Practical Guidelines for the Treatment of Gestational Trophoblastic Disease: Collaboration of the European Organisation for the Treatment of Trophoblastic Disease (EOTTD)–European Society of Gynaecologic Oncology (ESGO)–Gynecologic Cancer InterGroup (GCIG)–International Society for the Study of Trophoblastic Diseases (ISSTD)

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DOI https://doi.org/10.1200/JCO-24-02326

ABSTRACT

Gestational trophoblastic diseases (GTDs) are a group of pregnancy-related premalignant and malignant diseases with generally a favorable prognosis when treated adequately. Many different treatment protocols exist worldwide. To our knowledge, this is the first set of global consensus-based guidelines for GTD. Four international organizations (European Organisation for the Treatment of Trophoblastic Diseases, European Society of Gynecologic Oncology, Gynecologic Cancer Intergroup, and International Society for the Study of Trophoblastic Diseases) delegated 53 expert GTD clinicians from 31 countries who formulated nine consensus-based definitions and the minimum criteria required to be a GTD center. Furthermore, 18 flow diagrams were developed to diagnose, treat, and follow up all forms of primary or recurrent GTD. The definitions and flow diagrams were drafted and adapted in consecutive (online) meetings until consensus was reached followed by an external review process. Here, the final guidelines are presented together with the available supporting evidence from the literature.

ACCOMPANYING CONTENT

Appendix

Accepted March 14, 2025
Published May 13, 2025

J Clin Oncol 43:2119-2128

INTRODUCTION

Gestational trophoblastic diseases (GTDs) are a group of rare premalignant and malignant diseases characterized by their origin in trophoblastic cells. Premalignant forms are complete (CHM), partial hydatidiform moles (PHM), and atypical placental site nodules (APSNs). Malignant forms are called gestational trophoblastic neoplasia (GTN) and include invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Although GTD is considered a rare disorder, based on the current world population, we estimate that annually 220,000 women are diagnosed globally including 22,000 with GTN.

GTN is highly curable when treated adequately. However, patients benefit from dedicated teams, multidisciplinary team (MDT) meetings, and, in complex cases, cross-border discussions.[1,2] Referral to experts is not possible everywhere considering geographic hurdles and socioeconomic disparities between and within countries. Currently, 50% of all people live in low- or middle-income countries (LMICs).[3,4] Therefore, GTD is often managed in low-resource settings where options for diagnostics and treatment are limited.

Many guidelines are formulated for and by medical specialists from high-income countries, but these do not necessarily serve LMICs well with their distinct health care settings. In addition, guidelines should preferably be based on high levels of evidence. However, in GTD, large-scale prospective randomized studies are lacking because of its rare occurrence. The absence of such data has led to differences in GTD treatment worldwide. Previously developed European guidelines were consulted many times but did not take the worldwide disparities into account nor covered all aspects of GTD care yet.[5] Here, we present the globally agreed guidelines covering nearly all aspects of GTD care applicable everywhere.

METHODOLOGY, SEARCH STRATEGY, AND SELECTION CRITERIA

Guidelines were developed using a five-step process as defined by the European Society of Gynaecological Oncology (ESGO) Guideline Committee Standard Operative Procedures manual (Appendix Fig A1, online only). Strengths of the process include a multidisciplinary international development approach and a robust external review process.

Nomination of the Multidisciplinary International Development Group

Four scientific organizations—ESGO, Gynecologic Cancer Intergroup (GCIG), International Society for the Study of Trophoblastic Diseases (ISSTD), and European Organisation for the Treatment of Trophoblastic Diseases (EOTTD)—nominated 53 experts (Appendix 1) involved in the management of GTD including medical and gynecologic oncologists, obstetricians, pathologists, geneticists, radiologists, and clinical chemists from 31 countries representing all continents.

Identification of Scientific Evidence

Literature was systematically reviewed and critically appraised. Relevant studies published between January 2019 and December 2022 were selected to complete the search of the previous European guideline,[5] which was carried out using the MEDLINE database. Bibliography was supplemented by additional older relevant references identified by members of the Expert Panel. The search strategy excluded publications in other languages than English, editorials, letters, and preclinical in vitro and in vivo studies. The reference list of each identified article was reviewed for other potentially relevant articles.

Formulation of Guidelines

The Expert Panel members drafted guidelines for assigned topics. The guidelines were discussed and retained if they were supported by sufficiently high-level scientific evidence and/or when consensus was reached among experts at a predefined level of at least two third of votes.

In five sessions between October 2022 and November 2023, 18 flow diagrams, nine definitions, and agreement for the minimum requirements for a GTD center were developed. Every flow diagram was discussed and adjusted until consensus was reached.

To generate guidelines applicable worldwide, flow diagrams were divided into minimal requirements and additional practice points including best practices. Minimal requirements should be possible everywhere in the world. Practice points and best practices should be considered but are acknowledged as not generally applicable depending on geographic location and socioeconomic situation.

FIGO 2000 scoring and staging classifications were used to determine the score and stage of GTN (Appendix Tables A1 and A2, online only).[6]

External Evaluation of the Guidelines—International Review

A multidisciplinary geographically diverse external review panel was established. The flow diagrams and definitions were sent to 63 experts, and 24 forms were returned (Appendix Table A6). Responses were discussed, and subsequent adjustments of the guidelines were consensus-based as previously defined.

FINALIZED GTD DEFINITIONS AND GUIDELINES

Definitions for GTD and Minimum GTD Center Requirements

Definitions are essential for research and clinical practice to enable selection of patients for the right treatment and comparison of data between different centers. Appendix Table A3 shows nine new or reconfirmed consensus-based definitions. Furthermore, the minimum requirements for a GTD center were defined (Appendix Table A4). We recognize that it is not possible everywhere in the world to establish a GTD center yet. In the flow diagrams, recommendations are made when to contact a GTD center. If a GTD center is not available, this advice can also be read as to contact a (inter)national GTD expert or to discuss the patients in a MDT of GTD experts.

Diagnostic and Management Pathways

Suspected Hydatidiform Mole and Transformation to GTN

Hydatidiform mole (HM) can be suspected when severe hyperemesis or symptoms of hyperthyroidism occur (Fig 1). However, most patients present with vaginal bleeding or are asymptomatic and undergo first trimester ultrasound (US).[7] While imaging may point to a diagnosis of HM pregnancy, histologic examination of products of conception is required. High serum human chorionic gonadotropin (hCG) levels may increase suspicion for the diagnosis. Thyroid function tests should be measured to exclude hyperthyroidism. The role of Doppler US is still unclear but is being investigated in the TITANIUM study.[8] With suspected HM, US-guided suction

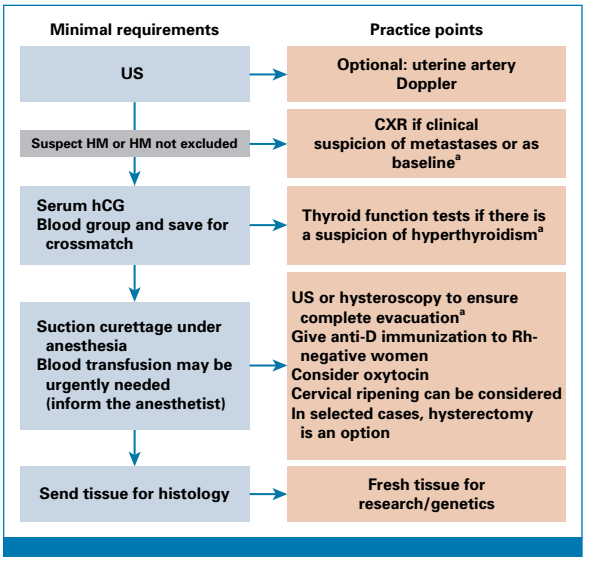

FIG 1. Diagnostic and management pathway for (first) HM. [a]Best practice. CXR, chest X-ray; hCG, human chorionic gonadotropin; HM, hydatidiform mole; US, ultrasound.

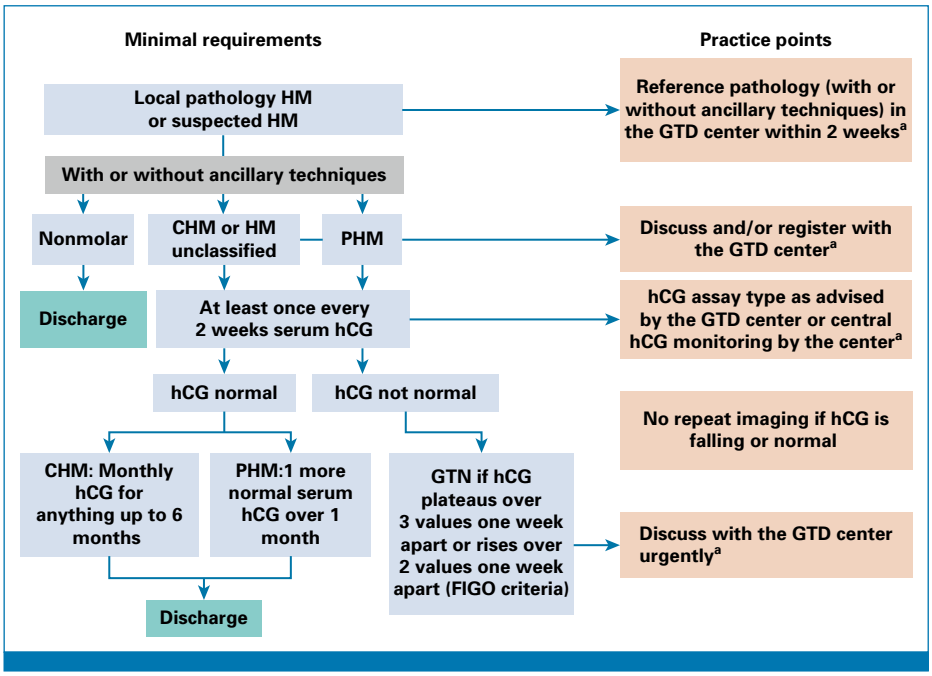

FIG 2. Diagnostic pathway for (suspected) HM to GTN. [a]Best practice. CHM, complete hydatidiform mole; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; HM, hydatidiform mole; PHM, partial hydatidiform moles.

curettage should be performed to ensure complete emptying of the cavity and avoid perforation. As these procedures potentially lead to significant blood loss, blood should be available preoperatively. Where possible, rhesus-negative women should receive anti-D immunization. There was no consensus on using cervical ripening before the procedure, and there is no literature to recommend either in favor or against this. Sometimes, hysteroscopic resection of residual tissue is an option. In older women without a wish to preserve their fertility, a hysterectomy can be considered.[9,10] In optimal settings, tissue can be biobanked and used for research or genetic testing (Fig 1).

Histologic examination is the basis for the diagnosis of either PHM or CHM. Differentiation between hydropic miscarriage, CHM and PHM can be difficult, and review by an experienced pathologist or ancillary techniques can be helpful.[11] These may include genetic analysis to confirm the type of molar pregnancy. After diagnosis of an HM, serum hCG should be monitored at least once every 2 weeks until normalization preferably using an hCG assay advised by the GTD center or centrally performed in a reference laboratory. PHM requires one more confirmatory normal hCG value before the patient can be discharged from monitoring. Serum hCG is mostly checked monthly up to 6 months after CHM although the risk of recurrence is very small.[9] Plateauing or rising of hCG levels suggests development of GTN (Fig 2).

