

# GESTATIONAL TROPHOBLAST NEOPLASIA AND MORTALITY RISK FACTORS

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## ABSTRACT

**Objective:** To analyze the risk factors associated with mortality in patients receiving treatment for Gestational Trophoblast Neoplasia (GTN).

**Material and Methods:** Retrospective, cross-sectional study done at Department of Obstetrics and Gynaecology, Hayatabad Medical Complex, Peshawar, Pakistan, from June 2005 to June 2014. Ninety women with the diagnosis of GTN were hospitalized and treated according to standard chemotherapeutic regimens. Hospital records of patients demographic profile, age, parity, antecedent pregnancy, serum  $\beta$ -hCG levels, site of metastasis, FIGO score, type of chemotherapy, and treatment outcomes including mortality were studied. Data analysis done through SPSS 16.

**Results:** In 90 patients diagnosed with GTN, 59(65.6%) patients were low risk and 31(34.4 %) were in high risk category. Nine out of 90 patients diagnosed with GTN died during initial treatment giving overall mortality of 10%. All patients who died were in high risk category with stage IV GTN. Six out of nine patients had term pregnancy as antecedent pregnancy. Five out of 9 patients that died had serum  $\beta$ -hCG levels of  $>100000$  IU/ml. Eight out of 9 patients had FIGO scored between 9-12. Metastasis was present in all the patients that died. Three patients had metastasis present both in Brain and Liver and two had metastasis only in liver, while other two had lung metastasis.

**Conclusions:** High FIGO score, high pretreatment serum  $\beta$ -hCG levels, previous term pregnancy, liver and brain metastasis have been associated with adverse outcome like mortality in patients with gestational trophoblast neoplasia: a rare but highly curable malignancy.

**Key Words:** Gestational, Trophoblast Neoplasia, FIGO Prognostic score (International federation of Gynaecologist and Obstetrician), Mortality, Chemotherapy.

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## INTRODUCTION

Gestational trophoblastic disease (GTD) consists of a range of pregnancy related disorders, that includes premalignant disorders of complete and partial hydatidiform mole, and malignant disorders of invasive mole, choriocarcinoma, placental site trophoblastic tumors, and epithelioid trophoblastic tumor. These malignant forms are termed gestational trophoblastic tumours or neoplasia (GTN), with typically low incidence and high cure rates.<sup>1</sup> Gestational trophoblastic disease (GTD)

arises more frequently in Asia than in North America or Europe. The incidence of GTD reported in Pakistani literature varies from 28-45 per 1000 livebirths<sup>2,3</sup>. Choriocarcinoma is a rare diagnosis with an incidence of 1 per 50,000-100,000 conceptions and PSST accounts for 0.2% of GTN in UK.<sup>1</sup>

GTN treatment has success rates exceeding 90% with preservation of fertility as it is highly sensitive to chemotherapy and one of most curable cancer.<sup>4</sup> An estimate of risk category can be obtained and patients offered initial treatment based on the International Federation of Gynecology and Obstetrics (FIGO) anatomic staging and prognostic scoring index.<sup>6</sup> The low risk group (prognostic score  $\leq 6$ ) can be treated with single-agent chemotherapy with survival rate approaching 100%. The high-risk group (prognostic score  $\geq 7$ ) requires initial multi agent combination chemotherapy to achieve a survival rate of 80-90%.<sup>5,6</sup> Any type of GTN can metastasize to elsewhere in the body but the most

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common metastatic site is lung (80%) followed by vagina (30%), brain and liver (10%).<sup>1</sup>

Most commonly, GTN is diagnosed following molar pregnancy with rising ( $\beta$ -hCG), but it can also occur after miscarriage or term pregnancies. Patients with molar pregnancies make up the large majority of the cases of GTN and approximately 10% of them will require additional therapy following uterine evacuation.<sup>7</sup> The patients who develop malignancy after a molar pregnancy should rarely prove difficult to treat and in areas with well organized and centralized care overall cure rates approaching 100% are reported.<sup>8,9</sup> Unfortunately an approach of 'no structured follow up' is still the case in many areas of the world including Pakistan where patients present with more advanced GTN and unfavorable outcomes.

Department of obstetrics and gynaecology has been a referral center and many patients were directed to our unit from all around the KPK and neighboring Afghanistan. The purpose of this study was to analyze the risk factors associated with adverse treatment outcomes like mortality in gestational trophoblast neoplasia patients.

