GESTATIONAL TROPHOBLASTIC NEOPLASIA: A CLINICO-EPIDEMIOLOGICAL PROFILE IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction

Gestational trophoblastic neoplasia (GTN) is a group of interrelated lesions that results from abnormal proliferation of placental trophoblastic cells. Early diagnosis and treatment of GTN results in successful outcomes with fertility preservation. This study was intended to stratify GTN cases using WHO scoring system, to diagnose and manage cases as per protocol and to identify complications of treatment of GTN.

Methodology

This was a single center prospective observational study conducted at Medical college Kolkata from June 2017 to December 2018. All the diagnosed cases of GTN fulfilling the inclusion criteria were incorporated in the study, data were collected from history, clinical examination and investigations. All the data were tabulated and analyzed by standard statistical methods

Result

In this study, primiparous were more prone to have GTN and molar pregnancy was the commonest antecedent event (71.4% of cases). 74.3% (26 out of 35) patients developed disease within four months of previous pregnancy. Anemia and vaginal bleeding were the presenting symptoms in >48.0% cases whereas hemoperitoneum, seizure, hemoptysis and respiratory distress were the rare presenting symptoms. In this study, the cases were diagnosed by histopathology or serial estimation of serum β-hcg. In our study, 91.4% patients were successfully treated with methotrexate and only three cases received EMACO.

Conclusion

To conclude this study established that cases of GTN can be successfully treated by early diagnosis and timely management.

KEYWORDS

Human chorionic Gonadotropin, treatment, clinical presentation, Gestational Trophoblastic Neoplasia.

INTRODUCTION

Gestational trophoblastic disease(GTD) is a heterogenous group of interrelated lesions arising out of abnormal proliferation of placental trophoblasts.[1] GTD is histologically divided into complete and partial moles and the aggressive subset collectively called GTN. Invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor are the different types of GTN.[2] Each of these types are histologically distinct and vary in its propensity to invade and metastasize. GTN most commonly arise following evacuation of a molar pregnancy (50.0%), but it may develop after any non-molar pregnancy (50.0%), including abortion or ectopic gestation (25.0%) and term or preterm pregnancies (25.0%).[3] GTN mostly present with persistent irregular bleeding following evacuation of molar pregnancy and there may be subinvolution of the uterus particularly if it occurs after term or preterm pregnancy. Diagnosis, treatment monitoring, early detection of relapse and remission of disease can be assessed primarily by serial estimation of serum β hcgalong with clinical findings.[4] GTN mostly affects women at extreme ages (teenage and advanced maternal age). After evacuation about 15.0% of complete moles turn into locally invasive GTN and four percent become metastatic disease, but metastatic GTN is more common after non-molar pregnancy.[5] Locally invasive GTN cases present with the features of irregular bleeding, theca lutein cyst, uterinesubinvolution or asymmetric enlargement, trophoblastic tissue may perforate the myometrium and serosa to cause intraperitoneal bleeding or it may erode into uterine vessels leading to excessive vaginal bleeding. Metastatic GTN has a tendency for early vascular invasion leading to widespread dissemination and symptoms result from spontaneous bleeding at metastatic foci, commonest sites of metastasis are lungs, vagina, pelvis, liver and brain in descending order of frequency. These neoplastic diseases are highly sensitive to chemotherapy with a cure rate of 100% in low risk cases and 80-90% in high risk cases.[6] Serum β hcg is used as a marker of treatment response as well as for follow up. In our study, clinical presentation, diagnosis, treatment modalities and complications arising from GTN and its management were thoroughly evaluated.

METHODOLOGY

The study was a single center prospective observational study conducted at a tertiary care hospital at Eastern India. 35 diagnosed cases of GTN attending the Department of Obstetrics and Gynecology (both indoor and outdoor) of our Hospital who fulfilled the inclusion criteria were observed in the study. Patients with comorbidities like pre-existing lung or liver diseases, anemia or other malignancies were excluded from the study.

Study was conducted at the department of Obstetrics and Gynecology, Medical College, Kolkata, a tertiary care hospital of Eastern India Study period was from June 2017 to Dec. 2018. Following criteria were used for diagnosis of GTN:

1. Less than 10% changes in β-hcg value for four measurements over a period of three weeks i.e day 1, 7, 14 & 21
2. More than 10% rise in β-hcg for three measurements over a period of two weeks day 1, 7 and 14
3. β-hcg remains detectable in serum even after six month.
4. Histological features of choriocarcinoma.

