Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) forms a group of disorders which range from molar pregnancies to malignant conditions such as choriocarcinoma. If there is any evidence of persistence of GTD the condition is referred to as gestational trophoblastic neoplasia (GTN).

Cure rates are excellent for this condition. This is due to central registration and monitoring in the UK, the use of beta human chorionic gonadotrophin (beta-hCG) as a biomarker, and the development of effective treatments [1].

Classification

GTD is classified as follows:

Premalignant - hydatidiform mole
- Complete hydatidiform mole (CHM).
- Partial hydatidiform mole (PHM).

Malignant - GTN
- Invasive mole.
- Choriocarcinoma.
- Placental site trophoblastic tumour (PSTT).
- Epithelioid trophoblastic tumour (ETT).

Aetiology

Normally at conception, half the chromosomes come from the mother and half from the father.

In complete molar pregnancies, all the genetic material comes from the father. An empty oocyte lacking maternal genes is fertilised. Most commonly (75-80%) this arises from a single sperm duplicating within an empty ovum [2]. Less often an empty ovum is fertilised by two sperm. There is no fetal tissue.

In partial molar pregnancies, the trophoblast cells have three sets of chromosomes (triploid). Two sperm are believed to fertilise the ovum at the same time, leading to one set of maternal and two sets of paternal chromosomes. Around 10% of partial moles are tetraploid or mosaic in nature. There is usually evidence of fetal tissue or fetal blood cells in a partial molar pregnancy. An embryo may be present at the start.

An invasive mole develops from a complete mole and invades the myometrium.

Choriocarcinoma most often follows a molar pregnancy but can follow a normal pregnancy, ectopic pregnancy or abortion, and should always be considered when a patient has continued vaginal bleeding after the end of a pregnancy. It has the ability to spread locally, as well as metastasise.

Placental site trophoblastic tumours most often follow a normal pregnancy but occasionally arise from molar pregnancies. These may also be metastatic.

Epidemiology [2, 3]

- GTD is rare in the UK, with a calculated incidence of 1 in 714 live births.
- Incidence of CHM is estimated at 1-3:1,000 pregnancies. 
- Incidence of PHM is estimated at 1:1,000 pregnancies.
- The incidence of GTN after a live birth is estimated at 1 in 50,000.
- After a molar pregnancy, the risk of a further CHM or PHM increases to around 1%. After two molar pregnancies the risk further rises to 15-20% and is not affected by a change in partner.
- PSTT is rare, representing about 0.2% of GTD in the UK.
- Around 0.5% of PHMs progress to malignant disease, whilst up to 20% of cases of CHM go on to need chemotherapy [4].

Risk factors

- Molar pregnancies may occur at any age but are more common in women aged over 45 years or under 16 years.
- There is also an increased risk with multiple pregnancy and previous molar pregnancy.
- Women with menarche over the age of 12, light menstruation and a history of use of the oral contraceptive pill may have higher risk.
- Asian women have a higher incidence of GTD.
Clinical presentation of gestational trophoblastic disease

- Most affected women in the UK develop vaginal bleeding in the first trimester and undergo uterine evacuation at about 10 weeks of gestation. Features such as hyperemesis, abnormal uterine enlargement, hyperthyroidism, anaemia, respiratory distress and pre-eclampsia are now rare as a result of routine use of ultrasound in early pregnancy.[6]
- All products of conception from a non-viable pregnancy should undergo histological examination, as ultrasound is not diagnostically reliable.
- Women with persistent abnormal vaginal bleeding after a non-molar pregnancy should undergo a pregnancy test to exclude persistent GTN, which should also be considered in any woman developing acute respiratory or neurological symptoms after any pregnancy.
- Metastatic disease very rarely presents with dyspnoea or abnormal neurology, including seizures.

Investigations

- **Urine and blood levels of hCG.** A urine pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event. Levels of hCG may be of value in diagnosing molar pregnancies but are far more important in disease follow-up.
- **Histology.** Definitive diagnosis is made by histological examination of the products of conception. All forms of GTD have distinctive morphological features, depending on which tissues they are derived from.
- **Ultrasound:**
  - Ultrasound in the first trimester may not be reliable. The typical 'snowstorm' appearance occurs mainly in the second trimester, showing a heterogeneous mass with no fetal development, and theca-lutein ovarian cysts.
  - Because of the lack of diagnostic reliability of ultrasound, products of conception from all non-viable pregnancies should undergo histological examination in order for diagnosis not to be missed, and the chance of monitoring to prevent complications.
  - When there is diagnostic doubt about the possibility of a combined molar pregnancy with a viable fetus then ultrasound examination should be repeated before intervention.
- **Staging investigations where metastatic disease is suspected:**
  - Doppler pelvic ultrasound for local pelvic spread and vascularity.
  - CXR or lung CT scan to diagnose lung metastases.
  - CT scanning for liver or other intra-abdominal metastases.
  - MRI scanning for brain metastases.
Staging

The staging system of the International Federation of Gynecology and Obstetrics (FIGO) is as follows:

- **Stage I**: disease confined to the uterus.
- **Stage II**: extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament).
- **Stage III**: extends to the lungs with or without genital tract involvement.
- **Stage IV**: all other metastatic sites.

