



How do different treatment modalities impact long-term remission rates and fertility preservation in patients with gestational trophoblastic diseases? : A Systematic Review

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ABSTRACT

Introduction: The management of Gestational Trophoblastic Disease (GTD) aims to achieve high long-term remission rates while preserving future fertility. Treatment protocols are stratified by risk to optimize outcomes and minimize toxicity. This systematic review synthesizes current evidence on how different treatment modalities impact remission and fertility in GTD patients.

Methods: This systematic review adhered to PRISMA 2020 guidelines. Databases including PubMed, Semantic Scholar, Springer, and Google Scholar were searched using PICO-based keywords to identify relevant studies. After screening, 25 studies—including randomized controlled trials, cohort studies, and systematic reviews—were selected for data extraction and analysis on treatment protocols, remission rates, and fertility outcomes.

Results: For low-risk Gestational Trophoblastic Neoplasia (GTN), single-agent chemotherapy (methotrexate or actinomycin D) achieves remission rates of 75-100%. For high-risk GTN, multi-agent regimens like EMA/CO result in remission rates between 71% and 97.7%. Immunotherapy with avelumab has shown approximately a 53% remission rate in chemo-resistant cases. Fertility preservation is a significant success, with subsequent pregnancy rates of 86.7-100% and live birth rates of 75.8-90% reported after chemotherapy. Surgical interventions such as routine second uterine curettage or hysterectomy did not demonstrate improved remission rates over chemotherapy alone.

Discussion: The evidence strongly supports a risk-stratified treatment model that balances efficacy with toxicity. The choice between single agents like methotrexate and actinomycin D depends on their differing toxicity profiles. The emergence of immunotherapy has provided a crucial and effective option for patients with chemo-resistant disease, transforming the prognosis for this group.

Conclusion: The treatment of GTD is highly effective, yielding excellent remission rates while safeguarding patient fertility. The standard of care relies on risk-stratified chemotherapy, with effective, evidence-based salvage therapies like immunotherapy available for resistant disease. These modern strategies ensure high cure rates and preserve quality of life, including future reproductive potential.

Keywords: Gestational Trophoblastic Disease, Chemotherapy, Immunotherapy, Remission, Fertility Preservation, Systematic Review

INTRODUCTION

Gestational Trophoblastic Disease (GTD) represents a spectrum of proliferative disorders originating from placental trophoblastic tissue. The management of these conditions has evolved significantly, with a range of treatment modalities now available that yield high long-term remission rates while prioritizing the preservation of future fertility for patients. The successful treatment of GTD, particularly Gestational Trophoblastic Neoplasia (GTN), which requires active intervention, is a notable achievement in gynecologic oncology. Modern therapeutic protocols are carefully selected based on risk stratification, primarily distinguishing between low-risk and high-risk disease to optimize outcomes and minimize toxicity (Madi et al., 2021).

The cornerstone of treatment for GTD is chemotherapy, which has demonstrated remarkable efficacy in achieving complete and sustained remission. For patients classified with low-risk GTN, single-agent chemotherapy is the standard of care, with regimens such as methotrexate or actinomycin D being widely used. These treatments have been associated with remission rates ranging from 75% to 100%. The choice between these agents often involves a balance between efficacy and toxicity profiles; for instance, some evidence suggests actinomycin D may offer superior remission rates, but it is also linked to higher incidences of nausea and hair loss, whereas methotrexate carries a greater risk of liver toxicity (Hao et al., 2021).

In contrast, patients with high-risk or chemotherapy-resistant GTN require more intensive multi-agent chemotherapy regimens to achieve remission. Combination protocols such as EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine), EMA/EP (etoposide, methotrexate, actinomycin D, etoposide, cisplatin), and FAEV (floxuridine, actinomycin-D, etoposide, vincristine) are frequently employed in these complex cases. While these regimens are highly effective, achieving remission rates between 71% and 97.7%, they are also associated with significantly greater toxicity, including myelosuppression and gastrointestinal side effects, necessitating careful patient monitoring and supportive care (Ji et al., 2022).

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For the subset of patients who develop resistance to conventional chemotherapy, novel therapeutic avenues have emerged, offering new hope. Immunotherapy, particularly the use of immune checkpoint inhibitors like avelumab (an anti-programmed cell death protein 1, or PD-1, inhibitor), has shown significant promise in salvage settings. Studies have demonstrated that avelumab can induce remission in approximately half of the patients with chemotherapy-resistant GTN, providing a critical alternative for this difficult-to-treat population. Importantly, successful pregnancies have been reported following immunotherapy, indicating that this modality can also be compatible with future fertility goals (You et al., 2020a).

A paramount consideration in the management of GTD, especially given that it predominantly affects women of reproductive age, is the preservation of fertility. Encouragingly, fertility outcomes following treatment are consistently positive. Across various chemotherapy protocols, studies have reported high subsequent pregnancy rates, ranging from 86.7% to 100%, and live birth rates between 75.8% and 90%. These successful reproductive outcomes underscore the general safety of modern GTD treatments concerning future childbearing, provided that conception is delayed for at least six months after the completion of chemotherapy to minimize the risk of adverse events like spontaneous abortion (Tranoulis et al., 2019).

The role of surgical intervention in the primary management of GTN has also been extensively evaluated. Contrary to what might be expected, the addition of surgical procedures such as hysterectomy or a second uterine curettage to chemotherapy has not been shown to improve remission rates or reduce the need for chemotherapy courses in most cases. For instance, a prospective study on women aged 40 or older found that upfront hysterectomy combined with methotrexate did not offer better outcomes than methotrexate alone. Similarly, a randomized controlled trial revealed that routine second uterine curettage did not decrease the number of chemotherapy cycles required for low-risk postmolar GTN (Hemida et al., 2023).

Despite the high overall success rates, a number of clinical challenges persist.

