# Management of molar pregnancy

**Alessandro Cavaliere**[1]
**Santina Ermito**[2]
**Angela Dinatale**[2]
**Rosa Pedata**[3]

[1] Department of Gynecology and Obstetrics, "Sapienza" University of Rome, Italy
[2] Operative Unit of Obstetrics and Gynecology, Policlinico Universitario "G. Martino", Messina, Italy
[3] Department of Gynecology, Obstetrics and Reproductive Sciences, Second University of Naples, Naples, Italy

Corresponding author: Alessandro Cavaliere, MD
Department of Gynecology and Obstetrics
"Sapienza" University of Rome, Italy
V.le Regina Elena, 324 - 00161 Rome, Italy
Ph. 0039 064997
E-mail: alessandro.cavaliere@libero.it

**Abstract**

**Gestational Trophoblastic Disease (GTD) originates from placental tissue and is among the rare human tumors that can be cured even in the presence of widespread metastases. GTD include a spectrum of interrelated tumors including complete and partial hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumor, that have different propensities for local invasion and spread. Although most GTD develop after a mole, they can follow any antecedent pregnancy.**
**Transvaginal ultrasound, routinary dosage of beta-hCG and current approaches to chemotherapy, let most women with malignant gestational trophoblastic disease to be cured and their reproductive function preserved.**

*KEY WORDS: gestational trophoblastic disease, human chorionic gonadotropin, chemotherapy.*

## Introduction

Gestational trophoblastic disease (GTD) is a tumor originating from the trophoblast, which surrounds the blastocyst and develops into the chorion and amnion. The main types of gestational trophoblastic diseases are:
– hydatidiform mole (complete or partial);
– invasive mole;
– choriocarcinoma;
– placental site trophoblastic tumor.
The most common form of GTD is hydatidiform mole, also known as molar pregnancy. There are 2 types of hydatidiform moles: complete and partial.

The *complete* hydatidiform mole is usually diploid and entirely androgenetic in origin. Most have 46,XX karyotype; a few have a 46,XY karyotype. A complete molar pregnancy consists of diffuse hydropic chorionic villi with trophoblastic hyperplasia, forming a mass of multiple vescicles. There is usually no evidence of a fetus and minimal embryonal development.
The *partial* hydatidiform mole is usually triploid, with one maternal and two paternal haploid sets, either from dispermic fertilization or from fertilization with an unreduced diploid sperm. There is usually a fetus and a large placenta. The hydropic villi show a less florid appearance than is seen with a complete hydatidiform mole and are interspersed with normal chorionic villi. The fetus usually dies within a few weeks of conception, and a recent review did not identify any case in which a fetus of paternal (diandric) origin survived to term (1). Very rarely, a partial molar pregnancy develops with two maternal and one paternal haploid set (digynic). In these cases, the placenta is small, the villi show minimal hydropic changes, and the fetus is growth-restricted. Some of these pregnancies have been reported to result in live births, with subsequent early neonatal death (2).
Of 3,000 women with partial hydatidiform moles, 0.1% had a choriocarcinoma. Persistent trophoblastic disease or malignant complications are much more common with a complete molar pregnancy than with a partial hydatidiform mole. The incidence of these complications is approximately 8% and 0.5% respectively, compared with a risk of 1:50,000 after a full-term pregnancy.

## Diagnosis

The diagnosis of a molar pregnancy might be suspected based on a number of clinical features: abnormal vaginal bleeding in early pregnancy is the most common presentation; uterus large for dates (25%); pain from large benign theca-lutein cysts (20%); vaginal passage of grape-like vescicles (10%); exaggerated pregnancy symptoms including hyperemesis (10%), hyperthyroidism (5%), early preeclampsia (5%).
Nowadays ultrasound scan often permits to diagnose molar pregnancy before 12 weeks, showing a fine vascular or honeycomb appearance. Later a *complete* mole is characteristically described as snowstorm appearance of mixed echogenicity, representing hydropic villi and intrauterine hemorrhage. The ovaries often contain multiple large theca-lutein cysts as a result of increased ovarian stimulation by excessive beta-hCG (3).
Ultrasound diagnosis of *partial* mole is more difficult: the fetus may be still viable, but may show signs consistent of triploidy, such as unusually early growth restriction or developmental abnormalities. There may be only scattered cystic spaces within the placenta, and ovarian cystic

changes usually much less pronounced. In case of doubt, the scan should be repeated in 1 to 2 weeks.
In women with a *complete* mole, the quantitative serum beta-hCG level is higher than expected, often exceeding 100,000 IU/L. In case of a *partial* mole, the level of beta-hCG is often within the wide range associated with normal pregnancy and the symptoms are usually less pronounced. For these reasons the diagnosis of a partial mole is often missed clinically and made from subsequent histologic assessment of the abortive material (4).

