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A PROSPECTIVE OBSERVATIONAL STUDY ON CLINICAL PROFILE AND OUTCOME OF GESTATIONAL TROPHOBLASTIC DISEASE IN A TERTIARY CARE CENTRE

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ABSTRACT

Aim and background: To study the demographics and clinical profile of women diagnosed with gestational trophoblastic disease. Also aims to study the outcome of gestational trophoblastic disease in a period of 1 year.

Methods: This prospective observational study was conducted in 76 women who were diagnosed with gestational trophoblastic disease (GTD) in a tertiary care centre in South Kerala. Detailed history, clinical findings, investigations like TSH level, serum βhCG levels,USG findings were noted. These women were followed up for 1 year with βhCG values and is assessed on each follow up visit for findings consistent with gestational trophoblastic neoplasia (GTN) and remission. Variables were compared with type of hydatidiform mole: complete and partial mole and statistical significance assessed. To show the differences between pre-evacuation and post evacuation βhCG values, paired t test was used.

Results: 76 patients were included in the study population and followed up for 1 year.76.4% of the patients belonged to 21-29yrs age group with mean age 25.4±4.29years.48.7% were primigravidae and the mean gestational age of presentation was 7±3weeks.61.8% presented with routine USG showing features of hydatidiform mole and 32.9% with vaginal bleeding.56.6%patients in the study group had a preevacuation βhCG >1lakh mIU/ml.76.3% patients were complete mole and 23.7% were partial mole. On follow up,14.47% of patients developed GTN;3 were invasive mole and one woman developed recurrent mole. Others had remission mostly within 8 weeks after evacuation. All patients with GTN treated with chemotherapy.6 patients were lost to follow up.

Conclusion: Early diagnosis of GTD is effectively possible with routine ultrasonography and the incidence of complications due to GTD is significantly reduced. Timely diagnosis, appropriate treatment, adherence to follow up and contraception ensures 100% cure. βhCG remains the reliable marker for diagnosis and follow up. Follow up of patients and awareness among population remains a challenging task.

Clinical significance: This study builds a platform to know the demography of GTD, its clinical features, various forms, importance of antenatal USG, βhCG monitoring, warning signs of GTN and to assess the compliance to follow up and contraception among GTD patients. Patient can be counselled regarding the natural history of this disease, its progression, need of follow up as well as contraception. Population based study should be proposed rather than hospital-based study to reveal the actual burden this disease in our population.

Keywords: Gestational trophoblastic disease, complete mole, partial mole, βhCG, Gestational trophoblastic neoplasia

INTRODUCTION

Gestational trophoblastic disease (GTD) is a spectrum of disorders associated with pregnancy characterized by abnormal proliferation of trophoblastic tissue and hydropic degeneration of villi with varying tendency to spontaneous remission, local invasion, and metastasis. It includes partial and complete hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), epithelioid trophoblastic tumour (ETT). The GTD spectrum has recently expanded to include atypical placental site nodule (APSN) as 10-15% may coexist or develop into PSTT/ETT. Molar

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pregnancies represent a significant burden of disease, benign in most cases, sometimes may develop into invasive mole or in rare cases, into choriocarcinoma, which is very sensitive to chemotherapy and has a good prognosis.

Recent studies shows that the routine use of antenatal ultrasound leads to early diagnosis of molar pregnancy. Diagnosis of molar pregnancy is based on a combination of clinical history, physical examination, serum βhCG levels, ultrasound. βhCG is an excellent marker of disease progression, response and subsequent post treatment surveillance. Suction evacuation is the treatment of choice and diagnosis is confirmed by histopathology. Early diagnosis of GTD is essential for timely and successful management with fertility preservation. The aim of this study is to determine the clinical profile and outcome of gestational trophoblastic disease. It is difficult to predict the outcome at the time of diagnosis, hence patient is followed up with serial quantitative βhCG measurements after suction evacuation to allow early diagnosis and treatment of persistent trophoblastic neoplasia. The serum βhCG level is expected to decline atleast by 6 to 8 weeks after uterine evacuation, and monitored weekly. After three consecutive normal results, serum βhCG levels are checked on a monthly basis for next six months, in order to detect recurrence and malignancy. According to International Federation of Gynecology and Obstetrics (FIGO), gestational trophoblastic neoplasia (GTN) is identified by the following criteria, a plateau in the serum βhCG level for 4 measurements, more than 3 consecutive weeks, an elevated serum βhCG level for more than two consecutive weeks, histopathological diagnosis of choriocarcinoma. The treatment of GTN essentially consists of chemotherapy.

