GESTATIONAL TROPHOBLASTIC NEOPLASIA

FLAME LECTURE: 224

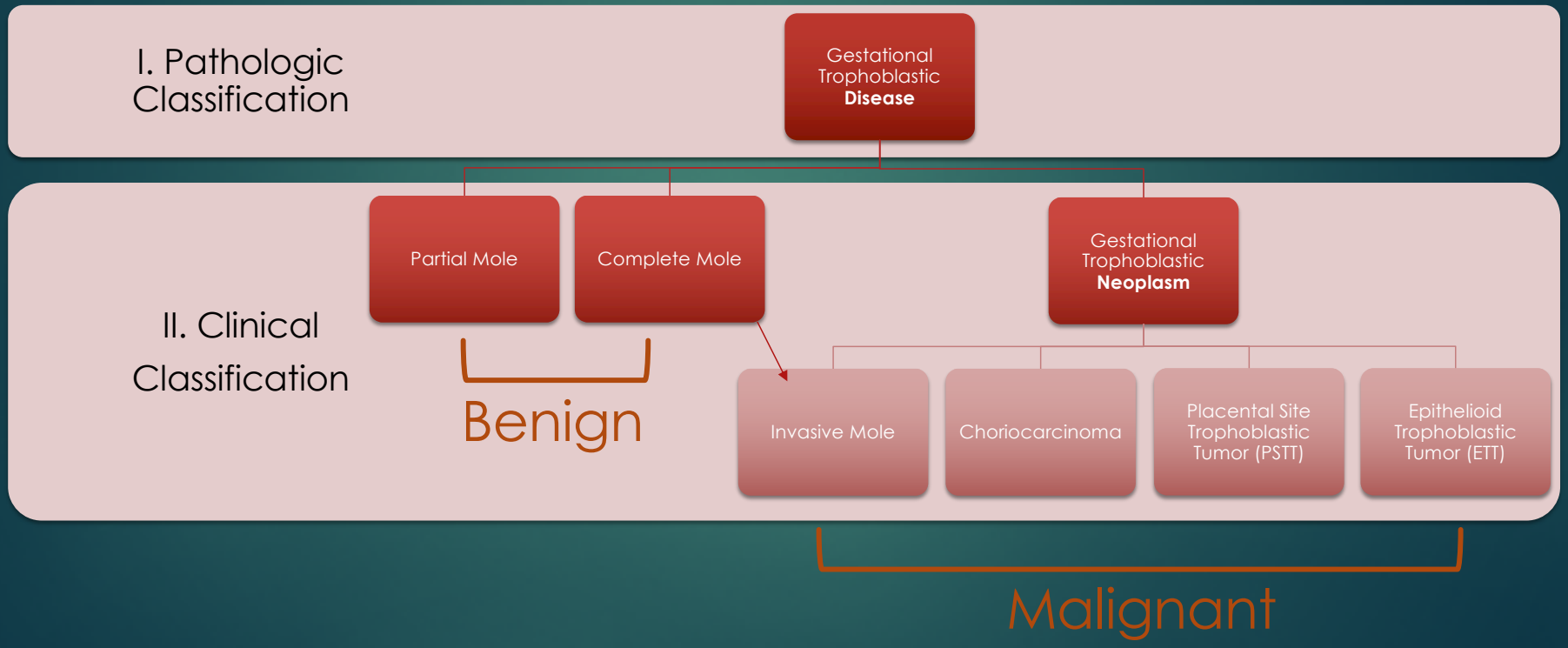
BERA / TSAI

EDITED BY: RAMCHANDRAN 9.29.21

LEARNING OBJECTIVES

- List the symptoms and physical examination findings of a patient with GTN
- Describe the diagnostic methods, treatment options and follow up for GTN
- Recognize the difference between molar pregnancy and malignant GTN
- Prerequisites
  - None
- See also – for related topics:
  - Other gynecologic oncology FLAMES

OVERVIEW


I. Pathologic Classification
Gestational Trophoblastic **Disease**
II. Clinical Classification
Partial Mole
Complete Mole
Gestational Trophoblastic **Neoplasm**
Benign
Invasive Mole
Choriocarcinoma
Placental Site Trophoblastic Tumor (PSTT)
Epithelioid Trophoblastic Tumor (ETT)
Malignant

