ICOG FOGSI Recommendations for Good Clinical Practice

The Management of Gestational Trophoblastic Disease

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Discussed by Committee:	28th March 2004
Discussed by Core Committee:	14th March 2009
Website:	ICOG & FOGSI
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1. Introduction

Gestational Trophoblastic Diseases comprises a spectrum of tumour and tumour like conditions that originate from the foetal chorion. Trophoblastic tumours are foetal allograft in maternal tissues and present unique biological, immunological and pathological problems. The spectrum of cellular proliferations includes the various forms of hydatidiform mole through invasive mole and choriocarcinoma to placental site tumours. The screening programs for Gestational Trophoblastic Neoplasia (GTN) following evacuation of hydatidiform mole have been instrumental in the near elimination of fatalities from the sequelae to mole.

2. Purpose

Gestational Trophoblastic Neoplasia (GTN) is highly curable, yet there are many patients succumbing to GTN in our country due to lack of proper organised follow up programmes. The purpose of this guideline is to provide the minimum standard of care of patients with gestational Trophoblastic Disease. It is important to have the regional registries for the proper understanding of this unique malignancy. This will help making decisions and optimizing management, and preventing treatment failure.

3. Background

It is well recognised that molar pregnancy comprises two distinct entities, the complete hydatidiform mole and partial hydatidiform mole which differ in their chromosomal pattern, gross and microscopic pathology and in the risk of developing GTN. Complete mole has 9 to 20 % risk of developing GTN while the risk in partial mole is only about 3 percent. Though it is desirable, histological verification is not mandatory for the diagnosis of GTN. GTN is diagnosed based on the clinical findings and hCG titre. Gestational Trophoblastic Neoplasia replaces the term invasive mole, choreoadenoma destruens, metastasizing mole and choriocarcinoma. GTN may be chemical only with persistent hCG level, or with evidence of tumour either confined to the uterus (non metastatic), or with metastasis to lungs, vagina, brain, liver or other organs (metastatic GTN). Besides post-molar GTN (60%), it may follow after abortion (30%) or after normal pregnancy or ectopic pregnancy (10%). Placental Site Trophoblastic Tumor (PSTT) is a variant of GTN and should be classified separately. The diagnosis of GTN in a patient who has not had a hydatidiform mole may be difficult. Non gestational trophoblastic disease is choriocarcinoma of the ovary or testes.

4. Diagnosis of hydatidiform mole

Ultrasonography is an accurate and sensitive method for the diagnosis of complete mole with the characteristic vesicular pattern due to generalized swelling of the chorionic villi. The vesicles in the first trimester complete mole tend to be smaller with less cavitations. The widespread use of ultrasound has led to earlier diagnosis of pregnancy and has changed the pattern of molar pregnancy. The majority of women present with symptoms of early pregnancy failure or anembryonic pregnancy while presentation with hyperemesis, early severe pre-eclampsia and hyperthyroidism is very rare. The specificity of sonographic findings in complete mole could be improved by correlation with high hCG levels.

Ultrasonography is of limited value in detecting partial mole, usually mistaken for missed abortion. The diagnostic features are a comparatively large placenta with cystic spaces within, gestational sac with amorphous echos or growth retarded fetus. The important diagnostic points are cystic spaces within the placenta and the ratio of the transverse to anterior-posterior dimension of the gestational sac will be more than 1.5. This change in the shape of the gestational sac may be part of the embryopathy of triploidy.

In rare situation of a twin pregnancy with one normal fetus and another mole, case should be repeatedly evaluated before intervention. 3-D ultrasound will be of help in diagnosing this condition. Conformation is by karyotyping which will show triploidy in partial mole and 23xx/23xy in case of mole with normal fetus.

Histopathological study of early mole may show blood vessels and nucleated RBCs. It is not correct to say that if there is fetal RBC, it is a partial mole.

5. Evacuation of the hydatidiform mole

Suction curettage under general anesthesia is the preferred method of choice for the primary management of complete mole. Use of PGE_1 analogue for cervical ripening is not contraindicated. Oxytocin infusion may be started at the end of the evacuation to minimize the bleeding. Routine repeat curettage after evacuation of the mole is not warranted. An ultrasonography after one week of evacuation is essential to see the completeness of the evacuation of the mole. If there is evidence of residual tissue, a repeat curettage has to be performed to ensure complete removal of all molar tissue so that the further bleeding and elevation or persistence of the hCG is a pointer for the diagnosis of GTN. Anti-D should be given to Rh-ve women

In partial mole, where the size of the fetus deters the suction curettage, medical termination is the method of choice.

In elderly multiparous patients who are not desirous of further reproductive function, hysterectomy with mole-in –situ may be an option. Though, hysterectomy will not prevent the risk of subsequent development of GTN, it reduces the risk. These patients are also advised to come for follow-up.

