Gestational trophoblastic disease updated management

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Introduction

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with abnormal pregnancy. Histologically, it includes the benign partial and complete hydatidiform mole, invasive and metastatic mole, as well as the malignant choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Molar pregnancies may develop persistent elevated serum human chorionic gonadotropin (hCG) levels after evacuation (complete mole 15%−20%, partial mole 0.1%−5% [1]-[3]), with a chance of progression to choriocarcinoma that may require treatment. Together with the malignant forms of GTD these are grouped under gestational trophoblastic neoplasia (GTN).

2.Epidemiology

Molar pregnancy is more common in some parts of Asia, with reported incidence rates as high as 2 per 1000 pregnancies[4],[5] compared with Europe and North American where the incidence is usually reported to be less than 1 per 1000 pregnancies [6],[7]. However, the incidence of molar pregnancy seems to be decreasing in Asian countries, possibly related to improvements in the economy and diet as well as a decrease in birth rates [4].

The incidence of choriocarcinoma is difficult to estimate because of its rarity and trouble in clinically distinguishing postmolarchoriocarcinoma from invasive mole owing to lack of histologic biopsy material. Although choriocarcinoma has been reported to affect approximately 1 in 40 000 to 9 in 40 000 pregnancies [3], the incidence rates have been declining. PSTT and ETT are rarer than choriocarcinoma.

3.Genetics and pathology

3.1-Molar pregnancy :

Histologically, complete mole has florid cistern formation, trophoblastic proliferation, and absence of fetal parts. In contrast, such histological features are less marked in partial mole and fetal parts are present, such as fetal cells [8]. Hydropic spontaneous abortion may mimic the appearance of partial mole.

Cytogenetics can help to differentiate complete mole from partial mole and hydropic spontaneous abortion. Typically, complete mole is diploid and has 46,XX chromosomes with both Xs from paternal origin whereas partial mole is triploid with maternal and paternal genetic origin. Hydropic spontaneous abortion normally has 46,XX or XY from both parents. Immunohistochemical staining of p57Kip2, which is an imprinted gene, can help to show the presence of maternal genes and enable complete mole to be excluded [8], [9].

Rarely, invasive and metastatic moles can be diagnosed by removal of the uterus or a metastatic lesion.

3.2- Choriocarcinoma :

Choriocarcinoma is a malignant tumor with absence of chorionic villi, abnormal syncytiotrophoblast and

cytotrophoblast, necrosis, and hemorrhage. It may invade the uterus and surrounding organs and it is common to have distant spread, particularly to the lung, but it may also involve the liver, spleen, kidneys, bowels, and brain [8].

3.3-Placental site trophoblastic tumor :

PSTT arises from the mononuclear intermediate trophoblast on the maternal side of the placental bed invading the myometrium. It has variable size and appearance, may be tan or yellowish with foci of necrosis, and on average is about 5 cm in size. Tumor cells have irregular nuclear membranes, hyperchromatic nuclei, and dense eosinophilic to amphophilic cytoplasm. Chorionic villi are absent. Tumor cells are strongly and extensively reactive to human placental lactogen (hPL) but only focally reactive to hCG. It has to be differentiated from the benign exaggerated placental site reaction where the Ki67 index is lower [8].

3.4- Epithelioid trophoblastic tumor :

ETT is a lesion of chorionic-type intermediate trophoblast. It usually appears as a discrete, hemorrhagic, solid, and cystic lesion.

It may be found in the fundus, lower uterine segment, or endocervix, or even the broad ligament. Histologically, islands of intermediate trophoblastic cells are surrounded by extensive necrosis and associated with a hyaline-like matrix. The tumor is focally immunoreactive to hPL, hCG, cytokeratin, and inhibin-alpha. It can be differentiated from PSTT by positive p63 immunostaining. ETT may coexist with choriocarcinoma or PSTT[10]-[12]. Emerging data indicate that atypical placental site nodules (APSN) can co-exist and/or preceded ETT and PSTT, suggesting that at least APSN cannot be regarded as benign [13].

