Curr Oncol Rep (2014) 16:408
DOI 10.1007/s11912-014-0408-y

GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Gestational Trophoblastic Tumours: An Update for 2014

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Abstract Gestational trophoblastic disease describes a variety of pregnancy-related diseases including the premalignant conditions of a partial and complete hydatidiform mole and the malignant disorders of invasive mole, choriocarcinoma and the rare placental-site trophoblastic tumour and epithelioid trophoblastic tumour. The availability of a highly sensitive tumour marker in the form of human chorionic gonadotrophin, the chemosensitive character of the disease with effective treatment strategies and centralization of care of a rare group of diseases has resulted in excellent survival rates, which can exceed 98 %. This review gives a general overview of gestational trophoblastic disease, the most recent insights in aetiology and pathology and a summary of the different management strategies.

Keywords Gestational trophoblastic disease · Molar pregnancy · Choriocarcinoma · Trophoblastic tumours · Pregnancy-related diseases · Gynaecological cancers · Oncology · Choriocarcinoma Trophoblastic tumours · Pregnancy-related diseases · Gynaecologic cancers

Introduction

A few days after conception, normal gestational trophoblasts arise from the peripheral cells of the blastocyst and invade the endometrium and uterine vasculature to form the placenta via well-controlled biological and immunological mechanisms. Gestational trophoblastic disease (GTD) is a rare complication of pregnancy during which these regulatory mechanisms are lost, resulting in vascularized tumours with possible metastases. It encompasses a group of interrelated diseases ranging from the premalignant partial and complete hydatidiform mole to the malignant diseases of an invasive mole, choriocarcinoma and the rare placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The malignant diseases are also collectively described as "gestational trophoblastic neoplasia" (GTN). In this review we give an overview of this rare group of diseases, discuss their epidemiology, pathological and genetic changes and clinical management.

Epidemiology

In the UK, a national register with central pathology review for all patients with GTD was established in 1973, resulting in the largest database worldwide. This has shown that the incidence of a partial hydatidiform mole (PHM) is approximately three per 1,000 pregnancies and that of a complete hydatidiform mole (CHM) is approximately one to three per 1,000 pregnancies [1]. Higher incidence rates have been reported in some Asian countries as well as in native American Indians, which can be due to dietary or genetic influences, but may also be a reflection of differences in reporting (hospital versus population-based data) or incorrect diagnosis in the absence of central pathology review [2]. Higher frequencies of molar pregnancies are also seen in both the lower and, in particular, the upper extremes of maternal age (younger than 16 years or older than 45 years, respectively), which has been a consistent finding in all regions and races [3]. After one molar pregnancy, the chance of a second complete or partial mole is 1–2 %. The risk of a third molar pregnancy increases substantially to 15–20 %, is not decreased by changing partner and may be related to familial or sporadic biparental molar disease (see later and Fig. 1c) [1].

This article is part of the Topical Collection on *Gynecologic Cancers*

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Published online: 16 October 2014

