Gestational Trophoblastic Disease/Neoplasia

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Trophoblasts

Is the outer layer of cells of the blastocyst. Trophoblasts are present four days after fertilization in humans. They provide nutrients to the embryo and develop into a large part of the placenta.

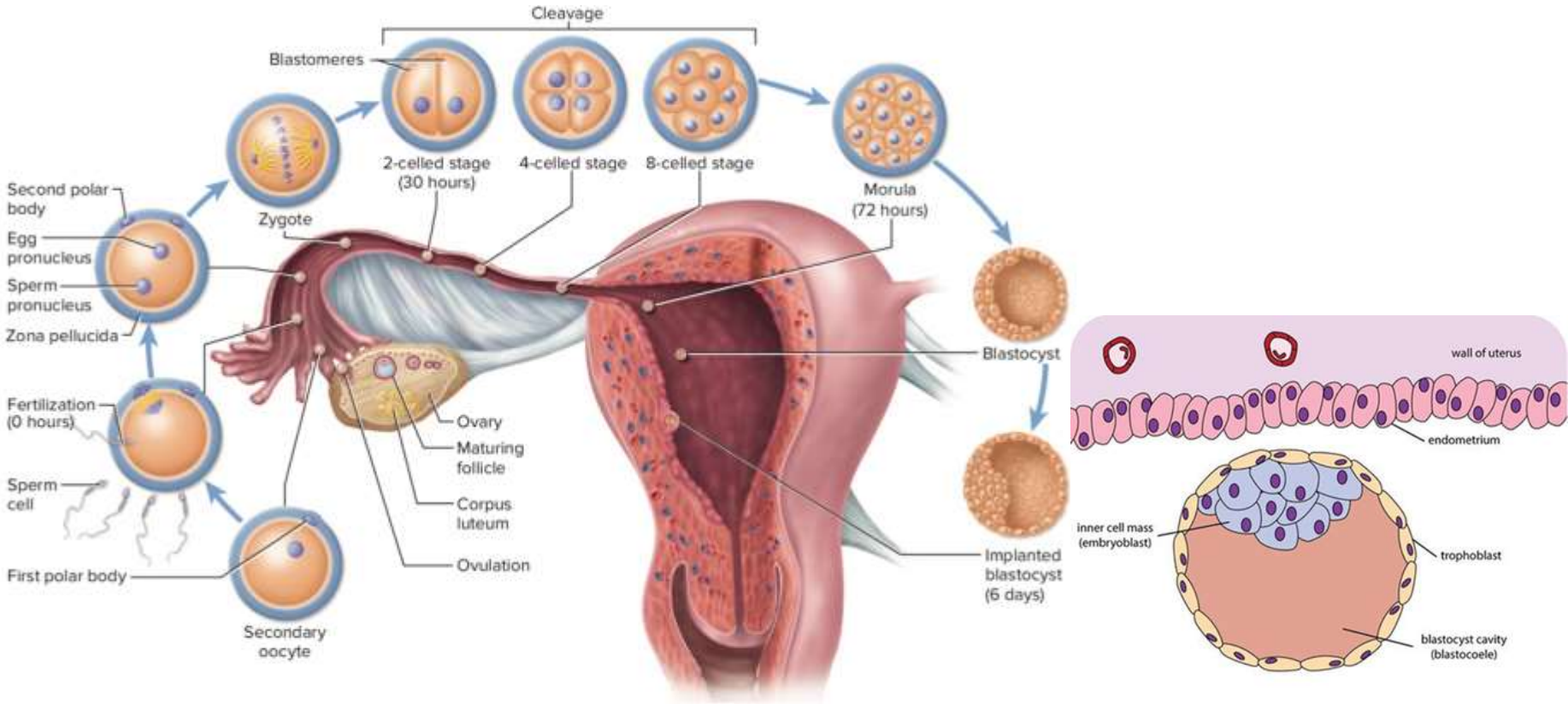


FIGURE 29.2 Migration of the Conceptus. The egg is fertilized in the distal end of the uterine tube, and the preembryo begins cleavage as it migrates to the uterus.

Gestational trophoblastic disease (GTD) and **gestational trophoblastic neoplasia (GTN)** comprise a heterogeneous group of related lesions arising from abnormal cellular proliferation of placental trophoblasts. Most, but not all, of these lesions produce human chorionic gonadotropin (hCG) at some level. The pathogenesis of GTD/GTN is unique because maternal lesions arise from fetal, not maternal, tissue, making them genetically distinct from the maternal host.

Gestational trophoblastic disease (GTD)

(1) Hydatidiform moles (HM)
(2) Exaggerated placental site(EPS)
(3) Placental site nodule (PSN)

- Benign lesions

Gestational trophoblastic neoplasia(GTN)

(1) Invasive mole
(2) Choriocarcinoma
(3) Placental site trophoblastic tumor (PSTT)
(4) Epithelioid trophoblastic tumor (ETT)

- Malignant lesions, Potential for local invasion and metastases

Hydatidiform moles (HM)

Is abnormal proliferation of trophoblasts that develop as a result of implantation of an aberrant fertilized oocyte in the uterus, not after a nonmolar pregnancy (abortion, ectopic pregnancy, or preterm or term birth). HM, although benign, are considered to be premalignant because they have the potential to develop into a malignancy.

It can be categorized as **complete mole or partial mole**, which differ by karyotypes, gross and microscopic histopathology, clinical presentations, risk of malignancy prognoses.

