Royal College of Obstetricians & Gynaecologists

The Management of Gestational Trophoblastic Disease

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The Management of Gestational Trophoblastic Disease

This is the third edition of this guideline. It replaces *The Management of Gestational Trophoblastic Neoplasia*, which was published in 2004.

1. Definitions

Gestational trophoblastic disease (GTD) forms a group of disorders spanning the conditions of complete and partial molar pregnancies through to the malignant conditions of invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumour (PSTT). There are reports of neoplastic transformation of atypical placental site nodules to placental site trophoblastic tumour.

If there is any evidence of persistence of GTD, most commonly defined as a persistent elevation of beta human chorionic gonadotrophin (βhCG), the condition is referred to as gestational trophoblastic neoplasia (GTN).

2. Purpose and scope

The purpose of this guideline is to describe the presentation, management, treatment and follow-up of GTD and GTN. It also provides advice on future pregnancy outcomes and the use of contraception.

3. Background and introduction

Molar pregnancies can be subdivided into complete (CM) and partial moles (PM) based on genetic and histopathological features. Complete moles are diploid and androgenic in origin, with no evidence of fetal tissue. Complete moles usually (75–80%) arise as a consequence of duplication of a single sperm following fertilisation of an 'empty' ovum. Some complete moles (20–25%) can arise after dispermic fertilisation of an 'empty' ovum. Partial moles are usually (90%) triploid in origin, with two sets of paternal haploid genes and one set of maternal haploid genes. Partial moles occur, in almost all cases, following dispermic fertilisation of an ovum. Ten percent of partial moles represent tetraploid or mosaic conceptions. In a partial mole, there is usually evidence of a fetus or fetal red blood cells.

GTD (hydatidiform mole, invasive mole, choriocarcinoma, placental-site trophoblastic tumour) is a rare event in the UK, with a calculated incidence of 1/714 live births.[1] There is evidence of ethnic variation in the incidence of GTD in the UK, with women from Asia having a higher incidence compared with non-Asian women (1/387 versus 1/752 live births). However, these figures may under represent the true incidence of the disease because of problems with reporting, particularly in regard to partial moles. GTN may develop after a molar pregnancy, a non-molar pregnancy or a live birth. The incidence after a live birth is estimated at 1/50 000. Because of the rarity of the problem, an average consultant obstetrician and gynaecologist may deal with only one new case of molar pregnancy every second year.

In the UK, there exists an effective registration and treatment programme. The programme has achieved impressive results, with high cure (98–100%) and low (5–8%) chemotherapy rates.

4. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. Medline, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Control Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews and Effects (DARE), the American College of Physicians' ACP Journal Club and Ovid database, including in-process and other non-indexed citations, were searched using the terms 'molar pregnancy', 'hydatidiform mole', 'gestational trophoblastic disease', 'gestational neoplasms', 'placental site trophoblastic tumour', 'invasive mole', 'choriocarcinoma' and limited to humans and English language. The date of the last search was July 2008.

Selection of articles for analysis and review was then made based on the relevance to the objectives. Further documents were obtained by the use of free text terms and hand searches. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency and applicability of the evidence base.

Owing to the rarity of the condition, there are no randomised controlled trials comparing interventions with the exception of first-line chemotherapy for low risk GTN. There are a large number of case–control studies, case series and case reports.

5. How do molar pregnancies present to the clinician?

Clinicians need to be aware of the symptoms and signs of molar pregnancy: ✓

- **The classic features of molar pregnancy are irregular vaginal bleeding, hyperemesis, excessive uterine enlargement and early failed pregnancy.**
- **Clinicians should check a urine pregnancy test in women presenting with such symptoms.**

Rarer presentations include hyperthyroidism, early onset pre-eclampsia or abdominal distension due to theca lutein cysts. Very rarely, women can present with acute respiratory failure or neurological symptoms such as seizures; these are likely to be due to metastatic disease. Evidence level 4

6. How are molar pregnancies diagnosed?

Ultrasound examination is helpful in making a pre-evacuation diagnosis but the definitive diagnosis is made by histological examination of the products of conception. D