Management

**Registration**

All women diagnosed with GTD should be provided with written information about the condition and the need for referral for follow-up to a trophoblastic screening centre. Since 1973, the UK has had a national system for registration, follow-up, and treatment of GTD. The gynaecologist treating affected women will register them with one of the three centres: Ninewells Hospital (Dundee), Charing Cross Hospital (London) and Weston Park Hospital (Sheffield).

**Management of hydatidiform moles**

- Suction curettage is the method of choice of evacuation for complete molar pregnancies.
- Suction curettage is the method of choice of evacuation for partial molar pregnancies except when the size of the fetal parts deters the use of suction curettage and then medical evacuation can be used.
- A urinary pregnancy test should be performed three weeks after medical management of failed pregnancy if products of conception are not sent for histological examination.
- Anti-D prophylaxis is required following evacuation of a PHM.
- Excessive vaginal bleeding can be associated with molar pregnancy and a senior surgeon directly supervising surgical evacuation is advised.
- The use of oxytocin infusion prior to completion of the evacuation is not recommended. A single dose of an oxytocic can be used following evacuation if there is excessive bleeding.
- If the woman is experiencing significant haemorrhage prior to evacuation, surgical evacuation should be expedited and the need for oxytocin infusion weighed up against the risk of tumour embolisation.

**Twin pregnancies with a viable fetus and a molar pregnancy**

- The pregnancy should be allowed to proceed if the mother wishes, following appropriate counselling.
- The probability of achieving a viable baby is poor (around 25%) and there is a high risk of complications such as premature delivery and pre-eclampsia.
- There is no increased risk of developing persistent GTD after this type of molar pregnancy and outcome after chemotherapy is unaffected.

**UK (Charing Cross Hospital) protocol for surveillance after hydatidiform mole**

- Two-weekly serum and urine samples until hCG concentrations are normal.
- In a partial mole, normal levels are confirmed four weeks later and if results remain normal, surveillance may end.
- For a complete mole, after hCG levels return to normal, monthly urine hCG testing is continued. This continues for six months from evacuation if levels have normalised within eight weeks; if not, monitoring continues for six months from when levels became normal.

All women should notify the screening centre at the end of any future pregnancy, whatever the outcome of the pregnancy. Levels of hCG are measured 6-8 weeks after the end of the pregnancy to exclude disease recurrence.
Indications for chemotherapy in GTD in the UK\textsuperscript{[3, 4]}

- Plateaued or rising hCG levels after evacuation.
- Histological evidence of choriocarcinoma.
- Evidence of metastases in the brain, liver, or gastrointestinal (GI) tract, or radiological opacities >2 cm on CXR.
- Pulmonary, vulval, or vaginal metastases unless hCG concentrations are falling.
- Heavy vaginal bleeding or evidence of GI or intraperitoneal haemorrhage.
- Serum hCG greater than 20,000 IU/L more than four weeks after evacuation, because of the risk of uterine perforation with further evacuation attempts.
- Raised hCG level six months after evacuation (even if falling).

Chemotherapy regimes

Women with evidence of persistent GTD should undergo assessment of their disease followed by chemotherapy. Disease risk is scored according to the FIGO staging for GTD.

<table>
<thead>
<tr>
<th>FIGO SCORING</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt; 40</td>
<td>≥ 40</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Abnormal pregnancy</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval months from end of index pregnancy to treatment</td>
<td>&lt; 4</td>
<td>4 – 7</td>
<td>7 – 13</td>
<td>≥ 13</td>
</tr>
<tr>
<td>Pretreatment serum hCG (IU/L)</td>
<td>&lt; $10^3$</td>
<td>$10^3$ – $10^4$</td>
<td>$10^4$ – $10^5$</td>
<td>≥ $10^5$</td>
</tr>
<tr>
<td>Largest tumour size, including uterus (cm)</td>
<td>&lt; 3</td>
<td>3 – 5</td>
<td>≥ 5</td>
<td>–</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastro-intestinal</td>
<td>Liver, brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>–</td>
<td>1–4</td>
<td>5–8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>–</td>
<td>–</td>
<td>Single drug</td>
<td>2 or more drugs</td>
</tr>
</tbody>
</table>

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The total score is obtained by adding the individual scores for each prognostic factor. Low-risk 0-6; high-risk ≥7.

Chemotherapy regimen for low-risk patients with GTD

- Methotrexate 50 mg intramuscularly; repeated every 48 hours (total of four doses) - courses are repeated every two weeks.
- Calcium folinate (folinic acid) 15 mg orally 30 hours after each injection of methotrexate.

