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GESTATIONAL TROPHOBLASTIC DISEASE AND NEOPLASIA: DILEMMA AND UPDATES!

Yashpal Verma

Medical Officer, Civil Hospital, Sonapat (INDIA)

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Corresponding author:

Dr. Yashpal Verma
Medical Officer,
Civil Hospital,
Sonapat (INDIA).
Email:

yashpverma@gmail.com

Abstract: Gestational trophoblastic diseases include hydatidiform moles and gestational trophoblastic neoplasia i.e. invasive mole, choriocarcinoma, placental site trophoblastic tumor and epitheloid trophoblastic tumor. Incidence from India has been reported up to 2.4/ 1000 pregnancies, 2.5/ 1000 deliveries and 2.6/ 1000 live births. The standard protocols for management exist and are evolving fast. Though all gestational trophoblastic diseases are not malignant, still these need to be managed intensively, because of their potentially life threatening complications and common occurrence in fertility age group females. The better aspect is that; if timely and standard interventions are made; these are highly curable conditions, even with preservation of reproductive function.

INTRODUCTION

Gestational trophoblastic diseases (GTDs) are conditions which arise as a result of abnormal fertilization and include six known to date clinico-pathological entities namely- complete hydatidiform mole (CHM), partial hydatidiform mole (PHM), invasive mole (IM) or chorioadenoma destruens, choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epitheloid trophoblastic tumor (ETT). These tumors are known for their potential life threatening nature in reproductive age group females. Incidence from India has been reported

up to 2.4/ 1000 pregnancies, 2.5/ 1000 deliveries and 2.6/ 1000 live births.^{1,2}

Gestational trophoblastic neoplasia (GTN) is the term used for malignant GTD's which include- invasive mole, choriocarcinoma, placental site trophoblastic tumor and epitheloid trophoblastic tumor. GTN may arise from pregnancy (normal/ ectopic/ molar) or may follow abortion (spontaneous/ induced). Most common antecedent event is molar pregnancy. Approximately 60% GTN follow molar pregnancy, 30% follow abortion (spontaneous/ induced) and 10% follow term pregnancy

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(normal/ ectopic). Overall estimated incidence of GTN is 1/40000 pregnancies.³

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CHMs are androgenic and diploid, with chromosomal pattern of 46XX or 46XY. **PHMs** have both paternal and maternal chromosomes and are triploid, with chromosomal pattern of XXY.

Myometrial wall is invaded in **IM** and may even lead to uterine rupture or intra-peritoneal hemorrhage. **IM** develops in approximately 15% patients of **CHM** and 5% patients of **PHM**.^{4,5}

CCA contains anaplastic trophoblastic tissue made up of cytotrophoblasts and syncytiotrophoblasts without villi. Approximately 50% cases of **CCA** follow molar pregnancy (though only 2-3% of hydatidiform moles progress to **CCA**), 25% follow ectopic pregnancy or spontaneous abortion and 25% follow a term delivery.⁶ **CCA** metastasize hematogenously, involving lungs in over 80% cases and vagina in about 30% cases. Distant metastasis constitutes high risk of death and is commonly seen in post-partum patients, where early diagnosis is frequently delayed.⁷

PSTT derives from intermediate trophoblastic cells and is seen commonly after non-molar abortion or term pregnancy but can also occur after a mole. **PSTT** is associated with less vascular invasion, necrosis, and hemorrhage than choriocarcinoma, and it has a propensity for lymphatic metastasis. Immunohistochemical staining reveals diffuse presence of cytokeratin (CK) and human placental lactogen (hPL), whereas hCG (human chorionic gonadotropin) is only focal. Contrary to **CCAs**, which secrete mainly hCG, **PSTTs** are known to secrete more placental lactogen (hPL) and free β -hCG.⁸

ETT is composed of intermediate trophoblasts and presents as solid-cystic, hemorrhagic discrete lesion/s; though coexistence of **ETT** with **PSTT** or **CCA** is known

also to occur. Positive p63 immuno-staining differentiates it from **PSTT**.⁹ Uterus is the primary site in 40% cases followed by cervix in 31% of cases. Lung is the most common extrauterine site, observed in about 19% of cases.¹⁰

RISK FACTORS

History of spontaneous abortion has been observed to bear two to three fold higher risk of molar pregnancy. Previous history of molar pregnancies is most important risk factor for development of **GTN**.^{3,5}

