State-of-the-Art Workup and Initial Management of Newly Diagnosed Molar Pregnancy and Postmolar Gestational Trophoblastic Neoplasia

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ABSTRACT

Gestational trophoblastic disease refers to a series of interrelated tumors arising from the placenta, including benign molar pregnancies as well as the malignant conditions termed *gestational trophoblastic neoplasia* (GTN). GTN most commonly follows a molar pregnancy but may develop after any gestation. The wide availability of first trimester ultrasound and serum human chorionic gonadotropin (hCG) measurement has changed the presentation of molar pregnancy in recent decades from a second trimester to a first trimester disease, such that most patients have few symptoms at diagnosis. With identification of molar pregnancy at earlier gestations, accurate diagnosis increasingly relies on expert histopathology coupled with ancillary molecular and genetic techniques. However, earlier diagnosis has not changed the risk of postmolar GTN. Although most molar pregnancies are treated with dilation and curettage, hysterectomy may be appropriate in select cases when future fertility is not desired. After treatment of molar pregnancy, close surveillance with serial hCG monitoring is essential to diagnose GTN and identify the need for chemotherapy. Physicians following hCG levels should understand the performance characteristics of the test, including common causes of false-positive and false-negative results. After a diagnosis of postmolar GTN is made, selection of single-agent or multiagent chemotherapy depends on accurate assignment of the clinical stage and risk stratification by the International Federation of Gynecology and Obstetrics (FIGO) prognostic scoring system. Surgical treatment of postmolar low-risk GTN, including both second uterine curettage and hysterectomy, may decrease subsequent need for or duration of chemotherapy. Cure rates for postmolar low-risk GTN approach 100%, and subsequent pregnancy outcomes for patients reflect those of the general population.

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Gestational trophoblastic disease includes a spectrum of interrelated tumors, including complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).[1–3] After CHM and PHM, gestational trophoblastic neoplasia (GTN) develops in 15% to 20% and 1% to 4% of patients, respectively, with local uterine invasion with or without metastases.[3,4] GTN most commonly follows a molar pregnancy but may develop after any gestation.

Molar Pregnancy: Complete Versus Partial

CHM and PHM differ based on their chromosomal pattern, gross morphology, and histopathology (Table 1).[5] CHM is generally diploid, and the molar chromosomes are generally entirely of paternal origin.[5] CHM is associated with more generalized trophoblastic hyperplasia and hydropic swelling of the chorionic villi and is not associated with fetal or embryonic tissues. PHM is generally triploid, in which the extra set of chromosomes is of paternal origin. PHM is associated with more focal trophoblastic hyperplasia and hydropic swelling of villi and is often associated with fetal or embryonic tissues. Rarely, in familial recurrent molar pregnancy CHM has a biparental chromosomal pattern and is associated with a mutation in the genes *NLRP7* or *KHDC3L*.[6,7]

Presentation of Molar Pregnancy

The classic description of CHM includes excessive uterine enlargement, theca lutein ovarian cysts, hyperemesis, preeclampsia, and hyperthyroidism. The medical complications of theca lutein ovarian cysts, preeclampsia, and hyperthyroidism are primarily associated with marked trophoblastic proliferation with particularly high human chorionic gonadotropin (hCG) levels and excessive uterine size. In recent years, CHM is more commonly diagnosed earlier in the first trimester, and these dramatic signs and symptoms are much less frequent.[8–11] Although excessive uterine size, preeclampsia, hyperemesis, and hyperthyroidism used to occur in 51%, 27%, 26%, and

Table 1. Genetic and Histopathologic Features of Molar Pregnancy

	Complete	Partial
Karyotype	Generally diploid or tetraploid; generally all chromosomes paternal	Generally triploid; extra set of chromosomes is paternal
Hydropic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of villi	Absent	Present
Fetal or embryonic tissue	Absent	Present
p57 expression	Negative	Positive

7% of cases, respectively, during the 1970s and 1980s, in recent years these symptoms have declined to 28%, 1.3%, 8%, and 0%, respectively.[8]

The availability of both ultrasonography and hCG measurement has led to the earlier diagnosis of CHM. If a patient presents with irregular bleeding during pregnancy, ultrasound and hCG measurement are commonly obtained and may diagnose an abnormal pregnancy, leading to pregnancy termination. Although approximately 50% of complete moles are associated with pre-evacuation hCG levels >100,000 mIU/mL, a single hCG level is seldom helpful in differentiating a complete mole from another type of pregnancy. Early diagnosis of CHM has also led to a change in pathology, with less prominent trophoblastic hyperplasia and hydropic villi.[12] Early CHM can be more difficult to distinguish pathologically from PHM and hydropic abortion. The absence of p57 expression on the maternal allele can be helpful in diagnosing early CHM. Importantly, early diagnosis of CHM has not led to a reduction in the development of GTN, although it has resulted in fewer medical and surgical complications.[8–11]

