Current management of gestational trophoblastic disease

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Abstract

Gestational trophoblastic disease is a rare pregnancy-related disorder. It comprises of partial mole, complete mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour. Novel immunohistochemical technologies have helped in the diagnosis of the disease and some of the genes may also serve as prognostic markers. Partial and complete moles can be treated by suction evacuation and most patients do not require further treatment. However, 10–20% of them may develop gestational trophoblastic neoplasia. The International Federation of Obstetrics and Gynaecology has adopted a staging system with incorporation of the modified World Health Organization scoring system. Low-risk disease is treated by single-agent chemotherapy while high-risk disease is treated by multi-agent chemotherapy. The overall cure rate is more than 90% and most patients can preserve fertility and anticipate normal pregnancy outcomes. Nevertheless, the disease can recur. Referral to a specialist centre is important to ensure proper monitoring and management.

Keywords choriocarcinoma; gestational trophoblastic disease; gestational trophoblastic neoplasia; hydatidiform mole; management

Introduction

Gestational trophoblastic disease (GTD) consists of a spectrum of pregnancy-related disorders ranging from benign hydatidiform mole to malignant conditions. In the report by the International Federation of Obstetrics and Gynaecology (FIGO) in 2012, gestational trophoblastic neoplasia (GTN) replaces the terms including chorioadenoma destruens, metastasizing mole, and choriocarcinoma, though a histological verification is still desirable. GTN also represents a condition when there is a plateau comprising of at least four persistently elevated human chorionic gonadotrophic (hCG) levels (day 1, 7, 14 and 21), or sequential rise of hCG for two weeks (day 1, 7 and 14) or longer, or lung metastases diagnosed by chest X-ray. Non-metastatic trophoblastic neoplasia refers to diseases localised within the uterus, while metastatic GTN refers to diseases spreading to other sites such as vagina, lungs, liver and brain. Placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) have distinct pathological and clinical presentation and should be classified separately. GTD was once a fatal disease. But with the advances in the disease diagnosis, better hCG assay, availability of effective chemotherapy, >90% patients can be treated successfully without the need of surgery even in the presence of metastatic diseases.

Hydatidiform mole

Epidemiology

Hydatidiform mole can be classified into complete (CHM) and partial (PHM) moles. Molar pregnancy is rare, and its incidence varies from 11.5 per 1000 deliveries in Indonesia to less than one per 1000 deliveries in the United States. In the United Kingdom, the incidence of CHM is 1–3 in 1000 pregnancies and that of PHM is 3 in 1000 pregnancy. The accuracy of these epidemiological data depends on reliability of the diagnostic techniques and the availability of a vigilant registry system. Besides, the incidence of molar pregnancy may be under-estimated if the tissue masses are not saved for histological examination after miscarriage or termination of pregnancy.

Molar pregnancy is more common at the extremes of ages. The risk of recurrent molar pregnancy increased to 1–1.8% after one molar pregnancy and to 15–20% after two molar pregnancies. Recent genetic studies also showed that mutation in NLRP7 (formerly known as NALP7) gene on chromosome 19q13 and rarely KHDC3L on chromosome 6, is associated with familial recurrent hydatidiform mole which is an autosomal recessive disorder causing CHM of diploid and biparental in origin. In addition, the use of oral contraceptive pills had been implicated to lead to an increased risk of molar pregnancy and such risk appears to increase with the duration of the use of the pills. On the other hand, the relationship of vitamin A precursor carotene deficiency, late menarache, light menstrual flow, parity, blood group, paternal age, smoking and alcohol consumption with molar pregnancy remains unclear.

Pathology

Cytogenetic studies have shown that CHM has a diploid karyotype and is paternal in origin. 80–90% of CHM are the result of fertilisation of an empty ovum by a haploid sperm which then duplicates its chromosomes. Hence, the karyotype configuration of the CHM zygote is 46, XX. In the remaining cases, an empty ovum is fertilised by two haploid sperms resulting in 46, XX or XY. In PHM, a haploid ovum is fertilised by two sperms. The zygote, therefore, becomes triploid containing 69, XXY, XXX and rarely XYY.

Although less conspicuous in early gestation, CHM is characterised by gross villous vesicles, diffuse hydropic villi and trophoblastic hyperplasia with stromal hypercellularity and...
karyorrhectic debris. The cytotrophoblasts may show nuclear pleomorphism. In contrast, gross villous vesicles are only occasionally seen in PHM and the hydropic villi tend to be smaller and less numerous compared with CHM. Trophoblastic hyperplasia is less obvious and there may be scalloping of chorionic villi and trophoblastic stromal pseudo-inclusion. Normal gestational products like gestational sac, embryo, foetus, foetal erythrocyte or placenta may be present. p57 (KIP2) is a paternally imprinted gene and is maternally expressed. CHM is composed of paternal DNA and there is absence of p57 (KIP2) nuclear staining in the cytotrophoblasts and villous stromal cells. On the other hand, since PHM and hydropic abortion contain maternal DNA, p57 (KIP2) is positive. Ploidy analysis using in situ hybridisation, flow cytometry or short tandem repeat genotyping can determine the paternal or maternal origin of the polymorphic alleles. Thus, it is possible to distinguish between androgenetic diploidy, diandrogenic triploidy and biparental diploidy in the diagnosis of CHM, PHM and non-molar pregnancy.

