15 years of progress in gestational trophoblastic disease: Scoring, standardization and salvage

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Introduction

- Gestational trophoblastic disease (GTD)
  - Neoplastic disorders that arise from placental trophoblastic tissue following abnormal fertilization
  - Pre-malignant disease: partial and complete hydatidiform moles
  - Malignant gestational trophoblastic neoplasia (GTN)
    - Choriocarcinoma
    - Placental site trophoblastic tumor
    - Epithelioid trophoblastic tumor
    - Invasive moles

GTD

Benign GTD
- Partial vs. Complete

Malignant GTN
- Invasive Mole
- Choriocarcinoma
- PSTT
- ITT
- Epithelioid TT

Metastatic
Non-metastatic
Epidemiology

- **Prevalence**
  - Varies with geography, maternal age, previous GTD history, socioeconomic factors, dietary factors and possibly blood grouping.
  - Incidence of molar pregnancy may be decreasing
    - Especially Asian population
    - Improved nutrition
  - North America, South America and Europe
    - 1 in 500-1000 pregnancies
  - East Asia
    - 1 in 120 pregnancies

- **Gestational trophoblastic disease**
  - 80% hydatidiform moles
  - 15% invasive moles
  - 5% choriocarcinomas
  - 0.2-2% placental site trophoblastic tumor
    - Highest mortality rate
Diagnosis

- **Signs and symptoms**
  - Serum B-hCG level that does not return to undetectable levels
  - Hyperthyroidism, ovarian theca lutein cysts, hyperemesis or preeclampsia
  - Abnormal uterine bleeding or amenorrhea
  - Pelvic pain or pressure due to enlarge uterus or ovarian cysts
- **Metastases**
  - Pulmonary (80%)- dyspnea, chest pain, cough or hemoptysis
  - Vaginal (30%)- vaginal bleeding or purulent discharge
  - CNS (10%)- headache, neuropathy, dizziness, nausea, slurred speech, visual disturbances or hemiparesis secondary to increased intracranial pressure or hemorrhage
  - Hepatic (10%)- Jaundice, epigastric or back pain

- **Ultrasound**
  - “Snowstorm” appearance due to hydropic villi
  - First trimester: mixed echogenic vascular mass
Diagnosis

- Histologic evaluation of tissue obtained early in gestation
- Cytogenetic techniques
  - Chromosomal banding and restriction fragment length polymorphism (RFLP) analysis of DNA
    - Negative immunostaining for P57KIP2 is diagnostic of complete mole; all other gestations demonstrate nuclear staining of cytotrophoblast and villous mesenchyme.
  - Ploidy analysis
    - Differentiate partial (triploid) vs. complete (diploid) mole.
  - Selective molecular genotyping
    - Comparison of alleles by evaluating molecular characteristics (microsatellite instability)
Diagnosis

- Placental site trophoblastic tumor
  - Develop after non-molar and molar gestations
  - Secretes placental lactogen and small amounts of B-hCG
  - Usually diploid
  - Intermediate trophoblastic cells: oval nuclei with abundant eosinophilic cytoplasm
  - No chorionic villi
  - Syncytiotrophoblastic and cytotrophoblastic populations are absent
  - Less vascular invasion, necrosis and hemorrhage (than choriocarcinoma)
Diagnosis

- **Laboratory testing**
  - Phantom hCG syndrome: persistent mild elevation of hCG when no true hCG or trophoblastic tissue is present
    - Heterophilic antibody can cause false positive
    - Urine pregnancy test can exclude false positive result
      - Large heterophile antibodies are filtered out at the level of the glomerulus
    - Serum test + urine test positive = real hCG is present.
Cell biology

- p53 dependent apoptosis may drive trophoblastic proliferation
- Human placental growth hormone has been detected in all variants of GTD
  - Biomarker for diagnosis
Staging and prognosis

- Federation of Gynecology and Obstetrics (FIGO) and WHO score
  - Score 0-6: likely to respond to single-agent therapy
    - Treated with dactinomycin or methotrexate
  - Score >6: higher resistance to single-agent therapy; best treated with combination therapy
- Trophoblastic Disease Centers
  - Superior outcomes with higher survival rates

<table>
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<th>Table 1: FIGO 2000 staging system for gestational trophoblastic disease.</th>
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<td><strong>Stage</strong></td>
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<td>I</td>
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<tr>
<td>III</td>
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<tr>
<td>IV</td>
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<tr>
<td><strong>WHO score</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Antecedent pregnancy</td>
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<tr>
<td>Interval months from index pregnancy</td>
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<tr>
<td>Pretreatment serum hCG (IU/mL)</td>
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<tr>
<td>Largest tumor size (including uterus)</td>
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<tr>
<td>Site of metastases</td>
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<tr>
<td>Number of metastases</td>
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<td>Previous failed chemotherapy</td>
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Treatment and surveillance