The use of ultrasound in early pregnancy has probably led to the earlier diagnosis of molar pregnancy. Soto-Wright *et al*. demonstrated a reduction in the mean gestation at presentation from 16 weeks, during the time period 1965–75, to 12 weeks between 1988–93.[2] The majority of histologically proven complete moles are associated with an ultrasound diagnosis of delayed miscarriage or anembryonic pregnancy.[3,4] In one study, the accuracy of pre-evacuation diagnosis of molar pregnancy increased with increasing gestational age, 35–40 % before 14 weeks increasing to 60% after 14 weeks.[4] A further study suggested a 56% detection rate for ultrasound examination.[5] The ultrasound diagnosis of a partial molar pregnancy is more complex; the finding of multiple soft markers, including both cystic spaces in the placenta and a ratio of transverse to anterioposterior dimension of the gestation sac of greater than 1.5, is required for the reliable diagnosis of a partial molar pregnancy.[6,7] Estimation of hCG levels may be of value in diagnosing molar pregnancies: hCG levels greater than two multiples of the median may help.[5]. Evidence level 2+

7. Evacuation of a molar pregnancy

7.1 What is the best method of evacuating a molar pregnancy?

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 3 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 molar pregnancy. ✓

Complete molar pregnancies are not associated with fetal parts, so suction evacuation is the method of choice for uterine evacuation. For partial molar pregnancies or twin pregnancies when there is a normal pregnancy with a molar pregnancy, and the size of the fetal parts deters the use of suction curettage, then medical evacuation can be used.

Evidence level 4

Medical evacuation of complete molar pregnancies should be avoided if possible.[8,9] There is theoretical concern over the routine use of potent oxytocic agents because of the potential to embolise and disseminate trophoblastic tissue through the venous system. In addition, women with complete molar pregnancies may be at an increased risk for requiring treatment for persistent trophoblastic disease, although the risk for women with partial molar pregnancies needing chemotherapy is low (0.5%).[10,11]

Evidence level 2+

Data from the management of molar pregnancies with mifepristone and misoprostol are limited.[9]

Evidence level 3

Evacuation of complete molar pregnancies with these agents should be avoided at present since it increases the sensitivity of the uterus to prostaglandins.

Because of poor vascularisation of the chorionic villi and absence of the anti-D antigen in complete moles, anti-D prophylaxis is not required. It is, however, required for partial moles. Confirmation of the diagnosis of complete molar pregnancy may not occur for some time after evacuation and so administration of anti-D could be delayed when required, within an appropriate timeframe.

Evidence level 4

7.2 Is it safe to prepare the cervix prior to surgical evacuation?

Preparation of the cervix immediately prior to evacuation is safe. D

In a case–control study of 219 patients there was no evidence that ripening of the cervix prior to uterine evacuation was linked to a higher risk for needing chemotherapy. However, the study did show a link with increasing uterine size and the subsequent need for chemotherapy.[12]

Evidence level 2+

Prolonged cervical preparation, particularly with prostaglandins, should be avoided where possible to reduce the risk of embolisation of trophoblastic cells.

Evidence level 4

7.3 Can oxytocic infusions be used during surgical evacuation?

Excessive vaginal bleeding can be associated with molar pregnancy and a senior surgeon directly supervising surgical evacuation is advised. ✓

The use of oxytocic infusion prior to completion of the evacuation is not recommended. ✓

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. ✓

Excessive vaginal bleeding can be associated with molar pregnancy. There is theoretical concern over the routine use of potent oxytocic agents because of the potential to embolise and disseminate trophoblastic tissue through the venous system. This is known to occur in normal pregnancy, especially when uterine activity is increased, such as with accidental haemorrhage.[13] The contraction of the myometrium may force tissue into the venous spaces at the site of the placental bed. The dissemination of this tissue may lead to the profound deterioration in the patient, with embolic and metastatic disease occurring in the lung. To control life threatening bleeding oxytocic infusions may be used.