MOLAR PREGNANCY
OVERVIEW

- Can be **BENIGN** or **PRE-MALIGNANT**
  - Caused by abnormal fertilization (overexpression of paternal genes)
    - All have double the paternal DNA
  - Characterized by abnormal chorionic villi and trophoblastic hyperplasia
  - Increased incidence in:
    - Maternal age <20 yo or >35 yo
    - History of hydatiform mole

MOLAR PREGNANCY

TYPES

COMPLETE MOLE

- Empty ovum + replicated paternal sperm (X) → 46 XX
- Less commonly, 2 paternal sperm fertilize an empty ovum → 46 XX or 46 XY
- "Snowstorm" appearance on ultrasound, no amniotic fluid
- hCG levels are higher than in partial moles
- 15-20% risk of developing invasive mole

PARTIAL MOLE

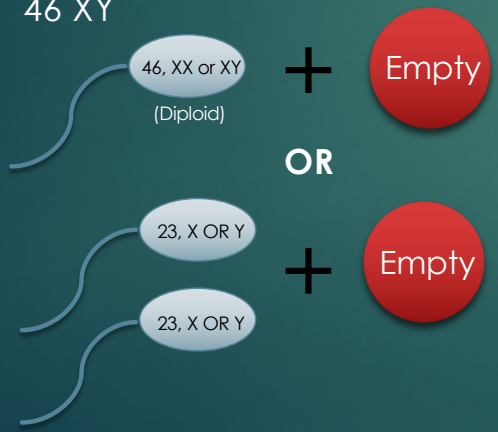
- Normal ovum + 2 paternal sperm OR 1 diploid sperm → 69 XXY, XXX, XYY
- Parts of the fetus are visible on ultrasound, amniotic fluid
- hCG levels are lower than in complete moles
- <5% risk of developing invasive mole

MOLAR PREGNANCY

TYPES

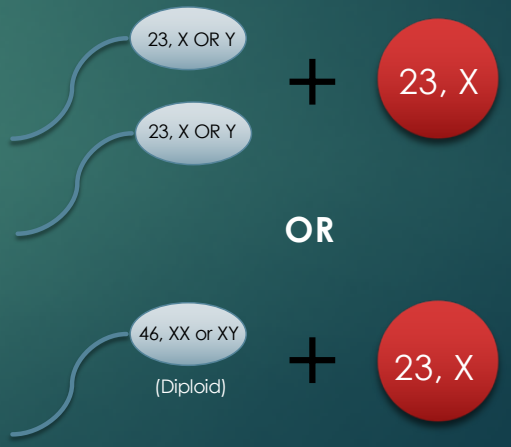
Complete Mole

- Empty ovum + replicated paternal sperm (X) → 46 XX
- Less commonly, 2 paternal sperm fertilize an empty ovum → 46 XX or 46 XY