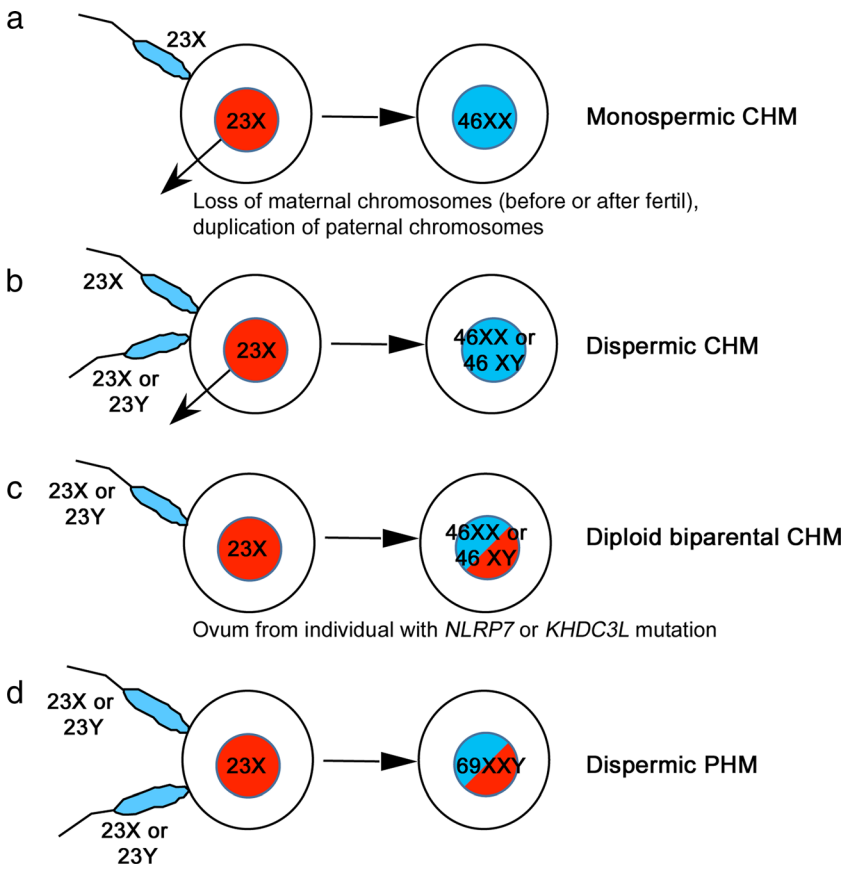

Fig. 1 Cytogenetic origin of complete hydatidiform mole (*CHM*) and partial hydatidiform mole (*PHM*). CHM develops after monospermic (**a**) or dispermic (**b**) fertilization of an ovum but maternal chromosomes have been lost either before or just after conception, resulting in a 46XX androgenetic (monospermic; **a**) or 46XY (dispermic; **b**) karyotype by duplication of the paternal genome. A biparental diploid CHM (**c**) is rare and occurs in females with recurrent CHM who are often homozygous, or a compound heterozygote, for mutations in *NLRP7* or *KHDC3L*. Dispermic fertilization of a normal ovum results in a PHM (**d**), which is generally triploid with a 69XXX, 69XXY or 69XYY karyotype

The incidence of choriocarcinoma and PSTT/ ETT is less well known. Following a term delivery, choriocarcinoma develops in approximately one in 50,000 women. However, genetic studies have shown that choriocarcinoma can arise from any pregnancy, including CHM and PHM pregnancies, and therefore the overall incidence of choriocarcinoma is likely much higher [4–6]. PSTT is the rarest form of GTD, representing 0.2 % of all registered cases of GTD in the UK [7].

Pathology and Genetics

Hydatidiform moles and choriocarcinoma arise from the villous trophoblast. In most cases (approximately 80 %), a CHM develops when an ovum is fertilized by one sperm but maternal chromosomes have been lost either before or just after conception, resulting in a 46XX androgenetic karyotype by duplication of the paternal genome (46YY products presumed not to be viable; Fig. 1a). The other cases of CHM most often arise from dispermic fertilization of one ovum with no maternal chromosomes (Fig. 1b) [1]. Some patients with recurrent CHM have a biparental diploid karyotype, which has been found to be an autosomal recessive disease, familial recurrent hydatidiform mole. Genetic studies in these families have found an association with mutations in two genes, *NLRP7* and, more rarely, *KHDC3L* (Fig. 1c) [8, 9]. Dispermic fertilization of a normal ovum results in a PHM, which is generally triploid and can be difficult to distinguish morphologically from a non-molar miscarriage. If a fetus is present, it often has features of triploidy, including growth retardation and multiple congenital malformations, and is never viable (Fig. 1d).

Morphologically, PHM and CHM have distinct features, but review by specialist histopathologists is recommended. In particular, as with earlier evacuation, the classic features may be less well developed and, for example, CHM can easily be incorrectly classified as PHM or non-molar abortions [10••]. CHM have characteristically been described as grape-like structures attributed to diffusely hydropic villi with diffuse trophoblast hyperplasia and stromal hypercellularity with stromal karyorrhectic debris and collapsed villous blood vessels. In contrast, PHM demonstrate a more patchy villous hydropic change with patchy

trophoblast hyperplasia and scattered, abnormally formed villi with trophoblastic pseudoinclusions. Abortions due to trisomy, monosomy, maternally derived triploidy and translocations often develop some degree of hydropic change, which can cause diagnostic confusion with molar pregnancies. Immunostaining with $p57^{KIP2}$, an imprinted marker expressed only by the maternal genome and therefore negative in CHM but positive in PHM or non-molar pregnancies, ploidy analysis by in situ hybridization or flow cytometry (triploid in PHM) or molecular genotyping can help to distinguish PHM from CHM and non-molar hydropic abortions [4].

