

# GESTATIONAL TROPHOBLASTIC DISEASE: EXPERIENCE AT A TERTIARY CARE HOSPITAL OF PESHAWAR

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## ABSTRACT

**Objective:** To find out the frequency, clinical presentation, type, extent and treatment modalities of Gestational trophoblastic disease.

**Material and Methods:** This was a descriptive study of 45 patient with Gestational trophoblastic disease admitted in Gynae "B" unit of Lady Reading Hospital over a period of one year from first of August 1992 to thirty first July 1993. The case records of all these patients were analyzed regarding their clinical presentation, investigation, treatment and follow up.

**Results:** The frequency of Gestational trophoblastic disease was 11.8/1000 pregnancies or 17.6/1000 deliveries. Out of 45 cases of Gestational trophoblastic disease, 38 were hydatidiform mole (H. Mole) and 7 were choriocarcinoma. The commonest age group was 21-39 yrs (68.5%). The disease was common in multigravida and grand multigravida (44%-40%). Variable period of amenorrhea associated with vaginal bleeding was the main presenting symptom (99.5%). Seventy three percent (73.3%) of patient had suction evacuation. Eighty percent (80%) of the patient did come for follow up. One patient died in case of choriocarcinoma due to complication.

**Conclusion:** Frequency of trophoblastic disease was high in this study compared to world and national literature. Regular follow up and counseling is essential to decrease the mortality and morbidity from this condition.

**Key Words:** Gestational Trophoblastic Disease (GTD), Gestational Trophoblastic Neoplasia (GTN), Hydatidiform Mole (H. Mole).

## INTRODUCTION

Gestational trophoblastic disease (GTD) is the general term for a spectrum of proliferative abnormalities of trophoblast. It includes hydatidiform mole (H. Mole) [complete and partial] invasive mole, choriocarcinoma and placental site trophoblastic tumor. In recent years, new entities like epithelioid trophoblastic tumors have been added<sup>1</sup>. The countess of Hennberg who delivered a hydatidiform mole on Easter 1276 is the first identifiable individual with this disease entity<sup>2</sup>. The exact etiology of the disease is not known but the cytogenetic studies show the stronger genetic association. Its incidence varies worldwide. The comparison between figures in different parts of the world is difficult, because some studies are population based while others are hospital based studies. In UK, H. Mole occurs in 1 in 714 pregnancies<sup>3</sup>. In North America the

incidence is 2.5/1000 pregnancies<sup>4</sup>. In Japan the incidence is 2/1000 deliveries while in Malaysia the incidence of molar pregnancy and gestational trophoblastic neoplasia (GTN) is 2.8/1000 and 1.59/1000 deliveries respectively<sup>5, 6</sup>. Highest incidence of 12.1/1000 deliveries is reported from Turkey<sup>7</sup>. In India the incidence of GTD was 1.31/1000 live birth and 1/967 pregnancies in one hospital based study<sup>8</sup>. In South Africa the incidence of molar pregnancy and choriocarcinoma is 1.2/1000 and 0.5/1000 deliveries respectively<sup>5</sup>.

The predisposing factors include low socioeconomic status, dietary deficiency in protein, folic acid and iron. Common clinical presentations include, vaginal bleeding in early trimester, uterus larger than period of gestation, absence of fetal parts after 20 weeks of gestation. GTD is characterized by the secretion of distinct tumour marker, the Beta human chorionic gonadotrophin

( $\beta$  HCG). Ultrasonography is a reliable non invasive tool for diagnosis of GTD in clinical setting.

Although no population based study is available from Pakistan but a few hospital based studies are available. One such study from Peshawar shows the frequency of GTN to be 1.88/1000 pregnancies<sup>9</sup> while a study from Jamshoro (Sindh) shows the frequency of GTD to be 1:45 live births<sup>10</sup>. Thus, the objective of this study was to find out the frequency, clinical presentation, type, extent and treatment modalities of GTD.

**MATERIAL AND METHODS**

This descriptive study was conducted in Department of Obstetrics and Gynaecology of Lady Reading Hospital Peshawar for period of one year from August 1992 to July 1993.