After recruiting in the study detailed history of each patient including their age, obstetrics history, medical history, family history and other relevant history were taken. Detailed clinical examination was carried out along with investigations like complete hemogram, pre-treatment β-hcg, liver function test(LFT), renal function test (RFT), serum Thyroid Stimulating Hormone (TSH), Ultrasonography (USG) whole abdomen, X-ray chest, Computed Tomography (CT) scan whole abdomen and brain(if required). All 35 patients were stratified into high and low risk according to the World Health Organization (WHO) prognostic scoring system. A score of 0 - 6 was considered low risk and those with score ≥ 7 were considered high risk cases. Objectives of our study was to find out the pattern of clinical presentation of cases of GTN, stratification of cases into low risk and high risk according to the WHO prognostic scoring system, diagnose and manage cases of GTN as per protocol as well as to identify the complications arising out of its management.

Low risk cases were treated with methotrexate and folinic acid high risk cases were given EMA-CO(Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide and Vincristine) or EMA-EP(Etoposide, Methotrexate, Actinomycin-D plus Etoposide and Cisplatin) according to the merit of the case. β-hcg reports was done at two weekly intervals during chemotherapy and continued till two consecutive reports become negative. There after monthly serum β-hcg were measured for six months. Considering the short duration of the study (one and half years) follow up for the study purpose was done for six months though all patients were followed up in our Oncology Outpatients department as per protocol (one year for low risk and 2 years for high risk GTN cases).[9]

RESULTS

Table 1: Demographic Distribution of cases of GTN

Age in Years	Frequency	Percent
≤ 20 Year	12	34.3%
21-30 Year	13	37.1%
31-40 Year	7	20.0%
>40 Year	3	8.6%
Parity		
0	10	28.6%
1	11	31.4%
2 or more	14	40%
Antecedent Pregnancy		
Abortion	10	28.6%
Molar Pregnancy	2571.4%	
Interval from Antecedent Pregnancy (months)		
<4	26	74.3%
4-6	5	14.3%
7-12	4	11.4%

Most of the patients were in the age group of 21 to 30 years (37.1%), 12 out of 35 patients (34.3%) were less than 20 years of age and only three patients were more than 40 years (8.6%). 40% of patients in our study were having two or more children and 28.6% i.e 10 out of 35 patients were nullipara. Molar pregnancy was the commonest antecedent event occuring in 25 patients (71.4%). Our study showed that 26 out of 35 patients(74.3%) had less than four months gap from previous pregnancy and only four patients develop GTN after an interval of 7-12 months from antecedent pregnancy.

Table 2: Case distribution according to clinical presentation

Mode of Presentation	Frequency	Percentage
Anemia, vaginal bleeding	17	48.6%
Respiratory distress	1	2.9%
Hemoptysis	1	2.9%
Hemoperitoneum	1	2.9%
Seizure	1	2.9%
Subinvolution	6	17.0%
Theca lutein cyst	8	22.8%
Total	**35**	**100%**

Almost half of the patients presented with anemia or vaginal bleeding (17 of the 35 patients). Six patients presented with complaints of uterine subinvolution(17.0%) and USG of eight patients revealed theca lutein cyst (22.8%). Hemoperitoneum, seizure, hemoptysis and respiratory distress were uncommon presentation found only in2.9% of patient each.

Table 3: Mode of Diagnosis of Cases

Mode	Frequency	Percent
HPE	3	8.5%
Increased β-hcg	15	42.9%
Persistent↑β-hcg> 6 m	5	14.3%
B-hcg Plateau	12	34.3%
Total	35	100%

GTN was diagnosed by HPE in three patients(8.5% of total cases) of which two were Choriocarcinoma and only one patient had an invasive mole. Apart from histopathology, cases of GTN were diagnosed by serial β-hcg i.e.>10% rise in three consecutive values over a period of two weeks on day 1,7 and 14; which was present in15 patients (42.9%).Plateau of β-hcg value (no or <10% decrease in four values over three weeks) was observed in 12 patients (34.3%).

Table 4: Risk Stratification of cases

WHO Prognostic Scoring	Frequency	Percent
High risk	3	8.6
Low risk	32	91.4
Total	**35**	**100**

All the cases were stratified according to the WHO scoring system. 91.4% of the patients (32 out of 35) were scored 0-6 and categorized as low risk. Three patients (8.6%) had a score ≥ 7.

