

GESTATIONAL TROPHOBLASTIC DISEASE

NEW ZEALAND GYNAECOLOGIC CANCER GROUP GUIDELINES

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1 BACKGROUND AND INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of disorders derived from a pregnancy. This term covers hydatidiform mole (including complete and partial moles), invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumour (PSTT).

Gestational trophoblastic neoplasia (GTN) is a term used to describe GTD requiring chemotherapy. GTN follows hydatidiform mole (60%), previous miscarriage/abortion (30%), normal pregnancy or ectopic gestation (10%). GTN most commonly follows hydatidiform mole as a persistently elevated hCG titre.

The incidence of GTD is 1:200-1000 pregnancies, with evidence of ethnic variation. Women from Asia have a higher incidence than non-Asian women (1/390 and 1/750 respectively). The incidence after a live birth is 1/50,000. Incidence is higher at both ends of the reproductive spectrum, ie, in women younger than 15 and older than 45.

2 PATHOGENESIS; PLOIDY

Partial moles are triploid, with 2 sets of paternal and 1 maternal haploid set. An embryo is usually present that dies by week 8-9. They most often occur following dispermic fertilisation.

Complete moles are usually diploid, derived from paternal duplication or dispermic fertilisation of an 'empty' ovum (lacking in maternal genes). The chromosome count is either 46XX, from one sperm (75%) that duplicates its DNA, or 46XX or 46XY from the presence of two different sperms (25%).

Placental site tumour is diploid from either the normal conceptus or a complete mole.

3 CLINICAL PRESENTATION

During Pregnancy

- Per vaginal bleeding in the first trimester
- High hCG values
- Large for dates uterus, hyperemesis, preeclampsia and hyperthyroidism
- Ultrasound: pathognomonic ultrasonographic changes, more often seen in complete moles

Macroscopic tissue appearance

- Partial mole often looks like normal products of conception and so the diagnosis may be missed.
- The characteristic 'bunch of grapes' appearance in complete moles is only seen in the second trimester and as most cases are diagnosed earlier, this is now rarely seen.

After Pregnancy Event

- Any woman who develops persistent vaginal bleeding after a pregnancy event is at risk of having GTN
- A urine pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event
- Symptoms of metastatic disease like dyspnoea or abnormal neurology occur rarely
- Vaginal GTN is most commonly located in the fornices or suburethrally. They are highly vascular and bleed heavily, and biopsy should be avoided.

4 DIAGNOSTIC FEATURES OF GTD SUBTYPES

- **Hydatidiform moles** are separated into complete and partial moles based on genetic and histopathological features. In early pregnancy (less than 8 -12 weeks gestation) it may be difficult to separate complete and partial moles on H&E microscopy, and other tests (e.g. ploidy, p57) will often be required to make the diagnosis.
- **Invasive moles** usually present with hCG elevation following a molar pregnancy, clinical features can include PV bleeding, abdominal pain or swelling. Quantitative estimation of hCG or tumour hCG (t -hCG) will be of use in the diagnosis.
- **Gestational choriocarcinoma** most commonly follows a complete molar pregnancy (25-50%), within 12 months of a non-molar abortion (25%), or after a term pregnancy (25-50%). Symptoms may include PV bleeding, pelvic mass, or symptoms from distant metastases such as liver, lung and brain metastases. hCG is always elevated. It may be a difficult pathological diagnosis because of the frequent haemorrhage and necrosis, which accompany it.
- **Placental Site Trophoblastic Tumour (PSTT)** is very rare. This frequently presents as a slow growing tumour a number of years after a molar pregnancy, non-molar abortion or term pregnancy. Usually PSTT presents with gynaecologic symptoms, about 1/3 present with metastases, and some patients present with hyperprolactinaemia or nephrotic syndrome. Usually the hCG levels are relatively low or normal in PSTT relative to the volume of the disease, and HPL is seen in cells on microscopy. This tumour is relatively chemoresistant.
- **Epithelioid Trophoblastic Tumour (ETT)** is extremely rare. It may be misdiagnosed as squamous cell cancer of the cervix, choriocarcinoma or PSTT. About 1/3 patients present with metastatic disease, usually in the lungs. The hCG levels are relatively low. It behaves most similarly to PSTT, has a spectrum of behaviour from benign to malignant, and is relatively chemoresistant.