Careful and reliable human chorionic gonadotrophin monitoring is essential and that remains challenging. At follow up, patient should be assessed for persistent bleeding per vaginum, hypertension, signs of preeclampsia, features of hyperthyroidism, presence of sub urethral nodules. The purpose of this research is to understand the clinical profile of gestational trophoblastic disease and to study outcome and compliance to βhCG monitoring and follow up in a period of 1 year.

OBJECTIVES
- To study the demographics and clinical profile of women diagnosed with gestational trophoblastic disease
- To study the outcome of gestational trophoblastic disease in a period of 1 year

METHODOLOGY
This is a hospital based prospective observational study conducted in the department of Obstetrics & Gynecology, Sree Avittom Thirunal Hospital,Thiruvananthapuram; a tertiary care centre after obtaining the ethical committee approval and written signed consent from the participants. The study period was 18 months from obtaining Institutional Ethical Committee Clearance, July 2021-December 2022. All study subjects were followed upto 1 year after evacuation. Women diagnosed with gestational trophoblastic disease histopathologically attending SAT hospital; Thiruvananthapuram were included in the study. Women with GTD who were not willing to give consent for study were excluded.

DATA COLLECTION TOOLS AND TECHNIQUE
Data collection was mainly done by using a structured proforma. Medical records were also used. 76 subjects were studied by taking detailed history including age, place, chief presenting complaints, gravidity, gestational age, outcome of previous pregnancies, menstrual history of each case.

The clinical examination includes nutritional status, height, weight, BMI, general examination findings, size of uterus per abdomen to check whether it corresponds to period of gestation. A difference of at least 4weeks between uterine size and gestational age is considered significant. Per speculum and per vaginal examination findings were noted.Blood investigations including Hb, blood grouping and Rh typing, TSH, serum βhCG levels were noted. Ultrasound findings were included. As a primary mode of management, suction evacuation was done followed by gentle curettage. The samples obtained were sent for histopathological examination and reports were collected. Serum βhCG was repeated after 48hrs of evacuation. Post evacuation USG be done for subjects with excessive or irregular vaginal bleeding and repeat evacuation was done for those subjects with evidence of retained molar tissue on post evacuation USG.

The subjects were followed up with proper counselling regarding the importance of follow up and contraception. Weekly follow up was done until normal βhCG values for 3 consecutive weeks, for one more month in case of partial mole and monthly until normal βhCG values for 6 consecutive months for complete mole. The normal level of βhCG will be taken as ≤5 m IU/mL. The time to achieve the first normal βhCG value after evacuation is noted. GTN is diagnosed during follow up either on the basis of rise in serum βhCG levels or histopathology or with evidence of metastasis. The patient is assessed on each follow up visit for findings consistent with GTN which include bleeding per vaginum, chest Xray, sub urethral nodule, theca lutein cysts, other systemic findings. Those diagnosed with GTN is classified as low risk or high risk using FIGO scoring system for GTN and were treated with chemotherapy.

