Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Guideline No. 38
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THE MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

This guideline replaces *The Management of Gestational Trophoblastic Disease*, issued in April 1999 as Guideline No. 18.

1. Purpose

Gestational trophoblastic neoplasia (GTN) (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. There is evidence of ethnic variation in the incidence of GTN in the UK, with women from Asia having a higher incidence compared with non-Asian women (1/387 versus 1/752 live births).[1] However, this may under-represent the true incidence of the disease because of problems with reporting, particularly with regard to partial moles. Persistent GTN may develop after a molar pregnancy, a nonmolar 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 may deal with only one new case every second year. The purpose of this guideline is to provide guidance on the management of women with GTN in the UK.

2. Identification and assessment of evidence

The Cochrane Database and Medline were searched, using the terms 'molar pregnancy,' 'hydatidiform mole,' 'gestational trophoblastic disease,' 'gestational neoplasms' and 'choriocarcimona', between the years 1966 and 2003.

The definitions of types of evidence used in this guideline originate from the US Agency for Health Care Research and Quality. Where possible, recommendations are based upon and explicitly linked to the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'good practice points'.

3. Background

Hydatidiform mole can be subdivided into complete and partial mole based on genetic and histopathological features. Complete moles are diploid and androgenetic in origin, with no evidence of fetal tissue. Complete moles usually arise as a consequence of duplication of the haploid sperm following fertilisation of an 'empty' ovum. Some complete moles arise after dispermic fertilisation of an 'empty' ovum. Partial moles are triploid in origin with two sets of paternal haploid genes and one set of maternal haploid

genes. They occur, in almost all cases, following dispermic fertilisation of an ovum. There is usually evidence of a fetus or fetal red blood cells.

The widespread use of ultrasound has led to earlier diagnosis of pregnancy and has changed the pattern of molar pregnancy. The majority of women present with symptoms of early pregnancy failure while presentation with hyperemesis, early severe pre-eclampsia and hyperthyroidism is very rare.

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.[2]

4. Diagnosis of gestational trophoblastic neoplasia

Early complete molar pregnancies are commonly associated with the ultrasound diagnosis of delayed miscarriage or anembryonic pregnancy. Complete moles may be associated with suggestive ultrasonographic changes in the placenta. However, ultrasound has limited value in detecting partial molar pregnancies. In twin pregnancies with a viable fetus and a molar pregnancy, the pregnancy should be allowed to proceed.

C

The increasing use of ultrasound in early pregnancy has probably led to the earlier diagnosis of molar pregnancy. However, the majority of histologically proven complete moles are associated with an ultrasound diagnosis of delayed miscarriage or anembryonic pregnancy.[3] The ultrasound features of a complete mole are reliable but 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 anterior-posterior dimension of the gestation sac of greater than 1.5 is required for the reliable diagnosis of a partial molar pregnancy.[4] Estimation of human chorionic gonadotrophin (hCG) levels may be of value in diagnosing molar pregnancies. 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. In the situation of a twin pregnancy, where there is one viable fetus and the other pregnancy is molar, the pregnancy should be allowed to proceed if the mother wishes, following appropriate counselling. The probability of achieving a viable baby is 40% and there is a risk of complications such as pulmonary embolism and pre-eclampsia. There is no increased risk of developing persistent GTN after such a twin pregnancy and outcome after chemotherapy is unaffected.[5]

Evidence level III

5. Evacuation of molar pregnancies

Surgical evacuation of molar pregnancies is advisable. Routine repeat evacuation after the diagnosis of a molar pregnancy is not warranted.

C

Suction curettage is the method of choice of evacuation for complete molar pregnancies. Because of the lack of fetal parts a suction catheter, up to a maximum of 12 mm, is usually sufficient to evacuate all complete molar pregnancies. Medical termination of complete molar pregnancies, including cervical preparation prior to suction evacuation, should be avoided where possible.[6,7] 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, e.g. with accidental haemorrhage.[8] 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 woman, with embolic and metastatic disease occurring in the lung. While it is recognised that significant haemorrhage may occur as a consequence of evacuating a large uterine

Evidence levels III/IV

cavity, it is recommended, where possible, that oxytocic infusions are only commenced once evacuation has been completed. If the woman is experiencing significant haemorrhage prior to evacuation and some degree of control is required then use of these agents will be necessary according to the clinical condition. Oxytocic infusions have been in common use for this purpose. It is suggested that prostaglandin analogues should be reserved for cases where oxytocin is ineffective. Because evacuation of a large molar pregnancy is a rare event, advice and help from an experienced colleague should be sought where appropriate. In partial molar pregnancies where the size of the fetal parts deters the use of suction curettage, medical termination can be used. These women may be at an increased risk of requiring treatment for persistent trophoblastic neoplasia, although the proportion of women with partial molar pregnancies needing chemotherapy is low (0.5%).[9]

Evidence levels III/IV

Data from the management of molar pregnancies with mifepristone are limited.[7] Evacuation of complete molar pregnancies with this agent should be avoided at present since it increases the sensitivity of the uterus to prostaglandins.

6. Histological examination of products of conception

All products of conception obtained after evacuation (medical or surgical) should undergo histological examination. Products of conception from therapeutic terminations of pregnancy should be examined if there is no evidence of fetal tissue.

