INVITED ARTICLE

UPDATE ON MOLAR PREGNANCY AND CHORIOCARCINOMA

A Ilancheran, P Singh

ABSTRACT

The term gestational trophoblastic disease encompasses a wide spectrum of disorders ranging from the benign hydatidiform mole to the malignant choriocarcinoma and placental site trophoblastic tumor. Recent advances in cytogenetics and pathological criteria have brought to light the occurrence of the partial mole, which is probably more common than the complete mole.

The World Health Organisation has proposed a classification to rectify the current confusion that exists with clinical and pathological terms.

Evacuation of the uterus followed by meticulous followup with sensitive beta subunit Human Chorionic Gonadotropin assay remain the cornerstone of management of molar pregnancy. Prompt chemotherapy is the most important aspect in managing malignant sequelae.Newer chemotherapy regimes have helped to salvage failures from the usual drugs. Judicial use of surgery in metastatic trophoblastic disease can reduce the duration and toxicity of chemotherapy. All patients with gestational trophoblastic disease should be managed in a tertiary care centre with the expertise and facilities easily available to manage these cases.

Keywords: Molar pregnancies, choriocarcinoma, evacuation of uterus, chemotherapy, surgery

SING MED J. 1989; NO 30: 473 – 475

INTRODUCTION

Molar pregnancy and choriocarcinoma consitute the two most important entities in the spectrum known as gestational trophoblastic disease. The former is a completely benign condition but predisposes to the development of the latter, a malignant disease, which till three decades ago was uniformly fatal. The impact of the disease was all the more as it affected young women in their reproductive years. Advances in diagnosis, treatment and followup have made choriocarcinoma the first human malignancy to be cured completely and, in most cases, permanently. This review will present an update on recent advances in this interesting and complex disease, especially with respect to the nomenclature, cytogenetics of molar pregnancy, diagnosis, management, newer chemotherapy regimes and the role of surgery in metastatic gestational trophoblastic disease.

NOMENCLATURE

It can be said that there is more confusion in the classification of gestational trophoblastic disease (GTD) than in any other gynaecological disorder. Clinical and histopathological terms have been used interchangeably and indiscriminately leading not only to conflicting reports on the incidence of the disease but also to confusion in the management of the various entities of GTD. In an effort to bring about order to this chaos, the World Health Organisation has proposed that the following terms be used universally (1).

A. Histopathologic terms

1. Hydatidiform Mole (HM). This is a term which includes two different entities, complete HM and partial HM. Features common to both forms are a hydropic state of some or all villi trophoblastic hyperplasia.

i) Complete HM (CHM). This is a conceptus without an embryo or fetus. There is gross hydropic swelling of the villi with pronounced hyperplasia of both the cyto and syncytiotrophoblastic layers. Cytogenetically, most are XX.

ii) Partial HM (PHM). This is an entity which has only recently been recognised and it appears that it may be much more common than CHM. It is a conceptus with an embryo or fetus that tends to die early with a placenta subject to focal swelling and trophoblastic hyperplasia involving the syncytiotrophoblast only. Cytogentically these are most often triploid.

2. Invasive Mole (IM). This is a tumor characterised by trophoblastic hyperplasia and persistence of placental villous structure, and invasion of the myometrium. It commonly results from CHM but may do so from PHM also. It does not often progress to choriocarcinoma. It may metastasize but does not exhibit the progression of a true cancer, and may regress spontaneously when the primary is removed. The old terminology for this entity include chorioadenoma destruens and malignant mole.

Department of Obstetrics & Gynaecology
National University of Singapore
National University Hospital
Lower Kent Ridge Road
Singapore 0511

A Ilancheran, M Med, MRCOG,
Senior Lecturer

P Singh, M Med, MRCOG,
Senior Lecturer

Correspondence to: Dr Ilancheran

3. **Choriocarcinoma (CC).** This is a carcinoma arising from the trophoblastic epithelium of a conceptus including those which result in a live birth, an abortion at any stage, ectopic pregnancy and hydatidiform mole.

4. **Placental Site Trophoblastic Tumour (PSTT).** This is a very rare tumour that arises from the placental bed, composed mainly of cytotrophoblast.

