

Evaluation and management of gestational trophoblastic disease

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Failure to cure patients with gestational trophoblastic disease (GTD) has been attributed mainly to the presence of extensive choriocarcinoma at the time of diagnosis, lack of initial high-risk therapy, and the inability of presently used chemotherapy protocols to control disease. However, with accurate initial treatment, GTD is considered to be highly curable. In this article, the authors explore the diagnostic approaches to and current management options for patients with hydatidiform moles and GTD.

Gestational trophoblastic disease (GTD) is considered highly curable, but accurate initial management is essential. The general gynecologist will most commonly encounter hydatidiform molar pregnancies, which are classified as either partial or complete and may progress to gestational trophoblastic neoplasia (GTN), including choriocarcinoma. According to the American College of Obstetricians and Gynecologists (ACOG), "Practicing ob/gyns should be able to diagnose and manage primary molar pregnancies, stage malignant trophoblastic disease, and assess risk in women with malignant trophoblastic disease to allow referral for appropriate initial treatment."¹ Recently, the International Federation of Gynecology and Obstetrics (FIGO) reissued simplified guidelines for the staging and diagnosis of GTD.²

Hydatidiform mole

Presentation

There is a significant increase in the incidence of molar pregnancy at the extremes of reproductive age. Vaginal bleeding is the most common symptom, resulting from the separation of the molar villi from the decidua and the interruption of the maternal vessels. Retained blood clots and molar tissue can distend the uterine cavity, resulting in size greater than expected for gestational age. GTD produces hCG (human chorionic gonadotropin), which can be measured in either urine or serum and will be elevated for gestational age.

With the advent of sensitive serum hCG testing and ultrasonography leading to earlier diagnosis, "classic" medical complications of a complete mole,

such as theca lutein cysts, preeclampsia, hyperemesis, and hyperthyroidism, are no longer seen as frequently in the United States, though they may be seen in up to 25% of patients with a uterine size greater than 14–16 weeks.³ According to data from the New England Trophoblastic Disease Center (NETDC) throughout the 1960s and 1970s, enlarged uterine size was noted in 51% of cases, theca lutein cysts in 50%, preeclampsia in 27%, hyperemesis in 26%, and hyperthyroidism in 7%.⁴ A subsequent report from 1993–1998 at the same institution revealed uterine size was greater than dates in 28% of the more recent cases, theca lutein cysts in 9%, preeclampsia in 1%, hyperemesis in 6%, and there were no hyperthyroid-related or respiratory events.⁵ However, 84% of the more recent cases had uterine evacuation in the first trimester, compared with 30%–57% in the prior study.

The need for routine histopathologic examination of spontaneous miscarriage has generated controversy, especially as women present earlier in pregnancy. Although the results of most first-trimester ultrasonographic studies of complete moles will demonstrate a typical diagnostic appearance, degenerating products of conception may resem-

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ble early molar disease.^{6,7} This is especially true for partial molar pregnancies, for which ultrasonographic characteristics may be difficult to identify prior to the second trimester; they are often diagnosed as missed abortions. There is no evidence that routine use of pathologic or early ultrasonographic studies is cost-effective or will decrease the incidence of GTN, but some investigators recommend submitting all tissue obtained for histopathologic evaluation and/or follow-up with hCG testing.⁸ Similar concerns have been expressed for women undergoing early elective termination of pregnancy.

Evaluation and management

Initial evaluation for molar disease should include a work-up for anemia, preeclampsia, electrolyte imbalance, and hyperthyroidism as well as a baseline chest x-ray. Pulmonary complications have been noted in patients with a gestational size greater than 16 weeks and are associated with preeclampsia, fluid overload, anemia, hyperthyroidism, or emboli at the time of evacuation.

Suction curettage is standard treatment, unless fetal structures (ie, a partial mole) preclude the use of this method.⁹ Medical methods are associated with a higher rate of chemotherapy and should not be used.⁹ If the patient does not wish future child-bearing, a hysterectomy decreases the risk of malignant sequelae to 3%–5% but does not eliminate the need for close follow-up. A laparotomy set and facilities for hemodynamic monitoring should be available during evacuation of the mole with significant uterine enlargement. Oxytocin should be initiated in the operating room before the procedure is performed, and blood products should be readily available.

Hypertension and hyperthyroidism usually resolve acutely after evacuation, although it may take ovarian cysts from hCG stimulation several months to resolve.

Follow-up

Approximately 20% of complete molar pregnancies and 5% of partial molar pregnancies have malignant sequelae requiring chemotherapy after uterine evacuation.¹⁰ Clinical features associated with such an increased risk include pre-evacuation hCG levels, uterine size, theca lutein cysts, associated medical factors, maternal age > 40 years, and previous molar pregnancy.

