CLINICAL PRACTICE

Molar Pregnancy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A healthy 37-year-old woman presents at 10 weeks of pregnancy with vaginal bleeding. Physical examination shows that the uterine size is appropriate for gestational age. The level of serum human chorionic gonadotropin (hCG) is 22,000 mIU per milliliter. Ultrasonography does not show an identifiable fetal heartbeat. After receiving a clinical diagnosis of missed abortion, the patient undergoes evacuation of the uterus; pathological examination indicates a complete molar pregnancy. How should this case be managed?

THE CLINICAL PROBLEM

Molar pregnancy comprises two distinct entities, partial and complete mole, which can be distinguished by means of gross morphologic and histopathological examination and according to chromosomal pattern (Table 1).[1-4] Complete moles have no identifiable embryonic or fetal tissues. Classically, the chorionic villi have diffuse trophoblastic hyperplasia and generalized swelling, and the trophoblast at the implantation site has diffuse, marked atypia. Complete moles usually have a 46,XX karyotype, and the molar chromosomes are derived completely from the father.[5] Most complete moles are homozygous and appear to arise from an anuclear empty ovum that has been fertilized by a haploid (23X) sperm, which then replicates its own chromosomes.[6] Whereas chromosomes in the complete mole have a paternal origin, the mitochondrial DNA has a maternal origin.[7]

In contrast to complete moles, partial moles are characterized by the following pathological features: chorionic villi that vary in size and are characterized by focal swelling and focal trophoblastic hyperplasia; focal, mild atypia of trophoblasts at the implantation site; marked villous scalloping and prominent stromal trophoblastic inclusions; and identifiable fetal or embryonic tissues.[2-4] Partial moles usually have a triploid karyotype that develops after the fertilization of an apparently normal ovum by two spermatozoa.[3] When fetuses with partial moles are identified, they usually have the congenital anomalies associated with triploidy, such as syndactyly and cleft lip.

Complete moles once were generally diagnosed in the second trimester, and certain symptoms and signs were common at the time of presentation, including excessive uterine size, anemia, toxemia, hyperemesis, hyperthyroidism, and respiratory failure.[8-11] However, the clinical presentation and pathological features of a complete mole have changed substantially over the past two decades. In a case series of patients presenting between 1965 and 1975 at the New England Trophoblastic Disease Center, at a mean gestational age of 16.5 weeks, the frequency of excessive uterine size was 51%, anemia 54%, toxemia 27%, hyperemesis 26%, hyperthyroidism 7%, and respiratory failure 2%.[12]

With the availability of accurate and sensitive tests for the detection of hCG and the use of early ultrasonographic examination, the diagnosis is now typically made

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Table 1. Chromosomal and Histopathological Features of Complete and Partial Moles.*

Characteristic	Complete Mole	Partial Mole
Karyotype	Diploid; 46,XX (usually), 46,XY	Triploid
Results on immunostaining of maternally expressed gene products (*p57, PHLDA2*)	Negative	Positive
Fetal or embryonic tissue	Absent	Present
Hydropic swelling of villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Trophoblast at implantation site	Marked atypia	Mild atypia

* Data are from Berkowitz and Goldstein.[1]

in the first trimester, often before classic clinical signs and symptoms develop.[12,13] For example, in a series of cases diagnosed between 1988 and 1993,[12] the mean gestational age at diagnosis was 11.8 weeks. Excessive uterine size, anemia, toxemia, and hyperemesis were detected in only 28%, 5%, 1%, and 8% of the patients, respectively, and no patient had clinical hyperthyroidism or respiratory insufficiency. The incidence of vaginal bleeding as a symptom at presentation also decreased, from 97% in the earlier case series to 84% in the later case series.