"Invasive mole" describes the condition where a CHM or, less frequently, a PHM invades the myometrium. It is clinically identified by a persistently elevated or rising level of human chorionic gonadotrophin (hCG) following uterine evacuation and an abnormal uterine ultrasound scan; pathological confirmation is rarely required. In occasional cases where histological information is available, invasive mole can be distinguished from gestational choriocarcinoma by the presence of chorionic villi.

Gestational choriocarcinomas are characterized by invasion of the myometrium with a dimorphic population of both cytotrophoblasts and syncytiotrophoblasts without the presence of formed chorionic villi. They have a grossly abnormal karyotype with various ploidies and chromosome rearrangements, none of which are specific for the disease [11]. Choriocarcinomas can originate from any type of pregnancy, including a previous hydatidiform mole or from a normal conception [5, 6, 12]. Intraplacental choriocarcinoma is rarely discovered, probably because placentas are not routinely sent for pathology review, so their true incidence is unknown. When it is discovered, the subsequent development of metastatic disease does not invariably occur. However, in patients presenting with metastatic choriocarcinoma following a term delivery, it seems likely that the preceding lesion was intraplacental. Consequently, patients with these lesions need monitoring. Fortunately, all choriocarcinomas secrete hCG, which serves as a very sensitive tumour marker. Subsequent biopsy of metastatic choriocarcinomas, which are highly vascular, can cause life-threatening haemorrhage, so obtaining tissue to make a formal histological diagnosis of choriocarcinoma is often not appropriate. Where tissue can be safely obtained, this can make possible a pathological diagnosis and also genotyping. The latter can provide useful information about the causative pregnancy and confirm gestational choriocarcinoma rather than non-gestational tumours, such as gastric or lung cancers, which can occasionally present as choriocarcinoma [13]. Unfortunately, there are no pathological or molecular features that can reliably predict which patients will develop a malignant change in a CHM or PHM, and therefore all patients with an evacuated molar pregnancy will need hCG surveillance [10••, 14].

Different in clinical behaviour are the PSTT, and a newly recognized variant termed "epithelioid trophoblastic tumour" (ETT). PSTT are characterized by monomorphic infiltrating nests and sheets of interstitial trophoblasts, with less necrosis and haemorrhage and lower concentrations of hCG compared with choriocarcinoma. Immunohistochemisty shows a positive staining for human placental lactogen and other extravillous trophoblast markers. ETT, which clinically behave similarly to PSTT, have a distinctive hyaline-like matrix and a slightly different immunohistochemical profile [15]. After the placenta is lost from the uterus, small nodules of placental tissue can remain in the myometrium, and usually resorb over time. However, occasionally they persist as placental-site nodules and can develop atypical features (atypical placental-side nodules) with increased mitoses and possible progression to PSTT or ETT [10••].

Diagnosis

Most patients with a CHM or PHM present with unexpected vaginal bleeding in the first trimester and subsequent abnormal findings on ultrasonography. Because of the routine use of ultrasonography in early pregnancy, previously reported symptoms such as hyperemesis, anaemia, pre-eclampsia, excessive uterine size, hyperthyroidism and respiratory distress are now rarely seen [16]. The classic ultrasonographic appearance of a CHM as a "snowstorm", a uterine cavity filled with a heterogeneous mass without associated fetal development and with theca lutein ovarian cysts, is seen only in the second trimester [17]. Findings in the first trimester are less specific and non-diagnostic, with high false-positive and false-negative rates, in particular for PHM, and therefore all products of conception from non-viable pregnancies must undergo histological examination [17–19].

Choriocarcinoma and PSTT/ETT, which all can develop months or years after a prior pregnancy, can be more difficult to diagnose. They can present with irregular vaginal bleeding or with symptoms related to metastatic disease with, for example, seizure, headaches or hemiparesis due to brain metastases or haemoptysis and respiratory symptoms related to pulmonary disease. Gestational choriocarcinoma metastasizes widely, particularly to the lungs, pelvic organs and brain. PSTT and ETT secrete less hCG, grow slowly and metastasize later in their disease course, with a propensity for involving the lymphatic system [10••].