6. Chemoprophylaxis

The routine use of prophylactic chemotherapy at the time of evacuation of the mole is not recommended. Although it may reduce the incidence of GTN in high-risk patients, there is no benefit in low-risk patients. If any of them develop GTN in spite of the prophylactic chemotherapy, they will have a more resistant disease requiring multi-agent chemotherapy. Hence if at all prophylactic chemotherapy is given to any high-risk cases, they should be continued with the chemotherapy till hCG remains negative.

7. Histological examination of products of conception

All products of conception obtained after evacuation of an abortion should be subjected to histological examination because of the difficulty in making a diagnosis of molar pregnancy in all cases prior to evacuation.

8. Follow-up

Serum hCG Assay- it is essential to have a reliable hCG assay system to monitor the patients after evacuation of the mole to detect the development of GTN at the earliest so that complete cure could be achieved with single agent chemotherapy with preservation of fertility potential.

Ideally serum for hCG should be taken prior to and one day after the evacuation to detect the initial hCG level. There after serum hCG level should be estimated at least every two weeks till it becomes undetectable. Then it is sufficient to check the urine for hCG once a month for 6 months if it remains negative without any clinical symptoms like abnormal vaginal bleeding and patient having regular cycles. During the initial follow up period clinical signs and symptoms like vaginal bleeding, sub involution of the uterus, persistence and appearance of lutein cysts are warning signs of development of GTN.

Patients are advised to use reliable contraception during the follow up period. Low dose OCP is not contraindicated once the hCG has be come negative.

Follow up may be required for 6 months to 2 years depending on the situation.

If the hCG becomes negative by 8 weeks after evacuation, a further follow up of 6 more months is sufficient.

If hCG remains positive for more than 8 weeks after evacuation, such patients should have 2 years follow up.

Estimation of hCG should be performed 6 to 10 weeks after any future pregnancy as these patients are at higher risk of developing GTN.

9. Criteria for diagnosis of post-molar GTN

The diagnosis of GTN is made on the basis of elevated hCG levels supported, but not necessarily, by histologic or radiologic evidence.

- When there is plateau of hCG for more than 4 weeks
- When there is rise in hCG on three consecutive measurements.
- If hCG is >20,000 IU/L 4 weeks after evacuation.
- If hCG remains positive after 16 weeks after evacuation.
- When there is histological evidence of choriocarcinoma.

Metastatic work up in GTN:

- Chest X-Ray is appropriate for diagnosis of lung metastasis.
- Liver metastasis may be diagnosed by CT scan or USG.
- Brain metastasis is diagnosed by MRI or CT SCAN.

FIGO staging of GTN:

Stage I	Disease confined to the uterus.
Stage II	GTN extends outside the uterus, but limited to genital organs.
Stage III	GTN extends to the lungs.
Stage IV	All other metastatic sites

The modified WHO scoring system is used to decide on management. In the new risk scoring system, blood groups are considered and liver metastasis is given a score of 4. Low risk group is a score of 6 or less and high risk patients will have a score of 7 and above.

Low Risk GTN:

- WHO score of 6 or less
- FIGO stage I, II, and III.
- Duration less than 4 months
- hCG value is less than 40,000 IU/L

Low risk GTN is treated with single agent chemotherapy.

Drug Schedules: single agent chemotherapy

1. Methotrexate with Leucovorin rescue –
   Methotrexate 1mg/kg im every alternate day for 4 days with Folinic acid 0,1mg/kg 24 hours after each dose of Methotrexate. Course could be repeated every two weeks depending on the response.
2. Actinomycin-D, 9-12 micrograms/kg IV daily for 5 days repeated every two weeks.
   - Complete blood count, RFT and LFT should be done prior to each course.
   - Weekly serum hCG measurements.
   - Chest X-ray.
   - Brain CT/MRI when there is suspicion of metastasis.
   - At least one course, usually two to three courses of chemotherapy should be given beyond first negative hCG level, especially if the fall of hCG was slow.

High Risk GTN:

- FIGO stage I, II, III with WHO risk Score of 7 or greater.
- FIGO stage IV.

Patients with high risk GTN are treated with combination chemotherapy, EMA-CO as the primary combination therapy. Risk of leukaemia with EMA-CO used for more than 6 courses has been reported.

It is safer to treat the patients with high risk GTN at higher centers.

Placental site trophoblastic tumor must be treated at higher centers with surgery and combination chemotherapy.

Pregnancy after chemotherapy for GTN:

Patients must be advised to wait for twelve months after completion of chemotherapy before undertaking pregnancy.

Establishment of Trophoblastic disease registries:

It is essential to have regional registries for trophoblastic disease to monitor follow up and outcome in GTN management in our country. This could be established at the society level with the guidance and help of FOGSI and ICOG.

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