THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Gestational Trophoblastic Disease for the General OB/GYN

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Learning Objectives

1. Describe clinical features and diagnostic criteria for gestational trophoblastic disease and gestational trophoblastic neoplasia
2. Improve understanding of pathology reports, including immunohistochemical analysis
3. Discuss surveillance in accordance with national guidelines
4. Discuss appropriate and timely transfer of care to gynecologic oncologist

Disclosures

I have no conflicts of interest to declare.

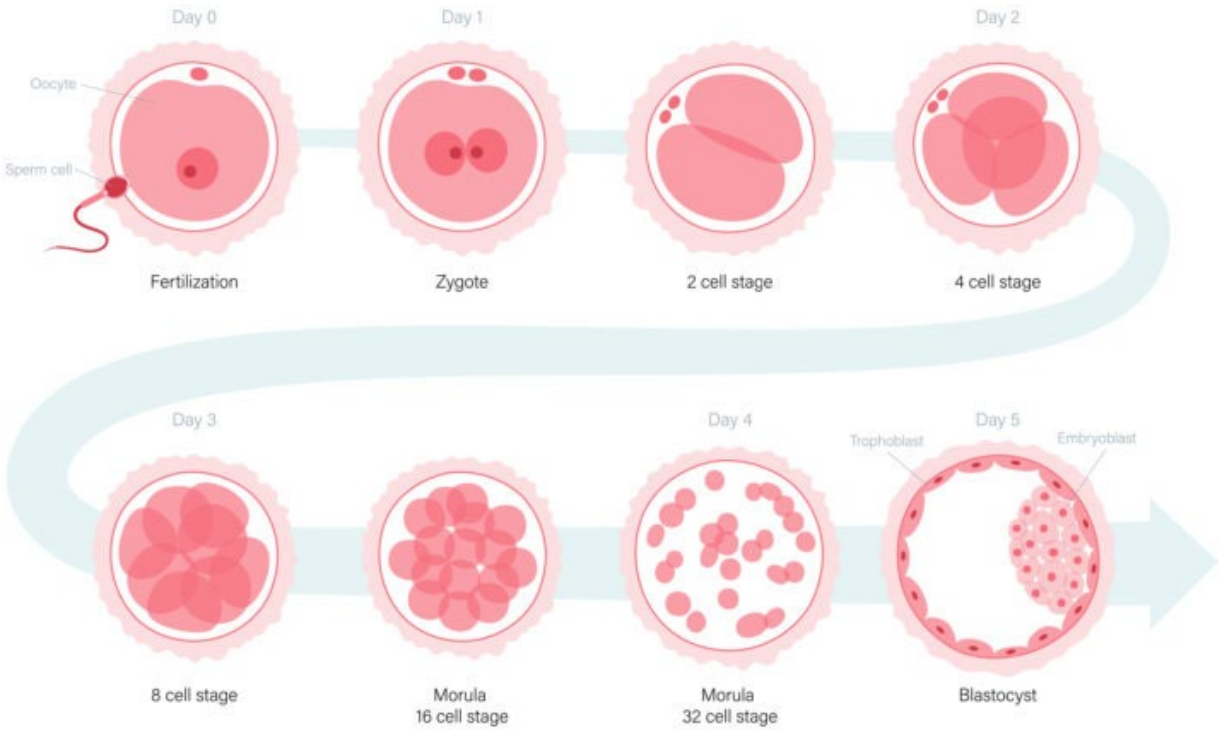
Terminology

- Gestational trophoblastic disease (GTD):
  - Benign:
    - Complete molar pregnancy
    - Partial molar pregnancy
    - Placental site nodule
  - Malignant:
    - Invasive mole
    - Choriocarcinoma
    - Placental site trophoblastic tumor
    - Epithelioid trophoblastic tumor

Gestational Trophoblastic Neoplasia (GTN)

What are trophoblasts?

