Gestational Trophoblastic Neoplasia: Evaluation of Prognostic Factors, Mode of Treatment and Responses

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Abstract

Background: Gestational Trophoblastic Disease (GTD) represents a spectrum of neoplastic disorders that arise from placental trophoblastic tissue after abnormal fertilization. The exact etiology of gestational trophoblastic disease is yet unknown. It arises from placental villous and extra villous trophoblast. Proper evaluation and appropriate treatment canreduce the complication of GTD. To evaluate the risk factorsfor optimum treatment according to risk group and response to treatment.

Materials and methods: This observational cross-sectional study was conducted in Dhaka Medical College Hospital between 27th April 2019 and 26th October 2019.A total of fifty patients having Gestational Trophoblastic Disease (GTD) admitted in Department of Obstetrics & Gynecology indoor during study period were included. Follow up of the patients was done who were treated by suction evacuation or chemotherapy. Data were collected from the informant and recorded in structured case report form. Clinical examination and relevant investigation were done meticulously. Data were analyzed by using Statistical Package for Social Science (SPSS) version 22.0.

Results: Among 50 patients with gestational trophoblastic disease 10 (20.0%) have below 20 years age group, 28 (56.0%) havebetween 20 and 30 years age and 3(6%) have >40years age group. Mean age ± SD of the responders was 25.94 ± 6.97 years and range was 17-45 years. Among them 11 (22.0%) were nulliparous, 39 (78.0%) were multiparous, 11 (22.0%) were primigravida, 10 (20.0%) were 2nd gravida, 29 (58.0%) were 3rd gravida and onwards. Out of 50 respondents, 18 (36.0%) had previous history of abortion and 32 (64.0%) had no previous abortion. Economically middle class of socioeconomic status was predominant (e.g., 44%). Among the respondents 46 (92.0%) patients presented with amenorrhea, 48 (96.0%) presented with per vaginal bleeding, 26 (52.0%) presented with per vaginl expulsion of grape like vesicles and 17 (34.0%) presented with abdominal distenstion.76.0% of patients had pretreatment serum β hCG level more than 100000 m IU/ml. Most of cases (46.0%) have more than 20 weeks of uterine size. Theca lutein cysts in adnexa was detected in 23(46.0%) patients, among them size of cyst was 6-8 cm in 28% cases. Most of the patients (70%) have the diagnosis of hydatidiform mole and serum β hCG levelreaches normal range within 6-8 weeks in 80% cases, but in 20% patients developed persistent GTN and 10% patients developed choriocarcinoma. Among the patients 70% treated only by sucction,evauation and curettage, 20% treated only by chemotherapy and 10% need both Sucction, evacuation, curettage followed by chemotherapy. Among the patients who needed chemotherapy 10(66.66%) patients were treated by single agent chemotherapy and 5(33.33%) patients were treated by combination chemotherapy.

Conclusions: GTD largely remains an etiologic enigma. The risk factors for the disease are unclear. In this study an attempt has been made to identify some risk factors, clinical presentation and level of serum a βhCG and ultrasound findings of GTD and response to the current mode of treatment. It will also provideinformation about awareness of the disease and it's monitoring and surveillance.

Key words: Fertilization; Gestational trophoblastic disease; Neoplastic disorder; Placenta.

Introduction

Gestational trophoblastic disease constitutes a spectrum of tumor and tumor like condition characterized by proliferation of pregnancy associated trophoblastic tissue of progressive malignant potential.[1] GTD comprise a spectrum of interrelated tumors including complete and partial

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hydatidiform mole, Placental Site Trophoblastic Tumor (PSTT) and choriocarcinoma. Trophoblastic tumors are all potentially malignant or malignant.[2] There are some epidemiological features of GTD which include age (Less than 20 years and above 40 years), parity, blood group, race, socioeconomic condition.[3] Women with previous history of one hydatidiform mole seem to have a tenfold risk for subsequent hydatidiform mole in comparison to women who have no history of hydatidiform mole.[4]

