

# Gestational Trophoblastic Neoplasia

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## Background

Gestational trophoblastic disease (GTD) refers to a group of pregnancy-related tumours that develop from the proliferation of trophoblastic cells of the placenta. GTD encompasses the conditions of partial and complete mole to the malignant entity of invasive mole, choriocarcinomas, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumours (ETT). Persistence of GTD is referred to as Gestational Trophoblastic Neoplasia (GTN)<sup>1</sup>.

ETT is an extremely rare subtype of GTN and arises from chorionic type intermediate trophoblast cells. PSTT is also rare and arises from implantation site intermediate trophoblast cells. The incidence of hydatidiform mole is less than 10 per 1000 pregnancies<sup>2</sup>. As many as 20% of complete hydatidiform moles will develop into GTN, whereas the rate in partial hydatidiform moles is 0.5-1%<sup>3, 4</sup>.

Metastases can occur in patients with GTN, the most common site being the lungs (81%). Other sites include the vagina (5%), the central nervous system (7%), the gastrointestinal tract concurrent with the lungs (4%), and the liver concurrent with the lungs (1.5%)<sup>5</sup>. When detected and managed early, cure rates for GTN are greater than 90%<sup>6, 7</sup>. The purpose of this guideline is to recommend options for the management of GTN, based on the best evidence available.

## Guideline Questions

1. Which patients should be referred to a gynecologic oncologist after evacuation of a hydatidiform mole?
2. What investigations are appropriate for the work-up of gestational trophoblastic neoplasia (GTN)?
3. How should GTN be staged and scored prognostically?
4. How should GTN be managed? What investigations are recommended for the follow-up of patients with GTN?

## Search Strategy

The Ovid Medline, PubMed, EMBASE, and Cochrane databases were searched for relevant articles published between 1965 – 2021. Clinical practice guideline databases (e.g. National Guidelines Clearinghouse, CancerView, etc.) were also searched for evidence relevant to this topic, published between 2006 – April 2021.

For the evidence on work-up, search terms included: gestational trophoblastic neoplasia AND workup or chest x-ray or magnetic resonance imaging or computed tomography or pelvic ultrasound or complete blood count or beta hCG or liver function tests or renal function tests or marrow function tests. A total of 1086 citations were returned; only studies that looked at blood work or imaging tests in a cohort of patients (i.e., ten or more) with diagnosed gestational trophoblastic neoplasia (no case studies) and were published in English from 2000 to 2021 were included. The terms, gestational trophoblastic neoplasia AND metastases, were also searched, with the results limited to clinical trials only. In total, nine articles and four guidelines were included as evidence. For the evidence on

staging and prognostic scoring, as well as evidence on follow-up, the term gestational trophoblastic neoplasia was searched using the National Guidelines Clearinghouse database as well as individually searching Canadian cancer guidelines developers' websites. For the evidence on management, the terms *gestational trophoblastic neoplasia* and *chemotherapy* were searched in the EMBASE, Ovid Medline and PubMed databases, with results limited to clinical trials published from 2000 to 2021 April that looked at a single agent or multi-agent regimen in a cohort of patients (i.e., ten or more) with diagnosed gestational trophoblastic neoplasia.

In addition to the ECRI Guidelines Trust Clearinghouse database, existing guidelines considered for this review included those published by the following groups: Society of Obstetricians and Gynaecologists of Canada (2002)<sup>8</sup>, National Cancer Institute (2020)<sup>9</sup>, and American College of Obstetricians and Gynecologists (2008)<sup>10</sup> and BC Cancer Agency (2020)<sup>11</sup>. An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence-based perspective was used to draft proposals. Where evidence was weak, recommendations were based on group consensus.

## Target Population

The recommendations outlined in this guideline apply to women with gestational trophoblastic neoplasia, including invasive mole, choriocarcinoma, epithelioid trophoblastic tumours, epithelioid trophoblastic tumours and placental site trophoblastic tumours.