EPIDEMIOLOGY

The incidence of HM is difficult to establish with certainty because of the low frequency of the disease and regional variation in reported rates.

- North American and European countries report low or intermediate rates of HM (66 to 121 per 100,000 pregnancies)
- Latin American, Asian, and Middle Eastern nations report a wide range, including high rates (23 to 1299 per 100,000 pregnancies)

RISK FACTORS

(1) Extremes of maternal age

-The risk of complete mole is highest at extremes of maternal age (≤15 and >35 years).

-Most cases of HM, however, still occur in patients under age 35 because of the greater number of pregnancies in this age group.

-The risk for molar pregnancy and its relation to maternal age is much greater in complete mole than partial mole.

-Paternal age does not appear to influence the risk of HM.

(2) Prior molar pregnancy

-The risk for repeat molar pregnancy after the first mole is approximately 1 to 1.5 percent (approximately 10 to 15 times the risk for the general population).

-The recurrence rate after two molar pregnancies has been reported to range from 11 to 25 percent.

(3) Others : history of prior spontaneous abortion and infertility, Dietary factors (vitamin A deficiency).

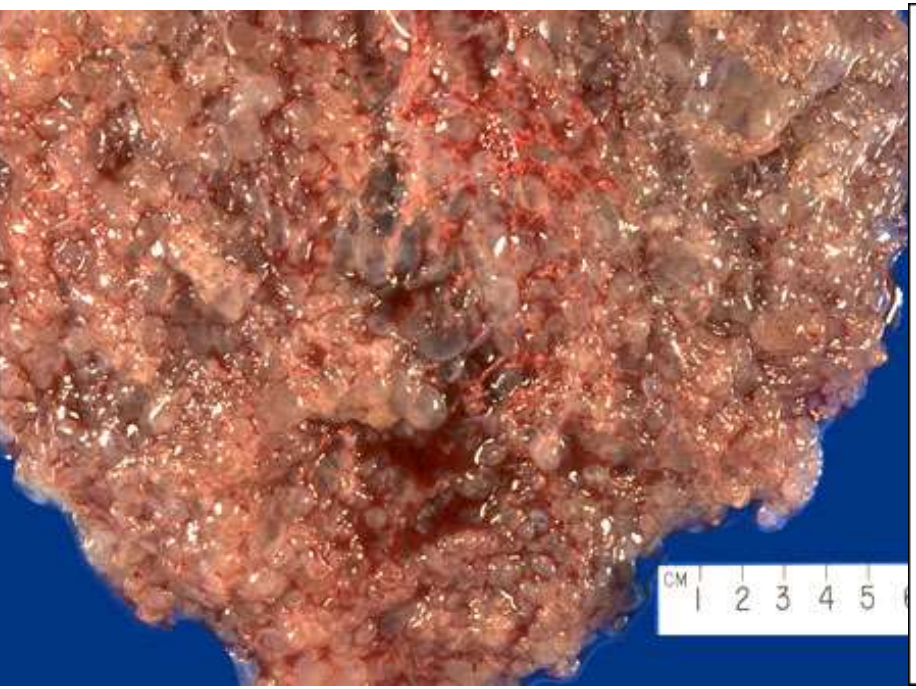
Complete hydatidiform mole

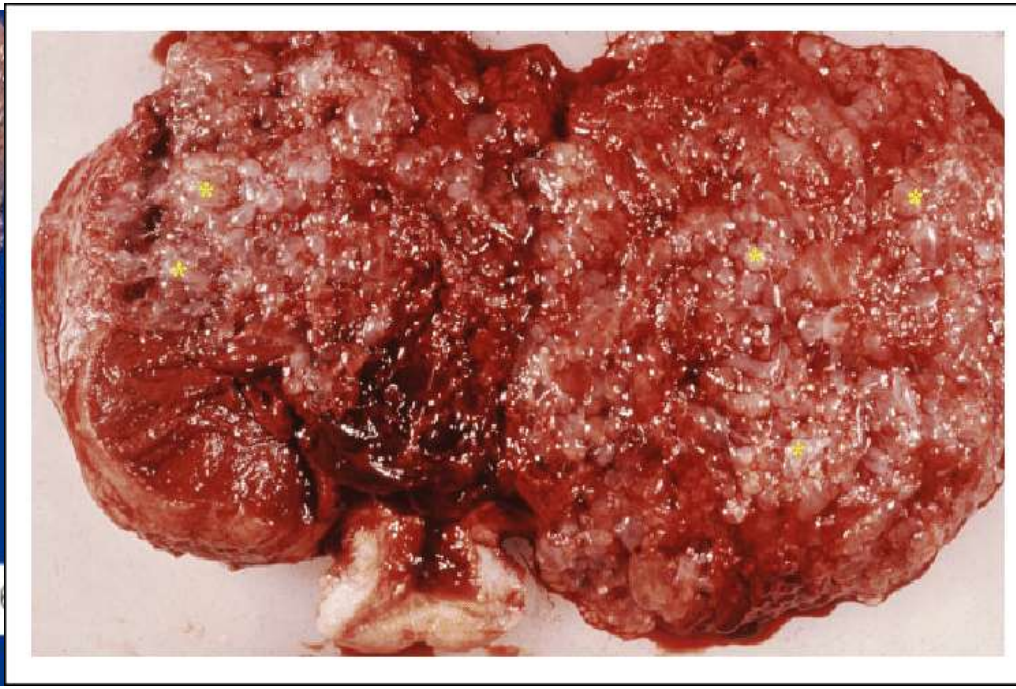
• **Pathogenesis**

- Most commonly this results from fertilization of an **"empty" egg** (ie, absent or inactivated maternal chromosomes) by a **haploid sperm that then duplicates**. It has a 46,XX karyotype, with all chromosomes of paternal origin.
- A small number (3 to 13 percent) of complete moles have a 46,XY chromosome complement. This is thought to occur when an **empty ovum** is fertilized by **two sperm**, one of which carries the Y chromosome.
- Complete moles with a 46,YY karyotype do not occur, presumably because they are nonviable.