Unexplained Persistent Low-Level Elevated hCG

Low unexplained hCG can be a diagnostic dilemma requiring a structured workup (Fig 3). Careful history taking is necessary to summarize medical and obstetric history and exclude exogenous hCG use. If there are no signs of pregnancy or retained products of normal conception on US, a negative urine hCG is suggestive of a false-positive serum result because of assay-interfering molecules such as human antimouse antibodies. Reference laboratories can advise on the use of another hCG assay, dilution testing, or perform a test with addition of blocking agents.[12] A true-positive hCG blood test requires measurement of additional tumor markers for germ cell tumors, hormones to identify menopause/pituitary hCG, and kidney function to exclude renal failure. Familial elevated hCG is a rare inheritable syndrome where mutated nonfunctional forms of hCG are produced. The diagnosis necessitates hCG measurements in parents.[13,14]

Combined oral contraceptives will normalize hCG in the case of menopausal-induced pituitary hCG production. However, vascular thromboembolism in menopausal women with other risk factors can make gonadotropin-releasing hormone a better option. Functional hCG levels >50 IU/L will normally suppress ovulation, whereas nonfunctional hCG does not exert this effect. Serial weekly pelvic US and hormone profiling will reveal whether ovulation occurs. After exclusion of assay-interfering molecules, pituitary hCG, and elevated hCG in renal failure, extensive imaging is required to localize potential hCG-producing gestational or nongestational tumors. Sometimes, a fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) can help.

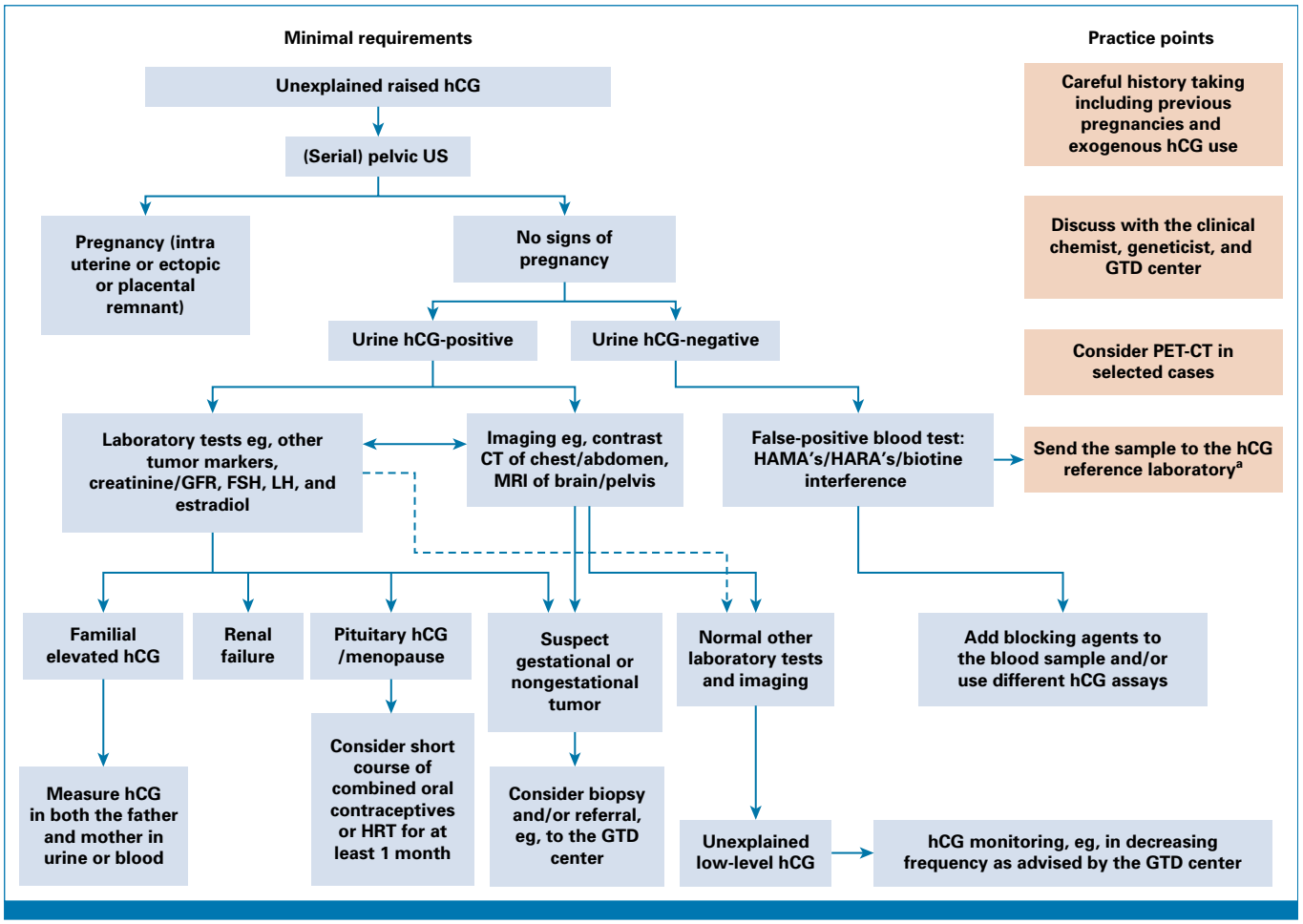

FIG 3. Diagnostic pathway unexplained persistent low-level elevated hCG. [a]Best practice. CT, computed tomography; FSH, follicle-stimulating hormone; GFR, glomerular filtration rate; GTD, gestational trophoblastic disease; hCG, human chorionic gonadotropin; HRT, hormone-replacement therapy; LH, luteinizing hormone; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound.

Twin Pregnancies Comprising a CHM With a Normal Cotwin

Twin pregnancy comprising suspected CHM with a cotwin is estimated to occur in 1:20,000-100,000 pregnancies (Appendix Fig A2).[15] If expert US reveals an abnormal cotwin fetus, termination of pregnancy is often chosen, but if the fetus appears to be normal, this will cause a dilemma. Early termination does not decrease the risk of subsequent GTN, and although maternal complications such as pre-eclampsia occur more often, these can be managed as usual with a 40%-60% chance of a healthy baby. Whatever the patient's choice, tissue should be obtained after the end of the pregnancy for histology to confirm the diagnosis and allow genetic analysis. Early pregnancy termination should be performed by suction curettage. In late pregnancy, termination is more complex and depends on gestational age, size of uterus, and maternal risks. Ongoing pregnancies should be managed in high-risk obstetric units with regular clinical follow-up and monitoring to detect early onset of pre-eclampsia. Serial hCG and US help to assess the degree of molar overgrowth and fetal compromise. PHM with coexisting fetus is extremely rare and requires counseling on maternal and fetal risks to determine how to proceed.

Low-Risk GTN Staging/Scoring Investigations and Treatment

After diagnosis of GTN, the extent of disease should be determined using a chest X-ray (CXR) and pelvic US (Fig 4).[16,17] The number of metastases is calculated based on visible metastases on the CXR. Small lung metastases <1 cm can be missed with CXR, but this does not appear to influence the outcome of treatment.[18] If lung metastases are found on CXR, CT thorax is required. If lung metastases are ≥1 cm, magnetic resonance imaging (MRI) brain plus CT or MRI of abdomen is required to assess further potential metastatic disease sites. The presence of lung metastases increases the risk of brain involvement. MRI of pelvis can be helpful to assess pelvic disease. PET-CT should not be routinely performed. In case of very high hCG concentrations (eg, >400,000 IU/L), even in the absence of metastases on CXR, the risk of metastases elsewhere is increased and additional imaging could be considered.[19] Imaging and

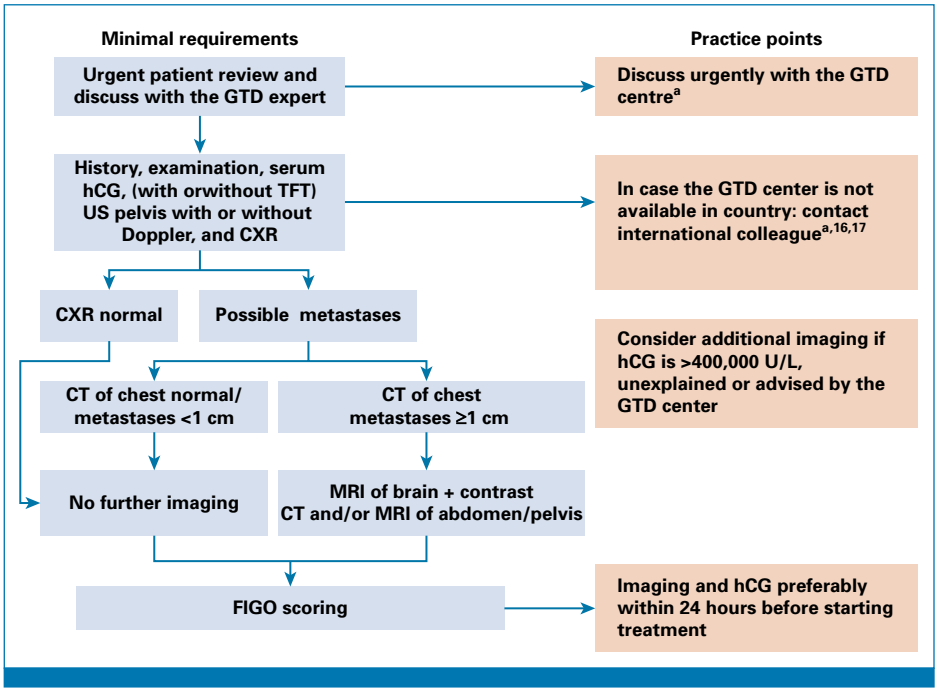

FIG 4. Postmole GTN staging. [a]Best practice. CT, computed tomography; CXR, chest X-ray; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; TFT, thyroid function test; US, ultrasound.

measurement of hCG levels to calculate FIGO score should be performed just before the start of treatment.

First choice of treatment depends on the FIGO score.[20] Low-risk GTN with a score of ≤6 is treated with monotherapy. High-risk and ultrahigh-risk GTN requires treatment with multiagent chemotherapy in a referral center (Appendix Fig A3).

