Bangladesh J Obstet Gynaecol, 2012; Vol. 27(2) : 50-56

Experience of Persistent Gestational Trophoblastic Disease in a Tertiary Medical College Hospital, Bangladesh

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Abstract:

Objectives: *To study the clinical presentation and risk factors of persistent trophoblastic disease and its outcome of treatment with chemotherapy.*

Materials and methods: *This observational study was carried out on fifty patients of persistent trophoblastic disease who were admitted in the Department of Obstetrics & Gynaecology, Mymensingh Medical Hospital (MMCH) during one year period. Evaluation of disease was done by thorough clinical examination and a set of investigations including chest radiography, ultrasound scan of abdomen and pelvis and estimation of serum â hCG. The four factors under analysis of PTD were age of the patient, clinical presentation, gestational age at diagnosis of molar pregnancy and nature of antecedent pregnancy.*

Patients with non-metastatic trophoblastic disease and low risk metastatic trophoblastic disease were offered single agent chemotherapy with methotrexate and folinic acid rescue in consultation with the oncologist. When β hCG response was inadequate, multi-agent chemotherapy was given. Complications of chemotherapy were also observed and supportive treatment was given.

Results: *Out of 50 patients, 49 (98%) patients had antecedent molar pregnancy and 1(2%) had missed abortion. In cases of post molar trophoblastic disease, 28 (57.58%) were in 20-30 yrs. Mean ± SD was 31.35 ± 7.25. In these cases gestational size of molar pregnancy was between 16-20 weeks in 24 (48.98%), <16 wks in 19 (38.78%) and >20 wks in 6 (12.24%) cases. Mean ± SD was 16.78 ± 4.45 wks (p<0.001). Associated theca lutein cysts were present among higher number of cases (57.14%) but not statistically significant. Regarding clinical presentation, 40 (80%) patients presented with irregular pervaginal bleeding, 3(6%) patients with features of metastasis. Most of the of the study subjects 43 (86%) were treated with chemotherapy and 7 (14%) had undergone both hysterectomy and chemotherapy. Single agent methotrexate was given in 47 (94%) cases and multiple agent (EMA-CO) in 3 (6%). After giving 4 cycles of chemotherapy 11 (22%) patients were cured, 38 (76%) had declining â hCG level and one had static β hCG level. Overall remission was 98 %. Complication of chemotherapy was observed in 5 (10%) patients.*

Conclusion: *Theca lutein cyst are important in the prediction of persistent disease after molar pregnancy. Methotrexate chemotherapy is effective and well tolerated in treating patients with nonmetastatic and low risk metastatic gestational trophoblastic neoplasia.*

Key Words: *Persistent trophobtastic disease, risk factor, chemotherapy.*

Introduction:

Gestational trophoblastic disease is a spectrum of tumors with a wide range of biologic behaviour and potential for metastasis. It refers to both the benign and malignant entities of the spectrum and includes hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumour (PSTT). The last three are termed gestational trophoblastic tumours

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(GTT); all may metastasize and are potentially fatal if untreated[1]. The incidence of hydatidiform mole varies in different regions of the world, but now has been falling[1]. Highest incidence of 12.1/1000 deliveries was reported from Turkey. The malignant potential of this disease is higher in South East Asia where it can be as high as 10-15% in comparison to 2-4% in the western countries[2].

In persistent trophoblastic disease (PTD), trophoblastic activity remains after evacuation of hydatidiform mole as shown by subsequent high or even rising βhCG concentration in blood. The reported frequency of PTD is 20% in complete hydatidiform mole and 0.5 to 9.9% in partial hydatidiform mole. In order to prevent complication from metastatic disease, PTD needs to be treated early. Prophylactic chemotherapy (started immediately after evacuation of the mole) reduces the incidence of PTD to 4-12%[1]. Because of the large proportion of patients show spontaneous remission of molar pregnancy after evacuation and because of the side effects of chemotherapy, clinicians are reluctant to use prophylactic chemotherapy. It would therefore be helpful to identify the patients at risk for developing PTD[3].