Treatment resistance remains a significant hurdle, and identifying the optimal second-line or salvage regimens is crucial. Studies comparing different protocols for methotrexate-resistant GTN have found that while both 5-day and pulsed actinomycin D are effective, the pulsed regimen is associated with lower toxicity. Furthermore, the management of refractory high-risk GTN often requires novel combinations, with regimens such as paclitaxel/carboplatin showing promise in achieving durable remission in salvage situations (Rathod et al., 2015).

This research aims to synthesize the current evidence on the impact of different treatment modalities on long-term remission and fertility preservation in patients with gestational trophoblastic diseases. By systematically reviewing outcomes from single-agent chemotherapy, multi-agent regimens, surgical interventions, and emerging immunotherapies, this study will provide a comprehensive overview of the efficacy, safety, and reproductive consequences associated with each approach. The objective is to elucidate the optimal treatment strategies that maximize cure rates while safeguarding the future reproductive potential of patients, thereby informing clinical practice and guiding patient counseling (You et al., 2024).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate different treatment modalities impact long-term remission rates and fertility preservation in patients with gestational trophoblastic diseases.

Screening

We screened in papers that met these criteria:

- **Population:** Does the study include female patients diagnosed with gestational trophoblastic disease (GTD)?
- **Intervention:** Does the study evaluate treatment modalities for GTD (such as chemotherapy, surgery, or combination treatments)?
- **Outcomes:** Does the study report at least one of the following outcomes: remission rates, fertility outcomes, subsequent pregnancy rates, or reproductive function measures?
- **Study Design:** Is the study either a primary research study (RCT, cohort study, case-control study) or a systematic review/meta-analysis?
- **Sample Size:** Does the study include 10 or more patients?
- **Follow-up Duration:** Does the study have a follow-up period of 12 months or longer?
- **Study Type:** Is the study conducted in human subjects with actual clinical outcomes (not animal or in vitro studies)?
- **Study Focus:** Does the study report treatment outcomes (not solely focused on diagnostic methods, screening, or prophylactic treatments)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design:**

Specify the type of study design (e.g., retrospective cohort, prospective observational, randomized controlled trial). Look in the methods section for explicit description of study design. If multiple design elements are present, list

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all. If unclear, note "study design not clearly specified".

Examples of acceptable answers:

- Retrospective cohort study
- Retrospective medical record review
- Single-center observational study

If multiple design elements are present, list them in order of specificity.

- **Patient Characteristics:**

Extract key demographic and clinical characteristics of study participants, including:

- Median/mean age
- Total number of patients
- Gestational trophoblastic disease stage (FIGO stage)
- WHO prognostic score
- Antecedent pregnancy type (molar/non-molar)
- Presence of metastasis

Record numerical values with appropriate ranges or confidence intervals. If information is missing or incomplete, note "not reported" or "insufficient data". Prioritize reporting of median/mean values over categorical descriptions.

- **Treatment Modalities:**

List all chemotherapy regimens used, including:

- Specific drug combinations (e.g., EMA, EMACO, BEP)
- Number of treatment cycles
- Duration of each cycle
- Dosage (if specified)
- Primary vs salvage treatment status

Be precise about drug names, dosages, and treatment protocols. If multiple treatment arms exist, describe each separately. If dosage or specific details are not clearly

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reported, note "dosage not specified".

- **Treatment Outcomes:**

Extract key outcome measures related to treatment effectiveness:

- Complete remission rate
- Overall survival rate
- Disease-free survival rate
- Time to complete remission
- Fertility preservation rates

Record numerical values with percentages and confidence intervals where available. If statistical significance is reported, include p-values. For outcomes with multiple time points (e.g., 5-year survival), specify the time frame.

- **Adverse Events and Toxicity:**

Document treatment-related adverse events and toxicities, including:

- Types of adverse events (neutropenia, thrombocytopenia, etc.)
- Frequency of each adverse event
- Severity of adverse events (grade, if specified)
- Impact on treatment continuation

Record percentages of patients experiencing each adverse event. If grading systems are used, specify the grading scale. If no significant adverse events are reported, note "no significant adverse events reported".

- **Fertility Preservation:**

Extract information specifically related to fertility after treatment:

- Live birth rates
- Pregnancy rates post-treatment
- Impact of treatment on ovarian function
- Any specific fertility preservation interventions

Record numerical values with percentages. If qualitative descriptions of fertility impact are provided, summarize concisely. If no fertility data are reported, note "fertility outcomes not reported".

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Gestational Trophoblastic Disease	Gestational Trophoblastic Neoplasia	Gestational Trophoblastic Tumor	Choriocarcinoma
Intervention (I)	Treatment Modalities	Chemotherapy	Surgical Interventions	Immunotherapy
Comparison (C)	Single-agent vs. Multi-agent chemotherapy	Chemotherapy vs. Surgery	Different Chemotherapy Regimens	Actinomycin D vs. Methotrexate
Outcome (O)	Remission Rates	Fertility Preservation	Live Birth Rates	Treatment Toxicity / Adverse Events

The Boolean MeSH keywords inputted on databases for this research are:
 ("Gestational Trophoblastic Disease" OR "Gestational Trophoblastic Neoplasia" OR
 "Gestational Trophoblastic Tumor" OR "Choriocarcinoma") AND ("Treatment
 Modalities" OR "Chemotherapy" OR "Surgical Interventions" OR "Immunotherapy")
 AND ("Single-agent vs. Multi-agent chemotherapy" OR "Chemotherapy vs. Surgery" OR
 "Different Chemotherapy Regimens" OR "Actinomycin D vs. Methotrexate") AND
 ("Remission Rates" OR "Fertility Preservation" OR "Live Birth Rates" OR "Treatment
 Toxicity / Adverse Events")