- **Hydatidiform mole**
  - Initial treatment is surgical- suction dilation and curettage
    - Use of ultrasound guidance to remove all molar tissue and avoid uterine perforation.
    - >16 weeks size, risk of pulmonary embolization
  - **Weekly serum B-hCG obtained until 3 consecutive values are normal**
    - Usually occurs within 8 weeks. 20% have elevated levels 14-16 weeks post-evacuation.
    - Complete moles- monitored with monthly serum B-hCG levels for 6 months.
    - Partial moles- serial hCG until two normal values obtained.
      - Risk of GTN 0.5-1%
      - Risk once hCG levels normalize 1:3000
Treatment and surveillance

- Subsequent pregnancy
  - Previous guidelines: avoid pregnancy for 12 months after normalization of hCG
    - No increased risk of molar pregnancy between 6-12 months
  - Caution used with IUDs due to potential for uterine perforation
  - OCPs for contraception and suppression of endogenous LH
    - LH may interfere with detection of low levels of B-hCG
Treatment and surveillance

- **Malignant GTN**
  - **Risk factors**
    - Pre-evacuation hCG >100,000 IU/L
    - Excessive uterine growth
    - Theca lutein cysts >6cm diameter
    - Age >40yrs
  - **Identification**
    - Rising/plateaued B-hCG level after normal result or for 2 weeks measured over three separate intervals
    - Evidence of metastatic disease
    - Tissue diagnosis of choriocarcinoma
    - Post-evacuation bleeding not due to retained tissue

- **Evaluation**
  - History, physical exam
  - Serum hCG
  - Imaging:
    - Pelvic US, chest x-ray/CT, MRI of brain
    - Non-molar pregnancy: add MRI pelvis, CT abdomen and +/- PET/CT
  - Score patient with WHO score and FIGO 2000 system
    - Low risk 0-6
    - High risk >6
Treatment and surveillance

- **Low risk (score 0-6)**
  - May consider repeat suction D&C
    - Follow weekly hCG titers until 3 negative then monthly for 6 months
  - When confined to uterus, 38% patients avoided need for chemotherapy
  - Hysterectomy: treatment of choice when future fertility is not desired
- **Low risk chemotherapy regimen**
  - Methotrexate: better side effect profile
    - No alopecia, less N/V, less myelosuppression
  - Dactinomycin: may have better efficacy with less frequent infusion schedule

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<tr>
<th>Treatment Regimen</th>
<th>Description</th>
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<tr>
<td><strong>Methotrexate 8 day regimen</strong></td>
<td>• 50-mg (or 1 mg/kg) total dose intramuscular days 1, 3, 5, 7 with folinic acid rescue</td>
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<td>• 15 mg given 24 or 30 h alter on days 2, 4, 6, 8; repeated every 14 days.</td>
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<tr>
<td><strong>Pulsed dactinomycin</strong></td>
<td>• Dactinomycin 1.25 mg/m² intravenously every 14 days</td>
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<tr>
<td><strong>Dactinomycin 5 day regimen</strong></td>
<td>• Dactinomycin 0.5 mg intravenously every 14 days</td>
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<tr>
<td><strong>Low-dose methotrexate</strong></td>
<td>• 30-50 mg/m² intramuscular weekly</td>
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<td><strong>Methotrexate 5 day regimen</strong></td>
<td>• Methotrexate 0.4 mg/kg (maximum 25 mg/day) intravenously days 1-5 repeated every 14 days</td>
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<tr>
<td></td>
<td>• High dose infusion Methotrexate: 100 mg/m³ intravenous push followed by 200 mg/m³ over 12 h + folinic acid</td>
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Treatment and surveillance

- **Low risk (score 0-6)**
  - Weekly IM Methotrexate
    - Score 0-1: 70% successful
    - Score 2-4: 40% successful
    - Score 5-6: 12% successful
  - Biweekly pulsed Dactinomycin
    - Score 5-6: 44% successful
  - Once serum hCG has normalized, 3 additional treatments of chemotherapy administered to minimize recurrence

- **Resistance**
  - Persistent elevation of serum hCG levels over 3 consecutive samples of an increase over 2 consecutive samples lasting >2 weeks
  - Low levels- must rule out phantom hCG syndrome
  - Failed methotrexate
    - B-hCG <300 IU/L may be considered for single therapy dactinomycin
Treatment and surveillance