Various risk factors for post molar trophoblastic disease has been reported such as pre evacuation β hCG level, maternal age, gestational age, histologic grade of molar tissue, uterine size, ovarian cyst, presence of medical complication, previous molar pregnancy and ABO blood groups were evaluated[4].

Gestational trophoblastic disease can occur after any type of antecedent pregnancy. The most frequent antecedent pregnancy is that of a patient presenting with a hydatidiform mole. Nearly 45% of choriocarcinomas follow evacuation of hydatidiform mole, 25% follow after full term normal pregnancy, 25% follow spontaneous abortion and 5% ectopic pregnancy[5].

The leading symptom of persistent trophoblastic disease is irregular uterine haemorrhage coming sooner or later after the expulsion of a mole or a normal pregnancy. Often the disease presents by way of its metastasis. Thus the occurrence of a haemothorax, a complaint of dyspnoea or haemoptysis or the appearance of neurological signs and symptoms such as headache , visual disturbances or focal neurological deficits can be the first evidence of choriocarcinoma[6].

Patients with gestational trophoblastic tumors are stratified into low and high risk groups which have different treatments and outcomes. A number of factors are used to stratify patients into high and low risk groups. Each factor scores numerical points. A score >6 (FIGO score) or >8 (Charring cross score) defines high risk disease[7]. Low risk patients are usually treated with single agent chemotherapy. Approximately 85-90% of patients in this group are cured by the initial chemotherapy regimen. Most of the others respond to alternate drugs; combination chemotherapy is rarely needed. High risk patients require combination chemotherapy with a selective use of surgery and radiotherapy[1].

Since there are well known side effects of all the chemotherapeutic drugs, a careful check is made before a course of treatment is commenced or continued. The principal adverse effects are on the bone marrow, liver and kidney, so regular checks are made on white cell count, platelets, liver function and blood urea[6].

Materials and Methods:

This prospective observational study was carried out in the department of Obstetrics & Gynaecology, Mymensingh Medical College Hospital, Bangladesh. from July, 2008 to June, 2009. Fifty patients of persistent trophoblastic disease, who were admitted during this period were selected as study population. In this study, there were 49 patients with histologically confirmed molar pregnancies; complete moles in 46 patients and partial moles in 3 patients. One patient had antecedent missed abortion which was not histologically confirmed.

Persistent disease was determined on the basis of the following criteria-

(a) Two or more consecutive weekly increase in beta hCG level.

(b) Plateauing of the beta hCG level for three or more consecutive weeks.

(c) Persistent or recurrent uterine haemorrhage and a persistently detectable beta hCG titre.

(d) Clinical or histological evidence of metastasis.

Evaluation of disease was done by thorough clinical examination and a set of investigations including chest radiography, ultrasound scan of abdomen and pelvis and estimation of serum β hCG. The four factors under analysis of PTD were age of the patient, clinical

presentation, gestational age at diagnosis of molar pregnancy and nature of antecedent pregnancy.

Patients with non metastatic trophoblastic disease and low risk metastatic trophoblastic disease were offered single agent chemotherapy with methotrexate and folinic acid rescue in consultation with the oncologist. When β hCG response was inadequate, multi-agent chemotherapy was given. Complications of chemotherapy were also observed and supportive treatment was given.

Sampling Method was Purposive non randomized method. A structured questionnaire was developed addressing all the variables of interest which was finalized following pre-testing.

Data was processed using software SPSS (Statistical Package for Social Science).

Results:

A total of 50 subjects of persistant trophoblastic disease were included in the present study. Subjects were categorized into different groups, their frequencies with percentages were calculated, significance levels and mean ± SD were determined by chi square test and one sample "t" test with the help of computer windows SPSS.