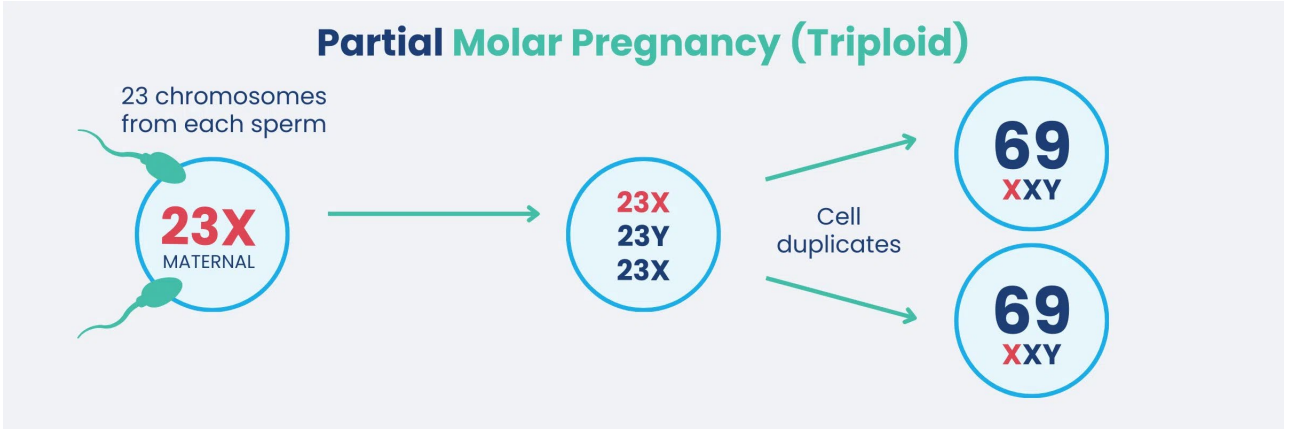
- Trophoblasts:
  - First cells to differentiate from fertilized egg
  - Supply embryo with nutrients
  - Form fetal portion of placenta