Presentation
The most common presentation of molar pregnancy is vaginal bleeding complicating pregnancy. Some may also have passage of vesicles and the uterus may be larger than date on examination. With more popular use of early ultrasound and hCG measurement, molar pregnancy can be diagnosed earlier. Therefore, florid symptoms like hyperemesis gravidarum, hyperthyroidism, early-onset pre-eclampsia, thromboembolism, large ovarian theca lutein cysts and neurological and chest symptoms due to bleeding complicating pregnancy. Some may also have passage of vesicles and the uterus may be larger than date on examination. With more popular use of early ultrasound and hCG measurement, molar pregnancy can be diagnosed earlier. Therefore, florid symptoms like hyperemesis gravidarum, hyperthyroidism, early-onset pre-eclampsia, thromboembolism, large ovarian theca lutein cysts and neurological and chest symptoms due to bleeding complicating pregnancy. 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Human chorionic gonadotrophin
hCG is a glycoprotein produced by syncytiotrophoblasts containing α and β subunits joined by non-covalent bonds. In normal pregnancy, most hCG is intact. In GTD, there is a higher proportion of β-hCG compared with that in normal pregnancy. Various forms of β-hCG exist in GTD, including free-β, β-core, nicked free-β and carboxyl-terminal fragments. Therefore, an ideal hCG assay for GTD should detect all portions of β-hCG, particularly the free beta subunit, hyperglycosylated hCG (HCG-H), nicked hCG, and hCG missing the terminal carboxyl segment. False-positive and false-negative results can occur. Phantom hCG (pseudohypergonadotropinemia) is a result of the presence of heterophilic antibodies in serum that react with the normal-derived antigens used in commercial hCG immunoassay kits giving rise to a falsely elevated hCG. Heterophilic antibodies may be present in approximately 3.4% of healthy individuals. If there is discrepancy with the clinical presentation, hCG levels should be rechecked with a different immunoassay. The other easy alternative is to measure the urine hCG or its derivatives (free-β subunit or β-core fragment) either quantitatively or qualitatively because heterophilic antibodies have a large molecular size and are not excreted into the urine. So if the serum hCG is persistently positive while the urine hCG is negative, it implies the presence of interference with the serum hCG immunoassay. The lack of linear parallelism with serial serum dilutions can also help to corroborate the presence of false-positive hCG, as heterophilic antibodies react with reagents in the immunoassay and not hCG. Serum can also be pre-absorbed to eliminate the heterophilic antibodies. If the serum hCG returns to negative after the pre-absorption, inference with the immunoassay is confirmed. Low level of pituitary-derived hCG may also be detected in serum in 1.3% peri-menopausal and 6.7% post-menopausal women due to the lack of oestrogen and progesterone negative feedback on the luteinizing hormone and follicle-stimulating hormone (FSH) production. Interpretation of the concurrent FSH level and the use of oral contraceptive pills to suppress the pituitary may be useful to determine the origin of the hCG production.

On the other hand, high dose hook effect can occur with a falsely low serum hCG level. When the serum hCG level is too high, there are not enough antibodies in the solution to bind the hCG molecules and hence much of them are being washed away without being measured. If a very high hCG level is suspected, the laboratory should be informed and the serum should be diluted before measurement.

In a retrospective study on 153 patients, 46% of the patients with CHM had hCG level over 100,000 IU/l before evacuation. However, a cut-off level for diagnosing pregnancy is not known, though some studies showed that molar pregnancy was likely if the hCG level was higher than two multiples of the median or more than 80,000 mIU/ml.

Treatment
Suction evacuation of the uterus can aid histological diagnosis and treatment. Cervical priming immediately before uterine evacuation does not increase the need of subsequent chemotherapy. Medical induction is not recommended for molar pregnancy because of the theoretical risk of myometrial contraction and tumour embolism through the venous system. Besides, medical induction might incur higher risk of incomplete abortion and hence the need of subsequent chemotherapy. Nevertheless, medical abortion may be considered in PHM at second trimester because the foetal parts may obstruct the evacuation and the risk of persistent trophoblastic disease after the procedure is low. Because the uterus is usually vascular and bigger than date, uterine evacuation should be performed by an experienced gynaecologist. If the gestation is more than 16 weeks, the evacuation should be performed in a trophoblastic disease centre. In case of heavy bleeding during the procedure, oxytocic agents can be given, preferably after the evacuation has been completed. Anti-D prophylaxis should be given where appropriate.
Up to date, there is still no strong evidence about the role of prophylactic chemotherapy. A meta-analysis including three randomised trials of 613 patients showed that prophylactic chemotherapy might reduce the risk of progression from CHM to GTN. However, two of the three studies had problems with the methodology. Besides, the prophylactic chemotherapy might delay the diagnosis of GTN and these patients appeared to require more courses of chemotherapy if GTN is subsequently diagnosed. Prophylactic chemotherapy might only be restricted to patients who cannot be followed and the decision should be made after discussion with experts in treating GTD.

Mole in multiple pregnancy
Hydatidiform mole can co-exist with a live foetus. An option of continuing the pregnancy can be given to the patient after informing the risks of miscarriage (40%), pre-term delivery (36%), pre-eclampsia (20%) and rarely pulmonary embolism. The patient should be referred to a maternal–foetal medicine unit for close antenatal check-up and the chance of achieving a live baby is 25–40%. There is no increased risk of persistent GTD. Hydatidiform mole has also been reported in triplet and quadruplet pregnancies. However, the risk of foetal loss is more than 90% and selective feticide might have to be considered.