GTD is considered to be the first and only disseminated solid tumors which is highly curable by chemotherapy.Several studies have been conducted since 1960 to determine the success or failure of the treatment.[5] WHO modified the scoring system in 1983.[6] According to this system GTD is divided into three groups-Low risk group (Score <5), medium risk group (Score 5-7), High risk group (Score >7). FIGO modified WHO scoring system at 25th annual meeting in 2000.[7] In this FIGO accepted system blood group has been omitted and hepatic metastasis has given a score.[5] The cut off score for low risk and high-risk neoplasia was ratified on June 2002. According to FIGO committee on Gynecology and oncology announcement 'A score of 6 or less is low risk disease and a score of 7 or greater is high risk diseases' whereas medium risk disease has been eliminated.[7]

Treatment modalities used for GTD are:

i) Suction and evacuation-

ii) Chemotherapy- Either prophylactic or primary chemotherapy treatment following evacuation.

iii) Chemotherapy with surgery: Chemotherapy can be given before and after surgery (Abdominal / pelvic surgery, craniotomy, lobectomy of lung etc.)

iv) Surgery alone: Only hysterectomy with normalization - βhCG level, in patient who did not undergo chemotherapy before and/or after hysterectomy.

v) Radiation: In cerebral metastasis or unresectable lesion.

At present it is possible to achieve almost 100% success of survival for low-risk group with single agent chemotherapy.

Single regimen used:

Inj. Methotrexate 50mg IM in D1, D3, D5, D7 and Tab. Folinic acid 30 mg PO in D2, D4, D6 and D8.[2]

This regimen is usually tolerable without toxicity. This cycle should be repeated at the 15 days interval. During treatment weekly βhCG titer should be done and before each course Complete Blood Count (CBC), liver and renal function tests should be done. After reaching to normal βhCG level another 3 cycle should be continuedfor complete eradication of the disease. When there is rising or plateau (βhCG level) after initial treatment then either single agent actinomycin D can be added or patient may need shifting to combination EMA-CO therapy.[2]

For high risk GTD, EMA-CO has been the most preferred treatment of choice with increasing survival rate to 80%. EMA-CO schedule is

D1: Actinomycin-D 0.5mg I/V
Etoposide 100mg/m2 I/V
Methotrexate 300mg/m2 I/V

D2: Actinomycin-D 0.5mg I/V
Etoposide 100mg/m2 I/V
Folinic acid 15mg PO BD 4 doses

D8: Vincristine 1.4mg/m2 I/V
Cyclophosphamide 600mg/m2 I/V[2]

This regimen should be repeated at an interval of 15 days and after each cycle toxicity is monitored. Toxicity developed by EMA-CO are bone marrow depression, elevated liver enzymes, diarrhea and vomiting, dermatitis, alopecia, neuropathy bodyache etc. so before starting each cycle of chemotherapy CBC, Hepatic and Renal function tests must be done. During treatment weekly βhCG level should be done and after achieving normal βhCG level another three cycle should be given to eradicate the disease. If βhCG level did not decrease after two courses of EMA-CO or if the βhCG level drew a plateau for four consecutive weeks it should accepted as drug resistance.[2] About 17% cases of high risk GTD developed resistance of this EMA-CO and require a change to second line drug treatment.

When three consecutive weekly normal βhCG titers have been achieved, complete remission is documented. Then patient should be regularly followed by βhCG level every month, pelvic examination and X-ray chest (If indicated) every three months during the first year and after the remission. β–hCG level, Pelvic examination and X-ray chest are repeated every six months during the second year and then yearly for the years to follow.[2]

Gestational trophoblastic neoplasia have become highly curable human malignancies because of the development of effective systemic chemotherapy regimen and the ability to monitor the treatment progress with sensitive assays for hCG Diagnosis and treatment of GTN in developing countries is challenging due to numerous factors .This study was conducted with the aim to determine the risk groups by evaluation of the prognostic factors and response to the current mode of treatment. It will also provide Information about awareness of the disease and it's monitoring and surveillance.