ANALYSIS

The data thus collected were analyzed with statistical software SPSS Version 25.0. Various statistical methods like descriptive statistics (mean, median, range and standard deviation), chi square test, independent t test and paired t test were employed for analysis. Descriptive analysis was performed for summarizing demographic and clinical variables of study patients. Continuous variables were summarized by using mean, standard deviation, median, minimum and maximum, while categorical variables were summarized by using proportions. The descriptive analysis results were demonstrated graphically wherever necessary. Clinical variables were compared using Chi square tests between pre-defined sub groups of the study cohort. To show the differences between pre-evacuation and post evacuation βhCG, paired t test was used. For several continuous variables, comparison of means between sub groups was performed using independent t test. All p-values reported are based on two-sided tests, and p-values <0.05 are considered to be significant, unless otherwise specified.
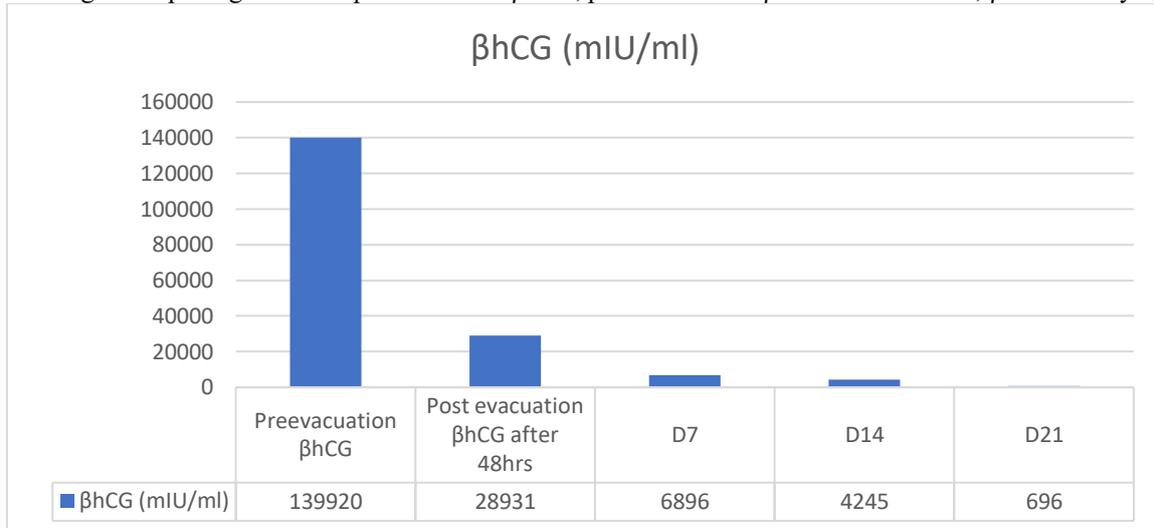
RESULTS

During the study period from July 2021 to December 2022,76 study subjects diagnosed with GTD were studied and followed up. Clinical variables were analyzed using Chi square tests between pre-defined subgroups. 76.4% subjects belonged to the age group 20-29 years. 44.8% primi gravida and 55.2% multigravida were diagnosed with complete mole.61.1% primi gravida and 38.9% multigravida were diagnosed with partial mole. Most of the subjects were diagnosed with GTD at a period of gestation 9 to 12 weeks.61.8% were diagnosed to have hydatidiform mole by using early antenatal USG. It was found that age, BMI, blood group, gravidity, gestational age at diagnosis, antecedent pregnancy, uterine size at diagnosis, hemoglobin level, thyroid status, presence of theca lutein cyst have no statistically significant association with type of hydatidiform mole. Among the hyperthyroid subjects, 90% were diagnosed to have complete mole. There is no statistically significant association between need of blood transfusion and type of hydatidiform mole. All the subjects presented with persistent bleeding per vaginum after abortion evacuation were finally diagnosed to have partial mole (5.3%). There is significant association between clinical presentation and type of hydatidiform mole (p value <0.05). 65.5% subjects with complete mole had preevacuation βhCG ranges from 1 lakh to 10 lakhs mIU/ml. Maximum value is 6,59,205 mIU/ml and minimum value is 1032 mIU/ml. This study shows significant association between preevacuation βhCG and type of hydatidiform mole (p value=<0.05). No significant association found between need of reevacuation and type of hydatidiform mole. Out of 11 patients who developed GTN during follow up period,7 subjects (63.6%) required reevacuation. But 2 subjects who required reevacuation had spontaneous remission. This study shows significant association between need of reevacuation and final outcome of GTD (p value <0.05)(Table 2). Among the subjects who developed GTN,8 subjects were complete mole and 3 were partial mole. This study shows no association between outcome during follow up and type of hydatidiform mole.