Patients with a partial mole usually present with the signs and symptoms of missed or incomplete abortion, including vaginal bleeding and a uterine size that is small or appropriate for gestational age, rather than the classic features of a complete mole.[14-16] The symptoms and gestational age at the diagnosis of a partial mole, unlike those at the diagnosis of a complete mole, have not changed appreciably in recent years.[17]

The pathological features of complete moles in the first trimester are also less readily identifiable than those of complete moles in the second trimester. One series compared the pathological findings in 23 complete moles diagnosed between 1994 and 1997, at a mean gestational age of 8.5 weeks, with 20 historic complete moles diagnosed between 1969 and 1975, at a mean gestational age of 17 weeks.[18] The more recent cases, as compared with the older cases, had a smaller mean maximal villous diameter (5.7 mm vs. 8.2 mm). The more recent moles were also less likely to have circumferential trophoblastic hyperplasia (39% vs. 75%) and global necrosis (22% vs. 54%) and were more likely to have primitive villous stroma (70% vs. 10%). Persistent neoplasia may develop in either a complete or partial mole and may require chemotherapy.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Ultrasonographic Examination

Because a complete molar pregnancy is characterized by marked swelling of the chorionic villi, the ultrasonographic finding of a vesicular pattern is strongly suggestive of the diagnosis (Fig. 1). As compared with complete moles that are diagnosed later, complete moles that are diagnosed in the first trimester show less cavitation and have smaller villi.[18] Nevertheless, ultrasonography can still be used to detect most of these cases.[19] For example, in one report of 24 cases of complete mole in the first trimester (mean gestational age, 8.7 weeks), 17 cases (71%) were correctly diagnosed on the basis of the initial ultrasonographic examination. Ultrasonographic findings that do not include the characteristics of a molar pregnancy are usually presumed to indicate a missed abortion. An elevated hCG level at the time of ultrasonographic examination may help to distinguish an early complete mole from a missed abortion.[20] However, a definitive diagnosis requires confirmation by a pathologist.

A partial mole is also associated with characteristic ultrasonographic findings[21,22] (Fig. 2). Such findings that have been shown to be significantly associated with the presence of a partial mole include focal cystic changes in the placenta and a ratio of the transverse to anteroposterior dimension of the gestational sac that is more than 1.5[21]; the latter finding may be related to triploidy. In one study, when both findings were noted, the

positive predictive value for a partial mole was 87%,[21] although this finding has not been validated.

Measurement of hCG

Since trophoblastic cells (which produce hCG) are hyperplastic in a molar pregnancy, the presence of a complete mole is strongly suggested by markedly elevated hCG values. Levels of hCG that were greater than 100,000 mIU per milliliter before evacuation were observed in 30 of 74 patients with complete moles (41%) in one series[23] and in 70 of 153 patients with complete moles (46%) who were followed at the New England Trophoblastic Disease Center.[24]

As compared with complete moles, partial moles are characterized by less prominent trophoblastic hyperplasia. Accordingly, patients with a partial mole present infrequently with substantially elevated hCG levels. We reported serum hCG levels greater than 100,000 mIU per milliliter at presentation in only 2 of 30 patients with partial moles at our center.[14] Similarly, only 1 of 17 patients with a partial mole in another study was noted to have a urinary hCG level that was greater than 300,000 mIU per milliliter.[15]

Challenges of Pathological Diagnosis

The shift to earlier detection and evacuation of complete moles has made the pathological diagnosis more challenging.[25] Early complete moles have subtle morphologic features that may lead to their misclassification as partial moles or nonmolar hydropic abortions.

Accurate pathological diagnosis can be greatly facilitated through the use of flow cytometry to determine ploidy (i.e., diploid vs. triploid moles) and through assessment of biomarkers of paternally imprinted and maternally expressed gene products. Whereas complete moles and hydropic abortions are both diploid, partial moles are generally triploid. Biomarkers that take advantage of imprinted genes to distinguish complete moles from other gestations have been identified. Because complete moles generally have no maternal chromosomes, paternally imprinted gene products, which are normally expressed only by maternal chromosomes, should be absent.[26-28] For example, in complete moles, the nuclei of the villous stroma and cytotrophoblastic cells do not express *p57* or *PHLDA2* (Pleckstrin homology-like domain, family A, member 2), which are paternally imprinted, maternally expressed gene products, whereas all other gestations, including partial moles, are characterized by nuclear immunostaining in these cells. Thus, a complete mole is diploid and negative for *p57* and *PHLDA2*, a hydropic abortion is diploid and positive for *p57* and *PHLDA2*, and a partial mole is generally triploid and positive for *p57* and *PHLDA2* (Table 1).