Evidence level 3

8. Histological examination of the products of conception in the diagnosis of GTD

8.1 Should products of conception from all miscarriages be examined histologically?

The histological assessment of material obtained from the medical or surgical management of all failed pregnancies is recommended to exclude trophoblastic neoplasia. D

In view of the difficulty in making a diagnosis of a molar pregnancy before evacuation, it is recommended that, in failed pregnancies, products of conception are examined histologically.[14]

As persistent trophoblastic neoplasia may develop after any pregnancy, it is recommended that products of conception, obtained after all repeat evacuations, should also undergo histological examination.

Evidence level 4

Ploidy status and immunohistochemistry staining for P57 may help in distinguishing partial from complete moles.[15]

Evidence level 3

8.2 Should products of conception be sent for examination after surgical termination of pregnancy?

There is no need to routinely send products of conception for histological examination following therapeutic termination of pregnancy, provided that fetal parts have been identified on prior ultrasound examination.

D

Seckl *et al.* reviewed the risk of GTN developing after confirmed therapeutic termination.[16] The rate is estimated to be 1/20 000. However, the failure to diagnose of GTD at time of termination leads to adverse outcomes with a significantly higher risk of life threatening complications, surgical intervention, including hysterectomy and multi-agent chemotherapy.

Evidence level 3

Guidance from the RCOG recommends the use of ultrasound prior to termination of pregnancy to exclude non-viable and molar pregnancies. There is no indication to send products of conception from a terminated viable pregnancy routinely for histological examination.[17]

The Royal College of Pathologists recommends that specimens should not be routinely sent for examination if fetal parts are visible.[18]

Evidence level 4

9. How should persisting gynaecological symptoms after an evacuation for molar pregnancy be managed?

Consultation with the relevant trophoblastic screening centre is recommended prior to second evacuation.

C

There is no clinical indication for the routine use of second uterine evacuation in the management of molar pregnancies.

If symptoms are persistent, evaluation of the patient with hCG estimation and ultrasound examination is advised. Several case series have found that there may be a role for second evacuation in selected cases when the hCG is less than 5000 units/litre.[19,20,21]

Evidence level 2+

10. Which women should be investigated for persistent GTN after a non-molar pregnancy?

Any woman who develops persistent vaginal bleeding after a pregnancy event is at risk of having GTN.

D

A urine pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event.

✓

Symptoms from metastatic disease, such as dyspnoea or abnormal neurology, can occur very rarely.

D

Several case series have shown that vaginal bleeding is the most common presenting symptom of GTN diagnosed after miscarriage, therapeutic termination of pregnancy or postpartum.[22,23,24,25,26]

The prognosis for women with GTN after non-molar pregnancies may be worse, in part owing to delay in diagnosis or advanced disease, such as liver or CNS disease, at presentation.[22,23,24,25,26]

Evidence level 2+

11. How is twin pregnancy of a fetus and coexistent molar pregnancy managed?

When there is diagnostic doubt about the possibility of a combined molar pregnancy with a viable fetus, advice should be sought from the regional fetal medicine unit and the relevant trophoblastic screening centre. ✓

In the situation of a twin pregnancy where there is one viable fetus and the other pregnancy is molar, the woman should be counselled about the increased risk of perinatal morbidity and outcome for GTN. D

Prenatal invasive testing for fetal karyotype should be considered in cases where it is unclear if the pregnancy is a complete mole with a coexisting normal twin or a partial mole. Prenatal invasive testing for fetal karyotype should also be considered in cases of abnormal placenta, such as suspected mesenchymal hyperplasia of the placenta. D

The outcome for a normal pregnancy with a coexisting complete mole is poor, with approximately a 25% chance of achieving a live birth. There is an increased risk of early fetal loss (40%) and premature delivery (36%). The incidence of pre-eclampsia is variable, with rates as high as 20% reported. However, in the large UK series, the incidence was only 4% and there were no maternal deaths.[27,28] In the same UK series, there was no increase in the risk of developing GTN after such a twin pregnancy and outcome after chemotherapy was unaffected.[27,28] Evidence level 3