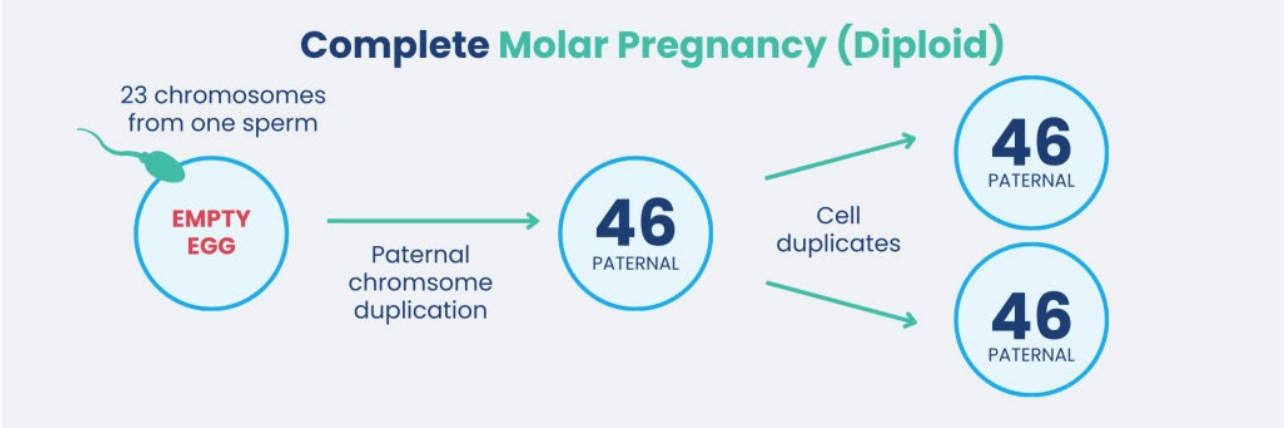


GTD: An Abnormal Fertilization Event

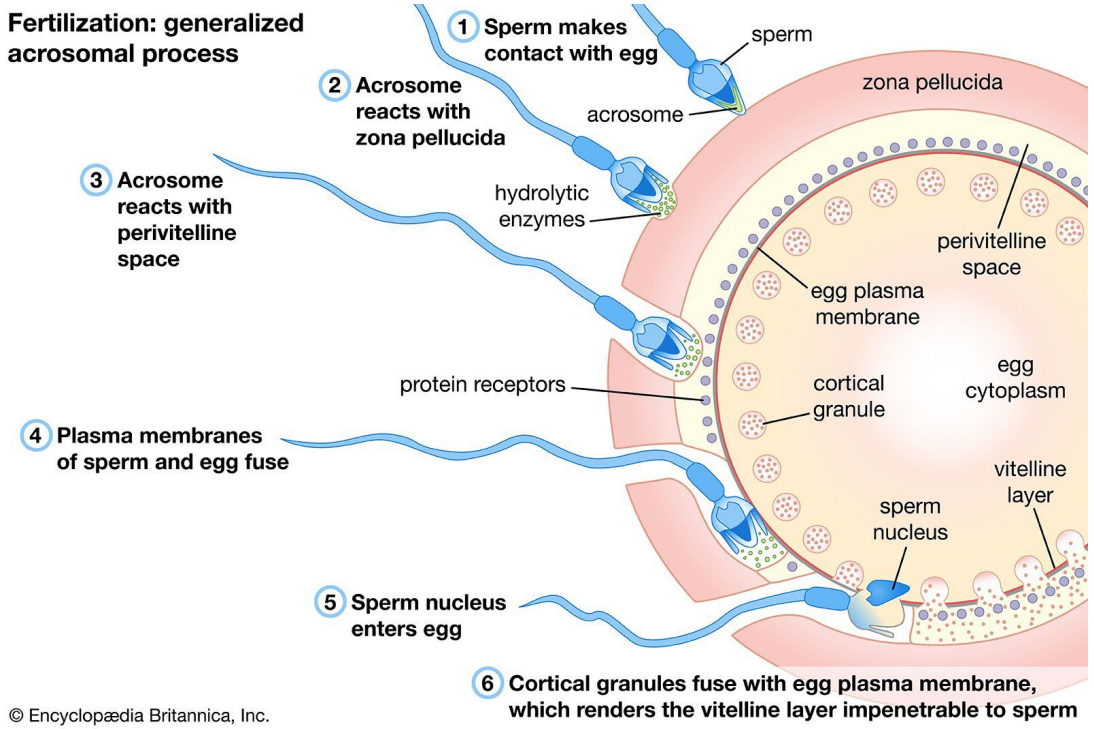
- Partial mole:
  - Simultaneous fusion of 2 sperm and 1 egg
  - Triploid genotype (69X??)

- Complete mole:
  - Blighted ovum + duplication of 1 sperm (80%)
  - Blighted ovum + 2 sperm (20%)
  - Diploid genotype (46XX, 46XY)
  - **All genes paternally derived**





