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Guideline No. 408: Management of Gestational Trophoblastic Diseases

(En français : Prise en charge des maladies gestationnelles trophoblastiques)

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

This Clinical Practice Guideline was prepared by the authors and overseen by the Society of Gynecologic Oncology of Canada (GOC) Guideline Committee and the Society of Obstetricians and Gyaecologists of Canada (SOGC) Gynaecology Clinical Practice Committee. It was reviewed by the SOGC's Guideline Management and Oversight Committee and Family Physicians Advisory Committee and approved by the GOC Executive and Board of Directors and the SOGC Board of Directors.

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Keywords: gestational trophoblastic disease, molar pregnancy, gestational trophoblastic neoplasia, hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor, human chorionic gonadotropin, trophoblastic neoplasms, uterine neoplasms, chemotherapy

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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed Consent: Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that they provide their patients with information and support that is evidence-based, culturally appropriate, and personalized.

Language and Inclusivity: This document uses gendered language in order to facilitate plain language writing but is meant to be inclusive of all individuals, including those who do not identify as a woman/female. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

Recommended Changes in Practice

1. Measure serum human chorionic gonadotropin (hCG) levels in women of reproductive age presenting with abnormal uterine bleeding, including bleeding >6 weeks after pregnancy (i.e., after term or preterm birth, ectopic pregnancy, termination of pregnancy, evacuation of a nonviable pregnancy, or spontaneous abortion) or with evidence of metastatic disease in order to promptly diagnose and manage gestational trophoblastic disease.
2. After evacuation of a molar pregnancy, begin weekly hCG monitoring 2 weeks post-procedure and continue until levels remain undetectable for 3 consecutive weeks. For complete hydatidiform mole, continue to monitor hCG monthly for 6 months. For partial hydatidiform mole, measure hCG 1 month after the first undetectable result in order to confirm resolution.
3. Discuss all cases of gestational trophoblastic neoplasia at multidisciplinary cancer case conferences and register in a regional and/or centralized database.

Key Messages

1. Any products of conception that appear abnormal at the time of uterine evacuation should be examined histologically, and any pathology suggestive of gestational trophoblastic disease should be reviewed by a gynaecologic pathologist to differentiate complete hydatidiform mole from partial hydatidiform mole and to look for evidence of malignancy, as these distinctions will affect patient follow-up, treatment, and referral.
2. Initial workup for post-molar gestational trophoblastic neoplasia requires a chest X-ray to detect lung metastases and a pelvic ultrasound scan to assess extent of disease in the pelvis. Initial workup for suspected choriocarcinoma, gestational trophoblastic neoplasia after a non-molar pregnancy, and/or post-molar gestational trophoblastic neoplasia with lung metastases on chest X-ray requires pelvic ultrasound scan, computed tomography scan of the chest and abdomen (with arterial phase through the liver), and magnetic resonance imaging of the brain.
3. Women diagnosed with gestational trophoblastic disease should be referred to a gynaecologist for initial evaluation and consideration for primary surgery (uterine evacuation or hysterectomy) and follow-up.
4. Women undergoing follow-up after molar pregnancy should receive reliable contraception throughout the entire duration of follow-up.
5. Women diagnosed with gestational trophoblastic neoplasia should be referred to a gynaecologic oncologist for staging, risk scoring, and consideration for primary surgery or systemic therapy (single- or multi-agent chemotherapy) with the potential need for additional therapies.

Abstract

Objective: This guideline reviews the clinical evaluation and management of gestational trophoblastic diseases, including surgical and medical management of benign, premalignant, and malignant entities. The objective of this guideline is to assist health care providers in promptly diagnosing gestational trophoblastic diseases, to standardize treatment and follow-up, and to ensure early specialized care of patients with malignant or metastatic disease.

Intended Users: General gynaecologists, obstetricians, family physicians, midwives, emergency department physicians, anaesthesiologists, radiologists, pathologists, registered nurses, nurse practitioners, residents, gynaecologic oncologists, medical oncologists, radiation oncologists, surgeons, general practitioners in oncology, oncology nurses, pharmacists, physician assistants, and other health care providers who treat patients with gestational trophoblastic diseases. This guideline is also intended to provide information for interested parties who provide follow-up care for these patients following treatment.

Target Population: Women of reproductive age with gestational trophoblastic diseases.

Options: Women diagnosed with a gestational trophoblastic disease should be referred to a gynaecologist for initial evaluation and consideration for primary surgery (uterine evacuation or hysterectomy) and follow-up. Women diagnosed with gestational trophoblastic neoplasia should be referred to a gynaecologic oncologist for staging, risk scoring, and consideration for primary surgery or systemic therapy (single- or multi-agent chemotherapy) with the potential need for additional therapies. All cases of gestational trophoblastic neoplasia should be discussed at a multidisciplinary cancer case conference and registered in a centralized (regional and/or national) database.

Evidence: Relevant studies from 2002 onwards were searched in Embase, MEDLINE, the Cochrane Central Register of Controlled Trials, and Cochrane Systematic Reviews using the following terms, either alone or in combination: trophoblastic neoplasms, choriocarcinoma, trophoblastic tumor, placental site, gestational trophoblastic disease, hydatidiform mole, drug therapy, surgical therapy, radiotherapy, cure, complications, recurrence, survival, prognosis, pregnancy outcome, disease outcome, treatment outcome, and remission. The initial search was performed in April 2017 and updated in May 2019. Relevant evidence was selected for inclusion in the following order: meta-analyses, systematic reviews, guidelines, randomized controlled trials, prospective cohort studies, observational studies, non-systematic reviews, case series, and reports. Additional significant articles were identified through cross-referencing the identified reviews. The total number of studies identified was 673, with 79 studies cited in this review.

Validation Methods: The content and recommendations were drafted and agreed upon by the authors. The Executive and Board of Directors of the Society of Gynecologic Oncology of Canada reviewed the content and submitted comments for consideration, and the Board of Directors for the Society of Obstetricians and Gynaecologists of Canada approved the final draft for publication. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology framework. See the online appendix tables for key to grading and interpretation of recommendations.

Benefits: These guidelines will assist physicians in promptly diagnosing gestational trophoblastic diseases and urgently referring patients diagnosed with gestational trophoblastic neoplasia to gynaecologic oncology for specialized management. Treating gestational trophoblastic neoplasia in specialized centres with the use of centralized databases allows for capturing and comparing data on treatment outcomes of patients with these rare tumours and for optimizing patient care.