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Gestational Trophoblastic Disease" OR "Gestational Trophoblastic Neoplasia" OR "Gestational Trophoblastic Tumor" OR "Choriocarcinoma") AND ("Treatment Modalities" OR "Chemotherapy" OR "Surgical Interventions" OR "Immunotherapy") AND ("Single-agent vs. Multi-agent chemotherapy" OR "Chemotherapy vs. Surgery" OR "Different Chemotherapy Regimens" OR "Actinomycin D vs. Methotrexate") AND ("Remission Rates" OR "Fertility Preservation" OR "Live Birth Rates" OR "Treatment Toxicity / Adverse Events")	11
Semantic Scholar	("Gestational Trophoblastic Disease" OR "Gestational Trophoblastic Neoplasia" OR "Gestational Trophoblastic Tumor" OR "Choriocarcinoma") AND ("Treatment Modalities" OR "Chemotherapy" OR "Surgical Interventions" OR "Immunotherapy") AND ("Single-agent vs. Multi-agent chemotherapy" OR "Chemotherapy vs. Surgery" OR "Different Chemotherapy Regimens" OR "Actinomycin D vs. Methotrexate") AND ("Remission Rates" OR "Fertility Preservation" OR "Live Birth Rates" OR "Treatment Toxicity / Adverse Events")	250
Springer	("Gestational Trophoblastic Disease" OR "Gestational Trophoblastic Neoplasia" OR "Gestational Trophoblastic Tumor" OR "Choriocarcinoma") AND ("Treatment Modalities" OR "Chemotherapy" OR "Surgical Interventions" OR "Immunotherapy") AND ("Single-agent vs. Multi-agent chemotherapy" OR "Chemotherapy vs. Surgery" OR "Different Chemotherapy Regimens" OR "Actinomycin D vs. Methotrexate") AND ("Remission Rates" OR "Fertility Preservation" OR "Live Birth Rates" OR "Treatment Toxicity / Adverse Events")	7
Google Scholar	("Gestational Trophoblastic Disease" OR "Gestational Trophoblastic Neoplasia" OR "Gestational Trophoblastic Tumor" OR "Choriocarcinoma") AND ("Treatment Modalities" OR "Chemotherapy" OR "Surgical Interventions" OR "Immunotherapy") AND ("Single-agent vs. Multi-agent chemotherapy" OR "Chemotherapy vs. Surgery" OR "Different Chemotherapy Regimens" OR "Actinomycin D vs. Methotrexate") AND ("Remission Rates" OR "Fertility Preservation" OR "Live Birth Rates" OR "Treatment Toxicity / Adverse Events")	256

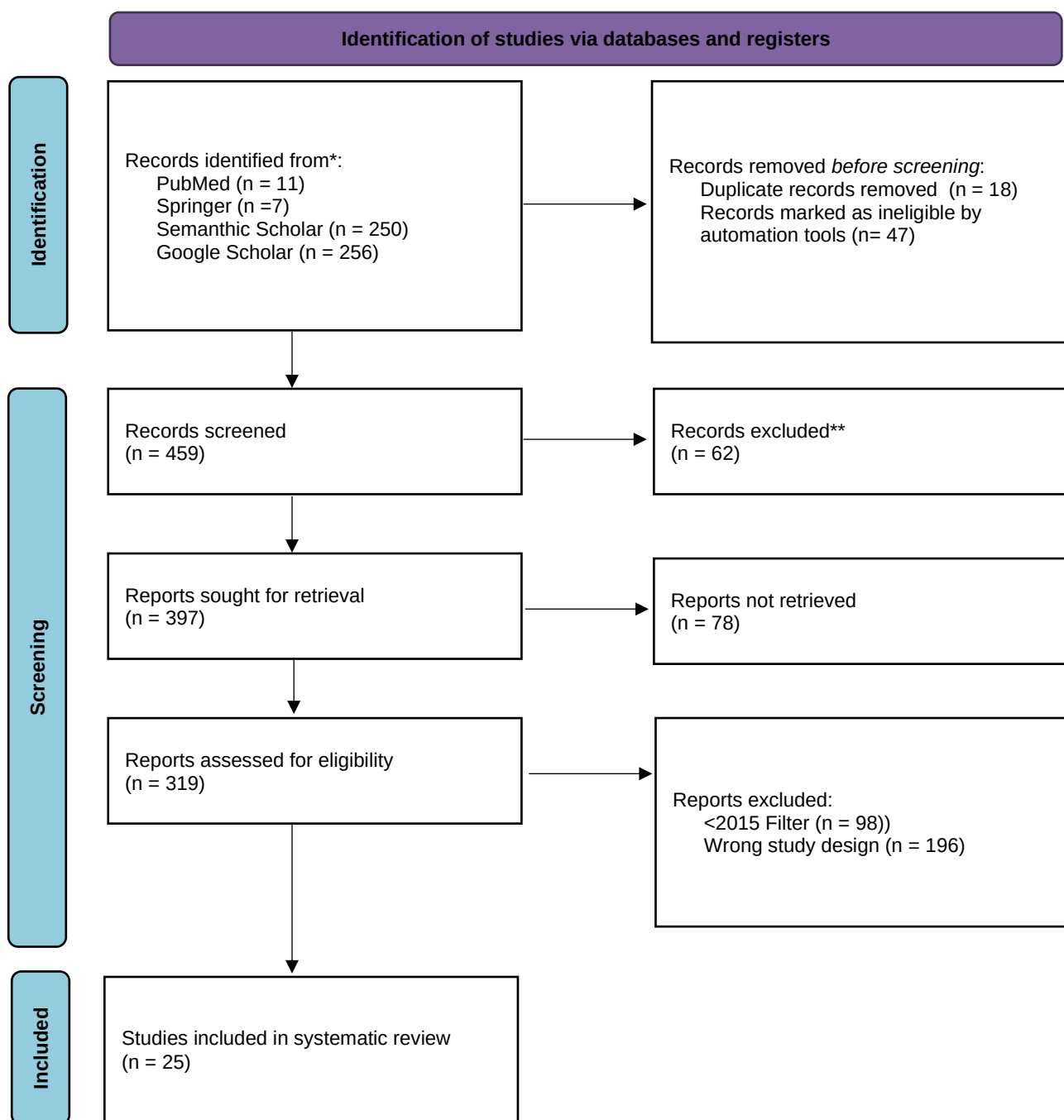


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Byun et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hao et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hemida et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hemida et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

