Gestational trophoblastic disease: An overview

Introduction
Gestational trophoblastic disease (GTD) represents a group of tumours arising from the trophoblastic tissue of the placenta. It comprises a spectrum of clinical entities ranging from non invasive molar pregnancy, to metastatic gestational trophoblastic neoplasm, and can follow any type of pregnancy.

Classification
The classification of GTD is a confusing subject as GTD and gestational trophoblastic neoplasia (GTN) are often used interchangeably as the same term. In this overview we will refer to the whole spectrum of disease as GTD and the malignant or invasive disease will be referred to as GTN.

Gestational trophoblastic disease can be classified according to the different histological types of the disease:

1. Hydatiform mole
   - Complete hydatiform mole
   - Partial hydatiform mole
   (Most cases of molar pregnancy will have a benign course.)
2. Persistent or invasive hydatiform mole
3. Choriocarcinoma
4. Placental site trophoblastic tumours
5. Miscellaneous trophoblastic tumours

Epidemiology and risk factors
Accurate epidemiologic data on the incidence of GTD is difficult to obtain due to the rarity of the disease, and because data are being compiled mainly from hospital reports and case series. Other unknown environmental factors may also play a role. The incidence of GTD differs widely in different regions of the world. In Italy the prevalence is 66 per 100 000 pregnancies1 and in the United States it is 122 per 100 000 pregnancies.2,3 In South America the prevalence has been reported ranging between 23 and 265 cases per 100 000 pregnancies.4,5 Data from Africa is scarce, with two studies from Nigeria reporting a prevalence ranging from 99 to 335 cases per 100 000 pregnancies.6 One South African study estimates the incidence of molar pregnancy at 1.2 and for choriocarcinoma at 0.5 cases per 1 000 deliveries. This is a report from a single tertiary referral hospital and the authors acknowledge that the figures are influenced by the referral patterns and are not representative of an incidence.7

Maternal age is a well established risk factor for the development of GTD. Women above the age of 35 years have a significantly increased risk, while women younger than 20 years are also at increased risk.8 Most cases of GTD will still occur in women under 35 years of age, as most pregnant women are younger.

A history of a previous episode of GTD also increases the risk in subsequent pregnancies.9 The use of oral contraceptives, even after evacuation of a molar pregnancy, does not increase the risk of developing GTD in subsequent pregnancies.10,11 Diet and lifestyle factors such as smoking, alcohol consumption and ß-carotene consumption are not recognised as risk factors.9

Pathology

Hydatiform mole
A complete hydatiform mole (CHM) is genetically derived from paternal genes and consists of a diploid 46XX karyotype. This occurs after fertilisation of an empty or anuclear ovum by a haploid (32X) sperm and then undergoes duplication. Alternatively, an empty ovum gets fertilised by a diploid sperm. This happens in 4 to 15% of CHM giving rise to 46XX or 46XY karyotypes.12 Recurrent molar pregnancies have also been described. These women are also more prone to develop persistent trophoblastic disease. Recurrent molar pregnancies are associated with an autosomal recessive condition characterised by molar pregnancies consisting of biparental diploid chromosomes. These women have significant under expression of p52(KIP2), which has an important role in apoptosis and tumour expression.13

Characteristics of CHM include diffuse hydropic swelling, trophoblastic hyperplasia on the chorionic villous surfaces, and abnormal distribution of trophoblast.13,14

In partial hydatiform mole (PHM), there are chorionic villi with a normal appearance as well as villi with hydropic changes and focal trophoblastic hyperplasia. The differential diagnosis of a PHM includes placental angiomatous malformation, twin gestation with complete mole and existing fetus, early complete mole and hydropic spontaneous miscarriage.13,14

The genetics in PHM is different to that of a CHM. Fertilisation of a 23X haploid ovum by two spermatozoa takes place, resulting in a triploid zygote with 69 chromosomes, 23 of maternal and 46 of paternal origin (69XXY, 69XXX, 69XYY).13,14

Gestational trophoblastic neoplasia (GTN)
This group consists of invasive mole, choriocarcinoma and placental site trophoblastic tumour. It usually follows after complete hydatiform mole and very seldom after partial hydatiform mole but can also occur after non molar pregnancy.