- **High risk (score >6)**
  - **EMA**: Etoposide, Methotrexate, Dactinomycin
    - **Day 1**
      - Etoposide 100 mg/m² intravenously over 30 min
      - Methotrexate 100 mg/m² intravenous bolus
      - Methotrexate 200 mg/m² intravenous as 12 h continuous infusion
      - Dactinomycin 0.5 mg intravenous bolus
    - **Day 2**
      - Etoposide 100 mg/m² intravenously over 30 min
      - Folinic acid 15 mg intravenously or intramuscular or orally every 6 h for 4 doses, beginning 24 h after the start of methotrexate
      - Dactinomycin 0.5 mg intravenous bolus
  - **CO**: Cyclophosphamide and Vincristin
    - **Day 8**
      - Cyclophosphamide 600 mg/m² intravenously over 30 min
      - Vincristine 1 mg/m² (maximum dose 2 mg) intravenous bolus

- Regimen to be repeated every 14 days as toxicity permits.
- Once hCG normalizes, 3 additional consolidation cycles (6 weeks) are administered
Treatment and surveillance

- **Very high risk (score >12)**
  - Significant risk for pulmonary, intraperitoneal or intracranial hemorrhage
  - May benefit from low dose induction chemotherapy prior to EMA- CO
    - Etoposide 100mg/m2 and Cisplatin 20mg/m2

- **CNS metastases**
  - Low dose induction chemotherapy
  - Neurosurgical intervention

- **Ultra-high risk (score >13, liver metastases)**
  - EMA-EP may be superior EMA-CO
  - 20-25% of patient with high-risk metastatic disease have persistent or recurrent disease
Treatment and surveillance

- Placental-site trophoblastic tumor
  - FIGO scoring not used to determine treatment
  - Non-metastatic disease
    - Hysterectomy with ovarian conservation preferred treatment with sampling and removal of suspicious lymph nodes
  - Metastatic disease
    - EMA-EP with surgical resection of residual disease and hysterectomy
    - Unresectable recurrent disease: radiation or combination chemotherapy

- Worst prognostic factor
  - Time from previous pregnancy
    - 98% long-term survival of patient presenting within 4 years
    - 100% mortality for patients presenting >4 years
Fertility preservation

- Risk of future molar pregnancy: ~1% for women successfully treated for molar pregnancy
  - Most risk with complete moles
- Pregnancy acceptable after 6 month surveillance with disease-free status
- EMA-CO induces menopause ~3 years earlier
Conclusion

- Significant improvements in treatment and understanding of GTN have occurred in the last 15 years.
- GTD and GTN are almost always curable.
- Refractory patients have more options for salvage therapy.
Review Article

15 years of progress in gestational trophoblastic disease: Scoring, standardization, and salvage

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HIGHLIGHTS
• Gestational trophoblastic neoplasia represents a spectrum of diseases with an excellent prognosis.
• Outcomes depend on appropriate scoring and treatment.
• Fertility preservation is an option for most women with gestational trophoblastic neoplasia.

ABSTRACT
Significant improvements in treatment and the understanding of gestational trophoblastic neoplasia have occurred in the last 15 years. These diseases are almost always curable, and refractory patients have more options for salvage therapy. Recent improvements in the understanding of epidemiology, diagnosis, and cell biology have resulted in changes in staging, advances in treatment options, and opportunities for fertility preservation.

Keywords:
Gestational trophoblastic disease
Choriocarcinoma
Placental site trophoblastic tumor
Hydatidiform mole

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1. Introduction

Gestational trophoblastic disease (GTD) comprises a wide spectrum of neoplastic disorders that arise from placental trophoblastic tissue after abnormal fertilization (Fig. 1). These disorders include pre-malignant disease (complete and partial hydatidiform moles) and malignant gestational trophoblastic neoplasia (GTN), which includes choriocarcinoma, placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT), and invasive moles [1]. GTN may be nonmetastatic or metastatic [2], with the cure rate approaching 100% and fertility preservation usually possible with individualized management based on careful scoring and multidisciplinary team planning [1,3,4].

As is often the case with rare tumors, research and advances are sporadic in nature and are rarely publicized in a coordinated manner. Nevertheless, significant achievements in the treatment and understanding of GTD have occurred in the last 15 years. These changes and improvements with regard to epidemiology, diagnosis, cell biology, staging, surveillance, treatment, and fertility preservation are detailed here based on all relevant publications during this time period, providing the clinician with an updated understanding and optimal treatment of the patient with GTD.