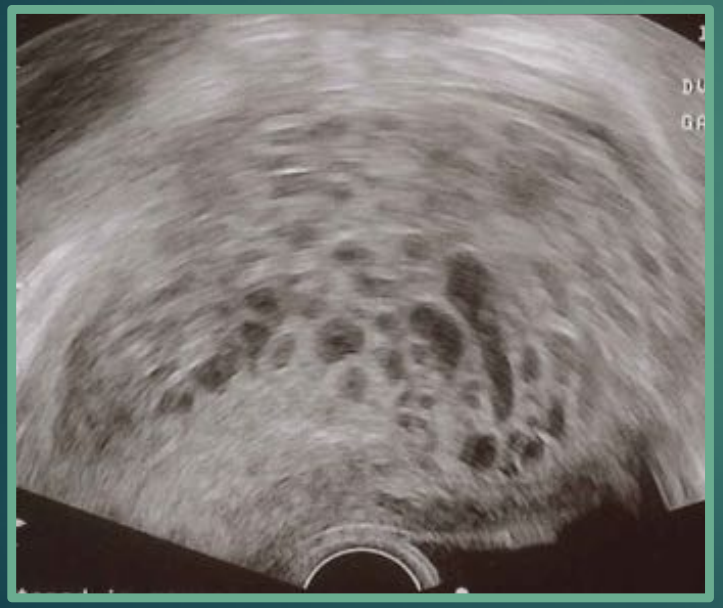
Partial Mole

- Normal ovum + 2 paternal sperm OR 1 diploid sperm → 69 XXY, XXX, XYY



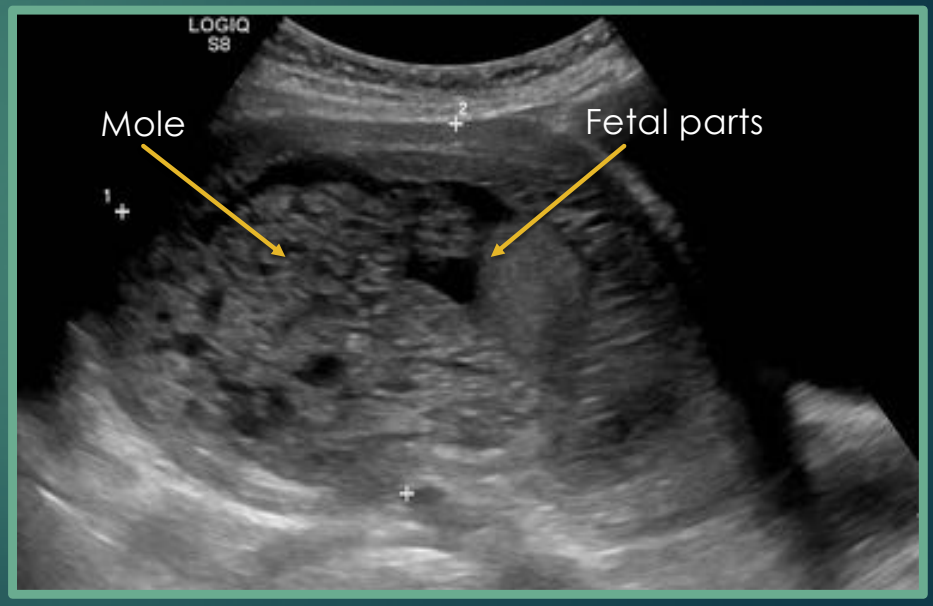
MOLAR PREGNANCY
TYPES

COMPLETE MOLE



"Snowstorm" on TUVS

PARTIAL MOLE



Transabdominal US

INVASIVE MOLE

- Is **MALIGNANT**
  - Arises most commonly from complete moles
  - Characterized by abnormal, *hydropic villi* invading the myometrium, uterine vessels, or extra uterine spaces
  - Metastasizes to vagina and lungs (hematogenous)
  - Presents similarly to molar pregnancy, with uterine rupture and intraperitoneal hemorrhage
  - May regress spontaneously

CHORIOCARCINOMA

- Is **MALIGNANT**
  - Arises from any trophoblastic tissue
    - Is most common neoplasia after a non-molar pregnancy
    - Can arise from tissue remaining after a delivered or failed pregnancy (e.g. ectopic pregnancy, abortion, ectopic)
    - More common after complete moles than partial moles
  - Presents with postpartum hemorrhage that is delayed (can hemorrhage *months* after pregnancy delivery)
  - Characterized by sheets of trophoblastic cells *WITHOUT villi*
  - Metastasizes to **lung**, brain, liver, pelvis, vagina, spleen, intestine, and kidney
  - Invasion into body tissues causes necrosis and *hemorrhage*

PLACENTAL SITE TROPHOBLASTIC TUMOR

- Can be **PREMALIGNANT** or **MALIGNANT**
  - Arises most commonly after non-molar abortion or pregnancy
  - Characterized by extra-villous trophoblastic cells; chorionic villi are usually *absent*
  - Most tumors are benign and limited to the uterus; 30% metastasize to local lymph nodes, lungs, pelvis
  - Causes inflammation and necrosis *without* hemorrhage
  - Generally resistant to chemotherapy – hysterectomy if contained to uterus