After the diagnosis of low-risk GTN, single-agent chemotherapy can consist of either methotrexate (MTX) with folinic acid (FA) rescue (MTX/FA) or actinomycin-D (Act-D; Fig 5, Appendix Table A5). Outcomes of both treatments are excellent[21] with the once every 2 weeks intravenous Act-D having a higher primary complete response (70%-94%) than an intramuscular (IM) MTX regimen[22,23] in two studies. However, the IM MTX regimen used is considered to be underdosed. Indeed, in the only randomized phase III trial available using adequate MTX dosing, the complete response rates of MTX/FA and Act-D were not significantly different (88% and 79%, respectively) and showed a 100% overall survival.[24] A secondary curettage can be considered as prospective research showed a cure rate of GTN of 40% independent of endometrial thickness.[25] Multiple curettages should be avoided to prevent endometrial scaring. Profuse bleeding may stop after performing a second curettage. Hysterectomy is an alternative treatment in women with completed families and disease confined to the uterus.[26]

If resistance or toxicity develops to the first single agent, then the other single-agent or multiagent chemotherapy should be started based on the hCG level[27] after reimaging. Act-D is able to induce remission in 74% of the patients with MTX resistance[28] and even 93% in patients with an hCG level of ≤1,000 IU/L.[24] The chances of success with the second agent falls with higher hCG levels.[24] Carboplatin as an alternative single-agent therapy was not very efficacious and is therefore not recommended.[29,30] Non-randomized phase II data suggest that avelumab will induce remission in 53% of patients failing one single-agent therapy and may be an option in some centers.[31] In patients with a FIGO score of 5-6, the chance of sustained remission with one or two sequential single agents is 60%. However, in three situations, combination-agent chemotherapy should be considered from the outset: (1) histology of metastatic choriocarcinoma, (2) no metastatic disease or choriocarcinoma but with a pretreatment hCG concentration of >410,000 IU/L, and (3) metastases or choriocarcinoma and a pretreatment hCG concentration of >150,000 IU/L.[32] After normalization of the hCG, at least two courses of MTX or Act-D should be given. Some centers advocate three courses as a study comparing two versus three courses showed a lower recurrence rate (4% *v* 8%) after three courses.[33] However, groups were not entirely comparable and other reports suggest that two consolidation courses are sufficient.[33,34]

High- and Ultrahigh-Risk Staging Investigations and Treatment

Incidence of high- and ultrahigh-risk GTN is low, management is complex, and treatment should be given in a GTD

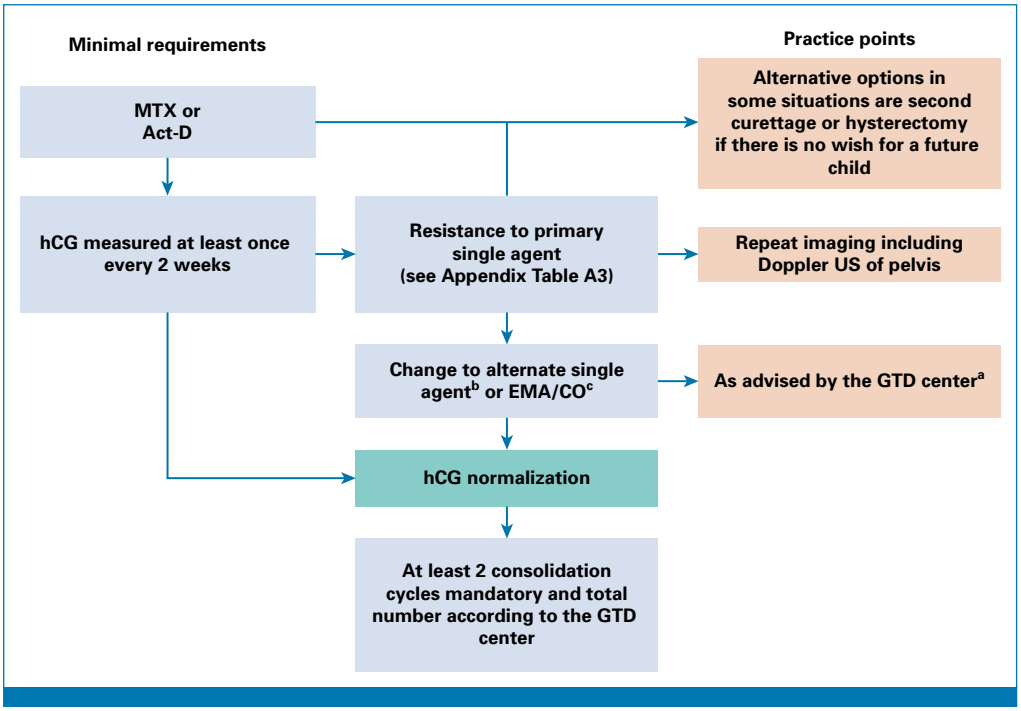

FIG 5. Treatment of low-risk GTN to remission. [a]Best practice. [b]If hCG plateaus/rises using serial local hCG test results and ≤1,000 IU/L, consider switch to other single agent, but if >1,000 IU/L, consider EMA/CO. For completely resected (low-risk) choriocarcinoma with hCG falling by half every 2 days to normal, no additional treatment is required. [c]Or other standard multichemotherapy schedule as advised by the GTD center. Avelumab can be an option in some countries to prevent multiagent chemotherapy. Act-D, actinomycin-D; EMA/CO, etoposide, MTX, Act-D, cyclophosphamide, and vincristine; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; US, ultrasound, MTX, methotrexate.

center (Fig 6 and Appendix Fig A4). More extensive investigation including MRI of head and pelvis and CT of chest and abdomen is necessary. Metastases are often highly vascular, and biopsies can cause life-threatening bleeding and should only be obtained when it is safe. High-risk GTN requires treatment with multiagent chemotherapy. Etoposide, MTX, and Act-D (EMA) alternating with cyclophosphamide and vincristine (CO [EMA/CO]; Appendix Table A5) are often used, but other schedules are possible. On starting chemotherapy, severe bleeding and metabolic disturbance may arise and can be mitigated by using low-dose etoposide and cisplatin (EP) chemotherapy before starting EMA/CO.[35] If bleeding occurs, embolization of the affected vessels is often helpful. Adapted chemotherapy is required for brain metastases, and neurosurgical intervention may be needed.[36]

There is no consensus because of lack of evidence on the exact number of consolidation courses, but the minimum recommended is two cycles. Survival rates are >96%.[37]

In ultrahigh-risk GTN (FIGO score ≥13), 1-3 cycles of low-dose EP are frequently used for the reasons discussed above (Appendix Fig A4). After this, it is usually safe to commence schedules such as EMA/CO or EMA/EP. In China, floxuridine, Act-D, etoposide, and vincristine (FAEV) are often used as an alternative effective regimen.[38] In the presence of CNS metastases, the dosage of MTX should be increased.[36] Some centers add intrathecal MTX (IT-MTX) although there is no consensus on the value of IT-MTX. Neurosurgery may be indispensable to control raised intracranial pressure, remove bleeding metastases, or insert an Ommaya reservoir to facilitate the delivery of IT-MTX. Stereotactic radiation therapy can be considered for vital brain lesions at the end of treatment, which are not safe to remove surgically. In the case of nonmolar choriocarcinoma, an increased risk of CNS metastases (20%) has been reported, and therefore, routine imaging of the CNS should be performed.[36] After normalization of hCG, 3-4 courses of consolidation should be administered. Survival up to 80%-85% has been reported.[37,39]

Diagnosis and Management of APSN, PSTT, and ETT

APSN was first described in 2015 (Appendix Fig A5).[40] Since then, more cases have been identified and the WHO introduced it in their classification, but diagnostic criteria remain unclear and not well defined.[41] Molecular profiling suggests that APSN should be considered a transitional stage between PSN and ETT.[42]

Because of its association with PSTT or ETT in 14%, pelvic US and MRI are necessary (Appendix Fig A5). Hysteroscopy may show the extent or multifocality of the lesion and allows tissue

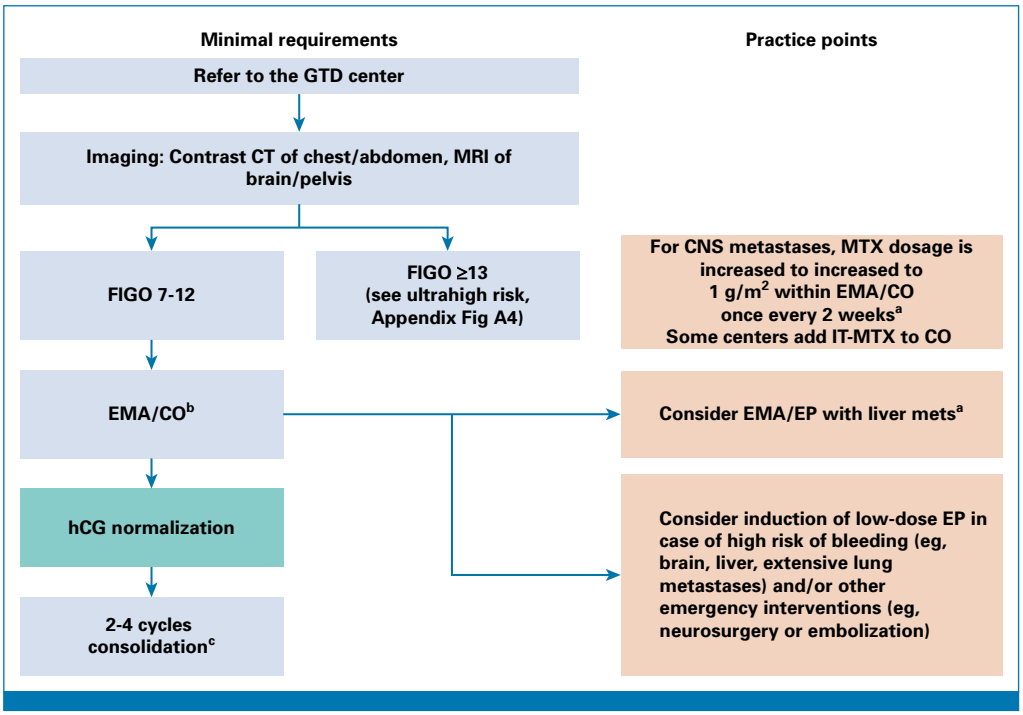

FIG 6. High-risk GTN treatment to remission. [a]Best practice. [b]Most often used, but other multichemotherapy schedules are possible, reassuring on fertility; in selected cases, referral to the fertility specialist might be appropriate. [c]Evidence uncertain. CO, cyclophosphamide and vincristine; CT, computed tomography; EMA, etoposide, MTX, and actinomycin-D; EP, etoposide and cisplatin; FIGO, International Federation of Gynecology and Obstetrics; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; IT-MTX, intrathecal MTX; MRI, magnetic resonance imaging; MTX, methotrexate.

collection for diagnosis and ancillary techniques. In patients wishing to retain fertility, follow-up with hysteroscopy, hCG measurements, and imaging is advised. There is no evidence available that guides optimal length of follow-up or frequency of imaging. For those patients with completed families, hysterectomy is advised as the APSN can be asymptomatically present in the myometrium and can develop into ETT. If subsequent histologic examination shows no ETT/PSTT and either just APSN or no residual APSN, the patient can be discharged. However, if ETT/PSTT is present, then those guidelines should be followed (Appendix Figs A6 and A7).

PSTT/ETT should be suspected in women with normal or only slightly elevated hCG levels in comparison with the volume of visible disease on imaging (Appendix Fig A6). Tissue should be obtained from the tumor and sent for specialist review. In difficult cases, histology review by a second expert should be considered. National or international MDT meetings can help to reach an accurate diagnosis.[43] If PSTT or ETT is confirmed, imaging of the brain, chest, and abdomen should be performed. The FIGO scoring system (Appendix Table A1) is *not* applicable for PSTT/ETT. Instead, treatment is determined by the FIGO 2000 stage (Appendix Table A2) and by the interval from the end of the last known or causative pregnancy to diagnosis (Appendix Fig A7). Stage IV disease or an interval longer than 48 months are two independent adverse prognostic factors for survival.[44–46] In patients with stage I disease with an interval of <48 months, hysterectomy with salpingectomy is indicated. In all other cases, surgery followed by 12-16 weeks platinum-based chemotherapy is advised. Pembrolizumab or high-dose chemotherapy can be considered.[47] PSTT and ETT can be indolent diseases, and the antecedent pregnancy is not necessarily the origin of the PSTT or ETT. Genetics can be used to determine the origin of the disease to define the interval with the causative pregnancy.[48] Fertility-sparing surgery should be considered experimental as limited reports show that because of poor visualization of intrauterine disease, surgical margins are often not free after fertility-sparing surgery, still requiring salvage hysterectomy.[49] Registration in the international database for PSTT and ETT is strongly advised.