Materials and methods

This descriptive type of cross sectional studywas carried out in the Department of Obstetrics & Gynecology, Dhaka Medical College Hospital between 27th April 2019 and 26th October 2020. Ethical clearance for the study was obtained from the institutional review board, Dhaka Medical College. A total of 50 women between 17 and 45 years of agewith GTD admitted in Department of Obstetrics & Gynecology were enrolled in the study. These women came with amenorrhea and per vaginal bleeding or passage of grapes like structure vaginally. After taking history with particular attention to aspects relevant to this study, clinical examinations were carried out. Diagnosis was confirmed by ultrasonography of lower abdomen and serum beta hCG. They had either recent history of suction and evacuation for molar pregnancy with rising or plateau β-hCG titer or past history of molar pregnancy who came to take chemotherapy for GTN.Patient with GTD with spontaneous regression of serum beta hCG level to normal level within 6 weeks of evacuation were excluded from the study.Purposive sampling was done according to the availability of the participants who had voluntarily joined this study. The purpose and procedure of study was discussed with the participants and informed written consent was taken.An interviewer administered questionnaire was used for data collection. Statistical analysis of the results was obtained by using Windows based computer software devised with Statistical Packages for Social Sciences (SPSS-20).

Results

Regarding age distribution, out of 50 patients with gestational trophoblastic disease 10 (20.0%) were below 20 years age group, 28 (56.0%) were in between 20 and 30 years, 9 (18.0%) were in between 30 and 40 years and rest 3 (6.0%) were in the age above 40 years. Mean age ± SD of the responders was 25.94 ± 6.97 years and age range was 17-45 years. Among the 50 patients, middle class of socioeconomic status was predominant (44%), followed by poor socioeconomic status 38% and upper socioeconomic status belongs 18% of respondents.

Out of 50 patients, 27 (54.0%) patients had A+ve blood group, 16 (32.0%) had O +ve, 03 (6.0%) had B +ve, 2 (4.0%) had AB +ve, 1 (2.0%) had A –ve and 1 (2.0%) had O –ve blood group.

Regarding Obstetric history among 50 respondents, 11 (22.0%) were nulliparous, 39 (78.0%) were multiparous, 11 (22.0%) were primigravida, 10 (20.0%) were 2nd gravida, 29 (58.0%) were 3rd gravida and onwards. Out of 50 respondents, 18 (36.0%) had previous history of abortion and 32 (64.0%) had no previous history of abortion.

Regarding personal history of the respondents among 50 patients 35 (70.0%) had the history of oral contraceptive use, 08 (16.0%) had the family history of GTD, 01 (2.0%) had the history of PE, 35 (70.0%) had positive smoking history.

Table I Distribution of chief complaints of the respondents (n=50)

Chief complications	Frequency	Percent
History of amenorrhea	46	92.0
Per vaginal bleeding	48	96.0
Expulsion of grape like vesicles	26	52.0
Abdominal distention	17	34.0

Table I shows among the 50 respondents 46 (92.0%) were presented with amenorrhea, 48 (96.0%) were presented with per vaginal bleeding, 26 (52.0%) were presented with expulsion of grape like vesicles and 17 (34.0%) were presented with abdominal distension.

Table II Physical sign of the respondents (n=50)

Sign	Frequency	Percent
Anemia	22	44.0
Enlarged uterus	28	56.0
Doughy consistency	12	24.0
Vesicles with the vaginal discharge	38	76.0
Cervical os open	45	90.0
Tenderness	30	60.0

Table II shows among 50 respondents 28 (56.0%) were detected enlarged uterus and 12(24.0%) had found doughy in consistency. Per-vaginal examination revealed that, 38(76.0%) had vesicle with vaginal discharge, Cervical os was found open in 45(90.6%) cases and tenderness was present in 30(60.0%) patients.

Table III Range of serum βhCG of the respondents (n=50)

Serum hCG	Frequency	Percent
< 1000 m IU/ml	2	4.0
1000 - 10000 m IU/ml	3	6.0
10000 - 100000 m IU/ml	7	14.0
> 100000 m IU/ml	38	76.0

Table III shows highest percentage (76.0) of patients had pretreatment serum β βhCG level is > 100000 m IU/ml.