C

In view of the difficulty in making a diagnosis of a molar pregnancy before evacuation, the histological assessment of material obtained from the medical or surgical management of incomplete miscarriage is recommended in order to exclude trophoblastic neoplasia.[10] Ploidy status may help in distinguishing partial from complete moles. Because persistent trophoblastic neoplasia may develop after any pregnancy it is recommended that all products of conception obtained after repeat evacuation should undergo histological examination.[11]

Evidence level IV

7. The management of women with gynaecological symptoms after evacuation of a molar pregnancy

In cases where there are persisting symptoms, such as vaginal bleeding, after initial evacuation, consultation with the screening centre should be sought before surgical intervention.

C

There is no clinical indication for the routine use of a second uterine evacuation in the management of molar pregnancies.[7] Uterine evacuation may be recommended, in selected cases, by the screening centre as part of the management of persistent trophoblastic neoplasia.

Evidence level IV

8. Persistent GTN after a nonmolar pregnancy

Women with persistent abnormal vaginal bleeding after a nonmolar pregnancy should undergo a pregnancy test to exclude persistent GTN. Persistent GTN should be considered in any woman developing acute respiratory or neurological symptoms after any pregnancy.

C

Persistent GTN can occur after nonmolar pregnancies. Vaginal bleeding is a common presenting symptom but symptoms from metastatic disease, such as dyspnoea or abnormal neurology, can occur. The prognosis for women with GTN after nonmolar pregnancies may be worse (21% mortality after a live birth, 6% after a nonmolar miscarriage) and in part due to the delay in diagnosis (0.5–58.0 months).[10] Urgent referral of such cases should occur.

Evidence levels III/IV

9. Registration of women with molar pregnancy

Registration of any molar pregnancy is essential. ✓

The Health Departments of England, Scotland, Wales and Northern Ireland and the RCOG have agreed that registration of women with a molar pregnancy is desirable. Women with the following molar pregnancies should be registered and require follow up for 6–24 months 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.

Evidence level IV

Registration forms can be obtained from the screening centres listed in Appendix 1.

10. Treatment of persistent GTN

Women with persistent GTN should be treated at a specialist centre with appropriate chemotherapy. ✓

The need for chemotherapy following a complete mole is 15% and 0.5 % after a partial mole.[9] Persistent GTN requiring chemotherapy after other pregnancies is rare precluding accurate assessment.

Women with evidence of persistent GTN should undergo assessment of their disease followed by chemotherapy. Disease risk is scored according to the FIGO staging for GTN.[12] Women scoring six or less (low risk) receive intramuscular methotrexate on alternate days, followed by six rest days, with each course consisting of four injections.[13] Women who develop resistance to methotrexate are treated with a combination of intravenous dactinomycin and etoposide. Women scoring seven or more (high risk) receive combination chemotherapy. At the Charing Cross Hospital, London, the treatment is intravenous etoposide, methotrexate, dactinomycin for two days followed by vincristine and cyclophosphamide (EMA-CO) one week later. The course is then repeated after six days. At Weston Park Hospital, Sheffield, the treatment is intravenous methotrexate followed by dactinomycin and etoposide one week later. The course is then repeated after one week.[2] Treatment is continued, in all cases, until the hCG level has returned to normal and then for a further six consecutive weeks.

Evidence level III

11. Placental site trophoblastic tumour

Advice on the management of these rare tumours should be sought from the appropriate registration centre. C

Placental site trophoblastic tumour is now recognised as a variant of gestational trophoblastic neoplasia. Surgery and multi-agent chemotherapy play major roles in the clinical management of this tumour.[14,15]

Evidence level III

12. Future pregnancy

Women should be advised not to conceive until the hCG level has been normal for six months. **C**

Women should be advised not to conceive until their hCG levels have been normal for six months. The risk of a further molar pregnancy is low (1/55) 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, in 68–80% of cases it will be of the same histological type.[16] After the conclusion of any further pregnancy, at any gestation, further urine or blood samples for hCG estimation are requested to exclude disease recurrence. Women who undergo chemotherapy are advised not to conceive for one year after completion of treatment.

Evidence level III

13. Contraception and hormone replacement therapy

The combined oral contraceptive pill and hormone replacement therapy are safe to use after hCG levels have reverted to normal. **C**

The combined oral contraceptive pill, if taken while hCG levels are raised, may increase the need for treatment. However, it can be used safely after the hCG levels have returned to normal.[9] Other forms of hormonal contraception do not appear to be linked to an increased need for treatment. The small potential risk of using emergency hormonal contraception, in women with raised hCG levels, is outweighed by the potential risk of pregnancy to the woman. Hormone replacement therapy may be used safely once hCG levels have returned to normal.

Evidence level IV

14. Auditable outcomes

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.

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APPENDIX 1

Screening centres

Trophoblastic Tumour Screening and Treatment Centre
Department of Medical Oncology
Charing Cross Hospital
Fulham Palace Road
London W6 8RF.
Tel: 020 884 61409
Fax: 020 874 85665

Trophoblastic Tumour Screening and Treatment Centre
Weston Park Hospital
Whitham Road
Sheffield S10 2SJ
Tel: 0114 226 5205
Fax: 0114 226 5511

Trophoblastic Tumour Screening Centre
Department of Obstetrics and Gynaecology
Ninewells Hospital
Dundee DD1 9SY
Tel: 01382 632748
Fax: 01382 632096

Further information may also be obtained from the Hydatidiform Mole and Choriocarcinoma UK information service website at www.hmole-chorio.org.uk and the Sheffield Trophoblastic Tumour Screening and Treatment Centre website at www.sheffield.ac.uk/~co/troph

APPENDIX 2

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: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). 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.

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.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

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

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

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unless otherwise indicated