Analysis of 58 Cases of GTT from 2000-2013 at A Tertiary Cancer Center in India

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Synopsis
Fifty eight cases of Gestational Trophoblastic Tumor were studied regarding their epidemiological background and necessary investigations were carried out. Appropriate management was instituted with close follow up.

Abstract
Gestational Trophoblastic tumor is a rare condition mainly among females in the reproductive age group which was almost fatal before the advent of chemotherapy but now has a better outlook. This retrospective study analyses a group of patients with gestational trophoblastic tumor in a tertiary care unit.

Data Source
Fifty eight cases were collected from the statistical department of Saroj Gupta Cancer Center and Research Institute, Kolkata, India from all cases registered at the gynae-oncology clinic between 01.01.2000 and 31.12.2013.

Method of study
Epidemiological factors were studied in detail. After relevant investigations and assessing the score, appropriate therapy was instituted, mainly with chemotherapeutic agents. Response to treatment was assessed.

Results
All cases were diagnosed and treated- partly or incompletely – prior to registration. All patients received methotrexate initially. Multi-drug therapy was given to patients with high scores not responding to methotrexate. There were two deaths before any therapy could be initiated. Response to chemotherapy did not always coincide with risk score. Seventeen patients underwent surgical procedures other than dilatation and evacuation. There were five deaths in the series, mostly from brain metastasis.

Conclusion
Mainstay of salvaging a patient with Gestational trophoblastic tumor is suspicion, early diagnosis and referral. All patients with recurrence/persistent vaginal bleeding following spontaneous or induced abortion should be referred to secondary or tertiary healthcare centre to exclude GTT. All tubal pregnancies should have histology to exclude molar pregnancy.

Materials and Methods
The study, a retrospective one, was undertaken at Saroj Gupta Cancer Center and Research Institute, a tertiary care cancer center in Kolkata, serving humanity since its inception in 1973. Apart from the city of Kolkata, the institute is the drainage point of cancer patients from the adjoining districts and neighboring states of eastern India. Many patients from adjacent countries of Bhutan, Nepal and Bangladesh also avail the facilities of the institute. Fifty eight cases of Gestational Trophoblastic Tumor were collected from hospital registry at Saroj Gupta Cancer Center and Research Institute, Thakurpukur, Kolkata during the period 2000-2013.

Epidemiological factors like age, residence, religion, socio-economic strata, marital status, and educational qualifications were assessed. A detailed history of the presenting complaints including the time of onset, preceding pregnancy event, any treatment, chemotherapy or operation, related to the disease was taken. Any report of blood test or radiological investigation was taken into account. A detailed clinical examination was followed with routine blood haematocrit and biochemistry, including beta-Human Chorionic Gonadotropin (beta HCG) and thyroid function tests. A chest x-ray and ultrasound study of the abdomen was routinely done to assess the baseline values at registration. Detailed investigations like ophthalmoscopy, lumbar puncture, computerized tomography and magnetic resonance imaging studies were done in selected cases.

Patients were stratified into high risk and low risk groups according to points as described in the latest FIGO Scoring System. Primary therapy with Methotrexate in the dose of 0.4mg/kg body weight was started with appropriate rescue factors. High risk patients not responding to methotrexate was put on EMA-CO regime. A few cases were put on MAC and other approved protocols. Intensive clinical and laboratory monitoring was undertaken during the course of treatment and follow-up. The services of a psychologist were credited.

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were utilized routinely.

**Results**

Data of the study was accrued on a data sheet. The disease had prevalence across all socio-economic groups. Forty three percent (43%) cases presented from the high income group, 28% from the middle income group while the rest 29% came from a low socio-economic background. Figure I

![Figure I: Categorization of patients according to socio-economic status](image)

It is to be mentioned that all patients were housewives and had no clinical evidence of vitamin A deficiency.

It was found that 52% cases came from Kolkata and the neighboring districts, 10% came from neighboring states while the rest 38% were international patients mainly from Bangladesh. Figure II

![Figure II: Drainage of cases on basis of domicile](image)

Sixteen percent (16%) patients were illiterate, 53% had been to school and 31% were graduates and post-graduates. The mean age of patients at presentation was 27.8 years; the range from 18 years to 48 years. Eight patients were married in the age group 10-14 years, 27 patients were married in the age group 15-19 years, and 18 patients were married in the age group 20-24 years while 5 cases were married in the age group 25-29 years. Thirteen patients (22.41%) were nulliparous, 32 (55.17%) had one to three children, 4 (6.9%) patients had six or more children while 9 (15.52%) patients had history of one or more miscarriages without any living issue. Fifty eight percentage patients had one or more abortions.