All those patients having gestational trophoblastic disease were included in the study. These patients were diagnosed by their typical clinical features i.e variable period of amenorrhoea associated with vaginal bleeding or passage of vesicles and with or without disproportionately enlarged uterus; higher than normal level ( $>10^3$  mIU/ml) of serum HCG; ultrasonographic (snowstorm appearance in case H.mole) or histopathological evidence of the disease. The diagnosis of GTD was based on presence of at least two or more of the above mentioned features. Patient having irregular bleeding per vagina without any evidence of trophoblastic disease were excluded from the study.

The case records of all these patients were analyzed. For this purpose a detailed proforma was printed which included age, parity clinical features, presenting symptoms, antecedent pregnancy, investigations, histopathology, type of trophoblastic disease, surgical treatment and follow up of the patient. Suction curettage was the method of choice for evacuation of mole.

All those patients who were diagnosed as choriocarcinoma were referred to cancer institute for further management. There these patients were admitted and all the necessary investigations including CAT scan (Computerized axial tomography) were carried before putting them on chemotherapy. Patients were classified as low and high risk group according to modified WHO (World Health Organization) prognostic criteria including features like age, antecedent pregnancy and its duration from diagnosis, size, site and number of metastasis, serum HCG level and any prior chemotherapy. Each criterion carries 0,1,2,4 numbers. The patients with score 0-6 were considered low risk and those with score 7

were considered high risk. Low risk patients were treated with single agent chemotherapy i.e. methotrexate 50mg per day on days 1,3,5,7 with folinic acid on days 2, 4, 6 and 8. Multiagent chemotherapy EMA-CO (Etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine) was used in high risk patients. EMA alternate with CO every week.

Follow up of the patients in case of H. Mole was carried out by clinical examination, serial HCG level, ultrasound and X-Ray chest. Initially it was carried out monthly till HCG was undetected then every 3 month for 6 month, then every 6 month for 1 year. Contraceptive pill was advised for 1 year after HCG become normal. After 1 year pregnancy was allowed. During follow up period these patients were readmitted when indicated.

Data entry and analysis was done using SPSS version 10.0. A chi-square as used for correlation analysis between different variable and values of 0.05 were considered statistically significant.

**RESULTS**

A total of 3815 pregnant patients were admitted during the study period including 45 cases of trophoblastic disease. Total deliveries were 2554 during this period. Hence frequency of GTD was 1:85 or 11.8/1000 pregnancies while frequency per delivery was 1:57 or 17.6/1000. Out of 45 cases of GTD 31(68.8% were complete mole, 7(15.5%) were partial mole and 7 (15.5%) were choriocarcinoma. Age ranges from 18 – 45 years with mean age of  $29.7 \pm 7.6$  years Thirty one (68.8%) were in between 21-39 years of age, 7 (15.5%) were 20 year and less and an equal number 7 (15.5%) were 40 years and above. Out of 45 patients 7 (15.5%) were primipara, 20 (44.4%) were multipara ( $P_{2-4}$ ) and 18 (40.00%) were grand multipara ( $P_5$  and above).

Seventeen (44.6%) patient had gestational period between 4-12 weeks, 15 (39.5%) between 13-24 weeks while in only 6 (15.8%) patient, it was 25 weeks or above (Table 1).

**Table 1: Gestational status in molar pregnancy (n=38)\***

Gestational amenorrhea (weeks)	Complete Mole	Partial Mole	Total
4 – 12	14	3	17 (44.6%)
13 – 24	13	2	15 (39.5%)
25 & above	4	2	6 (15.8%)

\*Amenorrhea was not a consistent feature in choriocarcinoma and only 2 patients had amenorrhoea out of 7

Most common presenting symptom was bleeding per vagina in 44 patients (98%). Other associated symptoms included nausea and vomiting, passage of vesicles, hypertension and dyspnoea in 32, 4, 3 and 2 cases respectively (Table 2).

Anemia was a consistent feature of GTD and 30 patients required blood transfusion. The

antecedent pregnancy was term pregnancy in 32 (71%), abortion in 8 (17%) and hydatidiform mole in 5 patients (11.1%). Out of 45 cases 51% had serum  $\beta$  HCG level between  $10^3$ - $10^4$ , 33.3% had between  $10^4$ - $10^5$  and 15.5% had more than  $10^5$  (Table 3).