4.Clinical presentation, investigation, and diagnosis

4.1-Molar pregnancy :

The most common presentation of a hydatidiform mole is abnormal vaginal bleeding in pregnancy. With the advent of ultrasound assessment of early pregnancy complications, molar pregnancy is usually diagnosed during the first trimester. Hence, the previous classical presentations of hyperemesis gravidarum, hyperthyroidism, pre-eclampsia, pulmonary trophoblastic embolization, and uterine size larger than dates are rarely seen nowadays.

The typical snow storm appearance of complete mole may not be seen in early first trimester complete mole. Absence of fetal parts, cystic appearance of the placenta, and deformed gestational sac may indicate early molar pregnancy. Hence, some molar pregnancies are only diagnosed on histological examination after dilation and curettage for a spontaneous abortion.

4.2- Gestational trophoblastic neoplasia :

Postmolar GTN is usually diagnosed by hCG surveillance. Patients are generally asymptomatic. At the 2000 FIGO Gynecology Oncology Committee meeting the definition of postmolar GTN based on hCG-level changes, histology, and specific investigations was agreed upon (1, 1) [14].

• When the plateau of hCG lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21.
• When there is a rise in hCG for three consecutive weekly measurements over at least a period of 2 weeks or more; days 1, 7, 14.
• When the hCG level remains elevated for 6 months or more.
• If there is a histologic diagnosis of choriocarcinoma.
a Abbreviation: hCG, human chorionic gonadotropin.

Box 1- FIGO criteria for diagnosis of postmolar gestational trophoblastic neoplasia :

• Chest X-ray is appropriate to diagnose lung metastases and it is chest X-ray that is used for counting the number of lung metastases to evaluate the risk score. Lung CT may be used.
• Liver metastases may be diagnosed by ultrasound or CT scanning.
• Brain metastases may be diagnosed by MRI or CT scanning.

Box 2- Tools for investigation of gestational trophoblastic neoplasia:

4.3- Human chorionic gonadotropin monitoring :

For monitoring of GTN, an hCG assay that can detect all forms of hCG, such as beta-hCG, core hCG, C-terminal hCG, nicked-free beta, beta core, and preferably the hyperglycosylated forms, should be used; these are different from those used for a routine pregnancy test. A persistent low hCG level should be followed up, after exclusion of false positives due to heterophile antibodies, as some may progress to GTN with rising hCGlevel[15], [16].

4.4- Gestational trophoblastic neoplasia after non-molar pregnancy :

As only about 50% of GTN follows molar pregnancy, the rest can occur after a spontaneous abortion, ectopic pregnancy, or a term pregnancy where no hCG monitoring would be recommended. Therefore, clinical presentations vary from abnormal vaginal bleeding; bleeding from metastatic sites in the abdomen, lung, or brain; pulmonary symptoms; and neurological signs from spine or brain metastasis [3]. GTN should be considered in the differential diagnosis of patients with unusual presentations and serum hCG should be performed as part of the workup of such patients.

5.Treatment

5.1- Molar pregnancy :

Suction evacuation of molar pregnancy should be carried out by an experienced gynecologist, especially if the uterus is larger than 16 weeks gravid size and ideally under ultrasound guidance. The risk of heavy bleeding can be reduced with use of oxytocics given after dilation and the onset of suction curettage. If there is no persistent bleeding, second evacuation is usually not needed

Hysterectomy is rarely indicated unless there is a co-existing indication.

Follow-up with hCG monitoring is essential for early diagnosis of postmolar GTN. Recent data show that GTN rarely occurs after the hCG has spontaneously returned to normal and hence contraception for only 6 months rather than 1 year is now recommended [3], [17]. Termination of pregnancy is not indicated if accidental pregnancy occurs during surveillance after the hCG level has returned to normal. Also, data now show that it is safe to recommend oral contraceptives[18].

The risk of recurrence is low (0.6%–2%) after one molar pregnancy, although much increased after consecutive molar pregnancies [19]-[21]. Mutations in NLRP7 and KHDC3L have been reported in women with recurrent molar pregnancy[22]-[24].