GTD: Origins

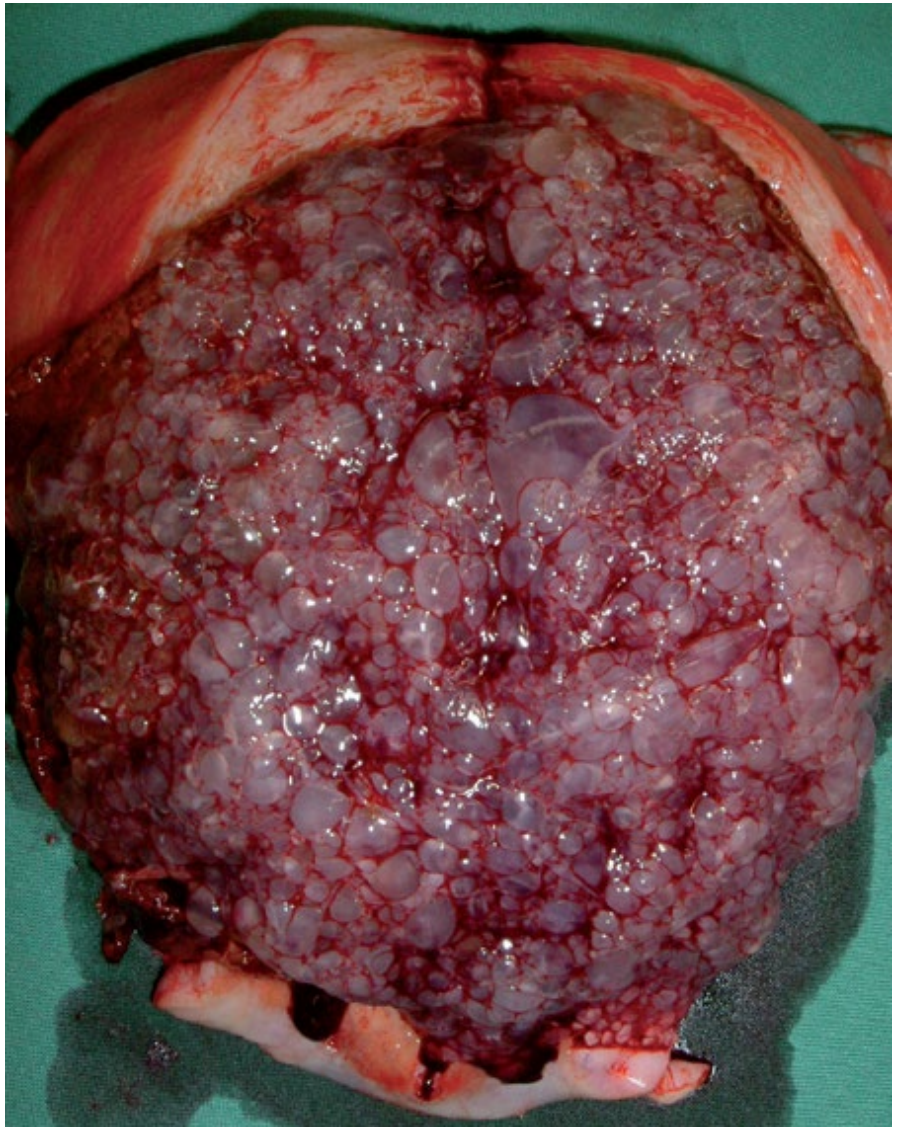


Mechanisms for prevention:

- Electrostatic:
  - Depolarization of cell membrane upon sperm contact
- Physical:
  - Cortical granules fuse with plasma membrane
- Altered membrane protein expression:
  - Sperm binding sites deactivated

Clinical Findings

- Clinical Presentation:
  - First-trimester bleeding
  - Elevated hCG for gestational age
  - Size > dates
  - No FHT
  - Symptoms of hyperthyroidism
  - Incidental finding on ultrasound