## Recommendations

Follow-up after evacuation of a molar pregnancy (complete or partial hydatidiform mole) should include:<sup>8</sup>

1. Weekly quantitative hCG until normalization. For complete hydatidiform mole, continue weekly monitoring for two further weeks, then monthly for 6 months. For partial hydatidiform mole, conclude follow-up after confirming normal hCG at 4 weeks after first normal result.
2. Follow-up for partial molar pregnancy is concluded once the hCG has returned to normal on two samples, at least 4 weeks apart (Level of Evidence III Strength of recommendation C)
3. Regular pelvic examination, at 1, 3, and 6 months post-evacuation
4. Contraception during hCG follow-up (preferably OCP)
5. Standard Chest X-ray for the work-up of complete and partial moles is not required. A chest x-ray is recommended only if GTN develops after a molar pregnancy (as may be detected from the serial HCG monitoring).

### **I. Indications for Referral to a Gynecologic Oncologist Following Evacuation of a Hydatidiform Mole** (Level of Evidence: II Strength of Recommendation: B)<sup>1, 3</sup>

Patients who have undergone evacuation of a hydatidiform mole *and* who present with any of the following should be referred to a gynecologic oncologist: <sup>1, 3</sup>

- an abnormal  $\beta$ -hCG regression pattern (a 10% or greater rise in  $\beta$ -hCG levels over three weeks or a plateauing  $\beta$ -hCG of three stable values over two weeks)
- a rise in  $\beta$ -hCG following a normal regression pattern for two weeks.
- a histologic diagnosis of choriocarcinoma, placental site trophoblastic tumour, or epithelioid trophoblastic tumour
- persistently elevated  $\beta$ -hCG levels six months post-evacuation
- the presence of metastases in addition to abnormal  $\beta$ -hCG levels.

## II. Work-up for Gestational Trophoblastic Neoplasia

History and physical exam should be performed, along with the following investigations:

- Blood work: serum  $\beta$ -hCG, complete blood count (CBC) with differential, platelet counts, PT/PTT, liver function tests, and renal function tests.
- Imaging to check for metastases: Staging and scores are based on the chest X-ray and not on the CT of the chest. Also brain imaging is required if there is confirmed lung disease.

## III. Staging and Prognostic Scoring for Gestational Trophoblastic Neoplasia (*Level of Evidence: I Strength of Recommendation: A*)<sup>9, 10, 12</sup>

Staging of GTN is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) system (2018): <sup>12</sup>(Table 1)

**Table 1.** Anatomic staging of gestational trophoblastic neoplasia (based on FIGO 2018)

FIGO Anatomic Staging	
Stage I	Disease confined to the uterus
Stage II	Disease extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	Disease extends to the lungs with or without genital tract involvement
Stage IV	Disease involves other metastatic sites

Risk assessment is based on several indicators, including age, antecedent pregnancy, interval months from index pregnancy, pretreatment serum  $\beta$ -hCG, largest tumor size (including uterus), site of metastases, number of metastases, and previous failed chemotherapy (see Table 2).<sup>12</sup>

**Table 2.** Prognostic scoring for gestational trophoblastic neoplasia (FIGO, 2018; modified from WHO)

Scores	0	1	2	4
age	<40	≥40	–	–
antecedent pregnancy	mole	abortion	term	–
interval months from index pregnancy	<4	4–6	7–12	>12
pretreatment serum β-hCG (mIU/ml)	<10 <sup>3</sup>	10 <sup>3</sup> –10 <sup>4</sup>	10 <sup>4</sup> –10 <sup>5</sup>	>10 <sup>5</sup>
largest tumor size (including uterus)	<3	3–4 cm	≥5 cm	–
site of metastases	lung	spleen, kidney	gastrointestinal	liver, brain
number of metastases	–	1–4	5–8	>8
previous failed chemotherapy	–	–	single drug	≥2 drugs

- Low-risk: individuals with a score ≤6. <sup>9, 10, 12</sup>
- High-risk: individuals with a score ≥7. <sup>9, 10, 12</sup>
- To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, i.e., stage II:4, stage IV:9. This stage and score will be allotted for each patient.