• **Histology**

- **The chorionic villi** of a "classic" (ie, fully developed) complete mole are diffusely enlarged and surrounded by hyperplastic, often atypical, trophoblasts. Many villi have internal cavities filled with watery fluid.
- Embryonic and yolk sac development are usually absent.(No fetus)
- Immunohistochemistry, particularly staining for p57, is a key tool for improving diagnostic accuracy and differentiating complete moles from partial moles. The p57 protein is a product of the maternally expressed allele, but not of the paternally silenced allele. Thus, immunohistochemical staining for p57 is absent (or nearly so) in complete mole.





A complete hydatidiform mole, No fetus develops, but there is an abnormal placenta consisting of a mass of tissue with grape-like, swollen chorionic villi.

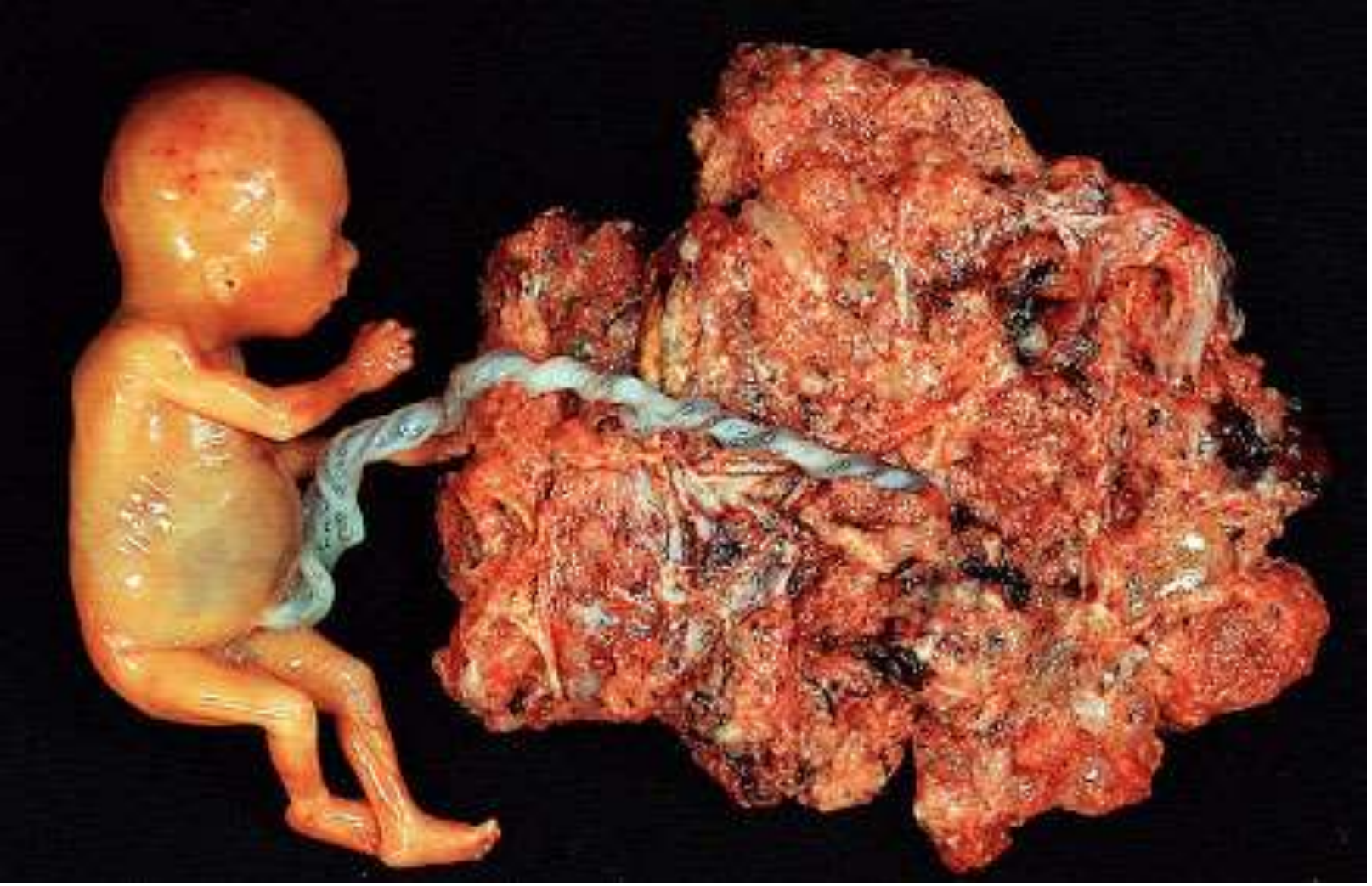
Partial hydatidiform mole

• **Pathogenesis**

- Most commonly result from the fertilization of an **ovum** (with one set of haploid maternal chromosomes) by **two sperm** (with two sets of haploid paternal chromosomes). Karotype (69,XXX, 69,XXY, rarely 69,XYY).
- In about 10% of cases, a tetraploid gestation with three paternal and one maternal genomes.

