RISK FACTORS FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA: A CASE CONTROL STUDY IN A TERTIARY HOSPITAL

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ABSTRACT

BACKGROUND

Gestational trophoblastic disease is a spectrum of proliferative abnormalities of the trophoblast. GTD represents a benign form of the disease while GTN is the malignant often metastatic lesion. 75-80 per cent of patients initially diagnosed as GTD will follow a benign course after dilatation and curettage. 15-20 per cent develop locally invasive disease and 3-5 per cent develop metastatic lesions. The study aims to assess the proportion of gestational trophoblastic neoplasia among women with gestational trophoblastic disease and identify the risk factors for chemotherapy in gestational trophoblastic neoplasia.

MATERIALS AND METHODS

This is a case-control study conducted in a tertiary hospital during a 5-year period. Cases are gestational trophoblastic neoplasia diagnosed by either rising beta-HCG levels or plateauing beta-HCG levels or by histological evidence of choriocarcinoma. Controls are cases of gestational trophoblastic disease post evacuation with normal HCG regression at 8 weeks. There were 306 controls and 57 cases.

RESULTS

Tabulated and analysed using SPSS package. Of the 363 patients of gestational trophoblastic disease, 57 (15.7%) needed chemotherapy. 98.2% belonged to the age group of 20-35 years. 63% had gestational age of more than 12 weeks, 56.1% had pre-evacuation HCG of more than 40,000. 15.7% needed combination therapy.

CONCLUSION

1. 83.1% of patients belonged to age group of 20-30 years.
2. Blood group distribution of patients with gestational trophoblastic disease did not show any significance.
3. 15.7% of total patients were diagnosed to have gestational trophoblastic neoplasia that necessitated chemotherapy.
4. When uterine size was more than 12 weeks, a statistically significant number of patients needed chemotherapy compared to non-chemotherapy group.
5. When BHCG values were more than 40,000, a statistically significant number of patients needed chemotherapy.
6. A risk score of seven or more was found to have a significant association in the chemotherapy group.
7. The major indications for chemotherapy were plateauing of HCG, rising HCG, rise in HCG 6 months after evacuation and invasive mole.
8. Single agent chemotherapy with methotrexate and folinic acid was used in 84.2% cases.
9. Combination therapy with EMACO was used in 15.7%.
10. Indication for combination therapy was methotrexate resistance-3 cases and high risk WHO score (>7)-6 cases.

KEYWORDS

Risk Factors, Gestational Trophoblastic Neoplasia, Gestational Trophoblastic Disease, Human Chorionic Gonadotropin, Methotrexate, Chemotherapy.

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BACKGROUND: Gestational trophoblastic disease is the general term for a spectrum of proliferative abnormalities of the trophoblast. Hydatidiform mole represents the benign form of the disease while choriocarcinoma represents the malignant often metastatic lesion.

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This neoplasia arises from the trophoblastic elements of the developing blastocyst and retain certain characteristics of the normal placenta such as invasive tendencies and the ability to recreate the polypeptide human chorionic gonadotropin. The disease is almost always related to some pregnancy event and thus specifically differs from choriocarcinoma found in germ cell tumours of the ovary. These proliferative trophoblastic abnormalities are classified as hydatidiform mole, invasive mole or choriocarcinoma based on their histopathological appearance.

Approximately, 75-80% of patients initially diagnosed as having hydatidiform mole will follow a benign course with spontaneous resolution after dilatation and curettage, but 15-20% subsequently develop locally invasive disease and 3-5% eventually prove to have metastatic lesions.

Gestational trophoblastic neoplasia is the malignant counterpart of Gestational Trophoblastic Disease. They maybe locally invasive or metastatic invasive mole and choriocarcinoma, but placental site trophoblastic tumour and epithelioid trophoblastic tumours are rare. Majority of Gestational Trophoblastic Neoplasia occur after a complete mole, but they may occur after partial mole, normal pregnancy, miscarriage or termination of pregnancy. The diagnosis of Gestational Trophoblastic Neoplasia is made on clinical presentation, elevated HCG and presence of metastasis on imaging. Tissue for histopathology is seldom obtained. Hence, a definite histological diagnosis of Gestational Trophoblastic Neoplasia is not made in most cases.