Fig 1: Pie diagram showing histopathological diagnosis of study subjects
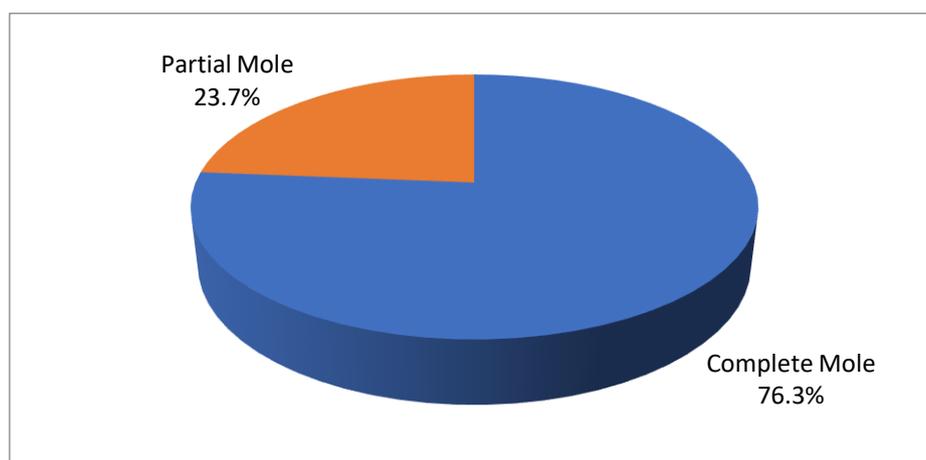
Clinical comparison was done between complete mole & partial mole using paired t test. Maternal age showed no statistical significance. The association between mean βhCG value on day7 and type of hydatidiform mole is statistically significant. A significant association is noted between mean βhCG value after 48hrs, day 7, day 14, day 21 of evacuation and final outcome of GTD. Also,there is significant association between mean time to attain first βhCG and final outcome. Among these study subjects,the mean±SD of preevacuation βhCG is 139920.8 ± 102193.4 mIU/ml,median is 116766, minimum value is 1032 and maximum value is 659105.The mean Post evacuation βhCG after 48hrs is 28931.7 ± 36376.1mIU/ml.

Fig 2: Bar diagram depicting the mean preevacuation βhCG, post evacuation βhCG after 48hours, βhCG on day 7,14,21

βhCG (mIU/ml)

	Preevacuation βhCG	Post evacuation βhCG after 48hrs	D7	D14	D21
βhCG (mIU/ml)	139920	28931	6896	4245	696

The line showing βhCG pattern of patients who developed GTN during follow up highlights the plateauing of βhCG levels during first 2 weeks post evacuation (Fig 3). Partial mole and invasive mole demonstrate similar regression pattern.