• **Histology**

- A partial mole is comprised of two populations of chorionic villi: one population is histologically **normal** whereas the second population is **enlarged**, irregularly shaped, and infrequently cavitated (cystic). Marked scalloping of chorionic villi and trophoblastic inclusions (defined as deep, narrow invaginations of the surface trophoblasts deep into the villous stroma.
- With less cavitation, trophoblastic hyperplasia, and atypia when compared with complete moles.
- Fetal tissue or an intact fetus are often found macroscopically or microscopically. Such triploid fetuses may have multiple congenital abnormalities.
- positive p57 immunostaining.



Partial mole

CLINICAL FEATURES

Common Symptoms :

1) Vaginal bleeding :

-Is a common symptom, which results from separation of the molar villi from the underlying decidua.

-At early gestational ages, the timing, volume, or pattern of bleeding in HM does not differ from other pregnancy-associated etiologies (spontaneous abortion, ectopic pregnancy).

-At later gestational ages, with complete mole, vaginal bleeding was often heavy and prolonged and resulted in anemia.

-Vaginal passage of hydropic vesicles.

2) Pelvic pressure or pain

-Is a common symptom, due to the enlarging uterus and/or enlarged cystic ovaries.

3) Hyperemesis gravidarum

-Due to high hCG levels.

-More common in complete mole.

-May develop earlier than in a nonmolar pregnancy and/or be more severe.

On physical examination, On bimanual examination

Uterine size greater than gestational age

-The enlargement is due to both large volumes of molar tissue and retained blood.
-Is more likely with a complete mole than partial mole.
-Patients with a partial mole may have a uterine size that is small for gestational age, due to slow growth of a fetus with triploidy.
-This finding was present in only 21 of 74 (28 percent) patients in one series. Uterine enlargement is a nonspecific finding and may also be present for other reasons (eg, incorrect estimate of gestational age, multiple gestation, uterine leiomyomas).

Bilateral adnexal masses may be present if ovarian theca lutein cysts have developed due to hCG stimulation.

Less common or late clinical features

Anemia – HM may be associated with significant bleeding at later gestational ages, resulting in iron deficiency anemia. Anemia is uncommon when HM is diagnosed in the first trimester.

sequelae associated with the high hCG levels (especially in complete mole) : theca lutein cysts, hyperthyroidism, and early onset of preeclampsia

-These complications occur in approximately 25 percent of patients with uterine size greater than 14 to 16 weeks of gestation.
-hCG levels are typically far lower in partial mole. Thus, partial mole is less likely to be associated with sequelae of hCG stimulation.

Preeclampsia <20 weeks of gestation: Preeclampsia typically develops after 34 weeks of a normal gestation. When it occurs at <20 weeks, complete mole should be suspected.

Hyperthyroidism : Clinical hyperthyroidism is present in HM primarily at later gestational ages. The development of hyperthyroidism requires the elevation of hCG >100,000 U/L for several weeks. These patients may present with tachycardia, warm skin, and tremor. Laboratory evidence of hyperthyroidism is commonly detected in asymptomatic patients with HM. Hyperthyroidism may be accompanied by thyroid storm when the patient undergoes anesthesia, due to the release of catecholamines from the adrenal gland. When pre-evacuation hCG levels exceed 400,000 U/L, administration of beta blockers and antithyroid drugs before complete molar evacuation may avert thyroid storm during or after surgery.

Ovarian theca lutein cysts: are a form of ovarian hyperstimulation resulting from high circulating levels of hCG. These cysts are multiloculated, often bilateral, and resolve a few weeks or months after treatment of HM.
Bilateral theca lutein ovarian cysts may be noted on pelvic examination or pelvic ultrasound. When the uterus is markedly enlarged, theca lutein cysts are difficult to palpate and are usually detected by ultrasonography.

INVESTIGATIONS

Laboratory evaluation

- hCG: A quantitative serum hCG should be measured. The serum hCG concentration in patients with HM is usually higher than that observed with singleton intrauterine or ectopic pregnancies of the same gestational age.

-Markedly elevated hCG levels are more commonly seen in patients with complete mole in contrast to partial mole (e.g > 100,000 U/L).

- Complete blood count, renal panel, liver function tests, urine protein, and thyroid function tests.

-For patients who present in the second trimester, there is a higher risk of complications.

Pelvic ultrasound:

If molar pregnancy is suspected, a transvaginal ultrasound should be performed.