Figure-I: Antecedent Pregnancy (n=50): 49(98%) of them were due to post molar trophoblastic disease and 01(02%) due to missed abortion (Fig I). Among the post - molar trophoblastic disease 46 (92%) due to complete mole and 3 (06%) due to partial mole. Complete mole was statistically significant (p=0.001).

Table-I: Maternal age of the post trophoblastic subjects (n=50): Maternal age <20 yrs, 20 – 30 yrs, 31 – 40 yrs and >40 yrs were 01(2.04%), 28(57.58%), 14(28.58%) and 06(12.24%) respectively of the post molar trophoblastic subjects where 20-30 yrs age group were significantly higher.

Table-I

Maternal age of the post trophoblastic subjects (n=50)

Years	No. of subjects	Percent (%)	P value
<20	01	2.04	<0.001
20 – 30	28	57.14	
31 – 40	14	28.58	
>40	06	12.24	
Total	49	100	

Mean ± SD 31.35 ± 7.25

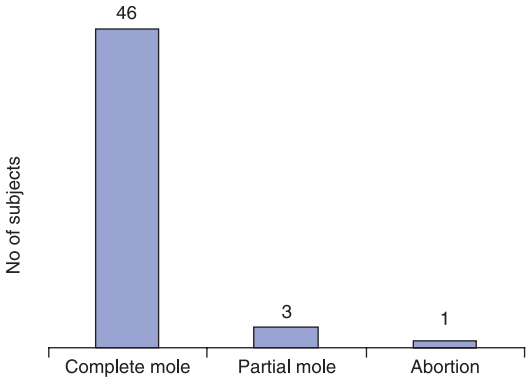

Fig.-1: *Antecedent Pregnancy (n=50)*

Figure-2: Association between past gestational size with the post- molar trophoblastic disease (n=50): Gestational size <16 wks, 16 – 20 wks, and >20 wks were 19(38.78%), 24(48.98%) and 06(12.24%) respectively in the post molar trophoblastic subjects. 16-20 wks group were significantly higher.

Fig.-3: Associated theca lutein cyst of the post trophoblastic subjects (n=50): Associated theca lutein cyst were present in 28(57.14%) but absent in 21(42.86%) in the presentation of trophoblastic subjects which was not statistically significant.

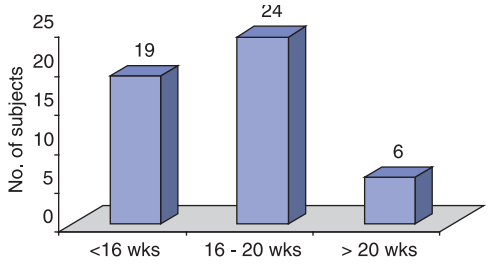

Fig.-2: *Association between past gestational Size with the post- molar trophoblastic disease (n=50)*

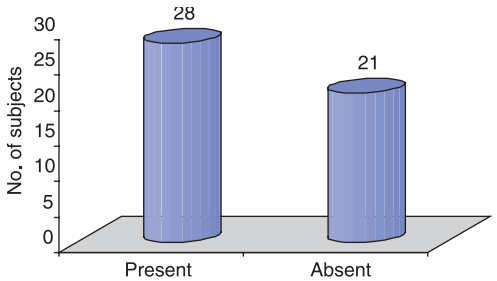

Fig.-3: *Associated theca lutein cyst of the post trophoblastic subjects (n=50)*

Figure-IV Menstrual cycle of the study subjects (n=50): Menstrual cycle were regular in 05(10%), irregular in 40(80%) amenorrhea in 04(08%) and amenorrhea due to surgery in one (02%) case. Incidence of irregular menstruation was significantly higher.