12. Which women should be registered at GTD screening centres?

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 should be explained. ✓

Registration of women with GTD represents a minimum standard of care. ✓

Women with the following diagnoses should be registered and require follow-up as determined by the screening centre:

- complete hydatidiform mole
- partial hydatidiform mole
- twin pregnancy with complete or partial hydatidiform mole
- limited macroscopic or microscopic molar change suggesting possible partial or early complete molar change
- choriocarcinoma
- placental-site trophoblastic tumour
- atypical placental site nodules: designated by nuclear atypia of trophoblast, areas of necrosis, calcification and increased proliferation (as demonstrated by Ki67 immunoreactivity) within a placental site nodule.

Recent reports suggest that a proportion of atypical placental-site nodules may transform into placental-site trophoblastic tumours so all women with this condition should be registered with the GTD screening service.

After registration, follow-up consists of serial estimation of hCG levels, either in blood or urine specimens.

In the UK, there exists an effective registration and treatment programme. The programme has achieved impressive results, with high cure (98–100%) and low (5–8%) chemotherapy rates.[29] Evidence level 3

Registration forms can be obtained from the listed screening centres or registration can be made online at http://www.hmole-chorio.org.uk.

13. What is the optimum follow-up following a diagnosis of GTD?

Follow up after GTD is increasingly individualised. ✓

If hCG has reverted to normal within 56 days of the pregnancy event then follow up will be for 6 months from the date of uterine evacuation. D

If hCG has not reverted to normal within 56 days of the pregnancy event then follow-up will be for 6 months from normalisation of the hCG level. D

All women should notify the screening centre at the end of any future pregnancy, whatever the outcome of the pregnancy. hCG levels are measured 6-8 weeks after the end of the pregnancy to exclude disease recurrence. ✓

Two large case series of just under 9000 cases have shown that, once hCG has normalised, the possibility of GTN developing is very low.[30,31] GTN can occur after any GTD event, even when separated by a normal pregnancy.[10] Evidence level 3

14. What is the optimum treatment for GTN?

Women with GTN may be treated either with single-agent or multi-agent chemotherapy for GTN. Treatment used is based on the FIGO 2000 scoring system for GTN following assessment at the treatment centre. D

The need for chemotherapy following a complete mole is 15% and 0.5 % after a partial mole. The development of postpartum GTN requiring chemotherapy occurs at a rate of 1/50 000 births.[11] Evidence level 3

Women are assessed before chemotherapy using the FIGO 2000 scoring system (Table 1).[32] Women with scores ≤ 6 are at low risk and are treated with single-agent intramuscular methotrexate alternating daily with folinic acid for 1 week followed by 6 rest days. Women with scores ≥ 7 are at high risk and are treated with intravenous multi-agent chemotherapy, which includes combinations of methotrexate, dactinomycin, etoposide, cyclophosphamide and vincristine. Treatment is continued, in all cases, until the hCG level has returned to normal and then for a further 6 consecutive weeks.

The cure rate for women with a score ≤ 6 is almost 100%; the rate for women with a score ≥ 7 is 95%.[11] Evidence level 3

Placental site trophoblastic tumour is now recognised as a variant of gestational trophoblastic neoplasia. It may be treated with surgery because it is less sensitive to chemotherapy.

15. When can women whose last pregnancy was a complete or partial hydatidiform molar pregnancy try to conceive in the future and what is the outcome of subsequent pregnancies?

