

GESTATIONAL TROPHOBLASTIC DISEASE

This document has been reviewed and approved by the Policy and Practice Guidelines Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC), the Gynaecologic Oncologists of Canada (GOC), the Society of Canadian Colposcopists (SCC), and by the Executive and Council of the SOGC.

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Abstract

Objective: To provide standards for the diagnosis and treatment of patients with hydatidiform mole and gestational trophoblastic tumours (GTT).

Options: Prognostic factors useful for treatment decisions in GTT are defined with patients classified as low-, medium-, and high-risk groups.

Outcomes: Improved mortality and morbidity.

Evidence: Evidence was gathered using Medline for relevant studies and articles from 1980 to 2001 with specific reference to diagnosis, treatment options, and outcomes. The quality of evidence of Recommendations has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.

Recommendations:

1. Suction curettage is the preferred method of evacuation of the hydatidiform mole (III-C). Post-operative surveillance with hCG assays is essential (II-3B).
2. Low-risk patients with both non-metastatic and metastatic disease should be treated with single-agent chemotherapy, either methotrexate or dactinomycin (II-3B).
3. Medium-risk patients should usually be treated with multi-agent chemotherapy, either MAC or EMA (III-C); single-agent chemotherapy may also be used (III-C).
4. High-risk patients should be treated with multi-agent chemotherapy EMA/CO, with selective use of surgery and radiotherapy (II-3B). Salvage chemotherapy with EP/EMA and surgery should be employed in resistant disease (III-C).
5. Placental site trophoblastic tumour that is non-metastatic should be treated with hysterectomy (III-C). Metastatic disease should be treated with chemotherapy, most commonly EMA/CO (III-C).

6. Women should be advised to avoid pregnancy until hCG levels have been normal for six months following evacuation of a molar pregnancy and for one year following chemotherapy for gestational trophoblastic tumour. The combined oral contraceptive pill is safe for use by women with GTT (III-C).

Validation: These guidelines have been reviewed and approved by the Policy and Practice Guidelines Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC), the Gynaecologic Oncologists of Canada (GOC), the Society of Canadian Colposcopists (SCC), and by Executive and Council of the SOGC.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

INTRODUCTION

Gestational trophoblastic disease (GTD) is a spectrum of tumours with a wide range of biologic behaviour and potential for metastases. GTD refers to both the benign and malignant entities of the spectrum and include hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumour. The last three are termed gestational trophoblastic tumours (GTT); all may metastasize and are potentially fatal if untreated. The incidence of hydatidiform mole varies in different regions of the world, but has been falling.¹ In North America the incidence is approximately 0.6 to 1.1 per 1000 pregnancies; the rate is approximately three times higher in Asia.¹ Choriocarcinoma in North America occurs in one of every 20,000 to 40,000 pregnancies.¹

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The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table 1).²

HYDATIDIFORM MOLE

Hydatidiform mole is classified as complete (CHM) or partial mole (PHM), which are distinguished by differences in clinical presentation, pathology, genetics, and epidemiology.³ The risk of malignant sequelae requiring therapy ranges from 8% to 15% with complete mole, to 1.5% to 6% with partial mole.⁴ The most common symptom is vaginal bleeding, which occurs in 84% of patients with complete moles.⁴ Fifty percent of patients with CHM show uterine enlargement and high levels of human chorionic gonadotropin (hCG).³ In contrast, patients with partial mole present with signs and symptoms of an incomplete or missed abortion, and have bleeding, a small uterus, and low hCG levels.⁴

Cytogenetic studies have characterized the two molar syndromes.⁴ In 90% of complete moles there are paternally derived chromosomes with a 46XX karyotype.⁴ Partial moles are most commonly due to a fertilization error in which a normal ovum is fertilized by two spermatozoa, resulting in a triploid karyotype (69XXY).⁴ Flow cytometry has been employed to differentiate the two molar types,³ but is not widely available.

DIAGNOSIS

In centres where ultrasound is available, the characteristic appearance of a vesicular molar pattern in CHM can often be identified in the first trimester before vaginal spotting or the

passage of macroscopic vesicles.³ There is no evidence of a fetus.

The early diagnosis of a partial mole is more complex and less likely, although ultrasound may demonstrate focal cystic spaces in the placenta and an increase in the transverse diameter of the gestational sac.³ A fetus may be seen in an advancing gestation.

TREATMENT

In both CHM and PHM, after diagnosis and workup, which includes a complete blood count (CBC), β -hCG, and chest X-ray, evacuation of the uterine contents is carried out by means of suction curettage followed by blunt curettage of the uterine cavity. Intravenous oxytocin should be administered during and after the evacuation procedure.