SUMMARY STATEMENTS (GRADE ratings in parentheses)

1. If symptoms of pregnancy persist 4 to 6 weeks after termination of pregnancy, evacuation of a nonviable pregnancy, or spontaneous abortion, measurement of serum or urine human chorionic

gonadotropin may allow for earlier diagnosis of gestational trophoblastic disease if products of conception are not sent routinely for pathology (moderate).
2. The differentiation of complete hydatidiform mole, partial hydatidiform mole, and malignant trophoblastic disease by a gynaecologic pathologist allows for tailored follow-up and management of gestational trophoblastic neoplasia (low).
3. The treatment of hydatidiform mole consists of surgical evacuation by suction dilatation and curettage or hysterectomy followed by human chorionic gonadotropin surveillance (moderate).
4. Prophylactic chemotherapy is considered only for high-risk patients who are unlikely to return for regular follow-up (very low).
5. Post-molar follow-up consists primarily of serial human chorionic gonadotropin monitoring (high).
6. Hormonal contraception can be safely prescribed and intrauterine contraceptive devices can be inserted after normalization of human chorionic gonadotropin levels (low).
7. Referral for genetic counseling and testing should be arranged for women with recurrent gestational trophoblastic disease as this is a rare scenario that may be associated with a familial gene mutation (moderate).
8. The finding of a persistent low-level human chorionic gonadotropin may be benign (e.g., false-positive human chorionic gonadotropin or pituitary production of human chorionic gonadotropin), premalignant (e.g., quiescent gestational trophoblastic disease), or malignant (e.g., placental site trophoblastic tumour or epithelioid trophoblastic tumour) (moderate).
9. Long-term follow-up may eventually reveal a diagnosis of gestational trophoblastic neoplasia for patients with a true positive human chorionic gonadotropin result but no immediate evidence of disease at the time of testing (low).

RECOMMENDATIONS (GRADE ratings in parentheses)

1. Women of reproductive age presenting with abnormal uterine bleeding, bleeding >6 weeks following pregnancy, or evidence of metastatic disease should have serum human chorionic gonadotropin levels tested in order to promptly diagnose and manage gestational trophoblastic disease (strong, low).
2. Any products of conception that appear abnormal at the time of dilatation and curettage should undergo histologic examination to rule out gestational trophoblastic disease (strong, very low).
3. Initial workup for post-molar gestational trophoblastic neoplasia requires a chest X-ray to look for lung metastases and a pelvic ultrasound scan to assess extent of disease in the pelvis (strong, moderate).
4. Initial workup for suspected choriocarcinoma, gestational trophoblastic neoplasia after a non-molar pregnancy, and/or post-molar gestational trophoblastic neoplasia with lung metastases on chest X-ray requires pelvic ultrasound scan, computed tomography scan of the chest and abdomen (with arterial phase through the liver), and magnetic resonance imaging of the brain (strong, moderate).
5. Women with suspected hydatidiform mole should be offered either suction evacuation of the uterus or hysterectomy for initial management (strong, moderate).
6. All Rh-negative women should be offered anti-D immune globulin after uterine evacuation to prevent alloimmunization (strong, high).
7. For all patients after evacuation of a molar pregnancy, weekly monitoring of serum quantitative human chorionic gonadotropin should begin 2 weeks post-procedure and continue until levels remain undetectable for 3 consecutive weeks. For complete hydatidiform mole, human chorionic gonadotropin should continue to be monitored monthly for 6 months. For partial hydatidiform mole, human chorionic gonadotropin should be measured 1 month after the first undetectable result to confirm resolution (strong, high).
8. Women undergoing follow-up after molar pregnancy should receive reliable contraception throughout the entire duration of follow-up (strong, moderate).
9. For women with previous gestational trophoblastic neoplasia or recurrent molar pregnancy, follow-up in a subsequent pregnancy should include early ultrasound scan, close examination of the placenta, and histologic examination of any nonviable pregnancy (strong, high).
10. Women diagnosed with gestational trophoblastic neoplasia should be promptly referred to a specialist in gynaecologic oncology for staging, risk scoring, and treatment (strong, high).
11. Women with low-risk gestational trophoblastic neoplasia should undergo treatment with single-agent chemotherapy, although hysterectomy is an option for select patients (strong, high).
12. Women with high-risk gestational trophoblastic neoplasia should undergo treatment with multi-agent chemotherapy at a centre with expertise in managing this disease (strong, high).
13. Ultrahigh-risk gestational trophoblastic neoplasia with liver or brain metastasis or a modified World Health Organization score as adapted by the International Federation of Gynecology and Obstetrics (FIGO),[56] of ≥13 should undergo low-dose induction chemotherapy with etoposide and cisplatin weekly for 1 to 3 weeks to avoid complications of uncontrolled hemorrhage followed by multi-agent chemotherapy at a centre with expertise in managing this disease, preferably at a reference centre (strong, high).
14. Women who become pregnant during follow-up for gestational trophoblastic disease or gestational trophoblastic neoplasia should be referred to gynaecologic oncology and maternal–fetal medicine for assessment and management (strong, very low).
15. The care of patients with gestational trophoblastic disease should be managed in specialized centres and their data recorded in centralized (regional and/or national) registries, where possible (strong, high).

INTRODUCTION

Gestational trophoblastic disease (GTD) is characterized by an abnormal proliferation of the placental trophoblast. Placental site nodules and exaggerated placental site tumours are non-neoplastic entities. Complete and partial hydatidiform moles are considered premalignant given their potential for persistence and invasion. Atypical placental site nodules also have malignant potential.[1] Malignant subtypes are categorized as gestational trophoblastic neoplasia (GTN). GTN can be preceded by a molar or non-molar pregnancy and includes several diagnoses: invasive moles, choriocarcinomas, placental site trophoblastic tumours, and epithelioid trophoblastic tumours (Figure).

GENETICS

Hydatidiform moles result from an excess of paternal haploid chromosome sets in the gestation. Complete hydatidiform moles are typically characterized by the absence of a maternal haploid chromosome set and the presence of 2 paternal haploid sets (androgenesis) that occurs either from fertilization of an empty ovum by a single sperm with duplication of its chromosomes (i.e., monospermy: 46,XX) or through fertilization by 2 sperm (i.e., dispermy: 46,XX or 46,XY). Partial hydatidiform moles result from similar processes but contain 1 maternal haploid chromosome set, resulting in a triploid gestation (i.e., 69,XXX, 69,XXY, or 69,XYY). In partial hydatidiform moles, a fetus or fetal membranes may be present, but the conceptus is nonviable. This is in contrast to a triploid pregnancy with 2 maternal sets and only 1 paternal haploid set, where the conceptus is a non-molar triploid gestation exhibiting hydropic villi but no trophoblastic proliferation. Immunohistochemical staining for the $p57^{KIP2}$ gene product of *CDKN1C* can be used to differentiate complete hydatidiform moles from partial hydatidiform moles and hydropic abortus. *CDKN1C* is a paternally imprinted, maternally expressed gene. The $p57^{KIP2}$ gene product is entirely absent in the villous trophoblast of the complete hydatidiform mole because of its androgenetic origin. An exception to this is the diploid biparental complete hydatidiform mole resulting from familial recurrent hydatidiform mole. This autosomal recessive condition affects genes *NLRP7* or *KHDC3L*, the former being an important contributor to maternal imprinting.[2,3] The condition is diagnosed through fluorescent microsatellite genotyping in which biparental contribution is identified. Patients with this condition are unable to conceive a normal pregnancy without the assistance of egg donation; they account for 50% to 80% of patients with recurrent hydatidiform mole.[4] Recent bi-allelic deleterious mutations have been identified in genes *MEI1*, *TOP6BL/C11orf80*, and *REC114*, with roles in the formation of meiotic double-strand breaks in women with recurrent androgenetic complete hydatidiform moles.[5] Research to identify other novel contributing genes is ongoing.[4]