Imaging Findings

- **Greatly enlarged placenta (relative to cavity)**

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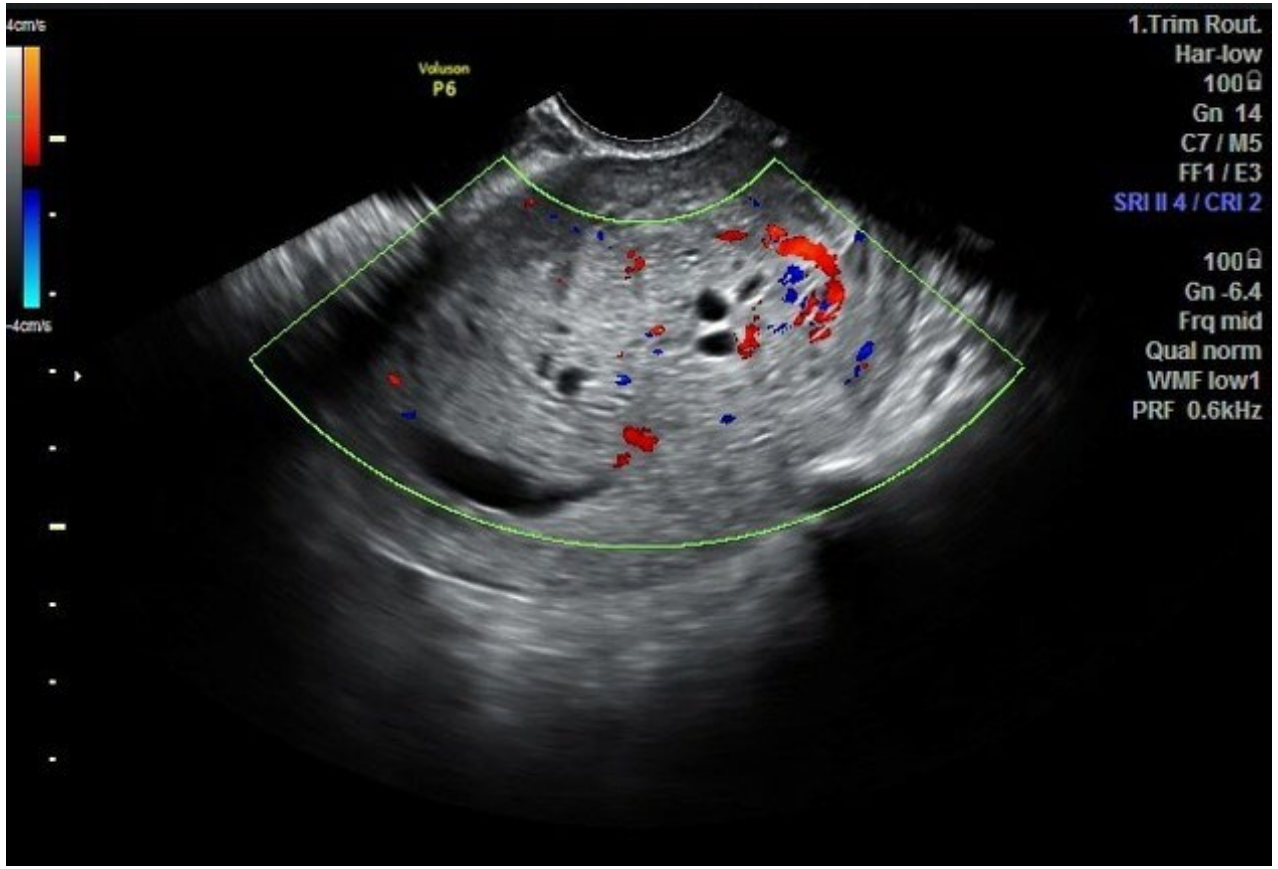
- **Cystic spaces within placenta (hydropic villi)**



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- **Amniotic cavity containing fetal parts surrounded by thick rim of placenta**

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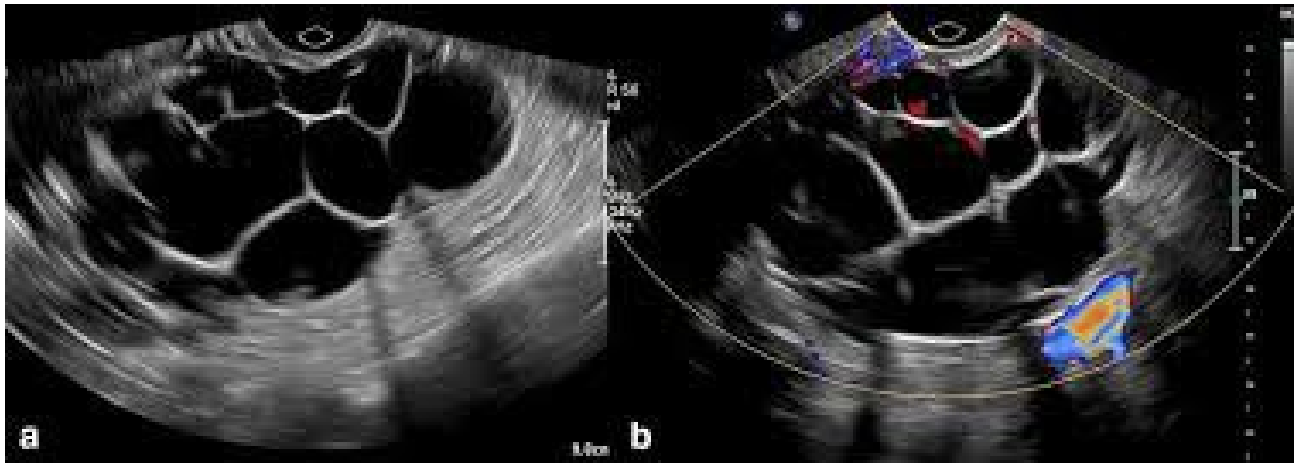
- Cystic spaces within placenta (hydropic villi)
- Amniotic cavity containing fetal parts surrounded by thick rim of placenta
- **Theca lutein ovarian cysts**