Follow-Up After Chemotherapy

In low-risk GTN, after confirmation of a normal hCG, at least 1 year of monthly hCG measurements is advised (Appendix Fig A8). Remaining lesion(s) on imaging should not be treated if hCG is normal. Risk of recurrence depends on histology (higher after choriocarcinoma) and the presence of lung metastases at presentation.[50] Most recurrences occur in the first year.[51]

Fertility is not harmed after treatment for low-risk GTN.[49] Fertility after EMA/CO is generally unchanged,[52] but increased age at the time of starting treatment is an important factor. Early pregnancy can make diagnosis of recurrence difficult. The initially exponentially rising hCG levels seen with healthy pregnancies should help differentiate this from recurrence. US around 6-7 weeks can exclude a new molar pregnancy. The risk of a second molar pregnancy is around 1% for CHM and for PHM much lower.[53] There was no consensus on the use of placental review after the subsequent pregnancy. Six weeks after the end of pregnancy, hCG should have normalized based on small series and a repeat hCG is recommended at this time to ensure no reactivation of GTN.[54]

After completion of high- and ultrahigh-risk GTN treatment, early post-treatment imaging should be obtained (Appendix Fig A9). Residual lesions do not appear to be predictive of recurrence and do not require removal if the serum hCG is normal. However, in the event of serially rising hCG indicating relapse, new imaging can then be compared with the post-treatment imaging. This comparison may reveal one growing lesion which can be surgically removed to effect a cure.[55] Protocols for hCG follow-up varied in frequency and duration between GTD centers. However, consensus was reached to monitor the hCG at least monthly for a year or more after 4-8 weeks of normal hCG values after completion of treatment. During follow-up, pregnancy is discouraged although early pregnancy is not associated with a higher risk of recurrence or unfavorable pregnancy outcome.[56] In a study among 255 women conceiving within 12 months after GTN treatment, 73.3% of live births were reported, with no increased risk of miscarriage or recurrence.[57] However, a higher risk of miscarriage in the first 6 months after treatment has been reported in another study[58] and in a meta-analysis. This meta-analysis including 23 studies showed an incidence of miscarriage of 15.5% after chemotherapy and a significantly higher occurrence in pregnancies <6 months after the end of chemotherapy.[59] Since most recurrences will occur in the first year of monitoring,[51] it seems sensible to avoid conception during this time. Any form of contraception can be used. Discussion regarding recovery from a temporary chemotherapy-induced menopause is helpful to deal with fertility and timing of subsequent pregnancies. Assisted reproductive technology (ART) should not be withheld although reproductive outcomes in secondary infertile couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment were shown to be less favorable with a reduced live birth rate (34.1% *v* 66.7%).[60] Women can sometimes receive support from other women dealing with GTN.[61]

The optimal follow-up after PSTT/ETT treatment is currently unclear. Monitoring of serum hCG or other biomarkers such as human placental lactogen, especially if elevated before treatment, can be helpful. Imaging is advised in all patients except stage one patients diagnosed within <48 months of the causative pregnancy. No data on the value of imaging after PSTT or ETT exist, but a suggested schedule is provided in Appendix Figure A10.

Diagnosis and Management of Recurrent GTN

A new pregnancy should always be excluded first when recurrence is suspected based on a rising hCG level (Appendix Fig A11). Imaging is necessary to define disease extent and differentiate resectable from nonresectable disease. A FDG-PET-CT can sometimes be helpful to exclude multiple metastases.[62] Normalization of hCG after surgical resection may avoid the need for chemotherapy. If the recurrence is not visible on imaging or considered nonresectable, multiagent chemotherapy is the only proven effective option in relapsed low-risk GTN.[35,63] The role of second single-agent treatment to salvage a patient who has relapsed after successful remission to another single-agent treatment is unclear.[64] In relapsed high-risk GTN, surgery is often less beneficial because the disease is more widespread, but still important to consider.[9,65]

Patients should be extensively discussed for individualized surgical plans such as pulmonary resection, craniotomy, or resection of liver metastases.

If the surgical procedure does not lead to hCG normalization or there is nonresectable disease, then patients who have relapsed after EMA/CO should be offered platinum-based chemotherapy (Appendix Fig A12). After failure to this treatment or FAEV, anti–PD-1 immunotherapy is indicated (Appendix Fig 13).[66] Immunotherapy is quickly becoming more important. The number of patients treated with such agents is growing, and response rates seems to be around 70%. This is why these treatments have been investigated earlier in the disease, for example, in the TROPHAMET phase I to II trial, showing a promising alternative for multiagent chemotherapy. After failure of previous immunotherapy, either a rechallenge or combination with chemotherapy can be tried. In selected patients with a response to platinum/etoposide schedules, high-dose chemotherapy can still be beneficial.[47] If the hCG is increasing despite rechallenge with platinum and etoposide, the only treatment options currently remaining are clinical trials or palliation. In cases with mixed response, salvage surgery or radiotherapy can be considered. Cured patients should be offered surveillance for at least 2 years.

In conclusion, our international multidisciplinary panel has produced a set of globally agreed definitions and guidelines for the diagnosis, management, and follow-up of patients with GTD. The widespread adoption of these standards across the world should improve the outcome of women with GTD and reduce unwanted practice variation and unnecessary deaths. The flow diagrams and definitions may also help to educate and train health professionals around the world and help new centers to be established. Finally, this work will help to ensure that data reported between centers are more comparable to facilitate future research.

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C.L. and N.v.T. shared first authorship. R.B. and M.S. shared last authorship.

SUPPORT

Supported by the European Society of Gynaecological Oncology, which provided an epidemiologist and a project manager who were involved in the development of the guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-02326.

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ACKNOWLEDGMENT

A complete list of the EOTTD-ESGO-GCIG-ISSTD Guideline Committee members can be found in Appendix 1. The list of reviewers is presented in Appendix Table A6.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Practical Guidelines for the Treatment of Gestational Trophoblastic Disease: Collaboration of the European Organisation for the Treatment of Trophoblastic Disease (EOTTD)–European Society of Gynaecologic Oncology (ESGO)–Gynecologic Cancer InterGroup (GCIG)–International Society for the Study of Trophoblastic Diseases (ISSTD)

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Research Funding: AstraZeneca (Inst), GlaxoSmithKline (Inst), Clovis Oncology (Inst), MSD (Inst), Tesaro (Inst), Roche Molecular Diagnostics (Inst), AbbVie (Inst), Iqvia (Inst), Daiichi Sankyo Europe GmbH (Inst), Eisai Europe (Inst)
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No other potential conflicts of interest were reported.

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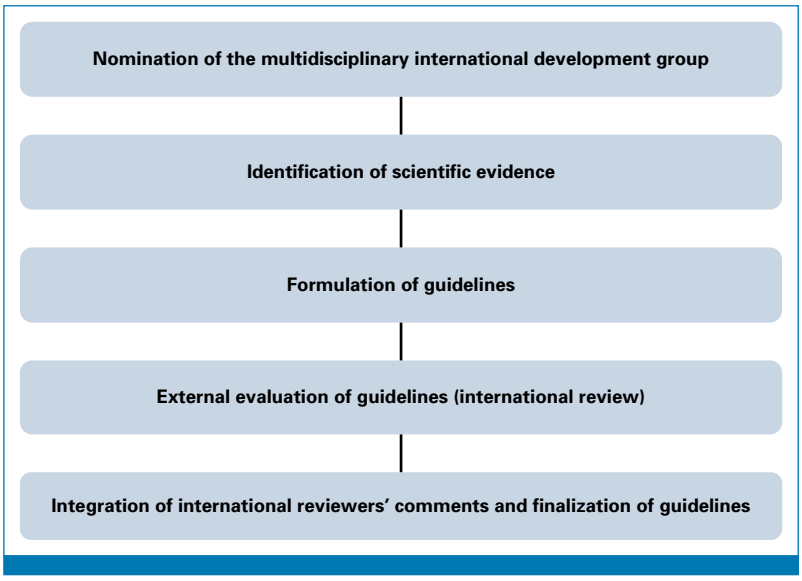

FIG A1. Development process.

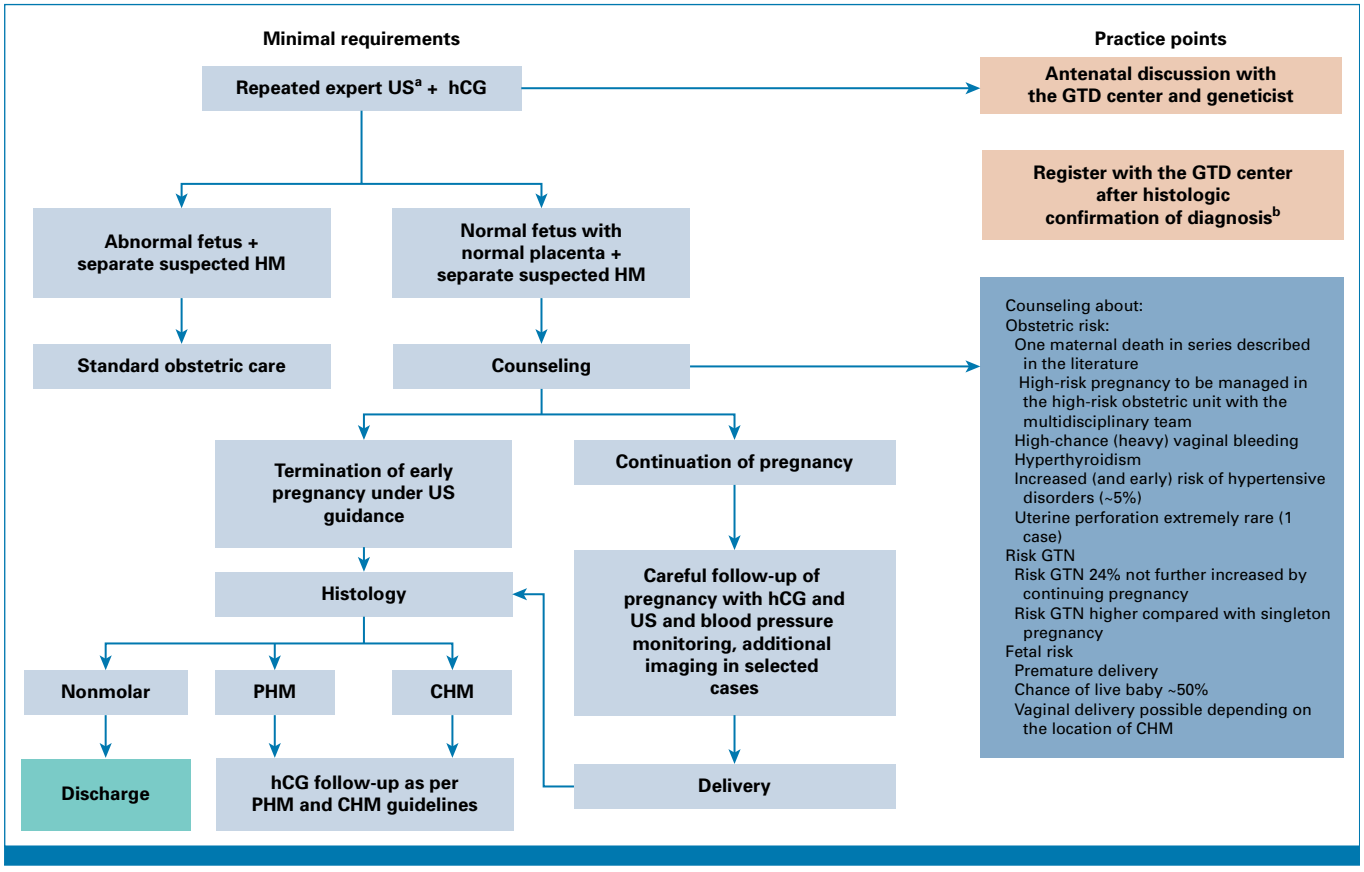

FIG A2. Suspected complete hydatidiform mole with viable fetus. [a]US can be highly suggestive but is not diagnostic of CHM. [b]Best practice. CHM, complete hydatidiform mole; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; HM, hydatidiform mole; PHM, partial hydatidiform moles; US, ultrasound.