#### IV. Treatment of Gestational Trophoblastic Neoplasia

Options for the management of GTN are dependent on prognostic scoring and include the following:

**Non-metastatic (Stage I) and Low-risk Metastatic (Stages II and III, FIGO score ≤6) (Level of Evidence: I Strength of Recommendation: A)**<sup>9, 13, 14</sup>

- Actinomycin 10-12 mcg/kg (or 0.5 mg flat dose) IV daily x 5 days repeat every 14 days.
- Actinomycin-D (1.25 mg/m<sup>2</sup> IV), (max 2 mg) given every 2 weeks for 1 to 3 cycles beyond negative β-hCG
- Methotrexate (50 mg/m<sup>2</sup> IM), given weekly for 1 to 3 cycles beyond negative β-hCG<sup>13</sup>
- Actinomycin D is considered more effective and preferred than methotrexate. <sup>13</sup>
- Methotrexate 0.4 mg/mkg/day IV or IM (max 25 mg/day) daily x 5 days; repeat every 14 days
- Methotrexate 1 mg/kg IM every other day x 4 days (day 1,3,5 and 7) Alternating every other day with leucovorin 15 mg po 30 hours after each methotrexate dose on days 2,4,6 and 8; repeat every 14 days

- Actinomycin-D and methotrexate with folinic acid, given every 2 weeks for 1 to 3 cycles beyond negative  $\beta$ -hCG
  - Actinomycin-D (0.5 mg/m<sup>2</sup> IV) given days 1-2
  - Methotrexate (100 mg/m<sup>2</sup> IV push + 300 mg/m<sup>2</sup> IV) on day 1
 Folinic acid (15 mg PO, q 6 h x 9 doses starting 24 hours after methotrexate bolus)
- Surgery (i.e., hysterectomy with salpingectomy). Hysterectomy as alternative if childbearing complete - Permanent sterilization and decrease need for subsequent chemo or reduce number of cycles of chemotherapy.<sup>15, 16</sup>
- Dactinomycin q 14 days regimen should not be used as secondary therapy for methotrexate-resistant disease. It also shouldn't be used as the primary therapy in patients with choriocarcinoma<sup>9</sup>.

**High-risk Metastatic (Stages II and III, FIGO score  $\geq 7$  and Stage IV) (Level of Evidence: I Strength of Recommendation: A)<sup>9, 14, 17</sup>**

- Preferred regimens include:
  - EMA/CO multi agent chemotherapy, given every 2 weeks for 3 cycles beyond negative  $\beta$ -hCG
    - Etoposide (100 mg/m<sup>2</sup> IV, days 1, 2)
    - Actinomycin-D (0.5 mg IV push days 1, 2)
    - Methotrexate (300 mg/m<sup>2</sup> IV, day 1)
    - Folinic acid (15 mg PO, q 12 h, 4 doses starting 24 hours after methotrexate)
    - Vincristine (0.8–1.0 mg/m<sup>2</sup> IV, day 8)
    - Cyclophosphamide (600 mg/m<sup>2</sup> IV, day 8)
    - Consider GCS-f 5 mcg/kg on days 4-6(&) and 10-12(13) of each cycle
  - EMA/EP multi agent chemotherapy, given every 2 weeks for 3 cycles beyond negative  $\beta$ -hCG
    - Course 1: same as EMA/CO
    - Course 2: etoposide (150 mg/m<sup>2</sup> IV, day 8), cisplatin (75 mg/m<sup>2</sup> IV, day 8), plus magnesium supplementation (30 ml PO, q 12 h, day 1) and Filgastrim (GCS-f 5 mcg/kg SC on days 9-14)
  - TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide (Repeat every 2 weeks)
  - MACE multi agent chemotherapy
    - Cisplatin (30 mg/m<sup>2</sup> IV, days 1-3)
    - Etoposide (50 mg PO, days 1-10)
    - Actinomycin-D (0.5 mg/m<sup>2</sup> IV, days 8 and 9)
    - Methotrexate (100 mg/m<sup>2</sup> bolus + 300 mg/m<sup>2</sup> IV, day 8)
    - Folinic acid (15 mg PO, q 6 h x 9 doses starting 24 hours after methotrexate bolus)
  - Paclitaxel 135 mg/m<sup>2</sup> IV infusion on Day 1
  - Cisplatin 75 mg/m<sup>2</sup> IV on Day 1
  - Alternating every 2 weeks with