**Management**

In case of a suspected mole, further investigations include a complete blood count, measurement of creatinine and electrolytes, liver - kidney - thyroid function tests, and a baseline quantitative beta-hCG measurement. A careful pelvic and abdominal ultrasound scan should be done to look for evidence of an invasive mole, exclude a coexisting pregnancy, and look for possible metastatic disease. Computed tomography or magnetic resonance imaging may provide further information. Chest radiography or computed tomography should be considered if there are symptoms that suggest pulmonary metastases (5).
Suction curettage is the preferred method of evacuation regardless of uterine size in patients who desire to preserve fertility (6). It is best to avoid prior cervical preparation, oxytocic drugs and sharp curettage or medical evacuation, to minimize the risk of dissemination of tissue leading to metastatic disease (7). Oxytocic agents and prostaglandin analogues are best used only after uterine evacuations when there is significant hemorrhage.
Total abdominal hysterectomy is a reasonable option for patients who do not wish to preserve their fertility. Hysterectomy is particularly advisable for patients >40 years whose risk of developing GTD is significantly increased. Though hysterectomy eliminates the risk of locally invasive disease, it does not prevent metastases and reduces the subsequent risk of persistent trophoblastic disease by up to 50% (8).
Guidelines from the Royal College of Obstetricians and Gynecologists and the British Blood Transfusion Society recommend that all Rhesus-negative women who have a molar pregnancy should be given 250 IU anti-D immunoglobulin after surgical evacuation (9).

**Follow-up**

The aims of follow-up are to confirm successful treatment and to identify women with persistent or malignant GTD who may require adjuvant chemotherapy or surgery at an early stage. Persistent vaginal bleeding and above all elevation of serum beta-hCG levels are the main indicators of residual disease.
The outcome of a *partial* hydatidiform mole after uterine evacuation is almost always benign. Persistent disease occurs in 1.2% to 4% of cases; metastasis occurs only in 0.1% of cases (10). In *complete* moles, these risks are approximately 5 times greater after treatment with uterine evacuation and 2-3 times greater after hysterectomy (11). The risk of persistent or recurrent GTD is greatest in the first 12 months after evacuation, with most cases presenting within 6 months.
A variety of hCG criteria have been used to diagnose postmolar gestational trophoblastic disease. Recently, the International Federation of Gynecologists and Obstetricians (FIGO) standardized the following hCG criteria for the diagnosis of postmolar gestational trophoblastic disease (12):
– An hCG level plateau of four values ±10% recorded over a 3-week duration (days 1, 7, 14, and 21).
– An hCG level increase of more than 10% of three values recorded over a 2-week duration (days 1, 7, and 14).
– Persistence of detectable hCG for more than 6 months after molar evacuation.

Use of reliable hormonal contraception is recommended while hCG values are being monitored. Oral contraceptives do not increase the incidence of postmolar gestational trophoblastic disease or alter the pattern of regression of hCG values (13). Frequent pelvic examinations are performed while hCG values are elevated to monitor the involution of pelvic structures and to aid in the early identification of vaginal metastases. Although pregnancies after molar evacuation usually are normal gestations, pregnancy obscures the value of monitoring hCG levels during this interval and may result in a delayed diagnosis of postmolar malignant gestational trophoblastic disease. A new intrauterine pregnancy should be ruled out on the basis of hCG levels and ultrasonography, especially when there has been a long delay in follow-up of serial hCG levels and noncompliance with contraception. After completion of documented remission for 6-12 months, women who desire pregnancy may discontinue contraception, and hCG monitoring may be discontinued. Patients with prior partial or complete moles have a 10-fold increased risk (1-2% incidence) of a second hydatidiform mole in a subsequent pregnancy (14). Therefore, all future pregnancies should be evaluated by early obstetric ultrasonography.