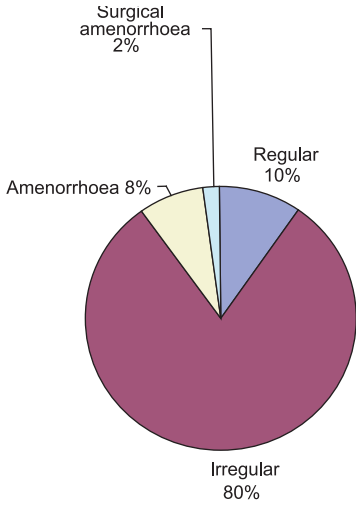

Fig.-4: *Menstrual cycle of the study subjects (n=50)*

Figure-5: Features of distant metastasis of the study subjects (n=50): 47(94%) of the study subjects have no features of distant metastasis but 02(04%) had pulmonary metastasis and one (02%) case had metastatic nodules in vagina. Non metastatic cases were significantly higher.

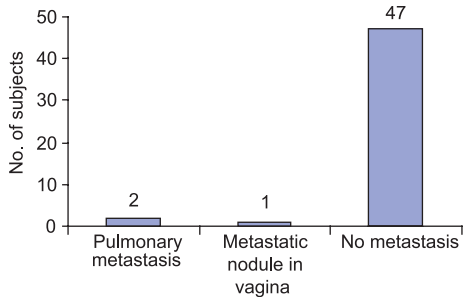

Fig.-5: *Features of distant metastasis of the study subjects (n=50)*

Table-2 Uterine size of the study subjects (n= 50): Uterine size were normal in 17(34%), 6-8 wks in 30(61%), 9-12 wks size in 2(4%) and >12 wks were in 1(2%) case. Uterine size 6-8 wks group were significantly higher.

Figure-6: Treatment given to the study subjects (n=50): 43(86%) of the study subjects were treated with chemotherapy alone and 07(14%) had both hysterectomy and chemotherapy.

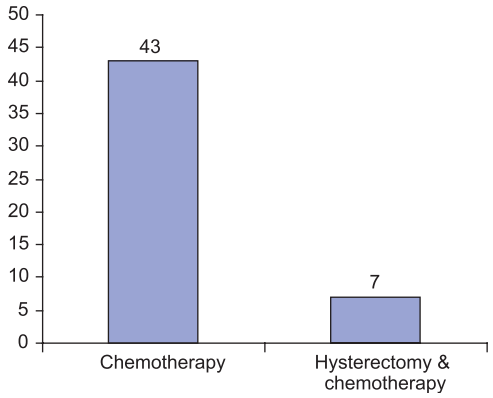

Fig.-6: *Treatment given to the study subjects (n=50)*

Table-II

Uterine size of the study subjects (n= 50)

Size	No. of subjects	Percent (%)	P value
Normal	17	34	<0.001
6 – 8 wks	29	58	
9 – 12 wks	02	04	
>12 wks	01	02	
Hysterectomy	01	02	
Total	50	100	

Figure-7: Type of chemotherapy given to the study subjects (n=50): Single agent chemotherapy were received by 47(94%) and multiple agent (Etoposide, Methotrexate, Actinomycin D and Cyclophosphamide) by 03(06%) of the study subjects.

Figure-8: The outcome of the study subjects (n=50): After chemotherapy, 11(22%) patients were cured, 38(76%) had declining â hCG level, and 1(2%) had static β hCG level. Declining β HCG level was significantly higher.