GTN can follow a molar pregnancy, a term/preterm pregnancy, an abortion, or an ectopic pregnancy. Postpartum choriocarcinoma is typically composed of biparental chromosomes identical to those of the fetus, whereas choriocarcinoma after complete mole is androgenetic. Genotyping may be beneficial to rule out primary gastric, ovarian, or pulmonary choriocarcinoma, depending on the clinical circumstances, such as absence of either a pelvic mass or preceding gestational event. Non-gestational choriocarcinomas are rare and can be distinguished by the absence of paternal DNA.[6] They are associated with nondurable treatment responses and an overall poor prognosis.[7]

PATHOPHYSIOLOGY

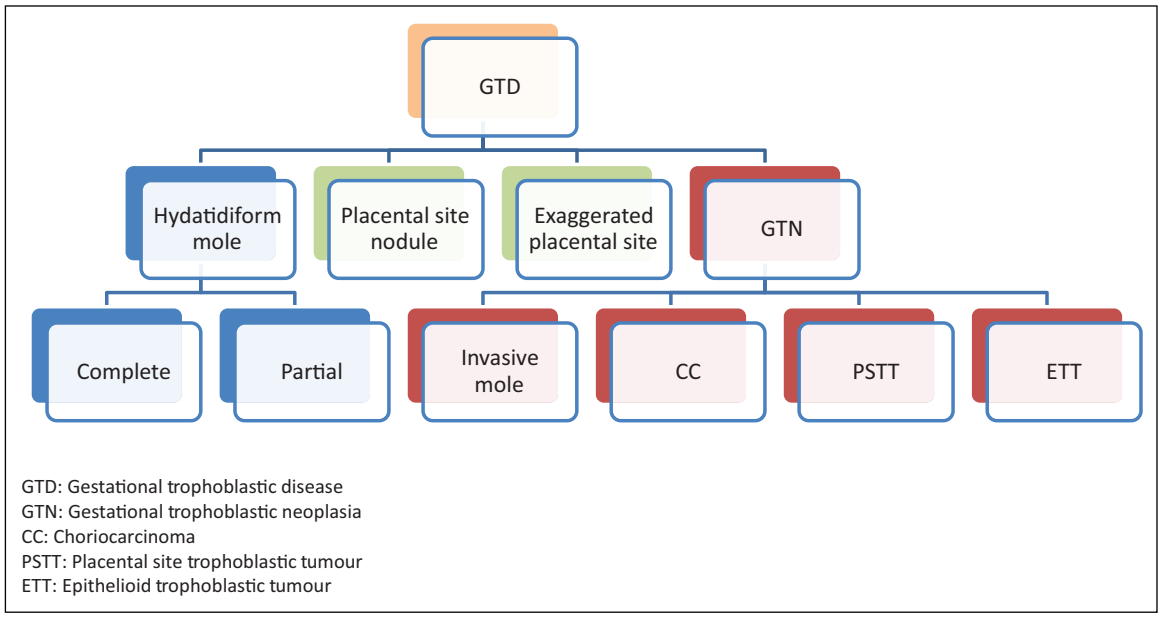
Gestational trophoblastic tumours secrete human chorionic gonadotropin (hCG). It is initially secreted by the primitive cytotrophoblast mostly as hyperglycosylated hCG until week 4. After week 4, most hCG is secreted by the syncytiotrophoblast (a layer derived from the invading cytotrophoblast layer). This layer is gradually lost as a gestation matures, declining from about the 12th week of gestation until term. Because placental site trophoblastic tumours arise from the implantation-site intermediate trophoblast, they contain very little syncytiotrophoblast and secrete very low levels of hCG. Epithelioid trophoblastic tumours, arising from the chorionic-type intermediate trophoblast, similarly secrete very low levels of hCG. Otherwise, serum hCG highly correlates with tumour burden and is therefore an important and useful marker in the diagnosis and treatment of GTN.

The glycoprotein hCG is made up of a unique beta subunit and an alpha subunit that is shared with other hormones, including thyroid-stimulating hormone and luteinizing hormone. Overstimulation from elevated levels of hCG (typically >100 000 mIU/mL) can result in the development of

ABBREVIATIONS

GTD	Gestational trophoblastic disease
GTN	Gestational trophoblastic neoplasia
hCG	Human chorionic gonadotropin
hCG-H	Hyperglycosylated human chorionic gonadotropin

Figure. Gestational trophoblastic diseases.



theca lutein cysts of the ovary, hyperemesis gravidarum, preeclampsia, and hyperthyroidism with the associated risk of thyroid storm, particularly at the time of uterine evacuation. Most hCG assays use antibodies to detect the beta subunit, which in normal pregnancy is mostly present in the intact form. With malignant change, however, the hCG molecule becomes increasingly disrupted, resulting in fragments such as core hCG, nicked free-beta, and C-terminal peptide. Hyperglycosylated forms are also increased. Commercially available hCG assays detect some of the different forms of hCG, but there is wide variation in the relative proportions that each test reports. This may cause variations in the hCG levels reported if different hCG assays are used in the follow-up of patients with GTN.[8]

The differential diagnosis of an elevated hCG level includes pregnancy, GTD, pituitary production of hCG, phantom hCG from cross-reaction with a circulating heterophile antibody, or ectopic production of hCG (e.g., non-gestational choriocarcinoma).

EPIDEMIOLOGY

The incidence of GTD is generally reported to be 1 in 1000 pregnancies; however, this varies by population.[9,10] The only Canadian study reports a risk of hydatidiform mole of 1 in 454 pregnancies in Nova Scotia between 1990 and 2005 using provincial databases of GTDs, pregnancies, and births.[11] GTDs are more common in patients at the extremes of age (<20 years or >40 years) and particularly in women over the age of 45.[11,12] The incidence of GTD appears to be highest in Asian populations.[10] The risk of invasive mole is 15% to 20% after a complete hydatidiform moles and 0.5% to 1% after a partial hydatidiform moles.[13–16] The risk of invasive mole increases to 40% to 50% in patients with any one of the following risk factors: age >40 years, uterine size >4 weeks above expected for gestational age, hCG ≥100 000 mIU/mL, and bilateral theca lutein cysts ≥6 cm.[17,18] The incidence of choriocarcinoma is approximately 1 in 20 000 pregnancies in North America but varies globally.[19,20] The most rarely diagnosed GTN are placental site trophoblastic tumours and epithelioid trophoblastic tumours, which make up less than 1% of all GTN; they can occur after molar and non-molar pregnancies, often years after the antecedent pregnancy.