Follow-up
According to the FIGO recommendation, patients with molar pregnancy should be followed up with weekly hCG until normal and then two more weekly specimens should be checked. After that, the hCG should be monitored monthly for six months and then every two months for six more months. In the UK, all patients with GTD should be registered in one of three specialist centres for follow-up: Weston Park Hospital (Sheffield), Ninewells Hospital (Dundee) or Charing Cross Hospital (London). A retrospective study involving 6701 patients showed that among the 422 patients (6%) who developed persistent GTN, 412 (98%) presented within 6 months after evacuation and only one woman was detected by routine extended follow-up. The current UK practice is to ask the patients to send their serum and urine samples for hCG assay every 2 weeks until the hCG levels return to normal. If the hCG levels return to normal within 56 days after evacuation, urine hCG will be checked monthly for 6 months from the date of evacuation. If the hCG levels return to normal more than 56 days after evacuation, urine hCG will be checked monthly for 6 months after the date when the levels drop to normal.

The patients should practice reliable contraception for at least 6 months after the hCG levels become normal, because raised hCG levels during pregnancy will confuse the clinical picture. A longer delay of subsequent pregnancy may be necessary if the decline of hCG is slow. A summary of the United Kingdom Medical Eligibility of Contraceptive Use (UKMEC) recommendations of the use of different contraceptive methods is illustrated in Table 1. Although it suggests that hormonal methods can be safely used even when the hCG level is persistently elevated or in the presence of malignant disease, it is generally advised to defer their use until the hCG level becomes normal. Similarly, intra-uterine contraceptive devices are not recommended when hCG is high because of the risk of abnormal vaginal bleeding and uterine perforation. If the patient happens to get pregnant within 6 months, the pregnancy may be allowed to continue because the risk of foetal abnormality or persistent trophoblastic disease is minimal.

Patient should notify the screening centres after each pregnancy regardless of the outcomes, and the serum and urine hCG level should be measured at 6 weeks and 10 weeks after the pregnancy until undetectable.

A summary of the management of hydatidiform mole is shown in Table 2.

GTN
Similar to molar pregnancy, GTN is more common in Southeast Asia than the West. The incidence in India and Indonesia varies from 15–19 per 1000 pregnancies and that in the West is 0.2–0.7 per 1000 pregnancies. 25% of it is associated with antecedent miscarriage or abortion, 5% with ectopic pregnancy, 20% with full-term pregnancy and 50% with hydatidiform mole. About 0.5 –1% of PHM and 15% CHM patients progress to GTN necessitating chemotherapy. Retrospective studies have shown that maternal age, previous history of molar pregnancy and elevated post-evacuation hCG levels were associated with higher risk of GTN. Recently, there were several studies showing that the regression rate of serum and urine hCG might be a predictor for the development of GTN.

Staging and scoring
There are few staging systems for GTN such as the ones developed in the Charing Cross Hospital and by Hammond. In 2000, the FIGO Gynaecological Oncology Committee recommended a clinical and anatomical staging system and accepted the incorporation of the WHO scoring system based on the prognostic factors modified from the one devised by Bagshawe. Each patient with GTN should be allotted with a stage (I–IV) and a score separated by a colon (e.g. stage I: 3). The staging and scoring systems are shown in Table 3.

The overall 5-year survival for patients with GTN is estimated to be 92.7%, and is 97.3%, 85.7%, 82.8% and 61.9% for stage I, II, III and IV patients respectively. Using 6 as the cut-off as ratified by the FIGO in June 2002, the 5-year survival for low-risk patients is similar to stage I patients, while that for high-risk patients is 79.5% overall (84% for those with score 7–12 and 68% for those with score >12).

Pre-chemotherapy work-up
The usual indications for chemotherapy used in the UK are listed in Table 4. In the past, raised hCG level 6 months after evacuation was an indication for chemotherapy even if it was falling. However, in a large review of 13,960 patients with molar pregnancy, only 76 patients (<1%) had persistently raised hCG of >5 IU/L six months after evacuation. 66 of them did not receive chemotherapy and the hCG of 65 patients returned to normal spontaneously. Therefore, this indication has been omitted in the recent FIGO and UK guidelines. In general, it is recommended that low-risk disease should be treated by single-agent chemotherapy while high-risk disease and choriocarcinoma by combination chemotherapy.

Physical examination is carried out to check if there is any systematic involvement, to assess the uterine size and look for
any vaginal metastasis or adnexal mass. Full blood count, clotting profile, liver function test, urea and electrolytes are taken to assess the general condition of the patients. Thyroid function test has to be checked when indicated. The serum hCG level is taken as a baseline for subsequent monitoring of the response to chemotherapy. Doppler ultrasound of the pelvis is needed to exclude any pregnancy or retained products of conception that might otherwise cause a rise of hCG, and to measure the uterine volume and the size of any intrauterine lesion. There is also emerging evidence that pulsatility index of the uterine artery can predict the resistance to methotrexate especially for those at increased risk. As a normal hCG value implies that there are still occult metastases but there is clinical suspicion, cerebrospinal fluid (CSF) can be aspirated to measure the hCG level. A CSF: serum hCG ratio of 1:60 suggests central nervous system metastasis.

Positron emission tomography (PET)-CT, tagging fluorodeoxyglucose with a positron-emitting isotope of fluorine (18F), could detect neoplastic tissues that have high metabolic rate and glucose uptake. In a recent retrospective study, it showed that PET-CT did not have additional value comparing to conventional imaging. However, it may be useful in locating the primary source of unexplained high hCG level that may not be detected by conventional imaging tools. It might also be potentially useful in mapping the metastatic sites and monitoring the treatment response.