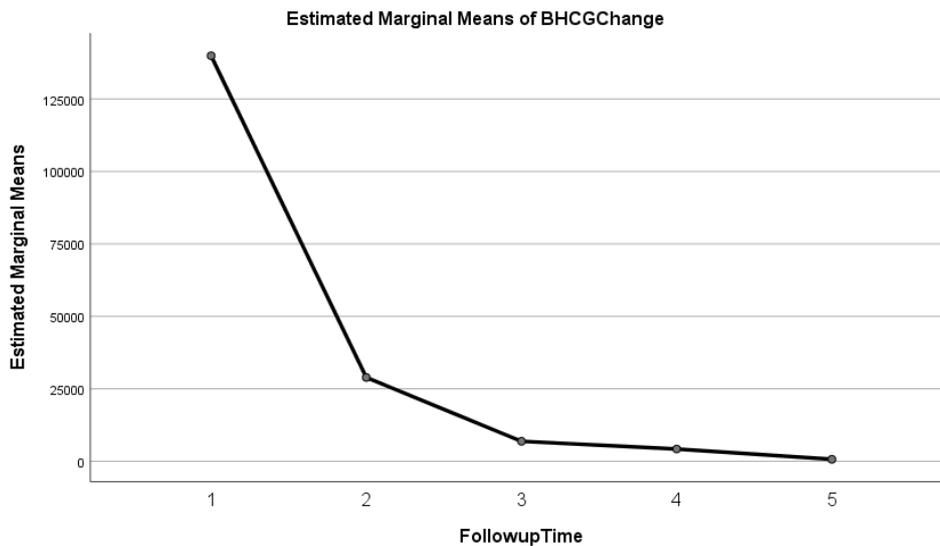Fig 3: Line diagram depicting the estimated marginal mean of βhCG fall

Estimated Marginal Means of BHCGChange

Fig 4: Line diagram depicting the βhCG regression in 1st 3 weeks of follow up

βhCG REGRESSION PATTERN

250000
200000
150000
100000
50000
0

Preevacuation bhCG | Post evacuation after 48hrs | D7 | D14 | D21

— Complete mole — Partial mole — Invasive mole — GTN
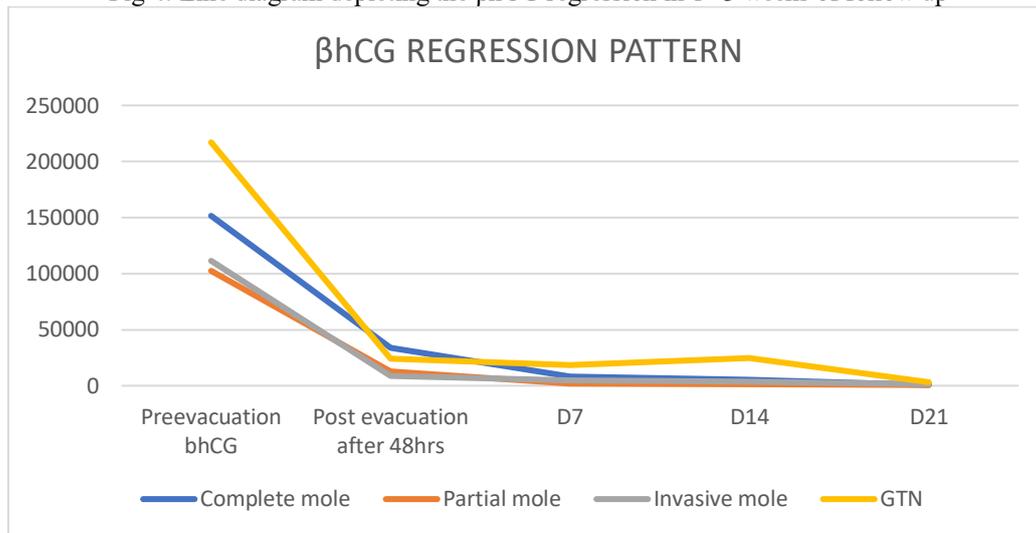
Table:1