Ultrasonography reports are given in Table 4.

**Table 2: Clinical Presentation**

Clinic Features	Complete Mole	Partial Mole	Choriocarcinoma	Total
Bleeding per vagina	31	7	6	44 (98%)
Nausea vomiting	31	1	0	32 (71%)
Passage of vesicles	4	0	0	4 (8.8%)
Hypertension	3	0	0	3 (6.6%)
Dyspnoea	0	0	2	2 (4.4%)

**Table 3: Serum  $\beta$  HCG level (miu/ml)**

Serum $\beta$ HCG level	Complete Mole	Partial Mole	Choriocarcinoma	Total
$10^3$ - $10^4$	17	4	2	23 (51%)
$10^3$ - $10^4$	10	3	2	15 (33.3)
$10^3$ - $10^4$	4	0	3	7 (15.5%)

**Table 4: Ultrasonography Findings in GTD (n=45)**

S. No	Findings	Complete Mole (31) (CM)	Partial Mole (7) (PM)	Choriocarcinoma (7) (CC)
1.	<b>Uterus Size</b>			
	Enlarged for POG	15	0	3
	Consistent with POG	10	3	2
	Small for POG	6	3	0
2.	<b>Uterine Contents</b>			
	Fluid filled vesicles (snowstorm pattern)	27		
	Vesicles with Placental tissue		3	
	Missed abortion		3	
	Intrauterine Pregnancy (Fetus with partial Mole with Placenta praevia)		1	
	Normal Intrauterine pregnancy of 36 weeks			1
	Hypoechoic mass			3
3.	<b>Ovarian corpus luteum cyst</b>			
	Present Bilateral	10	1	1
	Present Unilateral	0	0	1
	Not Present	21	6	5

**Note:**

- POG = Period of gestation
- CM = 4 cases had h/o passage of vesicles p/v
- PM = 3 cases was diagnosed on histopathology.
- CC = 2 cases had normal u/s findings.
- 1 case had h/o hysterectomy for H. Mole 3 years back.

**Table 5: Surgical Management of the sample (n=41)**

Type of Management	Complete Mole	Partial Mole	Choriocarcinoma	Total
Suction evacuation	27	6	0	33 (73.3%)
Abdominal Hysterectomy(± BSO)	4	0	2	6 (13.3%)
Caesarean Section	0	1	1	2 (4.4%)

Out of 45 cases, 41 under went surgical treatment. In 33 (73.3%) patients suction evacuation was done and in 6 patients' hysterectomy was performed. Including 4 patients with molar pregnancy and 2 patients with choriocarcinoma. In 2 patients cesarean section (C-section) was done. Both presented with ante partum hemorrhage (APH). One with partial mole coexisting with a normal fetus. The other presented with 36 weeks pregnancy and bleeding per vaginum due to metastasis in the vagina. Biopsy taken and report showed choriocarcinoma (Table 5).

Out of 38 cases of H. Mole, 30 patients (80%) did come for follow up and disease subsided in all of them within 3 months except 4 patients who required readmission and hysterectomy was done because of persistent vaginal bleeding after evacuation.

Out of 7 cases of choriocarcinoma 5 received low risk regimen while 2 received high risk regimen. One patient died because of complication. 5 patients recovered. One patient lost to follow up.

## DISCUSSION

The frequency of GTD in this study was 1:85 pregnancies, while the rate per delivery was 1:57 which is quite significant. This frequency is also higher within our country if compared to hospital based studies from Peshawar<sup>9</sup> and Jamshoro (Sindh)<sup>10</sup>. The reason for the high frequency of the GTD in this study might be the fact that the hospital is a major referral centre with large catchment area. There is ethnic variation in the incidence of GTD with increased rates in Asian women. However the high incidence in Asia is generally attributed to low socioeconomic status and malnutrition, although such dietary etiology is not supported by conclusive data<sup>3</sup>.