After molar evacuation, patients should be followed with serial serum hCG values and are considered to have achieved remission when hCG levels decline to undetectable levels for 6 months.¹¹ The NETDC has suggested that postevacuation monitoring for women with uncomplicated molar pregnancy may be shortened without compromising risk, as no patient at this center recurred after achieving two consecutive undetectable hCG levels.¹² Patients also should use reliable contraception so as not to obscure the diagnosis of persistent or recurrent disease. Use of oral contraceptives neither increases the risk of GTN nor causes a delay in achieving normal hCG values.¹³ Pelvic examination should document uterine involution and may identify early vaginal metastasis.

Gestational trophoblastic neoplasm

Diagnosis

After a complete molar pregnancy, the majority of cases of GTN will consist of nonmetastatic persistent or invasive moles. The minority of cases will involve metastatic disease, which may manifest histologically as a choriocarcinoma. The diagnosis of GTN after molar pregnancy is most commonly determined by persistently rising or plateauing hCG levels after evacuation; alternatively, GTN can be diagnosed if histologic results from the uterine evacuation show invasive molar proliferation, choriocarcinoma, or tro-

phoblastic tumor of the placental site. New intrauterine pregnancy should be ruled out on the basis of hCG levels and ultrasonographic findings.

The FIGO Council 2000 criteria for the diagnosis of posthydatidiform mole GTN follow:

- A rise in hCG level of 10% or higher of three values recorded over 2 weeks (days 1, 7, and 14)
- A plateau in hCG level (\pm 10%) of four values recorded over 3 weeks (days 1, 7, 14, and 21)
- The persistence of a detectable hCG level at 6 months or more after evacuation of the mole
- A histologic diagnosis of choriocarcinoma

Less commonly, choriocarcinoma will develop after a nonmolar gestation, including normal pregnancy, abortion, or ectopic pregnancy. Cases not following a known prior molar pregnancy may present many years after an antecedent pregnancy, and diagnosis can initially be baffling. Having a high index of suspicion may avoid an unnecessary thoracotomy or craniotomy for diagnostic purposes when a simple hCG level can be diagnostic. Any woman of reproductive age with brain metastasis or cerebral hemorrhage of unexplained etiology should be screened for GTN with an hCG level. For the patient with abnormal bleeding for more than 6 weeks after pregnancy, dilation and curettage may be helpful, although disease is sometimes deep in the myometrium and unobtainable by curettage. Additionally, disease may sometimes be confined to metastatic implants.

False-positive or phantom hCG level results

In 2001, the Society for Gynecologic Oncologists issued a warning regarding phantom hCG results. Laboratory assays for hCG levels may yield false-positive results, which have been reported to be as high as 800 mIU/mL or possibly higher. These

false-positive results may be caused by antimouse antibodies, heterophile antibodies, and a nonspecific protein interface. Furthermore, false-positive results have been reported with many different assay kits (platforms) from numerous manufacturers.¹⁴

Since the management of GTD is often guided by the hCG level, it is important to consider the possibility of a false-positive result, especially in discordant clinical situations. The presumptive diagnosis of either ectopic pregnancy or GTN has been the basis of unnecessary treatment. A prime consideration is to obtain a urinary hCG level, since the substances do not appear to be excreted in their interfering form in the urine.

Classification

The work-up of GTN must establish whether the disease is locally invasive or metastatic and whether the risk of therapeutic failure is high or low. The pattern of metastatic spread is hematogenous, and metastasis to the lungs is most common initially, followed by systemic dissemination, often to the brain and liver. At this point, the work-up to identify metastatic disease should include the following:

- Complete blood cell count (CBC), liver function tests, examination for clotting deficiency
- Neurologic and fundoscopic examinations
- Examination of the vaginal fornices and suburethral areas
- Chest x-ray, brain MRI or CT, abdominal CT, and liver MRI or CT.

Several classification systems for GTN exist, all of which identify patients at risk for therapeutic failure. The clinical classification system has been traditionally used in the United States and separates metastatic GTN according to prognosis (Table 1).¹⁵ However, in March 2002, the FIGO Council published the revised classification system for GTN combining the previous anatomic FIGO staging with the modified World Health Organization (WHO)

TABLE 1

Traditional classification system for gestational trophoblastic disease

Stage	Description
Stage I	Nonmetastatic gestational trophoblastic disease
Stage II	Metastatic gestational trophoblastic disease
	A. Good prognosis
	1. Urinary hCG level < 100,000 IU/24 h or serum hCG level < 40,000 IU/L
	2. Symptoms present for < 4 months
	3. No brain or liver metastases
	4. No prior chemotherapy
	5. Pregnancy is not term delivery (ie, mole, ectopic, or spontaneous abortion)
	B. Poor prognosis
	1. Urinary hCG level > 100,000 IU/24 h or serum hCG level > 40,000 IU/L serum
	2. Symptoms present for > 4 months
	3. Brain or liver metastases
	4. Prior chemotherapeutic failure
	5. Antecedent term pregnancy

hCG = human chorionic gonadotropin

TABLE 2

Revised FIGO classification system for gestational trophoblastic neoplasia

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

Variable	FIGO risk factor score			
	0	1	2	4
Age (years)	–	40	> 40	–
Antecedent term pregnancy	Hydatidiform mole	Abortion	Term	–
Interval (months) from index pregnancy	< 4	4–6	7–12	> 12
Pretreatment hCG level (mIU/mL)	< 10 ³	10 ³ –10 ⁴	> 10 ⁴ –10 ⁵	> 10 ⁵
Largest tumor size, including uterus	–	3–4 cm	5 cm	–
Site of metastases	–	Spleen/kidneys	GI tract	Brain/liver
Number of metastases identified	0	1–4	5–8	> 8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