In previous years, PHM rarely presented with the classic signs and symptoms of CHM. Patients with PHM generally presented with irregular bleeding and were usually thought to have a missed or incomplete abortion.[13,14] In a series of 81 patients with PHM, 74 (91%) were thought to have a missed or incomplete abortion before uterine evacuation.[13] In more recent years, however, similar to CHM, PHM is generally diagnosed in the first trimester. Sun et al[15] reported that, at Brigham and Women's Hospital from 1994 through 2013, the median gestational age at uterine evacuation for CHM and PHM was 9 and 12 weeks, respectively.

Ultrasound and Molar Pregnancy

Ultrasound is the most precise method of diagnosing CHM and PHM before evacuation. Classic sonographic findings of CHM include a heterogeneous uterine mass with cystic spaces, no identifiable fetus or embryo, and no amniotic fluid. Ovarian theca lutein cysts may also be present. However, the classic ultrasound features may be subtle or absent in an early first trimester CHM. Estimates of the sensitivity of pelvic ultrasound in diagnosing complete mole range from 70% to 90%, and increase with gestational age.[16–18] A study of 1,053 patients reported that an ultrasound finding of a molar pregnancy had a specificity of 74% for the diagnosis of CHM or PHM.[16]

PHM is more frequently misdiagnosed as an incomplete or missed abortion compared with CHM, because PHM is associated with the presence of fetal or embryonic tissue and amniotic fluid. PHM is diagnosed as an incomplete or missed abortion in 15% to 60% of cases.[16–18] Ultrasound findings suggesting PHM include the presence of cystic spaces in the placenta, an increase in the transverse diameter of the gestational sac, and the presence of fetal and embryonic tissue and amniotic fluid.[19]

Measuring hCG level at ultrasound may help distinguish CHM or PHM from a missed abortion. An hCG level >100,000 mIU/mL in the first trimester should strongly raise the suspicion of a molar pregnancy.[20]

Treatment of Molar Pregnancy

Once molar pregnancy is suspected, the patient should be evaluated for the presence of possible medical complications, such as preeclampsia, electrolyte imbalance from hyperemesis, anemia, and hyperthyroidism. After the patient is stabilized, a decision must be made concerning the most appropriate method of evacuation.

Patients wishing to preserve fertility should undergo suction curettage through either manual or electric vacuum aspiration regardless of uterine size.[21] For uteri larger than 14 weeks' size, evacuation under ultrasound guidance is recommended to ensure complete emptying of the uterine cavity. Medical induction of labor or hysterotomy are strongly discouraged because both techniques increase maternal morbidity, especially risk of hemorrhage. If the patient has a very high hCG level (>500,000 mIU/mL) or is suggestive of being hyperthyroid, anesthesia or surgery may precipitate thyroid storm. For these patients, a beta-adrenergic blocker should be administered at anesthesia. Patients with high hCG levels and excessive uterine enlargement may also be at increased risk for respiratory distress during and after evacuation. This risk is due to multiple factors, including heavy bleeding with high fluid replacement, trophoblastic pulmonary embolization, preeclampsia, and thyroid storm with high-output heart failure. The anesthesia and recovery room staff should be alerted to these possible complications. If the patient is Rh-negative, Rho (D) immunoglobulin should be administered after the procedure.

Hysterectomy may be considered in patients who do not desire future fertility, particularly among women of advanced maternal age. The risks of developing GTN after suction evacuation of CHM in patients aged >40 and >50 years are 54% and 60%, respectively; hysterectomy appears to reduce this risk and the subsequent need for chemotherapy. Hysterectomy may therefore be particularly reasonable to consider in patients aged >40 years with CHM.[22,23] If the ovaries have prominent theca lutein cysts, these can be aspirated and preserved.

Prophylactic Chemotherapy

Patients with CHM with very high hCG values and other signs of marked trophoblastic growth, such as excessive uterine size (>20 weeks) or theca lutein cysts, are at high risk (40%–50%) of developing GTN. Patients with CHM who present with medical complications (eg, preeclampsia, marked hyperthyroidism, respiratory insufficiency) and those with repeat molar pregnancy are also at increased risk for GTN. Prophylactic chemotherapy at evacuation of high-risk CHM has reduced the incidence of GTN from approximately 40% to 10% to 15% in randomized controlled trials.[24–26] We consider using chemoprophylaxis in patients with high-risk CHM when there is a significant concern about the reliability or availability of hCG follow-up.

