An update on gestational trophoblastic disease

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Abstract
Gestational trophoblastic disease is a rare pregnancy-related disorder. It comprises of partial mole, complete mole, invasive and metastatic 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 Gynecological Oncology Committee 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; management; mole

Introduction
Gestational trophoblastic disease (GTD) consists of a spectrum of pregnancy-related disorders ranging from benign hydatidiform mole, clinically malignant conditions like invasive mole and metastatic mole, to neoplastic conditions including choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). GTD can be subdivided into those with and without chorionic villi (see Table 1). In 2003, the World Health Organization (WHO) also developed a classification system (see Table 2). GTD was once a potentially fatal disease, however, with more understanding about the disease, most patients can now be treated conservatively and have a favourable prognosis.

Hydatidiform mole
Epidemiology
Hydatidiform mole can be classified into complete and partial moles. Molar pregnancy is a rare disease. Its incidence varies worldwide, the reported incidence is one in 125 livebirths in Taiwan, two in 1000 pregnancies in South East Asia and Japan while it is one in 1000 in Europe and one in 1500 in the United States, respectively. However, the accuracy of these epidemiological data depends on how vigilant and reliable the registry system is. 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. Previous history of molar pregnancy increases the risk of recurrent molar pregnancy to 1.8%, around 20 times higher than the background risk. Case-controlled studies had suggested that vitamin A precursor carotene deficiency was associated with increased risk of complete mole but not partial mole. Recent genetic studies also showed that mutation in NLRP7 (formerly known as NALP7) gene — a CATERPILLER protein family involved in pathogen-induced inflammation and apoptosis — on
chromosome 19q13.4 was associated with familial and recurrent hydatidiform mole. In addition, the use of oral contraceptive pills increases the risk of molar pregnancy (relative risk (RR) 1.3–2.6) and such risk appears to increase with the duration of the use of the pills. On the other hand, it is still controversial about the effects of parity, blood group, paternal age, smoking and alcohol consumption in molar pregnancy.

Pathology
Cytogenetic studies have shown that complete mole has a diploid karyotype and is paternal in origin. It is the result of fertilization of an empty ovum by a haploid sperm, which then duplicates its chromosomes and the karyotype configuration of the complete mole zygote is 46, XX. In about 4–20% of cases, an empty ovum is fertilized by two haploid sperms resulting in 46, XX or XY. In partial mole, a haploid ovum is fertilized by two sperms. The zygote, therefore, becomes triploid containing 69, XXY, XXX and rarely XYY.

Complete mole is characterized by gross villous vesicles although sometimes these may not be present in early gestation. Histologically, there are diffuse hydropic villi and trophoblastic hyperplasia. The cytotrophoblasts may show nuclear pleomorphism. There are no foetal tissues identified. In contrast, gross villous vesicles are only occasionally seen in partial mole and these tend to be smaller and less numerous compared with complete mole. Normal gestational products like gestational sac, embryo, foetus or placenta may be present. Hydropic villi and trophoblastic hyperplasia are less conspicuous in partial mole and foetal tissues like erythrocyte may be found. There may also be scalloping of chorionic villi and trophoblastic stromal inclusion. p57 (KIP2) is a paternally imprinted gene and is maternally expressed. Complete mole is composed of paternal DNA and so there is absence of p57 (KIP2) nuclear staining in the cytotrophoblasts and villous stromal cells. On the other hand, since partial mole and hydropic abortion contain maternal DNA, p57 (KIP2) is positive. Genotyping such as the use of short tandem repeats can identify the paternal or maternal origin of the poly-morphic alleles. Thus, it is possible to distinguish paternal diploidy or biparental diploidy as well as diandrogenic triploidy allowing for a diagnosis of complete, partial or 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, molar pregnancy may just be incidentally shown and the patients may not be symptomatic at all. And due to the early diagnosis, florid symptoms of hyperemesis gravidarum, hyperthyroidism, early-onset pre-eclampsia, thromboembolism, large ovarian theca lutein cysts and neurological and chest symptoms due to brain and lung metastasis are rarely seen nowadays.