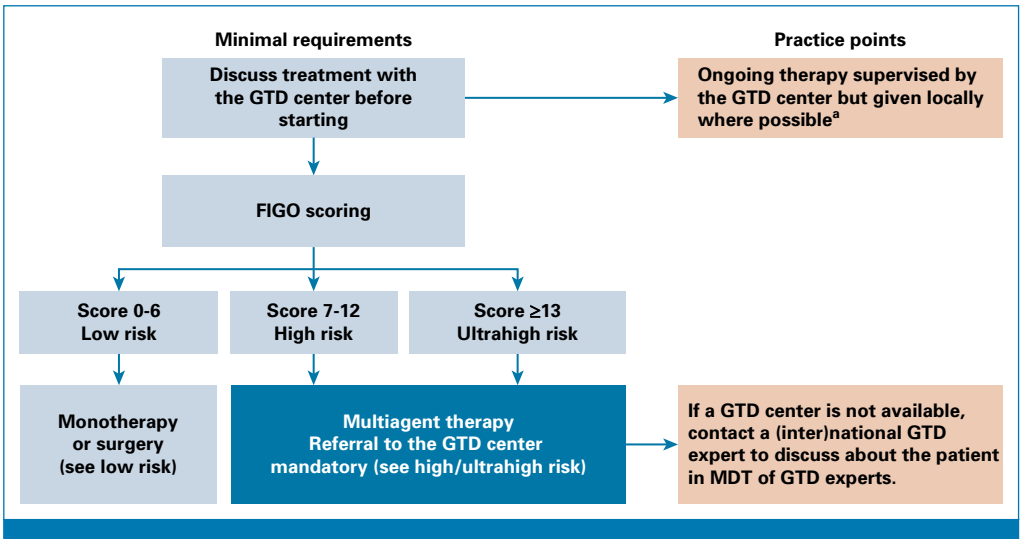

FIG A3. Postmole GTN treatment. [a]Best practice. FIGO, International Federation of Gynecology and Obstetrics; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; MDT, multidisciplinary team.

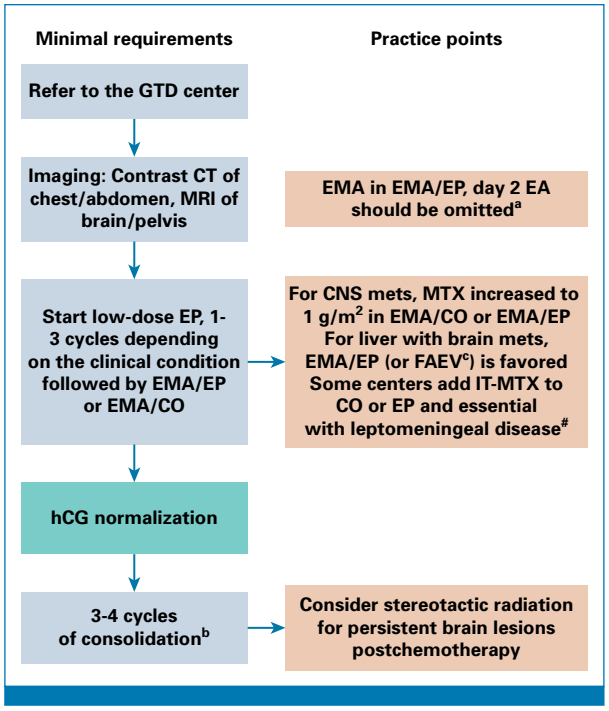

FIG A4. Ultrahigh-risk GTN treatment to remission. [a]Best practice. [b]Evidence uncertain. [c]Favored in some regions. CO, cyclophosphamide and vincristine; EA, etoposide and actinomycin-D; EMA, etoposide, methotrexate, actinomycin-D; EP, etoposide and cisplatin; FAEV, floxuridine, actinomycin-D, etoposide, and vincristine; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; MTX, methotrexate.

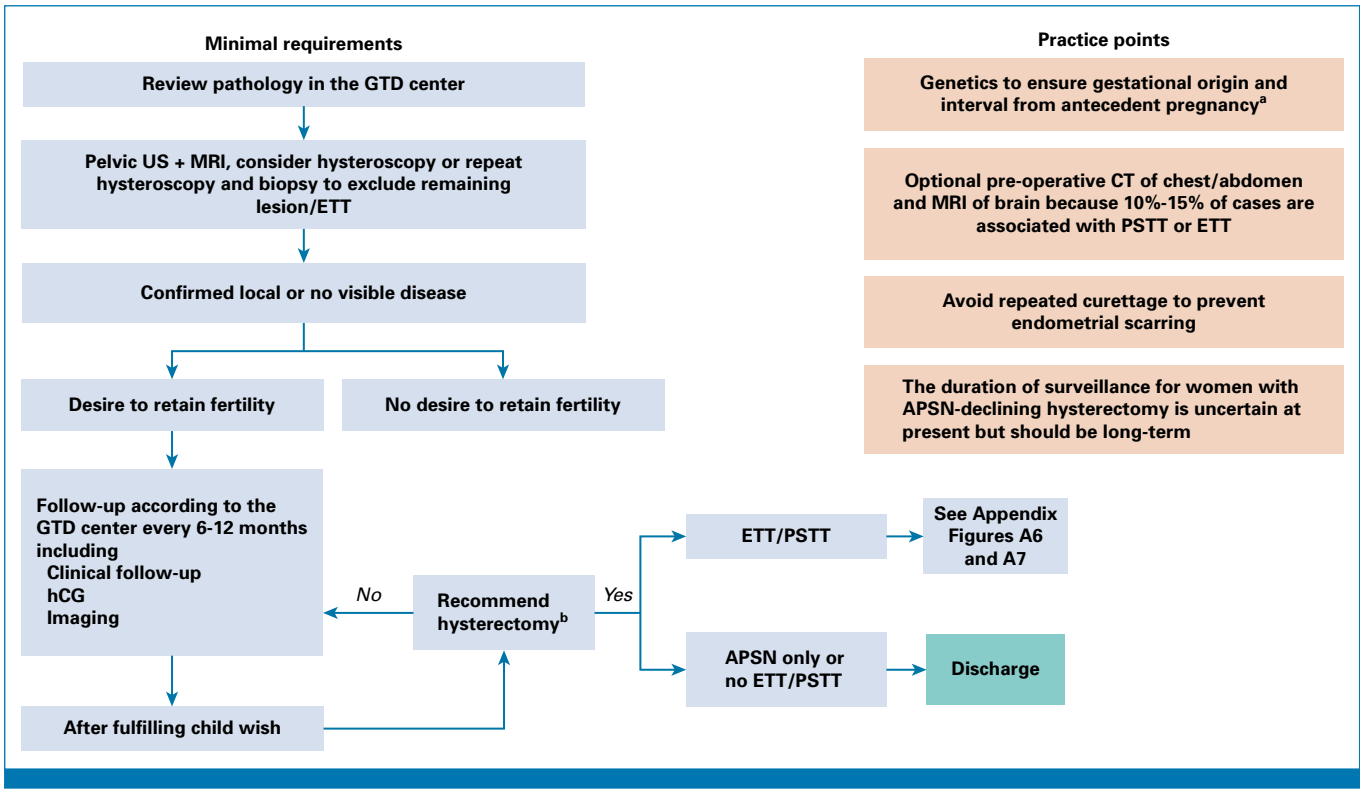

FIG A5. APSN. Only small case series, so low level of evidence. [a]Best practice. [b]Fertility-sparing surgery is experimental and should only be performed in the GTD center by experienced surgeons in selected cases. APSN, atypical placental site nodule; CT, computed tomography; ETT, epithelioid trophoblastic tumor; GTD, gestational trophoblastic disease; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; PSTT, placental site trophoblastic tumor; US, ultrasound.

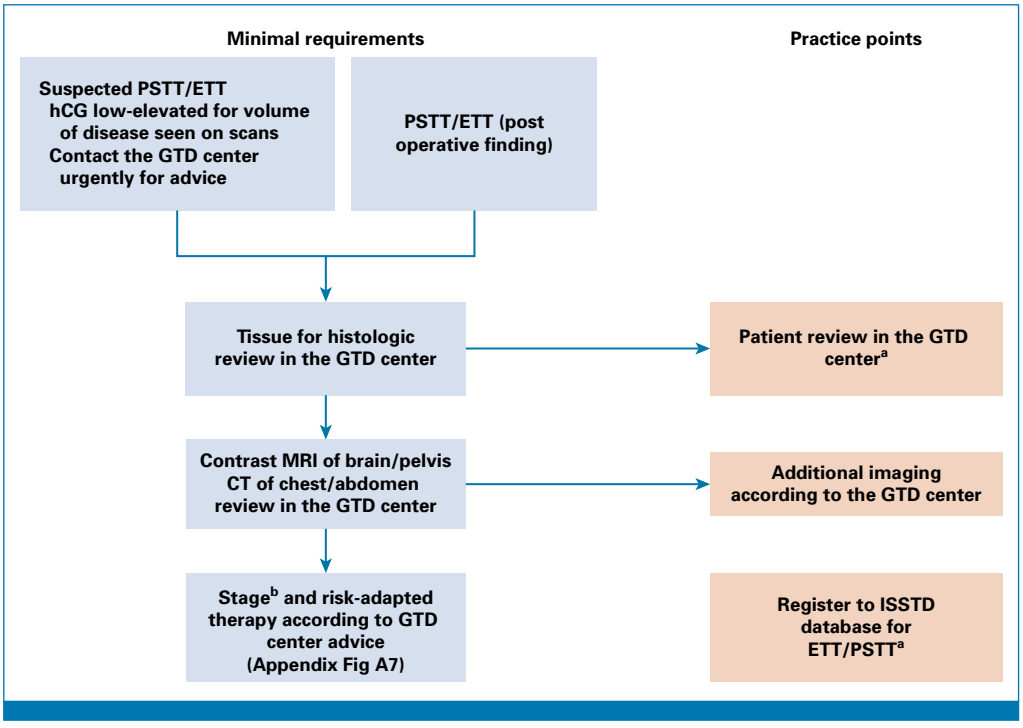

FIG A6. Diagnosis of PSTT/ETT. [a]Best practice. [b]Based on the FIGO 2000 staging system. CT, computed tomography; ETT, epithelioid trophoblastic tumor; FIGO, International Federation of Gynecology and Obstetrics; GTD, gestational trophoblastic disease; hCG, human chorionic gonadotropin; ISSTD, International Society for the Study of Trophoblastic Disease; MRI, magnetic resonance imaging; PSTT, placental site trophoblastic tumor.