Various risk factors have been identified from time to time for development of GTD<sup>11</sup>. Women 15 and 40 are at high risk<sup>12</sup>. In our study the common age group was 21-39 years. This may be because this was a small hospital

based study and this is the common reproductive age group. Altman AD et al concluded from their study that maternal age was a significant factor in the risk of molar pregnancy<sup>13</sup>. Increasing gravidity does not increase the risk of H. Mole. However following one mole the risk of subsequent pregnancy being a H. mole rises<sup>11</sup>. In our series 5 patients had history of previous molar pregnancy.

Vaginal bleeding is the most common presenting symptom of GTD, it occurred in 98% of our patients and it was also reported by other studies such as Khaskheli M et al<sup>10</sup>, Rauf B<sup>9</sup> et al and Moddley et al<sup>5</sup>.

Most of patients in this study were having hydatidiform mole (84.3%) and 15.5% had choriocarcinoma. Same result was also reported by Khaskheli M et al from Sindh<sup>10</sup>. No case of invasive mole was diagnosed. Suction curettage for H. Mole was the management of choice in most series<sup>5, 6, and 10</sup>. Similarly we did suction curettage in 33 (86.8%) patients of H. Mole. Prophylactic hysterectomy was done in 4 patients. The main indication was persistent vaginal bleeding after evacuation. These patients had completed their family. Currently there is no role of prophylactic hysterectomy<sup>6</sup>. Alazzan M et al was of the opinion that hysterectomy is valuable in managing persistent GTD as primary or adjuvant treatment<sup>14</sup>.

The repeat curettage was performed in 7 patients. The main indication was retained molar tissue documented by ultrasound. Routine repeat evacuation exposes patients to the risk of surgical procedure without the benefits of increased chance of cure. However it may be useful for symptoms control in selected patients with heavy bleeding or curative if the recurrent molar tissue is confined to the uterine cavity<sup>15, 16</sup>.

Patients with GTN or GTD should be managed in consultation with an individual experienced in the complex multimodality treatment of these patients<sup>17</sup>. In our series patients with choriocarcinoma were managed in cancer institute. They received single agent chemotherapy in low risk disease while multiagent therapy in high risk diseases.

Close HCG follow up after molar pregnancy is required to rule out development of post molar GTN or GTD. Recent studies suggest that a shorter period of post molar follow up may be reasonable for patient with both complete and partial molar pregnancy<sup>18,19</sup>. We recommend follow up for 1 year in case of molar pregnancy.

Rarely the choriocarcinoma can also present during pregnancy<sup>11</sup>. In our series one patient with choriocarcinoma presented during pregnancy. C. Section was done, the baby was normal. Patient was referred to cancer institute for chemotherapy. The current management protocols which include accurate diagnostic and monitoring methods together with effective treatment regimen have turned the prognosis highly favourable. The patient is classified at diagnosis and divided into two categories according to the WHO prognostic criteria into low risk (0-6) and high risk ( 7). Low risk patients are treated primarily with single agent chemotherapy (Methotrexate with Folinic Acid rescue) and high risk receive combination therapy (EMA-CO). Response to chemotherapy is determined by serial HCG level. Complete remission is diagnosed when three consecutive HCG levels achieved within normal limit. During treatment patients are monitored by physical examination, haematology and biochemistry profile. On completion of chemotherapy, patients are followed up regularly with HCG estimation. Contraception in the form of oral pills is advised once the HCG levels come to normal. Pregnancy is allowed after one year of completion of chemotherapy. Follow up by annual HCG is life long. Management of resistant and relapsed high risk patients is usually multidisciplinary and includes surgical debulking plus postoperative chemotherapy or salvage chemotherapy alone<sup>11, 12</sup>. Izhar R et al<sup>20</sup> and Rauf B et al<sup>9</sup> from Peshawar reported cure rate of 80%. In our series, 5 patients out of 7 recovered.

Most women with GTD can be successfully managed with preservation of their normal reproductive function<sup>17</sup>. Fertility after chemotherapy is reported to be unaffected. However these patients have significant level of anxiety, fatigue, anger, confusion problem for protracted period of time<sup>21</sup>.

## CONCLUSION

Frequency of GTD was higher in this study compared to world and national literature. Emphasis should be given to diagnose the disease in early stages. Regular follow up and counseling is essential to decrease the mortality and morbidity from this condition.

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