Women should be advised not to conceive until their follow-up is complete. D

Women who undergo chemotherapy are advised not to conceive for 1 year after completion of treatment. D

The risk of a further molar pregnancy is low (1/80): more than 98% of women who become pregnant following a molar pregnancy will not have a further molar pregnancy nor are they at increased risk of obstetric complications. If a further molar pregnancy does occur, in 68–80% of cases it will be of the same histological type.[33] Evidence level 3

Table 1 – FIGO Scoring system[32]

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

In a study of 230 women who conceived within 12 months of completing chemotherapy, there was an increased risk of miscarriage and higher rate of termination in women who received multi-agent chemotherapy. The rate of congenital abnormality was low (1.8%), irrespective of the type of chemotherapy used.[34] The rate of stillbirth was elevated compared with the normal population (18.6/1000 births).[35]

Evidence level 3

16. What is the long-term outcome of women treated for GTN?

Women who receive chemotherapy for GTN are likely to have an earlier menopause. D

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. D

The age at menopause for women who receive single-agent chemotherapy is advanced by 1 year and by 3 years if they receive multi-agent chemotherapy.[36]

An early study of 1377 women treated between 1958 and 1990 showed a 16.6 relative risk of developing acute myeloid leukaemia.There was also a 4.6 relative risk for developing colon cancer, 3.4 relative risk for melanoma and 5.79 relative risk for breast cancer in women surviving for more than 25 years.[37] If combination chemotherapy is limited to less than 6 months there appears to be no increased risk of secondary cancers.[38]

Evidence level 3

17. What is safe contraception following a diagnosis of GTD and when should it be commenced?

Women with GTD should be advised to use barrier methods of contraception until hCG levels revert to normal. D

Once hCG level have normalised, the combined oral contraceptive pill may be used. There is no evidence as to whether single-agent progestogens have any effect on GTN. D

If oral contraception has been started before the diagnosis of GTD was made, the woman can be advised to remain on oral contraception but she should be advised that there is a potential but low increased risk of developing GTN. ✓

Intrauterine contraceptive devices should not be used until hCG levels are normal to reduce the risk of uterine perforation. ✓

Two randomised controlled trials using the combined oral contraceptive pill have demonstrated no increased risk of developing GTN.[39] A much larger UK case series reported a 1.19 relative risk for developing GTN.[8]

Evidence level 1+

18. Is hormone replacement therapy safe for women to use after GTD?

Hormone replacement therapy may be used safely once hCG levels have returned to normal. ✓

There is no evidence of risk that the use of hormone replacement therapy affects the outcome of GTN.

Evidence level 4

19. Auditable outcomes

1. The proportion of women with GTN registered with the relevant screening centre.This would include:

- complete hydatidiform mole
- partial hydatidiform mole
- twin pregnancy with complete or partial hydatidiform mole
- limited macroscopic or microscopic molar change suggesting possible partial or early complete molar change
- choriocarcinoma

- placental site trophoblastic tumour
- atypical placental site nodules.

2. The proportion of women with a histological diagnosis of molar pregnancy who have an ultrasound diagnosis of molar pregnancy prior to uterine evacuation.

3. The proportion of women who undergo medical management for evacuation of products of conception with an ultrasound diagnosis of molar pregnancy.

20. Screening centres

Trophoblastic Tumour Screening and Treatment Centre
Department of Medical Oncology
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Tel: +44 (20) 8846 1409
Fax: +44 (20) 8748 5665
Website: www.hmole-chorio.org.uk

Trophoblastic Screening and Treatment Centre
Weston Park Hospital
Whitham Road
Sheffield S10 2SJ
Tel: +44 (0) 114 226 5205
Fax: +44 (0) 114 226 5511
Website: www.chorio.group.shef.ac.uk/index.html

Hydatidiform Mole Follow-up (Scotland)
Department of Obstetrics and Gynaecology
Ninewells Hospital
Dundee DD1 9SY
Tel: +44 (0) 1382 632748
Fax: +44 (0) 1382 632096

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated within the appropriate health services.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme. Once adapted for local use, these guidelines are no longer representative of the RCOG.

Classification of evidence levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies; e.g. case reports, case series

4 Expert opinion

Grades of recommendations

A At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++ and directly applicable to the target population; or
A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good practice point

✓ Recommended best practice based on the clinical experience of the guideline development group

This Guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
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The final version is the responsibility of the Guidelines Committee of the RCOG.

The Guidelines review process will commence in 2013
unless otherwise indicated