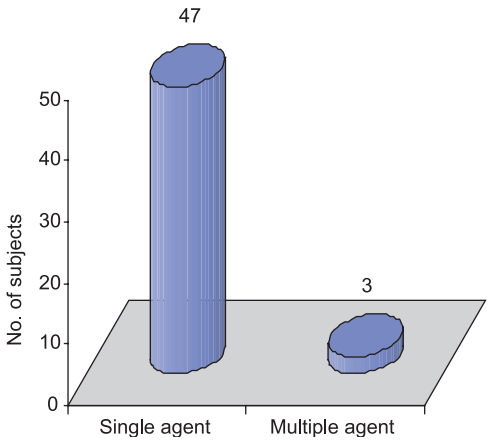

Fig.-7: *Type of chemotherapy given to the study subjects (n=50)*

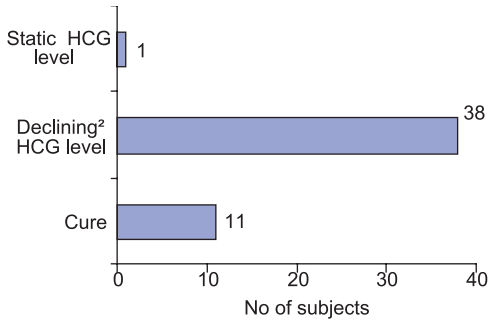

Fig.-8: *The outcome of the study subjects (n=50)*

Figure-9: The complication of chemotherapy of the study subjects (n=50): 45(90%) had no complication of chemotherapy. 02(04%) had liver dysfunction (Hepatitis and Elevated Transaminases), 02(04%) had stomatitis and 01(02%) had both GIT upset and stomatitis.

Figure-10: The effect of chemotherapy on β hCG of the study subjects (n=50): Mean ± SD of post evacuation β hCG was 84551 ± 39901, mean ± SD of β hCG levels after 1st dose of chemotherapy was 19854±14808 and mean ± SD of β hCG levels after 4th dose of chemotherapy was 84 ± 50 (Fig X). The differences were statistically significant.

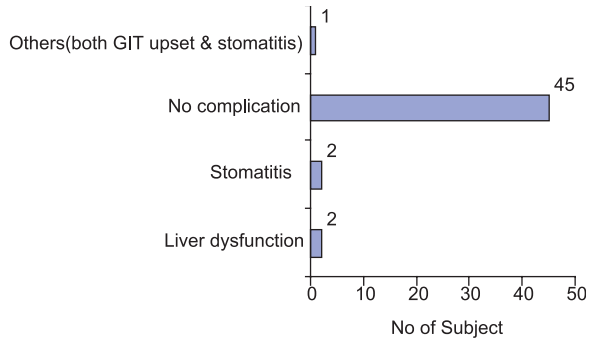

Fig.-9: *The complication of chemotherapy of the study subjects (n=50)*

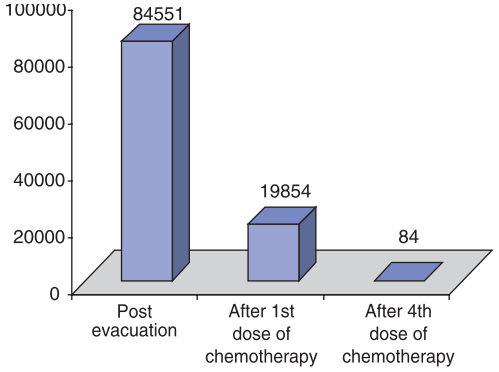

Fig.-10: *The effect of chemotherapy of the study subjects (n=50)*

Discussion:

Risk factors of post molar trophoblastic disease In the present study, among 49 patients of PTD, 28 (57.14%) were in 20-30 yrs of age group statistically significant (p<0.001), 14 (28.58%) in 31-40 yrs of age and only 7 (14.28%) were in extremes of age. Mean age was 31.35 yr. Similar findings were reported in Australia and in New England Trophoblastic Disease Centre (1990-2003) where patient's extreme age (below 20 yrs or above 35 yrs) were not found to be strongly associated with risk of persistent disease[7, 8]. In another study in India, 47.47 % patients were in between 20 and 25, 28% were less than 20 years of age and 24% were in > 25 years[9]. In Philippines, one study reported 44% of cases in between 25- 34 years and least number of cases in extremes of age[10].

In this study, 28 (57.14%) patients had associated theca lutein cyst. But it was statistically in significant. But Tchan Kyu Park found the presence of theca lutein cyst as a significant risk factor[4].

Antecedent pregnancy

In this study, among 50 patients of PTD, the antecedent pregnancy was molar in 49 (98%) and missed abortion in one (2%) case. Among PTD, 46 (92%) were due to complete mole and 3 (6%) due to partial mole.