- Paclitaxel 135 mg/m<sup>2</sup> IV infusion on Day 15 • Etoposide 150 mg/m<sup>2</sup> IV on Day 15
- Pegfilgrastim 6 mg SC on Days 2 and 16
- Other regimens include:
  - BEP multi agent chemotherapy
    - Bleomycin: 30 units per week
    - Etoposide: 100 mg/m<sup>2</sup>, days 1-5
    - Cisplatin: 20 mg/m<sup>2</sup>, days 1-5
  - 5-FU/actinomycin-D multi agent chemotherapy (as second-line therapy), given every 2 weeks for 4-7 cycles beyond negative β-hCG
    - 5-FU: 1500 mg/m<sup>2</sup> IV, days 1-5
    - Actinomycin-D: 0.5 mg/m<sup>2</sup> IV push
  - VIP multi agent chemotherapy
    - Etoposide (75 mg/m<sup>2</sup> day IV on days 1-5)
    - Isofamide (1200 mg/m<sup>2</sup>/day IV on days 1-5)
    - Cisplatin (20 mg/m<sup>2</sup> IV, days 1-5)
  - ICE multi agent chemotherapy
    - Isofamide (1.2 g/m<sup>2</sup> day IV on days 1-3)
    - Carboplatin (AUC 4 IV on day 1)
    - Etoposide (75 mg/m<sup>2</sup> day IV on days 1-3)
  - TIP multi agent chemotherapy
    - Paclitaxel (250 mg/m<sup>2</sup> IV on Day 1)
    - Isofamide (1500 mg/m<sup>2</sup> day IV on days 2-5)
    - Cisplatin (25 mg/m<sup>2</sup> IV, days 2-5)
- Adjuvant surgery for resection of metastases in selected patients
- Radiotherapy in selected patients

**V. Induction therapy for high risk GTN patients (Score ≥12 or those at significant risk of pulmonary, intraperitoneal or intracranial hemorrhage):** *(Level of Evidence: II Strength of Recommendation: B)*

- Consider induction low-dose EP, for 1-3 cycles prior to starting EMA/CO <sup>9, 14</sup>
- Etoposide 100mg/m<sup>2</sup>/day IV and cisplatin 20 mg/m<sup>2</sup>/day IV on Days 1 and 2 every 7 days for 1-3 courses prior to starting EMA/EP or EP/EMA
- Increase the methotrexate infusion dose in the EP/EMA or EMA/EP protocol to 1000 mg/m<sup>2</sup> and extend the infusion from 12 to 24 hours. Give leucovorin (folinic acid) 15 mg po every 6 hours for 12 doses starting 32 hours after the start of the methotrexate infusion

**VI. Management of High risk Gestational Trophoblastic Neoplasia who have failed EMA-CO** *(Level of Evidence: I Strength of Recommendation: A)<sup>17</sup>*

Most of the patients recovered well from EMA-CO. Patients scoring of ≥7 (based on FIGO scoring) are at high risk of developing drug resistance with up to 30% of patients developing resistance from EMA-CO.



- Preferred regimens include:
  - TP/TE is effective for high-risk GTN patients
  - Paclitaxel (135 mg/m<sup>2</sup> 3h, + Etoposide 150 mg/m<sup>2</sup>, 30 min, Day 1)
  - Paclitaxel (135 mg/m<sup>2</sup> 3h, + Cisplatin 75 mg/m<sup>2</sup>, 1hour, Day 15). This regimen is preferred to EMA-EP as it is less toxic.
  - EMA-EP/ EP/EMA multi agent chemotherapy, given every 2 weeks for patients who initially responded to EMA-CO but have low  $\beta$ -hCG or developed re-elevation of  $\beta$ -hCG.
    - Etoposide (100 mg/m<sup>2</sup> IV, days 1, 2,8)
    - Actinomycin-D (0.5 mg IV push days 1, 2)
    - Methotrexate (300mg/m<sup>2</sup> IV infusion over 12 hours on day 1)
    - Folinic acid (15 mg PO, q 12 h, for 4 doses beginning 24 hours after the start of methotrexate infusion)
    - Cisplatin (75 mg/m<sup>2</sup> IV, day 8)
- Other regimens include:
  - BEP multi agent chemotherapy
    - Bleomycin: (30 units IV days 1,8,15)
    - Etoposide: (100 mg/m<sup>2</sup>, IV days 1-4)
    - Cisplatin: (20 mg/m<sup>2</sup>, IV days 1-4)