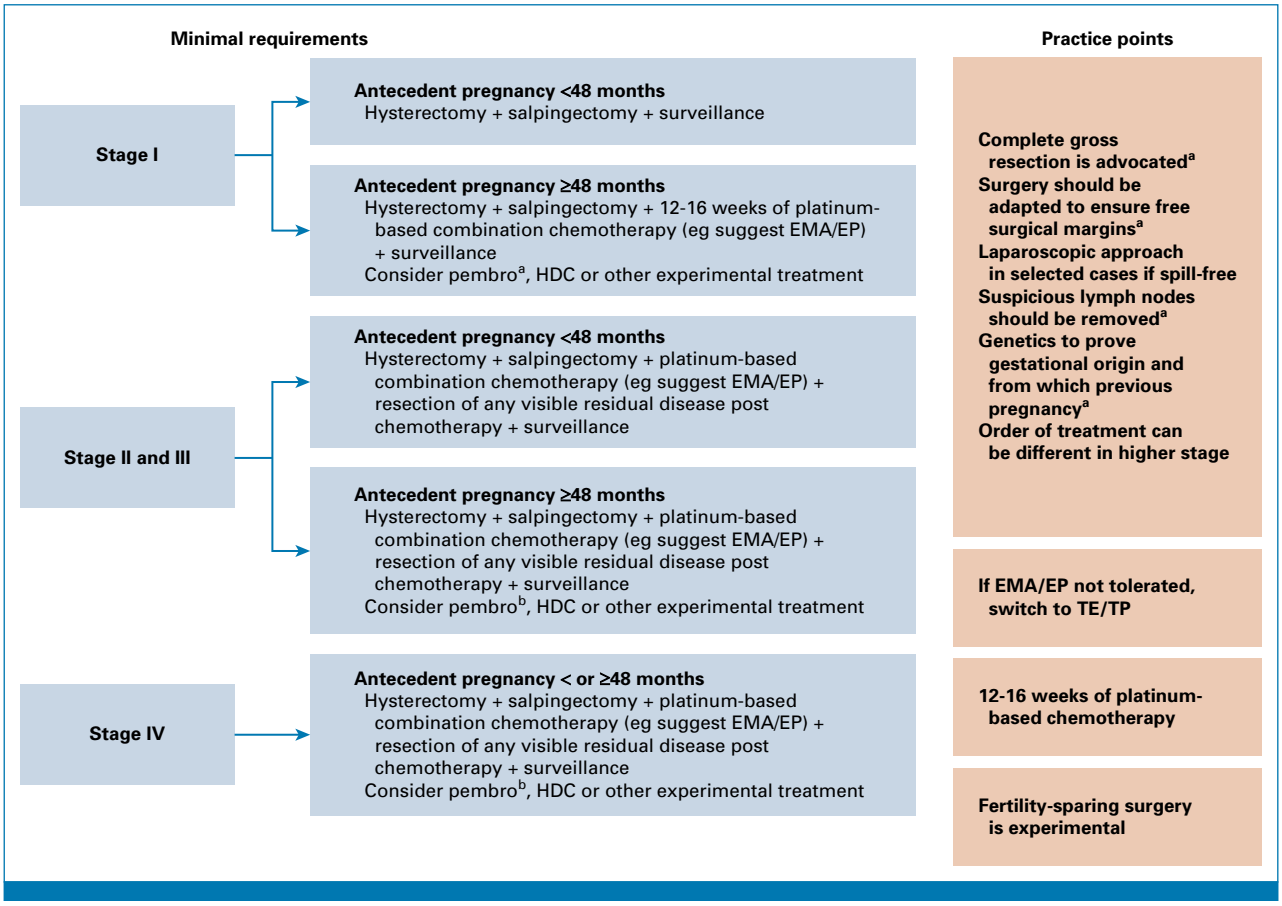

FIG A7. Treatment of PSTT/ETT. [a]Best practice. [b]Or other PD-1–targeted therapies, if available. EMA/EP, etoposide, methotrexate, actinomycin-D, etoposide, and cisplatin; ETT, epithelioid trophoblastic tumor; HDC, high-dose chemotherapy; pembro, pembrolizumab; PSTT, placental site trophoblastic tumor; TE, paclitaxel and etoposide; TP, paclitaxel and cisplatin.

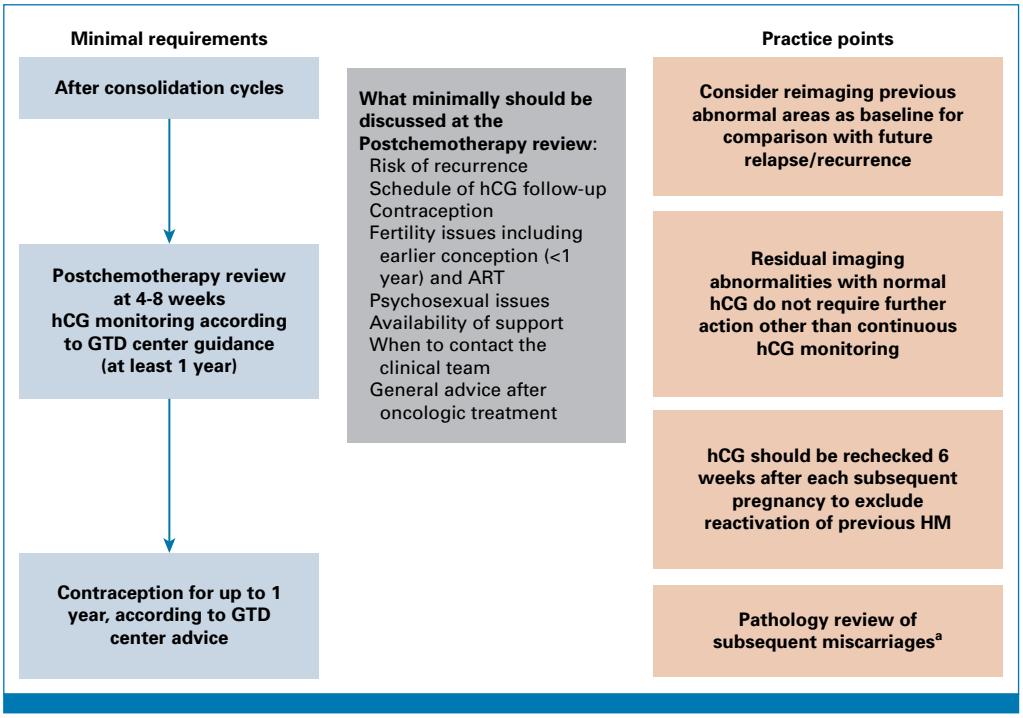

FIG A8. Follow-up after low-risk GTN. [a]Best practice. ART, assisted reproductive technology; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; HM, hydatidiform mole.

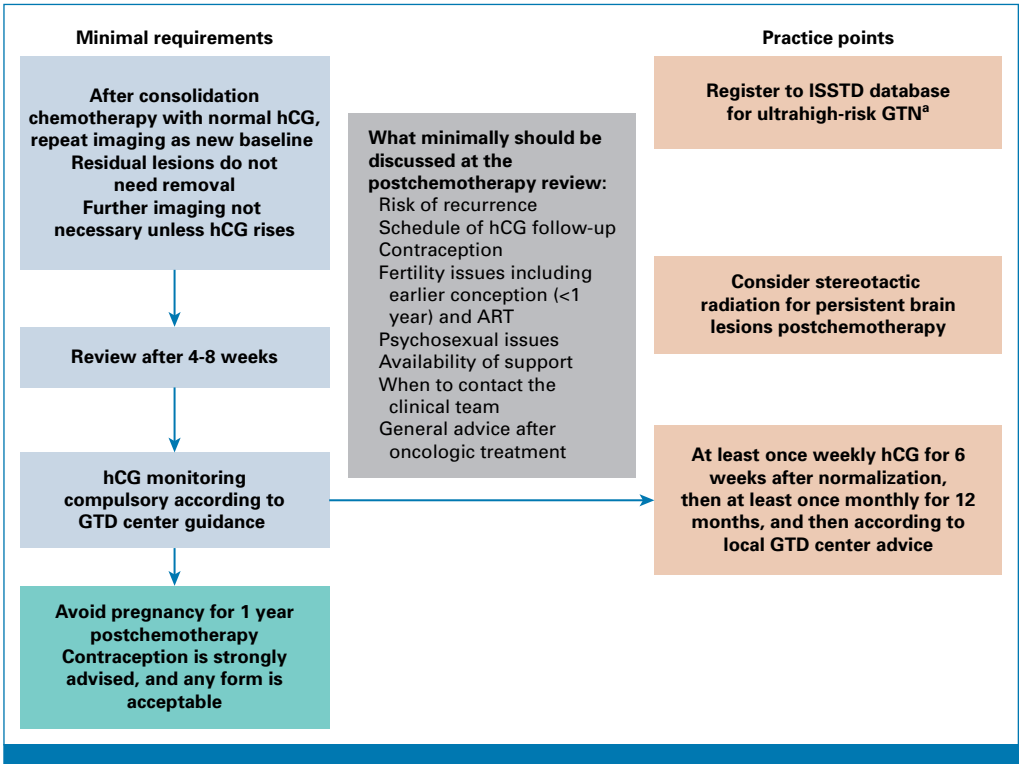

FIG A9. Follow-up after high-risk and ultrahigh-risk GTN. [a]Best practice. ART, assisted reproductive technology; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; ISSTD, International Society for the Study of Trophoblastic Diseases.

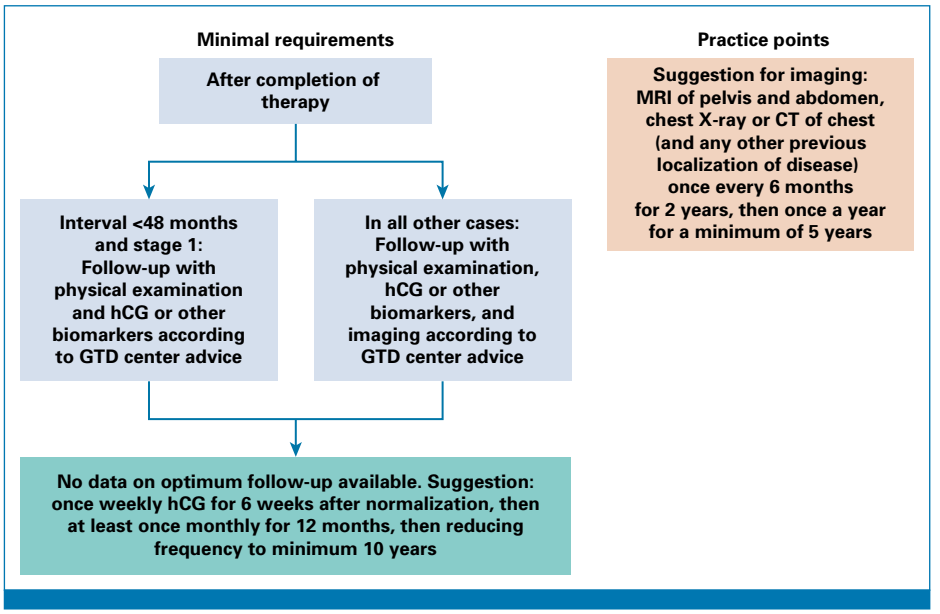

FIG A10. Follow-up after PSTT/ETT treatment. CT, computed tomography; ETT, epithelioid trophoblastic tumor; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; PSTT, placental site trophoblastic tumor.