Rarely, in partial molar pregnancies, where the size of the fetus precludes suction curettage, medical termination may be used; these patients, however, may be at an increased risk of persistent trophoblastic disease (III-C).⁵

In patients who desire surgical sterilization, an abdominal hysterectomy with the mole *in situ* can be considered (III-C).⁴

Routine repeat evacuation after the diagnosis of molar pregnancy is not warranted (III-C).³

In twin pregnancies with a viable fetus and a molar pregnancy, the pregnancy may be allowed to continue (III-C).⁶

Careful follow-up is critical after evacuation of a molar pregnancy, to identify those at risk of developing malignant sequelae. Repeated weekly assays of hCG levels should be carried out until three negative levels are obtained, and then followed by monthly hCG levels times six, along with regular pelvic examinations. A chest X-ray is indicated if the β -hCG rises.

TABLE 1 QUALITY OF EVIDENCE ASSESSMENT ²	CLASSIFICATION OF RECOMMENDATIONS
<p>The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.</p> <p>I: Evidence obtained from at least one properly randomized controlled trial.</p> <p>II-1: Evidence from well-designed controlled trials without randomization.</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</p> <p>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.</p> <p>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</p> <p>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</p> <p>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</p>

Contraceptive measures should be instituted, ideally using oral contraceptives, and the patient advised to avoid pregnancy until hCG values have remained normal for six months (III-C).⁷ An early ultrasound should be performed in all subsequent pregnancies because of the 1–2% risk of a second molar pregnancy.⁴

INDICATIONS FOR THERAPY

Widely accepted indications for therapy after evacuation of a mole⁴ are:

- an abnormal hCG regression pattern (a 10% or greater rise in hCG levels or a plateauing hCG of three stable values over two weeks)
- an hCG rebound
- histologic diagnosis of choriocarcinoma or placental site trophoblastic tumour
- the presence of metastases
- high hCG levels (greater than 20,000 mIU/mL more than four weeks post-evacuation)
- persistently elevated hCG levels six months post-evacuation.

GESTATIONAL TROPHOBLASTIC TUMOURS

Diagnostic procedures for staging gestational trophoblastic tumours (GTT) begin with a sensitive β hCG assay and a chest X-ray to detect pulmonary metastases. If the chest X-ray is clear, the presumptive diagnosis of non-metastatic tumour is made.

Pelvic ultrasonography is useful in detecting extensive uterine disease.⁵

If pulmonary metastases are present, CT scans of the brain and abdomen are indicated. A pulmonary CT scan may reveal disease undetectable by a regular chest X-ray in 40% of patients with GTT.⁸ An ultrasound of the liver may detect metastatic disease suspected on CT scan. CSF (cerebrospinal fluid)/serum hCG levels greater than 1:60 may be more sensitive in detecting cerebral metastases.⁴ If gastrointestinal bleeding is present, upper and lower gastrointestinal tract endoscopy is indicated. An arteriogram is also useful. If hematuria is present, an IVP and cystoscopy are indicated.

CLASSIFICATION AND STAGING

Prognostic factors useful for treatment decisions have been defined from the beginning of the chemotherapeutic era in GTT. Subsequently, these criteria were refined by Hammond into the NIH clinical classification, in wide use in North America.⁹ The high-risk (poor prognosis) group is unlikely to be cured by single agents and requires initial aggressive combination therapy.⁹

Bagshawe subsequently developed a complex scoring system of prognostic factors.¹⁰ Adapted by the World Health Organization (WHO) in 1983, this classification became the most widely used prognostic scoring system (Table 2). The WHO score is a dynamic system; the weighting of scores assigned to some items, as well as the definition of subgroups, has been changed recently by the Charing Cross Group.¹¹

An anatomic staging system was adopted by FIGO in 1982, with two risk factors added in 1992.¹¹

Multivariate analysis found the WHO score to be the strongest predictor of survival outcome, with the NIH classification less predictable, and FIGO staging the least predictable.¹² However, a current study concluded that the revised FIGO system is capable of selecting patients who will respond poorly to single-agent chemotherapy.¹³ A recent proposal has been made to FIGO that combines the FIGO staging system with the WHO scoring system.

TREATMENT

LOW-RISK PATIENTS (WHO SCORE: 4 OR LESS)

Almost all patients in this category are ultimately cured, most with single-agent chemotherapy.

