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GESTATIONAL TROPHOBLASTIC NEOPLASIA – AN EXPERIENCE OF A TERTIARY MEDICAL COLLEGE IN EASTERN INDIA

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ABSTRACT Gestational Trophoblastic Neoplasia is a rare gynaecological tumour. Between March 2016 and June 2018, fourteen (14) Gestational Trophoblastic Neoplasia patients, diagnosed either histopathologically or by imaging and raised serum β hCG level were evaluated. After risk categorization according to WHO guideline, nine patients with low risk disease were treated with Inj. Methotrexate. Two of them required Inj. Actinomycin – D due to Methotrexate resistance. Five high risk patients were treated with EMACO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine) regimen. One resistant case was treated with second line EMA/EP regimen (Etoposide, Methotrexate, Actinomycin D, Cisplatin). After treatment patients were followed with serial serum β hCG level for one year. All the patients were asymptomatic with normal β hCG level during the period. Treatment related toxicities were manageable. Gestational Trophoblastic Neoplasia is a highly chemosensitive and curable disease even in high risk patients with acceptable toxicities.

KEYWORDS : 1) Gestational Trophoblastic Neoplasia, 2) β hCG level, 3) Risk Scoring

INTRODUCTION: Gestational Trophoblastic Neoplasia arises from trophoblastic tissue and consists of six distinct clinicopathological entities – a) Complete Hydatidiform Mole, b) Partial Hydatidiform Mole, c) Invasive Mole, d) Choriocarcinoma, e) Placental Site Trophoblastic Tumour, f) Epitheloid Trophoblastic Tumour. Gestational Trophoblastic Neoplasia is a relatively rare gynecological tumour comprising fewer than 1% of all gynecological malignancies. [1] Although Gestational Trophoblastic Neoplasia is most commonly associated with molar pregnancy, it can also occur following normal or ectopic pregnancy and spontaneous or induced abortion. The overall incidence of Gestational Trophoblastic Neoplasia following all types of pregnancies is approximately 1: 40000. [2] Hydatidiform mole may affect women throughout the reproductive age. But it is more common at the extremes of the age range.

Patients with Gestational Trophoblastic Neoplasia commonly presents with 1) Vaginal bleeding during early pregnancy, 2) Passage of grape like structures per vagina in case of molar pregnancy, 3) Persistent vaginal bleeding after term delivery or miscarriage, 4) Features of metastatic disease in lung, brain, liver, vagina etc. and 5) Rarely as hyperemesis and abnormally enlarged uterus. Some patients may be incidentally diagnosed at the time of routine ultrasonography during pregnancy. As Gestational Trophoblastic Neoplasia is a proliferative disorder of trophoblastic tissue, it produces a high level of β hCG. β hCG is thus used for diagnosis, for assessing treatment response and as a part of post – treatment follow up.

Patients with rising β hCG level following non – molar pregnancy are considered to be having Gestational Trophoblastic Neoplasia until proven otherwise. Following molar evacuation the diagnosis of Gestational Trophoblastic Neoplasia is done on the basis of FIGO guidelines. [3]

All patients are subjected to FIGO staging and treated according to WHO scoring system based on Prognostic Factors. [4] Patients with score upto 6 are considered Low Risk and are treated with single agent chemotherapy. Patients with score of 7 or more are considered High Risk and are treated with multi-agent chemotherapy.

MATERIAL AND METHODS: Between March 2016 and June 2018, a total of fourteen (14) patients with diagnosed Gestational Trophoblastic Neoplasia were referred from Gynaecology and Obstetrics department of our institute to our outpatient department. All the fourteen patients were meticulously treated and followed up during this period.

RESULTS: Diagnosis of Gestational Trophoblastic Neoplasia and treatment of each and every case was done by FIGO guidelines and WHO scoring system. Pre-treatment patient profile is given in Table no. 1

Table 1. PRETREATMENT PATIENT PROFILE.