Role of hCG Surveillance

After uterine evacuation, patients should be enrolled in a serum hCG surveillance protocol. Serum hCG levels are a highly sensitive marker for trophoblastic proliferation. While on surveillance, patients should use a reliable form of contraception to avoid confusing a new pregnancy with GTN.

Patients under hCG surveillance should have serum hCG levels checked weekly until the value is below the reference range for the assay. Traditionally, this level has been 5 mIU/mL. However, recent higher-sensitivity assays may produce values even <1 mIU/mL. Because most studies on hCG surveillance were performed with a cutoff value of 5 mIU/mL, we have continued to use this as the clinically actionable result.

Similarly, it is important that patients obtain serial hCG measurements at the same reference laboratory. This laboratory should use an assay that can detect all of the various isoforms of hCG (eg, total hCG, nicked hCG, free beta subunit).[27] Detection of hCG beta and hCG beta core fragment are particularly variable among assays.[28] Reference ranges, calibration, and assay sensitivity may differ markedly among laboratories, which can lead to either false-negative results or overdiagnosis of persistent disease.[29] This is especially true when results are compared among different laboratories. When patients present to our center, we always confirm an hCG result on our local assay. However, for patients who will be monitored in the community setting, we advise continued use of the same reference laboratory.[28]

Markedly elevated hCG values can also produce falsely low hCG results through a phenomenon known as the "hook effect,"[30] which generally occurs when the hCG level exceeds 1,000,000 mIU/mL. This occurs because most hCG tests are based on sandwich enzyme-linked immunosorbent assay or radioimmunoassay techniques. Excess analyte saturates both the fixed, solid-phase antibodies and the labeled, soluble antibodies, preventing sandwich formation. If a hook effect is suspected, a true hCG value can be obtained by performing a serial dilution of the sample before analysis.[31]

In cases of persistent low-level hCG, false-positive results or "phantom hCG" must also be considered.[32] One common cause of phantom hCG is heterophile antibodies.[33] In this case, the patient may have antimouse antibodies that interfere with the immunoassay. Heterophile antibodies can be excluded by obtaining a urine hCG test result, because heterophile antibodies do not cross the glomerulus. Heterophile antibodies can also be controlled for by using heterophile-blocking tubes. Another common cause of persistent low-level elevations in hCG is pituitary hCG, especially in perimenopausal women,[29,34] in whom the prevalence of detectable hCG levels up to 14 mIU/mL is 8%.[35] Pituitary hCG can be distinguished from real hCG by placing a patient on oral contraceptive pills, which will suppress pituitary hCG production.

Duration of hCG Surveillance

Patients should be followed up with weekly serum hCG measurements until the result is below the reference range for 3 weeks, and then with monthly testing thereafter. The American College of Obstetricians and Gynecologists recommends continuing postmolar hCG surveillance until 6 months of "normal" values are obtained.[36] However, the optimal duration of hCG surveillance has been debated. In studies performed at Brigham and Women's Hospital, we found that the risk of GTN for both CHM and PHM is <1% after a single normal hCG value.[37,38] Similar findings were identified in Brazil, where the risk of GTN after hCG normalization was 0.6% after CHM and 0.1% after PHM.[39]

In the largest series, >20,000 patients with molar pregnancy from the Charing Cross Hospital in London underwent testing. After a single normal value, the risk of GTN after CHM was approximately 0.25%, and after PHM was approximately 0.03%.[39,40] Based on these data, our practice has been to shorten the duration of hCG surveillance to 3 months for CHM and 1 month for PHM. However, this recommendation is only for patients experiencing spontaneous hCG remission. For patients

diagnosed with and treated for GTN, we continue hCG surveillance for 1 year.

Diagnosis of Postmolar GTN

The 2002 International Federation of Gynecology and Obstetrics (FIGO) guidelines present hCG monitoring criteria for the diagnosis of persistent neoplasia after evacuation of a molar pregnancy.[41] Progressively increasing hCG levels across 3 values at least 14 days apart (ie, days 1, 7, and 14) or plateaued hCG values within a 10% range across 4 values at least 21 days apart (ie, days 1, 7, 14, and 21) establish a diagnosis of GTN. The 2002 FIGO guidelines also recommend treatment of GTN if hCG levels remain elevated >6 months after uterine evacuation. However, this last recommendation has been challenged by evidence from British and Brazilian referral centers for gestational trophoblastic disease suggesting that among women with persistently elevated but decreasing hCG levels at 6 months postevacuation, >80% of patients may experience spontaneous remission without chemotherapy.[42,43] Notably, extended surveillance does not appear associated with an increased risk of metastases, chemotherapy resistance, or need for multiagent chemotherapy.[42,43] Based on recent studies, FIGO no longer recommends starting chemotherapy when hCG is still elevated but declining 6 months after molar evacuation.[3,42]