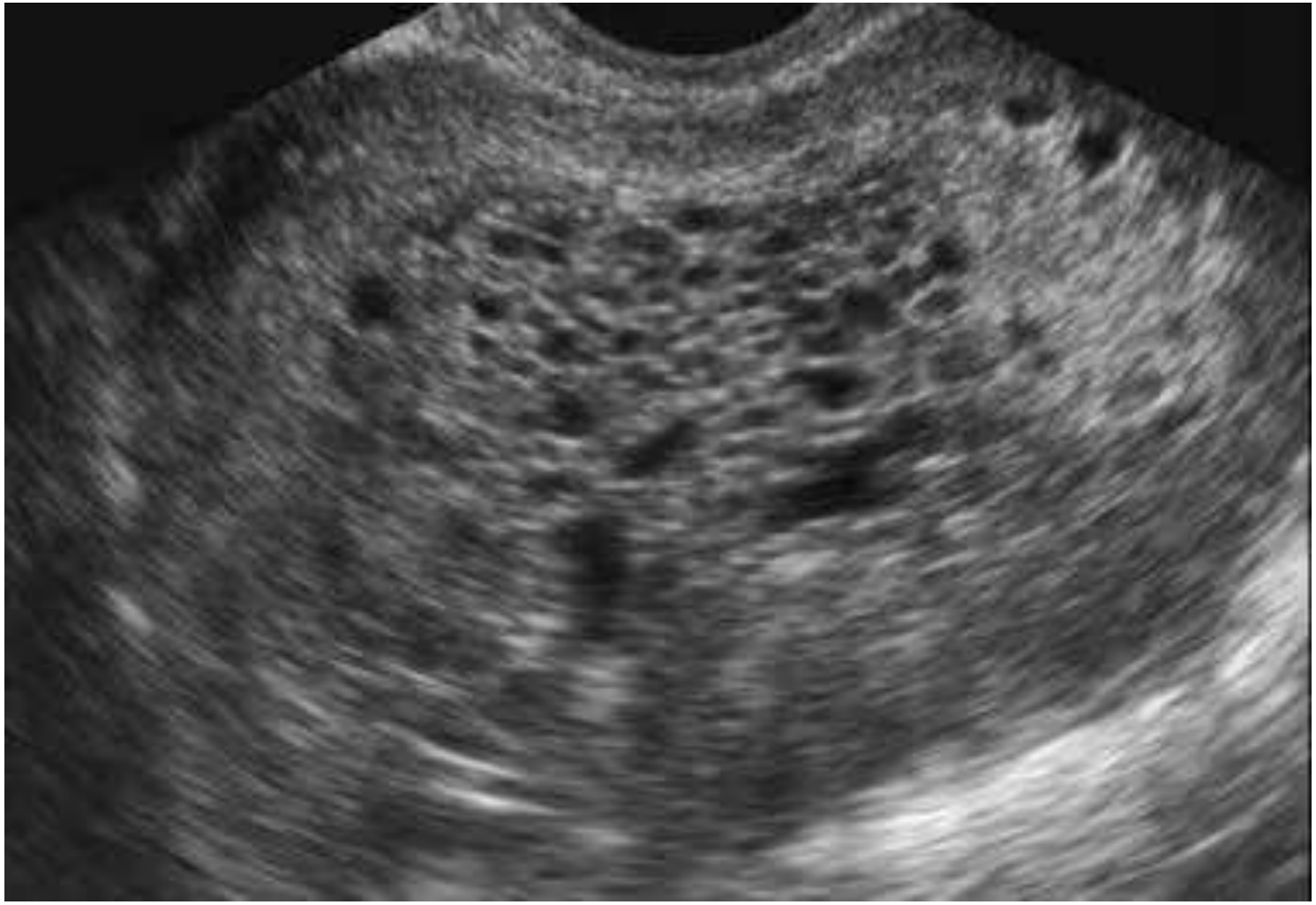
Sonographic features suggestive of a complete mole include:

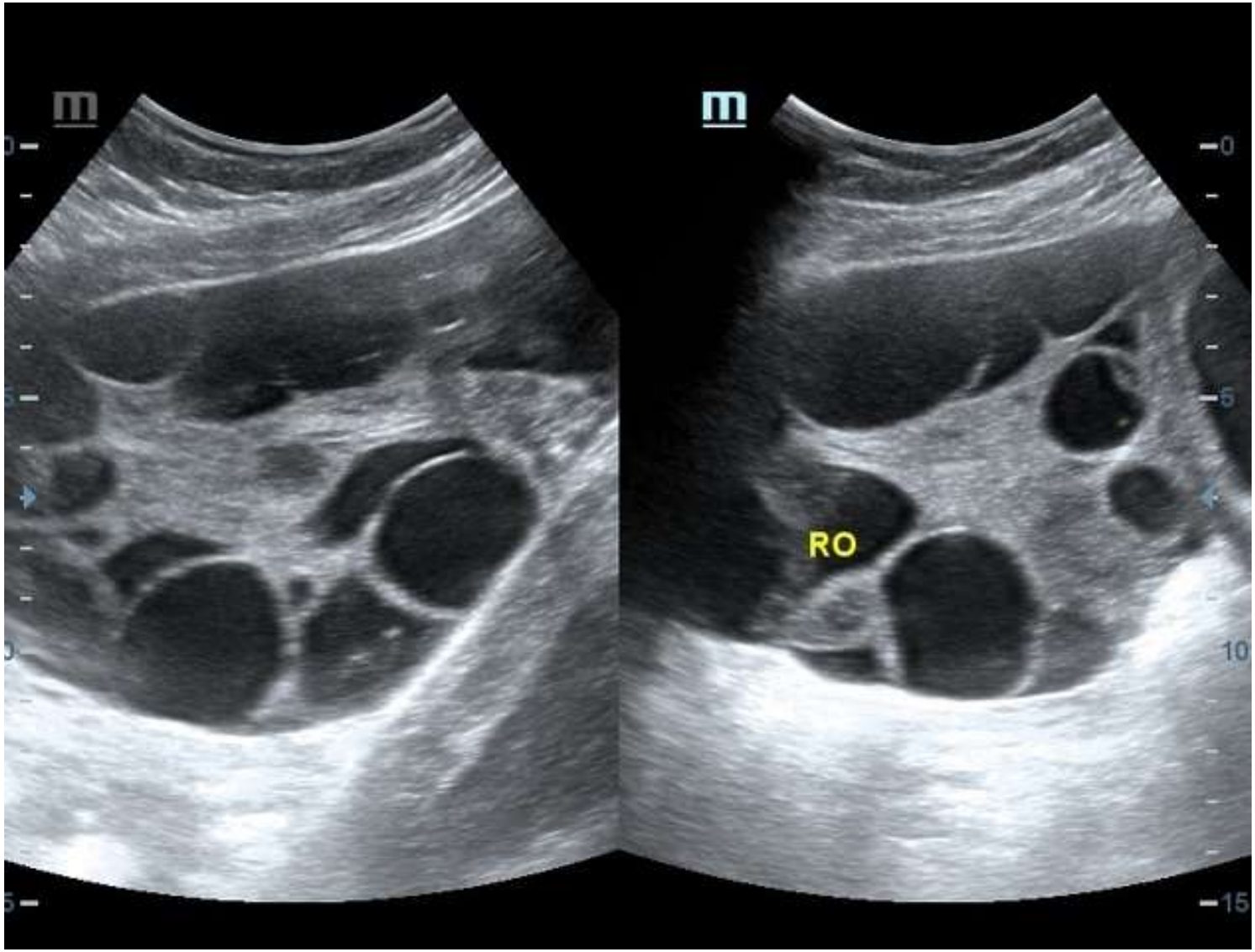
1-Absence of an embryo or fetus.