The types of Gestational Trophoblastic Neoplasia are:

1. Invasive mole.
2. Choriocarcinoma.
3. Placental site trophoblastic tumour.
4. Epithelioid trophoblastic tumour.

Chemotherapy is the main stay of treatment of Gestational Trophoblastic Neoplasia, but surgical intervention is warranted in some situations. Women who have low-risk Gestational Trophoblastic Neoplasia by the World Health Organization scoring system are treated with single agent chemotherapy and those with high-risk Gestational Trophoblastic Neoplasia are treated with multiagent chemotherapy. For single agent, methotrexate and actinomycin are the commonly used agents. The multiagent regimen consists of Etoposide, Methotrexate, Actinomycin Cyclophosphamide and Vincristine with folinic acid rescue (EMACO). Each course is given over eight days and next course started on day 15. Gestational Trophoblastic Neoplasia has a good prognosis with 100% complete remission in low-risk disease. With multiagent therapy, survival in high-risk disease is about 80-90%. When brain metastasis is present, survival reduces to 50-60%. Outcome of pregnancies after chemotherapy has been found to be normal. This study aims to determine the proportion of gestational trophoblastic neoplasia among the patients attending the trophoblastic clinic and to identify the indications for chemotherapy in this group.

AIMS AND OBJECTIVES

1. To study the proportion of gestational trophoblastic neoplasia among women diagnosed with vesicular mole at the vesicular mole clinic of a tertiary care hospital.
2. To identify the risk factors for chemotherapy in the gestational trophoblastic neoplasia group.

Sri Avittom Thirunal Hospital has a vesicular mole clinic where all cases of vesicular mole diagnosed by ultrasound and HCG values post evacuation are followed up according to FIGO guidelines by serial HCG and clinical examination in indicated cases.

MATERIALS AND METHODS

CASES:

Are gestational trophoblastic neoplasia diagnosed by the following criteria.

1. Plateauing of HCG on 4 occasions over a 3-week period or longer-days 1, 7, 14, 21.
2. Rise of HCG on 3 consecutive weekly measurements over a period of 2 weeks or longer on days 1, 7, 14.
3. Histological evidence of choriocarcinoma.

Controls: Are patients diagnosed to have vesicular mole who underwent evacuation and are on follow-up with normal regression of HCG, i.e. values touching normal by 8 weeks. This is a case control study done on patients attending the trophoblastic clinic of Sri Avittom Thirunal Hospital during a 5-year period. Cases of gestational trophoblastic neoplasia are compared with diagnosed cases of vesicular mole post evacuation on follow up to detect the high-risk factors in the former group, which necessitated chemotherapy. This is done by case-control approach.

STATISTICAL ANALYSIS: The data is entered in excel sheet and analysis done using SPSS package.

RESULTS:

Observations: There were a total of 363 patients registered in the vesicular mole clinic in the 5-year observation period at Sri Avittom Thirunal Hospital. The high number of patients attending the clinic maybe because Sri Avittom Thirunal Hospital is the only referral centre in South Kerala. Increased awareness about the seriousness of the disease among doctors at primary health centres and private nursing homes maybe the reason for increased referral of trophoblastic disease.

The Following were the Observations:

Maternal Age Distribution of Patients		
<20 years	57	15.7%
20-25 years	302	83%
25-35 years	4	1.3%
>35 years	Nil	
Total	**N = 363**	

Majority of patients belonged to the age group of 20-25 yrs.

Blood Group		
A	109	30.1%
O	130	35.8%
B	94	25.9%
AB	30	8.2%
Total	**N = 363**	

35.8% of the patients belonged to group O, 30.1% belonged to group A.

Gravidity		
Primi Gravida	151	41.6%
2nd Gravida	132	36.4%
3rd Gravida	63	17.4%
4th Gravida	17	4.6%
Total	**N = 363**	

41.6% of patients were primigravidas and 36.4% were second gravidas.

Gestational Age at Diagnosis		
<12 weeks	187	51.5%
>12 weeks	176	48.5%
Total	**N = 363**	

51% of the patients were diagnosed at a gestational age of less than 12 weeks. 48% had the disease diagnosed at more than 12 weeks.

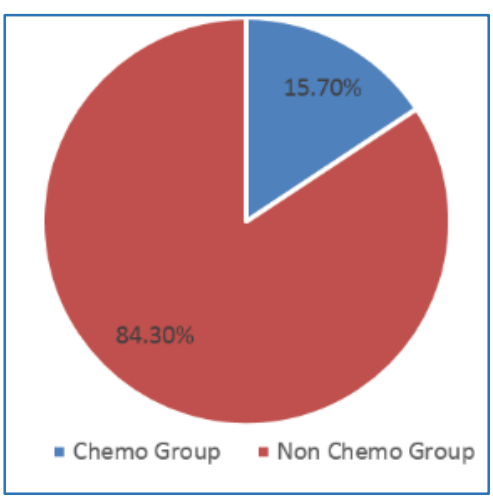
Re-Evacuation		
Not needed	328	90.3%
Needed	33	9.7%
Total	**N = 363**	

Majority of the patients did not require re-evacuation.