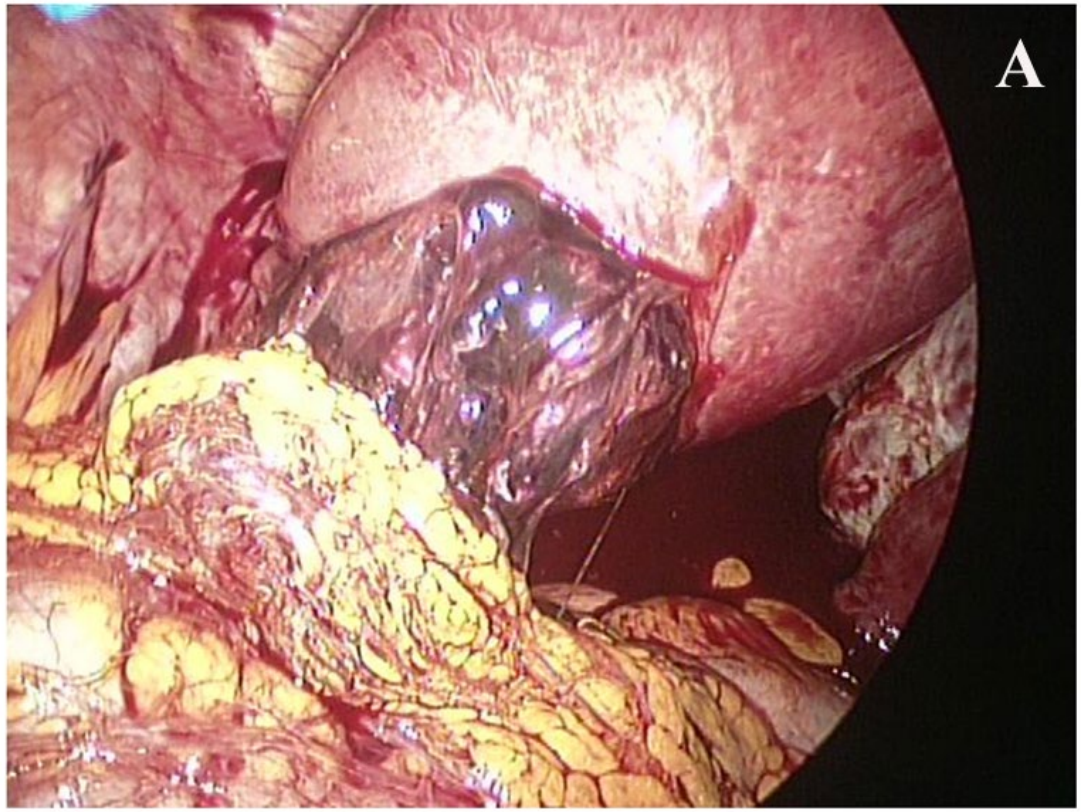


Treatment

- Treat based on suspicion of disease
  - **Do not biopsy suspected molar pregnancy!**
- Pre-operative workup:
  - hCG
  - CBC
  - Coagulation factors
  - Type & crossmatch
  - Chest XR