## VII. Management of patients who have Resistance to 2<sup>nd</sup> line combination chemotherapy

Pembrolizumab: 200 mg IV Q 3 weeks or 400 mg Q 6 weeks. Give 3 extra treatments beyond a negative HCG

- Consider High dose chemotherapy with autologous stem cell transplant if immunotherapy fails.
- Surgical resection can be considered if a focus of resistant disease is identified – hysterectomy, pulmonary resection.

## VIII. Epithelioid Trophoblastic tumours (ETT)

- These are extremely rare subtypes of GTN and account for less than 2% of all GTNs.
- They arise from chorionic intermediate trophoblastic cells. Surgery is recommended for non-metastatic ETT.
- A combination of chemotherapy with surgery should be considered in metastatic disease. However, these tumours are often refractory to standard chemotherapy.
- There may well be a role for immunotherapy in these patients, especially if chemorefractory<sup>18</sup>.

## IX. Placental site trophoblastic tumor (PSTT)

- PSTTs are malignant and develop from extravillous, intermediate trophoblasts.
- On microscopy there are no chorionic villi. They have a proliferation of intermediate trophoblastic cells. They produce very little HCG. Their clinical behavior is similar to ETT.



- They usually occur after a non-molar abortion or pregnancy, although they can also occur after a molar gestation. This time interval from antecedent pregnancy is highly prognostic for PSTT. They remain localized for a long time although 30 % may present with metastasis<sup>19</sup>.
- Surgery is recommended for non-metastatic PSTT.

## X. Follow Up for Gestational Trophoblastic Neoplasia

During chemotherapy  $\beta$ -hCG measurements should be measured every 2 weeks prior to the start of the next cycle. Middle of the cycle  $\beta$ -hCG measurements can be spuriously elevated. This should be Continue systemic therapy for 2-3 treatment cycles past normalization of  $\beta$ -hCG

Serial serum  $\beta$ -hCG measurements should be determined as follows:

- q 1-2 weeks during chemotherapy until levels have normalized, continue chemotherapy for another 2-3 cycles of normal  $\beta$ -hCG. Follow  $\beta$ -hCG weekly for the first month then monthly for 1 year after GTN.
- Patients should be advised about future pregnancy: (*Level of Evidence: II Strength of Recommendation: B*)<sup>7, 8, 10</sup>
- Pregnancy should be avoided until  $\beta$ -hCG levels have been normal for a minimum of six months up to one year (depending on risk score – low risk resolved with first line chemotherapy follow for 6 months, high risk disease should be followed for a year) following chemotherapy for gestational trophoblastic neoplasia; however, among patients who do conceive within 6-12 months of treatment, a favorable outcome is likely.
- The combined oral contraceptive pill and the IUD are for use by women with GTN.
- A intrauterine contraceptive device should only be used once the hCG has returned to normal as it is more likely to cause a perforation in the uterus if it is put in too soon after treatment for a molar pregnancy.
- First trimester ultrasound and serum  $\beta$ -hCG testing is recommended for women who become pregnant for the first time after treatment for GTN. In addition,  $\beta$ -hCG testing at 6-8 weeks after delivery should be performed.

In patients for whom hormone replacement therapy (HRT) is indicated, it may be used safely once  $\beta$ -hCG levels have returned to normal.

- Rarely, the occurrence of a twin pregnancy with hydatidiform mole should be considered during prenatal care. Normal fetuses in the presence of a molar placenta should raise suspicion. Treatment to an appropriate referral centre will be helpful in the analysis of these patients. In addition, it will facilitate systematic post-molar monitoring and appropriate chemotherapy if warranted.