FIGO = International Federation of Gynecology and Obstetrics; GTN = gestational trophoblastic neoplasia; hCG = human chorionic gonadotropin; GI = gastrointestinal

risk factor scoring system (Table 2).²

Management

Initial treatment of low-risk GTD consists of single-agent chemothera-

py, usually methotrexate with or without folic acid rescue or dactinomycin (Cosmegen), and is continued for 1 cycle after the first normal hCG value.¹⁶ If the tumor is resistant to ini-

tial single-agent therapy, and the patient is still at low risk, the alternative single agent is utilized. If alternative single-agent therapy fails, the patient is treated with multiagent regimens. Although 10%–15% of patients with low-risk disease will require multiagent chemotherapy with or without surgery to achieve remission, nearly all patients can be salvaged.

The combination chemotherapy EMA-CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine [Oncovin]) has widely become accepted as the treatment of high-risk disease,¹⁷ although there is a dearth of randomized studies in patients with this disease. EMA-CO may improve the primary response rate and lower the acute toxicity rate, compared with MAC (methotrexate, dactinomycin, and cyclophosphamide), especially among patients at high risk, but theoretically may increase the risk of leukemia.¹⁸ Twenty-five percent of patients with high-risk disease will have an incomplete response to or relapse from a methotrexate-containing regimen such as EMA-CO. These patients should be treated with salvage chemotherapy regimens employing platinum, often in conjunction with surgical resection of sites of persistent tumor in the uterus or lungs.¹⁹ Many patients with resistant tumors are initially treated ineffectively; therefore, the importance of appropriate referral of patients with high-risk GTD to clinicians who have experience with this relatively rare disease cannot be overemphasized.

The use of a second evacuation is limited in the United States to patients with persistent uterine bleeding, although the Sheffield Trophoblastic Disease Center in the United Kingdom has reported that second curettage eliminated the need for chemotherapy in 60% of patients with persistent GTD.²⁰ Second evacuation is most useful in patients with retained partial molar tissue. Hyster-

ectomy will shorten the duration and lower the dosage of chemotherapy administered and may be considered for patients who do not desire fertility.²¹ Disease refractory to chemotherapy and confined to the uterus may also be treated with hysterectomy.

Subsequent pregnancy

Most patients can expect a normal reproductive outcome for pregnancies occurring at least 6 months after the completion of treatment, although for unclear reasons, several series have reported a higher stillbirth rate for such patients.^{22–25} No differences in pregnancy outcomes have been noted between those treated with combination chemotherapy and those treated

For more information

Visit the comprehensive and authoritative Web site of the International Society for the Study of Trophoblastic Diseases (www.isstd.org). The site includes an online reference book written by world renowned experts and information for patients.

with single-agent chemotherapy. No increase in congenital malformations has been reported in those who have received chemotherapy. Infertility rates after chemotherapy for GTN appear to be no higher than those for the general population.

As the risk of recurrence is about 1% with one molar pregnancy and 15%–28% with two molar pregnancies, late first-trimester ultrasonography should be performed with all subsequent pregnancies.²³ Six weeks after delivery, an hCG level should be obtained to exclude occult choriocarcinoma. Although all products of conception should be examined pathologically after a subsequent spontaneous or therapeutic abortion, the utility of routine placental examination after a subsequent normal pregnancy is questionable. Patients should be counseled that pregnancy prior to the completion of follow-up

is likely safe, but a relapse would be more difficult to detect. Any vaginal bleeding or systemic symptoms should be promptly evaluated.

As recurrent molar pregnancies have been documented with a change of partner, and even with donor insemination, a primary oocyte is probable in such cases.²⁴ Patients with repetitive molar pregnancies may benefit from assisted reproductive techniques, such as intracytoplasmic sperm injection combined with preimplantation genetics, to confirm the biparental origin or alternatively the donor ovum²⁵; these patients also have a high risk of developing GTN with each subsequent episode of molar disease.

Conclusion

The past 40 years have seen significant advances in the treatment of GTD. Regional treatment centers have been created to provide excellent management and follow-up care; new therapies and clinical classifications related to therapy have also been developed. Failure to cure patients with GTD is attributable mainly to the presence of extensive choriocarcinoma at the time of diagnosis, lack of initial high-risk therapy, and the inability of presently used chemotherapy protocols to control disease.

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