5.2- Co-existing normal pregnancy with mole :

Molar pregnancy rarely co-exists with a normal pregnancy. The diagnosis is usually made on ultrasound. Although there is a high risk of spontaneous abortion, about 40% result in live births without significantly increasing the risk of GTN [25]. Hence, in the absence of complications and normal genetic and ultrasound findings, pregnancy can be allowed to proceed.

5.3- Gestational trophoblastic neoplasia :

Treatment of GTN is generally by chemotherapy. The best regimen to use depends on stage and classification. In the 2000 FIGO staging and classification (Tables 1 and 2), a risk score of 6 and below is classified as low risk and above 6 is considered high risk.

FIGO Stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus
II	Gestational trophoblastic tumors extending to the adnexae or to the vagina, but limited to the genital structures
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement
IV	All other metastatic sites

Table 1. FIGO staging and classification for gestational trophoblastic neoplasia :

FIGO/WHO risk factor scoring with FIGO staging	0	1	2	4
Age	< 40	> 40	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Interval from index pregnancy, months	< 4	4–6	7–12	> 12
Pretreatment hCGmIU/mL	< 13	> 103–104	> 104–105	> 105
Largest tumor size including uterus, cm	–	3–4	≥ 5	-
Site of metastases including uterus	lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	–	1–4	5–8	> 8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

Table 2. FIGO/WHO scoring system based on prognostic factors

Notes: To stage and allot a risk factor score, a patient's diagnosis is allocated to a Stage as represented by a Roman numeral I, II, III, or IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals e.g. Stage II:4, Stage IV:9. This Stage and score will be allotted for each patient.

5.3.1- Low-risk gestational trophoblastic neoplasia :

Patients with low-risk GTN should be treated with one of the single-agent methotrexate or actinomycin D protocols listed in 1. The Cochrane Review in 2012, including 513 patients in five randomized controlled trials, showed that actinomycin D (Act-D) appeared to be superior to methotrexate (MTX) (risk ratio [RR] 0.64; 95% confidence interval, [CI] 0.54−0.76) [26]. Methotrexate was associated with significantly more treatment failure than actinomycin D (RR 3.81; 95% CI, 1.64−8.86). A further trial is ongoing, comparing not only efficacy, but toxicity and quality of life of pulsed actinomycin D and multiday methotrexate regimens [27].

• MTX-FA 8- day regimen (50 mg MTX intramuscularly on days 1,3,5,7 with folinic acid 15 mg orally 24 h after MTX on days 2,4,6,8); repeat every 2 weeks.
• MTX 0.4 mg/kg (max. 25 mg) intravenously or intramuscularly for 5 days every 2 weeks.
• Actinomycin D pulse 1.25 mg/m2 intravenously every 2 weeks.
• Actinomycin D 0.5 mg intravenously for 5 days every 2 weeks
• Others: MTX 30–50 mg/m2 intramuscularly weekly, MTX 300 mg/m2 infusion every 2 weeks, 5-fluorouracil, etoposide.

Box 3 : Single-agent chemotherapy regimens for low-risk gestational trophoblastic neoplasia :

a Abbreviations: MTX-FA, methotrexate−folinic acid.

Chemotherapy should be changed to the alternative single agent if there has been a good response to the first agent but the hCG level plateaus above normal during treatment or if toxicity precludes an adequate dose or frequency of treatment. If there is an inadequate response to the initial single agent, a significant elevation in hCG level, development of metastasis, or resistance to sequential single-agent chemotherapy, multi-agent chemotherapy as for high-risk disease should be initiated [2]. Studies in the UK showed that if the hCG level is less than 100 IU/L or 300 IU/L, change to single-agent Act-D gives a good response [2], [28], [29]; otherwise, multiple agents need to be used.

After the hCG level has returned to normal, consolidation with 2–3 more cycles of chemotherapy will decrease the chance of recurrence. The overall complete remission rate is close to 100%[2],[30].

5.3.2- High-risk gestational trophoblastic neoplasia :

Multiple agent chemotherapy regimens are used to treat high-risk GTN. The most commonly used is EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) (Table 3), although the Cochrane Database review [31] failed to conclude what combination was best. The complete remission rate was approximately 85% and the five-year overall survival rate was 75%−90%. However, patients with liver and/or brain metastasis have poorer outcomes [32]-[34].