5 SURGICAL TREATMENT OF MOLAR PREGNANCIES

Evacuation of the uterus.

- Suction evacuation of the uterus is the preferred initial management regardless of uterine size.
 - Medical methods of uterine evacuation have been associated with higher rates of chemotherapy (1).
- Preparation of the cervix immediately prior to the evacuation is safe.
- The cervix should be carefully dilated to accommodate a cannula appropriate for the volume of trophoblastic tissue. A suction catheter up to a maximum of 12mm is satisfactory for the rapid evacuation and involution of the uterus.
- Oxytocin infusion can be used after evacuation, especially if brisk bleeding occurs.
 - Concern has been raised that oxytocin may promote metastases of trophoblastic tissue (2). However it has been reported that stimulation before evacuation did not increase the risk of persistent disease (3).
- It is advisable for the procedure to be carried out in the presence of, or by an experienced colleague, especially if the uterine size is large.
- Patients who are Rh -ve should receive Rh immunoglobulin
 - The Rh factor is expressed in the trophoblast.

Second evacuation of the uterus

- Second curettage evacuation of the uterus may be considered in select low risk patients after discussion at a Multidisciplinary meeting. Patients meeting the following criteria may be considered.
 - Hydatidiform mole following initial curettage
 - Persistently elevated b HCG
 - No evidence of metastatic GTN (CxR)
 - FIGO risk score of 0-4
 -

A multicentre prospective phase 2 trial of 85 pts showed that 40% of patients avoided chemotherapy with second curettage. There was 1 uterine perforation (1.6%) managed conservatively (4).

6 HISTOLOGICAL EXAMINATION OF PRODUCTS OF CONCEPTION

- All spontaneous miscarriages and retained products of conception managed through a hospital should undergo histological examination. Routine termination of pregnancy does not require histological review.
- If no histological examination was performed after medical evacuation, hCG test is recommended after three weeks (urine test sufficient)
- Because GTD can also develop after any pregnancy, it is recommended that products of conception obtained after any repeat evacuation are also examined histologically.
- Expert pathological opinion, by a pathologist with an interest in gynaecologic pathology, is always recommended in the diagnosis of GTD.
- Pathology must be reviewed at a multidisciplinary meeting.

7 INITIAL ASSESSMENT

- All patients diagnosed with a molar pregnancy should be seen for consultation by a local, named clinician responsible for the local GTD Service, typically a gynaecologist. This should happen in conjunction with the Regional GTD Service
- The establishment of a local registry to capture all GTD patients is recommended.
- All patients should be asked to consent to centralised registration once a central registry is available.
- Visit should include:
 - full history, including antecedent and all pregnancies, LMP date, evacuation date, oral contraceptive intake and symptoms
 - Information and discussion about the diagnosis and the need for regular follow up
 - Written information (see appendix 1)
 - Clinical examination for metastatic disease, pelvic exam
 - Chest X-ray
 - tumour hCG test as new baseline
 - Offering of counselling (5)
 - Socially disadvantaged women and those who do not conceive subsequent to GTD diagnosis require greater psychosocial support.

8 FOLLOW-UP IN MOLAR PREGNANCY (Partial and Complete Mole)

General Aspects

- Patients must be followed up with regular tumour hCG after any diagnosis of molar pregnancy.
- Follow-up should preferably be undertaken in consultation with or by a specialist centre (Gynaecological Oncologist, and/or Medical Oncologist) with experience in the management of GTD.
- Responsibility for follow up of tumour hCG results must be delegated to a specific clinician or GTD Clinical Nurse Specialist, with robust procedures in place for the monitoring of the results.