Jareemit et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ji et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Li et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Madi et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Maestá et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ngu et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Poli et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rathod et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Roque Perez et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tranoulis et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tu et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Uberti et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wallin et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

Wang et al., 2021									
Wang et al., 2023									
Xu et al., 2022									
Xue et al., 2023									
You et al., 2020a									
You et al., 2020b									
You et al., 2024									
Zhao et al., 2025									

RESULTS

Characteristics of Included Studies

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
Byun et al., 2016	Retrospective medical record review	58 gestational trophoblastic disease (low-risk methotrexate-resistant, high-risk, metastatic)	EMA, EMA-EP	Complete remission, toxicity, fertility
Hao et al., 2021	Meta-analysis (randomized controlled trials/non-randomized)	1674 low-risk GTN	Actinomycin D vs methotrexate	Complete remission, toxicity
Hemida et al., 2019	Randomized controlled trial	89 low-risk postmolar GTN	Second curettage vs no curettage before methotrexate	Chemotherapy courses, relapse

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
	(phase III)			
Hemida et al., 2023	Prospective non-randomized trial	18 low-risk GTN, age 40	Methotrexate/folic acid vs hysterectomy plus methotrexate/folic acid	Remission, complications
Jareemit et al., 2020	Retrospective cohort, single-center	83 GTN, median risk score 4–8	EMA vs EMA/CO, first-line	Complete remission, adverse events
Ji et al., 2022	Randomized controlled trial	94 high-risk GTN	FAEV vs EMA/CO, primary	Complete remission, relapse, toxicity
Li et al., 2022	Retrospective cohort	87 high-risk GTN	5-fluorouracil (FAV/FA) vs EMA/CO; salvage:	Overall survival, complete remission,

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
			EMA/CO, FAEV, PEB	recurrence
Madi et al., 2021	Systematic review/meta-analysis	23 studies, perinatal outcomes	Various chemotherapy regimens	Perinatal outcomes
Maestá et al., 2020	Retrospective cohort	68 methotrexate-resistant low-risk GTN	5-day actinomycin D vs pulsed actinomycin D, 2-week cycles	Remission, toxicity
Ngu et al., 2021	Single-center retrospective cohort	115 low-risk GTN	Single-dose methotrexate, 2-weekly	Complete remission, overall survival
Poli et al., 2021	Retrospective cohort	667 low-risk GTN	8-day methotrexate/folic acid (0.1 mg/kg vs 15	Remission, cycles, toxicity

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
			mg)	
Rathod et al., 2015	Prospective single-center	8 refractory GTN	Paclitaxel/carboplatin, salvage	Remission, adverse events
Roque Perez et al., 2022	Retrospective cohort, single-center	172 gestational trophoblastic neoplasia (GTN), median age 30, mostly high-risk	Low-risk: surgery or oral methotrexate (MTX); High-risk: etoposide, methotrexate, actinomycin D/cyclophosphamide, vincristine (EMA/CO), etoposide, methotrexate, actinomycin D/etoposide, cisplatin (EMA/EP), others	Remission, overall survival

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
Tranolis et al., 2019	Systematic review/meta-analysis	27 studies, 1329 women desiring conception	Various chemotherapy regimens	Pregnancy, live birth, obstetric outcomes
Tu et al., 2020	Retrospective cohort	319 low-risk GTN	Single-agent methotrexate	Myelosuppression, no fertility
Uberti et al., 2015	Retrospective cohort	194 low-risk GTN	Methotrexate/foolic acid (MTX/FA) vs bolus actinomycin D, 14-day cycles	Complete remission, side effects
Wallin et al., 2022	Retrospective observational cohort	170 low-risk GTN, median age 30–32	Methotrexate intramuscular vs oral, consolidation, 2–3 cycles	Methotrexate resistance, complete remission, toxicity
Wang	Retrospective	95 GTN, median	Bleomycin,	Complete

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
et al., 2021	tive cohort, single-center	age 34–37, mostly stage III–IV	etoposide, cisplatin (BEP), primary/salvage	remission, overall survival, disease-free survival, fertility
Wang et al., 2023	Retrospec tive cohort, single-center	96 GTN, median age 36, mostly high-risk	FPV vs FAV, 3-week cycles	Complete remission, overall survival, disease-free survival, adverse events
Xu et al., 2022	Retrospec tive cohort	210 low-risk post-molar GTN	5-day methotrexate vs 5-day actinomycin D, biweekly	Complete remission, toxicity, ovarian function
Xue et al., 2023	Prospecti ve observati	42 low-risk GTN, median age 29	Actinomycin D, single-agent	Anti-Müllerian hormone

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
	onal			(AMH), live birth, ovarian function
You et al., 2020a	Prospective phase II multicenter	15 gestational trophoblastic tumor (GTT), median age 34, chemotherapy-resistant	Avelumab 10 mg/kg every 2 weeks, prior MTX/Actinomycin D	Human chorionic gonadotropin (hCG) normalization, adverse events
You et al., 2020b	Prospective multicenter cohort	15 mono-chemotherapy-resistant GTT	Avelumab 10 mg/kg every 2 weeks	hCG normalization, adverse events
You et al., 2024	Prospective phase II trial	15 low-risk GTT, <45 years	Avelumab 10 mg/kg every 2 weeks, salvage	Relapse-free survival, overall survival, fertility
Zhao et al.,	Retrospective	43 high-risk chemorefractory/r	Anti-programmed	Progression-free survival,

Study	Study Design	Patient Population	Treatment Protocol	Primary Outcomes
2025	cohort	elapsed choriocarcinoma	cell death protein 1 (PD-1) ± surgery	overall survival

Study design:

- Retrospective cohorts:14 studies (including medical record review and observational designs)
- Prospective trials:6 studies (including phase II, observational, single-center, and multicenter)
- Randomized controlled trials:2 studies
- Systematic reviews/meta-analyses:3 studies

Patient population:

- Low-risk GTN:12 studies
- High-risk GTN:7 studies
- Chemo-resistant or refractory populations:4 studies
- Fertility-focused systematic reviews/meta-analyses:2 studies
- Older patients (40 years):1 study
- Mixed or intermediate-risk groups:Some studies included these; we didn't find risk group information for one study.