Serial no.	Patient Characteristics		Number
1.	Age	<20	5
		20 - <40	6
		≥40	3
2.	Parity	Nulliparous	8
		Multiparous	6
3.	Thyroid Status	Euthyroid	9
		Hypothyroid	5
		Hyperthyroid	0
4.	Presenting Features	Asymptomatic	4 (Treated after USG finding and persistently raised serum β hCG level)
		Symptomatic	10
5.	Stage of Disease	I	13
		II	1
		III	0
		IV	0
6.	Pretreatment serum β hCG	<1000	2
		1000 - <10000	2
		10000 - <100000	5
		≥100000	5
7.	Pretreatment Liver Function Test	Normal	14
		Abnormal	0

Following suction and evacuation of twelve patients, histopathological examination of the products showed complete hydatidiform mole in seven patients, partial hydatidiform mole in four patients and choriocarcinoma in one patient. In two patients biopsy could not be done due to fear of heavy bleeding as radiological imaging showed a highly vascular intra-uterine mass. In these two patients treatment was started as radiological imaging showed highly vascular intra-uterine mass suggestive of choriocarcinoma along with raised serum β hCG levels. Pathological appearance of hydropic villi of one of the patients is shown in fig. 1.

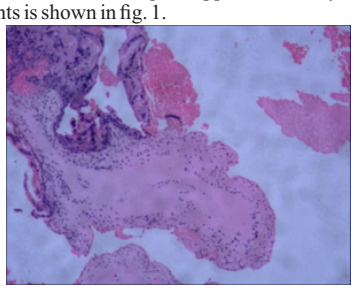

Fig. 1 Extensive Hydropic Change

Apart from the serum β hCG level, 1) Complete Blood Count, 2) Liver Function Test, 3) Kidney Function Test and 4) Thyroid Profile were done in each patient. Each patient was subjected to contrast enhanced Computerized Tomography (CT) Scan of whole abdomen and pelvis along with contrast enhanced CT scan of thorax. None of the patients showed any evidence of distant metastasis. In two patients CT scan suggested a highly vascular intra-uterine mass likely choriocarcinoma. CT scan image of one such patient is given in Fig no. 2. Three patients complained of occasional headache. So Magnetic Resonance Imaging (MRI) of brain was done in those three patients. But there was no evidence of brain metastasis. During treatment serum β hCG level was done weekly.

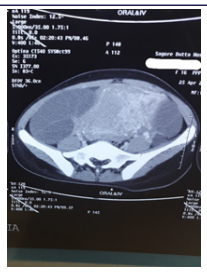

Fig. 2 CT scan suggestive of vascular intra-uterine mass

Risk scoring of patients is given in Table no. 2. Nine patients belonged to the low risk group and five patients belonged to the high risk group.

Table 2 RISK SCORING OF PATIENTS

Patient No.	SCORE FOR								Final Score
	Age in years	Antecedent Pregnancy	Interval (Months)	Pretreatment serum β hCG (mIU/ml)	Largest Tumour including uterine	Site of Metastasis	Number of metastasis	Prior failed chemotherapy	
1	0	0	0	1	1	0	0	0	**2**
2	0	0	0	2	1	0	0	0	**3**
3	0	0	1	1	2	0	0	0	**4**
4	0	0	0	2	2	0	0	0	**4**
5	0	0	1	4	2	0	0	0	**7**
6	0	0	1	4	2	0	0	0	**7**
7	0	0	0	2	1	0	0	0	**3**
8	0	0	0	2	2	0	0	0	**4**
9	1	0	0	4	2	0	0	0	**7**
10	0	0	1	2	2	0	0	0	**5**
11	1	0	1	4	2	0	0	0	**8**
12	0	0	0	0	2	0	0	0	**2**
13	0	0	0	0	2	0	0	0	**2**
14	1	0	0	4	2	0	0	0	**7**

Nine patients with low risk disease were treated with eight days alternating Inj. Methotrexate / Leucovorin regimen. Cycles were repeated at two weeks interval and continued for two more additional cycles after β hCG level became undetectable. All but two patients responded to this treatment. Those two patients who were found to be resistant to Inj. Methotrexate were treated with Inj. Actinomycin D. Both patients responded to Inj. Actinomycin D. Two further cycles of Inj. Actinomycin D were given after β hCG level became undetectable.

