GESTATIONAL TROPHOBLAST DISEASE (HYDATIDIFORM MOLE)

1. PURPOSE
To outline the diagnosis and treatment of women presenting with molar pregnancies and gestational trophoblast disease.

NB: These are guidelines and do not preclude the use of clinical judgement and discussion in a tumour board setting for unique cases which may require treatment deviating from this document.

KEY POINTS

1. A pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event (particularly after 6 weeks)
2. Suction evacuation is the preferred initial management regardless of uterine size. Ideally this should be performed by an experienced Obstetrician / Gynaecologist.
3. In selected cases a second evacuation may be necessary for histological confirmation in difficult cases and/or because of the problematic bleeding, but it has been shown that there is still a 70% chance of requiring chemotherapy and an 8% chance of uterine perforation.
4. Repeat curettage is not recommended if hCG > 5000 or in the presence of metastases.
5. All products of conception obtained at evacuation should be sent for histology.
6. Vaginal gestational trophoblastic neoplasia is most commonly located in the fornices or suburethrally. Due to their highly vascular nature, biopsy should be avoided.
7. Ploidy status and immunohistochemistry staining for P57 may be useful for differentiation between an partial or complete mole.
8. Use of prostaglandins to ripen the cervix is appropriate.
9. Avoid oxytocic use until after evacuation.
10. It is recommended that all patients who are RhD negative receive RhD Immunoglobulin prophylaxis.
11. To minimise the risk of perforation of the uterus, insertion of an intrauterine device should be delayed for at least 6 weeks after evacuation of the uterus and the hCG levels have returned to normal.
12. One person or team should be made responsible for the patient regarding monitoring of hCG levels.
13. An obstetrician / gynaecologist should undertake the monitoring of the post evacuation hCG levels and counselling of the patient.
14. Weekly quantitative hCG levels should be undertaken until 3 consecutive normal levels are seen and then monthly levels should continue until cleared of ongoing monitoring.
15. A rise of greater that 10% over 2 weeks (3 weekly hCG levels) or a fall of less than 10% over 3 weeks (4 weekly hCG levels) confirms a diagnosis of persistent GTD. Patients must be referred to the Gynaecologic Oncologist for further management.
16. Oestrogen and/or progestogens taken between evacuation of the mole and return to normality of hCG values appear NOT to increase the risk of invasive mole or choriocarcinoma developing. Therefore, women may use oral contraceptives after molar evacuation, before hCG returns to normal. Pregnancy should be avoided until after the completion of the surveillance period.
17. A diagnosis of a gestational choriocarcinoma and PSTT requires referral to the Gynaecologic Oncology team.
18. Women who receive multi agent chemotherapy for invasive mole may be at increased risk of early pregnancy complications if conception occurs within 12 months of completion of treatment.
19. For women who conceive again there is a 1:70 chance of having a subsequent molar pregnancy. An ultrasound scan early in pregnancy at 6 weeks gestation is recommended. Also obtain hCG levels 6 weeks after the conclusion of any future pregnancy, regardless of outcome.

BACKGROUND

Gestational Trophoblast Disease (GTD) forms a spectrum of illnesses that are rare, almost always highly curable but not always well understood by non-specialists. The types of trophoblast disease range from the usually benign partial molar pregnancy through complete molar pregnancy and invasive mole to the malignant choriocarcinoma and placental site trophoblastic tumours. All of these illnesses share the characteristic that they arise from a pregnancy.

Gestational trophoblastic neoplasia (GTN) is a term used to describe GTD requiring chemotherapy or excisional treatment because of the persistence of hCG or the presence of metastases. GTN follow hydatidiform mole (60%), previous miscarriage / abortion (30%), normal pregnancy or ectopic gestation (10%).

CLASSIFICATION

The World Health Organisation classification divides trophoblast disease into the pre-malignant and malignant forms as shown below:-

- **Pre-Malignant**
  - Partial Molar Pregnancy
  - Complete Molar Pregnancy

- **Malignant**
  - Invasive mole
  - Choriocarcinoma
  - Placental site trophoblastic tumours (PSTT)

PRE-MALIGNANT TROPHOBLAST DISEASE

Molar Pregnancy

The incidence of molar pregnancies in Europe and North America is in the order of 0.2-1.5 per 1000 live births although these figures are of limited accuracy. There may be a higher incidence of molar pregnancies in Africa and Asia; however the varying standards in the frequency and accuracy of pathology and demographics make accurate comparisons difficult.

The relative risk of molar pregnancy is highest in those pregnancies at the extremes of the reproductive age group. There is a modestly increased incidence in teenagers (1.3 fold) but a 10 fold increased risk in those aged 40 and over. The risk of a complete molar pregnancy increases more than the risk of developing a partial mole.

Historically the relative incidence of partial and complete molar pregnancies has been reported as approximately 3:1000 and 1:1000. This situation may well represent an over diagnosis of partial mole as data from CXH demonstrates that nearly 40% of partial moles referred for expert review are reclassified as either complete moles or non-molar pathologies.
Partial Mole

Partial moles are triploid with 2 sets of paternal and 1 set of maternal chromosomes.

