

Gestational Trophoblastic Diseases: Outcome at a Tertiary Care Centre in Central India.

Dr. Rohit S. Dimbar¹, Dr. Aparna Wahane², Dr. Dharmendra R. Raut³,
Dr. Madhuri G. Dhakne⁴, Dr. Sushma S. Deshmukh⁴

¹ Junior Resident, Department of Obstetrics and Gynecology, Government Medical College Akola.

² Professor and Head of Department, Department of Obstetrics and Gynecology, Government Medical College Akola.

³ Associate Professor, Department of Obstetrics and Gynecology, Government Medical College Akola.

⁴ Assistant Professor, Department of Obstetrics and Gynecology, Government Medical College Akola.

Abstract:

Background: Gestational trophoblastic disease (GTD) is a spectrum of disorders arising from the placenta which hold good prognosis if diagnosed and treated on time. The Indian subcontinent is under reported for this disorder, so a study to understand the demographic pattern and incidence of GTD in the region was necessary.

Materials and Methods: This was prospective and observational study carried out in the Department of Obstetrics and Gynaecology, Government Medical College Akola, Maharashtra, India from January 2019 to January 2021. Diagnosis of gestational trophoblastic diseases was made by ultrasonography or histopathological examination. The demographic details, presentation, management and follow up were studied.

Results: During the study period 19828 pregnant ladies were registered of which 17587 were deliveries and live births were 16,953, respectively. Fifty-five women were diagnosed of Gestational trophoblastic disease. The incidence of GTD came out to be 2.77 per 1000 pregnancies, 3.12 per 1000 deliveries and 3.24 per 1000 live births. Most patients were primigravidae presenting in First trimester with Ultrasonography features. All women had raised hCG levels and treated mostly with Suction and Evacuation.

Conclusion: Newer diagnostic imaging and biochemical testing have aided in reducing the time of presentation of GTD and decreased the mortality and morbidity due to GTD. Ultrasonography plays a key role in earlier diagnosis and better management of GTD. Majority of the cases are treated by suction evacuation. To determine the actual prevalence of GTD in India, a multi centric study and centralized disease specific registry for GTD should be established.

Key Word: Gestational Trophoblastic disease, Hydatidiform mole, GTD Follow up

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I. Introduction

Gestational trophoblastic disease (GTD) comprises a spectrum of disorders characterized by an abnormal proliferation of trophoblastic tissue with varying tendencies for spontaneous remission, local invasion and metastasis. Variation in the worldwide incidence rates results due to discrepancies in population based and hospital-based data(1).

Hydatidiform moles are being diagnosed at early gestational ages in the past 10 years due to the widespread use of routine first-trimester ultrasound examination and ultrasound investigation of threatened miscarriages(2,3). Most of the cases of GTD are cured by simple surgical intervention while those requiring chemotherapy are generally cured with very low toxicity regimen. Unlike other gynaecological malignancies, fertility can be preserved, and normal pregnancy outcome achieved in future. The curability of this condition is a milestone of success in the history of modern medicine(4). Even after being highly curable, many patients succumb to Gestational Trophoblastic Neoplasia (GTN) in our country due to the lack of proper and organized follow up programs. It is therefore important to have the regional registries for the proper understanding of this unique malignancy. This will help in making decisions, optimizing management, preventing treatment failure(5) and identifying possible areas of improvement.

Regular monitoring is needed to ensure full regression of disease. However, a lengthy timeframe for follow-up results in poor compliance and an increased number of defaulters. Women are highly recommended to continue follow-up for up to 6 months to enable detection of relapses or persistent gestational trophoblastic disease (pGTD)(6). The long protocol may create a significant burden to the woman and her family and may also delay future conception(7). GTD has a discrete pool of epidemiological and clinico-pathological entities. Some predisposing factors have a specific geographic character. Therefore, every geographical region should be

studied separately. The Indian subcontinent is under-reported for this disease. The Asian descent has been reported as a risk factor for GTD(8). This indicates that emphasis on detailed study of GTD and its follow up in Asian countries may help in revealing its geographical distribution in a clearer way(9).The present study pertains to a tertiary health care center in Central India.