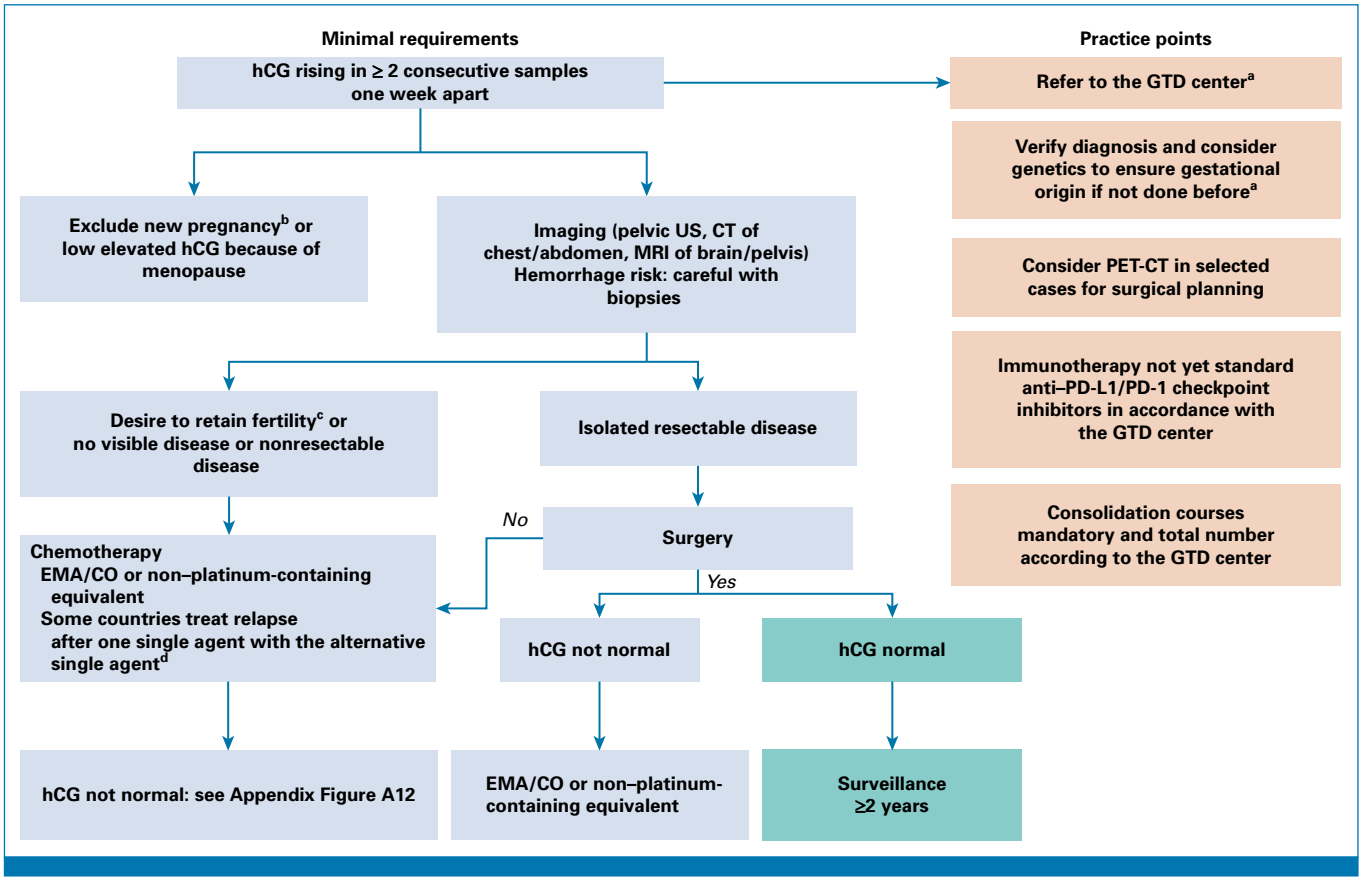

FIG A11. Recurrence *after remission* of low-risk GTN after treatment with *one or two lines* of monotherapy with MTX or Act-D. [a]Best practice. [b]Including incidental second molar pregnancy. [c]In the case of uterine disease. [d]There are limited published data on the use of second-line monotherapy after relapse after one single agent. Act-D, actinomycin-D; CT, computed tomography; EMA/CO, etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; MTX, methotrexate; PET, positron emission tomography; US, ultrasound.

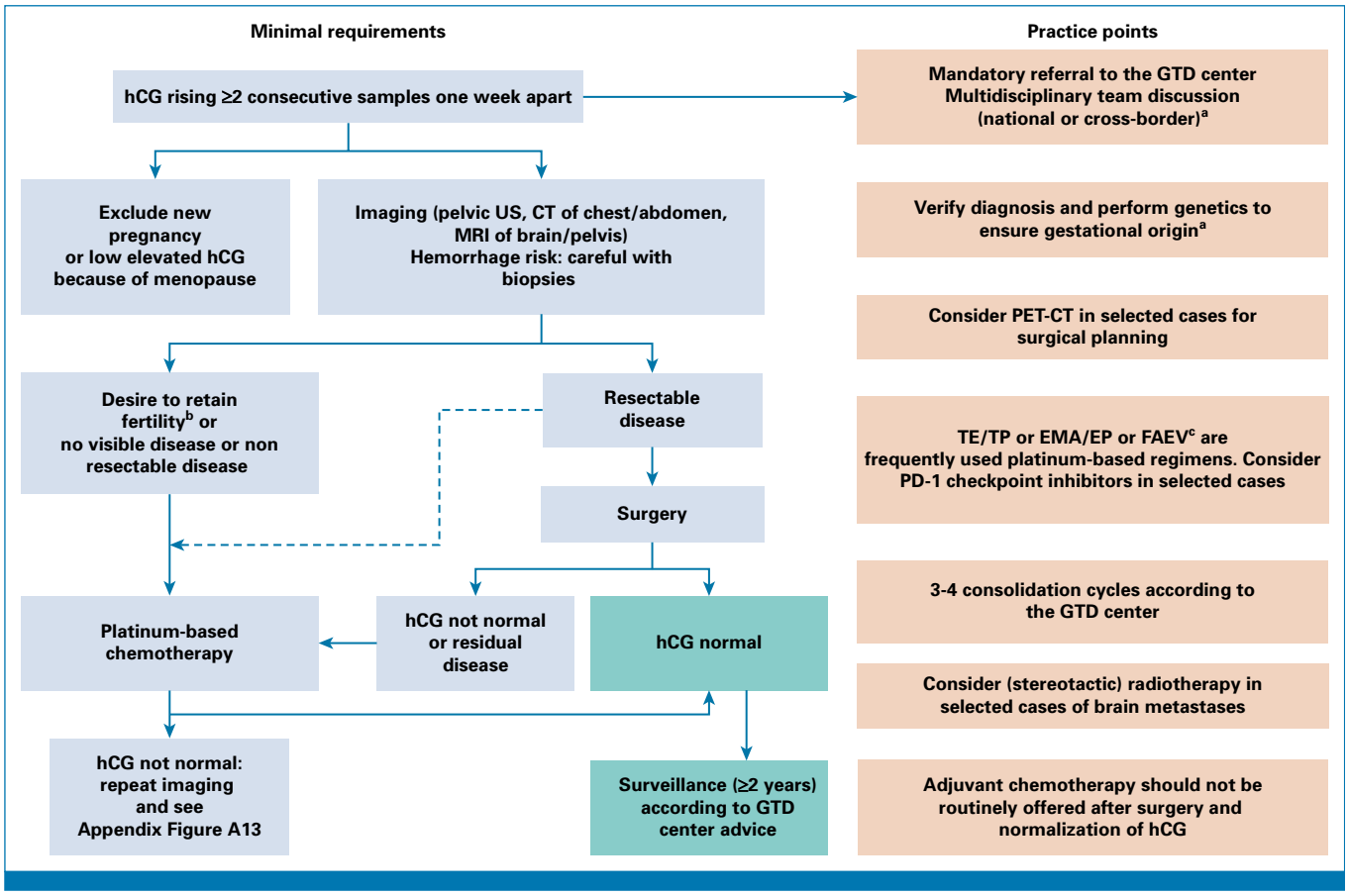

FIG A12. Recurrence of high-risk GTN after treatment with EMA/CO or platinum-free equivalent. [a]Best practice. [b]In the case of uterine disease. [c]Only used in China. CT, computed tomography; EMA/EP, etoposide, methotrexate, actinomycin-D, etoposide, and cisplatin; FAEV, floxuridine. actinomycin-D, etoposide, and vincristine; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; PET, positron emission tomography; TE, paclitaxel and etoposide; TP, paclitaxel and cisplatin; US, ultrasound.