Table 2

**Management of hydatidiform mole**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>CHC</th>
<th>POP</th>
<th>DMPA/NET-EN</th>
<th>IMP</th>
<th>Cu-IUD</th>
<th>LNG-IUD</th>
<th>Barrier methods</th>
<th>Female sterilisation</th>
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<tbody>
<tr>
<td>Serum and urine hCG</td>
<td>1</td>
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<td>1</td>
<td>A</td>
<td>D</td>
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<td>Full blood count</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>D</td>
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<td>Clotting profile</td>
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<td>Liver function test, urea, creatinine and electrolytes</td>
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<td>Group and saver</td>
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<td>Thyroid function test</td>
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<td>HIV and HBV serology</td>
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<td>Chest X-ray</td>
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<td>Ultrasound Doppler of pelvis</td>
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</table>

**Treatment**

**Low-risk GTN:** second uterine evacuation is usually unnecessary unless in selected patients who are symptomatic with retained products of conception, or when the hCG level is below 5000 IU/L and the tumour is confined in the endometrium. This has to be balanced against the risk of bleeding and uterine perforation and so the decision of repeated evacuation should only be made after being reviewed in specialist centres. Hysterectomy may be considered for those who have no fertility wish or have life-threatening haemorrhage. Hysterectomy can provide permanent sterilization and prevent local myometrial invasion, but it cannot obviate the risk of metastasis and the need of chemotherapy.

Patients at stage I—III with WHO score <7 are treated with single agent. Methotrexate (MTX) is the traditional first-line agent. One common regimen used in the UK is 50 mg MTX intramuscular injection on days 1, 3, 5 and 7, with 0.1 mg/kg or 15 mg oral folic acid 24—30 h after MTX on days 2, 4, 6 and 8, repeated every 2 weeks for four courses. Serum and urine hCG levels should be checked at least once per week to monitor the response. As a normal hCG value implies that there are still <10⁷
tumour cells in the body, at least one and preferably three more courses of chemotherapy should be given for consolidation after hCG normalisation in order to eliminate any residual trophoblastic cells and reduce the chance of relapse. The complete response rate is 72% with 20–25% primary failure rate. Less than 5% of patients develop grade III/IV toxicity including mucositis, stomatitis, pleuritic chest pain, thrombocytopenia, uterine bleeding, abdominal pain, liver derangement, rash and pericardial effusion. Other regimens of MTX have also been reported, for example, 0.4 mg/kg MTX intramuscularly for 5 days and repeated every 2 weeks where the primary failure rate is 2c% for metastatic disease, and 27–33% for metastatic diseases, and weekly intramuscular MTX 50 mg/m² where the primary failure rate is 30%. Direct comparison of these regimens is difficult because there are no randomised controlled trials and the indications of chemotherapy and scoring systems are different in different centres. Some may also administer.

intrathecal methotrexate (12.5 mg) prophylaxis every 2 weeks for three doses for those low-risk women with pulmonary but not central nervous system metastasis, although this practice is still being questioned.

Actinomycin-D is also widely used. It can be given as an intravenous bolus of 1.25 mg/m² or an intravenous infusion of 0.5 mg for 5 days every 2 weeks until documented complete response. About 75–80% of patients resistant to methotrexate attained complete response with minimal toxicity. Using as first-line treatment, the response rate was even up to 90%. A recent randomized controlled trial comparing weekly intramuscular methotrexate 30 mg/m² and biweekly intravenous actinomycin D 1.25 mg/m² showed a better response in the latter group (complete response rate 53% Vs 70%, p = 0.01) with modest toxicity. A Cochrane review including 513 patients in 5 randomized controlled trials showed that actinomycin D appeared to be superior to methotrexate (risk ratio [RR] 0.64, 95% confidence interval [CI] 0.54–0.76), and methotrexate was associated with significantly more treatment failure than actinomycin D (RR 3.81, 95% CI 1.64–8.86). However, caution should be taken in interpreting the results as the review included different regimens and direct comparison was difficult. In the past, 5-fluorouracil and etoposide were also used to treat low-risk GTN but they are now seldom used alone because of toxicity.

It has been demonstrated that only about 30% of patients with score 5–6 or hCG between 100,000–400,000 IU/L would respond to single agent chemotherapy. For those whose initial hCG is >400,000 IU/L, single agent is unlikely to be effective and therefore combined chemotherapy is recommended.

In a retrospective study on 328 low-risk post-molar GTN patients, the median time to remission was 46 days (28–77 days). The diagnosis of CHM, presence of metastatic disease, the use of multi-agent therapy and FIGO score were independently associated with longer time to remission. And each one-point increase in the WHO score would lead a 17-day increase in time to achieve.

### Indications for chemotherapy after GTD

- Rising hCG of >10% in two consecutive serum samples over at least 2 weeks (days 1, 7 and 14)
- hCG plateau in four or more consecutive serum samples after evacuation over at least 3 weeks (days 1, 7, 14 and 21)
- Serum hCG ≥20,000 IU/l more than 4 weeks after evacuation
- Brain, liver, gastrointestinal or lung metastases > 2 cm on chest X-ray
- Histological evidence of choriocarcinoma
- Heavy vaginal bleeding or gastrointestinal/intraperitoneal bleeding
- Pulmonary, vulval or vaginal metastases, unless the hCG level is falling

hCG, human chorionic gonadotrophin.