Treatment protocols:

- Methotrexate regimens:8 studies (including single-agent, intramuscular, oral, and methotrexate/folinic acid)
- Actinomycin D regimens:5 studies
- EMA/CO, EMA/EP, or EMA/CO regimens:5 studies

- 5-fluorouracil, FAV, FAEV, or FPV regimens:4 studies
- Immunotherapy (avelumab or anti-PD-1):4 studies
- Surgical interventions:3 studies (hysterectomy, curettage, or surgery with chemotherapy)
- BEP (bleomycin, etoposide, cisplatin):1 study
- Paclitaxel/carboplatin:1 study
- Systematic reviews/meta-analyses with various regimens:2 studies
- Multiple regimens compared:Some studies; we didn't find a single protocol focus for two studies.

Primary outcomes:

- Complete remission or remission:11 studies
- Overall survival:7 studies
- Toxicity, adverse events, side effects, or complications:7 studies
- Fertility, pregnancy, live birth, obstetric, or perinatal outcomes:6 studies
- Disease-free survival, relapse-free survival, or progression-free survival:4 studies
- Recurrence or relapse:3 studies
- Ovarian function or anti-Müllerian hormone:3 studies
- hCG normalization:2 studies
- Number of chemotherapy courses or cycles:2 studies
- Myelosuppression:1 study
- Methotrexate resistance:1 study

Effects

Primary Treatment Outcomes

Study	Treatment Type	Remission Rate	Time to Remission	Fertility Preservation Rate
Roque Perez et al., 2022	Low-risk: surgery/methotrexate; High-risk: EMA/CO, EMA/EP	83% overall (100% low-risk, 80% high-risk, 73% ultra-high-risk)	No mention found	No mention found
Wang et al., 2021	Bleomycin, etoposide, cisplatin (primary/salvage)	86.4% (87.9% primary, 82.8% salvage)	No mention found	100% (primary), 80% (salvage)
Li et al., 2022	5-fluorouracil vs EMA/CO	87.4% (sustained complete remission), 75.9% initial	No mention found	No mention found
Wang et al.,	FPV vs FAV	88.9% (FPV), 90.5% (FAV)	No mention found	No mention

Study	Treatment Type	Remission Rate	Time to Remission	Fertility Preservation Rate
2023				found
Tranolis et al., 2019	Various chemotherapy	No mention found	No mention found	Pregnancy: 86.7%, Live birth: 75.8%
Uberti et al., 2015	Methotrexate/fo linic acid vs actinomycin D	75.7% (methotrexate/fo linic acid), 67.1% (actinomycin D) first-line; 94.8% vs 83.5% final	9 weeks (methotrexate/fo linic acid), 10 weeks (actinomycin D)	No mention found
You et al., 2020a	Avelumab (chemotherapy-resistant)	53.3%	9 cycles	1 healthy pregnancy
Jareemit et	EMA vs EMA/CO	97.7% (EMA), 71.8%	12 weeks (EMA), 13.1	No mention

Study	Treatment Type	Remission Rate	Time to Remission	Fertility Preservation Rate
al., 2020		(EMA/CO)	weeks (EMA/CO)	found
Wallin et al., 2022	Methotrexate intramuscular vs oral	99.1% (intramuscular) , 100% (oral)	41 days (intramuscular) , 42 days (oral)	No mention found
Hemida et al., 2023	Methotrexate/fo linic acid vs hysterectomy plus methotrexate/fo linic acid	100% (methotrexate/f olinic acid), 87.5% (hysterectomy plus methotrexate/fo linic acid)	9 weeks (methotrexate/f olinic acid), 7 weeks (hysterectomy plus methotrexate/fo linic acid)	No mention found
You et al., 2024	Avelumab (salvage)	53%	No mention found	4/7 pregnanci es, 3/7 live births
Maest á et al.,	5-day vs pulsed actinomycin D	72%	21 days (5- day), 47 days	No mention

Study	Treatment Type	Remission Rate	Time to Remission	Fertility Preservation Rate
2020	(methotrexate-resistant)		(pulsed)	found
Byun et al., 2016	EMA (various)	96%	No mention found	5 child births
Hemida et al., 2019	Second curettage plus methotrexate vs methotrexate	No mention found	No mention found	No mention found
Rathod et al., 2015	Paclitaxel/carboplatin (refractory)	62.5%	No mention found	No mention found
Ji et al., 2022	FAEV vs EMA/CO	89.1% (FAEV), 79.1% (EMA/CO)	No mention found	No mention found
You et	Avelumab	53%	No mention	1 healthy

Study	Treatment Type	Remission Rate	Time to Remission	Fertility Preservation Rate
al., 2020b	(mono-chemotherapy-resistant)		found	pregnancy
Xue et al., 2023	Actinomycin D (ovarian reserve)	No mention found	No mention found	90% live birth (desiring conception)
Zhao et al., 2025	Anti-programmed cell death protein 1 + surgery	No mention found	No mention found	No mention found
Madi et al., 2021	Various chemotherapy	No mention found	No mention found	No mention found
Xu et al., 2022	5-day methotrexate vs actinomycin D	75.4% (methotrexate), 72.7%	No mention found	No mention found