Sand et al. in an epidemiological study observed that the incidence of repeat **GTD** was 1.33 per cent. After a second trophoblastic disease episode, the risk for a subsequent event rose to 28 per cent.¹¹

Berkowitz et al observed that after having one molar pregnancy, the risk of molar pregnancy in a later conception was about 1per cent. The incidence of a molar gestation after two molar pregnancies was around 23.1per cent.¹²

Age is another important factor related to risk for development of **GTDs**. The risk of complete mole is 1.9 times higher for women both >35 years and <21 years, compared to women aged 21-35 years. Risk of partial mole, invasive mole and choriocarcinoma increases with advancing age. Women with long-term oral contraceptive use and blood group A also seem to be at increased risk of choriocarcinoma.^{5,13}

DIAGNOSIS

Though all **GTDs** are not malignant, still these need to be managed intensively, because of their potentially life threatening complications. The better aspect is that; if timely and standard interventions are made; these are highly curable conditions, even with preservation of reproductive function.

The cut-off line between benign **GTD** and **GTN** must be kept in mind and both the terms should not be considered synonymous.

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Ultrasound (USG) and serum or urinary hCG has made early detection of most GTDs feasible and easy.

Role of hCG

Serial estimation of hCG in serum or urine is essential for diagnosis, monitoring of treatment and follow up. Beta subunit (β -hCG) of this glycoprotein is hormone specific. hCG levels become undetectable within 3-6 weeks after normal delivery or non-molar miscarriage and 8-10 weeks after evacuation of molar pregnancy. Persistence or rise after this period should therefore indicate residual or metastatic disease. During treatment, the level of hCG guides for continuation or switch of chemotherapy agent/s. Follow up rising levels indicate relapse. Hyperglycosylated form of hCG (hCG-h) is now considered as more specific marker of malignant GTD and its concentration corresponds to probability of good response to chemotherapy.^{14,15}

Rarely, in peri-menopausal women, false positive results are observed with serum hCG. The patient may be mis-diagnosed or may not have anticipated response to treatment. Urine levels of hCG in such situations are more guiding and rule out *Phantom* serum hCG.¹⁶

MANAGEMENT OF BENIGN GTD

Evacuation is the standard procedure; mode of evacuation may be a choice. Tidy et al, in a study conducted to assess whether there was a change in the mode of evacuation of GTD over two time periods and to assess whether mode of evacuation influenced the subsequent need for chemotherapy, concluded that suction curettage was a safe method of uterine evacuation in GTD. Medical methods of uterine evacuation were associated with higher rates of need of chemotherapy. This was probably due to a higher rate of incomplete evacuation. Medical methods of evacuation should not be used in cases of complete hydatidiform mole.¹⁷

Repeat, but meticulous, evacuation may be carried out in case symptoms exist and ultrasound shows evidence of retained tissue/incomplete evacuation. Hysterectomy may be offered to patients who do not wish to preserve fertility, are aged more than 40 years & having completed family, present with massive life threatening hemorrhage and/or have severe sepsis. Though, hysterectomy eliminates the risk of local invasion, it does not ensure against possibility of metastasis.¹⁸

Since, myometrium is usually not obtained at suction/evacuation or curettage and hysterectomy is not the preferred surgery in patients with GTD, the diagnosis is less often made by histology. Most often, it is diagnosed clinically based on persistent or elevation of hCG after molar evacuation and is frequently treated with chemotherapy even without a histopathologic diagnosis.^{19,20}

Prophylactic Chemotherapy

The use of prophylactic chemotherapy at the time of molar evacuation is controversial. Kashimura et al evaluated the effectiveness of prophylactic chemotherapy in 420 patients with molar pregnancy. All patients were followed up for 5 to 15 years after evacuation. Results showed that 7.5% patients with prophylactic chemotherapy compared to 18.1% patients without prophylactic chemotherapy developed secondary trophoblastic disease. It was concluded that prophylactic chemotherapy could reduce the occurrence of secondary trophoblastic disease. However, prophylactic chemotherapy did not eliminate the occurrence of choriocarcinoma. The complication/s of prophylactic chemotherapy was observed in 27.3% of the patients.²¹

Prophylactic administration of either Methotrexate or Actinomycin D at the time of or immediately after evacuation of a hydatidiform mole is associated with a reduction in incidence