EPITHELIOID TROPHOBLASTIC TUMOR

- Can be **BENIGN** or **MALIGNANT**
  - Originally called "atypical choriocarcinoma"
  - Histologically resembles squamous cell cancer of the cervix
  - Clinical behavior similar to PSTT
  - Usually a discrete, hemorrhagic, solid, and cystic lesion
  - 50% present with metastases; mostly to the lungs
    - Usually late diagnosis

SYMPTOMS

- Abnormal vaginal bleeding during pregnancy
- Abnormal uterine bleeding or amenorrhea after non-molar pregnancy
- Hyperemesis gravidum
- Pelvic discomfort from uterine size larger than gestational age
- Passage of hydropic vesicles from vagina in molar pregnancies
- High levels of hCG stimulate thyrotropin and lactogen secretion leading to increased risks of:
  - Hyperthyroidism
  - Ovarian theca lutein cysts (>6 cm)
  - **Preeclampsia <20 weeks gestation**
- Metastasis: headache and other neuropathy; cough, chest pain, hemoptysis; jaundice, back pain

DIAGNOSTIC CONSIDERATIONS

- hCG
  - High levels in molar disease and choriocarcinoma
  - Low levels in placental site tumors
  - Can be substantially higher than expected with normal pregnancy (>100,000 IU/L)
- Pelvic ultrasound
  - Invasive mole: poorly defined masses with anechoic areas
  - Choriocarcinoma: heterogeneous with necrosis and hemorrhage
  - PSTT/ETT: cystic and solid components can both be present
- Chest X-ray and CT abdomen and pelvis for staging

NORMAL HCG LEVELS WITH GA

GA	hCG mIU/ml
3 wk	5-50
4 wk	5-426
5 wk	18-7340
6 wk	1080-56,500
7-8 wks	7,650-229,000
9-12 wks	25,700-288,000
13-16 wks	13,300-254,000
17-24 wks	4,060-165,400
25-40 wks	3,640-117,000

GTN STAGING

FIGO Prognostic Scoring	0	1	2	4
Age (years)	<40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from end of index pregnancy to treatment	< 4	4 - 6	7 - 12	>12
Pretreatment serum hCG (iu/l)	$<10^3$	10^3-10^4	10^4-10^5	> 10^5
Largest tumor size (including uterus – cm)	< 3	3 - 4	≥ 5	-
Site of metastases	Lung	Spleen, kidney	Gastro-Intestinal	Liver, brain
Number of metatases	-	1-4	5-8	> 8
Previously failed chemotherapy	-	-	Single drug	Multi-drug

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High risk >= 7, Low risk < 7

MANAGEMENT

- Molar Pregnancy: Dilation and Curettage
- Low risk treatment (Stage I or Stage II/III FIGO Score 0-6)
  - Lower risk of resistance to monotherapy
  - **Methotrexate**
  - Dactinomycin as second line
  - Overall >99% cure rate
- High risk treatment (Stage II/III FIGO Score ≥7)
  - EMA/CO Regimen
    - Etoposide, methotrexate, dactinomycin/cyclophosphamide, vincristine
- Follow up: monitor ß-hCG levels for recurrence x1 year
  - Need to prevent pregnancy during this time to not complicate hCG monitoring so provide birth control

IMPORTANT LINKS / REFERENCES

- UpToDate: Gestational trophoblastic neoplasia: Epidemiology, clinical features, diagnosis, staging, and risk stratification
- UpToDate: Hydatidiform mole: Epidemiology, clinical features, and diagnosis
- UpToDate: Initial management of low-risk gestational trophoblastic neoplasia
- UpToDate: Initial management of high-risk gestational trophoblastic neoplasia
- Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekhara PK, Lurain JR. FIGO CANCER REPORT 2015: Update on the diagnosis and management of gestational trophoblastic disease. *International Journal of Gynecology and Obstetrics* 2015(131): S123-S126.
- PDQ Adult Treatment Editorial Board. Gestational Trophoblastic Disease Treatment (PDQ®): Health Professional Version. National Cancer Institute. Published online: February 25, 2015.
- Gestational Trophoblastic Neoplasia. NCCN Clinical Practice Guidelines in Oncology. Version 2.2021 - March 31, 2021.