The standard five-day regimens of methotrexate and dactinomycin have evolved from hospital-administered parenteral regimens, to single-day outpatient regimens given over a shorter time, to oral regimens, to single courses of treatment. Present studies focus not on remission rates but rather on cost-effectiveness, toxicity, and patient convenience.

WHO SCORING SYSTEM ¹⁰				
	0	1	2	4
AGE	≤ 39	> 39		
Antecedent pregnancy	Hydatidiform Mole	Abortion	Term pregnancy	
Interval months from index pregnancy	4	4–6	7–12	> 12
Pretreatment hCG (IU/mL)	$< 10^3$	10^3 – 10^4	10^4 – 10^5	$> 10^5$
Largest tumour size including uterus		3–4 cm	5 cm	
Site of metastases		spleen, kidney	gastrointestinal tract	brain, liver
Number of metastases identified		1–4	4–8	> 8
Previously failed chemotherapy			single drug	two or more drugs

Non-Metastatic Disease

Hysterectomy, in selected cases, may be used as primary therapy in those patients with non-metastatic tumours who have completed childbearing or are not concerned about preserving fertility (III-C).⁴ The surgery is carried out in most centres during a course of single-agent chemotherapy to eradicate any occult metastases and reduce the likelihood of tumour dissemination or implantation (III-C).⁴

Single-agent chemotherapy with methotrexate or dactinomycin is the treatment of choice for patients wishing to preserve their fertility.

Methotrexate 0.4 mg/kg (maximum 25 mg) intravenously or intramuscularly daily for five days per treatment course has been widely employed. A similar regimen of methotrexate 1 mg/kg intramuscularly given days 1, 3, 5, and 7 with calcium leucovorin rescue 0.1 mg/kg days 2, 4, 6, and 8 is an alternative; advantages are decreased toxicity but disadvantages are increased cost and patient inconvenience. Courses are repeated every 14 days dependent on toxicity.^{7,11}

Methotrexate can also be given as a weekly regimen, 30 mg/m² intramuscularly.¹⁴

Dactinomycin 9–13 µg/kg intravenously daily for five days every two weeks (maximum 500 µg/d) is an alternative regimen and the primary therapy for patients with hepatic and renal disease or in circumstances contraindicating the use of methotrexate.⁷ Alternatively, pulsed dactinomycin 1.25 mg/m² intravenously every two weeks has the added benefit of patient convenience.¹⁴

Etoposide 200 mg/m² per os daily for five days every 12 to 14 days has been found to be highly effective and less toxic.¹⁵ However, side effects, primarily alopecia, prevent its widespread use. Recent data have also identified associated secondary tumours.¹⁶

Chemotherapy is changed from methotrexate to dactinomycin if the hCG level plateaus or if toxicity precludes adequate chemotherapy. With the development of metastases or an elevation in hCG, combination chemotherapy should be started. Treatment is continued one to two courses past the first normal hCG level.¹⁷

Approximately 85–90% of patients in this group are cured by the initial chemotherapy regimen. Most of the others will respond to alternate drugs; combination chemotherapy is rarely needed.

Low-Risk Metastatic Disease

Single-agent chemotherapy is employed as in non-metastatic disease. If resistance to single-agent chemotherapy develops, combination chemotherapy is employed.⁵ Approximately 30–50% of patients in this category will develop resistance to the first drug and require alternative treatments.¹¹ Hysterectomy may be necessary to eradicate a focus of resistant disease in the uterus. Approximately 5–15% of patients will require combination therapy with or without surgery to achieve remission.¹¹

MODERATE-RISK PATIENTS (WHO SCORE: 5 TO 7)

Traditionally, moderate-risk patients have been treated with multi-agent chemotherapy.^{7,16,18} MAC-based combinations (methotrexate, dactinomycin, cyclophosphamide or chlorambucil) are used, as is EMA (etoposide, methotrexate, dactinomycin).^{7,16,18}

The Charing Cross group has recently treated moderate-risk patients with methotrexate and folinic acid, similar to low-risk patients. No late sequelae have been demonstrated and there are no adverse prognostic factors if these patients are changed to multi-agent therapy later on.¹¹

If resistance develops in moderate-risk patients on treatment with the above regimens, they are reclassified into the high-risk category and combination chemotherapy with EMA/CO is initiated (see below).¹¹

HIGH-RISK PATIENTS (WHO SCORE: 8 OR GREATER)