Trophoblastic disease is virtually unique in that it produces a highly specific marker in the form of hCG, which can be measured in urine and/or blood and correlates with the amount of disease present. It is a large placental glycoprotein composed of an alpha subunit, which is similar to those of other pituitary glycoprotein hormones, and a beta subunit that is specific to hCG. Assays to detect hCG therefore use antibodies that detect

the beta subunit. In healthy pregnancy, the beta subunit is intact and is hyperglycosylated in the first trimester. However, in trophoblastic disease or cancer, the beta hCG can exist in a number of fragments, including nicked hCG, beta-core, C-terminal segment and free beta subunit; an assay used to monitor hCG values in these cases should therefore detect all forms of beta hCG preferably equally well. Unfortunately, many of the commercial assays fail to detect all forms of beta hCG and/or overdetect or underdetect certain forms, which may give false-negative results in patients with cancer. Some other assays are more susceptible to false-positive results, often owing to cross-reacting heterophile antibodies. As monitoring of hCG has a crucial role in the management of GTD, it is important for clinicians to be aware of these potential problems [1].

Treatment

Surgical Evacuation

Suction dilation and curettage (D&C) with ultrasound guidance to ensure complete uterine evacuation is the treatment of choice for patients with a suspected hydatidiform mole. Since the trophoblast expresses rhesus D, patients who are rhesus negative should receive anti-rhesus D prophylaxis during the procedure. Twin pregnancies comprising a normal fetus and a hydatidiform mole are estimated to occur in one per 20,000–100,000 pregnancies. Although these pregnancies have a high risk of spontaneous abortion, a case series of 77 twin pregnancies showed a successful pregnancy outcome in approximately 40 % of cases with no obvious increased risk of malignant change [20].

Following evacuation, all patients with a hydatidiform mole should be registered with a specialist centre for hCG surveillance. In most cases, the hCG level will normalize after evacuation, and no further treatment is indicated. However, malignant change may occur, resulting in what is often termed "persistent GTD" or "GTN after hydatidiform mole", as reflected by a plateaued or rising hCG level, and further treatment will be needed. Data from the UK have shown that this occurs after 15 % of CHM and 0.5–1 % of PHM [6, 21, 22]. Other countries have reported higher rates, but this is likely due to differences in hCG assays, criteria used for the diagnosis of GTN or lack of centralized pathology review and whole population demographics rather than due to a true difference in disease biology [1]. Various hCG surveillance programmes exist in different countries, but the principles are similar. In the UK, serum and urine hCG levels are measured every 2 weeks until the hCG level is normal, after which monthly urine hCG values are recorded. Patients who reach a normal hCG level within 56 days of evacuation have a lower risk of GTN after hydatidiform mole and are monitored for 6 months from the evacuation date; when the first normal hCG reading is after 56 days, hCG monitoring continues for 6 months from that day for patients with CHM [23]. The same principle was previously applied for patients with PHM. However, recent data from over 10,000 PHM show that the risk of subsequent GTN once the hCG level is normal is only 1:3000, so currently surveillance is discontinued after a second confirmatory normal value 1 month later. With each subsequent pregnancy, ensuring a normal hCG level once the pregnancy has ended can help to detect rare relapses of dormant disease. In the UK, this hCG sample is taken 6 weeks after the end of each future pregnancy regardless of the pregnancy outcome.

Indications To Start Treatment

The commonest indication to start treatment is a plateaued hCG level (three or more equivalent hCG values over at least 3 weeks) or rising hCG levels (two consecutive rises in hCG level of 10 % or greater over at least 2 weeks) after evacuation. Other reasons to initiate treatment are histological evidence of choriocarcinoma, metastatic spread to the brain, liver or gastrointestinal tract, or radiological opacities larger than 2 cm on chest X-ray. In the UK, other indications for treatment include heavy vaginal bleeding that requires transfusion, even if the hCG level is falling, and a serum hCG level of 20,000 IU/L more than 4 weeks after evacuation because of a risk of uterine perforation and our prior experience that such disease is unlikely to remit spontaneously [1, 24]. If 6 months after evacuation the hCG level is still elevated but falling, continued surveillance has been shown to be clinically safe as in all patients the hCG level eventually returned to normal without the need for chemotherapy [25••].