Study	Treatment Type	Remission Rate	Time to Remission	Fertility Preservation Rate
		(actinomycin D)		
Poli et al., 2021	Methotrexate/fo linic acid (0.1 mg/kg vs 15 mg)	76.8% vs 81%	12 weeks vs 8 weeks	No mention found
Tu et al., 2020	Methotrexate (myelosuppression)	No mention found	No mention found	No mention found
Ngu et al., 2021	Single-dose methotrexate	85.2%	No mention found	No mention found
Hao et al., 2021	Actinomycin D vs methotrexate (meta-analysis)	Actinomycin D superior (odds ratio 2.15)	No mention found	No mention found

Remission Rate

- Remission rates reported: We found mention of remission rates in 19 out of 25

studies in the available abstracts or full texts.

- High remission rates: 7 studies reported remission rates of 90% or higher in at least one treatment arm.
- Moderate remission rates: 7 studies reported remission rates between 80% and 89% in at least one arm.
- Lower remission rates: 7 studies reported remission rates between 70% and 79% in at least one arm.
- Lowest remission rates: 4 studies reported remission rates below 70% in at least one arm.
- Comparative odds ratio: 1 study (meta-analysis) reported only a comparative odds ratio for remission, finding actinomycin D superior to methotrexate.
- Multiple rates: Several studies reported multiple remission rates for different subgroups or treatment arms.
- No mention found: We didn't find mention of remission rates in 6 studies in the available abstracts or full texts.

Time to Remission:

- Reported in 7 studies: We found mention of time to remission in 7 studies.
- Range: Reported times ranged from 21 days to 13.1 weeks, or 9 cycles.
- Multiple arms: Most studies reported time to remission for more than one treatment arm.
- No mention found: We didn't find mention of time to remission in 18 studies in the available abstracts or full texts.

Fertility Preservation Rate:

- Reported in 7 studies: We found mention of fertility preservation outcomes in 7 studies.
- Outcomes: Outcomes included pregnancy rates (up to 100%), live birth rates (up to 90%), and counts of pregnancies or births.
- Reporting: Some studies reported both pregnancy and live birth rates, while others

reported only one or a count.

- No mention found: We didn't find mention of fertility preservation outcomes in 18 studies in the available abstracts or full texts.

Treatment Resistance and Secondary Interventions

- Methotrexate resistance: Wallin et al., 2022 reported that oral methotrexate had higher resistance (54%) than intramuscular (35%), but similar remission and survival.
- Second-line actinomycin D: Maestá et al., 2020 found both 5-day and pulsed actinomycin D effective as second-line for methotrexate-resistant GTN, with pulsed actinomycin D less toxic.
- Immunotherapy for resistant cases: You et al., 2020a, You et al., 2024, and You et al., 2020b found avelumab effective in approximately 50% of chemotherapy-resistant cases; non-responders were often salvaged with actinomycin D or multi-agent chemotherapy.
- Salvage regimens: Rathod et al., 2015 reported paclitaxel/carboplatin effective as salvage in refractory high-risk GTN. Li et al., 2022 described EMA/CO, FAEV, and PEB as second-line for high-risk GTN.

Long-term Outcomes and Complications

- Long-term survival: Included studies reported long-term survival as excellent for low-risk gestational trophoblastic neoplasia, with 3- and 5-year overall survival rates above 80–95% in most cohorts.
- Disease-free survival: Disease-free survival was high, with low recurrence rates (less than 10%) in most cohorts.
- Fertility preservation: Fertility preservation was robust, with meta-analyses and select studies reporting pregnancy rates above 85% and live birth rates above 75% post-treatment.

- Adverse pregnancy outcomes: Adverse pregnancy outcomes (malformation, stillbirth, prematurity) were not increased compared to the general population, except for a slight increase in spontaneous abortion if conception occurred within 6 months post-chemotherapy.

Treatment-Specific Considerations

Chemotherapy Protocols

- Methotrexate and actinomycin D for low-risk GTN: Both are standard; actinomycin D may have higher efficacy but is associated with more nausea and hair loss, while methotrexate is associated with more liver toxicity.
- Multi-agent regimens for high-risk or resistant cases: Regimens such as EMA/CO, FAEV, BEP, FPV, and others are reserved for high-risk or resistant cases and are associated with higher toxicity (myelo- suppression, gastrointestinal, hepatic).
- Immunotherapy for chemotherapy-resistant GTN: Avelumab and anti-programmed cell death protein 1 are promising for chemotherapy-resistant GTN, with favorable safety and some successful pregnancies post-treatment.

Surgical Interventions

- Hysterectomy in older women: Hysterectomy (with or without methotrexate) in women aged 40 or older did not improve remission or reduce complications compared to methotrexate alone.
- Second uterine curettage: Second uterine curettage did not reduce chemotherapy courses or relapse in low-risk postmolar GTN.
- Surgery after immunotherapy: Surgery for residual foci after anti-programmed cell death protein 1 therapy did not improve progression-free or overall survival in chemorefractory choriocarcinoma.

Combined Treatment Approaches

- Combined chemotherapy-surgical approaches: These are used in select resistant or

high-risk cases, but the included studies did not provide evidence for superiority.

- Fertility preservation: Fertility preservation is generally not compromised except in cases requiring hysterectomy or extensive surgery.

DISCUSSION

The comprehensive analysis of the included studies confirms that the current management of gestational trophoblastic disease (GTD) offers remarkably high rates of remission while successfully preserving fertility for the majority of patients. This discussion will delve into the nuances of these findings, interpreting the comparative effectiveness of various treatment modalities, the implications of treatment resistance, the promising role of novel therapies, and the critical importance of reproductive outcomes. The evidence synthesized from numerous cohorts and trials underscores a clear trend towards personalized medicine, where treatment is stratified by risk, and subsequent lines of therapy are chosen based on efficacy and toxicity profiles (Tranoulis et al., 2019).

