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Original Research Article

A study of factors affecting regression of βhCG in gestational trophoblastic disorders

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ABSTRACT

Background: Gestational trophoblastic disorders are among the rare human tumors that can be cured even in the presence of widespread dissemination. Authors can anticipate the development of persistent trophoblastic disease by identifying high risk factors affecting βhCG regression in vesicular mole. The study of this aim was to determine the incidence of gestational trophoblastic disorders and persistent trophoblastic disease in our institution. Factors affecting regression of βhCG and thereby leading to persistent disease are assessed.
Methods: The study was conducted for a period of 2 years at a tertiary care centre in central Kerala. The factors affecting progression to persistent disease are assessed by a case control study. Those developing persistent trophoblastic disease were taken as cases and those with normal regression of βhCG were taken as controls. Variables studied were age, sociodemographic factors, obstetric history, histopathological report, βhCG value, post evacuation USG and clinical features.
Results: The incidence of gestational trophoblastic diseases was 1 in 178 births and of persistent trophoblastic disease was 18.6%. Fourteen cases with persistent trophoblastic disease were studied and 61 controls were recruited. Incidence increased in older age group (>30) and low socio-economic group. Pre-evacuation βhCG> 40000 and presence of theca lutein cyst are important factors affecting βhCG regression. Strong association with uterine size >poa, post evacuation uterine subinvolution and presence of hyperthyroidism was found.
Conclusions: Progression to persistent trophoblastic disease was associated with low socioeconomic status, high pre-evacuation βhCG values, uterine size>poa and presence of theca lutein cysts. Identification of these risk factors helps in proper counseling and meticulous follow up of patients.

Keywords: βhCG, Persistent trophoblastic disease, Risk factors

INTRODUCTION

Gestational trophoblastic disorders are among the rare human tumors that can be cured even in the presence of widespread dissemination. It comprises a group of interrelated conditions that arise from placental trophoblastic tissue after abnormal fertilisation of oocyte. The placental tissue forms a grape like mass in the uterus. It comprises a spectrum of clinical entities from non-invasive molar pregnancy to metastatic gestational trophoblastic neoplasia and characterised by tumor marker βhCG. The incidence is approximately 1-3 in 1000 pregnancies for CHM and 3 in 1000 pregnancies for PHM in North America and Europe, both conditions appear to be diagnosed more often in Asia and Latin America. This could be due to differences in hospital systems and population data, availability of pathological expertise or genetic effects.

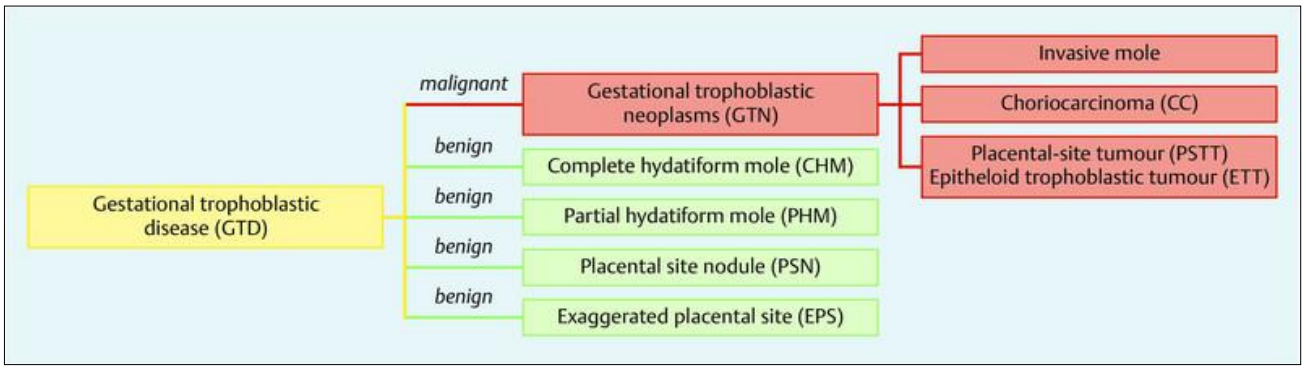

Figure 1: WHO classification.[1]

The risk for molar pregnancy is increased by 1-2% after one, and by 15-20% after two prior molar pregnancies, respectively.[2]

GTD was historically associated with significant morbidity and mortality. Hydatidiform moles were often accompanied by serious bleeding and other medical complications prior to the development of early detection and effective uterine evacuation in the 1970s. The outcomes for GTN were likewise poor before the introduction of chemotherapy into their management 50years ago. The mortality rate for invasive mole approached 15%, most often because of hemorrhage, sepsis, embolic phenomena, or complications from surgery. Choriocarcinoma had a mortality rate of almost 100% when metastases were present and approximately 60% even when hysterectomy was done for apparent nonmetastatic disease. Gestational trophoblastic neoplasms are now some of the most curable of all solid tumors, with cure rates >90% even in the presence of metastasis.[3]

This success is due to the sensitivity to chemotherapy and use of βhCG as tumor marker for monitoring. Management of molar pregnancy is by suction evacuation. This is followed by monitoring of β hCG. After evacuation, βhCG normalises by 8-10 weeks. Persistance indicate invasive or metastatic disease. It is known as persistent trophoblastic disease.