Table IV Ultrasonography findings of the molar pregnancy (n=50)

USG findings	Frequency	Percentage (%)
Enlarged uterus	32	64.0
Echogenic central uterine mass containing many 'grape-like' anechoic (Cystic) spaces	50	100.0
Theca lutein cysts in adnexa	23	46.0
Ovarian enlargement	27	54.0
No associated embryonic or fetal structures	50	100.0

Table IV shows USG findings of molar pregnancy. Echogenic central uterine mass containing many 'grape-like' anechoic (cystic) spaces and no associated embryonic or fetal structures had typical findings and present in all cases. It was evident that, theca lutein cysts in adnexa had detected in 23(46.0%), enlarged uterus in 32(64.0%) cases and ovarian enlargement detected in 27(54.0%) cases.

Table V Frequency distribution of different spectrum of GTD (n=50)

Type of GTD	Frequency	Percent
Hydatidiform mole	35	70%
Persistent H.mole	10	20%
Choriocarcinoma	5	10%
Total	50	100%

Table V shows that most of the patients (70%) had developed hydatidiform mole, 20% patients had persistent H. mole and 10% patients had choriocarcinoma.

Table VI Mode of treatment of participants (n=50)

Mode of treatment	Frequency	Percentage
Sucction and Evacuation	35	70%
Sucction and Evacuation + Chemotherapy	5	10%
Chemotherapy	10	20%

Table VI shows 70% have got only Sucction and Evacuation, 20% have got only chemotherapy and 10% have got both Sucction and Evacuation + chemotherapy.

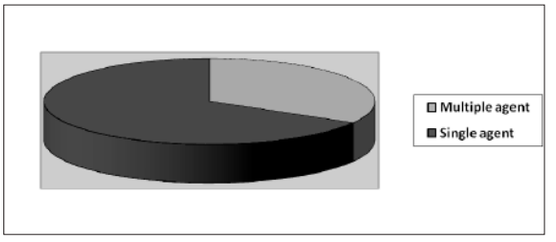

Figure 1 Frequency distribution of chemotherapy schedule (n=15)

Figure 1 shows among patients with chemotherapy 10(66.66%) patients were treated by single agent and 5(33.33%) patients were treated by combination chemotherapy.

Table VII Frequency distribution of completion of chemotherapy (n=15)

Chemotherapy	Frequency	Percentage
Not completed	3	20.0
Completed	12	80.0
Total	15	100

Table VII shows most of the patients 80.0% have completed their chemotherapy.

And out of 12 patients who completed chemotherapy10(83.3%) patients have got complete remission and only 2(16.7%) patients developed drug resistance.

Discussion

In this study, among 50 patients 70% patients had hydatidiform mole, 20% patients had persistent Hydatidiform mole and 10% patients had choriocarcinoma. The age range of patients was found between 18 and 45 years. Maximum numbers of patients (60%) were in 20-29 age groups, 16.66% in the 30-39 years age group, 13.33% were below 20 years and 10% were found above 40 years.

According to FIGO oncology committee report, FIGO staging for gestational trophoblastic neoplasia 2000, data analysis indicates that GTD is a disease of reproductive age group women with highest percentage of cases occurring between ages of 25 and 29 years. The findings of this study are consistent with previous study. Majority of GTD occurred between 21-30 years which is the peak period of fertility.[7] A study of Khatoon RA and colleagues showed that 63.75% were in 21-30 years age group.[8] Regarding Obstetric history among 50 respondents, 11 (22.0%) were nulliparous, 39 (78.0%) were multiparous, 11 (22.0%) were primigravida, 10 (20.0%) were 2nd gravida, 29 (58.0%) were 3rd gravida and onwards. Out of 50 respondents, 18 (36.0%) had previous history of abortion and 32 (64.0%) had no previous history of abortion.In this study it was also showed that there was no significant relationship between blood group and risk group. Most of the patients of this study had blood group B +ve (40%), next 26% had blood group A +ve. Another 23.33% had O +ve and 10% AB +ve. In 1983 WHO modified system blood group was included as prognostic factor.[6] But in 2000 at the 25th annual meeting FIGO modified this system and blood group was omitted.[7] A study by Rahman F in 2003 at DMCH showed among 100 patients or GTD, 35% had blood group A +ve, 34% had B +ve, 19% had O +ve and 12% had AB +ve.[9] The above findings were consisted with the current study.