Investigation
Ultrasound is commonly performed in pregnancy. Complete mole may be diagnosed by features such as anembryonic pregnancy, delayed miscarriage and snow-storm appearance. It is difficult to detect partial mole by ultrasound, although some have described soft markers such as cystic spaces in placenta, ratio of transverse to antero-posterior diameters of the gestational sac more than 1.5. In general, the detection rate of molar pregnancy by ultrasound is poor. In one retrospective study involving more than 1000 patients, the sensitivity, specificity, positive predictive value and negative predictive value for ultrasound in detecting hydatidiform mole were 44%, 74%, 88% and 23%, respectively.

Human chorionic gonadotrophin (hCG): it is a glycoprotein produced by syncytiotrophoblasts. It contains 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. β-hCG not only reflects trophoblastic activity but also promotes tumourigenesis. Various forms of β-hCG exist in GTD, including free-β, β-core, nicked free-β and carboxyl-terminal fragment. Therefore, an ideal hCG assay for GTD should detect all forms of β-hCG. False-positive and false-negative results can occur. Phantom hCG (pseudo-hypergonadotropinemia) is a result of the presence of heterophilic antibodies in serum giving rise to a falsely elevated hCG. If there is discrepancy with the clinical presentation, hCG levels should be measured again with a different immunoassay. The other alternative is to measure the urine hCG level because heterophilic antibodies are not excreted into the urine. The serum hCG can also be diluted serially. The lack of dilutional parallelism also indicates the presence of phantom hCG. On the other, 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 very high hCG level is suspected, the laboratory should be informed and the serum should be diluted before measurement. The role of hyperglycosylated hCG in predicting the presence of GTN needs further confirmation as no commercial assay is available at the moment.

It had been shown that 46% of 153 patients with complete mole had elevated hCG level over 100,000 IU/l before evacuation. However, there is no consensus on a cut-off level for making the diagnosis, though some studies showed that molar pregnancy was suggested if the hCG level was higher than two multiples of the median. While hCG may not be diagnostic of molar pregnancy, it should be measured as a baseline for subsequent monitoring if molar pregnancy is suspected before evacuation.

Treatment
Suction evacuation of the uterus can obtain tissues for histologic diagnosis and treat the condition completely under most circumstances. A case-control study showed that cervical priming immediately before uterine evacuation did 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, which might increase the need of subsequent chemotherapy. Nevertheless, medical abortion may be considered in partial mole at second trimester because the foetal parts may obstruct the evacuation and the risk of persistent trophoblastic disease is low. Because the uterus is usually

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vascular and bigger than date, uterine evacuation should be performed by an experienced gynaecologist. In case of heavy bleeding during the procedure, oxytocic agents can be given, preferably after the evacuation has been completed. Second uterine evacuation is usually unnecessary unless in selected patients who are asymptomatic with retained products of conception or when the hCG level is below 5000 IU/l, after being reviewed in specialist centres.

Mole in multiple pregnancy
Hydatidiform mole can co-exist with a live foetus. In this situation, an option of continuing the pregnancy can be given to the patient, provided that she understands there are 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
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 gestational trophoblastic neoplasia (GTN), 412 (98%) presented within 6 months after evacuation and only one woman was detected by routine extended follow-up. The current practice of the Charing Cross Hospital is to ask the patients to send their serum and urine samples for hCG assay every 2 weeks until the hCG levels become normal.

At the 2000 International Federation of Obstetrics and Gynecology (FIGO) meeting, the term ‘gestational trophoblastic neoplasia’ was designated to the condition where hCG levels failed to drop in the absence of a normal pregnancy. In addition, in order to diagnose GTN, there should be: a plateau comprising of at least four persistently elevated hCG values (day 1, 7, 14 and 21); a sequential rise of hCG for 2 weeks (days 1, 7 and 14 or longer; or lung metastases diagnosed by chest X-ray. GTN also includes invasive mole, choriocarcinoma and PSTT, which is associated with antecedent miscarriage or abortion in 25% of cases, ectopic pregnancy in 5%, full-term pregnancy in 20% and hydatidiform mole in 50%. Similar to molar pregnancy, GTN is more common in South East Asia than the West. The incidence in India and Indonesia is 15–19 per 1000 pregnancies and that in the West is 0.2–0.7 per 1000 pregnancies.