B. Clinical terms

Except for CHM and PHM, the diagnosis of other entities of GTD is often clinical. There is a misconception that any patients with metastic disease after a CHM has choriocarcinoma, for example, patients with lung shadows or a vaginal nodule. Most of these patients are actually cases of invasive mole, the secondaries being made up of molar tissue. Hence, their excellent response to chemotherapy. However, if the secondaries were detected after an abortion or term pregnancy, then they are likely to be true choriocarcinomas. However, since the treatment is the same whether it is invasive mole or choriocarcinoma, in practice, the terms have been used indiscriminately. Treatment is instituted on the basis of radiological or biochemical evidence of GTD. With decreasing emphasis on hysterectomy as the primary treatment for CHM, it is becoming increasingly difficult, if not impossible, to make a diagnosis of invasive mole. An extremely vigorous curettage may reveal the diagnosis at the expense of unacceptable complications. Besides, the presence of an excellent tumour marker, namely Human Chorionic Gonadotrophin (HCG), has made histological confirmation of malignancy obsolete. The WHO proposes the following clinical terms:

1. **CHM, PHM, IM and CC:** These terms are used whenever positive histological diagnosis is available.

2. **Gestational Trophoblastic Tumour (GTT):** This term includes patients with only clinical evidence of IM or CC (i.e. biochemical or radiological evidence but no histological proof). This is further subdivided according to antecedent pregnancy such as post mole (PM), post abortion (PA), post term (PT) or unknown (U). GTT may be non metastatic or metastatic. The WHO has recommended that these patients should not be labelled as choriocarcinomas or clinical choriocarcinomas. It must be stressed that treatment should be instituted promptly once the diagnosis of GTT is made.

Cytogenetics of hydatidiform mole

Hydatidiform mole is the most common variety of GTD. Until recently, only the complete hydatidiform mole (CHM), commonly known as molar pregnancy, was recognised as a pathological entity. Now, the occurrence of a much more common variant, the partial hydatidiform mole (PHM), has been documented with increasing frequency (2). There are strict histological criteria for the diagnosis of PHM but this is not always easy. Cytogenetic examination has revealed the distinct difference between the two entities. The CHM are always diploid whilst the PHM are almost always triploid. What is more interesting is the fact that most of the CHM have two X chromosomes, both derived from the father! The PHM, on the other hand, have two paternally derived chromosomes (XY) and a maternally derived X. This dominant zygosity in moles has led to speculation of the existence of a "high risk" male. The cytogenetic makeup of the moles has led Szulman (2) to postulate that, in PHM, "the presence of the maternal chromosomes produces a "dilution" of the total molar syndrome, causing the appearance of a checkerboard distribution of hydatidiform changes in the villi of trophoblastic hyperplasia, as well as the attenuation of other features: a delay in the demise of the embryofetus, a milder clinical course including the infrequency of invasive complications and an apparently total absence of choriocarcinoma".

DIAGNOSIS

Passage of vesicles per vaginum is the sine qua non for the clinical diagnosis of CHM. In the absence of this, a high index of suspicion is needed. Any patient presenting with bleeding in early pregnancy, uterus larger than dates or absence of fetal movements must be considered to have CHM until proven otherwise. Rarely, these patients may present with severe hypertension in early pregnancy or hyperthyroidism. Confirmation of diagnosis is best done by ultrasound examination of the uterus which will show the characteristic "snow storm" appearance with absence of a gestational sac or fetal echoes. Routine ultrasound scanning of early pregnancy by many obstetricians has led to earlier diagnosis of this condition which usually presents clinically in the second trimester. Coexistent fibroids with normal pregnancy or missed abortions may mimic the ultrasound picture of CHM.

Majority of PHM present as incomplete or missed abortions and the diagnosis is seldom made preoperatively. It is of vital importance that the entire contents of the aborted material be sent for pathological examination as the changes only affect portions of it. With increasing experience of ultrasound, a few cases of PHM are being diagnosed before abortion.

As mentioned above in the discussion on nomenclature, histological diagnosis of invasive mole or choriocarcinoma of the uterus, without hysterectomy, is extremely difficult. Histological access to choriocarcinomatous deposits in other parts of the body is even more difficult. Pelvic angiography, high resolution ultrasonography and CT scans may be of value in suggesting the diagnosis. However, the most important parameter for the diagnosis of the above malignant sequelae is raised levels of HCG in the serum and this alone is enough for the diagnosis and to start therapy. In fact, choriocarcinoma is the only malignancy that is treated without histological diagnosis! Whilst most doctors are aware of the malignant potential of hydatidiform mole, it is important to remember that choriocarcinoma can occur after any pregnancy such as term delivery, abortion or ectopic pregnancy. In such instances a high index of suspicion is needed to make the diagnosis.

MANAGEMENT

Molar pregnancy is best treated by vacuum aspiration. Aborting the mole prior to vacuum suction with prostaglandins or oxytocin is not only not necessary but may predipose to metastatic disease (3). Primary hysterectomy may be indicated in older women, but this does not reduce the need for close followup subequently.