2-Absence of amniotic fluid.

3-Central heterogeneous mass with numerous discrete anechoic spaces – This has classically been described as a "snowstorm or Swiss cheese pattern" on older ultrasounds.

4-Ovarian theca lutein cysts.

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Sonographic features suggestive of a partial mole include:

1-A fetus may be identified, may be viable, and is often growth restricted.

2-Amniotic fluid is present, but the volume may be reduced.

3-Placenta with one or more abnormal findings – Enlarged, cystic spaces ("Swiss cheese pattern") and/or increased echogenicity of chorionic villi.

4-Increased transverse diameter of the gestational sac – These changes in the shape of the gestational sac may be part of the embryopathy of triploidy.

5-Theca lutein cysts are usually absent.

- Based on ultrasound findings, a partial mole is diagnosed as a missed or incomplete abortion in 15 to 60 percent of cases.

Chest radiograph — When patients present with HM, a chest radiograph is performed only if the patient has pulmonary symptoms such as dyspnea or chest pain.

DIAGNOSIS

HM is a histologic diagnosis, based on a uterine evacuation specimen.

An initial clinical diagnosis and the exclusion of a viable intrauterine pregnancy allows the clinician to proceed with a uterine evacuation. This can be made based on pelvic ultrasound findings characteristic of complete or partial mole and associated clinical features:

●Complete mole – If the ultrasound is indeterminate, a clinical diagnosis of complete mole can be made based on a human chorionic gonadotropin (hCG) >100,000 U/L. Additional supportive findings are theca lutein cysts or hyperthyroidism without another likely etiology. Patients who present with preeclampsia at <20 weeks should be considered to have gestational trophoblastic disease unless proven otherwise.

●Partial mole – Partial mole is difficult to diagnose on ultrasound. A fetus may be present, but may be growth restricted or have low amniotic fluid. Characteristic sonographic findings are present in a minority of cases. The hCG may be elevated above the expected level, but if it is <100,000 U/L, it is not informative. hCG levels vary in normal pregnancy and there is not a standard level for each gestational age. A uterine curettage may be performed if a fetal heartbeat is not present at an appropriate hCG level and gestational age. For earlier gestations, the patient should be followed with serial ultrasound and hCG levels (eg, weekly) until a normal pregnancy can be ruled out.

Distinction between complete and partial molar pregnancy

Feature	Complete mole	Partial mole
Incidence	1/1500 pregnancies	1/750 pregnancies
Karyotype	Diploid: 46,XX (less than 15 percent are 46,XY)	Triploid: 69,XXX, 69,XXY (rarely 69,XYY)
Embryonic/fetal tissue	Typically absent (may be present in few cases)	Present
Villi	Diffusely hydropic	Hydropic villi with marked scalloping mixed with normal appearing chorionic villi and fetal tissue; hydropic changes are focal and less prominent than in complete mole
Trophoblastic proliferation	Hyperplastic	Less trophoblastic hyperplasia than in complete mole; trophoblastic stromal inclusions can be seen
Trophoblastic atypia	Often present	Infrequent
Immuncoytochemistry	hCG*, rare PLAP•	hcG, PLAP, p57
Uterine size	Often large for dates	Often small for dates
Theca lutein cysts	Present in ≤25 percent	Rare
Persistent mole	15 to 20 percent	3 to 5 percent
Choriocarcinoma	3 percent	0.1 percent

Treatment and follow-up of HM

Surgical removal of the HM is the central component of treatment and can be accomplished by either **uterine evacuation** or **hysterectomy.**

-Surgical uterine evacuation(Suction evacuation) for most patients, it is effective, preserves childbearing capacity, and is less morbid.