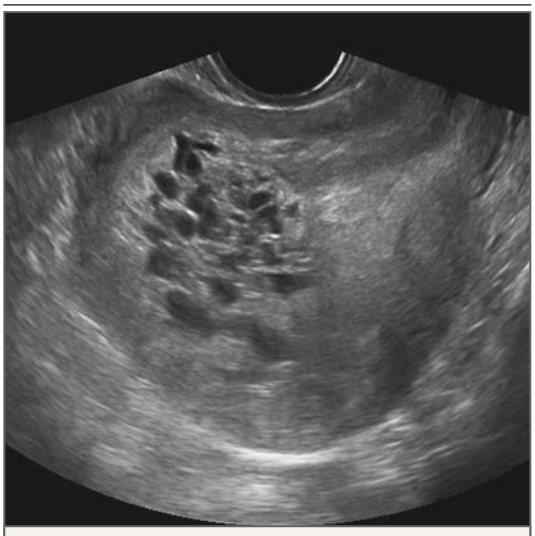

Figure 1. Ultrasonographic Scan from a Patient with a First-Trimester Complete Molar Pregnancy.

The scan shows diffuse vesicular changes in the placenta; the gestational sac is absent. (Image courtesy of Carol B. Benson, M.D., Dept. of Radiology, Brigham and Women's Hospital, Boston.)

MANAGEMENT

Patients who receive a diagnosis of molar pregnancy should be evaluated for potential medical complications such as anemia, toxemia, or hyperthyroidism. All patients should undergo a complete physical examination and laboratory testing, including determination of the blood type and hematocrit and evaluation of thyroid, liver, and renal function.

After any medical complications have been addressed, a decision must be made concerning the best method of evacuation. Suction curettage is the optimal method of evacuation, regardless of uterine size, in patients who wish to retain reproductive function, because it carries a significantly lower risk of excessive bleeding, infection, and retained molar tissue than methods involving induction with oxytocin or prostaglandin.[29,30] Because the RhD antigen is present in trophoblasts, patients with an Rh-negative blood type should receive Rh immune globulin at the time of evacu-

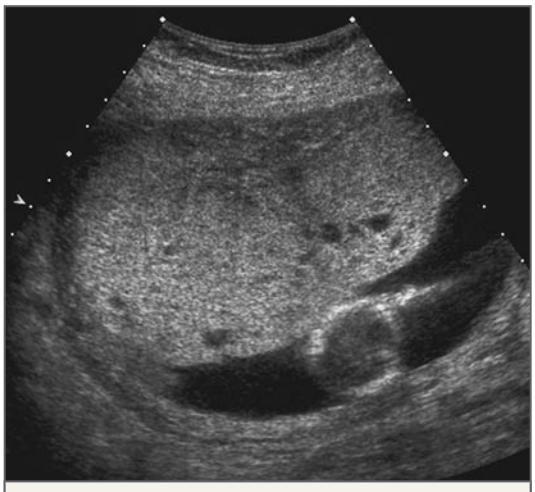

Figure 2. Ultrasonographic Scan from a Patient with a First-Trimester Partial Molar Pregnancy.
The scan shows focal vesicular changes in the placenta and a fetus with a gestational sac (bottom). (Image courtesy of Carol B. Benson, M.D., Dept. of Radiology, Brigham and Women's Hospital, Boston.)

ation of the uterus. Patients who have completed or do not have an interest in childbearing may undergo hysterectomy. Although hysterectomy prevents the development of local invasion, it does not eliminate metastatic disease. Therefore, careful monitoring of hCG levels is still required to ensure that persistent neoplasia does not develop.