Risks factors for patients with hydatidiform mole
About 0.5% of partial mole and 15% complete mole patients progress to GTN requiring chemotherapy. Retrospective studies have shown that maternal age, previous history of molar

### Recommendations from the UKMEC 2009

<table>
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<tr>
<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 sterilization</th>
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<td>A</td>
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<td>Persistently elevated β-hCG level or malignant disease</td>
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UKMEC, United Kingdom Medical Eligibility of Contraceptive Use. CHC, combined hormonal contraception; POP, progestogen-only pills; DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate; IMP, progestogen-only implant; Cu-IUD, copper-bearing intrauterine device; LNG-IUD, levonorgestrel-releasing IUD; hCG, human chorionic gonadotrophin; Category 1, a condition for which there is no restriction for the use of the contraceptive method; Category 2, a condition where the advantages of using the method generally outweigh the theoretical or proven risks; Category 3, a condition where the theoretical or proven risks usually outweigh the advantages of using the method; Category 4, a condition which represents an unacceptable health risk if the contraceptive health risk if the contraceptive method is used; Category A, there is no medical reason to deny sterilization to a person with this condition; Category D, the procedure is delayed until the condition is evaluated and/or changes. Alternative temporary methods of contraception should be provided.

Table 3
pregnancy and elevated post-evacuation hCG levels were associated with higher risk of GTN. However, it is controversial about the prognostic value of factors like maternal age, histological type, previous history of molar pregnancy, initial uterine size, gravidity, presence of theca lutein cysts and initial β-hCG levels.

Prognostic factors and staging
There are few staging systems for GTN such as the ones developed in the Charing Cross Hospital and by Hammond. In 2000, the FIGO Gynecological Oncology Committee recommended a clinical staging system and accepted the incorporation of the WHO scoring system modified from the one devised by Bagshawe, which combines the anatomical distribution and prognostic factors. 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 5. The overall 5-year survival for patients with GTN is estimated to be 92.7%. The 5-year survival for stage I, II, III and IV patients is 97.3%, 85.7%, 82.8% and 61.9%, respectively. Using six 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 Charing Cross Hospital are listed in Table 6. Essentially, it is recommended that low-risk disease should be treated by single-agent chemotherapy while high-risk disease and choriocarcinoma by combination chemotherapy. Investigation is, therefore, important in calculating the risk scores for the patients to assess the need and choice of chemotherapy.

Physical examination is carried out to assess the uterine size, to look for any vaginal metastasis or adnexal mass. Full blood count, clotting profile, liver function test, urea and electrolytes, and thyroid function tests are taken to assess the general condition of the patients. 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 that might otherwise cause the rise of hCG. It is also needed to locate and measure the size of any intrauterine lesion. It has been suggested that the uterine volume and pulsatility index of the uterine artery can predict the response to chemotherapy. Chest X-ray is crucial in looking for pulmonary metastasis and the role of routine computed tomography (CT) of...
Indications for chemotherapy after molar pregnancy

- 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
- Rising hCG in two consecutive serum samples
- Serum hCG >20,000 IU/L more than 4 weeks after evacuation
- hCG plateau in three consecutive serum samples after evacuation
- Raised hCG level 6 months after evacuation even if it is falling

hCG, human chorionic gonadotrophin.

Table 6

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Table 7

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<th>EMA-CO chemotherapy</th>
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<tr>
<td>Regimen 1</td>
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<td><strong>Day 1</strong></td>
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<tr>
<td>Etoposide 100 mg/m² intravenous infusion over 30 min</td>
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<tr>
<td>Actinomycin-D 0.5 mg intravenous bolus</td>
</tr>
<tr>
<td>Methotrexate 300 mg/m² intravenous infusion over 12 h</td>
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<tr>
<td><strong>Day 2</strong></td>
</tr>
<tr>
<td>Etoposide 100 mg/m² intravenous infusion over 30 min</td>
</tr>
<tr>
<td>Actinomycin-D 0.5 mg intravenous bolus</td>
</tr>
<tr>
<td>Folinic acid rescue 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><strong>Regimen 2</strong></td>
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<td><strong>Day 8</strong></td>
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<tr>
<td>Vincristine 1 mg/m² intravenous bolus (maximum 2 mg)</td>
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<tr>
<td>Cyclophosphamide 600 mg/m² intravenous infusion over 30 min</td>
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<td>The two regimens alternate each week</td>
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EMA-CO chemotherapy, etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine with folinic acid rescue. In recent studies, the complete remission
rate was about 85% and the overall survival rate was about 90%. However, survival was only 27% with liver metastasis and 70% with brain metastasis. Prognosis was even worse (10%) with both brain and liver metastasis. The major side effects included mucositis, pleuritis, alopecia, liver derangement, myelosuppression and vincristine-associated peripheral neuropathy. In addition, one health questionnaire study carried out in the UK showed that combined chemotherapy containing etoposide was associated with a slight increased risk of secondary malignancy (RR = 1.5; 95% confidence interval (CI), 1.1–2.1) with the greatest risk in myeloid leukaemia (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 minimize 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). As first-line chemotherapy regimens, 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 select the best regimen because of the lack of randomized controlled trials and the heterogeneous and unclear quality of the studies.