Staging Investigations and Risk Stratification

Once the decision has been made that chemotherapy is needed, the regimen is chosen in most countries by assessing the patient's prognostic score as defined by the International Federation of Gynaecology and Obstetrics (FIGO). Scores given to various factors from the history, examination and investigations give a combined score that predicts the potential of developing resistance to single-agent chemotherapy (Table 1). To allow comparison between centres, all physicians managing GTN should now use this scoring system [26]. The most important prognostic variables include the serum hCG concentration (correlation with viable tumour tissue), the duration of the disease (risk of drug resistance of GTN varies inversely with time) and the presence of liver and/or brain metastases. Most patients with GTN following a hydatidiform mole are identified early via hCG monitoring and have a FIGO score of 0–6, which indicates disease that is at low risk of becoming resistant to single-agent chemotherapy with methotrexate or actinomycin D. A Doppler pelvic ultrasonography

Table 1 International Federation of Gynaecology and Obstetrics (FIGO) scoring system for gestational trophoblastic neoplasia

Prognostic factor	Score			
	0	1	2	4
Age (years)	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval from end of antecedent pregnancy to chemotherapy (months)	<4	4–6	7–12	>12
hCG (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Number of metastases	0	1–4	5–8	>8
Site of metastases	Lung	Spleen and kidney	GI tract	Brain and liver
Largest tumour mass (cm)		3–5	>5	
Previous chemotherapy			Single-agent therapy	Combined therapy

The total score is calculated by adding the individual scores for each prognostic factor. Low risk, 0–6; high risk, 7 or greater.
GI gastrointestinal, *hCG* human chorionic gonadotrophin

will confirm the absence of pregnancy, measure uterine size and the extent of the disease and its vascularity by the Doppler pulsatility index. The latter has been suggested to be a further independent prognostic factor for resistance to single-agent therapy (Fig. 2a) [27]. All patients will need a chest X-ray, but as possible pulmonary micrometastases do not influence the outcome, computed tomography (CT) of the chest is not needed if the chest X-ray is normal. However, if pulmonary lesions are seen, complete staging with body CT and magnetic resonance imaging (MRI) of the brain is indicated to exclude more widespread disease [10••].

Women who present with suspected choriocarcinoma or PSTT/ETT following a prior pregnancy require full staging investigations with Doppler pelvic ultrasonography, body CT and brain MRI at presentation. If lung metastases are present and the brain MRI is normal, a lumbar puncture to measure the ratio of cerebrospinal fluid to serum hCG (normal <1:60) can help to rule out occult CNS disease. For choriocarcinomas, the FIGO scoring system is the same as for GTN following hydatidiform mole as described above, and therapeutic choices are not guided by anatomical staging. However for PSTT and ETT, which have a different biological behaviour as described above, this scoring system is not helpful, and the FIGO anatomical staging is used to help make treatment decisions (Table 2) [10••]. In PSTT, univariate analysis has identified stage, hCG value, mitotic index and a duration of more than 4 years from a prior pregnancy as prognostic factors, but on multivariate analyses, only