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**Table 3**

<table>
<thead>
<tr>
<th>FIGO staging and classification</th>
<th>Disease confined to the uterus</th>
<th>GTN extends outside of the uterus, but is limited to the genital structures (adnexal, vagina, broad ligament)</th>
<th>GTN extends to the lungs, with or without known genital tract involvement</th>
<th>All other metastatic sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified WHO prognostic scoring system as adapted by FIGO</strong></td>
<td></td>
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<tr>
<td>Scores</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;40</td>
<td>≥40</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>mole</td>
<td>abortion</td>
<td>term</td>
<td>—</td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt;4</td>
<td>4—&lt;7</td>
<td>7—&lt;13</td>
<td>—</td>
</tr>
<tr>
<td>Pre-treatment serum hCG (IU/l)</td>
<td>&lt;103</td>
<td>103—&lt;104</td>
<td>103—&lt;104</td>
<td>≥105</td>
</tr>
<tr>
<td>Largest tumour size (including uterus)</td>
<td>—</td>
<td>3—&lt;5 cm</td>
<td>≥5 cm</td>
<td>—</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>lung</td>
<td>spleen, kidney</td>
<td>gastro-intestinal</td>
<td>liver, brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>—</td>
<td>1—4</td>
<td>5—8</td>
<td>&gt;8</td>
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<tr>
<td>Previous failed chemotherapy</td>
<td>—</td>
<td>—</td>
<td>single drug</td>
<td>≥2 drugs</td>
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FIGO, Federation of Obstetrics and Gynaecology; GTN, gestational trophoblastic neoplasia; WHO, World Health Organization; hCG, human chorionic gonadotrophin.
HCG remission. The role of uterine artery pulsatility index, HCG normogram and HCG kinetic models in predicting resistance to MTX needs to be further evaluated.

High-risk GTN: patients in stage I–III with WHO score ≥7 or stage IV are treated with combined chemotherapy. The most popular regimen used nowadays is the EMA-CO (Table 5). The complete remission rate was about 85% and the 5-year overall survival rate was 75–90%. However, cause-specific survival was only 68% for those with liver metastasis. The overall survival was 50–70% with brain metastasis, and was worse for those with symptoms compared to those without symptoms (41% vs 100%, p = 0.0005). If both brain and liver metastases are present, the 5-year survival is only 10%. The major side effects include mucositis, pleuritis, alopecia, liver derangement, myelosuppression and vincristine-associated peripheral neuropathy. One health questionnaire study conducted in the UK showed that combined chemotherapy containing etoposide was associated with a slight increased risk of secondary malignancy (RR 1.5; 95% CI 1.1–2.1) with the greatest risk in myeloid leukemia (RR 16.6; 95% CI 5.4–38.9), colon (RR 4.6; 95% CI 1.5–10.7), and breast cancer when the survival exceeded 25 years (RR 5.8; 95% CI 1.2–16.9). Some centres lower the dosage of etoposide after normalization of the HCG level to minimise the risk of secondary malignancies.

Examples of other regimens include MEA (methotrexate, etoposide, and actinomycin-D); MAC (methotrexate, actinomycin-D and cyclophosphamide or chlorambucil); CHAMOMA (cyclophosphamide, hydroxyurea, actinomycin-D, methotrexate with folinic acid, vincristine, melphalan and doxorubicin); and CHAMOC (cyclophosphamide, hydroxyurea, actinomycin-D, methotrexate with folinic acid, vincristine). Used as primary treatment, the response rate was around 60–80%. Although some studies attempted to compare the response rate and toxicity of different regimens, a Cochrane review failed to draw any conclusion because only one randomised controlled trial comparing MAC and CHAMOC was identified and there was no randomised controlled trial comparing EMA-CO with other regimens.

Those patients presenting at very advanced stage involving organs like the lungs, brain, and/or liver, might be commenced on reduced-dose chemotherapy, such as etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2 and repeated weekly for 1–3 weeks before returning to the usual chemotherapy regimen, to avoid life-threatening complications such as pulmonary, cerebral, or liver decompensation from tumour oedema or haemorrhage.

A review containing 22 patients with MTX-resistant GTN and 24 patients with primary high-risk diseases using EMA-CO showed that half of each group would be able to achieve HCG remission before the 3rd and 6th course, respectively. The 90th percentile was below the normal before the start of the 4th cycle for those MTX-resistant patients and before the start of the 8th cycle for those primary high-risk patients. Such normogram might potentially be useful in predicting resistance to EMA-CO but further validation is needed.

Resistant or relapsed high-risk GTN: Chemo-resistance is featured by a plateau or a rise in HCG level with or without new metastasis while the patient is receiving chemotherapy, and relapse is defined by >2 consecutive rise of HCG not related to pregnancy after complete remission from primary treatment. The relapse rate is about 3% in low-risk GTN, and 7–10% and up to 25% in some case series in high-risk GTN. Although 20–30% of these patients eventually fail to respond to treatment and progress, the rest are salvageable by further chemotherapy with or without surgery. Those who are resistant to chemotherapy have worse prognosis than those who relapse. The overall 5-year survival for patients with relapsed GTN is more than 90% (nearly 100% for low-risk GTN and around 85% for high-risk GTN).