Resistant or relapsed high-risk GTN: the relapse rate is about 3% in low-risk GTN and 7–10% in high-risk GTN. Although 20% of these patients eventually fail to respond to treatment and die, the rest are salvageable by further chemotherapy. 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).

For patients who are resistant to methotrexate or have relapse in low-risk GTN, actinomycin-D can be given if hCG is less than 300 IU/l and combined chemotherapy like EMA-CO can be given if hCG is higher than 300 IU/l. For those who are resistant to first-line chemotherapy or have relapse in high-risk GTN, salvage combined chemotherapy can be given, such as EP-EMA (etoposide, cisplatin, etoposide, methotrexate and actinomycin-D), MBE (methotrexate, bleomycin and etoposide), TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide), BEP (bleomycin, etoposide and cisplatin), VIP or ICE (etoposide, ifosfamide and cisplatin or carboplatin). Myelosuppression remains the dose-limiting factor and granulocyte-colony stimulating factor may be needed.

Role of surgery: although GTN is chemosensitive, surgery is occasionally indicated. Surgery may have a role 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; treat infection; 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 still be needed if patients complain of sudden abdominal pain related to ovarian theca lutein cyst complications. About one in 140 patients require hysterectomy for GTN. One-third of them are performed because of resistance to chemotherapy, and another third because of heavy bleeding. The remission rate of patients undergoing hysterectomy is around 90%. 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 hCG drop and many patients still had a persistent chest lesion for years despite clinical remission. However, if there is chemoresistance related to the pulmonary metastasis and the lung lesion is amenable to operation, thoracotomy and 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 requiring emergency decompression, or when there are multiple metastases where early removal of solitary superficial tumour can stabilize the patients before contemplating further treatment.

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 embozation to control the bleeding and disease in a patient with low-risk GTN that eliminated the need for 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 mainly used to treat brain metastasis to prevent unexpected bleeding. When whole brain irradiation is given concurrently with combined chemotherapy, the overall survival rate is around 40–90%. A retrospective study compared the outcomes of those receiving chemotherapy and irradiation, chemotherapy alone and no treatment, and found that the survival rate 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 showed that the 5-year overall survival rate for those receiving less than 2200 cGy was 39%, and for those receiving more than 2200 cGy was 100% \( (p = 0.03) \). In general, the usual dosage is 2000–4000 cGy given in 10 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 delivered at around 2000 cGy concurrently with
chemotherapy. However, the prognosis of these patients is poor with an overall 5-year survival rate of less than 30%. Radiotherapy to liver probably does not provide any benefit and it is seldom given nowadays.

**Follow-up**

Reurrence 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 8. As it is unclear when it is safe to stop the surveillance, the monitoring is life-long.

**Fertility**

Most of the 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 recent 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 counselling 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 first group (median 50, range 25–56 years) had menopause 3 years earlier than the second 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 for patients receiving single and multiple agents, the overall fertility rate is more than 80% and about 70% can achieve a full-term live pregnancy. The rate of foetal congenital abnormality is similar to that of the normal population and it is only 1.8% even for patients conceiving within 1 year of chemotherapy completion. Nevertheless, 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%, \( p = 0.14 \)). 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 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 8.