Tumour Marker follow-up

- Take serum tumour hCG
 - Differs from pregnancy test with beta-hCG (β -hCG) , as it measures all hCG isoforms
 - The 2 assays are not comparable
 - Patients undergoing follow-up after diagnosis of GTD should preferably have tumour hCG measured. Consistency is essential as treatment decisions might be based on small changes in the hCG.
 - The serum half-life of hCG is ~24-36 hours. The level is roughly linked to the number of tumour cells; 5IU/l ~104 – 105 tumour cells.
- Schedule t-hCG
 - On the day of diagnosis
 - Weekly thereafter until normal levels are obtained twice
 - Monthly once normal levels are obtained.

- Duration
 - The duration of Follow up should be dependent on type of GTD (6)
This follow up plan can be followed if a central/MDM review of pathology has confirmed the diagnosis
 - Partial mole: stop as soon as tHCG negative (7)
 - Complete mole: 6 months after normalisation
 - any mole with a multiple pregnancy: monthly for 12 months
 - If no central /MDM pathology review has been performed
 - assume complete mole 6 months after normalisation.
- See appendix 2 for a form to record tumour hCGs.

Clinical Follow-up

- After the initial consultation, and provided the tumour hCG is falling appropriately, the patient should be seen again at 8-10 weeks to check that menstruation has returned, and that adequate contraception is being followed.
- If t hCG has not fallen to normal by this point patients should be referred to a molar clinic or discussed with a gynaecologic oncologist
- For pregnancy advice during follow-up, see “Pregnancy advice after Molar pregnancy” below.
- In a large series, the risk of GTN after end of follow-up as described above is 0% for partial moles, and 0.3% for complete moles (6, 7).

9 CRITERIA FOR REFERRAL TO MEDICAL ONCOLOGY FOR (SUSPECTED) GTN

The following criteria for immediate referral apply at any time during diagnosis or follow-up:

- Histological diagnosis invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT).
- Plateau of tumour hCG lasts for 4 measurements over a period of 3 weeks or longer, ie, days 1,7,14,21 (plateau is usually defined as +/- 10%)
- Rise of tumour hCG on three consecutive weekly measurements, over a period of two weeks or longer, days 1,7,14 (usually defined as > 10%)
 - Consider possibility of new pregnancy if tumour hCG is rising
- Serum hCG >20,000 >4 weeks after evacuation (because of risk of uterine perforation)
- Evidence of metastases in the brain, liver or GI tract, or >2cm on Chest X-ray.

Most molar pregnancies spontaneously remit after evacuation; however persistence or change into malignant disease requiring chemotherapy (Gestational trophoblastic neoplasia or GTN) occurs in:

- 0.5 - 4% Partial moles
- 15 - 20% Complete moles.

10 HYSTERECTOMY FOR PERSISTENT GESTATIONAL TROPHOBLASTIC DISEASE?

Hysterectomy for treatment of molar pregnancy is not recommended as routine practice

- Patients who have completed their families may ask about hysterectomy to avoid the possibility of chemotherapy or surveillance.
- Two small American studies (8, 9) have shown that the chances of needing chemotherapy after hysterectomy for molar pregnancy are 3-10%, i.e. about halved, but certainly not eliminated
- Need for careful surveillance remains essential after hysterectomy
- In patients being considered for hysterectomy, full staging investigation including CT thorax/ abdomen/pelvis and MRI pelvis should be performed to exclude obvious evidence of extra-uterine spread which would be a contra-indication to treatment by hysterectomy.

! A Gynaecologic Oncologist must be consulted before deciding to proceed to an elective hysterectomy!

11 PROPHYLACTIC CHEMOTHERAPY IN MOLAR PREGNANCY?

Prophylactic chemotherapy is not recommended as routine practice (10).

- Four prospective randomised trials (11-14) have shown that the risk of post molar GTD (i.e. persistence, invasion, choriocarcinoma, GTN) dropped in patients with molar pregnancy treated after surgery with prophylactic chemotherapy.
- **However,**
 - Prophylactic chemotherapy does not obviate the need to monitor patients after evacuation as the risk does not drop to zero.
 - There is a suggestion that patients who received prophylaxis need more chemotherapy if their disease recurs (14).
 - The 'risk scales' used to determine high risk patients for prophylaxis have been subject to much criticism.