Macroscopically partial moles may resemble the normal products of conception with initially an embryo present, which dies by week 8-9. The histology shows less swelling of the chorionic villi than in complete mole and there are usually only focal changes. As a result the diagnosis of partial mole can often be missed after an apparently straightforward miscarriage or termination.

The clinical presentation of partial mole is most frequently via irregular bleeding or by detection on routine ultrasound. The obstetric management is by suction or medical evacuation and these all partial mole patients should be followed up with serial hCG.

Partial moles rarely becomes malignant with generally only one or two cases of malignant disease seen per year at CXH with an overall risk of 0.5% of requiring chemotherapy after a partial mole.

Complete Mole

In most complete moles the genetic material is entirely male in origin and results from the fertilisation of an empty ovum lacking maternal genes. The chromosome complement is most commonly 46XX, which results from one sperm that duplicates its DNA, or less frequently 46XX or 46XY from the presence of two different sperm. On very rare occasions complete moles can be biparental with genetic contributions from both the mother and father (ref). Whilst this type is extremely rare, biparental mole is associated with a high risk of further molar pregnancies and patients who have had more than 2 molar pregnancies may benefit from investigation at an expert centre.

The diagnosis of complete mole is most often made as a result of bleeding, a large for dates uterus, or an abnormal ultrasound. Macroscopically there is no fetus and the histology shows the characteristic oedematous villous stroma. However the textbook 'bunch of grapes' appearance is seen in the second trimester and as now most cases are diagnosed earlier, this is rarely seen. The obstetric management is by suction evacuation followed by serial hCG measurement and surveillance registration.

In contrast to a partial mole, a complete mole more frequently proceeds to invasive disease with 8-20% of patients requiring chemotherapy.

MALIGNANT TROPHOBLAST DISEASE

Invasive Mole (chorioadenoma destruens)

Invasive mole is a very rare condition. The use of routine ultrasound, the early evacuation of complete moles and effective hCG surveillance means that very few women have this diagnosis.

Invasive mole usually arises from a complete mole and is characterised by invasion of the myometrium, which can lead to perforation of the uterus. Microscopically invasive mole has a similarly benign histological appearance as complete mole but is characterised by the ability to invade in to the myometrium and the local structures if untreated.

The usual presentation is with hCG elevations following a previous molar pregnancy; other clinical features can include abnormal bleeding, abdominal pain or swelling.
Gestational Choriocarcinoma

Choriocarcinoma is clinically and histologically overtly malignant and presents the most common emergency medical problems in the management of trophoblast disease.

The diagnosis most frequently follows a complete mole when the patients are usually in a surveillance programme but can also arise in unsupervised patients after a non-molar abortion or a normal pregnancy.

The clinical presentation of choriocarcinoma can be from the disease locally in the uterus leading to bleeding, or from distant metastases that can cause a wide variety of symptoms with the lungs, central nervous system and liver the most frequent sites of distant disease.

Choriocarcinoma presenting with distant metastases can present some diagnostic challenges, however the combination of the reproductive/gynaecology history and elevated serum hCG usually makes the diagnosis apparent and so avoid a biopsy which can be hazardous from the risk of haemorrhage.

On the occasions that pathology is available the characteristic findings show the structure of the villous trophoblast but with sheets of syncytiotrophoblast or cytotrophoblast cells, haemorrhage, necrosis and intravascular growth is common.

In contrast to molar pregnancies the genetic profile of choriocarcinoma gives a range of gross abnormalities without any specific characteristic pattern.

Placental Site Trophoblastic Tumour (PSTT)

Placental site trophoblast tumours were first described in 1976 (Kurman 1976) and are the least common form of gestational trophoblast disease comprising less than 2% of all cases. PSTT most commonly follows a normal pregnancy but may occur after a non-molar abortion or a complete molar pregnancy.

In contrast to the other types of trophoblast disease which characteristically present fairly soon after the index pregnancy, in PSTT the average interval between the prior pregnancy and presentation is 3.4 years. The clinical presentation of PSTT can range from slow growing disease limited to the uterus to more rapidly growing metastatic disease that is similar in behaviour to choriocarcinoma.

The most frequent presentations are abnormal bleeding or amenorrhea. Usually the hCG levels, whilst elevated, are relatively low in PSTT relative to the volume of the disease compared to the other types of GTT.

PSTT is diploid and arises from the non-villous trophoblast and the pathology is characterised by intermediate trophoblastic cells with vacuolated cytoplasm, the expression of PLAP rather than hCG and the absence of cytotrophoblast and villi.

Postpartum and Infantile Choriocarcinoma

Choriocarcinoma is an uncommon but curable cancer that develops during pregnancy and although it most often occurs with a complete hydatidiform mole, may occur after a normal pregnancy. Postnatal women who present with persistent postpartum bleeding which does not appear to be related to the recent pregnancy should be tested to exclude choriocarcinoma. This may include

- Quantitative serum HCG
- Full Blood Picture
Kidney Function Tests
Liver Function Tests

In suspected/confirmed cases the neonate should have a urine test for quantitative HCG.