In the United Kingdom, in case of resistance to methotrexate or relapse in low-risk GTN, actinomycin-D will replace methotrexate if the HCG level is less than 300 IU/l and combined chemotherapy like EMA-CO will be given if HCG is higher than 300 IU/l. For those high-risk patients who are resistant to first-line chemotherapy or have relapse, salvage combined chemotherapy can be given. The most commonly used regimen in this scenario is EP-EMA (etoposide, cisplatin, etoposide, methotrexate and actinomycin-D), which has been shown to have 66–75% complete remission rate and 88% survival rate. EP may be replaced by doxorubicin and cisplatin in selected cases. Another regimen consisting of TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide) is also gaining favour, which has a response rate of 50% and survival rate of 44% in those who failed previous chemotherapy and the side effects are tolerable. The survival rate increases to 70% for those who had not exposed to platinum-based chemotherapy before. Other alternative regimens include MBE (methotrexate, bleomycin and etoposide), FA (5-fluorouracil, dactinomycin), BEP (bleomycin, etoposide and cisplatin), FAEV (fluoruridine, dactinomycin, etoposide, and vincristine), VIP or ICE (etoposide, ifosfamide, and cisplatin or carboplatin) and capetitabine. Myelosuppression remains the dose-limiting factor and granulocyte-colony stimulating factor may be needed. Some authors have also used high-dose chemotherapy and autologous stem cell support as salvage treatment though this practice has not been evaluated in clinical trials. The Cochrane review published in 2012 could not identify any randomised control study and so no conclusion could be drawn to suggest the most optimal therapy.

Quiescent GTD: it has been suggested that hyperglycosylated HCG (HCG-H), produced by extra-villous cytotrophoblast cells, can enhance trophoblast invasion in choriocarcinoma, and trigger trophoblast growth and placental implantation during pregnancy. It is elevated in GTN. In the recent decades, a condition called ‘quiescent GTD’ has been described. It is thought to be an ‘inactive’ form of GTD which can be diagnosed by persistently low HCG, usually in the range of 50–100 IU/l and typically below 207 IU/l, for at least three consecutive months. It is postulated that the low level of HCG is due to the presence of differentiated syncytiotrophoblasts which produce a small amount of HCG. Because there is no significant amount of cytotrophoblast cells, the HCG-H level is negligible. Chemotherapy is not needed and the condition usually will disappear within 6 months. It has been estimated that approximately 20% of women with quiescent HCG will have a rise in HCG months to years later when the HCG-H constitutes a large proportion of the total HCG.
and treatment should then be initiated. However, whether quiescent GTD is a new disease entity and whether it is reliable to utilise hCG-H in managing this condition are still under debate.

**Role of surgery**

About 50% of high-risk GTN patients may require surgery during the course of their treatment. Surgery may be indicated to remove resistant or persistent disease in the uterus or metastatic sites, decrease the uterine tumour load in case of limited metastasis, control profuse tumour haemorrhage, and relieve symptoms like bowel or urinary obstruction due to the large tumour bulk.

Uterine evacuation only benefits a limited number of patients with low-risk GTN but may be useful in those who do not require immediate chemotherapy and where urinary hCG is < 1500 IU/l. Surgical bleeder plication and arterial ligation may be necessary in case of torrential bleeding from the tumours. Ovarian cystectomy or salpingo-oophorectomy may be required if the patients complain of sudden abdominal pain related to ovarian theca lutein cyst complications. About 1 in 140 patients require hysterectomy for GTN. About one-third of them are performed as primary treatment, one-third are because of resistance to chemotherapy, and another third because of heavy bleeding. The remission rate of patients undergoing hysterectomy is around 75—90%. Metastatic lesions outside lungs and pelvis, the number of metastases, chemo-resistance especially to combination chemotherapy and the use of ≥ 2 regimens, appear to adversely affect the therapeutic response after hysterectomy in high-risk patients.

Residual lung lesions after completion of chemotherapy may not need to be resected. Besides, it was postulated that the radiological finding of tumour regression lagged behind the decline of hCG and many patients still had a persistent chest lesion for years despite clinical remission. However, if the chemo-resistance is due to the pulmonary metastasis and the lung lesion is amenable to operation, lung resection may be justified. A remission rate of up to 90% has been reported. Craniotomy is usually performed when there is acute cerebral haemorrhage or other neurological complications requiring emergency decompression, or when there are multiple metastases where early removal of solitary superficial tumour can stabilise the patients before contemplating further treatment. A retrospective study showed that all chemo-resistant patients having treatment failure after salvage surgery had 2 out of the 4 risk factors: age older than 35, antecedent non-molar pregnancy, metastasis outside lungs and pre-operative β-hCG level > 10 IU/l.

**Role of selective arterial embolization**

Selective arterial embolization using modified Seldinger technique with gelfoam particles has been used to control intractable bleeding in uterine, vaginal, hepatic metastasis. There has also been a case report describing the use of embolization to control bleeding and disease in a patient with low-risk GTN, eliminating the need of subsequent chemotherapy. This technique is an attractive alternative to surgery because it is non-invasive and can be done under conscious sedation. Pregnancy has been reported after this treatment. However, complications can arise, including post-embolization syndrome like malaise, fever, pelvic pain and leucocytosis. If iliac vessels are embolized, severe complications such as perineal skin sloughing, recto-vesico-vaginal fistulae and neurological deficits in the lower limbs can occur.