12 CONTRACEPTION IN MOLAR PREGNANCY

- Patients should be strongly counselled to avoid pregnancy during follow-up. Pregnancy masks tumour persistence/recurrence.
- Oral contraceptives can be taken between evacuation and normalisation of HCG.
- Recent series and systematic reviews suggests there is NO increased risk of invasive mole or choriocarcinoma developing from the use of oral contraceptives before normalisation of HCG (15,16).
- IUCDs
 - should be avoided until the menstrual pattern and tumour hCG are normal to reduce risk of uterine perforation.
 - If chosen as contraception (after normalisation of hCG) advise insertion of IUCD by a gynaecologist.
- Barrier Methods are the preferred method of contraception during chemotherapy.

13 PREGNANCY ADVICE AFTER MOLAR PREGNANCY

- Women should be advised *not* to conceive until their follow up is complete
- Future pregnancies
 - In all subsequent pregnancies patients should have an early (6-8 week) and mid trimester scan looking for molar tissue
 - After all future pregnancy events (including TOP, miscarriage etc) patients should have a tumour hCG blood test 6-8 weeks
- The chances of conception after molar pregnancy do not differ from the general population.
- The risk of a further molar pregnancy in future pregnancies is 1:70.
- Subsequent pregnancies result in full-term live births in about 70% of women, with major and minor congenital malformations detected in 0.4-2.5% of infants. These figures do not differ significantly from the normal population.
- Outcomes other than full-term live births include first trimester spontaneous abortions in about 15%, 2-8% premature deliveries, and smaller numbers of stillbirths and ectopic pregnancies.

14 PREGNANCY DURING FOLLOW-UP AFTER MOLAR PREGNANCY

- Pregnancies occurring before completion of recommended follow-up may be allowed to continue under careful surveillance.
 - Background : Tuncer (17) reviewed 44 pregnancies conceived within 6 months of normal tumour hCG (mean 3 months normal hCG). Seventy five percent of 44 patients had live births and there were 10 spontaneous abortions. None of these patients developed

persistent or recurrent GTD, and none of the live births demonstrated any foetal abnormalities.

- Patients should have an early and mid-trimester scan looking for molar tissue.
- Other surveillance is difficult during pregnancy, and will depend on the managing specialist's estimation of the risk of recurrence.
- see also Pregnancy Advice after Molar Pregnancy
- Routine follow-up should be resumed after the pregnancy until the total follow-up duration initially planned.

15 COEXISTING VIABLE PREGNANCY AND MOLAR PREGNANCY

- The recommendation is that the pregnancy should be allowed to proceed after loss of the molar tissue, if it is otherwise safe and the mother wishes, following appropriate counselling.
- Background
 - rare occurrence 1 in 22,000 – 100,000 pregnancies (18)
 - higher risk of developing maternal complications
 - probability of achieving a viable baby 40% (most pregnancies result in preterm labour, or premature fetal death) (19, 20)

16 DIAGNOSIS OF GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)

The table below represents the criteria agreed for diagnosis of GTN by the Committee of the International Federation of Gynecology and Obstetrics (FIGO) in September of 2000

Gestational trophoblastic neoplasia is treated by chemotherapy.

Criteria for the diagnosis of post hydatidiform mole trophoblastic neoplasia (GTN)

1. GTN may be diagnosed* when the plateau of human chorionic gonadotrophin (hCG) lasts for 4 measurements over a period of 3 weeks or longer, that is days 1,7,14,21.
2. GTN may be diagnosed* when there is a rise of hCG on three consecutive weekly measurements, over a period of two weeks or longer, days 1,7,14.
3. GTN is diagnosed if there is histologic diagnosis of choriocarcinoma.
4. (GTN is diagnosed when the hCG level remains elevated for 6 months or more**)

*The actual level of hCG or the amount of rise will be determined by the individual Investigator, but a plateau is usually defined as +/- 10%, and rise >10%

**This has subsequently been removed as a criteria in 2013 (21)

Other factors may be also taken into account by the medical oncologist such as evidence of brain, liver, renal or gastro-intestinal tract metastases, lung metastases >2cm, or a serum tumour hCG > 20,000 IU/L more than four weeks after evacuation.