**Chemotherapy**

Complete molar pregnancy is well recognized to have the potential for local invasion and distant spread. After evacuation, local uterine invasion occurs in about 15% and metastases in 4%. *Complete* molar pregnancy is usually divided into low and high risk for persistence based on signs and symptoms of marked trophoblastic proliferation at the time of evacuation, i.e.: hCG >100,000 mIU/Ml; excessive uterine enlargement; theca-lutein ovarian cyst >6 cm in diameter; older maternal age; a previous molar pregnancy. The risk of postmolar GTD is significant less with partial molar pregnancy and is seen in approximately 1-6% (15). Unfortunately there are no distinguishing clinical or pathologic features for predicting persistence after complete molar pregnancy.
Although controversial, the use of chemoprophylaxis at the time of evacuation of high-risk complete molar pregnancy has been shown to significantly decrease the development of GTD from approximately 50% to 10-15%. A number of chemotherapy regimens are used for

treating the disease, but the best seems to be the association between methotrexate, actinomycin D and cyclophosphamide (16).

## Conclusion

The general understanding of the natural history and management of molar pregnancy has advanced considerably in recent years. The key-role in obtaining a high cure rate becomes an early diagnosis and the subsequent strictly follow-up. Efforts are still necessary to develop effective new second-line therapies for patients with drug-resistant disease.

## References


1. Petignat P, Billieux MH, Blouin JL, Dahoun S, Vassilakos P. Is genetic analysis useful in the routine management of hydatidiform mole? Hum Reprod. 2003 Feb;18(2):243-9.
2. Fryns JP, van de Kerckhove A, Goddeeris P, van den Berghe H. Unusually long survival in a case of full triploidy of maternal origin. Hum Genet. 1977 Sep 22;38(2): 147-55.
3. Benson CB, Genest DR, Bernstein MR, et al. Sonographic appearance of first trimester complete hydatidiform moles. J Ultrasound Obstet Gynecol. 2000;16:188-91.
4. Soper JT, Mutch DG, Schink JC; American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. Gynecol Oncol. 2004 Jun;93(3):575-85.
5. Schlaerth JB, Morrow CP, Montz FJ, d'Abling G. Initial management of hydatidiform mole. Am J Obstet Gynecol 1988;158:1299-306
6. Berkowitz RS, Goldstein DP. Chorionic tumors. N Engl J Med 1996;335:1740-8.
7. Stone M, Bagshawe KD. An analysis of the influences of maternal age, gestational age, contraceptive method, and the mode of primary treatment of patients with hydatidiform moles on the incidence of subsequent chemotherapy. Br J Obstet Gynaecol. 1979 Oct;86(10):782-92.
8. Bahar AM, el-Ashnehi MS, Senthilselvan A. Hydatidiform mole in the elderly: hysterectomy or evacuation? Int J Gynaecol Obstet. 1989 Jul;29(3):233-8.
9. Lee D, Contreras M, Robson SC, Rodeck CH, Whittle MJ. Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis. British Blood Transfusion Society and the Royal College of Obstetricians and Gynaecologists. Transfus Med. 1999 Mar;9(1):93-7.
10. Hancock BW, Tidy JA. Current management of molar pregnancy. J Reprod Med. 2002 May;47(5):347-54.
11. Curry SL, Hammond CB, Tyrey L, Creasman WT, Parker RT. Hydatidiform mole: diagnosis, management, and long-term followup of 347 patients. Obstet Gynecol. 1975 Jan; 45(1):1-8.
12. Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and clinical assessment. Int J Gynecol Cancer. 2001;11:73-7.
13. Curry SL, Schlaerth JB, Kohorn EI, Boyce JB, Gore H, Twiggs LB, et al. Hormonal contraception and trophoblastic sequelae after hydatidiform mole. A Gynecologic Oncology Group study. Am J Obstet Gynecol. 1989;160:805-9.
14. Berkowitz RS, Im SS, Bernstein MR, Goldstein DP. Gestational trophoblastic disease: subsequent pregnancy outcome, including repeat molar pregnancy. J Reprod Med. 1998;43:81-6.
15. Soper JT, Clarke-Pearson DL, Berchuck A, Rodriguez G, Hammond CB. 5-day methotrexate for women with metastatic gestational trophoblastic disease. Gynecol Oncol. 1994;54:76-9.
16. Deng L, Yan X, Zhang J, Wu T. Combination chemotherapy for high-risk gestational trophoblastic tumour. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD005196.