Criteria of persistent trophoblastic disease:[4]

- An abnormal hCG regression pattern (a 10% or greater rise in hCG levels or a plateauing hCG of three stable values over two weeks)
- An hCG rebound
- Histologic diagnosis of choriocarcinoma or placental site trophoblastic tumour
- The presence of metastasis
- High hCG levels (greater than 20,000mIU/mL more than four weeks post-evacuation)
- Persistently elevated hCG levels six months post-evacuation
- Persistent trophoblastic disease is treated with methotrexate
- High risk cases are given EMACO regime
- Some of the risk factors for persistent disease are age, blood group, period of gestation, socioeconomic factors, pre-evacuation βhCG, presence of theca lutien cysts. This study looks into the association of persistent trophoblastic disease with these risk factors.

The significance of finding out the factors affecting βhCG regression in vesicular mole is that detection of any definite established pattern in etiological factors helps identify high risk groups among the vesicular mole patients so that authors may be able to anticipate the development of persistent trophoblastic disease. Gestational trophoblastic tumors are important to recognize because, βhCG surveillance helps in finding out patients with abnormal regression curves. Normally βhCG is expected to fall to normal levels within 6 to 8 weeks after evacuation. In this study the factors affecting βhCG regression in vesicular mole are also studied.

The aim of the study was to find out the incidence of GTD and persistent trophoblastic disease in our institution. It also studies the factors affecting regression of βhCG in vesicular mole like age, socioeconomic factors, previous conception, period of gestation, uterine size, pre-evacuation βhCG, the calutein cysts.

METHODS

This study was conducted at the vesicular mole clinic conducted at a tertiary care center in central Kerala for 2 years. The study looks into the factors affecting progression to persistent disease by a case control study.

Inclusion criteria

- Authors included patients who had a histopathological diagnosis of vesicular mole and on

regular follow up in vesicular mole clinic were included in this study.

Exclusion criteria

- Those developing persistent trophoblastic disease as per FIGO criteria were taken as cases and those with normal regression βhCG were taken as controls. Patients with incomplete follow up in vesicular mole clinic and those referred from local hospital without a histopathologic report were excluded.

Authors collected data using a pretested questionnaire which included socio demographic variables and clinical characteristics like histopathological report, period of gestation, size of uterus, pre-evacuation βhCG value, post evacuation USG, presence of theca lutein cysts and clinical features. Study was done after approval from institutional ethics committee.

Statistical analysis

Data was using entered to Microsoft excel sheet and data analysis was done with the incidence is approximately 1-3 in 1000 pregnancies for CHM and 3 in 1000 pregnancies for PHM in North America and Europe, both conditions appear to be diagnosed more often in Asia and Latin America. This could be due to differences in hospital systems and population data, availability of pathological expertise or genetic effects. The risk for molar pregnancy is increased by 1-2% after one, and by 15–20% after two prior molar pregnancies, respectively. Two SPSS trial version software. Results were expressed as percentages and association was analysed using χ^2 test at p value 0.05.

RESULTS

Incidence of gestational trophoblastic disease at Medical College, Kottayam during the first year was 1 in 190 and next year was 1 in 168, i.e. an average of 1 in 179. Of these,32% cases were partial mole,65% were complete mole and 2% cases were choriocarcinoma. A 14 cases of persistent trophoblastic disease were identified ie,18.6%.

Factors affecting development persistent trophoblastic disorders

Fourteen cases with persistent trophoblastic disease were studied and 61 controls were recruited.

Maternal age

In this study, maximum number of cases was seen in the age group 20-30. Both cases and controls were comparable in this aspect. But the incidence significantly increased in older age group (>30) among those with persistent trophoblastic disease (21%) compared to controls (1.9%). Majority of cases in older age group developed persistent trophoblastic disease (Table 1).

In this study, majority of cases (78%) belong to low socio-economic status. A 58% of controls belonged to low socioeconomic status (Table 2). It was found in this study that both the cases and controls were comparable with respect to blood groups. Blood group was not found to affect regression.

Period of gestation was not found to be an important factor affecting regression. Both cases and controls had similar distribution in the POA > 12 weeks and <12 weeks group.57% of both persistent and nonpersistent trophoblastic disease were in the<12 weeks group.42% of both were in the >12 weeks group (Table 3).