In Pakistan one study reported among the persistent trophoblastic disease, in 40% cases antecedent pregnancy was hydatidiform mole, and while 60% cases it was spontaneous abortion[11]. In Charing Cross Hospital 602 patients treated between 1985 to 1994, there were 100 cases (16.6%) where the antecedent pregnancy was either a non-molar abortion or a live birth, rest of the cases were molar pregnancy[12].

Clinical Presentation

In the present study, 40(80%) patients presented with irregular pervaginal bleeding which was statistically significant. (p<0.001), 4 (08%) presented with amenorrhoea and 3(06%) presented with metastasis, 32 (64%) presented with uterine size more than normal, 28(56%) with tubo-ovarian mass.

In one study in India 20 cases with GTD were presented with abnormal vaginal bleeding[13].

In a study in Charring cross hospital, among 602 patients between 1985- 1994, approximately two-third (66.67%) presented with varying degrees of vaginal

bleeding but in one-quarter (25%) of these patients the primary complaint was associated with symptoms from metastatic disease involving lung, brain or abdomen[12].

Outcome of chemotherapy in persistent trophoblastic disease

In the present study 43 (86%) patients were treated with chemotherapy and 7(14%) patients were treated with hysterectomy followed by chemotherapy. All patients started with single agent methotrexate but subsequently 94% patients responded to single agent and 6% needed salvage therapy with multiple agent chemotherapy (EMA-CO). After 4 cycles of chemotherapy 22% patients cured completely, 76% had declining β hCG level and 2% had static β hCG level. Overall remission was 98%. Mean ± SD of â hCG levels after 1st dose of chemotherapy was 19854±14808 and after 4th dose of chemotherapy was 84 ± 50 (Table IX and Fig X). The differences were statistically significant.

In India one study showed almost 90% patient cured with methotrexate (MTX), 2.2% cases were treated with multiple agent chemotherapy. Case fatality was 2.02%[11]. Another study showed 92.9% remission rate of low risk GTN with MTX. Rest of the cases required multiagent chemotherapy[14].

In Manila, one study reported sustained remission rate 98.5% with chemotherapy for non metastatic GTN and LRM GTN (Low risk metastatic GTN)[12] while Wong reported 91.5% cure rate with MTX[15].

In United Kingdom, one study showed 94.4% cure rate of LRMGTN with MTX while 5.55% required salvage chemotherapy[16].

Chemotherapy complication: The toxicity of chemotherapy has been reported to occur in 16.9% to 70.2% of the cases. Some deaths due to drug toxicity has been reported. In Korea one study showed chemotherapy was well tolerated without serious toxicities[13]. Hepatotoxicity was observed frequently with MTX, CVF regimen. Gastro intestinal symptoms mainly nausea, vomiting occurred frequently when actinomycin D was given. Haematological toxicity was transient and mild. Alopecia was minimal and reversible. Stomatitis was also mild and transitory.[4]

In the present study, complications of chemotherapy were found only in 10% of patients. Among them 4%had liver dysfunction, 4%had stomatitis and 2% had both gastrointestinal symptoms and stomatitis.

In Pakistan one study showed after administration of EMA-CO therapy, 100% patient developed nausea, vomiting, anorexia; 60% patient developed alopecia and 20% patient developed bone marrow depression.[11]

In United Kingdom one study showed 25% patient developed serosal symptoms with low dose MTX and folinic acid regimen, among them pleurisy was the commonest complaint.[17] On the other hand Wong reported no significant side effects except Steven Johnson Syndrome in one case[15].

Conclusion:

Most common presenting complaint of PTD was irregular per vaginal bleeding. Serial β hCG levels remain the best monitor for following up a molar pregnancy and for determining response to treatment.

Methotrexate infusion therapy described in this study is effective in the treatment of non metastatic GTD and low risk metastatic GTD. Neither severe complication nor death occurred due to toxicity.

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