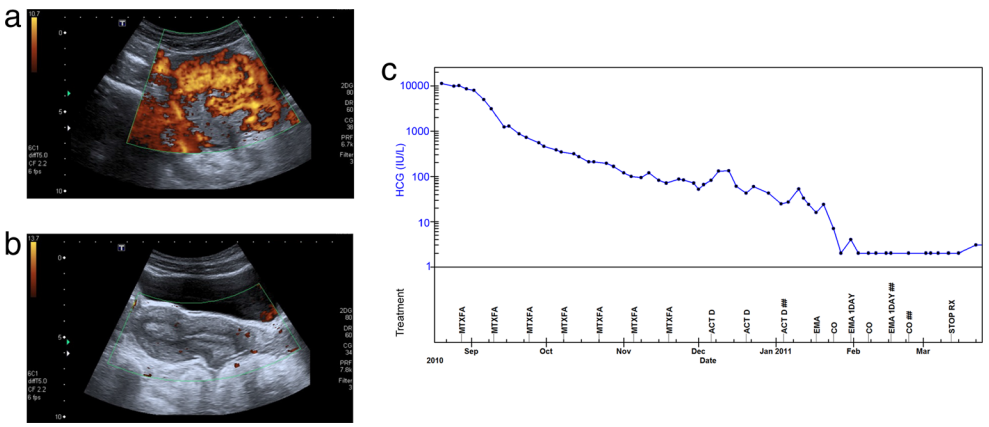

Fig. 2 Doppler pelvic ultrasonography of persistent gestational trophoblastic disease following a hydatidiform mole and the treatment graph. Doppler pelvic ultrasound image before chemotherapy (**a**) and after chemotherapy (**b**). The response to treatment after evacuation of a CHM, as measured by the human chorionic gonadotrophin (*hCG*) concentration, is shown in **c**. The time and type of intervention are shown below the *line*. Treatment was indicated for low-risk gestational trophoblastic neoplasia, and methotrexate/folinic acid (*MTXFA*) therapy was started. However, as demonstrated by at least two subsequent samples with a plateaued or rise in hCG concentration, resistance to therapy developed, and a change in treatment was indicated, first to actinomycin D (*ACT D*) (at hCG concentration below 300 IU/L) and later to etoposide, methotrexate and ACT D (*EMA*)/cyclophosphamide and vincristine (*CO*). Therapy was continued for 6 weeks after normal hCG concentration (below 5 IU/L) was recorded, after which surveillance with regular hCG monitoring continued. *RX* treatment

Table 2 FIGO anatomical staging (used for placental-site trophoblastic tumour/epithelioid trophoblastic tumour)

Stage	Description
I	Disease confined to the uterus
II	Disease extending into the pelvis
III	Disease spread to lungs and/or vagina
IV	All other metastatic sites, including liver, kidney, spleen and brain

the duration from the preceding pregnancy was predictive of survival [7].

Treatment of Low-Risk Disease

The role of a second D&C to reduce the need for chemotherapy is controversial, and a second D&C should be considered only if the disease is in the uterine cavity rather than the myometrium and the hCG level is below 5,000 IU/L. However, the relatively low efficacy of repeated D&C and small risks of introducing infection, haemorrhage or uterine perforation should be balanced against a nearly 100 % cure rate with chemotherapy [1].

Several treatment regimens have been developed for low-risk GTN, of which the most frequently used are methotrexate/folinic acid and actinomycin D. A few randomized trials have compared methotrexate-based regimens with actinomycin D, suggesting that the latter is more likely to induce remission, but these studies were underpowered and compared regimens that are not commonly used internationally [28]. A larger international randomized controlled trial to address the question of the optimal first-line treatment is currently open and is comparing the more frequently used methotrexate regimens methotrexate/folinic acid (Table 3)and methotrexate at 0.4 mg/kg (maximum 25 mg) administered intravenously on days 1–5 every 2 weeks in one arm with actinomycin D at 1.25 mg/m^2 administered intravenously every 2 weeks in the other arm [29]. Centres can choose which of the methotrexate regimens they wish to use. Efficacy, toxicity and quality of life will be examined. Whatever the outcome, fortunately, patients who do develop resistance and in whom first-line therapy fails are usually successfully treated with second-line or sometimes third-line therapy (Fig. 2b, 2c), and the overall survival rate approaches 100 % [30, 31]. It, therefore, seems reasonable to start with the least toxic treatment and work up from there. The methotrexate/folinic acid rescue regimen developed at Charing Cross Hospital (Table 3) is widely used as first-line treatment because of its simplicity and lack of toxicity. The first cycle is administered in hospital to monitor the patient for an increased risk of bleeding, after which subsequent cycles can be given at home, at the general practitioner's practice or at a local hospital. It is generally well tolerated, with only about 2 % of women developing toxicities, such as mouth ulcers, sore eyes and rarely serositis with pleuritic or peritoneal pains [30]. Patients who develop resistance to methotrexate/folinic acid, as demonstrated by at least two subsequent samples with a plateaued or rise in hCG level, can change to treatment with actinomycin D when the hCG level is below 300 IU/L; those with higher hCG values will need to start combination treatment as for high-risk disease [31]. Chemotherapy should be continued until the hCG level is normal, followed by three more consolidation cycles to minimize the chances of a relapse. Reduction of consolidation to just two cycles of therapy appears to double the risk of relapse [32•].