SUMMARY STATEMENTS 1, 2 and RECOMMENDATIONS 1, 2, 3, 4

DIAGNOSIS OF GESTATIONAL TROPHOBLASTIC DISEASE

Historically, patients with GTD typically presented with abnormal vaginal bleeding and a large-for-date uterus and occasionally with hyperemesis, preeclampsia, or hyperthyroidism. However, since the institution of routine first-trimester ultrasound scan, GTD is most often identified by imaging before the patient develops clinical symptoms

other than vaginal bleeding, or on histology post-evacuation of an abnormal pregnancy. If ultrasound findings are not clearly diagnostic of a molar gestation, a rising hCG level will differentiate GTD from diagnoses such as a blighted ovum or missed abortion.[21] Consideration should be given to the measurement of serum or urine hCG 4 to 6 weeks after any termination of pregnancy, evacuation of a nonviable pregnancy, or spontaneous abortion if symptoms of pregnancy persist, such as ongoing bleeding or amenorrhea. This would rule out retained products of conception or a new pregnancy in settings where products of conception are not routinely sent for pathology and can identify GTD, thus avoiding delayed diagnosis of GTN, which is associated with life-threatening complications and the need for surgical intervention and chemotherapy.[22]

Ultrasound features of a complete hydatidiform mole include absence of a fetus and no amniotic fluid in an enlarged uterus. The uterus is filled with a heterogeneous, predominantly echogenic, mass containing multiple hypoechoic foci in what is commonly described as a "snowstorm" pattern. The uterine mass contains multiple cystic spaces (hydropic villi) resulting in the "cluster of grapes" appearance. As the pregnancy progresses, the cystic areas enlarge and become more numerous. In addition to the cystic spaces, the mass may contain larger irregular fluid collections. In complete hydatidiform moles, ovarian theca lutein cysts may occur when the hCG level is elevated given the ability of the intact hCG molecule to mimic luteinizing hormone. Partial hydatidiform moles may present as an empty gestational sac or a sac containing amorphous fetal parts or a growth-restricted/nonviable fetus. There is decreased amniotic fluid and an enlarged placenta relative to the size of the uterus, with cystic spaces often referred to as having a "Swiss cheese" appearance. The gestational sac in the partial hydatidiform mole may have an ovoid appearance, as determined by an increased transverse diameter (ratio of transverse diameter to anteroposterior diameter >1.5). Theca lutein cysts are typically absent owing to the lower hCG level. Misdiagnosis of a partial hydatidiform mole may occur in the rare case of a twin pregnancy consisting of a molar pregnancy and a biparental diploid (viable) fetus.[21]

Any products of conception that appear abnormal at the time of uterine evacuation should be examined histologically.[22] Any pathology results suggestive of GTD should be reviewed by a gynaecologic pathologist to differentiate complete hydatidiform moles, partial hydatidiform moles, and malignant trophoblastic disease; this distinction will affect patient follow-up and the management of GTN.

Workup of a suspected GTD includes a review of systems to identify complications such as anemia, preeclampsia, and hyperthyroidism, or symptoms suggestive of metastatic disease. The dates and outcomes of all preceding pregnancies should be recorded as part of the obstetrical history. Physical examination should include assessment of uterine size and the presence of adnexal masses or other metastases. Laboratory investigations include complete blood count, electrolytes, international normalized ratio, partial thromboplastin time, creatinine, liver enzymes, thyroid-stimulating hormone, quantitative total hCG, and urine protein. A reproductive-age woman with unexplained persistently elevated or rising hCG levels should be considered to have GTD until proven otherwise.

Imaging for patients with molar pregnancy typically includes only a pelvic ultrasound scan, with further investigations tailored to presenting symptoms. Imaging post-molar GTN requires a chest X-ray to look for lung metastases and a pelvic ultrasound scan to assess extent of disease in the pelvis. On chest X-ray, lesions ≥6 mm would be expected to be visible. If the chest X-ray findings are negative, no further imaging is required. The likelihood of clinically significant metastases is negligible in the absence of lung or vaginal metastases. Micrometastases in the lung identified on CT scan of the chest do not affect the clinical outcome of patients with otherwise stage I disease.[23,24] If the chest X-ray findings are suspicious or positive, a CT scan of the chest and abdomen with an arterial phase through the liver is recommended. If the chest X-ray results are positive, magnetic resonance imaging (MRI) of the brain should also be performed.

In suspected choriocarcinoma or GTN after a non-molar pregnancy, a more extensive workup is recommended because the incidence of metastases can be greater than 40%.[23] Pelvic ultrasound scan should be used in the initial assessment to determine the extent of pelvic disease after the physical examination. Additional workup requires a CT scan of the chest and abdomen (with arterial phase through the liver) and MRI of the brain.

There is no advantage of positron emission tomography/computed tomography scan over conventional imaging in tumour staging. However, positron emission tomography/computed tomography scan may be helpful in ambiguous cases presenting with elevated hCG levels.

GTN metastasizes primarily hematogenously. The lungs and vagina are the most common sites of metastases; the brain, liver, and other sites are far less frequently involved. Presenting symptoms of metastasis in GTN can include

vaginal bleeding, dyspnea, cough, chest pain, hemoptysis, abdominal pain, melena, headache, visual changes, dizziness, seizures, or neurological deficits. Respiratory failure, acute abdomen, severe anemia, or stroke may result from hemorrhage from these highly vascular tumours. Although clinical evaluation should be performed, including abdominal and pelvic examination, biopsy of suspicious lesions is *contraindicated* because of the risk of significant hemorrhage. After pregnancy, any persistent bleeding beyond 6 weeks postpartum should be investigated with hCG assay and pelvic ultrasound scan.

Women with suspected hydatidiform mole can be referred to general gynaecology for assessment and management. Women with suspected GTN should be referred directly to gynaecologic oncology for urgent staging and treatment.

SUMMARY STATEMENTS 3, 4 and RECOMMENDATIONS 5, 6

TREATMENT OF HYDATIDIFORM MOLE

The most common form of GTD is the hydatidiform mole. The recommended option for surgical management is uterine evacuation, but hysterectomy is an acceptable alternative. Medical methods of uterine evacuation are not recommended.[25] The treatment approach should be tailored to the needs and desires of the patient. If hysterectomy is selected, patients must be aware that they will still require serial hCG monitoring because the development of GTN requiring systemic treatment may still occur. A recent meta-analysis suggests that hysterectomy rather than uterine evacuation might be the ideal treatment option in patients over age 40 who have completed child-bearing.[26] If imaging findings are convincing for molar pregnancy, hysterectomy can be considered. The surgery must be performed by an experienced surgeon. The uterus must be removed intact (i.e., no morcellation). Follow-up must be the same as for those undergoing uterine evacuation, and treatment should be based on the final pathology results.