Followup of patients after evacuation of a mole is the most important part of the management as this is the only way to detect malignant sequelae early and institute prompt treatment. The prognosis for such patients is directly related to the time interval between the diagnosis of the malignant sequelae and the antecedent pregnancy. Besides a good history and physical examination, the measurement of HCG in the serum at every visit is the most critical part of the followup. The use of radioimmunoassay to measure the β subunit of HCG is currently the most sensitive method. A persistently high value, a plateauing or a secondary rise in the level of the hormone is sufficient to make a diagnosis of GTT and to start chemotherapy.

The frequency of followup is intensive in the first 6 months as majority of the malignant sequelae would occur within this period. Almost no one develops malignancy after 2 years. Recently, Bagshawe(4) had shown that in patients in whom the serum HCG becomes negative (<2.5miu/ml) by 8 weeks, the risk of recrudescence of the disease requiring chemotherapy is zero. If the test becomes negative after 8 weeks but before 12 weeks after evacuation and there is no rise in titre for the next 6 months, the risk is 1: 286. If patients have remained well for 2 years following the evacuation of the mole, it is reasonable to discharge them, with advice to come back if they become pregnant or develop irregular bleeding. Contraception is usually advised during that first year of followup mainly to avoid the confusion of interpreting rising levels of HCG which may be due to a normal pregnancy. Barrier methods are not very effective. Hormonal contraception is the choice in most centres.

If a diagnosis of invasive mole is made preoperatively, the standard treatment is a total hysterectomy followed by chemotherapy. However, in young patients desirous of further pregnancy and in whom the lesion is small, local resection may be used successfully.

The mainstay of treatment of choriocarcinoma and GTT is chemotherapy. Since methotrexate (MTX) was first used to treat choriocarcinoma in 1956, various new drugs and regimes have evolved. Currently, various centres use scoring systems to subclassify patients into low and high risk categories. Low risk patients are treated with single agent chemotherapy whilst the high risk patients are given combination chemotherapy with three or more drugs. In Singapore, MTX or actinomycin D (ACT-D) is used in single agent therapy. Our choice for high risk patients is a combination of MTX, ACT-D and etoposide. For details on the selection criteria, pretreatment investigations, dosages and complications, the reader should refer to Ilancheran et al (5).

Surgery has an important role in the management of trophoblastic disease. Vacuum aspiration and hysterectomy have been mentioned before. In choriocarcinoma and GTT, surgery may be resorted to in selected cases in whom chemotherapy does not achieve complete cure. The lungs are the most common sites of metastases in this disease. More than 90 percent of patients with pulmonary metastases will enter complete remission with chemotherapy alone. But in patients with solitary metastasis confined to one lung, who do not respond to chemotherapy, thoracotomy can produce permanent remission (6). Intracerebral metastases occur in about 20 percent of patients with GTT and usually carries a poor prognosis. Whilst the preferred treatment in these patients is combined chemotherapy and radiotherapy, selected patients with solitary, large metastasis in an accessible area and with no other extensive disease elsewhere in the lungs may be good candidates for an initial craniotomy.

The rare condition, placental site trophoblastic tumour, is best treated by hysterectomy and chemotherapy. This is one tumour which does not produce HCG consistently and hence followup HCG monitoring may not be useful.

Followup of patients after treatment for choriocarcinoma and GTT is identical to that mentioned for hydatidiform mole.

CONCLUSION

Recent advances in the understanding of the natural history of the disease, better diagnostic techniques, the use of the tumour marker HCG, more effective chemotherapy regimes and the judicial use of surgery have all contributed to transform trophoblastic disease from a dreaded disease to an eminently curable one. One other key factor for this progress was the setting up of regional centres with adequate facilities to manage this complex disease. All patients with gestational trophoblastic neoplasm should be referred to such centres.

REFERENCES

1. World Health Organisation Scientific Group on Gestational Trophoblastic Diseases: Gestational Trophoblastic Diseases, Technical Report Series No. 692. Geneva, World Health Organisation, 1983.
2. Szulman AE: Trophoblastic Disease: Clinical Pathology of Hydatidiform Moles. Obstet Gynecol Clin N Amer 1988; 15:443-56.
3. Curry SL, Hammond CB, Tyrey L, Creaseman WT, Parker RT: Hydatidiform mole: Diagnosis and management and long term followup. of 427 patients. Obstet Gynecol 1975; 45:1-8.
4. Bagshawe KD: High risk metastatic trophoblastic disease. Obstet Gynecol Clin N Am 1988; 15:531-43.
5. Ilancheran A, Singh P, Sen DK, Ratnam SS; Update on chemotherapy of gestational trophoblastic disease. Sing J Obstet Gynaecol 1988; 19:53-60.
6. Jones WB, Lewis JL: Integration of surgery and other techniques in the management of trophoblastic malignancy. Obstet Gynecol Clin N Am 1988: 15:565-76.