Table 3 Treatment for low-risk disease

Agent	Regimen
Methotrexate	50 mg intramuscularly, every 48 h for a total of 4 doses
Folinic acid	15 mg orally, 30 h after each methotrexate injection

Cycle repeated every 2 weeks

Treatment of High-Risk Disease

Patients with a FIGO score of 7 or more are at high risk of developing resistance to single-agent therapy and are therefore treated with combination-agent chemotherapy. The regimen developed by Charing Cross Hospital consisting of etoposide, methotrexate and actinomycin D (EMA) alternating weekly with cyclophosphamide and vincristine (CO) has been adopted by most centres across the world and is used for all high-risk patients in the UK as first-line treatment for high-risk disease (Table 4) [33]. Commencing chemotherapy gently with low-dose etoposide (100 mg/m^2) and cisplatin (20 mg/m^2) on days 1 and 2 repeated weekly for the first 1–3 weeks has been shown to reduce the chances of early death due to haemorrhage or metabolic complications in patients with very advanced disease from 7.2 % to 0.7 % [34•]. With an overall survival rate of 94 % in 196 high-risk patients treated in the UK, these patients have an excellent prognosis [35]. Poor prognostic factors include

Table 4 Treatment for high-risk disease

	Agent	Regimen
Day 1	Etoposide	100 mg/m^2 intravenously over 30 min
	Actinomycin D	0.5-mg intravenous bolus
	Methotrexate	300 mg/m^2 intravenously over 12 h
Day 2	Etoposide	100 mg/m^2 intravenously over 30 min
	Actinomycin D	0.5-mg intravenous bolus
	Folinic acid	15 mg intravenously or orally, every 12 h for 4 doses, starting 24 h after the start methotrexate infusion
Day 8	Vincristine	1 mg/m^2 intravenous bolus
	Cyclophosphamide	600 mg/m^2 over 30 min

Etoposide/methotrexate/actinomycin D therapy alternates with vincristine/cyclophosphamide therapy every week.

very extensive disease associated with a FIGO score greater than 12, disease involving the liver with or without brain involvement and duration greater than 2.8 years from the antecedent pregnancy [1, 36]. More specific treatment recommendations in challenging situations such as brain metastases or pulmonary failure are beyond the scope of this review, and are discussed elsewhere [37, 38]. However, it is worth pointing out that patients presenting with liver metastases after initial induction chemotherapy with low-dose etoposide and cisplatin (EP) will likely fair better if they are treated with EP alternating weekly with EMA (omitting actinomycin D and etoposide on the second day) rather than EMA/CO [39]. Similarly to low-risk disease, once the hCG level has normalized, treatment is continued for 6 or 8 weeks if poor prognostic factors such as liver or brain metastases are present.

Treatment of Drug-Resistant Disease

Regular hCG surveillance during and after chemotherapy allowsearly detection of progression of disease, resulting in excellent outcomes. Approximately a fifth of patients who present with high-risk disease will progress with first line chemotherapy, but with cure rates as high as 84 %, these patients still have an excellent outcome [40]. Fluorine-18 fluorodeoxyglucose PET scanning may help to identify sites of active disease, and selected patients with solitary lesions may benefit from surgical resection of chemotherapy-resistant metastases [41]. However, if the hCG level subsequently falls inappropriately (half-life longer than 2 days) or surgery is not possible, further chemotherapy will be needed. Several salvage regimens have been developed, including treatment with EP alternating weekly with day 1 EMA or the less toxic regimen of paclitaxel/etoposide and paclitaxel/cisplatin (TE/TP; Table 5). To determine the best treatment regimen for relapsed disease, the International Society of the Study of Trophoblastic Diseases has recently proposed an international, multicentre randomized trial of TE/TP versus EP/EMA following treatment with non-cisplatin- or non-paclitaxel-based combination therapies such as EMA/CO [10••]. Patients in whom TE/TP or EP/EMA therapy fails may benefit from high-dose chemotherapy with peripheral stem-cell transplantation, but the cure rates are comparatively low, and further studies to improve patient selection are needed [42]. Other salvage regimens/agents that have been tried with some effect include those used to treat germ cell tumours such as bleomycin/EP, gemcitabine and cisplatin, or breast cancer such as capecitabine. Radiotherapy is not curative, but can help when used as stereotactic Gamma Knife therapy as consolidation for deep non-resectable residual brain lesions.