Uterine evacuation is most safely performed in the operating room, with suction curettage, ideally ultrasound-guided, to ensure complete emptying and to minimize the likelihood of inadvertent uterine perforation. The anaesthesiologist and operating room team should be aware of the possibility of significant hemorrhage, thyroid storm, or acute respiratory dysfunction from trophoblastic emboli. Brisk bleeding is often encountered with serial dilatation of the cervix. A suction catheter appropriate to the size of the uterus is then used to evacuate the uterine contents, which are sent for histologic examination. A delicate sharp curettage is performed at the end of the procedure to ensure complete evacuation. Oxytocin can be used to increase uterine tone after evacuation. Fundal massage may be appropriate if the uterus is >12 to 14 weeks in size. Balloon tamponade and angioembolization have been described for uterine preservation in cases of severe hemorrhage post-evacuation.[27,28]

Before hospital discharge, effective contraception should be prescribed with a plan for immediate initiation. Follow-up arrangements must also be in place before discharge: a requisition for weekly quantitative serum total hCG (to be started 2 weeks after uterine evacuation and performed consistently at the same laboratory) and an appointment for a postoperative visit 3 to 6 weeks after treatment to review pathology results and adherence to contraception, to monitor hCG, and to perform a pelvic examination in order to ensure continued uterine involution.

Anti-D immune globulin should be administered to all Rh-negative patients to prevent alloimmunization. Although fetal tissue or blood is typically encountered only in a partial hydatidiform mole, it is not always possible to clinically distinguish partial hydatidiform moles from complete hydatidiform moles at the time of uterine evacuation. To offer prophylaxis within the appropriate 72-hour window, anti-D immune globulin is recommended post-procedure for all Rh-negative patients.

Prophylactic chemotherapy for all patients is not recommended because it exposes a majority to unnecessary systemic therapy and its adverse effects and may cause chemotherapy resistance in those who go on to develop persistent disease. Prophylactic chemotherapy can be considered in select high-risk patients who are unlikely to complete follow-up.[17,29–32]

SUMMARY STATEMENTS 5, 6 and RECOMMENDATIONS 7, 8

FOLLOW-UP OF HYDATIDIFORM MOLE

If the histology results confirm the diagnosis of hydatidiform mole without metastatic disease, close follow-up is recommended to ensure disease resolution. Quantitative serum total hCG should be measured by commercially available assays capable of measuring hCG levels lower than 5 mIU/mL and capable of detecting all forms of hCG, including beta-hCG, core hCG, C-terminal hCG, nicked-free

beta, and beta core. The same assay should be used each time during follow-up to avoid differences in results between laboratories. hCG should be measured weekly beginning 2 weeks post-procedure and continuing until hCG levels are undetectable for 3 consecutive weeks. Monthly monitoring should continue for 6 months for patients with complete hydatidiform moles.[33] For patients with partial hydatidiform moles, hCG should be measured 1 month after the first undetectable result to confirm resolution.[34] A shorter period of follow-up could be considered for patients with complete hydatidiform moles who wish to become pregnant, especially in women ≥35 and particularly those with a history of infertility. Several large retrospective studies have shown that the risk of GTN is <1% after complete or partial hydatidiform moles once hCG reaches undetectable levels and the risk is lowest in patients with normalization within the first 56 days.[35–39] Reliable contraception must be used to avoid pregnancy during follow-up because pregnancy would interfere with the interpretation of hCG results and complicate treatment should persistent disease be diagnosed. Hormonal contraception is safe to prescribe immediately after uterine evacuation and does not increase the risk of persistent disease. Oral contraceptives provide the added benefit of suppressing endogenous luteinizing hormone, which can interfere with the measurement of hCG at low levels.[40] Intrauterine contraceptive devices (IUDs) should be avoided until after normalization of serum hCG levels to reduce the risk of uterine perforation.[41]

SUMMARY STATEMENT 7 and RECOMMENDATION 9

GESTATIONAL TROPHOBLASTIC DISEASE IN A TWIN OR MULTIPLE GESTATION

The incidence of GTD in a twin or multiple gestation is rare. These patients carry an increased risk of preeclampsia, hemorrhage, thyrotoxicosis, preterm delivery, and subsequent GTN. In 72 cases of GTD with a twin pregnancy (out of 12 455 cases of GTD), 60% of pregnancies that continued resulted in live births. Progression to GTN was observed in 46% of patients. Elective termination did not alter the risk of subsequent GTN. Pregnancies terminated for complications such as preeclampsia or heavy bleeding were more likely to progress to GTN, as were those with higher presenting hCG levels.[42] A balanced discussion of the risks and benefits of continuing the pregnancy should take place, and if the pregnancy proceeds, it must be managed jointly by a gynaecologic oncologist and maternal–fetal medicine specialist.

SUBSEQUENT PREGNANCY POST-GESTATIONAL TROPHOBLASTIC DISEASE

The risk of recurrent GTD is approximately 1 in 100, or approximately 10-fold higher than in a patient with no prior GTD history. In subsequent pregnancies, an early ultrasound scan is recommended to confirm a normal intrauterine pregnancy. At the time of delivery, the placenta should be carefully examined and sent for pathology if there are any clinical abnormalities. In the event of an ectopic pregnancy or abortion of any type, the products of conception should be sent for histologic examination. A referral for genetic counseling and testing should be made upon diagnosis of recurrent molar pregnancy to rule out familial recurrent hydatidiform mole.

SUMMARY STATEMENTS 8, 9 and RECOMMENDATION 10

DIAGNOSIS OF POST-MOLAR GESTATIONAL TROPHOBLASTIC NEOPLASIA

During post-molar follow-up, persistent disease is diagnosed when any of the following criteria are met:

- A rising serum hCG level, defined as a >10% increase compared with the previous level for 2 consecutive weeks (3 levels measured on days 1, 8, and 15) [43]
- A plateau in serum hCG levels, defined as a <10% change compared with the previous level for 3 consecutive weeks (4 levels measured on days 1, 8, 15, and 22)[43]
- A histologic diagnosis of choriocarcinoma (note: re-biopsy is *not* recommended)[43]
- Evidence of metastatic disease[44]
- A serum hCG level ≥20 000 mIU/mL more than 4 weeks post-evacuation[44]

NOTE: The referral criterion of "elevated hCG 6 months after evacuation" is no longer listed. It appears to be safe to follow hCG levels beyond 6 months as long as the hCG level is declining.[45]

Patients diagnosed with GTN should be managed primarily by a gynaecologic oncologist or a medical oncologist with an interest in gynaecologic oncology. Improved patient outcomes depend on prompt referral and transfer of care for staging, risk scoring, and treatment.