Pre-Evacuation HCG		
<10,000	130	35.8%
10,000-40,000	125	34.4%
More than 40,000	108	29.8%
Total	**N = 363**	

30% of the patients had pre-evacuation HCG of more than 40,000, 34% had HCG values between 10,000 and 40,000.

Chemo	Non-Chemo
57	**306**
15.7%	**84.3%**
Total Patients Studied N = 363	



Of the 363 patients who attended the clinic, 57 patients needed chemotherapy (15.7%).

Characteristics of Chemotherapy Group: 56 patients, i.e. 98.2% fell in the age group of 20-35 years, which was statistically significant compared to 1 patient (1.8%) in the less than 20 age group.

Age	Chemo	Non-Chemo	P value
20-35	56 (98.2%)	250 (81.7%)	0.011 significant
<20	1 (1.8%)	56 (10.3%)	

31% patients among chemotherapy group had blood group A compared to 28.9% in the non-chemotherapy group. 31.3% patients belonged to O group in the chemotherapy group compared to 35.8% in the non-chemotherapy group. 29.8% patients belonged to B group in the chemotherapy group compared to 31.2% patients in non-chemo group.

Blood Group			
Blood Group	Chemo	Non-Chemo	p-Value
A	31%	28.9%	
O	31.3%	35.8%	0.2 not significant
B	29.8%	31.2%	
AB	7.9%	4.1%	

Gestational Age at Diagnosis: Compared to the non-chemo group, a large number of patients requiring chemotherapy was found to have uterine size more than 12 weeks and this difference was found to be statistically significant.

Gestational Age at Diagnosis			
Gestational Age	Chemo	Non-Chemo	p-Value
>12 weeks	36 (63%)	135 (46.3%)	0.02 significant
<12 weeks	21 (37%)	156 (53.6%)	

Pre-Evacuation HCG Values: A statistically significant number of patients needed chemotherapy when pre-evacuation HCG was more than 40,000.

Pre-Evacuation HCG Values			
	Chemo	Non-Chemo	p-Value
>40,000	32	76	0.0011 significant
<10,000	15	115	
10,000-40,000	10	115	

Uterine subinvolution was not found to be a risk factor among the patients requiring chemotherapy compared to the non-chemo group.

World Health Organization Risk Score:

	Chemo	Non-Chemo	
>7	6 (10.5%)	0	0.0009 significant
<6	51 (89.5%)	306 (100%)	

Indications for Chemotherapy:

1. Plateauing of HCG values-49%.
2. Rising HCG values-24%.
3. Rise in HCG 6 months after evacuation-17%.
4. Invasive mole-10%.

All patients in the chemo group had stage I disease at diagnosis.

Choice of Chemotherapy	
Single agent Methotrexate + Folinic Acid	48 cases (84.2%)
EMACO	9 cases (15.7%)

Indications for Combination Therapy:

1. Methotrexate resistance-3.
2. High-risk cases-6.

DISCUSSION: Incidence of gestational trophoblastic disease is much higher in Asian countries compared to the western world.[1] We had a total of 363 patients registered in the vesicular mole clinic in the 5-year study period. This high number is because Sri Avittom Thirunal Hospital is a major referral centre for South Kerala and part of Tamil Nadu. Both doctors at the peripheral health centres as well as patients are becoming increasingly aware of the seriousness of the need for early diagnosis and follow up. Out of 363 patients, 57 patients (15.7%) required chemotherapy.

Age: In the present study, maximum number of patients with gestational trophoblastic disease was found in the age group of 20-25 years (83%). This is comparable to the highest number of obstetric patients in this group. In the neoplasia group, 98.2% fell in the age group of 20-35 years, which was found to be statistically significant with a p value of 0.011. The youngest case of choriocarcinoma reported in literature is a 10-year-old girl.[2] In this study, there were no cases of metastatic disease. In the series, we did not come across a case of choriocarcinoma. The decreasing incidence of choriocarcinoma may be due to BHCG follow up and the timely intervention, which was not available till recently. It is reported that the higher prevalence in developing countries is due to the poor socioeconomic status, malnutrition and higher fertility. Prophylactic chemotherapy is no longer advocated routinely following pregnancies because of toxicity.

Before the advent of chemotherapy, choriocarcinoma was seen in not more than 3% of hydatidiform moles, but the number of patients who receive chemotherapy now after hydatidiform mole ranges in different series. In the present study, 41.6% of patients were nulliparous, 36.4% were second gravidas, 17.4% were third gravidas and 4.6% were fourth gravidas. No significant association with parity was noted in the 57 patients who required chemotherapy. The effect of parity on incidence and survival was studied by Bagshawe.