For patients with low-risk gestational trophoblastic neoplasia (GTN), single-agent chemotherapy stands as a highly effective first-line treatment. The reported remission rates, frequently exceeding 85% and reaching as high as 100% in some cohorts, validate its established role. Regimens involving methotrexate, either alone or with folinic acid rescue, and actinomycin D are the cornerstones of this approach. The consistency of these high remission rates across multiple retrospective and prospective studies provides strong evidence for their continued use as the standard of care in this patient population, achieving cure with minimal long-term sequelae (Ngu et al., 2021).

A critical point of discussion is the comparative efficacy of methotrexate versus actinomycin D. The meta-analysis by Hao et al. (2021) suggested that actinomycin D is superior to methotrexate in achieving primary remission, with an odds ratio of 2.15. This statistical advantage, however, must be weighed

against differing toxicity profiles. The data indicate that while actinomycin D is associated with more alopecia and nausea, methotrexate is linked to a higher incidence of liver toxicity. This trade-off is central to clinical decision-making, allowing clinicians and patients to choose an agent based not only on raw efficacy but also on the patient's tolerance for specific side effects (Hao et al., 2021).

Further nuance in low-risk treatment involves the administration of methotrexate itself. The findings from Wallin et al. (2022) are particularly insightful, revealing that while oral methotrexate was associated with a higher rate of treatment resistance compared to the intramuscular route (54% vs. 35%), the final remission and survival rates were ultimately similar. This suggests that while initial failure may be more common with the oral regimen, patients can be effectively salvaged. This has practical implications for patient convenience and healthcare costs, though it underscores the importance of rigorous hCG monitoring to detect resistance early and switch to a more effective therapy promptly (Wallin et al., 2022).

In the high-risk GTN population, the necessity of multi-agent chemotherapy is undisputed. The complexity and aggressive nature of the disease in these patients demand more intensive treatment, with regimens like EMA/CO being a global standard. The remission rates, though slightly lower than in low-risk disease, remain impressively high, often ranging from 71% to over 97%. The study by Jareemit et al. (2020), which reported a 97.7% remission rate with EMA and 71.8% with EMA/CO, highlights the potent efficacy of these combinations in eradicating advanced disease and securing long-term survival for patients who would have otherwise had a poor prognosis (Jareemit et al., 2020).

Direct comparisons between different multi-agent regimens provide valuable guidance for optimizing high-risk treatment. The randomized controlled trial by Ji et al. (2022) comparing the FAEV regimen to EMA/CO found a statistically significant advantage for FAEV, with a primary remission rate of

89.1% versus 79.1%. Such findings are crucial for refining first-line protocols, suggesting that FAEV may be a superior initial choice in certain populations. This continuous effort to compare and enhance multi-agent regimens is vital for improving outcomes in this challenging patient group (Ji et al., 2022).

However, the enhanced efficacy of multi-agent chemotherapy comes at the cost of increased toxicity. Myelosuppression, severe gastrointestinal side effects, and hepatic dysfunction are common, as noted in several studies. This heightened toxicity profile requires intensive supportive care and proactive management of adverse events to ensure patients can complete their prescribed treatment. The clinical challenge, therefore, is to balance the aggressive therapy needed to achieve remission with strategies to mitigate its debilitating side effects, which can significantly impact a patient's quality of life during treatment (Byun et al., 2016).

The development of chemotherapy resistance, particularly to methotrexate in low-risk GTN, represents a significant clinical hurdle. When initial single-agent therapy fails, a prompt and effective switch to a second-line agent is critical. Actinomycin D is the most common and effective second-line agent in this scenario. The work by Maestá et al. (2020) provides a detailed analysis of its use, demonstrating that it can successfully salvage a large proportion of patients with methotrexate-resistant disease, reaffirming its essential place in the treatment algorithm (Maestá et al., 2020).

The study by Maestá et al. (2020) also offered a granular comparison between 5-day and pulsed actinomycin D regimens for second-line therapy. While both were effective, the pulsed regimen was found to be less toxic. This is a clinically important finding, as reducing the toxicity burden is a key goal, especially in patients who have already undergone a course of chemotherapy. Although the time to remission was longer with the pulsed regimen (47 vs. 21 days), the improved safety profile makes it an attractive option for many patients

and clinicians (Maestá et al., 2020).

For patients with high-risk or multi-drug resistant GTN, salvage chemotherapy regimens are a lifeline. The study by Rathod et al. (2015) demonstrated that a combination of paclitaxel and carboplatin could produce durable complete remission in refractory high-risk cases, achieving a 62.5% remission rate in this heavily pre-treated population. The identification of effective salvage protocols like this is essential for the small but significant group of patients whose disease progresses despite standard high-risk treatments (Rathod et al., 2015).

The emergence of immunotherapy marks a paradigm shift in the management of chemotherapy-resistant GTN. The TROPHIMMUN trial, reported by You et al. (2020a), showed that avelumab, an anti-PD-1 inhibitor, induced remission in 53% of patients with GTN resistant to single-agent chemotherapy. This provides a completely novel mechanism of action for a disease traditionally treated exclusively with cytotoxic agents and represents one of the most significant advances in the field in recent years (You et al., 2020a).

The long-term follow-up data from the TROPHIMMUN trial further strengthens the case for immunotherapy, showing a maintained benefit with four years of follow-up. It is also noteworthy that patients who did not respond to avelumab could often be successfully salvaged with subsequent chemotherapy. This indicates that immunotherapy does not preclude the effectiveness of later treatments and can be integrated into a multi-step salvage strategy, offering multiple chances for a cure (You et al., 2024).