Variables	Complete mole		Partial mole		χ^2	p
	Count	Percentage	Count	Percentage		
Age group(yrs)						
16-19	5	8.6	2	11.1	3.613	0.461
20-24	25	43.1	4	22.2		
25-29	20	34.5	9	50		
30-34	6	10.3	3	16.7		
40-45	2	3.4	0	0		
BMI						
<15	2	3.4	0	0	1.948	0.745
15-19.9	24	41.4	10	55.6		
20-24.9	25	43.1	7	38.9		
25-29.9	6	10.3	1	5.6		
30-34.9	1	1.7	0	0		
Gravidity						
Primi	26	44.8	11	61.1	1.458	0.227
Multigravida	32	55.2	7	38.9		
Gestational age at diagnosis						
<8weeks	14	24.1	9	50	4.560	0.102
9-12weeks	36	62.1	8	44.4		
13-20weeks	8	13.8	1	5.6		
Clinical presentation						
Bleeding per vaginum	20	34.5	5	27.8	13.61	0.001
Routine USS finding	38	65.5	9			
Persistent bleeding after abortion evacuation	-	-	4	22.2		
Antecedent pregnancy						
Nullipara	26	44.8	11	61.1	1.641	0.650
Term delivery	22	37.9	5	27.8		
Abortion	9	15.5	2	11.1		
Ectopic	1	1.7	-	-		
Vesicular mole	-	-	-	-		
Uterine size						
Corresponding	35	60.3	13	72.2	4.704	0.095
>Gest age	23	39.7	4	22.2		

					χ^2	p
<Gest age	-	-	1	5.6		
Blood group						
A+	20	34.5	8	44.4	1.832	0.767
B+	14	24.1	3	16.7		
O+	16	27.6	6	33.3		
AB+	6	10.3	1	5.6		
O-	2	3.4	-	-		
Hemoglobin level(gm%)						
<7	1	1.7	-	-	4.46	0.216
7-9.9	4	6.9	1	5.6		
10-11.9	33	56.9	15	83.3		
>12	20	34.5	2	11.1		
Thyroid status						
Euthyroid	40	69	14	77.8	1.198	0.549
Hypothyroid	9	15.5	3	16.7		
Hyperthyroid	9	15.5	1	5.6		
Theca lutein cyst						
Present	7	12.1	-	-	2.393	0.122
Absent	51	87.9	18	100		
Preevacuation βhCG(mIU/ml)						
10^3-10^4	2	3.4	1	5.6	8.031	0.018
10^4-10^5	18	31	12	66.7		
10^5-10^6	38	65.5	5	27.8		
Need of reevacuation						
Yes	5	8.6	4	22.2	2.434	0.119
No	53	91.4	14	77.8		

Table 2: Association between need of reevacuation and final outcome of GTD

	Spontaneous remission		GTN		χ^2	p
Reevacuation	Count	Percentage	Count	Percentage		
Yes	2	3.1	7	63.6	33.05	<0.001
No	63	96.9	4	36.4		

Table 3: Comparison of groups-Spontaneous remission and GTN

	Spontaneous remission		GTN		t test	
	Mean	SD	Mean	SD	t	p
Age in years	25.8	5.6	24.0	3.6	1.009	0.316
Preevacuation βhCG	126859	77395.5	217104	179799.5	2.833	0.006
βhCG after 48 hrs	29709.8	38011.6	24333.4	25489.3	0.451	0.653
Day 7	4934.3	9003.0	18489.4	31675.3	2.899	0.005
Day 14	832.4	1228.0	24413.0	66690.9	2.947	0.004
Day 21	281.7	359.5	3146.1	3700.9	6.271	0.000
Time to attain 1st normal βhCG(weeks)	6.4	1.9	6.9	4.8	6.189	0.000

DISCUSSION

Gestational trophoblastic disease is a rare disorder which has malignant potential. There are geographical variations in the incidence of GTD and Asian women are at high risk to develop molar pregnancies than non-Asians. Many countries around the world assess the incidence, demographics and clinical progression of GTD and develops epidemiological data

reports on their population. But, in India only few studies have been conducted on GTD and national level infrastructure or programme for the detection, management, follow up and formulation of epidemiological data of GTD is not yet established. In such a scenario, institution-based studies will provide some light on the epidemiological data, clinical profile, outcome and compliance to follow up.