Stable or rising ß-hCG levels after molar pregnancy will be due to invasive mole in 75% of cases and in 25% of cases it will be because of choriocarcinoma. On the other hand, GTN developing after a non molar

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pregnancy will always be due to choriocarcinoma or placental site trophoblastic tumour.14

Invasive hydatiform mole

Invasive mole is mostly a clinical entity diagnosed on the post molar evacuation β-hCG trend. It is difficult to diagnose histologically, as myometrial tissue needs to be present in the specimen in order to facilitate this diagnosis. Histological diagnosis is made at time of hysterectomy, and is characterised by enlarged hydropic villi that infiltrate into the myometrium. The histopathology of invasive mole may closely mimic that of choriocarcinoma.15,16

Choriocarcinoma

Choriocarcinoma is a highly malignant tumour arising from the trophoblastic epithelium. It originates inside the uterus or in the Fallopian tube in the case of an ectopic pregnancy. Fifty percent of all cases of gestational choriocarcinoma follow a hydatiform mole, 25% follow a spontaneous abortion or ectopic pregnancy, and 25% follow a term pregnancy.

Metastases are to the lungs, brain, liver, pelvis and vagina. Microscopically there is invasive proliferation of syncytiotrophoblasts and cytotrophoblasts in the absence of choriocarcin villi.

Choriocarcinoma following molar pregnancies are mostly aneuploid containing only paternal DNA, while those cases following normal pregnancy consist of biparental chromosomes identical to the fetus.15,16

Placental site trophoblastic tumour

Occurs mostly after normal pregnancies or spontaneous miscarriages. Chorionic villi are usually absent as the neoplasm occurs in the non-villous trophoblast. There is invasion of the myometrium with a dissecting growth pattern.17 β-hCG levels are not always elevated, and these tumours can be of low–grade or high grade malignancy. Malignant placental site trophoblastic tumour is fairly resistant to chemotherapy.

Epithelioid trophoblastic tumour

This represents a very rare form of trophoblastic disease, and can occur after any type of pregnancy in younger women. It can also occur up to 10 years after the last known pregnancy and has also been described in post-menopausal women. The histological appearance is that of intermediate trophoblasts with cellular characteristics between primitive cytotrophoblast and terminally differentiated cyrsyntrophoblast. β-hCG levels are usually elevated and vaginal bleeding is often the presenting symptom.17,18

Miscellaneous trophoblastic tumours

These are rare and consist of exaggerated placental site and placental site nodule and plaque.

Clinical presentation and diagnosis of hydatiform mole

Pregnancy is the most common cause of a raised β-hCG in women, and therefore complicated pregnancy is frequently diagnosed in patients with molar pregnancy. The most common presenting symptom is abnormal vaginal bleeding, with a palpable uterus that is larger than the gestational age according to the last normal menstruation. Molar pregnancy can also present with theca lutein cysts, anaemia, hyperemesis gravidarum, hyperthyroidism, very high levels of β-hCG and pre-eclampsia before 20 weeks of gestation. Some patients will present with a history of passing hydropic vesicles or grape-like pieces of tissue.19

The elevated levels of β-hCG, especially in those women with enlarged uteri between 14 to 16 week size can give rise to complications such as theca lutein cysts, hyperemesis gravidarum and (subclinical) hyperthyroidism.19

Ultrasound has become the most important diagnostic tool in diagnosing molar pregnancy, especially CHM. The ultrasound picture shows a mixed echogenic pattern, comprising hydropic villi, an absent fetus and no amniotic fluid. Theca lutein cysts can often be demonstrated on ultrasound. However, the ultrasound appearance is non-specific, and therefore molar pregnancies are frequently misdiagnosed as incomplete miscarriages.