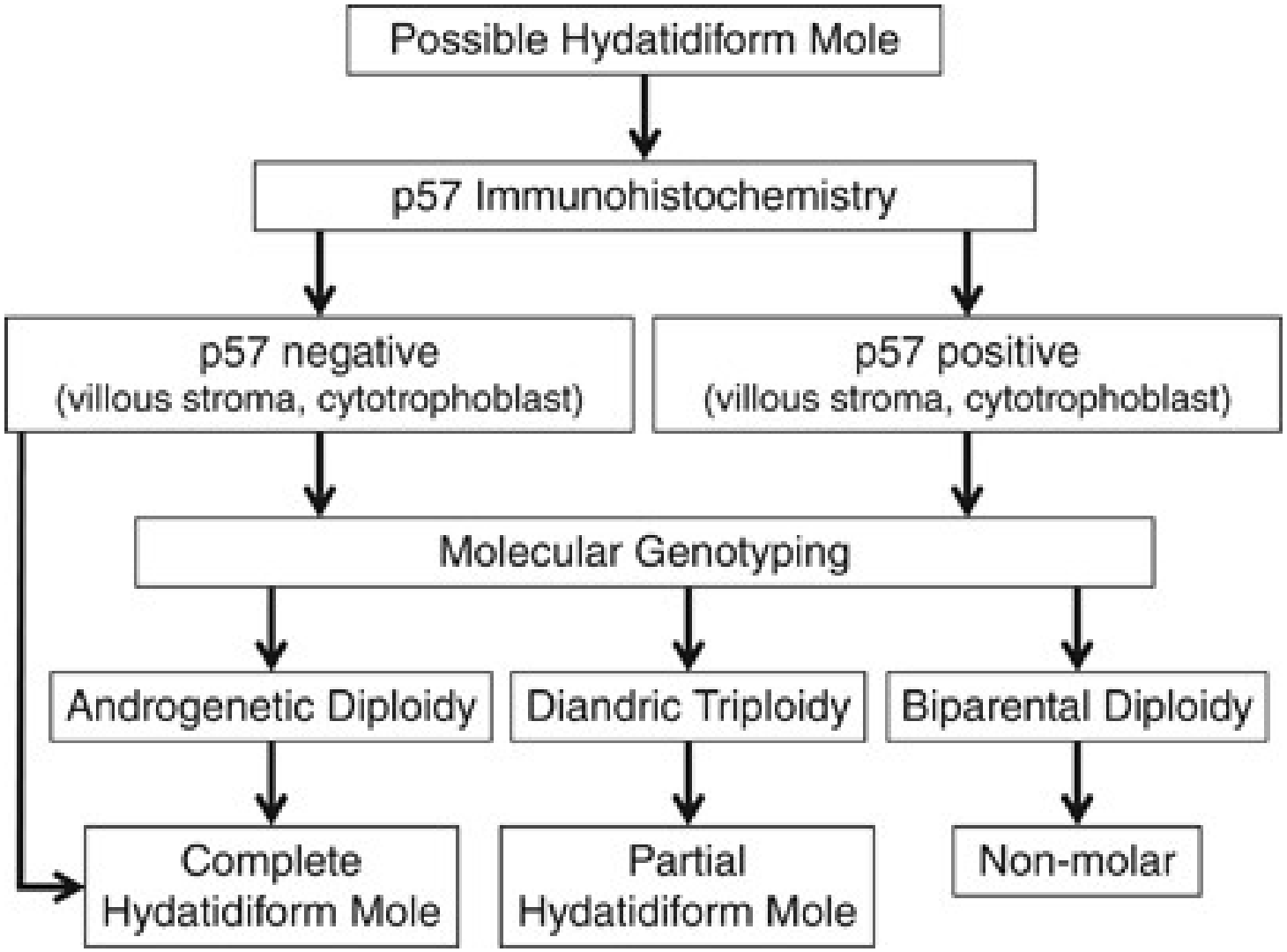
Treatment

- Suction D&C
  - Risks:
    - Perforation
      - Use largest cannula that is easily introduced
      - Conisder ultrasound guidance
    - Hemorrhage
      - Uterotonics available
- Hysterectomy?
  - 80% reduction in post-evacuation GTN
- Contraception!
- **No role for medical evacuation**
- **No role for prophylactic chemotherapy**



Diagnosis

- Hydropic villi alone non-diagnostic
  - Missed abortion may undergo hydropic degeneration
  - Diagnosis on morphology alone has high interobserver variability
- p57 immunohistochemical (IHC) staining
  - p57 is maternally expressed
    - If p57 negative (i.e. no maternal gene expression) → complete mole
    - If p57 positive (i.e. maternal and paternal gene expression)→ partial mole OR non-molar pregnancy
- Ploidy analysis
    - Triploid = partial mole
    - Euploid = hydropic abortion