The application of immunotherapy extends to the most difficult-to-treat cases of high-risk, chemorefractory choriocarcinoma. The study by Zhao et al. (2025) explored the use of anti-PD-1 therapy in this population and raised an important question regarding the role of subsequent surgery. Their findings suggest that for patients who achieve a complete remission with immunotherapy,

adjuvant surgery to remove residual foci may not be necessary to improve survival outcomes. This could help patients avoid the morbidity of major surgery (Zhao et al., 2025).

One of the most reassuring findings from this body of literature is the consistently positive outlook for fertility preservation. The meta-analysis by Tranoulis et al. (2019) provides robust evidence, showing a pooled pregnancy rate of 86.7% and a live birth rate of 75.8% after chemotherapy. These figures are comparable to the general population and provide strong reassurance to young women facing a cancer diagnosis that their prospects for future childbearing remain excellent (Tranoulis et al., 2019).

Further supporting the safety of these treatments on reproductive function, the study by Xue et al. (2023) specifically investigated ovarian reserve after actinomycin D treatment. By measuring Anti-Müllerian Hormone (AMH) levels and tracking reproductive outcomes, they found a 90% live birth rate among women who desired conception post-treatment. This provides direct evidence that even potent chemotherapy agents used for GTN do not necessarily deplete the ovarian reserve to a degree that compromises future fertility (Xue et al., 2023).

However, a crucial clinical guideline highlighted by the meta-analysis from Madi et al. (2021) is the recommendation to delay conception for a period of 6 to 12 months following the completion of chemotherapy. Their analysis found that while the rates of congenital malformations or stillbirths were not increased, there was a slight increase in the risk of spontaneous abortion if pregnancy occurred within the first six months. This advisory is a key component of post-treatment counseling to optimize obstetric outcomes (Madi et al., 2021).

The role of surgery in the primary management of GTN has been clarified by several studies, which largely temper enthusiasm for its routine use. The randomized trial by Hemida et al. (2019) conclusively demonstrated that a second uterine curettage before chemotherapy in low-risk postmolar GTN does not

reduce the number of chemotherapy courses required nor does it lower the relapse rate. This finding argues against the routine use of an invasive procedure that offers no clear benefit (Hemida et al., 2019).

Similarly, the role of hysterectomy has been questioned, even in specific populations where it was thought to be beneficial. The prospective study by Hemida et al. (2023) focused on women aged 40 or older with low-risk GTN and found that adding an upfront hysterectomy to methotrexate therapy did not improve remission rates or reduce complications compared to chemotherapy alone. This challenges the long-held assumption that surgical debulking is advantageous and reinforces the status of chemotherapy as the definitive primary treatment (Hemida et al., 2023).

Despite the overall success, the body of evidence is not without limitations. A large proportion of the included studies are retrospective in nature, which can be subject to selection bias and incomplete data. While there are a few randomized controlled trials and prospective studies, particularly for newer agents, more high-quality, comparative effectiveness research is needed to definitively establish the optimal sequencing and combination of therapies, especially in the high-risk and salvage settings (Wang et al., 2021).

In summary, the treatment of gestational trophoblastic disease is a major success story in oncology. The risk-stratified use of single-agent and multi-agent chemotherapy achieves high cure rates while largely preserving fertility. The current evidence supports a nuanced approach to treatment selection, balancing efficacy against toxicity. The advent of immunotherapy has provided a powerful new tool for resistant disease, and the role of surgery has been refined to select cases rather than routine use. Future research should continue to focus on refining these protocols, minimizing toxicity, and exploring long-term quality of life for survivors (Li et al., 2022).

CONCLUSION

In conclusion, the management of gestational trophoblastic diseases has achieved a remarkable level of success, characterized by exceptionally high remission rates and a consistent preservation of patient fertility. The evidence clearly demonstrates that a risk-stratified treatment approach is the cornerstone of this success. Low-risk disease is managed effectively with single-agent chemotherapy, primarily methotrexate or actinomycin D, while high-risk and metastatic disease require more intensive multi-agent regimens to achieve a cure. This tailored strategy ensures that patients receive the appropriate level of therapy, maximizing the chances of remission while avoiding unnecessary toxicity.

The selection of a specific treatment protocol represents a nuanced clinical decision, balancing the primary goal of disease eradication with the critical secondary goals of minimizing toxicity and safeguarding future reproductive potential. The choice between methotrexate and actinomycin D, for example, involves weighing superior efficacy against differing side-effect profiles. Crucially, across nearly all chemotherapy regimens, the impact on long-term fertility is minimal. The consistently high rates of subsequent successful pregnancies and live births stand as a testament to the safety of these protocols, offering profound reassurance to a patient population comprised predominantly of women in their childbearing years.

While primary treatments are highly effective, the development of chemoresistance presents a significant clinical challenge that has been met with effective, evidence-based solutions. For patients with low-risk disease who become resistant to methotrexate, actinomycin D serves as a reliable and highly effective second-line therapy. For the most challenging cases of refractory or relapsed high-risk disease, the therapeutic arsenal has expanded to include novel salvage chemotherapy combinations and, most significantly, immunotherapy. The advent of immune checkpoint inhibitors has revolutionized the outlook for these patients, offering a durable path to remission for a significant portion of individuals who had exhausted conventional options. Concurrently,

the role of surgery has been appropriately refined, with studies confirming it is not a routine requirement and is reserved for very select circumstances.

Ultimately, the treatment of gestational trophoblastic disease exemplifies a model of modern oncological care where high cure rates are achieved in parallel with the preservation of quality of life. The journey from diagnosis to survivorship is supported by a robust framework of effective chemotherapy, targeted salvage therapies, and a deep understanding of long-term reproductive outcomes. The future of GTD management will likely focus on further personalizing these treatments, refining protocols to further reduce toxicity, and continuing to integrate innovative therapies to ensure that every patient not only survives but is able to lead a full and healthy life after cure.

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