As is the case with other forms of complicated pregnancy, ultrasound findings need to be interpreted against the background of the β-hCG value. Suspicious ultrasound findings, together with an abnormally raised β-hCG must be regarded as highly suggestive of molar pregnancy.

Where ultrasound is available for patients who book early to confirm their pregnancy, the diagnosis will often be made before onset of symptoms typically experienced in complicated pregnancy.21,22

Ultrasound finding in cases of PHM, includes a fetus (sometimes growth restricted), amniotic fluid and focal areas of anechogenic spaces in the placenta. Theca lutein cysts are absent.21,23

It can be difficult to distinguish between a complete and partial hydatiform mole on ultrasound findings alone, and the diagnosis is usually confirmed after histopathological examination. Accurate diagnosis is not essential as the management of both PHM and CHM remains the same.

In the absence of vaginal metastases, vaginal ultrasound can be performed to try and exclude invasive hydatiform mole, where the interface between abnormal trophoblastic tissue and normal myometrium is carefully examined with the aid of high resolution.22

Management of molar pregnancy

Dilatation and suction curettage is the standard treatment of all patients presenting with a possible diagnosis of molar pregnancy. Before evacuation is performed, the following investigations should be performed:

- Full blood count
- Clotting studies
- Renal function assessment
- Liver function test
- Thyroid functions
- Quantitative β-hCG level
- Blood group compatibility
- Chest X-ray

Evacuation, usually under general anaesthesia and preferably under ultrasound guidance, should be performed as soon as possible after the patient has been assessed and stabilised. After dilatation of the cervix, a suction cannula is placed just past the internal os, suction is applied and the uterus allowed to contract as the products are being aspirated after commencing an intravenous oxytocin infusion (Figure 1). Suction curettage is safer than sharp curettage and more effective than medical or non-surgical methods of evacuation. As heavy bleeding can be encountered, it is always good practice to have blood for transfusion readily available.

Patients with uteri larger than 14 to 16 weeks are prone to develop respiratory complications at time of evacuation. Respiratory distress can occur due to trophoblastic embolisation and cardiac failure due to anaemia, hyperthyroidism or pre-eclampsia. Iatrogenic fluid overload can cause pulmonary oedema.19,25

In certain cases and where preservation of fertility is not required, hysterectomy is an alternative to dilatation and suction curettage. The risk of GTN after hysterectomy is 3–5%, and therefore post-operative monitoring of β-hCG remains crucial. Theca lutein cysts will resolve.
Following evacuation of a molar pregnancy the risk of persistent GTD is 18 to 28% of patients who had CHM and between 2 to 4% for those diagnosed with PHM. Serial assessment of β-hCG levels on a weekly basis until the level is normal on three consecutive occasions, then monthly for 6 to 12 months, is indicated to identify patients with GTN requiring adjuvant treatment. Figure 2 shows the time frames for β-hCG to return to normal after different types of pregnancies.26,27

The laboratory must use an appropriate hCG assay that is able to detect not only the β-hCG secreted in normal pregnancy, but also the variants associated with GTD (hyperglycosylated hCG, nicked hCG, and nicked hCG missing the C-terminal extension on beta-hCG). Dilutions should also be performed to avoid false positives and negatives.28

Reliable contraception is required during the surveillance of β-hCG levels. Combined oral contraceptive use is safe in the post evacuation period.20

Risk factors that predict an increased risk for the development of GTN include β-hCG values above 100 000 mIU/ml, teca lutein cysts > 6 cm in diameter and a significantly enlarged uterus. Prophylactic chemotherapy to prevent GTN in women with high risk molar pregnancies is effective.29,30 As not all women with high risk molar pregnancy will develop GTN, chemoprophylaxis in this group is not universally accepted, and close follow-up is widely recommended. However, there probably is a strong case for this practice in countries where close follow-up of patients is difficult. A patient living in rural South Africa will probably benefit from this approach as close follow-up in these patients is often not feasible.