2. Epidemiology

The prevalence of GTD varies depending on geography, maternal age, previous GTD history, socioeconomic factors, dietary factors, and possibly blood grouping. However, recent studies suggest that the incidence of molar pregnancy and choriocarcinoma are decreasing, especially in the Asian population, and that improved nutrition may be responsible for a decline in incidence and improvement in outcomes in some populations.

In North America, South America, and in Europe, GTD develops in approximately 1 in 500–1000 pregnancies [1,5]. The rate in East Asia is 5- to 15-fold higher, approaching 1 in 120 pregnancies [1]. Native American women in New Mexico had a higher incidence than other predominant ethnic groups there [6]. While these data suggest the importance of ethnicity, the causative factors may relate more directly to diet, diagnosis, and improved capture of population statistics. For example, in Kuala Lumpur, Malaysian, Indian, and Chinese ethnic groups all have similar incidence of GTD. Some recent analyses suggest that the incidence in Southeast Asia now approaches that in Europe [1,2,5]. Further supporting this claim is the observation that women of lower socioeconomic status in East Asia, the Middle East, the United States, and Brazil all have up to a 10-fold greater rate of molar pregnancy than their more affluent counterparts [2,7]. This relationship between GTD incidence and geographic region, culture, and socioeconomic status suggests that diet and nutrition may contribute to the etiology.

The most current evaluations confirm that the majority (80%) of GTDs are hydatidiform moles, 15% are invasive moles, and 5% are choriocarcinomas. The highest mortality rate is due to PSTT, which occurs in 0.2–2% of all GTD [8–10]. The precise rate of choriocarcinoma may be underreported, as the risk of hemorrhage with biopsy usually precludes tissue diagnosis [1,2].

3. Diagnosis

While a constellation of symptoms and signs has historically been associated with molar pregnancy, such events are becoming less common due to routine ultrasonography in early pregnancy and the resulting early diagnosis of molar pregnancy [11]. Tissue is often obtained early in gestation, and the diagnosis of molar pregnancies based on histology alone can be problematic [12]. Cytogenetic techniques, such as chromosomal banding and restriction fragment length polymorphism (RFLP) analysis of DNA, have allowed unique chromosomal patterns of complete and partial molar pregnancies to be identified and differentiated [13–15]. Negative immunostaining for P57KIP2, an imprinted gene expressed by the maternal allele, is diagnostic of a complete mole, as the placenta of all other gestations demonstrate nuclear staining of cytotrophoblast and villous mesenchyme [16]. Ploidy analysis can help differentiate partial (triploid) from complete (diploid) mole, but cannot distinguish between this and other etiologies of triploidy. Ploidy analysis is particularly useful with a missed abortion that has developed hydropic villi suggestive but not diagnostic of a partial mole. Selective molecular genotyping enables the comparison of alleles by evaluating molecular characteristics such as microsatellite instability. This allows for definitive diagnosis when histologic review is equivocal, but the cost of such testing may prohibit widespread adoption of this technique [17,18].

The detection of placental site trophoblastic tumor has improved. These tumors are rare and most often develop after non-molar gestations but can occur after evacuation of a complete or partial hydatidiform mole [8]. The intermediate trophoblastic cells have oval nuclei with abundant eosinophilic cytoplasm, and no chorionic villi are seen. Syncytiotrophoblastic and cytotrophoblastic populations are absent, and less vascular invasion, necrosis, and hemorrhage are seen than in choriocarcinoma (Supplementary material) [15]. Lymphatic metastasis is a little less rare than in choriocarcinoma, occurring in about 5% of PSTT cases. PSTT secretes placental lactogen and small amounts of β-hCG and is usually diploid [19,20]. Presenting symptoms of PSTT are most commonly irregular vaginal bleeding, amenorrhea and a pelvic mass [15].

Familial recurrent hydatidiform mole syndrome (FRHM) is a rare disorder that may lead to recurrent molar pregnancies. This is an autosomal recessive disorder with mutations in NLRP7 (70% of cases) or KHDC3L (5% of cases) resulting in diploid complete moles of biparental origin, as opposed to exclusively paternal origin. Live birth in these patients is rare, but egg donation from unaffected women may result in successful live birth [14].

Ultrasound imaging has been utilized for decades in the diagnosis of GTD. However, the classic “snowstorm” appearance due to hydropic villi is less commonly appreciated in current practice since the diagnosis of GTD is typically made early in the first trimester. The adoption of routine in the first trimester of pregnancy has allowed the diagnosis of GTD...
prior to the development of significant hydropic change when only a mixed echogenic vascular mass is present [1,12].