Staging of GTN

Once the criteria for postmolar GTN are met, FIGO stage and score should be determined.[44] Staging consists of 2 parts: a FIGO anatomic staging and a FIGO risk score to determine the risk of disease progression and resistance to single-agent chemotherapy. The score is calculated by adding the total points assigned to various clinical and tumor risk factors. Women with a FIGO score ≤6 are considered to have low-risk disease and can be treated with single-agent chemotherapy.[41,45,46] It is critically important to use a plain chest radiograph rather than a CT scan when staging patients, because approximately 30% to 40% of CT scans can show micrometastases that do not influence outcome and could lead to more aggressive chemotherapy than is needed.[47] Additionally, the hCG value used in the scoring system is the hCG level at persistence, not at the value at initial molar diagnosis or before evacuation of the mole. Again, failure to use the correct hCG value can result in an inappropriately elevated FIGO risk score.[45]

Treatment of Low-Risk Postmolar GTN

Most patients who are followed up with serial hCG levels after evacuation of a molar pregnancy and are determined to have postmolar GTN based on FIGO criteria will have low-risk GTN (FIGO score <7). Treatment of low-risk GTN consists of single-agent chemotherapy, typically with either methotrexate or actinomycin D. Multiple dosing and infusion schedules for both agents have been investigated, but given the heterogeneity of the data, no clearly preferred regimen has been determined. At our institution, we use the 8-day methotrexate regimen due to its low toxicity, ease of administration, and large reported clinical experience. Efficacy for both methotrexate and actinomycin D is similar, with complete remission rates of approximately 70% to 80%. Meta-analysis and randomized trials suggest that actinomycin D may have a higher rate of cure and require fewer cycles of therapy to achieve remission; however, much of these data come from studies comparing actinomycin D versus weekly intramuscular or infusional methotrexate rather than the more effective 5-day or 8-day regimens.[48–54] Weekly intramuscular methotrexate is no longer recommended for low-risk GTN because of lower reported efficacy rates compared with the other methotrexate dosing schedules. The improved toxicity profile of methotrexate can make it the preferred agent. Alternative single-agent chemotherapy options include etoposide and 5-fluorouracil.[55,56] Chemotherapy is continued until hCG normalization with an additional 3 cycles of consolidation chemotherapy administered to minimize recurrence.[57] For patients who do not experience remission or who develop toxicity to methotrexate or actinomycin D, an alternative single agent is often used with excellent results. However, transition to multiagent chemotherapy may be necessary if the hCG level at persistence is particularly elevated or if clear progression of disease is seen.[58]

Role of Second Dilation and Curettage

The potential role of second dilation and curettage rather than chemotherapy has been investigated in several studies with conflicting results. In a recent prospective study, approximately 40% of women undergoing a second dilation and curettage experienced cure without the need for chemotherapy.[59] FIGO score (5 or 6) and age (>39 or <19 years) have been identified as risk factors for failure of second curettage to avoid the need for chemotherapy.[59,60]

Role of Hysterectomy

Women with FIGO stage I nonmetastatic GTN who do not desire fertility preservation may be treated with hysterectomy.[61,62] The best approach (open vs minimally invasive) has not been established. Given the high rate of occult pulmonary metastases, one cycle of single-agent chemotherapy administered perioperatively may be considered to achieve sustained remission.[63] Hysterectomy is also the treatment of choice for women with the relatively chemotherapy resistant histologies of PSTT or ETT. These are uncommon tumors, and PSTT and ETT are rarely diagnosed during postmolar surveillance.

Those diagnosed with PSTT or ETT later than 48 months from antecedent pregnancy are at high risk for recurrence and poor outcome, leading some clinicians to offer postoperative high-dose chemotherapy with stem cell support.[64,65]

Follow-Up and Future Pregnancy

Regardless of treatment method, women with low-risk GTN should have serum hCG levels monitored monthly for 1 year after remission. During this time, effective birth control must be used. The type of birth control used does not seem to increase rates of recurrence.[66] GTN and use of chemotherapy do not seem to impact future fertility. Other than an increased risk of second molar pregnancy, subsequent pregnancies after GTN have been shown to have obstetrical outcomes similar to those for women without a history of GTN.[67–70] However, for any subsequent pregnancies, we recommend an early trimester ultrasound to assess for normal early development and to check hCG level approximately 6 to 8 weeks postpartum to ensure that it has normalized and a that second trophoblastic event did not develop.

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