76 patients diagnosed with gestational trophoblastic disease attending the vesicular mole clinic of department of obstetrics and gynecology at Sri Avittom Thirunal Hospital in Thiruvananthapuram district were recruited. This study is an effort towards understanding the clinical profile, management, follow up pattern, compliance to follow up of patient diagnosed with GTD. Majority of the patients belonged to the age group 20-29years (76.4%).38.2% in each age group of 20-24 years and 25-29 years. Mean age was found to 25.4±4.29 years ranging from 18 years to 45 years.There is no significant association noted between the age group and outcome of molar pregnancy. In a study conducted by Neeta Kumar et al. in India, majority of patients (66%) belonged to age group of 20-25years.Some studies consider extremes of age group as a risk factor for GTD.

In the present study, more than half of patients (51.3%) are multigravida and 48.7% patients are primigravida.35.5% had a previous term delivery,14.5% patients had previous abortion and 1 patient had previous ectopic pregnancy.None of the subjects had prior molar pregnancy. In a study conducted in Mysore, India;40.3% patients were primi gravida.
Majority of women (57.9%) presented at 9-12 weeks of gestation. In a study conducted in Malaysia by Nirmala C K et al., the mean gestational age of presentation is 11±3 weeks which is comparable with this study. But, a study in Uganda showed that mean gestational age of diagnosis was 17 weeks.In this study, 61.8% of the study subjects presented with routine USG showing features of molar pregnancy,32.9% presented with vaginal bleeding.The commonest symptom reported in majority of cases including large series study by Goldstein was vaginal bleeding. 51% patients presented with USG findings of GTD in a study conducted by Tasneem et al. In 2003, only 6.5% of study population were symptomless GTD presented with routine USG showing molar pregnancy. This early detection in first trimester of GTD is due to the effective use antenatal USG. None of the study subjects had passage of vesicles per vaginum.

In this study, 35.5% women had uterine size more than the period of amenorrhea when compared to 63.2% with uterine size corresponding to gestational age. A study by Nirmala C K et al.observed only 17.6% with larger uterine size while Fatima et al. and A A Al -Muhim etal. Saudi Arabia reported 70.6% and 62% subjects with larger uterine size respectively. Among 76 patients, only 9.2% had theca lutein cysts and only 2 of them developed GTN. But in some other studies like Kumar et al[65], 34.7 % had theca lutein cysts and 39% in a study conducted by Fatima et al. Majority (71%) of the patients in this study were euthyroid,15.8% were hypothyroid and 13.2% were hyperthyroid. Molar pregnancy induced hyperthyroidism is rare but potentially life threatening; presentations can range from thyrotoxicosis to thyroid storm. One patient in this study had features of thyrotoxicosis. None of the patients had features of preeclampsia and suburethral nodules.
Contrary to other published studies,63.2% patients had a hemoglobin level 10-11.9gm%. Only 6.6% required blood transfusion. In a study conducted in Mysore, India;78.85% patient had Hb <10gm%. In a study conducted in Nepal,60% of study subjects with GTD required blood transfusion. Chest Xray of each study subjects in this group showed no abnormal findings. Higher modality imaging was done in selected GTN cases and found to have metastatic lung lesions in a patient with invasive mole.
In this study,56.6% subjects showed preevacuation βhCG value more than 1,00,000mIU/mL.The mean preevacuation βhCG value is higher in complete mole when compared to partial mole.This study shows significant association between preevacuation βhCG and type of molar pregnancy with a p value 0. 018.Similar observations were seen in several studies conducted in India as well as other countries. In the present study, histopathological examination of 76 subjects reported that 76.3% were complete mole and 23.7% were partial mole. Nirmala C K et al. in Malaysia reported only 47.1% complete mole,but 52.95% partial mole.A study conducted by Krishnappa et al. observed 76.6% CHM,20% partial mole and 3.33% invasive mole. Charlotte Lybol et al.reported 30.2% CHM and 44.5% PHM and rest unspecified.
Among the 76 study subjects,36.8% achieved first normal βhCG in 8-10 weeks of follow up. The mean duration is 7±3.06 weeks with a minimum and maximum of 3 and 24weeks respectively. Complications associated with GTD like sepsis, hemorrhage, uterine perforation was few in this study. One patient developed torrential hemorrhage which was promptly managed with evacuation of uterus and multiple blood transfusion.9 patients required reevacuation due to persistent bleeding per vaginum and retained products of conception in follow up USG. All 76 study subjects were followed up with serial βhCG monitoring & clinical examination. 6 study subjects were lost to follow up. During the follow up period,3 subjects showed deviation from the mean βhCG regression pattern over 3 weeks postevacuation (D21); developed GTN. Hence it is important to monitor βhCG to facilitate early detection of GTN.
In this study,85.52% patients had spontaneous remission. 11 patients (14.47%) were diagnosed with GTN in the follow up period.8 complete mole and 3 partial mole cases developed into GTN. Among them 3 were diagnosed invasive mole and none developed choriocarcinoma. All 11 patients took chemotherapy;1 patient required multi agent chemotherapy with methotrexate, actinomycin D and leucovorin and rest of the patients were managed with single agent chemotherapy. One patient with GTN later developed recurrent mole within 1 year of follow up due to noncompliance to contraception. Krishnappa et al. studied 30 cases, observed 9 cases (30%) of GTN, out of which 6 were persistent trophoblastic disease,