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of post-molar GTN from approximately 15-20%
down to 3-8%. It should be limited, however, to
special situations in which the risk of post-molar
GTN is much greater than normal or where
adequate hCG follow-up is not possible²²

Prophylactic chemotherapy may reduce
the risk of progression to GTN in women with
CMs who are at a high risk of malignant
transformation; however, current evidence in
favor of prophylactic chemotherapy is limited by
the poor methodological quality and small size of
the included studies. As prophylactic
chemotherapy may increase drug resistance,
delay treatment of GTN and expose women
unnecessarily to toxic side effects, this practice
cannot currently be uniformly recommended.²³

Follow-up

Follow up after evacuation of a
hydatidiform mole is essential to detect
trophoblastic sequelae (invasive mole or
choriocarcinoma), which develop in
approximately 15-20% with complete mole and
1-5% with partial mole. Clinical findings of
prompt uterine involution, ovarian cyst
regression, and cessation of bleeding are all
reassuring signs. However, definitive follow-up
requires serial serum quantitative hCG
measurements every 1-2 weeks until 3
consecutive tests show normal levels, after which
hCG levels should be determined at monthly
interval for 6 months after the spontaneous return
to normal.⁵

Lurain et al published an epidemiological
study of 738 patients with hydatidiform mole
referred for follow-up and hCG testing after
evacuation. There was spontaneous regression of
trophoblastic disease in 596 (80.8%) patients. Of
these 596 patients, regression occurred in 11
(1.8%) by day 10 after evacuation, in 124
(20.8%) between days 11 to 30, in 255 (42.8%)
between days 31 to 60, and in 206 (34.6%)
between days 61 to 170. Treatment with

chemotherapeutic agents was required in the
remaining 142 (19.2%) patients; 125 (16.9%) of
these had invasive mole (107 non-metastatic and
18 metastatic) and 17 (2.3%) had
choriocarcinoma (13 non-metastatic and 04
metastatic).²⁴

Goto et al investigated the clinical
characteristics of 349 patients with molar
pregnancy, who developed invasive mole. The
comparison revealed that the incidence of
development of invasive mole after partial molar
pregnancy was significantly lower than that for
the development of invasive mole following
complete molar pregnancy (2.87% versus
12.34%; $p < 0.01$). The interval from molar
delivery to the diagnosis of invasive mole was
under 9 weeks for the patients with partial mole
and was significantly shorter than that for the
patients with complete mole, up to 18 weeks
(Mean 4.9 weeks versus 8.12 weeks; $p < 0.01$).²⁵

MANAGEMENT OF MALIGNANT GTD (GTN) DIAGNOSIS

International Federation of Gynecologists
and Obstetricians (FIGO) has established
guidelines for diagnosis of GTN.

In molar pregnancy, after evacuation:

(1) A plateau in β -hCG of four values \pm 10%
over 3 weeks, (2) A 10% or greater rise in β -hCG
for three or more values over at least two weeks,
(3) Persistence of β -hCG levels for more than six
months after molar evacuation, or (4)
Histological evidence of choriocarcinoma.²⁶

In non-molar pregnancy, β -hCG levels
are not routinely done. Patients following ectopic
pregnancy, past history of molar pregnancy or
suspicious symptoms (like abnormal bleeding,
altered sensorium or breathlessness etc) should
be evaluated to rule out CCA, unless proven
otherwise. Metastases are found in lungs (80%),
vagina (30%), pelvis (20%), brain (10%), liver
(10%) and other sites (<5%).¹⁸

Other than β -hCG levels; evaluation includes- general physical examination, vaginal per speculum examination, blood counts, liver and renal function tests, chest and brain imaging, sonography of abdomen and pelvis.

It is not necessary to obtain histopathologic confirmation of diagnosis, as the

tumor is highly vascular and may bleed profusely.