### MATERIAL AND METHODS

It is a retrospective cross sectional study. Hospital records of 90 patients with diagnosis of GTN from June 2005 to June 2014, treated at Department of Obstetrics and Gynaecology, Hayatabad Medical Complex, were studied. After the staging work-up, patients with GTN were categorized according to the World Health Organization (WHO) scoring system called the prognostic scoring index. The WHO/FIGO risk factor scoring system was determined by age, antecedent pregnancy, interval from antecedent pregnancy, pre-treatment hCG level, largest tumor size, site of metastasis, number of metastasis, and previous failed chemotherapy. Patients with score  $\leq 6$  were considered low-risk, whereas patients with score  $\geq 7$  or more were considered high-risk group.

At our institution, the first-line chemotherapy for patients with low-risk GTN, was usually started with single-agent chemotherapy consisting of methotrexate 1 mg/kg intramuscular (IM) injection repeated every 48 hours for four doses along with 15 mg calcium folinate orally 30 hours after each injection of methotrexate. Patients with high-risk GTN were treated with multiple agent combination chemotherapy, EMA-CO which is eight day regimen as per internationally tested and recommended regimens.<sup>9</sup>

Response to treatment/chemotherapy was evident by the decrease in hCG levels. When three consecutive weekly hCG levels were within the normal range ( $< 5$  IU/ml) patients were defined to have achieved complete remission. The clinical data about the patient disease characteristics, including age, antecedent pregnancy, interval from antecedent pregnancy, clinico-pathologic diagnosis, pre-treatment hCG, extent of tumor and treatment outcomes including mortality were retrieved from hospital records. Data was analyzed by statistical package for social sciences (SPSS) version 16.0. Mean and standard deviation were calculated for numerical data and percentages, frequencies for categorical variables. We retrospectively analyzed the clinical data of all the patient that died during the course of treatment.

### RESULTS

A total of 90 women were diagnosed with GTN. According to FIGO prognostic scoring index, 59(65.6%) patients were low risk and 31(34.4%) were in high risk category. Overall cure rates of 86.7% were observed when treatment outcomes were adjusted after successful second line management of resistant, and relapsed cases. Fourteen out of 59 patients in low risk category developed resistance to initial chemotherapy which were subsequently treated. Ten out fourteen patients that developed resistance had molar pregnancy as prior gestational even. Both category had one relapse each which were treated successfully. Nine out of 90 patients

**Table1: Antecedent Pregnancy (AP) \* Treatment outcome \* Diagnosis Cross tabulation count**

Dx		Treatment outcomes					Total
		"Clinical & biochemical remission"	"Resistance"	Relapse	Left Treatment	Mortality during Chemotherapy	
Low Risk GTN	Mole	32	10	1	1		44
	Miscarriage	8	2	0	1		11
	Term	2	2	0	0		4
	Pregnancy	42	14	1	2		59
High Risk GTN	Mole	5	0	0	0	1	6
	Miscarriage	6	0	0	1	2	9
	Term	8	1	1	0	6	16
	Pregnancy	19	1	1	1	9	31

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**Table 2: Age \* Treatment outcome \* Dx Crosstabulation**

Dx		Treatment outcomes					Total
		"Clinical & biochemical remission"	"Resistance"	Relapse	Left Treatment	Mortality during Chemotherapy	
Low Risk GTN	Age <40	34	12	1	2		49
	>40	8	2	0	0		10
	Total	42	14	1	2		59
High Risk GTN	Age <40	18	0	0	1	5	24
	>40	1	1	1	0	4	7
	Total	19	1	1	1	9	31

diagnosed with GTN died during initial treatment giving overall mortality of 10% in our case series. All patients who died were in high risk category. The diagnosis of disease and its outcome is shown in Table 1.

Five out of 9 patients were aged less than 40 years and four were more than 40 years of age. Six out of nine patients had term pregnancy as antecedent pregnancy while two patients had miscarriage and one patient had molar pregnancy as a prior gestational event. Interval from antecedent pregnancy was >13 months in three patients and between 7-12 months in other two patients that died. Five out of 9 patients that died had serum  $\beta$ -hCG levels of >100000IU/ml. Eight out of 9 patients had FIGO score between 9-12. Treatment outcome in relation to the age of the patients is shown in Table 2. Metastasis were present in all the patients that died. Three patients had metastatic deposits present both in Brain and Liver, Two had metastasis only in liver, other two had lung metastasis and one patient had metastasis in GIT.