Possible Hydatidiform Mole
p57 Immunohistochemistry
p57 negative
(villous stroma, cytotrophoblast)
p57 positive
(villous stroma, cytotrophoblast)
Molecular Genotyping
Androgenetic Diploidy
Diandric Triploidy
Biparental Diploidy
Complete Hydatidiform Mole
Partial Hydatidiform Mole
Non-molar

Post-Treatment Surveillance

- ACOG Guidelines
  - Weekly hCG until negative x3
  - Monthly x 6 months
- National Comprehensive Cancer Network (NCCN)
  - Weekly hCG until negative x3
  - 2 negative hCG assays in 3-month intervals (total 6 months after sustained normalization)
- If hCG normalizes in <56 days, risk of GTN 0.03% (complete mole) and 0.02% (partial mole)

Diagnosing Post-Molar GTN

Table 2
FIGO /WHO criteria for diagnosis of post-molar GTN (26).

1. Plateauing of hCG +/− 10% for 4 consecutive values over 3 weeks (i.e., days 1, 7, 14, 21)
2. A rise in hCG levels of ≥10% for 3 values over 2-week period (i.e., days 1, 7, 14)
3. Histologic diagnosis of choriocarcinoma or clinical and/or radiologic evidence of metastases

SEEK A SPECIALIST

Risk Factors for Post-Molar GTN

- Complete mole (20%) vs. partial mole (4%)
- hCG at diagnosis >100,000
- Excessive uterine size
- Theca lutein cysts
- Age >40
- Compounded risk factors = increased risk
  - Age >45 + hCG >175,000 – 85% risk of GTN
  - Age >50, 60% risk of GTN
  - May consider hysterectomy

What happens once GTN is diagnosed?

Table 3
FIGO staging (54):

Stage I	Disease confined to uterine corpus
Stage II	GTN extends outside of uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

What happens once GTN is diagnosed?

Table 4
WHO Risk Score (54).

	Scores			
	0	1	2	4
Age (yr)	<40	≥40	–	
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4	4–<7	7–<13	≥13
Pretreatment serum hCG (International Unit/L)	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	$>10^5$
Largest tumor size (including uterus)	3–<5 cm	≥5 cm		
Site of metastases	Lung	Kidney/spleen	Gastrointestinal/liver	Brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	2 or more drugs

What happens once GTN is diagnosed?

- FIGO Stage + WHO score
- Risk stratification
  - Low-risk: single-agent (methotrexate) chemotherapy
    - 5-year survival approaches 100%
  - High-risk: multi-drug (EMA-CO) chemotherapy
    - 5-year survival >80%
- Prolonged follow-up

GTD: Take-aways

- GTD is aberrant growth of placental tissue resulting from abnormal fertilization event.
- Suspicion for GTD typically arises on ultrasound, but may have significant clinical findings (bleeding, size > dates, elevated hCG, lack of FHT).
- Modern diagnosis is based on specimen from uterine evacuation via microscopic analysis, ploidy analysis, and IHC staining.
- Initial treatment is via surgical uterine evacuation.
- Surveillance is weekly hCG levels until negative x 3 values, then 3-monthly for 6 months (NCCN guidelines).
- Referral to gynecologic oncologist when hCG plateaus (<15% drop) over 3 weeks or rises (>10%) over 2 weeks.

References

1. Horowitz, N.S. et al. Epidemiology, diagnosis, and treatment of gestational trophoblastic disease: A Society of Gynecologic Oncology evidenced-based review and recommendation. Gynecologic Oncology, Volume 163, Issue 3, 605 – 613.
2. Donovan MF, Arbor TC, Bordoni B. Embryology, Yolk Sac. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555965/
3. Bruce S, Sorosky J. Gestational Trophoblastic Disease. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470267/
4. Quade, B. Gestational trophoblastic disease: Pathology and genetics. UpToDate

Thank you!