## Discussion

About 15% of all molar pregnancies will develop into gestational trophoblastic neoplasia (GTN)<sup>3, 4</sup>. Referral to a gynecologic oncologist should be initiated when, following evacuation of a hydatidiform mole,  $\beta$ -hCG levels show an abnormal regression pattern (i.e., a 10% or greater rise or a plateauing for three stable values over two weeks), rebound, are high (>20,000 mIU/mL) more than four weeks post-evacuation, or are persistently elevated six months post-evacuation<sup>1, 3</sup>. Other reasons for referral include a histologic diagnosis of choriocarcinoma, epithelioid trophoblastic tumor, or placental site trophoblastic tumour, or metastasis to one or more sites<sup>1, 3</sup>. Once a referral has been made, blood work should include at minimum a baseline  $\beta$ -hCG, complete blood count, and liver, renal, and marrow function tests<sup>9-11</sup>. Imaging to rule out metastases should also be performed<sup>8-11</sup>. Common sites of metastases include the lungs, the central nervous system, the vagina, and the liver concurrent with the lungs<sup>5</sup>. A positive chest x-ray is sufficient for the detection of lung metastases and CT doesn't offer any advantage in terms time to remission; the chest x-ray is also used for staging and scoring purposes<sup>20, 21</sup>. However, metastases are seen on chest CT scan in 30-40% of patients with normal chest x-rays, necessitating the need for chest CT to ensure adequate resolution of all lung metastatic disease<sup>7</sup>.

Depending on a number of risk factors, including age, antecedent pregnancy, interval months from index pregnancy, pretreatment serum  $\beta$ -hCG, largest tumor size (including uterus), site of metastases, number of metastases, and previous failed chemotherapy (Table 1), patients will be grouped into one of two risk categories: low risk (score of  $\leq 6$ ) or high risk (score of  $\geq 7$ )<sup>12</sup>. Treatment of non-metastatic (stage I) and low risk metastatic (stage II and III, risk score  $\leq 6$ ) GTN typically requires a less aggressive approach than treatment of high risk metastatic GTN (stage II and III, risk score  $\geq 7$  and stage IV).

Most groups recommend single agent actinomycin-D or methotrexate with or without folinic acid as primary therapy for non-metastatic or low risk metastatic GTN<sup>8-11</sup>. Single agent methotrexate typically achieves complete response rates ranging from 48 to 74%<sup>22-27</sup> after four to five cycles<sup>26</sup>. Single agent actinomycin-D has produced better complete response rates, which range from 70 to 100%<sup>22, 23, 26, 28</sup>. A phase III clinical trial comparing methotrexate with actinomycin-D found that actinomycin-D significantly improved the complete response rate by 17% ( $p=.01$ ), while both regimens were well tolerated<sup>22</sup>. A recent retrospective study by Eiriksson L, et al. at the Alberta Cross Cancer Institute and the BC Cancer Agency demonstrated a response rate of 98% using combination chemotherapy with actinomycin-D and methotrexate for a median three cycles, with limited grade 3 and 4 hematologic toxicities (12% and 8%, respectively)<sup>6</sup>

High risk metastatic GTN is treated with multi agent chemotherapy. Etoposide, actinomycin-D, methotrexate, vincristine, and cyclophosphamide is commonly used, alone (EMA/CO) or with cisplatin (EMA/CE), as first line therapy<sup>8-10</sup>. Among patients receiving EMA/CO as first or second line therapy for high-risk metastatic GTN, the complete response rate was 71%, with overall survival reaching 91%<sup>29</sup>. A retrospective study reported a cure rate of 86% for EMA/CO<sup>30</sup>. The addition of cisplatin

(EMA/CE) may produce a slightly better remission rate (88%) when used as first line therapy; however, EMA/CE is associated with greater hematologic toxicity<sup>31-33</sup>. As second line therapy, EMA/CE has achieved complete response rates, ranging from 67 to 73%<sup>32, 33</sup>.