### DISCUSSION

Relative rarity, unique biology and extremely effective therapies for gestational trophoblastic neoplasia (GTN) have made these tumours an interesting and important area of gynecological and oncological care<sup>1,9</sup> however, patients with metastatic disease still die more so in developing countries which lack centralized care for GTD often leading to late presentation and delayed diagnosis.<sup>10</sup>

In our study 90 women with the diagnosis of GTN were treated. Over all cure rates of 86.7% were observed, which is at par with local and international studies.<sup>3,5</sup> Nine out of 90 patients died during initial treatment. Mortality rate of 10% in our study is more than the reported figures of 1% and 4% from cancer centres of Sheffield, Charing cross respectively in UK<sup>11</sup>, and 3% in Swedish case series<sup>12</sup>. Lack of access to health care, poor budgetary allocation for health, lack of specialized

cancer care centers, lack of awareness in primary care physician about signs and symptoms of GTN, advanced stage at presentation are presumably the reasons behind GTN patients still dying in our set up.

Indian and South African case series had reported mortality rates of 9% and 10%, similar results in somewhat identical set ups.<sup>13,14</sup> However there is improvement from previously reported mortality figures in the study conducted at our institution from 20% to 10% due to improvement in medical care, social, economic and education changes<sup>15</sup>. Korean study showed improved outcomes in GTN in 30 years and mortality rates decreased significantly from 32.6% to 2.6%.<sup>16</sup> While Chinese 20 years case series of outcomes of GTN patients showed mortality rates of 28.6% because of larger sample size and increased prevalence of GTD in the country<sup>17</sup>.

Advanced maternal age has been implicated as an adverse prognostic factor in GTN patients. But in our study both age groups i.e less than or more than 40 years died from advanced disease. Five out of 9 patients were aged less than 40 years and 4 were more than 40 years of age.<sup>1,4,23</sup> Antecedent pregnancy as term pregnancy has been given highest risk score in FIGO prognostic scoring index, a fact that has been replicated in our study by showing that six out of nine patients died had term pregnancy as a gestational event prior to starting treatment.<sup>6</sup>

Serum  $\beta$ -hCG has been excellent tumor marker and has a pivotal role both in diagnosis and in monitoring response to treatment in GTN. High values indicated tumour burden and is adverse prognostic factor. Our study showed that five out of 9 patients that died had serum  $\beta$ -hCG levels of >100000IU/ml while other three had levels between 10,000-100,000IU/ml.<sup>18</sup> Increasing interval between antecedent pregnancy and starting chemotherapy in GTN patients has been associated

with higher risk of adverse prognosis. However in our study GTN patients had succumbed to death in all time interval ranges contrary to international literature.<sup>19,23</sup>

All of GTN patients that died in our study were high risk category and in stage IV, having FIGO score ranging from 9-12. All the patients had multiorgan metastasis associated with adverse prognosis. Liver and brain metastasis were associated with deaths in six out of nine patients. A study by Barber EL showed that survival was significantly decreased for patients with both intra abdominal and brain metastases.<sup>20</sup>

A study by Kingdon SJ et al also showed majority of deaths in GTN are due to non pulmonary metastasis. While pulmonary metastasis with respiratory failure resulted in death in two of our patients even before starting chemotherapy.<sup>21</sup> Dutch study showed that lung metastases increase the risk for recurrence and death from disease in GTN patients.<sup>22</sup>

### CONCLUSION

Advanced metastatic disease, high FIGO score, high pretreatment serum  $\beta$ -hCG levels, previous term pregnancy, liver and brain metastasis have been associated with adverse outcomes in patients with gestational trophoblast neoplasia: a rare but highly curable malignancy.

### RECOMMENDATIONS

Treatment at a specialized cancer centre in every province is the need of the hour.

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### **AUTHOR'S CONTRIBUTION**

Following authors have made substantial contributions to the manuscript as under:

**Arzoo Gul Bangash:** Conception of idea of study formulating objectives Performa, literature review of the topic ,Statistical analysis and methodology, Writing conclusion and recommendation at the end of Study.

**Rabeea Sadaf:** Involved in data collection,search of hospital records.

**Mehr-un-Nisa:** Involved in writing discussion, interpreting results.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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