Regimens **Regimen 1** **Day 1** **Etoposide** **Actinomycin-D** **Methotrexate**	**100 mg/m2 intravenous infusion over 30 minutes** **0.5 mg intravenous bolus** **100 mg/m2 intravenous bolus ?? 200 mg/m2 intravenous infusion over 12 hours**
Day 2 **Etoposide** **Actinomycin-D** **Folinic acid rescue**	**100 mg/m2 intravenous infusion over 30 minutes** **5 mg intravenous bolus** **15 mg intramuscularly or orally every 12 hours for four doses (starting 24 hours after beginning the methotrexate infusion)**
Regimen 2 **Day 8** **Vincristine** **Cyclophosphamide**	**1 mg/m2 intravenous bolus (maximum 2 mg)** **600 mg/m2 intravenous infusion over 30 minutes**
The two regimens alternate each week	

Table 3. EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy

5.3.3- Ultra high-risk gestational trophoblastic neoplasia and salvage therapy:

Among the high-risk group as defined by the FIGO staging and classification, a subgroup with a score greater than or equal to 12 as well as patients with liver, brain, or extensive metastases did poorly when treated with first-line multiple agent chemotherapy[35].

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 [36].
For those patients with liver or brain metastases or a very high-risk score, EP (etoposide and platinum)/EMA or another more intensive chemotherapy regimen (Table 4), rather than EMA, may yield a better response and outcome. Such regimens can also be used in treating relapse or progressive disease while on first-line chemotherapy. For such high-risk patients, a longer consolidation with four cycles of chemotherapy should be considered.

• EP-EMA (etoposide, cisplatin, etoposide, methotrexate and actinomycin-D)
• TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide)
• MBE (methotrexate, bleomycin and etoposide)
• VIP or ICE (etoposide, ifosfamide, and cisplatin or carboplatin)
• BEP (bleomycin, etoposide and cisplatin)
• FA (5-fluorouracil, actinomycin-D)
• FAEV (floxuridine, actinomycin-D, etoposide and vincristine)
• High-dose chemotherapy with autologous bone marrow or stem cell transplant

Table 4. Salvage chemotherapy

In patients with brain metastases, an increase in the methotrexate infusion to 1 g/m2 will help the drug cross the blood brain barrier and intrathecal methotrexate 12.5 mg can be given at the time of CO when EMA-CO is used. Some centers may give whole brain radiotherapy 3000 cGy in 200 cGy daily fractions concurrent with chemotherapy or use stereotactic radiation to treat brain metastases.

5.4- Role of surgery :

Surgery may have an important role in the management of GTN. Hysterectomy can be considered in uncontrolled uterine bleeding, although it can often be avoided with the use of uterine artery embolization. Laparotomy may be needed to stop bleeding in organs such as the liver, gastrointestinal tract, kidneys, and spleen. Neurosurgery is needed if there is bleeding into the brain or increased intracranial pressure. In patients with an isolated drug-resistant tumor, removal of isolated cranial or pulmonary nodules or hysterectomy can improve survival.

5.5- Role of radiotherapy :

Radiotherapy has a limited role in GTN, except in treatment of brain metastasis, although its efficacy compared with intrathecal methotrexate is controversial [33], [37].

5.6- PSTT/ETT :

Both PSTT and ETT are less chemosensitive than choriocarcinoma. Hysterectomy is the primary mode of treatment in most cases. However, if fertility preservation is desired, especially in a localized lesion, conservative management such as uterine curettage, hysteroscopic resection, and chemotherapy may be considered. Fertility preservation is not suitable in diffuse lesions. EP-EMA is the most commonly used chemotherapy. Interval from antecedent pregnancy of more than 48 months seems to be the most significant adverse prognostic factor.

5.7- Follow-up :

After treatment of GTN, frequent monitoring of hCG for at least 12 months with reliable contraception is essential for surveillance of relapse.
Future fertility, pregnancy, and offspring are not affected, although psychosocial and sexual counseling may be needed for some patients.

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