Staging and prognostic scoring of GTN

Staging of disease is done as per International Federation of Gynecologists and Obstetricians (FIGO) guidelines and World Health Organization (WHO) scoring system based on prognostic factors (Table 1)²

Table 1: FIGO Staging and WHO scoring system for Gestational Trophoblastic Neoplasm

Stage I	Disease confined to the uterus			
Stage II	Disease extends outside uterus, but limited to genital structures			
Stage III	Disease extends to lung/s, with or without genital tract involvement			
Stage IV	Metastasis to any other site/s			
Prognostic factor	Risk Score			
	0	1	2	4
<i>Age (years)</i>	< 40	≥ 40	-	-
<i>Antecedent pregnancy</i>	Mole	Abortion	Term	-
<i>Interval between end of antecedent pregnancy and start of chemotherapy (Months)</i>	< 4	≥ 4 but < 7	≥ 7 but < 13	≥ 13
<i>Pre-treatment serum hCG (mIU/mL)</i>	< 1000	1000 to < 10000	10000 to < 100000	≥ 100000
<i>Largest tumor (in cms) including uterine disease</i>	-	3 to < 5	≥ 5	-
<i>Site of metastases</i>	Lung	Spleen, Kidney	Gastrointestinal tract	Brain, Liver
<i>Number of metastases</i>	-	1-4	5-8	> 8
<i>Prior failed chemotherapy</i>	-	-	Single agent	Multi-agent
	<ul style="list-style-type: none"> • Risk score is numerical sum of all risk factor score. • Disease is described as 'Stage: Score'. For example- II:5 			

Prognostic scoring guides to opt for appropriate treatment protocol by finding risk of developing resistance to chemotherapy. Score of less than 7, bears low risk of resistance and is likely to achieve remission with single agent chemotherapy. Score of 7 or more indicates high risk of developing resistance to single agent chemotherapy and therefore is indication of treatment with multi-agent combination

chemotherapy. Stage IV disease is always high risk and CCA is always stage IV.

Uterine Artery Pulsatility Index (UAPI) ≤ 1 , suggestive of high vascularity, identifies women with GTN who are at increased risk of resistance to first-line single-agent Methotrexate (MTX-R). UAPI is shown to be an independent predictor of MTX-R in women with FIGO 5-6 GTN.²⁷

Treatment

As in most malignancies, best management is possible in a multidisciplinary setup. Chemotherapy is highly effective in most of the cases of GTN. Cure rates up to 100% in low risk and 80-90% in high risk cases have been reported.²⁸ Surgery and radiotherapy are used as adjunct.

Low risk disease

Single agent chemotherapy is recommended for treatment of disease with low risk of resistance. Methotrexate (MTX) and Actinomycin-D (ACTD) are the most preferred single agents.

MTX is usually used with Calcium Leucovorin/ Folinic Acid (FA) rescue to minimize its toxicity. Response is assessed by weekly serum hCG level, which should fall by 1

log (ten folds) within 18 days of completion of course. More than 70% patients respond to first course. Second course is given if serum hCG level- (a) doesn't fall by 1 log within 18 days, (b) plateaus for more than 3 weeks or (c) re-elevates.

ACTD is substituted, if patient shows evidence of altered liver function or resistance to MTX.

Cochrane Review in 2012, including 513 patients in five randomized controlled trials, showed that Actinomycin D appeared to be superior to Methotrexate (RR 0.64; 95% confidence interval, 0.54–0.76). Methotrexate was associated with significantly more treatment failure than Actinomycin D (RR 3.81; 95% CI, 1.64–8.86).²⁹ Few popular and convenient regimens are shown in Table 2.

Table 2. Single agent chemotherapy regimen for low risk gestational trophoblastic neoplasm

MTX	0.5 mg/kg (Max 25 mg), I/M or I/V daily for 5 consecutive days
MTX Folinic Acid	1 mg/kg, I/M or I/V on Day 1,3,5,7 0.1 mg/kg, P.O. on Day 2,4,6,8
ACTD	10 mcg/kg (Max 1000 mcg), I/V daily for 5 consecutive days
High dose MTX/ACTD alternate week	MTX- 100 mg/m ² , I/V loading followed by 200 mg/m ² I/V infusion over 12 hours, Day 1 Folinic Acid- 15 mg I/M or PO, 12 hourly Day 2 and 3 (4 doses) ACTD- 1.25 mg/m ² I/V

Role of surgery

Hysterectomy with ovarian preservation may be considered as primary treatment for the patient with stage I disease and having completed family.

Remission

When hCG level is undetectable for three consecutive weeks, it is designated as remission.

Follow up

Patient is followed up to one year with monthly hCG and contraceptive advice.

Resistance/ Relapse

Patients with any evidence of resistance or relapse at any stage should be treated like high risk disease, with multi-agent chemotherapy.

High risk disease

Multi-agent chemotherapy is indicated for the patients with high prognostic score (≥ 7) or following failure of single agent chemotherapy in low prognostic score patients.