**Diagnosis of GTN**

Following a molar pregnancy, which is mostly a benign disease, GTN is diagnosed as follows according to the FIGO consensus statement of 200031:

- When the plateau β-hCG lasts for 4 measurements over a period of 3 weeks or longer, that is day 1, 7, 14, 21.
- When there is a rise of β-hCG of three weekly consecutive measurements or longer, over at least a period of 2 weeks or more days 1, 7, 14.
- When the β-hCG level remains elevated for 6 months or more.
- GTN is diagnosed if there is a histological diagnosis of choriocarcinoma.

After the diagnosis has been made of GTN, the patient must then be investigated for staging. The following investigations can be used:

- Chest X-ray is appropriate to diagnose lung metastases and to assess the number of lung metastases to evaluate the risk score. Lung CT may also be used.
- Ultrasound or CT scan can be used to diagnose liver metastases.
- CT or MRI scan can be used for the diagnosis of brain metastases.

After the diagnostic investigations have been performed the patient is then staged according to the FIGO anatomical staging and allocated a prognostic score using the modified WHO prognostic scoring system.
The FIGO anatomical staging for GTN is as follows:

**Stage I**  
Disease confined to the uterus

**Stage II**  
GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)

**Stage III**  
GTN extends to the lungs, with or without known genital tract involvement

**Stage IV**  
All other metastatic sites

Table I shows the modified WHO prognostic scoring system as adopted by FIGO. In order to stage and allot a risk factor score, a patient’s diagnosis is allocated to a stage as represented by a Roman numeral I, II, III and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. A score of 0–6 is regarded as low risk, and a score of 7 or higher as high risk.

Most GTN following a molar pregnancy will be diagnosed on ß-HCG surveillance as discussed above. GTN can also follow after non-molar pregnancies, presenting with subtle symptoms and signs. Abnormal bleeding after any pregnancy needs to be investigated with quantitative ß-hCG testing. Choriocarcinoma can present with the symptoms and signs of the organ affected by metastases. Patients can present with intracerebral bleeding, or respiratory symptoms suggestive of pulmonary embolism. It should also be on the differential diagnosis of patients presenting with carcinoma of unknown primary.

A history and general examination is mandatory. A pelvic examination must be performed to rule out vaginal and/or pelvic metastases.

Apart from the imaging studies already mentioned above, the following investigations are also required:

- Full blood count
- Clotting studies
- Renal function assessment
- Liver function test
- Thyroid functions
- Quantitative ß-HCG level
- Blood group compatibility

Metastases to other sites are rare without respiratory metastases. Up to 40% of patients with negative findings for lung metastases on chest radiograph will have metastases diagnosed on CT scan of the chest.

The FIGO staging and prognostic scoring system is useful in making treatment decisions. Women with stage I disease generally have low risk scores and about 90% of these women will go in remission following single agent chemotherapy. Stage II and III with a low risk score (< 7) can be treated with single agent chemotherapy while those with a high risk score (≥ 7) as well as stage IV disease will require more than single agent chemotherapy.

**Chemotherapy**

GTN is very sensitive to chemotherapy and high cure rates are achievable with many patients requiring only single agent treatment. Stage of disease, risk score and previous exposure to chemotherapy will influence the decision of chemotherapeutic regimen.

**Single agent chemotherapy**

Methotrexate is still the most widely used single agent treatment. It can be administered as a single dose, eight day course or a weekly regimen until the ß-hCG levels return to normal. The different treating regimens are probably equally effective. Ten to 30% of patients will require a second treatment course if the serum beta-hCG does not fall by one log within 18 days, or if the value plateaus for more than two weeks before returning to normal.