In the post-molar monitoring of serum hCG, special consideration must be given to the detection of persistently low levels of hCG, a finding that may represent true GTN, "quiescent

GTD," pituitary gland production of hCG, or a false-positive hCG (i.e., "phantom hCG"). A persistent low level of hCG is defined as an hCG level <1000 mIU/mL for 3 or more months with no clear upward or downward trend and no evidence of disease.[46] Measurement of the proportion of hyperglycosylated hCG (hCG-H) has been proposed to distinguish between the presence of malignancy and quiescent GTD because the invasive cytotrophoblast is primarily responsible for the production of hCG-H.[47] Measurement of the proportion of free beta-subunit has been proposed as a means to identify patients with placental site trophoblastic tumours.[48] The use of hCG-H and free beta-hCG requires validation in large prospective studies to define their role in the management of GTN.[49] Cases suggestive of malignancy must be referred to gynaecologic oncology for further workup and management. Patients with quiescent GTD have hCG titres around 55 mIU/mL and require no active management other than regular hCG monitoring. Pituitary production of hCG is a biological phenomenon observed in some perimenopausal and postmenopausal women and averages 10–11 mIU/mL and <35 mIU/mL, respectively.[50,51] It can be suppressed by the administration of an estrogen-containing oral contraceptive pill for 3 weeks or detected in the laboratory because it is sulfated. Phantom hCG is a false-positive assay result caused by circulating heterophile antibody. This phenomenon can be confirmed by urinalysis, which is notably negative for hCG (the heterophile antibody is too large to be present in the urine); by using a dilution test; or by performing a specialized hCG assay. In the absence of pregnancy or evidence of malignancy, women with persistently elevated serum *and* urine hCG (i.e., excluding a false-positive hCG) should undergo long-term follow-up under the supervision of an expert in the management of GTN. Despite negative initial investigation results, 1 in 5 of these women will develop GTN several months or years after initial presentation. In the absence of identified disease, treatment should be avoided.[52]

RECOMMENDATION 11

STAGING AND RISK SCORING OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

After a diagnosis of GTN, the patient's disease is staged and a risk score is assigned in order to plan treatment. Invasive molar disease and choriocarcinoma are generally highly sensitive to chemotherapy, whereas placental site trophoblastic tumours and epithelioid trophoblastic tumours are much less so. In both cases, treatment may require a combination of systemic therapy and surgery.

At a minimum, the patient should have a chest X-ray and pelvic ultrasound scan, ideally with Doppler (the Doppler pulsatility index can be an independent predictor of resistance to single-agent methotrexate in cases of otherwise low-risk disease).[53] Although up to 41% of patients with a normal chest X-ray may have evidence of micrometastases (<6 mm) on CT scan, further imaging in otherwise low-risk patients is not warranted because the presence of metastases <2 cm does not affect chemotherapy resistance or time to remission.[54] If lung metastases are identified on chest X-ray *or* GTN is identified after a non-molar pregnancy *or* if histologic diagnosis of choriocarcinoma, placental site trophoblastic tumour, or epithelioid trophoblastic tumour is made *or* the case involves a relapse of previously diagnosed GTN, imaging requires a CT scan of the chest, abdomen, and pelvis in addition to MRI of the brain. MRI of the pelvis can also be considered. An arterial-phase CT scan of the abdomen is required in order to accurately identify liver metastases.

Neurologic symptoms are present in 87% to 100% of patients with brain metastases. If brain imaging is equivocal, lumbar puncture can be diagnostic if the cerebrospinal fluid to serum hCG ratio is >1:60. In a series of 27 patients with central nervous system metastases, 3 patients (11.1%) presented with central nervous system metastases as the only site of disease. Therefore, for patients with non-molar choriocarcinoma, brain imaging is recommended regardless of alternate locations of disease or the absence of symptoms.[55] Table 1 displays the International Federation of Gynaecology and Obstetrics (FIGO) staging of GTN, which applies to all subsets of the disease, including invasive molar disease choriocarcinoma, placental site trophoblastic tumours, and epithelioid trophoblastic tumours.

Patients with invasive moles or choriocarcinoma are deemed to be low or high risk based on the modified World Health Organization (WHO) prognostic scoring system as adapted by FIGO; see Table 2.[56] Patients with low-risk disease (scoring 0 to 6) are offered single-agent chemotherapy or hysterectomy (in the absence of evidence of metastatic disease). Patients with high-risk disease (scoring ≥7) are offered multi-agent chemotherapy, preferentially under the supervision of an oncologist with a special

Table 1. FIGO staging: gestational trophoblastic neoplasia

Stage I	Disease confined to the uterus
Stage II	GTN extends outside the uterus, but is limited to the genital structures
Stage III	GTN extends to the lungs
Stage IV	All other metastatic sites

Reproduced with permission.[56] FIGO: International Federation of Gynecology and Obstetrics.

Table 2. Modified World Health Organization prognostic scoring system as adapted by FIGO: gestational trophoblastic neoplasia

	Scores			
Risk factor	0	1	2	4
Age, years	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval, months	<4	4 to 6	7 to 12	>12
Pre-treatment serum hCG, mIU/mL	<1000	1000–10 000	10 000–100 000	>100 000
Largest tumour size, cm	<3	3–5	>5	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	0	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	≥2 drugs

Reproduced with permission.[56] FIGO: International Federation of Gynecology and Obstetrics; GI: gastrointestinal; hCG: human chorionic gonadotropin.

interest and expertise in the management of this disease. Surgery is offered to a small number of patients who develop drug resistance or disease-related complications. Patients with a risk score ≥12 are considered ultrahigh risk with an increased risk of death, particularly early death.[57] Ultra high-risk patients, who typically present with liver and/or brain metastases, require specialized treatment, preferably at a reference centre with expertise in managing GTN where a multidisciplinary team (e.g., interventional radiology, thoracic and neurosurgery, intensive care) can be involved. Table 2 displays the modified WHO prognostic scoring system as adapted by FIGO. Of note, only lung lesions visible on chest X-ray are scored. The WHO prognostic scoring system does not apply to placental site trophoblastic tumours or epithelioid trophoblastic tumours, which are considered separately.

TREATMENT OF LOW-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA

The primary chemotherapeutics used in single-agent therapy for low-risk GTN are methotrexate and dactinomycin (Table 3). Globally there are several regimens in use, including 5-fluorouracil, used commonly in China with good efficacy and low toxicity. Debate is ongoing as to the most effective chemotherapy regimen, with considerations being primary cure rates, patient convenience and quality of life, side effect profiles, and cost. The Gynecologic Oncology Group conducted a randomized controlled trial of dactinomycin (1.25 mg/m^2, maximum dose 2 mg) administered every 2 weeks (i.e., biweekly) versus weekly methotrexate (30 mg/m^2) and concluded that biweekly dactinomycin demonstrated superiority with a complete response rate of 70% versus 53% for methotrexate ($P = 0.01$).[58] This is compared with complete response rates of 70.8% for weekly methotrexate (50 mg/m^2) and 69.5% for an 8-day methotrexate–folinic acid regimen in a nonrandomized cohort study.[59] A Gynecologic Oncology Group study (GOG 275) comparing biweekly dactinomycin with 5- or 8-day methotrexate found similar complete response rates and toxicity profiles between regimens (with similar rates of alopecia), but it was closed early because of issues with accrual.[60] Overall there are no major differences in the toxicity profiles of methotrexate and dactinomycin. The most frequent adverse effects are nausea, fatigue, and anemia. However, alopecia is more common