PERSISTENT NEOPLASIA AFTER A MOLAR PREGNANCY

Nonmetastatic or metastatic gestational trophoblastic neoplasia may develop in a complete or partial molar pregnancy. Nonmetastatic neoplasia develops when molar tissue or choriocarcinoma invades the uterine wall and there is no evidence of disease beyond the uterus, whereas metastatic disease spreads beyond the uterus. In 2002, the International Federation of Gynecology and Obstetrics established new criteria for the diagnosis of persistent neoplasia after a molar pregnancy. These criteria include serum hCG levels that do not return to the normal range after evacuation, evidence of metastasis, and a pathological diagnosis of choriocarcinoma, any one of which establishes the diagnosis of persistent neoplasia.[31]

The incidence of gestational trophoblastic neoplasia after a complete molar pregnancy in the United States has been reported to be 18 to 29%[1,10,32-34] and has not been affected by the earlier diagnosis and treatment of complete moles.[12,35] At our center, after evacuation of a complete mole, local uterine invasion was diagnosed in 15% of patients, and metastases were diagnosed in 4% of patients.[9] Chemotherapy has been shown to be highly effective in the treatment of both nonmetastatic and metastatic disease, with cure rates ranging between 80 and 100%, depending on the extent of disease.[1]

Certain clinical features are predictive of tumors after molar pregnancy.[8] Among 858 patients with a complete mole who were followed at our center, persistent tumor after evacuation was significantly more likely among those with signs of marked trophoblastic proliferation (41% of the total cohort), including an hCG level greater than 100,000 mIU per milliliter, a uterine size that was larger than appropriate for gestational age, and theca lutein ovarian cysts larger than 6 cm in diameter, than among those without these clinical findings. The rate of subsequent uterine invasion among patients with signs of trophoblastic proliferation was 31.0%, as compared with 3.4% among patients without these signs, and the rate of metastasis was 8.8% as compared with 0.6%. Therefore, patients with a complete mole who have markedly elevated hCG levels and an abnormally large uterus before evacuation are categorized as being at high risk for subsequent gestational trophoblastic neoplasia.[10,36]

The reported risk of the development of gestational trophoblastic neoplasia after a partial molar pregnancy ranges from 0 to 11%.[9] Gestational trophoblastic neoplasia was reported in 73 of 7155 patients with a partial mole from 10 centers (1.0%)[37] and in 22 of 390 patients at our center (5.6%)[17]; in our case series, clinical symptoms at presentation did not distinguish patients who were at risk for persistent tumor from those who were not at risk.[17]

MONITORING OF HCG AFTER EVACUATION OF THE MOLE

After evacuation, serial hCG levels should be monitored in patients with either a complete or partial molar pregnancy in order to facilitate the early detection of persistent gestational trophoblastic neoplasia. To ensure that the patient has a complete, sustained remission, hCG tests are often performed weekly until levels have been undetectable (<5 mIU per milliliter) for 3 weeks, with subsequent monthly testing until levels have been undetectable for 6 months. Data from multiple centers for several thousand women with a molar

pregnancy indicate that once the level of hCG becomes undetectable, recurrent elevation of the level occurs in less than 1% of patients. The time of relapse has not been specifically indicated in most of these patients.[38-46] In one series involving 4754 patients with a mole, 27 (0.6%) had a relapse after at least one hCG test indicating an undetectable level (<5 mIU per milliliter in serum or <25 mIU per milliliter in urine).[47] In eight clinical series published since 2004, only 2 of more than 2000 patients with a molar pregnancy had persistent tumor after serum hCG levels had become undetectable. These data suggest that it may be possible to shorten the period of follow-up hCG testing after evacuation of the mole without compromising a patient's safety.