Better options for patients who develop resistance to EMA-CO include a 2-week alternating regimen of TC/TE or 5FU with actinomycin D(FA). Among 11 patients who relapsed after EMA-CO, the overall survival rate with FA was 82% after a mean follow-up of over 11 years<sup>34</sup>.

Many recent studies suggested that immune system play a critical role in the outcome of gestational trophoblastic diseases. This new concept is based on the expression of programmed death-ligand 1 (PD-L1) in all subtypes of gestational trophoblastic tumors, which could be a target for the immunotherapy. The TROPHIMMUN trial showed the effectiveness of Avelumab (PD-L1 inhibitor) in patients with methotrexate resistance. The Phase II trial showed a favorable safety profile and a 50% remission rate in patients after treatment with Avelumab. Pembrolizumab has shown a complete response of 75-80% in patients with chemotherapy resistant GTN. This includes a population that had failed high-dose chemotherapy(HDC) with peripheral stem cell support<sup>35-37</sup>.

The development of the premature ovarian failure (POF) and infertility are known side effects of chemotherapy in breast cancer patients. GnRH agonists used in young female breast cancer patients for temporary ovarian suppression. Based on the clinical evidence it is recommended that GnRH agonists can be considered as an effective option for ovarian function preservation in young premenopausal breast cancer patients. Three different clinical trials, namely, PROMISE-GIM6, POEMS/SWOG S0230, and Anglo Celtic Group OPTION, reported that the use of GnRH agonists showed a 15% reduction in POI rates after chemotherapy. Hence, GnRH agonists could be a good option for ovarian suppression in young gynecologic cancer patients receiving chemotherapy<sup>38-40</sup>.

Patients with gestational trophoblastic neoplasia are typically followed up monthly for one year after treatment, with a higher frequency (i.e., q 1 week for one month, then q 2 weeks for two months) for the first three months; serum  $\beta$ -hCG levels are monitored.<sup>8,10,11</sup> During follow up, patients report anxiety around fear of recurrence, of infertility, and of conceiving again; however compliance with recommended follow up is good<sup>41</sup>. The risk of abnormal pregnancy (i.e., spontaneous abortion, still birth, repeat mole) is greater during the first six months following treatment (for low risk or high risk GTN) than after a year following treatment;<sup>31, 42</sup> therefore, patients are normally advised to avoid pregnancy for the first year following treatment<sup>7, 8, 10, 43</sup>. Patients should be reassured, though, that if they do conceive early (within 12 months of treatment), outcomes will likely be favorable. Among 230 early pregnancies at the Charing Cross Hospital in London, 71% were delivered at full term, while 11% were spontaneously aborted, 1.3% developed into new hydatidiform moles, and 1% were still born (the remaining 15% were terminated); spontaneous miscarriages were more likely to occur in the multi-agent group ( $p=.04$ )<sup>44</sup>. Regarding the use of hormones, the combined oral contraceptive pill is considered safe for use by women who have been treated for GTN; further, patients taking hormone replacement therapy may do so safely once  $\beta$ -hCG levels have returned to normal<sup>8, 44</sup>.

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## Development and Revision History

This guideline was reviewed and endorsed by the Alberta GYNE Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2012 and updated in 2021.

## Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## Abbreviations

CBC, complete blood count; CT, computed tomography; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique ; FU, fluorouracil; GTN, gestational trophoblastic neoplasia; HRT, hormone replacement therapy; IM, intramuscular; IT, intrathecal; IV, intravenous; MRI, magnetic resonance imaging; POF, premature ovarian failure, PSTT, placental site trophoblastic tumour, ETT, epithelioid trophoblastic tumours, PDL-1, programmed death-ligand-1; PET-CT, positron emission tomography, computed tomography; serum  $\beta$ -hCG, serum beta-human chorionic gonadotropin; U/S, ultrasound

## Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GYNE Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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## Conflict of Interest Statements

**Dr. Helen Steed** has nothing to disclose

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**Dr. Tiffany Wells** has nothing to disclose

**Ritu Sharma**

**\* Guideline working group lead**