3.1. Laboratory testing

The sensitivity of laboratory testing has increased substantially in the last 15 years, and home pregnancy test kits can detect low levels of intact hCG. However, in GTD, hCG can exist as a free beta subunit, nicked free beta subunit, c-terminal peptide, beta-core, or hyperglycosylated form [21]. In order to accurately detect these forms, commercial assays which detect all of these forms equally well should be used for hCG monitoring in GTD [1,2]. Even so, some commercial assays may be unreliable for detecting hCG isoforms, occasionally leading to false negative readings or false positive results from cross reaction with heterophile antibodies (Fig. 2) [1,2]. Phantom hCG syndrome (phantom choriocarcinoma syndrome, pseudohypergonadotropinemia) refers to persistent mild elevation of hCG when no true hCG or trophoblastic tissue is present. It is important to recognize this scenario to avoid unnecessary treatment after primary evacuation of a molar pregnancy or after successful chemotherapy for GTN. Heterophilic antibodies can cause false-positive results by interfering with the assay, in which a mouse monoclonal immunoglobulin (IgG) binds to hCG and a second polyclonal antibody labeled with an enzyme or chemiluminescent agent, marks the first antibody. Heterophilic antibodies usually bind the assay of IgG at sites common to humans and other species, link the capture and tracer antibodies, and thereby mimic hCG immunoreactivity; that is, they take the place of the hCG molecule in linking the two antibodies, thereby causing a false positive. Since large heterophile antibodies are filtered out at the level of the glomerulus, the urine hCG test is negative in the setting of heterophile antibodies. Therefore, while urine pregnancy tests are not sufficient for making the diagnosis of GTD, they may be used to exclude a false positive result (serum positive, urine negative) by testing the urine sample in the laboratory with the same modality as serum testing [1]. If both the urine test and the serum test results are positive, then real hCG is present and occult malignant GTD must be excluded [22]. The differential diagnosis of genuinely elevated hCG includes all forms of GTD, germ cell tumours, any cancer that has undergone trophoblastic differentiation including epithelial cancers and very rarely familial elevated hCG. The latter is functionless and does not suppress ovulation.

4. Cell biology

Delineation of the activities of proto-oncogenes, tumor suppressor genes, cytokines, and growth factors is improving the understanding of GTN and tumor progression [13,17,20]. It appears that p53 dependent apoptosis may drive trophoblastic proliferation [13]. Human placental growth hormone has recently been detected in all variants of GTD and may serve as a novel biomarker for diagnosis [20].

5. Staging and prognosis

Staging for GTD defines prognostic groups to direct optimal therapy yielding the highest possible cure rate by identifying patients likely to be resistant to single-agent methotrexate or dactinomycin [2]. Patients are classified into different prognostic groups on the basis of histologic subtype, extent of disease, hCG titer, duration of disease, nature of the antecedent pregnancy, and extent of prior treatment and scored accordingly. The staging system of the International Federation of Gynecology and Obstetrics (FIGO 2000), developed from the World Health Organization (WHO) scoring system, is the most commonly used system (Table 1) [23,24]. Patients with a score of 0–6 are likely to respond to single-agent therapy and should be treated with a low risk regimen of dactinomycin or methotrexate. A score >6 implies a higher risk of resistance to single-agent chemotherapy, and these patients are best treated with combination chemotherapy [2,24,25].

The FIGO 2000 system is not universally predictive of individual patient outcome. While patients with a score of 0–4 will nearly all be cured with single agent chemotherapy, over 50% of patients who score 5–6 will fail single agent treatment and require combination chemotherapy. Since almost all failures can be cured by transitioning to combination chemotherapy, single agent therapy is still used initially for patients who score 5–6 in order to spare patients who respond the more toxic effects of combination chemotherapy [4].

Factors other than the WHO score have been identified that may predict drug resistance. Pulsatility index, measured with Doppler

![Fig. 2. A. True positive hCG assay. Normally, both the capture antibody and the label antibody binds the hCG molecule (the analyte), allowing the label antibody to signal the presence of the hCG. B. False positive hCG assay. The heterophile antibody links the capture antibody and label antibody in the absence of hCG, allowing the assay to read positive without the presence of analyte.](image-url)
ultrasonography, measures uterine vascularity and predicts methotrexate resistant disease [4]. Algorithms which utilize hCG regression nomograms and kinetics may predict early onset of resistant disease during treatment with a single agent, but this has not yet been widely adopted [26,27]. Patients infected with human immunodeficiency virus who have CD4 counts <200 cells/μL do not tolerate chemotherapy and have poor outcomes with higher mortality [28]. In practice, with modern retroviral therapy, this is no longer a real clinical issue for the majority of patients.