EMA/CO is most popular regimen, using Etoposide, MTX, ACTD, Cyclophosphamide and Oncovorin (VCR) with reported cure rates up to 90%. EMA/EP (including Cisplatin) is another commonly used regimen. Chemotherapy cycle is repeated 2 to 3 weeks, toxicity permitting.^{30,31} Treatment is continued if patient responds, until hCG levels are undetectable (remission) and remain so following three weeks. Additional 2-3 courses

for consolidation are recommended. Popular multi-agent regimens are shown in Table 3.

Table 3. Multi-agent chemotherapy regimen for high risk gestational trophoblastic neoplasm

Regimen	Protocol
EMA/CO	<p>Day 1 Etoposide: 100 mg/m² I/V infusion Actinomycin-D: 0.5 mg I/V push Methotrexate: 100 mg/m² I/V loading f/b 200 mg/m² infusion over 12 hours</p> <p>Day 2 Etoposide: 100 mg/m² I/V infusion Actinomycin-D: 0.5 mg I/V push Folinic Acid: 15 mg PO or I/M 12 hourly, 4 doses</p> <p>Day 8 Cyclophosphamide: 600 mg/m² I/V infusion Oncovorin (VCR): 1.0 mg/m² I/V push</p>
EMA/EP	<p>Day 1 Etoposide: 100 mg/m² I/V infusion Actinomycin-D: 0.5 mg I/V push Methotrexate: 100 mg/m² I/V loading f/b 200 mg/m² infusion over 12 hours</p> <p>Day 2 Etoposide: 100 mg/m² I/V infusion Actinomycin-D: 0.5 mg I/V push Folinic Acid: 15 mg PO or I/M 12 hourly, 4 doses</p> <p>Day 8 Etoposide: 100 mg/m² I/V infusion Cisplatin: 60 mg/m² I/V infusion, with prehydration and under Mannitol dieresis</p>
<i>Cycle is repeated every 2-3 weeks, toxicity permitting</i>	

In patients with brain metastases, an increase in the Methotrexate infusion to 1000 mg/m² may help the drug cross the blood brain barrier and intra-theal Methotrexate 12.5 mg can be given at the time of CO when EMA-CO is used. Some centers prefer to give whole brain radiotherapy 3000 cGy in 200 cGy daily fractions, concurrent with chemotherapy or use stereotactic radiation to treat brain metastases.

For those with massive disease, starting with standard chemotherapy may cause severe marrow suppression leading to bleeding, septicemia, and even multiple organ failure. This may be avoided by starting with a lower dose and a less intensive regimen, such as Etoposide 100 mg/m² and Cisplatin 20 mg/m² on days 1 and 2, repeated weekly for 1-3 weeks, before starting the usual chemotherapy regimen.³²

Follow up

Patient is **followed up** to two year with monthly hCG and contraceptive advice. Risk of relapse is about 3% in the first year following treatment completion, after which risk declines steeply.

Role of surgery

Placental site trophoblastic tumors are relatively chemo-resistant and surgery is primarily indicated. Hysterectomy with lymph node sampling is done.

For other GTNs; irrespective of parity, hysterectomy is indicated in- (1) bulky intrauterine disease, (2) pelvic sepsis (3) heavy bleeding (4) non-responding, adherent, solitary tumor in pelvic/ abdominal organ or brain.

Hysterectomy followed by adjuvant chemotherapy may be considered in stage I patients having completed family.

Hysterectomy may be used as an adjunct to the primary management of selected patients with malignant GTD. Other extirpative procedures, such as thoracotomy, may be integrated into the management of drug-resistant disease.³³

Hepatic resection, craniotomy-decompression may at times be required.

Role of radiotherapy

Radiotherapy is considered for brain metastases, which pose life threat and for palliation of local disease, especially which is bleeding profusely.

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LONG TERM OUTCOMES

Since chemotherapy is the most common modality, risk of secondary malignancy is the prime concern and depends on the chemotherapy agent/s used. Maximum risk is attributed to Etoposide, though short course up to six months appears to have no increased risk of secondary malignancy.³⁴

Early menopause has been observed in patients having received chemotherapy. It has been observed that the age at menopause is advanced by 1 year for women who receive single-agent chemotherapy and by 3 years if they receive multi-agent chemotherapy.³⁴

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