Because the occurrence of a new gestation would interfere with follow-up testing of hCG levels, patients with a molar pregnancy are strongly advised to use reliable contraception during the entire interval of hCG monitoring. An intrauterine device should not be inserted before gonadotropin remission because of the risk of perforating the uterus if tumor is present. The use of either barrier methods of contraception or oral contraceptives should be recommended after evacuation. Although limited data have suggested that the use of oral contraceptives before gonadotropin remission may be associated with an increase by a factor of two to three in the frequency of tumor after a molar pregnancy, as compared with the frequency among women who do not use oral contraceptives,[48] a more recent randomized trial showed no increase in the risk of gestational trophoblastic neoplasia after molar pregnancy with the use of these contraceptives.[49] Moreover, several other observational studies have likewise shown no significant association between the use of oral contraception and the risk of persistent tumor after molar pregnancy.[50,51]

SUBSEQUENT PREGNANCY

After a molar pregnancy, patients and their partners commonly express concern about the potential for a molar pregnancy in the future.[52] Case series indicate that most patients with a molar pregnancy who subsequently conceive will have a normal pregnancy, but there is an increased risk of another molar pregnancy.[53] The absolute risk that a subsequent pregnancy will be a molar pregnancy is about 1% after one mole and about 15 to 18% after two moles.[47,53]

Because of the increased risk of later molar disease, ultrasonographic examination is recommended in the first trimester of a subsequent pregnancy to confirm that the pregnancy is normal. It is considered safe for patients to attempt to conceive as soon as follow-up hCG testing has been completed.

AREAS OF UNCERTAINTY

The necessary period of follow-up hCG testing after evacuation of the mole remains uncertain. The use of prophylactic chemotherapy at the time of evacuation also remains uncertain. In two randomized trials, chemoprophylaxis in patients with high-risk complete molar pregnancies resulted in a significant reduction in the incidence of persistent gestational trophoblastic neoplasia (14% for both studies, vs. 47% and 50% among patients who did not receive chemoprophylaxis).[54,55] The use of chemoprophylaxis in patients with high-risk complete moles is generally considered in circumstances in which follow-up hCG testing is unavailable or patient compliance is a concern.

GUIDELINES

The American College of Obstetricians and Gynecologists (ACOG) has recommended that after evacuation of a mole, serum hCG levels should be monitored every 1 to 2 weeks in all patients while the levels are elevated and then at monthly intervals for an additional 6 months once the levels become undetectable (<5 mIU per milliliter).[56] The International Federation of Gynecology and Obstetrics has established the following guidelines for the diagnosis of persistent tumor after molar pregnancy: four or more measurements of the hCG level that show a plateau in the values over a period of at least 3 weeks, an increase in the hCG level of 10% or more in three or more measurements over a period of at least 2 weeks, the presence of choriocarcinoma on histologic analysis, and the persistence of detectable hCG levels 6 months after evacuation of a mole.[33]

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette presented with signs and symptoms of first-trimester missed abortion. She did not have the classic features of molar pregnancy (e.g., a uterus that is larger than appropriate for gestational age, a marked eleva-

tion of the hCG level, and a characteristic appearance of a mole on ultrasonographic examination); this absence of findings is common now that molar pregnancy is typically diagnosed in the first trimester. In cases in which the histologic findings are nondiagnostic, the use of flow cytometry to determine ploidy (a partial mole is generally triploid) and immunostaining for maternally expressed gene products (complete moles are negative for *p57* and *PHLDA2*) can facilitate an accurate pathological diagnosis.

Suction curettage is recommended for evacuation, after which serial hCG levels should be measured in all patients with molar pregnancy in order to ensure a return to undetectable levels, which are indicative of complete remission. The ACOG currently recommends continuation of follow-up testing for 6 months after the levels become undetectable, but the risk of recurrence once the levels are undetectable is extremely low (<1%), and it is possible that this duration of follow-up could be safely abbreviated. Patients should be instructed to use reliable contraception during the entire interval of hCG monitoring; data indicate that the use of oral contraceptives is safe during this period. Patients should be reassured that, although there is a slightly increased risk of a subsequent molar pregnancy after one molar pregnancy, in most cases, a subsequent pregnancy will be normal.

No potential conflict of interest relevant to this article was reported.

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