In this study, among cases 71% and among controls 34% has size of uterus more than period of amenorrhea (Table 4). This emphasizes the strong association between persistent disease and uterine size more than period of amenorrhea. In this study, 78% cases had pre-evacuation βhCG> 40000 and only 40% among controls had similar level. This was found to be statically significant. High pre-evacuation βhCG values are very important in determining the risk to develop persistent disease (Table 4). Presence of theca lutein cyst has been found to be an important factor affecting βhCG regression (Table 4). A 57% of those with theca lutein cysts developed persistent disease and only 26% of controls had lutein cysts.

Table 1: Maternal age and persistent trophoblastic diseases.

Age group	No. of persistent trophoblastic disease (N=14)	Percentage	No. of non-persistent trophoblastic disease (N=61)	Percentage
< 20	4	28.5	18	29.5
21-25	2	14.2	26	50.9
26-30	5	35.7	16	31.3
31-35	1	7.1	1	1.9
>35	2	14.2	0	0

($\chi 2 = 12.826$, $p = 0.012$)

Table 2: Socioeconomic status.

	No. of persistent trophoblastic disease	Percentage	No. of non-persistent trophoblastic disease	Percentage
Low	11	78.5	30	58.8
Middle	2	14.2	28	54.9
High	1	7.1	3	5.8

(χ2=4.75, p==0.093)

Table 3: Period of gestation.

	No. of persistent trophoblastic disease	Percentage	No. of non-persistent trophoblastic disease	Percentage
< 12 weeks	8	57.1	35	57.3
>12 weeks	6	42.8	26	42.6

(χ^2= 0.0, p = 0.987)

Table 4: Summary of all study variables affecting regression of βhCG.

Determinants	No. of PTD (N=14)		No. of non PTD (N=61)		Chi-square value	P- value
	Frequency	(%)	Frequency	(%)		
Maternal age						
<20	4	28.5	18	29.5	χ^2=11.176	p=0.010*
21-25	2	14.2	26	50.9		
26-30	5	35.7	16	31.3		
>30	3	21.3	1	1.9		
Socioeconomic status						
Low	11	78.5	30	58.8	χ^2=4.75	p=0.093
Middle	2	17.2	28	54.9		
High	1	7.1	3	5.8		
Period of gestation						
<12 weeks	8	57.1	35	57.3	χ^2=0.0	p=0.987
>12 weeks	6	42.8	26	42.6		
Type of mole						
Partial mole	2	14.2	22	36	χ^2=10.5	p=0.005*
Complete mole	10	71.4	39	63		
Choriocarcinoma	2	14.2	0	0		
Uterine size compared to period of gestation						
<period of amenorrhea (poa)	1	7.1	15	24.5	χ^2=6.56	p=0.038*
=poa	3	21.4	25	40.9		
>poa	10	71.4	21	34.4		
Pre-evacuation βhCG						
<40000	3	21.4	37	60	χ^2=6.56	p=0.038*
>40000	11	78.5	24	40		
Presence of theca lutein cysts						
Present	8	57.1	16	26	χ^2=5.001	p=0.025*
Absent	6	42.8	45	74		

(χ^2 = 2.65, p = 0.103)

Among cases 72% had complete moles and in controls 59% had complete moles.

Among cases 64% had post evacuation uterine subinvolution and 16% controls had subinvolution (Table 4).

Two patients each had hypertension and hyperthyroidism and they went on to develop persistent disease.

DISCUSSION

Incidence of GTD

One of the most interesting features of trophoblastic disease is the marked geographic variation in its distribution. These regional variations have been attributed to environmental factors and extrinsic factors. The incidence in our institution is 1 in178 deliveries.ie,

5.6 per1000 deliveries. Incidence in different parts of worldIndonesia-11.7/1000 pregnancies, Pakisthan-3.8/1000 pregnancies, USA-0.7/1000 pregnancies, middle east-4.5/1000.[5] The trophoblastic clinic in our institution caters to a large population of central Kerala. Our institution is a referral one. Also, there is increased awareness among medical personnel as well as the public and hence there are increased and early referrals. The incidence is quoted in the number of deliveries and not in the number of pregnancies. Ideally incidence must be found out using a population-based study and not a hospital based one, the denominator being pregnancies not delivery.

Age of the patient

Most authors agree that the risk of molar pregnancy increases sharply in women over the age of 40 years.[6,7] In young women under the age of 20 years, the risk is relatively increased, and this early peak may due to over reporting of pregnancies. Accordingly, to Remy et al, young women (20 years old) had significantly less malignant GTD and significantly less metastatic malignant GTD than did older women.[8] The present study shows that the mean age among patient was 24 years.