It should also be noted that outcomes tend to be superior with a higher survival rate for patients treated at a recognized Trophoblastic Disease Center. Specifically, patients treated primarily at a referral center have a lower mortality than patients referred after failure of primary treatment. This has prompted the recommendation for early referral to a trophoblast center when possible [29,30].

6. Treatment and surveillance

The simplified algorithm for treatment of GTD is presented in Fig. 3. The initial treatment of hydatidiform mole is surgical, but the desire to preserve reproductive capacity guides the optimal management in this mostly curable disease [31]. Most patients wish to maintain fertility and are treated with suction dilation and curettage, often with ultrasound guidance in order to remove all molar tissue and avoid uterine perforation, a procedure with <1% chance of mortality [1,10]. If the uterus is >16 weeks' size, there is a risk of pulmonary embolization of molar tissue, and care in a referral center is warranted [2]. Transient pulmonary insufficiency associated with pulmonary embolization or a systemic inflammatory response syndrome (SIRS) generally lasts for one to two hours and responds to appropriate supportive measures. Labor induction and hysterectomy are not recommended due to the increased incidence of post molar GTN requiring chemotherapy [32].

After primary surgical treatment, weekly serum β-hCG assays should be obtained until 3 consecutive weekly assays are normal. This usually occurs within 8 weeks, but 20% of patients have elevated levels for 14 to 16 weeks' post-evacuation. Subsequently, patients with complete moles should be monitored with monthly serum β-hCG levels for 6 months. The risk of subsequent GTN is between 0.5 and 1% in patients with partial moles, and once the hCG normalizes the risk of developing GTN falls to 1:3000. Consequently, most centers now follow up women with partial hydatidiform moles with serial hCG samples until two normal values have been obtained [2,4,30]. While earlier guidelines suggested the use of contraception to avoid pregnancy for 12 months after normalization of hCG, recent data have demonstrated no increased risk of recurrent molar pregnancy between 6 and 12 months. Therefore, most experts recommend only 6 months of contraception [2]. Intravaginal devices are not used because of the potential for uterine perforation. Oral contraceptives may be useful for contraception and to suppress endogenous LH during the period of surveillance, since luteinizing hormone (LH) may interfere with the detection of low levels of β-hCG. While historical reports linked post-evacuation oral contraceptive use to GTN, modern oral contraceptives appear to be safe with no increased risk of GTN [2,4]. Administration of prophylactic adjuvant chemotherapy after molar evacuation is controversial and usually not advised, as the risk outweighs the benefit, except in rare circumstances where follow-up compliance is unlikely [2,33].

Traditionally, GTN was separated into metastatic and non-metastatic subgroups. However, prognosis and treatment is probably best decided on the WHO prognostic score, regardless of the presence or absence of metastatic disease, and appropriate treatment can be defined by the

![Algorithm for the management of gestational trophoblastic disease. Following treatment of disease with chemotherapy, follow-up guidelines regarding frequency and duration of hCG testing vary among institutions. A reasonable guideline would be monthly hCG titers for 12 months, to be individualized according to the patient's risk profile [2].](Image)
FIGO 2000 staging (Table 1) [10]. Using these criteria, 81% of patients have low risk disease (WHO score ≤ 6), 18% have high risk disease (WHO score > 6), and 1% have PSTT. Patients with malignant GTN are identified by a rising or plateaued β-hCG level after a normal result or for 2 weeks measured over three separate intervals, evidence of metastatic disease, tissue diagnosis of choriocarcinoma, or postevacuation bleeding not due to retained tissues [2,25,30]. Of note, an elevated but falling hCG 6 months after molar evacuation does not mandate chemotherapy, as most of these patients will eventually normalize their hCG levels [34]. In the United Kingdom, chemotherapy is administered if the serum hCG level remains >20,000 IU/L more than four weeks after evacuation because the risk of uterine perforation and hemorrhage is substantial [1,2].

Risk factors for malignant GTN include a pre-evacuation hCG level over 100,000 IU/L, excessive uterine growth, thca lutein cysts over 6 cm in diameter, and age over 40 years [34,35]. Additionally, recent studies have indicated that the antecedent pregnancy was complete mole in 78% of patients, partial mole in 9% of patients, and choriocarcinoma in 8% of patients [10].