MANAGEMENT of GTD

NB: A Consultant must be notified for all suspected or confirmed molar pregnancies

Initial Management

1. Perform initial blood tests for
   - hCG levels
   - blood group and antibody screen
   - full blood count
   - coagulation studies
   - U & Es
   - Renal and liver function tests
   - Thyroid function test

2. Order a chest x-ray prior to surgery

3. Arrange surgical intervention with suction dilatation and curettage (D & C). Suction evacuation is recommended for complete and partial molar pregnancies. Avoid the use of oxytocic infusions until surgery has been completed. This reduces the risk of causing trophoblastic embolism to the placental bed.

   If evacuation is followed by excessive bleeding, a single dose of oxytocin can be used after complete evacuation. For persistent disease repeated evacuations bring reducing results and repeated procedures are rarely advised. Repeat curettage is not recommended if hCG > 5000 or in the presence of metastases

4. Send all products of conception for histology examination and consider cytogenetics

5. Administer RhD immunoglobulin to Rh-negative patients after surgery.

6. Register with the Oncology Unit if molar pregnancy is confirmed.

FOLLOW UP

- Following diagnosis patients should be followed by weekly serial serum hCG levels.

- Weekly quantitative hCG levels should be undertaken until 3 consecutive normal levels are seen and then monthly levels should continue until cleared of ongoing monitoring.

- A rise of greater than 10% over 2 weeks (3 weekly hCG levels) or a fall of less than 10% over 3 weeks (4 weekly hCG levels) confirms a diagnosis of persistent GTD. Patients must be referred to the Gynaecologic Oncologist for further management.
• Send a discharge letter to the GP. Provide information of discharge, the follow-up management and include management if the woman presents with a future pregnancy.

Molar Pregnancy Indications for Chemotherapy treatment during surveillance (Charing Cross Hospital UK)

1. Brain, liver, GI metastases or lung metastases >2cm on CXR
2. Histological evidence of choriocarcinoma
3. Heavy PV bleeding or GI/intraperitoneal bleeding
4. Pulmonary, vulval or vaginal metastases unless the hCG level is falling
5. Rising hCG in two consecutive serum samples
6. hCG > 20,000 IU/L more than 4 weeks after evacuation
7. hCG plateau in 3 consecutive serum samples

FIGO Indications for chemotherapy treatment

1. hCG plateau of 4 values +/- 10% over a 3 week period
2. hCG increase of >10% of three values over a 2 week period
3. Persistence of hCG for more than 6 months after molar evacuation.

Management of Placental Site Trophoblast Disease (PSTT)

This is a malignancy that can often metastasise but still be cured with effective therapy.

The management depends on careful staging. When the disease is limited to the uterus, curative treatment can be achieved with a hysterectomy.

For women with disseminated disease the recommended treatment is with EP/EMA chemotherapy continued for 6-8 weeks after the normalisation of the hCG level. Following successful chemotherapy treatment, a hysterectomy is recommended.

Initial Assessment at Admission for Women Admitted for Additional Treatment after a Documented Molar Pregnancy

• Full history to include: details of the antecedent and all other pregnancies, LMP date, evacuation date and method, OCP usage, bleeding and other symptoms particularly respiratory and CNS.
• Investigations: FBC, biochemistry, clotting, HIV, HBV serology, hCG serum levels are measured twice a week during the treatment, group and save.
• Doppler ultrasound of the pelvis to confirm disease presence and volume and to rule out the possibility of a new pregnancy and chest x-ray.
For women admitted for treatment for presumed choriocarcinoma or PSTT

As above plus

- CT scan thorax, abdomen and liver
- MRI brain scan
- Diagnostic CSF hCG level if brain or lung metastases
- GFR prior to EP /EMA or CNS EMA / CO chemotherapy
- Avoid biopsy of cerebral lesion if seen, as it may haemorrhage

Low Risk Disease Chemotherapy Management

- The treatment for patients with low risk trophoblast disease is methotrexate given intramuscularly with oral folinic acid rescue following the schedule shown below.
- The first course of treatment is administered in hospital, with the subsequent courses administered at home.
- Patients with a high hCG level of >10,000 iu/mL may need to stay in for 3 weeks as they have a higher risk of bleeding, particularly as the tumour shrinks rapidly with the initial chemotherapy. Bleeding usually responds well to bed rest.
- The low risk chemotherapy treatment is generally well tolerated without much major toxicity. Methotrexate does not cause alopecia or significant nausea and myelosuppression is extremely rare. Of the side effects that do occur, the most frequent problems are from pleural inflammation, mucositis and asymptomatic elevation of liver function tests.
- For low risk patients with lung metastases on their chest x rays, add CNS prophylaxis with intra-thecal methotrexate (12.5mg) administration on 3 occasions 2 weeks apart to minimise the risk of development of CNS disease.

REFERENCES (STANDARDS)

National Standards – 1.2 Care provided by the clinical workforce is guided by current best practice Legislation - Nil
Related Policies - Nil
Other related documents – Nil

RESPONSIBILITY
Policy Sponsor Director of Gynaecology KEMH
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Do not keep printed versions of guidelines as currency of information cannot be guaranteed.
Access the current version from the WNHS website