**Role of radiotherapy**

Radiotherapy is rarely needed in the treatment of GTN but it has a pivotal role in preventing unexpected bleeding in brain metastases. When whole brain irradiation is given concurrently with combined chemotherapy, the overall survival rate is around 40—90%. A retrospective study found that the survival rate of patients receiving chemotherapy and irradiation, chemotherapy alone and no treatment was 50%, 24% and 0%, respectively. A total of 58% and 74% of the second and third groups died of central nervous causes. Patients with neurological symptoms, prior treatment and brain metastasis during treatment had poor prognosis. The dosage of irradiation is also important. One study

<table>
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<tr>
<th>EMA-CO chemotherapy</th>
<th>Day 1</th>
<th>Day 2</th>
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<tbody>
<tr>
<td><strong>Regimen 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m² intravenous infusion over 30 min</td>
<td></td>
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<tr>
<td>Actinomycin-D</td>
<td>0.5 mg intravenous bolus</td>
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<tr>
<td>Methotrexate</td>
<td>300 mg/m² intravenous infusion over 12 h</td>
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<tr>
<td><strong>Regimen 2</strong></td>
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</tr>
<tr>
<td>Vincristine</td>
<td>100 mg/m² intravenous infusion over 30 min</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0.5 mg intravenous bolus</td>
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<tr>
<td></td>
<td>15 mg intramuscularly or orally every 12 h for four doses (starting 24 h after beginning the methotrexate infusion)</td>
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<tr>
<td></td>
<td>1 mg/m² intravenous bolus (maximum 2 mg)</td>
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<tr>
<td></td>
<td>600 mg/m² intravenous infusion over 30 min</td>
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Table 5
showed that the 5-year overall survival rate for those receiving less than 2200 cGy was 39%, whereas for those receiving more than 2200 cGy the survival rate was 100% (p = 0.03). In general, the usual dosage is 2000–4000 cGy given in 10–20 fractions of 200–300 cGy each and the radiotherapy is usually given under steroid cover to reduce cerebral oedema.

Radiotherapy has also been used in patients with liver metastasis to avoid haemorrhagic complications. Whole-liver irradiation is usually delivered at around 2000 cGy concurrently with chemotherapy over 2 weeks in an attempt to reduce the risk of radiation-induced hepatitis. However, the prognosis of these patients is poor with an overall 5-year survival rate less than 30%. Radiotherapy to liver probably does not provide any survival benefit and it is seldom given nowadays.

Follow-up
Recurrence usually occurs within 1 year. There is no recommendation for the best schedule of follow-up. The follow-up protocol used in the Charing Cross Hospital is shown in Table 6. As it is unclear when it is safe to stop the surveillance, the monitoring is life-long.

Fertility
Most patients with GTN belong to the reproductive age group and fertility is an important issue. There is concern that sexual performance, ovarian function and foetal outcomes may be affected after the completion of chemotherapy. A questionnaire survey involving 47 patients receiving chemotherapy and/or surgery for GTN showed that 70% experienced absent or low sexual desire, 42% had dyspareunia, 45% had lubrication problems and 53% had changes in the relationship with their partners within the first year after remission. This indicated that sexual dysfunction was a rather common phenomenon after treatment for GTN, which could be overlooked by clinicians. This problem could be partly attributed to the anxiety about disease recurrence and future pregnancy outcomes. Thorough counseling about the nature of the disease, care about the psychosocial aspect of patients, early detection of any distress in patients and the involvement of a multidisciplinary team are definitely needed.

On the other hand, another retrospective controlled survey compared the age of menopause between patients treated with and without chemotherapy. Although the former group
(median 50, range 25–56 years) had menopause 3 years earlier than the latter group (median 53, range 40–57 years) (log-rank Chi² test = 12.6, \( p = 0.0004 \)), there was no evidence of premature ovarian failure and the difference did not have great clinical significance. In addition, even if assisted reproductive technique is contemplated, there is no evidence of increased risk of recurrent GTD in spite of a small number of case reports.

As for the pregnancy outcomes of patients receiving single and multiple agents, the overall fertility rate is more than 80%. A review article summarising the data from 10 different international centres showed that patients with persistent GTN, regardless of the risk scores and the chemotherapy regimens used, had favourable pregnancy outcomes. The live birth rate was 76.4% and the term delivery rate was 71.5%, while the rate of premature deliveries, stillbirth, miscarriage and congenital abnormalities was only 5.0%, 1.3%, 14.0% and 1.3% respectively. But if patients conceive within 6 months of chemotherapy, the incidence of abnormal pregnancies, including miscarriage, stillbirth and repeated molar pregnancy, is significantly higher than those who conceive more than 12 months later (37.5% Vs 10.5%, \( p = 0.14 \)). Besides, the growth of primordial Graafian follicles is estimated to take more than six months. By waiting for one year, this may allow damaged DNA to be repaired. Therefore, patients should be advised to refrain from pregnancy for at least 1 year in order to avoid any misinterpretation of hCG results and possible harmful effects of chemotherapy on the ovarian function and foetal outcome. Nonetheless, if patients happen to conceive within 1 year, they can be reassured that the overall outcome is favourable and termination of pregnancy is not required.

A summary of the management of GTN is shown in Table 6.

Choriocarcinoma

In Europe and USA, the estimated number of choriocarcinoma is 1 in 50,000 pregnancies whereas in South East Asia and Japan it is 9.2 and 3.3 respectively. 25% of choriocarcinoma occurred after miscarriage, 25% after term pregnancy and the rest after molar pregnancy. It shows no chorionic villi, and abnormal cytotrophoblastic and syncytiotrophoblast with haemorrhage and necrosis invading myometrium and vessels are often seen.

Hematological spread is common. Unless developed following molar pregnancy, it is difficult to reach the diagnosis of choriocarcinoma and is usually made when there is an unexplained high hCG level and the presence of tumour in the lung, brain or liver on imaging. Some patients present with neurological or pulmonary symptoms and diagnosis is made histologically after removal of the tumour. A delay in diagnosis resulting in a delay in starting chemotherapy is a major cause of early death in patients with brain or liver metastasis.