The treatment of malignant GTN depends on the cell type, stage, level of serum β-hCG, treatment of the specific sites of metastases, and extent of prior treatment. Each patient must be stratified for risk prior to treatment, and the FIGO 2000 system incorporating the modified WHO scoring system is the most commonly used tool [23–25]; A score of 0–6 indicates a low risk of developing resistance to single agent chemotherapy, while a score over 6 indicates a high risk of resistance to single agent chemotherapy and therefore mandates combination chemotherapy as initial therapy.

Evaluation should include history, physical examination, serum hCG, and directed imaging (typically, pelvic ultrasound and chest X-ray). A chest CT may be useful in the rare patient with recurrent disease in whom a lesion posterior to the heart measuring 1 cm or greater would be expected if the tumor is limited to the uterus or the patients no longer desire fertility and should receive chemotherapy as primary treatment for low-risk disease. Each patient must be stratified for risk prior to initiating chemotherapy. Acceptable modern chemotherapy regimens expected to result in cure are listed in Table 2. Either methotrexate, with or without folinic acid rescue, or dactinomycin are acceptable with the provided schedules. Several studies have evaluated these regimens, but the differences in inclusion criteria among trials make determining the superior regimen problematic. The only published randomized trial compared a low dose of methotrexate (30 mg/m2) with dactinomycin and found dactinomycin to be superior with a complete response rate of 53.3% vs. 69.7%, respectively [36]. Despite this trial, debate continues, as methotrexate may have a better side effect profile (no alopecia, less nausea/vomiting, less myelosuppression). Conversely, dactinomycin may have better efficacy with a less frequent infusion schedule [2]. The likelihood of success of the weekly regimen is dependent on the WHO score. The weekly intramuscular methotrexate regimen is successful in 70% of patients with a WHO score of 0–1 [36]. However, the success rate falls to 40% for a WHO score of 2–4 and 12% for a WHO score of 5–6 [37]. This has led some to suggest that weekly methotrexate should never be administered, and a regimen other than methotrexate may be preferred for a patient with a WHO score ≤2.

During treatment, serum hCG levels should be monitored at least every 1–2 weeks to determine response [2]. Resistance to first line therapy is indicated by a persistent elevation over 3 consecutive samples or an increase over 2 consecutive samples lasting >2 weeks [2]. If the levels are low, phantom hCG syndrome must be excluded. Hysterectomy is offered if the tumor is limited to the uterus or the patients no longer desire fertility. A patient with low risk GTN who develops resistance to primary chemotherapy does not require rescoring, as the score is unlikely to change, unless levels have remained persistently elevated over a long period of time and PSTT or ETT is suspected [4]. If she wishes to retain fertility, alternate chemotherapy is recommended. Patients who fail methotrexate and have low hCG levels may achieve cure with dactinomycin. The initial conservative estimate suggests that only patients with hCG <100 IU/L be considered for single agent dactinomycin after failing methotrexate, but the updated data support using a cutoff of <300 IU/L [4,39]. Patients who fail single-agent treatment with higher levels of hCG should be treated with combination EMA-CO chemotherapy [4]. Once the serum hCG has normalized, 3 additional treatments of chemotherapy past normal are administered to minimize the chance of recurrence [2]. A comparison of 2 versus 3 cycles of methotrexate past normalization of the hCG (defined in this study as <5 IU/L) showed a doubling in recurrence rates in patients receiving only 2 consolidation courses, so it is important to administer 3 cycles past titer normalization (titer <5) [40]. When normal is defined as <1, as is reported in sandwich immunoassays, many trophoblastic disease centers administer two cycles of chemotherapy after the titer reaches <1.

### Table 2

| Treatment schedules for low-risk gestational trophoblastic neoplasia. |
|-----------------------------|-----------------------------|
| **Methotrexate 8 day regimen** |
| 50-mg (or 1 mg/kg) total dose intramuscular days 1, 3, 5, 7 with folinic acid rescue 15 mg given 24 or 30 h alter on days 2, 4, 6, 8; repeated every 14 days. |
| **Dactinomycin 1.25 mg/m2 intravenously every 14 days** |
| **Dactinomycin 5 day regimen** |
| Dactinomycin 0.5 mg intravenously every 14 days |
| **Low-dose methotrexate** |
| 30–50 mg/m2 intramuscular weeklyb |
| **Methotrexate 5 day regimen** |
| Methotrexate 0.4 mg/kg (maximum 25 mg/day) intravenously days 1–5 repeated every 14 days |
| High dose infusion Methotrexate: 100 mg/m2 intravenous push followed by 200 mg/m2 over 12 h + folinic acid |

**a Patients** who meet criteria for treatment (Table 1) and score 0–6 on FIGO 2000 scoring system (Table 2); patients with PSTT and ETT are not scored or treated for low-risk GTN.