### Management of gestational trophoblastic neoplasia

**Investigation**

- Serum and urine hCG
- Full blood count
- Clotting profile
- Liver function test, urea, creatinine and electrolytes
- Group and save
- Thyroid function test
- HIV and HBV serology
- Chest X-ray
- Ultrasound Doppler of pelvis
- Ultrasound of liver or CT abdomen and thorax
- CT or MRI brain if there are neurological symptoms or lung metastasis
- CSF hCG level in case of clinical suspicion

**Treatment**

- Low-risk: single-agent chemotherapy like methotrexate
- High-risk: multi-agent chemotherapy like EMA-CO
- Surgery, selective arterial embolization and radiotherapy are used in selected cases

**Follow-up**

- Serum and urine hCG are taken twice weekly during treatment
- After treatment stops, serum and urine hCG are measured weekly for 6 weeks
- At the 6th week, perform USS Doppler of pelvis, CXR or CT/MRI if they are abnormal at presentation
- Year 1 — Two-weekly serum and urine hCG at 0–6 months, and then two-weekly urine hCG at 7–12 months
- Year 2 — Monthly urine hCG
- Year 3 — Two-monthly urine hCG
- Year 4 — Three-monthly urine hCG
- Year 5 — Four-monthly urine hCG
- Year 6 and life-long — Six-monthly urine hCG
- Practice contraception for at least 12 months

hCG, human chorionic gonadotrophin; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; EMA-CO, etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine with folinic acid rescue.

### Table 8

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<th>Year</th>
<th>Follow-Up Schedule</th>
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<td>0–6</td>
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<td>Six-monthly urine hCG</td>
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<td>6</td>
<td>Life-long</td>
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Epidemiology

Incidence of choriocarcinoma is difficult to estimate because of its rarity. In Europe and USA, the estimated number of choriocarcinoma is one in 50,000 pregnancies whereas in South East Asia and Japan it is 9.2 and 3.3 respectively.

Pathology

Choriocarcinoma shows no chorionic villi. Abnormal cytotrophoblastic and syncytiotrophoblast with haemorrhage and necrosis invading myometrium and vessels are common. Haematological spread is common with metastasis to lung, liver, brain, bowel and pelvis.
Presentation
Choriocarcinoma is associated with pregnancy. It was estimated that 25% occurred after miscarriage, 25% after term pregnancy and the rest after molar pregnancy. Unless developed following molar pregnancy, a high index of suspicion is needed to make a diagnosis based on an unexplained high hCG level in the presence of tumour evidenced by imaging in the lung, brain or liver. Many patients present with neurological or pulmonary symptoms and diagnosis is made histologically after operation in removal of the tumour. A delay in diagnosis with delay in starting chemotherapy treatment is a common cause of early death in patients with brain or liver metastasis.

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

Tumours of intermediate trophoblast
PSTT
PSTT was first described in 1976 and is a rare neoplasm arising from the implantation site intermediate trophoblast. It is a unique form of GTN and constitutes 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, nephritic syndrome related to immunoglobulin deposits in the glomerular membranes, and virilization due to ovarian stromal hyperthecosis and paraneoplastic syndromes are also seen. 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. The diagnosis is often made in the hysterectomy or curettage samples. Lung metastasis, long interval from antecedent pregnancy (5-years or more), mitotic count more than five per 10 high power fields, and advanced FIGO stage appear to be the poor prognostic factors. The cornerstone treatment method is hysterectomy because PSTT is less sensitive to chemotherapy. However, if fertility preservation is desired, conservative management like uterine curettage, hysteroscopic resection and chemotherapy may be considered if the lesion is localized in the uterus, the mitotic count is low, there is no uterine enlargement and close monitoring is available. The most commonly used chemotherapy regimen is EMA-EP (etoposide, methotrexate, actinomycin-etoposide, and cisplatinum) and alternative is TE/TP.

ETT
ETT is derived from the chorionic-type intermediate trophoblast and was first described in 1998. The tumour is characterized 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 co-exist 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 chemosensitive and it is mainly treated by operation.

Conclusion
The management of GTD is a success in modern medicine. Because of the early diagnosis by different imaging tools, the availability of sensitive hCG assays and the introduction of effective chemotherapy, the once fatal malignancy is now curable. However, there is still a challenge about the management of chemoresistant patients. The rarity of the disease and the different staging systems and treatment criteria used in different centres also hinder the conduction of randomized controlled trials and systematic reviews. International collaboration and further studies are needed to define the best treatment protocol and explore other forms of treatment.

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, thromboembolism, 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, PSTT or ETT is found.

- The FIGO committee have recommended a clinical anatomical staging system together with the modified WHO risk scoring system. Global standardization 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 7–10% 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 jeopardized 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 chemosensitive and hence hysterectomy is the mainstay treatment.