Table 3. Low-risk, single-agent regimens

Regimen	Dosage
Methotrexate	
8-day (Charing Cross; modified Bagshawe)	1 mg/kg IM q 48 hours × 4 Folinic acid 30 mg PO q 48 hours × 4 (30 hours after MTX) repeated every 14 days
5-day	0.4 mg/kg (max 25 mg) IV or IM daily × 5 days repeated every 14 days
Weekly	30–50 mg/m^2 IM weekly
High dose	600 mg/m^2
Dactinomycin	
Every 2 weeks	1.25 mg/m^2 IV (max 2 mg) repeated every 14 days
5-day	9–13 μg/kg (max 0.5 mg) IV × 5 days repeated every 14 days

IM: intramuscularly; IV: intravenously: PO: orally.

with dactinomycin, whereas stomatitis is more common with methotrexate.[61] Further study is required to determine if there is a preferred regimen for low-risk patients and whether other regimens, such as a combination of methotrexate and dactinomycin, may prove beneficial in select patients.

Patients with stage I disease who have completed childbearing can be offered hysterectomy, although systemic therapy may still be required if post-surgery monitoring demonstrates persistent disease. A recent retrospective study showed that 82% of women with low-risk, nonmetastatic GTN treated with hysterectomy did not require salvage chemotherapy.[62] Patients aged 35 years and younger with a modified WHO prognostic score of ≤4 can also be offered a second curettage. This approach may spare over 40% of patients the need for chemotherapy and has a low incidence of complications such as uterine perforation or acute hemorrhage. The impact from this approach on future fertility is unclear, and concerns have been raised about the risk of uterine synechiae with a second procedure.[63]

Patients undergoing treatment require weekly quantitative serum hCG monitoring to promptly identify the development of resistant disease. An hCG assay able to detect all forms of hCG should be used (e.g., beta-hCG, core hCG, C-terminal hCG, nicked-free beta, beta core), and it is recommended that the same assay (i.e., same laboratory) be used each time to avoid differences in results between laboratories. Resistant disease is diagnosed if there is a plateau of or a rise in hCG levels, as per FIGO criteria. In the event of drug resistance, restaging and risk scoring will prompt a switch to an alternate single-agent (revised risk score ≤6) or multi-agent treatment. Therapy is continued until serum hCG levels normalize, followed by 2 to 3 cycles (4 to 6 weeks) of consolidation.[65] Overall cure rates for patients with low-risk disease, either with primary or subsequent therapies, approaches 100%.

Patients at risk of resistant disease include those with increased tumour vascularity seen on Doppler ultrasound scan,[53] those with a modified WHO prognostic score of 5 or 6,[57] those with pre-treatment hCG levels in excess of 400 000 mIU/mL,[65] those with non-molar choriocarcinoma, and those with suboptimal response as identified through nomograms/hCG kinetic analyses.[66] The risk of methotrexate resistance in patients with a modified WHO prognostic score of 6 and a uterine artery pulsatility index of ≤1 was 100%, compared with 20% in patients with a uterine artery pulsatility index of >1 ($P < 0.0001$).[43] These findings are useful for prognostic and counseling purposes; however, further study is needed to determine which of these patients may benefit from first-line multi-agent chemotherapy.

RECOMMENDATIONS 12, 13

TREATMENT OF HIGH-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA

High-risk GTN is treated with combination chemotherapy. Two commonly used regimens with high cure rates and acceptable toxicity profiles are etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine (EMA-CO) and etoposide, methotrexate, dactinomycin, etoposide, cisplatin (EMA-EP). These and alternate regimens are listed in Table 4. Toxic effects of concern are myelosuppression, which may respond to granulocyte colony-stimulating factor; alopecia; mucositis; and the development of secondary malignancies. Weekly hCG monitoring should be continued until normalization of serum hCG. With high-risk disease, it is recommended to consolidate treatment with 3 cycles (6 weeks) of chemotherapy after normalization of hCG.

High-risk patients with liver and brain metastases or those with a modified WHO score as adapted by FIGO[56] of >12 are considered ultra high risk. These patients may die during treatment as a result of acute hemorrhage or complications from extensive disease. Low-dose induction chemotherapy with etoposide and cisplatin for 1 to 3 weeks, followed by EMA-EP or EMA-CO chemotherapy, has been shown to reduce early death in ultrahigh-risk patients (Table 4). Consolidation chemotherapy after normalization of serum hCG continues for 8 weeks. Although no randomized data exist to compare regimens in ultrahigh-risk patients, those with liver and brain metastases may benefit from EMA-EP as a first-line, multi-agent treatment after induction chemotherapy.[67]

Adjunctive treatments to systemic therapy may be required to address life-threatening complications and achieve remission. Endovascular embolization by interventional radiology may be required to control massive hemorrhage.[68] Stereotactic radiation for central nervous system metastases may be required to prevent hemorrhage or neurologic deterioration, or to treat resistant foci of disease. Similarly, tailored surgery may be required to prevent acute deterioration (e.g., craniotomy to address increased intracranial pressure) or to treat resistant foci of disease (e.g., thoracotomy with pulmonary wedge resection). The potential for cure in high-risk patients is 70% to 95%. Previously, those with ultrahigh-risk disease were at risk of early death, with a survival rate of only 25% to 50%. If treated with induction chemotherapy, these ultrahigh-risk patients now have a prognosis similar to those with high-risk disease.[69]

Table 4. High-risk, multi-agent regimens

Regimen	Drug, dosage, and route	Administration
EMA-CO	Etoposide 100 mg/m^2 IV infusion	Days 1 and 2
	Dactinomycin 0.5 mg IV bolus	Days 1 and 2
	Methotrexate 100 mg/m^2 IV bolus	Day 1
	Methotrexate 200 mg/m^2 IV infusion	Day 1
	Leucovorin 15 mg IM or PO q 12 hours × 4	Days 2 and 3
	Cyclophosphamide 600 mg/m^2 IV infusion	Day 8
	Vincristine 1 mg/m^2 IV bolus	Day 8
EMA-EP	Etoposide 100 mg/m^2 IV infusion	Days 1 and 2
	Dactinomycin 0.5 mg IV bolus	Days 1 and 2
	Methotrexate 100 mg/m^2 IV bolus	Day 1
	Methotrexate 200 mg/m^2 IV infusion	Day 1
	Leucovorin 15 mg IM or PO q 12 hours × 4	Days 2 and 3
	Cisplatin 60 mg/m^2 IV infusion	Day 8
	Etoposide 100 mg/m^2 IV infusion	Day 8
TP/TE	Paclitaxel 135 mg/m^2 IV infusion	Day 1
	Cisplatin 60 mg/m^2 IV infusion	Day 1
	Paclitaxel 135 mg/m^2 IV infusion	Day 15
	Etoposide 150 mg/m^2 IV infusion	Day 15
ICE	Ifosfamide 5000 mg/m^2 IV infusion	Day 2
	Carboplatin AUC 5 IV infusion	Day 2
	Etoposide 100 mg/m^2 IV infusion	Days 1–3
BEP	Bleomycin 30 units IV	Days 1, 8, 15
	Etoposide 100 mg/m^2 IV infusion	Days 1–5
	Cisplatin 20 mg/m^2 IV infusion	Days 1–5
Low-dose induction	Etoposide 100 mg/m^2 IV infusion	Days 1 and 2, repeat weekly for 1–3 weeks
	Cisplatin 20 mg/m^2 IV infusion	

AUC: area under the curve; IM: intramuscularly; IV: intravenous: PO: orally.