According to him, the prognosis was best for those with more than 4 pregnancies, but prognosis worsened as parity increased up to 4.[3] In the present study, the blood group distribution of patients with gestational trophoblastic disease as well as neoplasia did not show much difference from the general population. Compared to the non-chemotherapy group, a large number of patients in the chemotherapy group was found to have uterine size more than 12 weeks and this difference was found to be statistically significant. There is a correlation between excessive uterine size and markedly elevated HCG levels as the uterus contains hyperplastic trophoblastic tissue. The greatly enlarged uterus is considered a risk factor for subsequent trophoblastic neoplasia. Also, the greatly enlarged uterus is a danger signal for possible embolisation of molar tissue.[4]

Paul Morrow, Oscar et al on their study on 128 women with hydatidiform moles evacuated at the Los Angeles County-University of Southern California Women's Hospitals concluded that of the 121 patients with follow-up, persistent Trophoblastic Disease (TD) was diagnosed in 32 (26.4 per cent). The risk of Gestational Trophoblastic Disease was significantly increased in pregnancies large for dates (47.8 per cent) with a uterus >20 weeks' gestational size (45.0 per cent) or with theca lutein cysts >5 cm. in diameter (50.0 per cent).[5]

A statistically significant number of patients needed chemotherapy where the HCG values were more than 4,00,000. When the pre-evacuation HCG is more than one lakh, the patient is classified as high-risk Gestational Trophoblastic Neoplasia.

Kang, Choi and Kim studied 467 patients with complete molar pregnancies. Persistent Gestational Trophoblastic Neoplasia was diagnosed in 24.2% on the basis of the 2000 FIGO criteria. The decline ratio in hCG level 2 weeks after evacuation in patients with complete molar pregnancies was found to be the most reliable predictor of persistent Gestational Trophoblastic Neoplasia.[5] A score of seven or more (WHO risk score) was found to have a significant association with multiagent chemotherapy compared to the non-chemotherapy group. 95% of patients with gestational trophoblastic neoplasia are low risk (Score 1-6). All low-risk Gestational Trophoblastic Neoplasia patients need chemotherapy with methotrexate or Actinomycin D.

Indications for Chemotherapy: The indications for chemotherapy in the study were:

a. Plateauing of HCG values in 49%.
b. Rising of HCG values in 24%.
c. Rise in HCG 6 months after evacuation-17%.
d. Invasive mole in 10%.

All patients in the study group had stage I disease at diagnosis. 84.2% of patients in the chemotherapy group received single agent chemotherapy with methotrexate and folinic acid while 15.7% cases received combination therapy with EMACO.

Indications for Combination Chemotherapy in the Study Group:

Methotrexate Resistance-3.
High-Risk Cases-6.

SUMMARY AND CONCLUSIONS

1. There were a total of 363 patients registered in the vesicular mole clinic of Sri Avittom Thirunal Hospital during the study period of 5 years.
2. Majority of patients (83.1%) belonged to the age group of 20-45 years.
3. Blood group distribution of patients with gestational trophoblastic neoplasia did not show any significance.
4. 41.5% of patients diagnosed to have gestational trophoblastic disease were nulliparas.
5. 51.5% of the patients had the disease diagnosed at a gestational age of less than 12 weeks and 48.4% had the diagnosis at a gestational age of more than 12 weeks.
6. 15.7% of the total patients were diagnosed to have gestational trophoblastic neoplasia that necessitated chemotherapy.
7. A statistically significant number of patients who underwent chemotherapy belonged to age group of 20-35 years.
8. When the uterine size was more than 12 weeks, a statistically significant number of patients needed chemotherapy compared to non-chemotherapy group.
9. When the HCG values pre-evacuation was more than 40,000, a statistically significant number of patients needed chemotherapy.
10. Uterine subinvolution was not found to be a risk factor among the chemotherapy group compared to the non chemotherapy group.
11. World Health Organization risk score of seven or more was found to have a significant association in the chemotherapy group compared to the non-chemotherapy group.
12. The major indications for chemotherapy were plateauing of HCG values (49%), rising HCG values (24%), rise in HCG 6 months after evacuation and invasive mole 10%.
13. Single agent chemotherapy with methotrexate and folinic acid was used in 84.2% cases.
14. Combination therapy with EMACO regime was used in 15.7%.
15. Indications for combination therapy were methotrexate resistance-3 cases and high-risk cases (World Health Organization score >7)-6 cases.
16. No case of choriocarcinoma was identified in the study group.

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