3 were invasive mole and none choriocarcinoma. Another study by Kumar et al. reported 23% invasive mole cases and 14% choriocarcinoma. A study conducted in Mysore reported 3 GTN (5.7%) cases and all of them were invasive mole.

In this follow up study,76 subjects were followed up,69 women (90.3%) showed compliance to follow up.6 women (8%) lost to follow up after 1st normal βhCG and none lost follow up prior to achieving 1st normal βhCG. One subject became pregnant during follow up period as a result non adherence to contraception and diagnosed recurrent mole. Krishnappa et al. observed 93.33% compliance to follow up and 3.33% lost to follow up before attaining first normal βhCG. Some studies have reported poor compliance to follow up (34.62%).

LIMITATIONS
- This study is based on hospital-based data that may not reflect the incidence and burden of GTD in the population
- Follow up remains a challenging task

CONCLUSION
Various epidemiological studies have found that Asian ethnicity is at high risk for gestational trophoblastic disease. Early diagnosis of gestational trophoblastic disease is effectively possible with routine antenatal ultrasonography, thereby the incidence of complications due to GTD is significantly reduced.

Timely diagnosis, appropriate treatment, strict adherence to follow up ensures 100% cure. βhCG remains the reliable marker for diagnosis as well as follow up. Suction evacuation, a simple surgical intervention is the preferred modality of treatment. Follow up of patients, adherence to contraception during follow up period and awareness among population remains a challenging task. Longer period of follow up for uncomplicated GTD must be avoided.

A multicentered population-based study is necessary in India to determine the incidence and burden of gestational trophoblastic disease in our population. A centralized registry, database, website, management protocol is a essential for the effective management and to ensure 100% cure of this rare completely curable disease.

CLINICAL SIGNIFICANCE
Molar pregnancies represent a significant burden of disease affecting the women in reproductive age group, mostly benign, but has a malignant potential, which is sensitive to chemotherapy and has a good prognosis. Most women with GTD can be successfully managed with fertility preservation. It is important to manage molar pregnancies properly to minimize acute complications and to identify GTN promptly. Routine antenatal ultrasonography facilitates early diagnosis of gestational trophoblastic disease. Thus, there is a tremendous decline in incidence of acute complications and appropriate treatment can be initiated timely. Follow up of GTD patients with serial monitoring of βhCG plays a major role in detection of GTN. Contraception advice should be effectively implemented. The duration of hCG monitoring varies depending on histologic type and regression rate.

This study builds a platform to know the demography of GTD, its clinical features, various forms of GTD, importance of antenatal USG, βhCG monitoring, warning signs of GTN. It is also a chance to assess the compliance to follow up and contraception among GTD patients. Patient can be counselled regarding the natural history of this disease, its progression, need of follow up as well as contraception until necessary. Population based study should be proposed rather than hospital-based study to reveal the actual burden this disease in our population.

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