The study shows among the 50 respondents 46 (92.0%) were presented with amenorrhea, 48 (96.0%) were presented with per vaginal bleeding, 26 (52.0%) were presented with expulsion of grape like vesicles and 17 (34.0%) were presented with abdominal distension.

On Ultrasound findings. Echogenic central uterine mass containing many 'grape-like' anechoic (cystic) spaces and no associated embryonic or fetal structures had typical findings and present in all cases. It was evident that, theca lutein cysts in adnexa had detected in 23(46.0%), enlarged uterus in 32(64.0%) cases and ovarian enlargement detected in 27(54.0%) cases.

The study reveals highest percentage (76.6%) of patients had pretreatment serum βhCG was >100000m IU/ml, 13.3% had between 10000-100000m IU/ml and 6.6% had between 1000-10000m IU/ml and only 3.3% had <1000m U/ml. There was relationship between serum β βhCG and risk group but not highly significant (p value-0.020) because most of the patients of all risk group had serum βhCG level >100000m IU/ml.

The study found Initial treatment that is 70% of all patients was treated by suction and evaluation and developed complete remission to this treatment. 20% patients got only chemotherapy and 10% patients got Sucction and Evacuation + chemotherapy. 80% of patient having chemotherapy had completed their chemotherapy. 20% had failed to complete their chemotherapy. It is mostly the economic factors that prohibit the patient to take regular chemotherapy.

The patient completing chemotherapy cycle 83.3% developed complete remission, 16.7% developed drug resistance.

A similar study conducted by McNeish IA and colleagues on low risk persistence trophoblastic disease showed 67% of low risk group was successfully treated by Methotrexate. The rest of the patients needed second line drug or combination drugs.[10] This study also reveals in medium risk group those patients (30.4%) who treated by MTX, only developed drug resistance in 15.2% cases and another 15.2% declared as complete remission. The resistance eases were treated by second line drug or combination therapy. Only 4.2% of this group getting EMA-CO developed drug resistance.

Limitations

The present study was conducted within a short period of time. The study population was selected from one selected hospital, so that the results of the study may not be reflect the exact picture of the country. Small sample size with purposive sampling was also a limitation of the present study.

Conclusion

GTD largely remains an etiologic enigma. The risk factors for the disease are unclear. In this study an attempt has been made to identify some risk factors, clinical presentation and level of serum βhCGand ultrasound findings of GTD. This study shows, there isassociation among maternal age, parity, ABO blood group , reproductive history and some risk factors .The study also detect most of the patients belong to low to middle socio-economic status. Treatment by Sucction & Evacuation to all low risk group gave very good response by proper follow up. Chemotherapy was given to medium and high risk groups which response was very satisfactory. Only 16.7% developed drug resistance by single agent chemotherapy.

Recommendations

Further longitudinal studies with larger sample size with multicentric approach and long duration are needed.This will strengthen the outcome of this study result.

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Contribution of authors

KKT-Cconception, design, data collection, data analysis, drafting manuscript & final approval.

NH-Data analysis, interpretation of results, critical revision & final approval.

NH-Data analysis, interpretation of data, critical revision & final approval.

SMS-Interpretation of data, critical revision & final approval.

NEA-Data collection, draft manuscript & final approval.

NFJN-Data analysis, interpretation of results, drafting & final approval.

MAK-Data analysis, interpretation of results, drafting & final approval.

Disclosure

All the authors declared no conflict of interest.

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