The exclusion of a new pregnancy is essential when evaluating patients with a tumour hCG rise.

17 STAGING OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

All patients with GTN should have history and physical examination as above outlined under GTD.

- Blood tests
 - Baseline t hCG
 - FBC, U&E
 - Thyroid function tests
 - Coagulation Status

- HBsAg
- Consider cross-match if heavy bleeding.
- Radiology
 - Chest X ray (relevant for scoring system below)
 - Pelvic ultrasound (trans-vaginal is preferable)
 - CT abdomen and pelvis and MRI Brain if pulmonary metastasis detected or abnormal findings on exam / symptoms
- Urine creatinine clearance_in patients for EP/EMA or high dose methotrexate.

Patients with recurrent GTN should be fully restaged, with all blood tests as above, CT chest abdomen and pelvis, MRI brain, and lumbar puncture for CSF hCG to exclude the CNS acting as a sanctuary site.

18 RISK ASSESSMENT IN GESTATIONAL TROPHOBLASTIC NEOPLASIA

If a patient on follow-up meets any of the criteria for chemotherapy, their risk will be assessed by the FIGO 2000 criteria below (22). Low risk patients are those with a score of 6 or below, High risk patients have a score of 7 or over.

FIGO score	0	1	2	4
Age	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4 mo	4-≤7	7-<13	≥13
Pre-treatment serum hCG (IU/l)	<10 ³	10 ³ < 10 ⁴	10 ⁴ -<10 ⁵	≥10 ⁵
Largest tumour size (including uterine tumour)	<3 cm	3-<5cm	≥5 cm	
Site of metastases	Lung *	Spleen kidney	GIT	Brain liver
Number of metastases	0	1 - 4	5 - 8	>8
Previous failed chemotherapy			Single drug	≥2 drugs

Notes:

1. The interval months from pregnancy is taken from when the pregnancy ended (not started)
2. The score for site of metastases is not additive. The highest scoring organ is taken to be the score (e.g. A patient with gastrointestinal and brain metastases scores 4, not 6)
3. * lung metastasis counted on CXR not on a Chest CT

19 CHEMOTHERAPY IN GESTATIONAL TROPHOBLASTIC NEOPLASIA

- All patients requiring chemotherapy including methotrexate should be managed by a Medical Oncologist
- Most patients will be low risk, and therefore treated with methotrexate intramuscularly
 - This is a generally well tolerated 2 weekly outpatient regimen with few side effects
 - This continues until hCG has normalised plus an additional 3 cycles (i.e 6 weeks after normalisation).
- About 1 in 3-4 of these women will become resistant to this chemotherapy, and will then generally then require combination chemotherapy with EMA-CO or Actinomycin.
- A small number of women may become intolerant of methotrexate and need to switch regimens.
- Patients with high risk score or recurrent disease need to be discussed at MDM

Sample guideline chemotherapy regimens are included in Appendix 3.

20 FOLLOW-UP POST CHEMOTHERAPY

- Medical Oncologist will often refer back to General Gynaecologist or Gynae Oncologists for further follow up after completion of chemotherapy
- Patients undergoing follow-up after diagnosis of GTD or GTN should only have thCG measured (if this is available).
- Consistency is essential as treatment decisions are based on small changes in the hCG.

- Initial post chemo follow-up is recommended to re-check the sites of original disease (e.g. TVUSS, CT, MRI as appropriate) and give advice as in the section below.
- If the tumour hCG becomes abnormal again at any time after chemotherapy, pregnancy should be excluded first. The tumour hCG should be checked again immediately, and an urgent referral made to Medical Oncology.
- **Follow up schedule:** based on European and USA international guidelines. (note Charing cross follow up indefinitely for data gathering purposes.)
 - Low risk GTN: (post Mtx/actinomycin):
 - Follow up with monthly tHCG's for 12 months.
 - High risk GTN: (post EMA-CO or equivalent):
 - Follow up with monthly tHCG's for 2 years.
 - PSTT/ETT: Follow up for minimum of 5 years - HCG's plus appropriate imaging.