-Hysterectomy is a reasonable alternative for patients who have completed childbearing, particularly those with a known or presumptive complete mole and the following risk factors for gestational trophoblastic neoplasia (GTN):

1-Signs of excessive trophoblastic proliferation (eg, uterine size greater than gestational age, serum human chorionic gonadotropin [hCG] levels >100,000 milli-international units/mL, ovarian theca lutein cysts >6 cm in diameter).

2-Evidence of myometrial invasion on diagnostic imaging studies.

3-Age >40 years.

OUTCOME

Frequency of gestational trophoblastic neoplasia after molar pregnancy

After a complete mole — approximately 15 to 20 percent of patients develop gestational trophoblastic neoplasia (GTN). Invasive disease is several-fold more common than metastatic disease.

After a partial mole — approximately 1 to 5 percent of patients develop GTN. Almost all patients with GTN have invasive disease; metastatic disease is rare.

POSTOPERATIVE MONITORING

Postoperative human chorionic gonadotropin (hCG) monitoring is performed to detect development of gestational trophoblastic neoplasia (GTN), which is indicated by an hCG level that does not return to undetectable. Persistent hCG elevation is usually due to molar tissue that invaded the myometrium (ie, invasive mole) and thus was not completely removed by aspiration and curettage, but a small proportion are due to metastatic invasive mole. Occasionally, persistent hCG elevation is due to development of choriocarcinoma and, very rarely, to development of placental site trophoblastic tumor or epithelioid trophoblastic tumor.

After surgical treatment of HM (evacuation or hysterectomy), measurements of serum hCG levels are obtained weekly in all patients until the level remains undetectable (< 5 U/L) then monthly (one to six months).

Contraception during monitoring — Patients with HM must be advised to use reliable contraception during the entire period of postoperative hCG monitoring. A new pregnancy during this time would make it difficult or impossible to interpret hCG results and would complicate management. Options include hormonal contraception (progestin-only or combined estrogen-progestin) or barrier methods.

Diagnosis of Postmolar GTN if any:

1-Increasing hCG levels : level that progressively increases >10 percent across three value during at least a two-week period (eg, on days 1, 7, and 14).

2-Plateaued hCG levels : is defined as four measurements that remain within ±10 percent over at least a three-week period (eg, days 1, 7, 14, and 21).

3-Persistence of detectable serum hCG for more than six months after molar evacuation.

4-The histologic identification of choriocarcinoma.

5-The presence of metastatic disease.

Obstetric outcomes of subsequent pregnancies — In general, patients with either a complete or partial mole can anticipate normal future reproductive outcomes.

Estimates of the risk of subsequent HM are:

- After one molar pregnancy: 1 to 1.9 percent.

- After two molar pregnancies: 15 to 17.5 percent.

OBSTETRIC MANAGEMENT OF SUBSEQUENT PREGNANCIES

Due to the risk of recurrent HM, in our practice, we do the following in patients with a prior HM who become pregnant:

- First-trimester ultrasound to confirm normal gestational development.

- After delivery, carefully examine the placenta and send to pathology for histologic examination if any gross abnormalities are present.

- Measure serum human chorionic gonadotropin (hCG) six weeks after the completion of any type of future pregnancy (eg, term delivery, miscarriage, pregnancy termination) to exclude choriocarcinoma.

- Send all products of conception from miscarriages and pregnancy terminations for examination by a pathologist.

Gestational trophoblastic neoplasia

Refers to a group of malignant neoplasms that consist of abnormal proliferation of trophoblastic tissue, and may follow a hydatidiform mole or a nonmolar pregnancy. GTN is comprised of the following histologic types:

- Invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumor (PSTT)
- Epithelioid trophoblastic tumor (ETT)

Invasive mole and choriocarcinoma are characterized by high levels of human chorionic gonadotropin (hCG), while PSTT and ETT typically have low hCG levels.

Prior to the development of effective chemotherapy for GTN, the majority of patients with disease localized to the uterus were cured with hysterectomy, but metastatic disease was almost uniformly fatal. With the use of sensitive quantitative assays for hCG and appropriate management with highly effective chemotherapy, most patients with GTN can be cured and their reproductive function preserved.

EPIDEMIOLOGY

The incidence of GTN is difficult to establish with certainty because data regarding the incidence of pregnancies and subsequent trophoblastic events are not available in most countries.

Approximately 50 percent of cases of GTN arise from molar pregnancy, 25 percent from pregnancy loss or tubal pregnancy, and 25 percent from term or preterm pregnancy.

GTN after a nonmolar pregnancy, usually choriocarcinoma but rarely PSTT or ETT, occurs in approximately 2 to 7 per 100,000 pregnancies in Europe and North America, whereas in Southeast Asia and Japan, the incidence is higher at 5 to 200 per 100,000 pregnancies, respectively.

Invasive mole

-Develops after a molar pregnancy and is characterized by the presence of edematous chorionic villi with trophoblastic proliferation invading the myometrium.
-Uterine rupture and severe intraperitoneal hemorrhage may occur if deep myometrial invasion is left untreated.
-Metastases of invasive moles spread hematogenously; the lungs and vagina are the most common sites.

Choriocarcinoma

-Consists of invasive, highly vascular, and anaplastic trophoblastic tissue made up of cytotrophoblasts and syncytiotrophoblasts without villi.