Table 5: Complications of GTN management

Complications of Treatment	Frequency	Percent
Abdominal pain	1	2.9
Leukopenia	1	2.9
Pancytopenia	1	2.9
Conjunctivitis	3	8.6
Alopecia	1	2.9
Stomatitis	4	11.4
Nil	24	68.4
Total	**35**	**100**

In our study, 32 low risk GTN cases were treated successfully with Methotrexate (MTX) along with folinic acid and three high risk patients received EMACO. Most of the patients tolerated chemotherapy without any adverse effect;23 out of 35 patients had no complications (65.7%), four patients (11.4%) had stomatitis; alopecia, pancytopenia, leukopenia, abdominal pain developed in a small number of patients (2.9%) but three (8.6%) of our patients suffered from conjunctivitis during treatment.

DISCUSSION

This study was intended to follow the course of Gestational Trophoblastic Neoplasia(GTN), in the context of a developing country like ours. In this study the mean age of patients was 26.4 with the most frequent age group being 21-30 years. Patients of this age group were younger in comparison to other studies like the study done by Gulia et al.[7] Segal et al.[8] The reason may be that most of the patients who attend our hospital have an early marriage as well as pregnancy at an early age. We mostly found GTN patients among primiparous (31.4%) and this finding was different from the findings observed by Rangwala et al.[19] Molar pregnancy was the antecedent event in the majority of cases observed in present study. Study by May et al.[9] Suprasert et al.[10] Ngan et al.[11] also showed similar finding. The median interval between development of GTN and antecedent pregnancy was four months in majority of cases of our study (74.3%) and it is very close to the study done by Suprasert et al.[10] in which the median interval was 2 months. The commonest presentation (48.6) in our study was anemia with vaginal bleeding. Theca lutein cyst was presenting symptom in 22.8% and sub involution in 17.0% of cases .These findings are almost similar with the studies of Goldstein et al.[12] Khoo et al.[13] Gilani et al.[14] and Maesta et al.[15] in which 30% of their cases presented with abnormal vaginal bleeding. please follow Vancouver style of referencing not Harvard style.

In our study 94.3% cases of GTN were preceded by molar pregnancy. Goldstein et al[12] observed that about 50% cases occurred following molar gestation and 25% after abortion. We had histopathology reports in only three cases (two were having choriocarcinoma and one invasive mole). A retrospective study by Srivastava et al.[1] found 11 cases of choriocarcinoma and four cases of invasive mole out of 28 patients. In our study, 15 cases(42.9%) of GTN were diagnosed on the basis of rising β-hcg over two weeks (day 1,

7 & 14) and 12 cases (34.3%) were diagnosed by plateauing of β-hcg over three weeks (day 1,7,14,21), whereas only 8.5% of GTN on the basis of histopathology. Ngan et al.[11] Biscaro et al diagnosed cases of GTN in their study in a similar way.[16] Studies by Suprasert et al;[10] had 90% referred cases and our study also had a large number of referred cases (68.4%). Lungs, vagina, brain and liver were main sites of metastasis in our study, this corroborates with study of lurain et al.[17] and Gulia et al.[7]

In our study, 32(91.4%) low risk cases were treated with Methotrexate and only three patients received EMACO (8.6%). Low risk cases treated with single agent had good outcome whereas patients with higher score needed combination chemotherapy which was found in other studies also like those done by Ngan et al,[11] Froeling et al;[18] Biscaro et al. In the present study 68.4% patients did not develop any complications after chemotherapy, stomatitis developed in 11.4% and conjunctivitis in 8.6% while only few patients developed abdominal pain, alopecia, leukopenia and pancytopenia. Shrivastavai et al.[1] found alopecia to commonly occur in EMACO treated patients, whereas study by Gulia et al. showed mucositis to be associated with Methotrexate(MTX) therapy.[7]

CONCLUSION

In this study we tried to diagnose the cases at the earliest and compared the patient profile as well as treatment outcome with other studies, it revealed that most patients can be treated successfully with single agent chemotherapy (Methotrexate), only a few required multidrug therapy and most of the patients did not develop any major complications. GTN represents one of the success stories of medical science and our study only strengthens the fact.

RECOMMENDATION

Our study showed that GTN cases require a high level of suspicion and can be diagnosed easily by a simple blood test of β-hcg. Treatment with Methotrexate can cure most of the cases with minimal complications. Case stratification using the WHO scoring system is essential for proper drug treatment.

LIMITATIONS OF THE STUDY

This was a single center study for one and half years, so we got only a few cases of GTN. As it was a hospital based study we did not get the exact picture of GTN in the community. Follow up cases were not done so a long term outcome of cases cannot be predicted.

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CONFLICT OF INTEREST

This study has no conflict of interest.

FINANCIAL DISCLOSURE

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