SUMMARY STATEMENTS 3, 4 and RECOMMENDATIONS 5, 6

RECOMMENDATIONS 14

TREATMENT OF PLACENTAL SITE TROPHOBLASTIC TUMOURS AND EPITHELIOID TROPHOBLASTIC TUMOURS

Placental site trophoblastic and epithelioid trophoblastic tumours are notable for their slower growth, late metastases, and greater resistance to chemotherapy. These tumours secrete lower levels of hCG because they are derived from intermediate trophoblast. The FIGO staging system is used to describe extent of disease. Staging investigations require CT scan of the chest, abdomen, and pelvis as well as Doppler ultrasound scan of the pelvis, MRI of the brain, and, if brain imaging is equivocal, lumbar puncture to measure cerebrospinal fluid to serum hCG ratio. Surgery should be offered to those with stage I disease, including simple hysterectomy with consideration given to ovarian preservation. The need for lymphadenectomy is unclear. The incidence of lymph node metastases was 5.9% in a series of 286 cases.[70] Eight weeks of adjuvant EMA-EP or paclitaxel-cisplatin/paclitaxel etoposide (TP/TE) chemotherapy should be offered to those with risk factors such as an antecedent pregnancy more than 48 months before diagnosis.[71] A combination of chemotherapy with EMA-EP or TP/TE and surgery should be offered to patients with stage II to IV disease, although the likelihood of response is low. Isolated residual disease identified in such patients is resected, and consolidation chemotherapy for 8 weeks after normalization of hCG would usually be recommended.

POST-TREATMENT FOLLOW-UP OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

At the completion of therapy, imaging is performed to serve as a baseline. Residual lesions may be present, particularly in the lung, but do not require resection or re-treatment if hCG levels remain undetectable.[72] The risk of relapse is approximately 3%, and relapse typically occurs during the first 12 months of follow-up.[73] The serum hCG is monitored weekly for the first 4 to 6 weeks and then monthly for a minimum of 12 to 24 months for low- and high-risk disease, respectively. Patients with placental site trophoblastic or epithelioid trophoblastic tumours may

require long-term follow-up. Pregnancy should be avoided with the use of reliable contraception, including hormonal methods and an intrauterine device, during the surveillance period. Insertion of an intrauterine device is acceptable only after normalization of hCG. A limited number of studies have been conducted on pregnancy outcomes after GTN treatment with chemotherapy.[74,75] Some report a higher risk of adverse outcomes in pregnancies conceived <6 months after completion of chemotherapy, such as miscarriage, recurrent mole, preterm labour, preeclampsia, and placental disease.[75] These risks appear to be lower for pregnancies conceived ≥1 year after the completion of chemotherapy.

Although exposure to EMA-CO chemotherapy may result in earlier menopause, fertility does not appear to be affected, and there is no increased risk of congenital malformation. There is an increased risk of developing a second cancer (e.g., leukemia, breast cancer, colon cancer, melanoma), highlighting the need for long-term follow-up and centralized registries.[76]

PREGNANCY DURING FOLLOW-UP FOR GESTATIONAL TROPHOBLASTIC DISEASE

On occasion, pregnancy will occur during the follow-up period after evacuation of a hydatidiform mole or treatment for GTN. Because serum hCG is the primary marker used in surveillance, pregnancy in the follow-up period poses a significant clinical challenge. Management in these cases must be individualized, and a balanced discussion of the risks and benefits of continuing the pregnancy must take place. Referral to gynaecologic oncology and maternal–fetal medicine is recommended. Depending on the individual patient's circumstances, preferences, and risk of disease recurrence, a management plan should be devised. Should the patient wish to continue the pregnancy, close follow-up with serum hCG monitoring and ultrasound scan are recommended to identify early evidence of GTN.

RECOMMENDATION 16

RECURRENT GESTATIONAL TROPHOBLASTIC NEOPLASIA

Recurrence of GTN requires restaging with CT scan of the head, chest, abdomen, and pelvis. Fluorodeoxyglucose positron emission tomography may be useful to localize foci of resistant/recurrent disease and target therapy.[77] The disease should be rescored using the modified WHO system as adapted by FIGO[56] and low- or high-risk treatment options selected. For high-risk disease, chemotherapy options include EMA-EP; TP/TE ifosfamide, carboplatin, and etoposide (ICE); and BEP, as listed in Table 4. For multi-drug-resistant disease, novel therapies can be prescribed, including targeted agents such as programmed death-ligand 1 inhibitors or human epidermal growth factor receptor 2/neu receptor antagonists.[78] A clinical trial of avelumab in chemotherapy-resistant GTN is ongoing. Surgical resection may be required for isolated foci of persistent tumour. The half-life of hCG is approximately 48 hours and could therefore be used to assess acute response to any surgical intervention. High-dose chemotherapy with autologous bone marrow or stem cell transplantation can also be considered. Patients with multi-drug-resistant disease are at risk for disease-related death, and therefore highly specialized, tailored care is imperative to achieve the best possible outcomes.

GESTATIONAL TROPHOBLASTIC DISEASE REGISTRY

The establishment of centralized (regional and/or national) registries, where possible, should be the next priority in the care of patients with GTD. Optimal disease management depends on the centralization of care at specialized centres, pathology review, consistent and evidence-based treatment decisions, and systematic follow-up.[79] Long-term data will not only contribute to improvements in our understanding and treatment of this rare disease entity but will also allow for consideration of survivorship issues.[80]

SUPPLEMENTARY MATERIAL

Supplementary material can be found in the online version of this article, available 10.1016/j.jogc.2020.03.001.

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APPENDIX

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

	Definition
Strength of Recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional (weak)[a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of Evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Do not interpret conditional (weak) recommendations to mean weak evidence or uncertainty of the recommendation.

Adapted from GRADE Handbook (2013), Table 5.1, available at gdt.gradepro.org/app/handbook/handbook.html.

Table A2. Implications of Strong and Conditional (Weak) Recommendations, by Guideline User

Perspective	Strong Recommendation "We recommend that. . ." "We recommend to not. . ."	Conditional (Weak) Recommendation "We suggest. . ." "We suggest to not. . ."
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policy makers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1, available at gdt.gradepro.org/app/handbook/handbook.html.