Incidence of persistent trophoblastic disease

In the present series incidence of persistent trophoblastic disease was 18.6%. This probably reflect the awareness of the condition by the patient and the meticulous follow up visits that they come for, thus enabling detection of any deviation from normal very early.

Factors affecting development of persistent trophoblastic disorders

A 14 cases with persistent trophoblastic disease were studied and 61 controls were recruited. In this study, maximum number of cases was seen in the age group 20-30. Both cases and controls were comparable in this aspect. But the incidence significantly increased in older age group (>30) among those with persistent trophoblastic disease (21%) compared to controls (1.9%). According to Ahyan et al, increase in post molar GTD is found in age group >35 years.[9]

Defects in premature or post mature ova are implicated for the risk. In this study, majority of patients belongs to low socio-economic status. Socioeconomic status was found to affect βhCG regression. Parazzini et al, reported that increase in risk of GTD was seen in lower socioeconomic status due to deficiency of Carotene.[10] It was found in this study that both the cases and controls were comparable with respect to blood groups. Number of vesicular mole cases was highest in B and O blood group. Blood group was not found to affect regression. According to study by Aziz MF et al, slow regression of βhCG was found in vesicular mole patients with B and O blood groups.[11]

Period of gestation was not found to be an important factor affecting regression. Among cases 57.1% had POA <12 weeks and among controls 57.3% had POA <12 weeks. Both cases and controls had similar distribution in POA >12 weeks.

In other studies, slow regression of βhCG was observed when diagnosed at late gestational age. In present study, the number of cases in the cell >12 weeks was less. This might be the reason that authors did not get results in concordance with other studies. According to Stone M et al, late regression of βhCG was seen at gestational age >12 weeks.[12] In this study, among cases 71% and among controls 34% has size of uterus more than period of amenorrhea. Among cases only 21% had uterine size = POA and 7.1% had uttering size <POA. This is seen as increased uterine size is associated with hydropic degeneration and increased trophoblastic hyperplasia with size of uterus more than POA. According to Tehan Kyu et al, large for dates uterus is associated with late regression of βhCG.[13] As found in other studies, presence of theca lutein cyst has been found to be an important factor affecting βhCG regression. In this study, it was found that 57% cases had theca lutein cysts and controls only 26% had theca lutein cyst. 42% cases did not have theca lutein cyst. This was found to be statistically significant. According to Gryzibowski et al, presence of prominent the calutein cyst is associated with late regression of βhCG.[14]Among cases 72% had complete moles and in controls 59% had complete moles. In cases 14.2% had partial moles. This finding was found in concordance with other studies. It was found to be statistically significant. Other studies like Rob et al, have found delay in βhCG regression in complete mole as statistically significant.[15] Studies like Neimann I et al, have found pre-evacuation βhCG as important factor in assessing regression.[16] In this study, 78% cases had pre-evacuation βhCG>40000 and only 40% among controls had similar level. This was found to be statistically significant. In this study, among cases 64% had post evacuation uterine subinvolution and 16% controls had subinvolution. This was found to be statistically significant. Similar finding was obtained by Tehan Kyu et al. In this study 14.2% cases had history of hyperthyroidism and preeclampsia. Thus, strong association was found between preeclampsia and hyperthyroidism, and late regression of βhCG. Number of cases of persistent trophoblastic disease was 14 proportion of persistent trophoblastic disease calculated was 18.6%. All these patients were given single agent chemotherapy with methotrexate. 12 patients (86%) responded well to chemotherapy. But two patients (14%) developed failure to single agent and combination chemotherapy was given. A patient had metastatic sub urethral nodule and responded well to single agent therapy. There was a rare case of primary choriocarcinoma of fallopian tube which presented with features suggestive of ruptured ectopic pregnancy for which laparotomy was done. During the follow up period, 5 patients came back to our clinic with next pregnancy of

which 3 delivered normally. One is an ongoing normal pregnancy. One patient who had persistent disease earlier ended up in missed abortion.

CONCLUSION

The incidence of gestational trophoblastic disease at Medical college, Kottayam was 1 in 178 births. There were 14 cases of persistent trophoblastic disorder among the 75 cases of vesicular mole studied over 2 years, i.e., 18.6%. The incidence of persistent disease was maximum at 26 -30 years. Age, blood group, period of gestation was not found to affect progression to persistent disease. Persistent trophoblastic disease was associated with low socioeconomic status and uterine size >POA. Pre-evacuation βhCG> 40000 and presence of theca lutein cysts were associated with persistent trophoblastic disease. Most of the patients responded well to single agent chemotherapy. The disease spectrum in GTN varies from benign to malignant. While it can almost always be treated successfully, even hydatidiform mole can be fatal if unattended. It is important that the condition be diagnosed early for intervention and chemotherapy.

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