Regarding age at first conception, it was found that 28 (48.3%) patients conceived in the age group 15-19 years, 25 (43.1%) patients conceived in the age group 20-24 years, 4 (6.9%) in the group 25-29 years and one between 30-34 years. Ten patients conceived within one year following marriage, 24 patients conceived within 2 years, 14 patients within 3 years and the rest beyond 3 years, implying that 83% patients conceived within 3 years of marriage. Forty three patients (74.1%) presented with molar pregnancy, two cases of ruptured tubal ectopic pregnancy, both on the right side, and one case of normal delivery as the antecedent pregnancy event. One patient had recurrent hydatidiform mole.

Vaginal bleedings was the commonest symptom found in 51 (87.93 %) cases. Haemoptysis was complained by 4 patients, haematuria by 1 patient while 1 patient presented with complaints of weakness of the limbs. Pallor with a bulky uterus was the commonest clinical finding.

Patients were often referred to this tertiary care institute with a provisional or final diagnosis of gestational trophoblastic tumor. Fifteen cases had a diagnosis of hydatidiform mole, 15 had choriocarcinoma, 2 had choriocarcinoma of the fallopian tube, 1 with placental site trophoblastic tumor, 15 had gestational trophoblastic neoplasia and 5 had gestational trophoblastic disease. One patient had concomitant cancer of the uterine cervix. Histopathological slides were reviewed where available. In 7 cases choriocarcinoma was confirmed of which in 2 cases, there was involvement of cervix. 1 case had associated cancer of the cervix while 1 case had confirmed choriocarcinoma with a ruptured uterus. Imaging revealed metastasis to the lungs in 6 cases, to the liver in 3 cases, to the pelvis in 3 cases, to the kidney in 1 case and one case had metastasis to the brain. Among the three cases with spread to the pelvis, one had disease in the rectum.

Eighteen patients underwent major surgery prior to referral to this institute. Twelve cases had total abdominal hysterectomy with bilateral salpingo-oophorectomy, 2 had total hysterectomy, 2 had subtotal hysterectomy and 2 had salpingo-oophorectomy for tubal ectopic pregnancy.

Fourteen patients were placed in the high risk group with a score above7, while there were 5 patients who scored above 12. All patients had methotrexate at the outset. Eleven patients with high risk scores were given EMA-CO, 3 patients received methotrexate and actinomycin D with chlorambucil, 1 case received etoposide with cisplatin, 1 received methotrexate with etoposide while 1 received paclitaxel with carboplatin. Intrathecal methotrexate was given in 1 case. At this institute, one patient underwent extra peritoneal internal artery ligation. The patient having concomitant cancer of the uterine cervix had appropriate radiotherapy. Cranial radiotherapy was administered in one case with cranial metastasis. There were 5 deaths (8.62 %) in the series. All the deaths occurred in patients with brain metastasis along with spread to liver, lungs and rectum. There was massive haemorrhage in one case. Another case died of severe neutropenia following chemotherapy. Both these cases of gestational trophoblastic tumour died following
gestational trophoblastic tumour in the tube and died before any definitive treatment could be initiated. Follow-up was very poor. Eight patients were free of disease till the completion of the second year after therapy, while there were 6 patients who were well after 3 years and beyond. There were two cases who conceived after treatment, one after 2 years and the other 5 years after therapy. No congenital anomaly was reported in the children of those who conceived.

**Discussion**

Gestational Trophoblastic tumor is a relatively new term. Trophoblastic tumor in the female has largely been seen to occur in germ cell ovarian tumor and is etiologically different from its gestational counterpart by the absence of any contribution from the spouse. In contrast, Gestational trophoblastic tumours have a typical chromosomal patterns derived from the paternal half. Various nomenclatures like hydatidiform mole, choriocarcinoma, chorioadenomadoestruens, and invasive mole are confusing. They are distinct histological entities. Since the diagnosis of gestational trophoblastic tumour is not totally histology based, such nomenclature is now becoming obsolete. Hydatidiform mole is now termed as gestational trophoblastic disease; the rest is gestational trophoblastic tumour. Placental site trophoblastic tumor is still regarded as a separate entity as it has unique features of its own.