The management of choriocarcinoma is similar to that of high-risk GTN.

Tumours of intermediate trophoblast

PSTT

PSTT was first described in 1976 by Kurman et al. and is a rare neoplasm arising from the implantation site intermediate trophoblast. It constitutes 0.1–2% of all GTN. Most cases of PSTT are at least focally infiltrative and myometrial smooth muscle cells are found in between the clusters or sheets of tumour cells. Unlike choriocarcinoma which is immunoreactive for hCG and has a high Ki-67 proliferative index, PSTT is only focally and weakly immunoreactive for hCG and the mean Ki-67 is around 15%. PSTT can be preceded by normal pregnancy, miscarriage or abortion, and less commonly molar pregnancy and ectopic pregnancy. Most patients present with vaginal bleeding, amenorrhoea and uterine enlargement. Rarely, patients may present with nephritic syndrome related to immunoglobulin deposits in the glomerular membranes, and virilisation due to ovarian stromal hyperthecosis and paraneoplastic syndromes.

About half and up to 90% of patients are diagnosed at early stage. Serum hCG may be high and 79% of patients have levels less than 1000 IU/l and 58% less than 500 IU/l. Serum human placental lactogen may be raised and this can be used as a tumour marker. Ultrasound may show an intra-uterine cystic or heterogeneous mass with various degree of vascular signal. The definite diagnosis is often made in the hysterectomy or curettage samples.

Age over 35, interval from preceding pregnancy over 24 months, deep myometrial invasion, advanced stage, maximum hCG level >1000 IU/l, mitotic count more than 5 per 10 high power fields, extensive coagulative necrosis and presence of clear cytoplasm have been suggested to carry a poor prognostic effect. However, a recent review showed that the only independent predictor of overall and recurrence-free survival was the interval from its antecedent pregnancy using 48 months as cut-off. On the other hand, another recent case series consisting of 17 PSTT patients showed that patients with FIGO stage IV had worse overall survival than those with stage I–III diseases (\( p = 0.009 \)).

The cornerstone treatment method is hysterectomy because PSTT is less sensitive to chemotherapy. However, conservative management like uterine curettage, hysteroscopic resection and chemotherapy may be considered provided that the patient has a strong desire of fertility, the lesion is localised in the uterus, the mitotic count is low, there is no uterine enlargement and close monitoring is feasible. It has been suggested that stage I diseases can be treated by surgery alone, while stage II–IV diseases have to be treated by surgery and chemotherapy, and the most commonly used regimen is EMA-EP and the alternative is TE/TP. In Charing Cross Hospital, adjuvant chemotherapy is also given to stage I patients after surgery if risk factors like interval from preceding pregnancy >4 years are present.

ETT

ETT is derived from the chorionic-type intermediate trophoblast and was first described in 1998. The tumour is characterised by uniform nests and cords of mononucleated intermediate trophoblastic cells surrounded by extensive necrosis and associated with an eosinophilic hyaline-like matrix creating a ‘geographical’ pattern. Because about half of the tumours are found in the lower uterine segment or endocervix, they are often mistaken for squamous cell carcinoma of the
cervix. Rarely, ETT can coexist with choriocarcinoma or PSTT. The majority of ETT occurs in the reproductive age group. Patients often have symptoms resembling those in PSTT and about 70% of them have abnormal vaginal bleeding. The serum hCG level is usually mildly elevated. Similar to PSTT, ETT is not chemo-sensitive and it is mainly treated by operation.

FURTHER READING


Practice points
- GTD is a spectrum of benign and malignant pregnancy-related conditions and is more common in Asia and Latin America.
- The common use of ultrasound has led to earlier diagnosis of GTD. The clinical presentation has, therefore, changed in the past few decades. Florid symptoms of hyperthyroidism, thrombocytopenia, pre-eclampsia and neurological symptoms are rarely seen nowadays.
- All patients should be referred to a specialist centre for subsequent management.
- Suction evacuation is the main treatment for molar pregnancy and most often no further treatment is required.
- Specimens should be examined by experienced pathologists. Ancillary tests with the use of paternally imprinted genes help to differentiate partial mole from complete mole.
- Serum and urine hCG should be monitored to detect any persistent trophoblastic disease. Patients should be advised to practice contraception for at least 6 months.
- The diagnosis of GTN is made when the hCG level is stationary or rising after a molar pregnancy or when choriocarcinoma is found. PSTT are ETT are separate disease entities as their cell origin and clinical behaviours are different.
- The FIGO committee have recommended a clinical anatomical staging system together with the modified WHO risk scoring system. Global standardisation of the staging systems and treatment criteria is important for comparison of treatment results.
- Low-risk disease is treated by single-agent chemotherapy and high-risk disease is treated by multi-agent chemotherapy. The overall response rate is more than 90%. However, systematic reviews have failed to identify the best regimen.
- The relapse rate is about 3% in low-risk GTN and 7–20% in high-risk GTN. More than 80% of patients are salvaged by further chemotherapy. The overall 5-year survival rate is more than 90%.
- Patients should be advised to refrain from pregnancy for at least 12 months. They can be reassured that their fertility potential is not jeopardised and that the risks of disease recurrence and foetal abnormality are small.
- The psychosocial aspects of these patients are often overlooked. Detailed explanation about the disease should be given and a multidisciplinary approach should be adopted.
- PSTT and ETT are rare intermediate trophoblast tumours. They are not very chemo-sensitive and hence hysterectomy is the mainstay treatment.