A 2016 Cochrane review found that dactinomycin (actinomycin D) is probably more likely to achieve a primary cure for low-risk disease, with fewer treatment failures than the methotrexate regimen, and that the side effect profile is similar\textsuperscript{[7]}. However, dactinomycin (actinomycin D) may be associated with a greater risk of severe adverse events. The review concluded that there were ongoing trials which are likely to contribute significantly to available evidence in this field and that higher-certainty evidence is still needed.

Prophylactic chemotherapy for women who have had complete moles to prevent GTN is not recommended\textsuperscript{[8]}.

Chemotherapy regimen for high-risk patients with GTD

There is no strong evidence to determine the best combination chemotherapy regimen for high-risk gestational trophoblastic tumour. A 2013 Cochrane review found that more multi-centre collaborative random controlled trials are needed and that the EMA/CO regime below is the most widely used currently\textsuperscript{[9]}.

Therefore, there are a number of different regimes in use. Charing Cross Hospital in the UK uses the following chemotherapy schedule\textsuperscript{[4]}.
Two regimens alternate each week:

- **Regimen 1:**
  - Day 1: etoposide, methotrexate and dactinomycin (actinomycin-D).
  - Day 2: etoposide, dactinomycin (actinomycin-D) and folinic acid rescue (starting 24 hours after beginning the methotrexate infusion).

- **Regimen 2:**
  - Day 8: cyclophosphamide and vincristine (on Day 8 only).

This schedule is known as EMA/CO (= etoposide/methotrexate/dactinomycin (actinomycin D)/cyclophosphamide/vincristine - formerly oncovin).

The alternative EP/EMA regime may be used second-line if resistance develops, where Day 1 of Regimen 1 is the same as above but Day 2 comprises folinic acid only, and in Regimen 2, etoposide and cisplatin are used.

Treatment is continued until hCG levels have returned to normal and then for a further six consecutive weeks.

**Follow-up after chemotherapy**[^3][^4]

- Women are followed up for life following chemotherapy because there is no certainty about when it is safe to stop monitoring.
- Initially urine and serum hCG levels are monitored weekly; this gradually drops to four-weekly urine levels in year 2, and through further gradual reductions in frequency to six-monthly levels from year 6.
- The highest risk of recurrence is in the first year.

**Future pregnancy**[^2]

- Women being monitored after molar pregnancy should be advised not to conceive until their hCG levels have been normal for six months. Women who undergo chemotherapy are advised not to conceive for one year after completion of treatment.
- The risk of a further molar pregnancy is low and more than 98% of women who become pregnant following a molar pregnancy will not have a further mole or be at increased risk of obstetric complications.
- If a further molar pregnancy does occur, it will be of the same histological type in 68-80% of cases.
- Women should notify the screening centre at the end of any future pregnancy, and hCG levels are measured 6-8 weeks after the end of the pregnancy to exclude recurrence.

**Contraception following treatment**[^4][^6]

Oestrogen and/or progestogens taken between evacuation of the mole and return to normality of hCG values do not appear to increase the risk of invasive mole or choriocarcinoma developing[^10]. Therefore the latest advice is that women may use oral contraceptives after molar evacuation, before hCG returns to normal. Women should use contraception until after the completion of the surveillance period in order to avoid pregnancy at this time.

**Prognosis**

- The need for chemotherapy following a complete mole is 8-20% and is 0.5% after a partial mole[^4]. Persistent GTD requiring chemotherapy after other pregnancies is rare.
- There is an almost 100% cure rate for women with low-risk GTN, which is the vast majority of cases. For high-risk GTN (5% of cases), five-year survival rates are lower but still up to 90%[^3]. Fertility is retained in the majority.
- Risk of relapse after chemotherapy is around 3% and mostly occurs in the first year[^11].
- The presence of brain or liver metastases is a poor prognostic feature, as is presentation more than four years after the antecedent pregnancy.
Women who receive chemotherapy for GTN are likely to have an earlier menopause. The age at menopause for women who receive single-agent chemotherapy is advanced by one year and by three years if they receive multi-agent chemotherapy. There is no evidence of risk that the use of hormone replacement therapy (HRT) affects the outcome of GTN.

Women with high-risk GTN who require multi-agent chemotherapy which includes etoposide should be advised that they may be at increased risk of developing secondary cancers.

Further reading & references

- International Society for the Study of Trophoblastic Diseases
- Service Specification - Gestational Trophoblastic Disease; NHS England

2. Management of Gestational Trophoblastic Disease; Royal College of Obstetricians and Gynaecologists (February 2010)
3. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis treatment and follow-up; European Society of Medical Oncology (Sept 2013)
4. Hydatidiform Mole and Choriocarcinoma UK Information and Support Service
6. The Sheffield Trophoblastic Disease Centre

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