advised to be avoided for 18 months. The intrauterine device is not recommended, because of fear of perforating the uterus and irregular bleeding [51].

Oestrogen containing pills can be started after β-HCG becomes normal.

19 Subsequent Pregnancy

Women who had GTD or had a history of previously treated GTN usually have no problem with fertility. Around 83% of patients become pregnant after treatment with methotrexate or EMACO regimen [51]. Familial gestational trophoblastic disease has been seen to run in families and is due to genetic mutation at 19q13.4. Coexistent molar pregnancy with live foetus is a rare condition but caries risk to foetus and hence managed judiciously at high-risk centres.

But they have a risk of developing a GTD in a future pregnancy. The following are recommended for such cases:

1. Sonographic evaluation is recommended in early pregnancy.
2. At delivery, the placenta or products of conception are to be sent for pathological evaluation.
3. Serum β-hCG measurement at 6 weeks postpartum.

20 Secondary Malignancies

There is an increased risk of secondary malignancies like leukaemia, colon cancer, melanoma, and breast cancer.

This increased risk is attributed to etoposide use.

But a study done at Charing Cross Hospital in 2006 for cases from 1958 to 2000 concluded that following chemotherapy either MTX-FA or EMA-CO, the cancer risks for patients who were cured of gestational trophoblastic tumours with current chemotherapy appear to be similar to those of the general population, with no overall increased risk of malignancy. However, based on small patient numbers, there was evidence of an elevated risk of leukaemia after EMA-CO and some indication of other site-specific higher risks. Except for MTX-FA, all effective therapies raised the likelihood of early menopause [52].

21 Conclusion

GTNs are a group of the curable malignancies. In India actual incidences are not known. So multicentred studies are required in India to determine the true incidence and overall outcome of gestational trophoblastic diseases that will help in understanding the burden of disease and to produce the optimal outcome.

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