-Choriocarcinoma can follow any type of pregnancy:

●Following a molar pregnancy, choriocarcinoma is more common after a complete mole rather than a partial mole.

●Following a nonmolar pregnancy, choriocarcinoma is the most common type of GTN; placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT) makes up only 1 to 2 percent of GTN following nonmolar pregnancy. Diagnosis is often delayed following a nonmolar pregnancy and thus, metastases are more common than after a molar pregnancy.

Choriocarcinoma is the most aggressive histologic type of GTN and is characterized by early vascular invasion and widespread metastases. The clinical presentation of choriocarcinoma depends upon extent of disease and location of metastases. Choriocarcinoma metastasizes hematogenously. The clinical presentation is often due to bleeding from a metastatic site.

Placental site trophoblastic tumor — PSTT

-Is a rare malignant and develop from extravillous, intermediate trophoblasts.
-Occurs most commonly after a nonmolar abortion or pregnancy, although it can also occur after a molar gestation.
-May be diagnosed several months or even years after the pregnancy. This time interval from antecedent pregnancy is highly prognostic for PSTT
-It secretes very low levels of hCG.
-Tends to remain localized in the uterus for long periods before metastasizing to regional lymph nodes or other metastatic sites. Approximately 30 percent of patients present with metastatic disease.

Epithelioid trophoblastic tumor

-Is a rare variant of GTN. Similar clinical presentation to PSTT.

In general, the sites of GTN metastases :

- **Pulmonary** (80 percent).
- Vagina (30 percent).
- Central nervous system (CNS) metastases (10 percent) are usually in the brain and, rarely, in the meninges. Virtually all patients with CNS metastases have concurrent pulmonary and/or vaginal involvement.
- Hepatic (10 percent).
- Other sites (kidney, gastrointestinal tract, spleen).

CLINICAL PRESENTATION

-GTN has a varied presentation depending upon the antecedent pregnancy, extent of disease, and histopathology. GTN may follow a molar pregnancy (complete or partial) or any other pregnancy event (pregnancy loss, induced abortion, preterm or term pregnancy).

1)GTN most commonly presents following evacuation of a hydatidiform mole.

2) GTN following a term or preterm gestation may present with amenorrhea, but usually presents with AUB due to invasion of uterine tumor or bleeding from a metastatic site. Bleeding from uterine perforation or metastatic lesions may result in abdominal pain, hemoptysis, or melena. Patients with central nervous system (CNS) metastases often exhibit evidence of increased intracranial pressure from intracerebral hemorrhage, leading to headaches, dizziness, seizures, or hemiplegia. Patients who develop extensive pulmonary metastases may present with dyspnea, cough, or chest pain. Rapid growth, widespread dissemination, and a high propensity for hemorrhage makes this tumor a medical emergency.

-Elevated human chorionic gonadotropin (hCG), At levels >100,000 milli-international units/Ml hCG stimulation effects may develop, These include symptoms or findings of hyperthyroidism, ovarian theca lutein cysts, and rarely, hyperemesis or preeclampsia.

STAGING AND RISK ASSESSMENT

All patients with GTN are classified according to FIGO staging and the WHO risk scoring system:

(A) <u>Low-risk GTN</u>
1-FIGO stage I GTN or
2-Stage II or III GTN with a WHO risk score <7.

(B) <u>High risk GTN</u>
1-Stages II and III with risk score >6 or
2-Stage IV disease

The International Federation of Gynecology and Obstetrics (FIGO) staging

Stage I — All patients with persistently elevated beta-hCG levels and tumor confined to the uterus.

Stage II — The presence of tumor outside of the uterus, but limited to the vagina and/or pelvis.

Stage III — Pulmonary metastases with or without uterine, vaginal, or pelvic involvement.

Stage IV — All other metastatic sites (eg, brain, liver, kidneys, gastrointestinal tract).

WHO scoring system based on prognostic factors

Score of 6 or less classified as low risk, score of 7 or more classified as high risk.

WHO risk factor scoring with FIGO staging	0	1	2	4
Age	<40	>40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from index pregnancy, months	<4	4-6	7-12	>12
Pretreatment hCG mIU/mL	$<10^3$	$>10^3$-10^4	$>10^4$-10^5	$>10^5$
Largest tumor size including uterus, cm	<3	3-4	>5	–
Site of metastases including uterus	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases identified	0	1-4	5-8	>8
Previous failed chemotherapy	None	None	Single drug	Two or more drugs

MDedge News

Note: WHO scoring system adapted by the International Federation of Gynecology and Obstetrics.

Source: Int J Gynecol Obstet. 2018;143[S2]:79-85

MANAGEMENT OF GTN

low-risk GTN

-Single-agent chemotherapy, using either methotrexate (MTX) or dactinomycin (ActD).

High risk GTN

-Multi-agent chemotherapy, etoposide, methotrexate (MTX), plus actinomycin D (ActD) alternating with cyclophosphamide and vincristine (EMA-CO).

- All women with GTN should be monitored with weekly serial measurements of serum beta-hCG during therapy. Remission is defined as three consecutive normal hCG values (less than 5 milli-international units/mL) over 14 to 21 days.

- After remission is achieved, serum beta-hCG should be measured monthly until monitoring has shown one year of normal hCG levels.

- Contraception, It is essential that women use contraception both during and for the entire duration of beta-hCG follow-up(at least one year). Estrogen-progestin contraceptives are preferred because of their low failure rate and relatively low incidence of irregular bleeding.