Women with high-risk GTT present considerable difficulty in management and require combination chemotherapy with a selective use of surgery and radiotherapy. This group may include patients with metastases to the brain, liver, and gastrointestinal tract; complications such as massive bleeding may occur early in the course of the disease. These patients are also likely to develop drug resistance after prolonged chemotherapy. Treatment should be administered by experienced personnel in a specialized Gestational Trophoblastic Disease Centre or by a qualified gynaecologic oncologist.⁴

The standard chemotherapy regimen is EMA/CO¹¹ (etoposide, dactinomycin, and methotrexate alternated at weekly intervals with vincristine and cyclophosphamide). Newlands *et al.*¹¹ reported a five-year survival rate of 86%. Adverse prognostic variables are liver metastases, brain metastases, term delivery in the antecedent pregnancy, and a long interval between the antecedent pregnancy and diagnosis. Drug resistance developed in 17% of patients, of whom 70% were salvaged with additional chemotherapy or surgery.¹¹ Surgery included removal of the sites of drug resistance (e.g., uterus, portion of lung, portion of brain), followed by chemotherapy. The commonly used regimen for resistant disease is EP/EMA (etoposide, cisplatin, etoposide, methotrexate, dactinomycin).^{11,19}

There are few reports of treatment with the newer anti-cancer agents. Paclitaxel has achieved remission in a small group of patients with resistant GTT.²⁰ Other treatment approaches in patients with refractory disease have been the employment of G-CSF and high-dose chemotherapy with autologous bone marrow support.^{11,19} Cisplatin, vinblastine, and bleomycin may also be effective as second-line therapy.²¹

Central nervous system (CNS) metastases are classified into those presenting early (before therapy) or late (during or after therapy). Survival of women with those in the former group is 80% and in the latter 25%.²² EMA/CO with a dose escalation of methotrexate to 1 g/m² is commonly employed.²² In the

presence of a large superficial CNS lesion, an elective craniotomy with surgical excision followed by EMA/CO has provided good results.²²

Radiotherapy with concurrent chemotherapy has been used for CNS metastases in North America with a five-year survival averaging 50%.²³

PLACENTAL SITE TROPHOBLASTIC TUMOURS

Placental site trophoblastic tumours (PSTT) are rare and usually diagnosed after dilatation and curettage for missed abortion, but have also been described following term pregnancies and a hydatidiform mole.²⁴ PSTT has a wide spectrum of clinical behaviour, ranging from a self-limited state to persistence to a highly aggressive metastatic neoplasm.²⁴ The majority of cases behave in a self-limited fashion.²⁴ Metastases to the lung, liver, peritoneal cavity, and brain have been described.²⁴ The origin of PSTT is the intermediate trophoblastic cell, which shows a characteristic histologic pattern.

The optimal treatment for non-metastatic PSTT is hysterectomy. Outcomes of patients with non-metastatic PSTT are excellent with hysterectomy, while those with advanced disease have a 30% survival.²⁴ Chemotherapy in the latter group has been disappointing, although remissions have been reported with the EMA/CO protocol.²⁴

SPECIAL CONSIDERATIONS

With increasing attention being paid to quality of life, patients with hydatidiform mole and other low-risk patients will benefit from referral to services providing supportive care.

Medium-risk and high-risk patients are best treated in cancer treatment centres that provide expertise in drug therapy and in managing drug toxicity. The patient should be directed to other services such as social services, nutritional support and spiritual support of the patient's choice.

RECOMMENDATIONS

1. **Suction curettage is the preferred method of evacuation of the hydatidiform mole (III-C). Post-operative surveillance with hCG assays is essential (II-3B).**
2. **Low-risk patients with both non-metastatic and metastatic disease should be treated with single-agent chemotherapy, either methotrexate or dactinomycin (II-3B).**
3. **Medium-risk patients should usually be treated with multi-agent chemotherapy, either MAC or EMA (III-C); single-agent chemotherapy may also be used (III-C).**
4. **High-risk patients should be treated with multi-agent chemotherapy EMA/CO, with selective use of surgery and radiotherapy (II-3B). Salvage chemotherapy with EP/EMA and surgery should be employed in resistant disease (III-C).**

5. **Placental site trophoblastic tumour that is non-metastatic should be treated with hysterectomy (III-C). Metastatic disease should be treated with chemotherapy, most commonly EMA/CO (III-C).**
6. **Women should be advised to avoid pregnancy until hCG levels have been normal for six months following evacuation of a molar pregnancy and for one year following chemotherapy for gestational trophoblastic tumour. The combined oral contraceptive pill is safe for use by women with GTT (III-C).**

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