Five patients with high risk disease were treated with multi-agent chemotherapy regimen – EMACO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine) with granulocyte colony stimulating factor support. Four patients responded to EMACO regimen and they were given three additional cycles of chemotherapy after β hCG level became undetectable. In one patient even after six cycles of EMACO (after initial response), β hCG level was not undetectable. Hence the patient was shifted to EMA/EP regimen (Etoposide, Methotrexate, Actinomycin D, Cisplatin). β hCG level was undetectable after 2 cycles of EMA/EP. Patient received 3 more cycles of EMA/EP after β hCG level became undetectable.

Four patients in low risk group and three patients in the high risk group developed Grade I oral mucositis and were managed conservatively. Two patients in the low risk group and all the five patients of the high risk group developed anaemia. They were treated with packed red blood cell transfusion. Two patients in high risk group, despite Inj. Filgastrim support developed febrile neutropenia during course of the treatment. They were treated conservatively. Chemotherapy cycles of those two patients were delayed.

Patients were then followed up initially with weekly serum β hCG level for one month and then with monthly till one year. Till date none of the patients showed any sign of recurrence. Normal menstrual cycle returned in all patients after three to four months of completion of chemotherapy.

DISCUSSION: Chemotherapy is highly effective in most patients with Gestational Trophoblastic Neoplasia. Cure rate reaches about 100% in case of low risk disease and about 80 – 90% in high risk disease as reported by a number of centers. [5] Placental Site Trophoblastic Tumour and Epitheloid Trophoblastic Tumour are relatively chemo-resistant and surgery is the initial treatment in these cases. [6]

Meticulous risk scoring is essential for treatment of Gestational Trophoblastic Neoplasia. Low risk disease is treated with single agent chemotherapy. New England Trophoblastic Disease Centre used Inj. Methotrexate and Folinic acid initially for low risk disease because it has least toxicity and a high response rate.[7] Inj. Actinomycin D is used in case of Inj. Methotrexate resistance or in case of deranged Liver Function Test due to Inj. Methotrexate. Patient resistant to both Inj. Methotrexate and Inj. Actinomycin D respond ultimately to multi-agent chemotherapy. [8] High risk diseases are treated with multi-agent chemotherapy. [9] Most common regimens are EMACO and EMA/EP. Patients treated with these regimens have high remission rate as well as high overall survival rate.

Surgery plays an important role in the management of certain cases of high risk disease. [10] Hysterectomy is done in cases of heavy bleeding, large intrauterine disease or presence of significant pelvic sepsis. Surgery of unresponsive metastatic disease in liver, kidney, spleen etc. may be considered. For brain metastasis radiotherapy is to be given.

This study focuses on patient profile, clinical presentation, management, treatment related toxicities and outcome of Gestational Trophoblastic Neoplasia patients in our hospital. 9/14 (64.3%) patients belonged to the low risk group and remaining 5/14 (35.7%) patients belonged to the high risk group. Low risk group patients responded well to Inj. Methotrexate. 2/9(22.2%) patients who did not respond to Inj. Methotrexate responded to Inj. Actinomycin D. High risk group patients responded well to EMACO. 1/5(20.0%) patient who did not respond to EMACO responded to EMA/EP. Most significant treatment related toxicities were 2/14(14.3%) cases of febrile neutropenia that occurred in high risk group. All the treatment related toxicities were managed conservatively. But patients developing febrile neutropenia had treatment breaks.

Most important pitfall of this study is that the follow up period is relatively short. So it is improper for us to comment on the long term treatment related toxicities of our study population. Also as the follow up period is short further pregnancy, that is patients' reproductive capacity after treatment are not shown in this study.

CONCLUSION: Gestational Trophoblastic Neoplasia is a life threatening condition. But early treatment produces very high cure rate. So its early diagnosis and management according to well established guidelines are of utmost importance.

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