**b Methotrexate** dosed at 30 mg/m2 remains in the literature but cannot currently be supported, and a higher dose should be used if methotrexate is given weekly. A preferred regimen.

**c Preferred regimens.**
The dose of methotrexate is escalated to 1 mg/m².

For 1

Instead initiate low dose etoposide and cisplatin repeated weekly.

Centers have successfully avoided the use of whole brain radiotherapy.

Given in EP.

Acute and chronic toxicity. Some evidence suggests that TE/TP is equally effective.

Placental-site trophoblastic tumor (PSTT) is a type of GTN that also requires special consideration. Treatment has progressed in the last 15 years. These tumors present with lung metastases in 10–29% of cases, and an additional 10% of patients develop metastases during follow-up [8]. FIGO scoring is not used to determine the treatment of PSTT. Salvage therapy for recurrent gestational trophoblastic disease plays a critical role in the salvage of these patients.

PET-CT may be useful to detect patients with isolated (1–3) metastatic sites who may benefit from surgical resection [48]. Surgical resection of resistant disease plays a critical role in the salvage of these patients. In one series, 39% of patients underwent resection of resistant foci of disease with a long term survival of 82% for the surgical cohort [49]. Approximately 90% of patients with primary drug-resistant and relapsed GTN can be cured with hysterectomy to remove the disease, with or without adnexectomy and lymphadenectomy [50].

Intrathecal methotrexate 12.5 mg may be given with the CO component of EMA-CO but not at the time of whole brain radiotherapy (20–30 Gy in two daily fractions) because of the risk of multifocal leukoencephalopathy [45].

Placental-site trophoblastic tumors (PSST) are a type of GTN that also requires special consideration. Treatment has progressed in the last 15 years. These tumors present with lung metastases in 10–29% of cases, and an additional 10% of patients develop metastases during follow-up [8]. FIGO scoring is not used to determine the treatment of PSST.
after the previous pregnancy, these patients should be considered for clinical trials or high dose chemotherapy, even when the disease is localized upon presentation [8]. Patients with limited disease who desire fertility may be considered for fetal ureteric resection with or without chemotherapy, but this is experimental and outcomes data are limited [1]. Of note, serum β-hCG level is not uniformly helpful in diagnosis, treatment, or follow-up [8]. Overall mortality from PSTT approximates 16–21% [10]. Another study reported a median overall survival of 86 months; 88% of patients with early stage disease and 11% of patients with advanced stage disease were disease-free 28 months after diagnosis [15].

Epithelioid trophoblastic tumor is distinct, and generally more aggressive than PSTT, but is treated similarly. The ISSTD database is collecting information on both of these histologic subtypes [2].

7. Fertility preservation

The risk of future molar pregnancy is about 1% for women successfully treated for molar pregnancy [35]. Most of this risk resides in women with complete rather than partial moles [51]. In general, after 6-months without recurrence, patients may conceive without increased risk, though close monitoring during future pregnancies is recommended. Once a 6-month surveillance establishes disease-free status, conception is acceptable, although these women are always at higher risk for future molar disease and will require close observation during future pregnancies. Contraception during this early window relates to the importance of hCG surveillance and not the risk of recurrence, as GTN-related outcomes, miscarriage, and the incidence of birth defects appear to be unrelated to time since treatment [35]. Importantly, 83% of patients are able to conceive despite prior chemotherapy, and most patients are able to carry a pregnancy to term successfully with a live birth [35]. Although a single study has noted a slight increase in stillbirths in pregnancies post-GTN chemotherapy, all other authors have found no increase in adverse events (e.g., first- or second-trimester abortions, stillbirths, prematurity, need for cesarean section, or fetal anomalies) [35]. Fertility treatment may be considered for patients with difficulty conceiving.

EMACO induces menopause approximately 3 years earlier than otherwise anticipated, though this is of limited clinical significance [4]. The risk of second primary cancers (e.g., acute myelogenous leukemia and thyroid cancer) has been inconsistent [1]. The most recent study with 30,000 patient years of follow-up shows no overall increased risk of malignancy following EMA-CO kept to <6 months’ total duration of therapy [52]. Issues of survivorship appear to be greater for socially disadvantaged patients and surround sexual dysfunction and reproductive quality of life [53].

8. Conclusion

Significant improvements in treatment and the understanding of GTN have occurred in the last 15 years. GTD and GTN are almost always curable, and refractory patients have more options for salvage therapy. The next 15 years should see refinement of treatment for advanced stage patients and continued improvement in fertility preservation.

Disclosures

None of the authors report any relevant disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jygyno.2016.08.330.

References