21 ADVICE TO PATIENTS AFTER CHEMOTHERAPY

- **Risk of relapse**
 In the largest published series of over 1700 patients, 60 (3.5%) relapsed 35 (58%) of initially low risk, and 25 (42%) of initially high risk. The median time to relapse was 4 months, 73% relapsed within a year of chemotherapy, and 85% within 2 years. Only 1 of the 60 relapses occurred after 5 years (23).

Time to relapse	N =	(%)	Cumulative (%)
0 - 3 months	31	51.6	51.6
3 - 6 months	10	16.6	68.2
6 - 12 months	3	5.0	73.2
12 - 24 months	7	11.7	84.9
1 – 5 years	8	13.5	98.4
> 5 years	1	1.6	100

- **Contraception**
 Any method may be used after chemotherapy. A delay of at least 6 weeks post chemotherapy is advisable before fitting an IUD. Contraception should be advised for at least one year after the last dose of chemotherapy. This is both to prevent pregnancy obscuring relapse, and to reduce the incidence of abnormal pregnancies.
- **Pregnancy**
 See section below.
- **Hormonal Replacment Therapy**
 Provided t hCG levels are normal, there is not known to be any increased risk of recurrence in the use of hormone replacement therapy for those patients with symptomatic premature menopause.
- **Risk of second malignancy**
 There is no apparent increased risk after Methotrexate and folinic acid. After EMA-CO, the risk ratio over the normal population is 1.5. Myeloid leukaemia is the most common second malignancy followed by breast and colon cancer, and melanoma.

22 PREGNANCY AFTER CHEMOTHERAPY FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA

Ability to conceive and effect on age of menopause

- Most women successfully treated with chemotherapy for GTN can be reassured that their fertility is unlikely to be significantly affected by chemotherapy.
 - A London study of 728 women treated with chemotherapy who subsequently wanted to become pregnant found that 93% conceived and 83% reported at least 1 live birth.

- There were no apparent differences in conception rates between those who received single agent, and multi-agent chemotherapy (24).
- While chemotherapy does hasten menopause, this is only by a small amount in the majority of patients (2-3 years) (25).

Pregnancy Advice and Outcome after Chemotherapy

- Women should be advised not to become pregnant for at least a year after the last dose of chemotherapy. About 90% of patients who want to become pregnant after chemotherapy will do so.
- There is a 1:70 (1-2%) chance of conceiving a further molar pregnancy.
- Most studies suggest that as a group, women have normal reproductive outcomes after chemotherapy for GTN.
 - Pregnancies result in about 70% term live births, with a 2.5% incidence of major and minor congenital abnormalities (26, 27).
These figures do not differ significantly from those in the normal population.
- Management future pregnancies see above

If a pregnancy (against advice) within 12 months after completion of Chemotherapy for GTN :

Recommendation

- There is no indication for a recommendation of a termination of pregnancy.
- The patient needs to be advised about increased risks (spontaneous abortion, stillbirth and repeat mole)
- Please see chapters “Pregnancy advice after molar pregnancy” and “Pregnancy during Follow up after molar pregnancy” for surveillance recommendations

Background

- < 12 months vs. > 12 months
No significant changes were found between women who conceived within 12 months of completing chemotherapy to the comparator groups, in a study conducted by the Charing Cross (28).
- < 6 months vs. > 12 months
Another retrospective analysis found incidence of abnormal pregnancies (spontaneous abortion, stillbirth and repeat mole) was higher in those women who conceived within 6 months vs > 12 months of completing chemotherapy (37.5% vs 10.5 %) Of these women 85% had been treated with methotrexate, the remainder with MEA (29).

23 PROGNOSIS IN GESTATIONAL TROPHOBLASTIC NEOPLASIA

- **low risk disease**
 - Chances of cure are close to 100%.
 - This is the case if they are treated with MTX alone, or if they require change to second line chemotherapy.
- **high risk disease**
 - Survival varies widely according to tumour burden and site of metastases
 - Overall cure is close to 85%.
 -

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APPENDICES

1. Patient information
2. Patient record

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