Pulsed dactinomycin is, according to some data, more effective than methotrexate as a single agent with comparable toxicity. Dactinomycin is also a very useful agent in patients where methotrexate is contraindicated. Etoposide and 5-fluorouracil are also drugs that are being used as single agents.

**Multiagent chemotherapy**

Women diagnosed with high risk GTD or women who are refractory to single agent chemotherapy will require combination chemotherapy.
The combination of etoposide, methotrexate and dactinomycin followed by cyclophosphamide and vincristine (EMA/CO) is the most widely used regimen for initial treatment of high-risk GTD in most countries. The regimen is repeated every two weeks until normalisation of β-hCG and disappearance of all radiographically evident disease, and then continued for an additional three cycles (six weeks).26 Besides alopecia, this well tolerated regimen is not associated with serious toxicity.36

Other multiagent regimens include EMA and MAC (triple therapy with methotrexate, dactinomycin plus either chlorambucil (original regimen) or cyclophosphamide (modified regimen)). There are no randomised trials comparing the different regimens.

Second line chemotherapy is indicated in patients who are resistant to initial chemotherapy (20–25%), can’t tolerate the initial regimen, or develop recurrent disease after chemotherapy. Most patients with relapsed stage I or low-risk disease, and 60 to 70% of high-risk patients who relapsed, can be successfully salvaged with additional chemotherapy.27,28

Patients who fail to have an initial response to treatment have a worse outcome than those who relapse after an initial response.29 MAC, EMA and EMA combined with etoposide and cisplatin (EMA/EP) are frequently used in this setting.40 Other regimens for salvage therapy include:

- Cisplatin, vinblastine, and bleomycin
- Bleomycin plus etoposide and cisplatin (BEP)
- Ifosfamide, either alone or in combination with etoposide and cisplatin (VIP)
- Ifosfamide, carboplatin, plus etoposide (ICE)
- High dose 5-FU plus dactinomycin
- Paclitaxel alone or in combination with ifosfamide, carboplatin, or cisplatin plus etoposide

**Post treatment monitoring**

All women with GTD should be monitored with weekly serial measurements of serum β-hCG during treatment. Remission is defined as three consecutive normal hCG values over 14 to 21 days. After remission is achieved, serum β-hCG should be measured monthly until the patient has had normal β-hCG levels for one year. After remission, the risk of tumour relapse in patients treated for persistent GTN is 3 to 9%. A significant number of patients with recurrent disease can be cured, and such cases should always be offered treatment with curative intent.41 Assays used for monitoring 8-hCG levels after treatment should be able to measure the 8-hCG variants. Failure to measure variant 8-hCG molecules associated with GTN may result in a false negative test as these are the major (and sometimes the only) sources of 8-hCG immunoactivity.23

**Surgery**

Repeat curettage is associated with risks of uterine perforation, haemorrhage, infection, intrauterine adhesions, and anaesthetic complications. The efficacy and benefit of repeat evacuation is doubtful and should only be performed if there is evidence of retained tissue in the uterus.

Hysterectomy is indicated in the following cases:

- Women diagnosed with choriocarcinoma who do not desire future fertility. Hysterectomy can be performed before chemotherapy, as this prevents the persistence of drug-resistant local disease, and can shorten the duration and amount of chemotherapy required to achieve remission.42
- Primary therapy for stage I or II placental site trophoblastic tumour as it is usually limited to the uterus and the response to chemotherapy is variable.
- Women who have chemotherapy-resistant disease.
- To control uterine bleeding or ongoing sepsis due to infection of necrotic tumour.

There is no proven benefit to performing a hysterectomy if the uterus has no disease demonstrable on imaging. Thus, radiographic imaging, with MRI and/or ultrasonography, should be performed prior to hysterectomy in women where this procedure is being considered.

Local excision is an option in women who need to retain fertility. Successful treatment of localised disease by hysterotomy, local tumour excision and uterine reconstruction has been described.

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