PSTT/ETT

In contrast to treatment of invasive molar disease or choriocarcinoma, surgery plays a major role in the treatment of the rare PSTT. As discussed before, these tumours have a slow growth rate and can present many years after term delivery, non-molar miscarriage or complete mole. Surgery in the form of a hysterectomy with removal of suspicious pelvic or abdominal lymph nodes and ovarian conservation (unless the patient is postmenopausal or there is a family history of ovarian cancer) is the treatment of choice for stage I disease. Patients with adverse risk factors such as tumours with high mitotic rates, disease within 1 mm of the resection margins or lymphovascular invasion are recommended to have 8 weeks of adjuvant chemotherapy with either EP/EMA or TE/TP, although there is no strong evidence for this. Moreover, patients with localized disease presenting more than 4 years after the last known pregnancy might wish to consider possible tandem high-dose chemotherapy with stem cell support given the very high risk of relapse and death from disease without therapy. Patients presenting with metastatic disease will need chemotherapy, and currently EP/EMA therapy until the hCG

Table 5 Treatment for relapsed gestational trophoblastic neoplasia

	Agent	Regimen
Day 1	Dexamethasone	20 mg orally 12 and 6 h before paclitaxel
	Cimetidine	30 mg in 100 mL NaCl intravenously over 30 min
	Chlorphenamine	10-mg intravenous bolus
	Paclitaxel	135 mg/m^2 in 250 mL NaCl intravenously over 3 h
	Mannitol	10 % in 500 mL intravenously over 1 h
	Cisplatin	60 mg/m^2 in 1 L NaCl intravenously over 3 h
	Post-hydration	1 L NaCl+20 mmol KCl+1 g $MgSO_4$ intravenously over 2 h
Day 15	Dexamethasone	20 mg orally 12 and 6 h before paclitaxel
	Cimetidine	30 mg in 100 mL NaCl intravenously over 30 min
	Chlorphenamine	10-mg intravenous bolus
	Paclitaxel	135 mg/m^2 in 250 mL NaCl intravenously over 3 h
	Etoposide	150 mg/m^2 in 1 L NaCl intravenously over 1 h

level is normal and 8 weeks of consolidation treatment is the recommended regimen. In contrast to choriocarcinoma, residual masses are surgically removed, including the uterus, which can have microscopic disease [1, 7]. Currently, ETT are thought to behave similarly to PSTT, and therefore they are treated as PSTT [10••]. Since these conditions are so rare, it will be a challenge to fully optimize their treatment, but to increase our understanding and improve treatment strategies, an international PSTT/ETT database has recently been established [43].

Follow-up After Treatment

Once treatment has been completed, post-treatment images should be obtained to document the post-therapy appearances for future comparison. For low-risk disease, this usually means a repeated Doppler ultrasound scan of the pelvis (Fig. 2b). The risk of relapse after chemotherapy is approximately 3 %, and resection of residual masses of choriocarcinoma does not reduce this risk, and is therefore not indicated. Most relapses occur in the first year of follow-up, and careful hCG monitoring should continue, with pregnancy ideally delayed until beyond this first year. However, patients who do become pregnant within 1 year of chemotherapy can be reassured of a likely favourable outcome, with risks similar to those of the general UK population [44, 45]. Worldwide, several schedules for hCG surveillance exist, but the basic principles are the same. In the UK, we continue surveillance for life, with a gradual decrease in frequency of blood and urine measurements from weekly for the first 6 weeks after chemotherapy to every 2 weeks until 6 months after chemotherapy, after which time only urine samples are assessed, with a gradual decrease in frequency to 6 monthly after 5 years [10••]. When patients become pregnant, surveillance is discontinued but repeated hCG measurement 6 and 10 weeks after delivery is important to ensure the hCG level has returned to normal.

Apart from EMA/CO bringing the menopause date forward by 3 years, fertility is not affected by chemotherapy, with similar fertility rates as for the general population and no increased risk of adverse outcomes [46–48]. Interestingly, the previously documented slight increased risk of second malignancies induced by EMA/CO [49] has disappeared in the latest, much larger analysis with over 30,000 patient-years of follow-up [50].

Conclusions

In summary, GTD is rare, and although most patients have a favourable outcome, some present with extensive or drug-resistant disease and die of the disease. Consequently, novel therapeutic strategies are still needed with better efficacy and less toxicity, in particular for those with drug-resistant disease. In addition, there is no prognostic test to identify patients who will need treatment after evacuation of a hydatidiform mole. The UK national register with centralized care has proven to be extremely valuable for optimizing patient treatment and facilitated important research to increase our understanding of the disease. The centralization of care, pathology review and hCG monitoring has been essential in enabling us to reach survival rates of 100 % and nearly 95 % for low-risk and high-risk disease, respectively. Similar efforts to establish centralized care of GTD should be made worldwide as this will likely save more young lives [51•].

Compliance with Ethics Guidelines

Conflict of Interest Fieke E. M. Froeling and Michael J. Seckl declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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