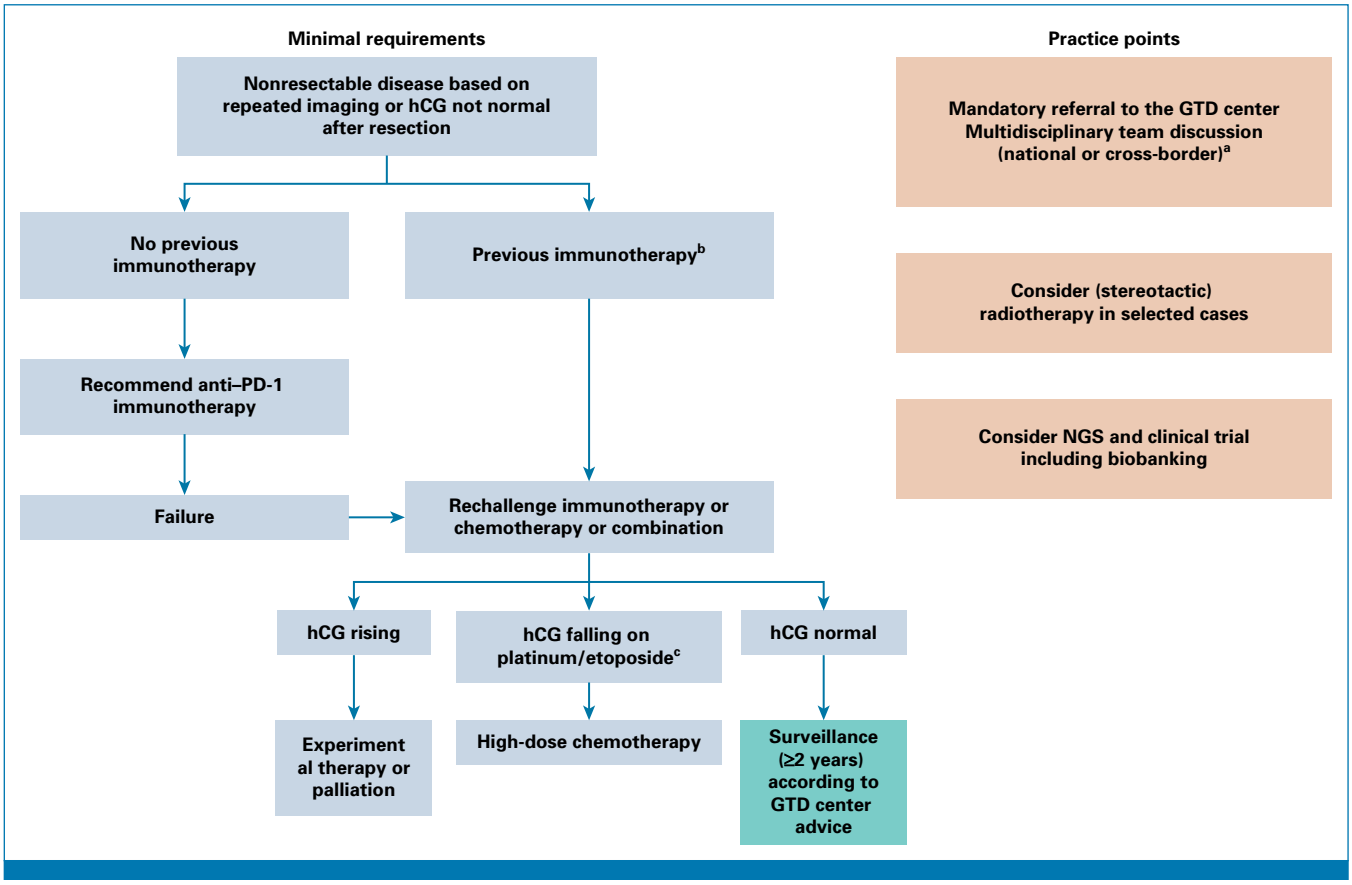

FIG A13. Recurrence of nonresectable disease after EMA/EP or TE/TP or FAEV. [a]Best practice. [b]There are no published data to guide the use of immunotherapy after long-term remission on previous immunotherapy. [c]No data on high dose after immunotherapy. EMA/EP, etoposide, methotrexate, actinomycin-D, etoposide, and cisplatin; FAEV, floxuridine, actinomycin-D, etoposide, and vincristine; GTD, gestational trophoblastic disease; hCG, human chorionic gonadotropin; NGS, next generation sequencing; TE, paclitaxel and etoposide; TP, paclitaxel and cisplatin.

TABLE A1. FIGO Scoring System

Score	0	1	2	4
Age, years	<40	≥40	—	—
Antecedent pregnancy	Mole	Miscarriage	Term	—
Interval from index pregnancy, months	<4	4 to <7	7 to <13	≥13
Pretreatment serum hCG, IU/mL	<1,000	1,000 to <10,000	10,000-100,000	≥100,000
Largest tumor size (including uterus)	—	3 to <5 cm	≥5 cm	—
Site of metastases	Lung	Spleen, kidney	GI	Liver, brain
Metastases, No.	—	1-4	5-8	>8
Previous failed chemotherapy	—	—	Single drug	≥2 drugs

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; hCG, human chorionic gonadotropin.

TABLE A2. FIGO staging system

Stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus
II	Gestational trophoblastic tumors extending to the adnexa or to the vagina but limited to the genital structures
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement
IV	All other metastatic sites

Abbreviation: FIGO, International Federation of Gynaecology and Obstetrics.

TABLE A3. Definitions of GTD

Term	Definition
GTD	All forms of premalignant or malignant neoplasia arising from the cytotrophoblast, syncytiotrophoblast, or intermediate trophoblast
GTN	All malignant forms of GTD including invasive mole, gestational choriocarcinoma, PSTT, and ETT
Low-risk GTN	FIGO score <7 (FIGO 0-6)
High-risk GTN	FIGO score ≥7 (FIGO 7-12)
Ultrahigh-risk GTN	FIGO score ≥13
Normalization of hCG	2 normal consecutive hCG levels at least 1 week apart within the normal range of the assay in a nonpregnant woman (preferably measured in a reference laboratory for hCG)
Remission after chemotherapy of hCG-secreting GTN	Normal hCG over a period of at least 4 weeks after completing chemotherapy
Remission after treatment of non–hCG-secreting GTN (eg, PSTT/ETT)	No evidence of disease/progression on physical examination and/or on (serial) imaging and/or pathologic examination of removed (metastatic) disease sites at least 4 weeks after treatment completion
Unexplained persistent real low-level hCG (in the absence of a lesion)	Serum hCG above the detection level measured in at least >3 samples in >3 months
Chemotherapy resistance in low- or high-risk disease	
Primary resistance	hCG increases despite 2 courses of systemic agent or hCG plateaus (<10% decrease over 2 weeks) despite 3 courses of systemic treatment
Acquired resistance	hCG plateau (<10% decrease over 2 courses [4 weeks]) or rise (at least 2 values over 2 weeks) after initial response
Recurrent GTN	Increase in hCG on at least two consecutive occasions (at least 1 week apart) and above the reference level of GTD center and at least 4 weeks after cessation of treatment (including consolidation) and exclusion of new pregnancy

Abbreviations: ETT, epithelioid trophoblastic tumor; FIGO, International Federation of Gynecology and Obstetrics; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; PSTT, placental site trophoblastic tumor.

TABLE A4. Requirements of a GTD center

Requirement
>5 patients should be discussed or treated in the center each year
At least one member of the GTD center should be a member of an international GTD society and regularly attend its meetings
The center should have an expert experienced in giving single-agent MTX and Act-D, EMA/CO, and EMA/EP (or equivalent)
The center should have (or easy access to) an expert pathologist; a nurse with special interest in GTD; a radiology department with CT, MRI, and interventional radiology; and an intensive care unit. Easy access to PET-CT would be desirable
The center should serve at least as a regional referral center for GTD

Abbreviations: Act-D, actinomycin-D; CT, computed tomography; EMA/CO, etoposide, MTX, Act-D, cyclophosphamide, and vincristine; EMA/EP, etoposide, MTX, Act-D, etoposide, and cisplatin; GTD, gestational trophoblastic disease; MRI, magnetic resonance imaging; MTX, methotrexate; PET, positron emission tomography.

TABLE A5. Dosing schedules

Drug	Dosage Regimen
MTX once every 2 weeks	
MTX with FA	MTX 1 mg/kg IM once daily on days 1, 3, 5, 7 or fixed-dose 50 mg once daily on days 1, 3, 5, 7 FA (leucovorin) 15 mg PO 24-30 hours after MTX once daily on days 2, 4, 6, 8
MTX alone	MTX 0.4 mg/kg/day once daily IV or IM days 1-5, not exceeding 25 mg/day
Actinomycin-D once every 2 weeks	
	1.25 mg/m^2 IV bolus (max 2 mg) or 0.5 mg IV once daily for days 1-5
EMA/CO once every 2 weeks	
EMA	
Day 1	Actinomycin-D 0.5 mg IV once daily
	Etoposide 100 mg/m^2 IV once daily
	MTX 300 mg/m^2 IV once daily
Day 2	Actinomycin-D 0.5 mg IV once daily
	Etoposide 100 mg/m^2 IV once daily
	Leucovorin 15 mg PO twice per day × 4 doses starting 24 hours after commencing MTX
CO	
Day 8	Vincristine 0.8 mg/m^2 (max 2 mg) once daily
	Cyclophosphamide 600 mg/m^2 once daily
TE/TP once every 4 weeks	
Day 1	Paclitaxel 135 mg/m^2 IV once daily
	Cisplatin 60 mg/m^2 IV once daily
Day 15	Paclitaxel 135 mg/m^2 IV once daily
	Etoposide 150 mg/m^2 IV once daily
EMA/EP once every 2 weeks	
Day 1	Actinomycin-D 0.5 mg IV once daily
	Etoposide 100 mg/m^2 IV once daily
	MTX 300 mg/m^2 IV once daily
Day 2	Leucovorin 15 mg PO twice daily × 4 doses starting 24 hours after commencing MTX
Day 8	Etoposide 150 mg/m^2 IV once daily
	Cisplatin 75 mg/m^2 IV once daily
Low-dose EP once weekly	
Day 1	Etoposide 100 mg/m^2 IV once daily
	Cisplatin 20 mg/m^2 IV once daily
Day 2	Etoposide 100 mg/m^2 IV once daily
	Cisplatin 20 mg/m^2 IV once daily
FAEV once every 3 weeks	
	Floxuridine 800-900 mg/m^2 once daily IV days 1-5
	Actinomycin-D 0.2 mg/m^2 once daily IV days 1-5
	Etoposide 100 mg/m^2 once daily IV days 1-5
	Vincristine 2 mg IV bolus, once on day 1
Immune checkpoint inhibition	
Avelumab	800 mg IV once every 2 weeks, 3 consolidation courses
Camrelizumab/apatinib	In each once every 4 weeks treatment cycle, camrelizumab IV once every 2 weeks and apatinib orally once per day
Pembrolizumab	200 mg once every 3 weeks until normalization, 5 cycles of consolidation
Pembrolizumab/ chemotherapy	Has been combined with TE/TP, EP, and FAEV, and pembrolizumab was continued for at least 4 months after completing combinations

Abbreviations: CO, cyclophosphamide and vincristine; EMA, etoposide, MTX, and actinomycin-D; EP, etoposide and cisplatin; FA, folinic acid; FAEV, floxuridine, actinomycin-D, etoposide, and vincristine; IM, intramuscular; IV, intravenous; MTX, methotrexate; PO, orally; TE, paclitaxel and etoposide; TP, paclitaxel and cisplatin.

TABLE A6. List of External Reviewers

Name	Specialty	Country
Cioffi Raffaella	Gynecologic Oncology, Obstetrics & Gynecology	Italy
Cortés Rafael	Obstetrics & Gynecology	Venezuela
de la Motte Rouge Thibault	Medical Oncology	France
Hemida Reda	Gynecologic Oncology	Egypt
Jamelot Mathieu	Medical Oncology	France
Kesic Vesna	Gynecologic Oncology	Serbia
Miedzińska Magdalena	Medical Oncology	Poland
Miller David	Gynecologic Oncology	USA
Morrison Shona	Nursing	Australia
Niimi Kaoru	Gynecologic Oncology	Japan
Patrier Sophie	Pathology	France
Pierre Marc Edy	Medical Oncology	Colombia
Rajaram Shalini	Gynecologic Oncology, Obstetrics & Gynecology	India
Rousset Pascal	Radiology	France
Rustin Gordon	Medical Oncology	United Kingdom
Sauthier Philippe	Gynecologic Oncology	Canada
Savage Philip	Medical Oncology	United Kingdom
Schink Julian	Gynecologic Oncology	United States
Slim Rima	Genetics	Canada
Tejada Berges Trevor	Gynecologic Oncology	Australia
Tsip Nataliya	Gynecologic Oncologist	Ukraine
Ulrikh Elena	Gynecologic Oncology, Obstetrics & Gynecology, Medical Oncology	Russia
Usui Hirokazu	Gynecologic Oncology, Obstetrics and Gynecology	Japan
Verheijen Rene	Gynecologic Oncology	France