Hydatidiform mole is rare in the western world; the incidence is about 1:1000 pregnancies while that of choriocarcinoma is 1:20,000 pregnancies in the United States. It is common in the Far East, the incidence being 9.9:1000 deliveries in Indonesia and 8.3:1000 deliveries in Taiwan [1, 2]. In terms of pregnancies as the denominator, the incidence varies from a low of 23 per 100,000 pregnancies in Paraguay to as high as 1,299 per 100,000 pregnancies in Indonesia [3]. Incidence of gestational trophoblastic tumor in South East Asia including India is low, but there is no official nationwide data available mainly due to absence of proper registries. There were 58 cases of gestational trophoblastic tumor registered at Saroj Gupta Cancer Center and Research Institute during the period 2000-2013. The total number of cases registered in the gyna-oncology department during this period was 10,379. The incidence of gestational trophoblastic tumour in this institute is about 1:200 gynecological registrations at the tertiary cancer care center.

The etiology of gestational trophoblastic tumour remains unknown. It is postulated that it is common in the low socio economic group (2), possibly due to a deficiency in carotene but this study could find no such validity. No clinical evidence of deficiency of vitamin A was found in the patients of this study. It is said that the disease affects patients at the extremes of age (2) and 21 patients (36%) in this study were teenagers. The antecedent pregnancy event was molar pregnancy in 74.1% of cases with one case of recurrent molar pregnancy. A case report with seven consecutive molar pregnancies has been published [4]. Vaginal bleeding with a history of amenorrhea was the commonest symptom at presentation, occurring in 51 cases (87.93%). This is at par with statistics presented by Soto Wright V. et al [5]. Pallor with a bulky uterus was the commonest sign at presentation. Among the radiological investigative modalities, ultrasonography was commonly used to detect molar tissue in the uterus. Typically it yields a snow storm appearance. Ski gram of the chest for presence of cannon-ball lesions was also done, though their presence did not alter risk assessment. Magnetic resonance imaging was done in isolated cases specially to rule out placental site trophoblastic tumor, while computerized tomography was done to detect brain metastasis. Magnetic Resonance Imaging and Computerized Tomograms facilities were not available in this institute during the early period of the study. Moreover, these are expensive modalities and may be out of reach of the poor patients.

Serum beta-human chorionic gonadotropin is a very valuable marker for diagnosis and prognosis of gestational trophoblastic tumour with almost 100% sensitivity and specificity. Often, therapy is commenced on finding a high level of the hormone even in the absence of any histology evidence. Persistently high serum beta-human chorionic gonadotropin after 3-6 weeks of termination of pregnancy is pathognomonic. A number of tests of human chorionic gonadotropin (hCG) have come up including intact hCG, free alpha hcg, free beta hCG, nicked hCG, nicked free beta hCG, beta core fragment of hCG and hyperglycosylatedhCG. HyperglycosylatedhCG is a marker for destructive cytotrophoblast cells in gestational trophoblastic tumour [6]. The beta hCG is a marker of syncytiotrophoblast activity. The measurement of apparent but spurious hCG has come up in the literature and has been referred to as phantom hCG. Typically, such false positive results show low levels of hCG (generally, <1,000miu/ml and usually <150 miu/ml and a negative urinary test for pregnancy [7]. Under such circumstances, no treatment is necessary.

The response to chemotherapy did not coincide with FIGO risk scoring. Some high risk patients responded to single drug treatment with methotrexate while some low scoring patients did not respond to single agent chemotherapy and needed multidrug treatment. Of the five deaths in this series, one had a FIGO risk score of 5. The first of the two patients with tubal ectopic choriocarcinoma died of brain metastasis while the other died of severe neutropenia and massive gastro-intestinal bleeding, though literature points at good outcome for these patients [8]. Uterine artery embolization for the control of haemorrhage from gestational trophoblastic tumour is an alternative to major surgical procedures like hysterectomy [9]. Hysterectomy is equivalent to metastatectomy and chemotherapy is the preferred choice especially in young patients desirous of future child-bearing.

Gestational trophoblastic tumour is a rare condition with 58 patients in 14 years. The two deaths of gestational trophoblastic tumour, arising from tubal ectopic gestation, occurring before any definitive treatment could be initiated prove that early referral to tertiary care centers may bring down the mortality. Molar pregnancy arises from fertilization of a nuclear oocyte which is often seen at the extremes of age. Prevention of teenage pregnancy
and pregnancy after 35 years of age may bring down the incidence of the disease. In this study, there was no impact of socio-economic status and education. Recurrent molar pregnancy may indicate a genetic cause [10]. and artificial reproductive techniques with donor oocyte may be the treatment of choice.

As metastasis may occur years after conception, serum ßhCG need to be assessed in case of convulsion or hemoptysis in women along with imaging for correct diagnosis. In young patients, aim should be fertility preserving surgery as in many cases, chemotherapy works wonders. Surgery becomes mandatory to control haemorrhage. Chemotherapy has its own hazards and should be undertaken in a tertiary center only.

Reference