II. Material And Methods

The present study was a Prospective and observational study carried out in the Department of Obstetrics and Gynaecology, Government Medical College Akola, Maharashtra, India from January 2019 to January 2021. Fifty-five (n=55) women with diagnosis of Gestational trophoblastic disease and admitted in Department of Obstetrics and Gynaecology, Government Medical College Akola, Maharashtra, India were enrolled in the study after fulfilling the inclusion criteria. Diagnosis of gestational trophoblastic diseases was made by ultrasonography or histopathological examination. Detailed study pattern and importance were explained to study participants. The baseline investigations were done after enrolment (day 0).

INCLUSION CRITERIA:

- Patients with diagnosis of gestational trophoblastic disease (ultrasonography or histopathological examination).
- Patients willing to take part in study and giving informed written consent.

METHOD OF COLLECTION OF DATA:

A pre-designed case record form was used to collect demographic details like name, age, address along with data about physical examination and clinical history. The patients were subjected to USG if not previously done and their findings were recorded in case record form. As a primary mode of management, suction and evacuation was done for all patients followed by gentle curettage. Injection Anti-D (50 mcg if pregnancy was 1st trimester and 300 mcg for pregnancy exceeding 1st trimester) was given to Rh negative women. The serum β -hCG was repeated 48 hours after evacuation.

Then the patients were counselled regarding the need for follow up and use of contraception for the entire period of follow up. Follow up was done with weekly Sr. β -hCG until normal for 3 consecutive weeks followed by monthly determination until the levels were normal for 6 consecutive months. The normal level of Sr. β -hCG was taken as less than 10 mIU/mL. GTN was diagnosed during follow up either based on a rise in Sr. β -hCG levels or histopathology or with evidence of metastasis. Those diagnosed as GTN were classified as low risk or high risk using FIGO scoring system for GTN.

STATISTICAL ANALYSIS:

Incidence rate was calculated by the number of cases of gestational trophoblastic diseases reported to the institution for treatment during the study period for every 1000 pregnant women during the same period. Descriptive analyses were performed for summarizing demographic and clinical variables of study patients. Continuous variables were summarized by using mean, standard deviation, while categorical variables were summarized by using proportions. 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 Sr. β -hCG levels, paired t test was used.

III. Result

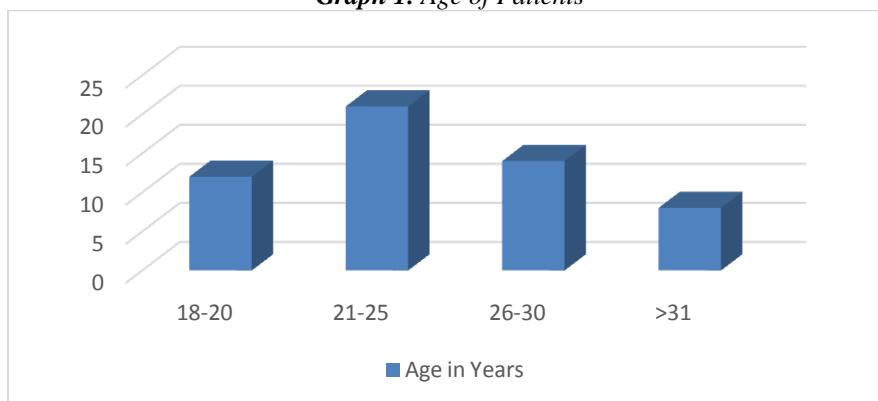
During the study period we had 19828 pregnant women which included live births, still births, abortions, MTP and ectopic pregnancies. Total number of deliveries and live birth were 17587 and 16953, respectively. Fifty-five (n=55) women were diagnosed of Gestational trophoblastic disease and enrolled in the study. So, the incidence of GTD came out to be 2.77 per 1000 pregnancies, 3.12 per 1000 deliveries and 3.24 per 1000 live births.

The mean age of the patients was 24.76 ± 4.02 years, median age was 23 years and 35 (63.63%) of the patients, belonged to 3rd decade of their life. Vaginal bleeding was the common presenting symptom. But 58.18% (32) patients were asymptomatic and presented with USG findings of Molar pregnancy. Other complaints like passing of grape like vesicles PV, excessive vomiting, pain in abdomen, mass in abdomen and hypertension were rarely found. In this study primigravida (24) patients were more when compared to multigravida (21). The antecedent pregnancy was term pregnancy in 36% (20) patients while 16% (9) and 3.63% (2) had history of abortion and mole respectively in previous pregnancy. Maximum number of patients presented in the first trimester of gestation with mean gestational age being 13.07 ± 3.83 weeks and majority of the patients had uterine size larger than the period of gestation. Table 1. summarizes the above findings.

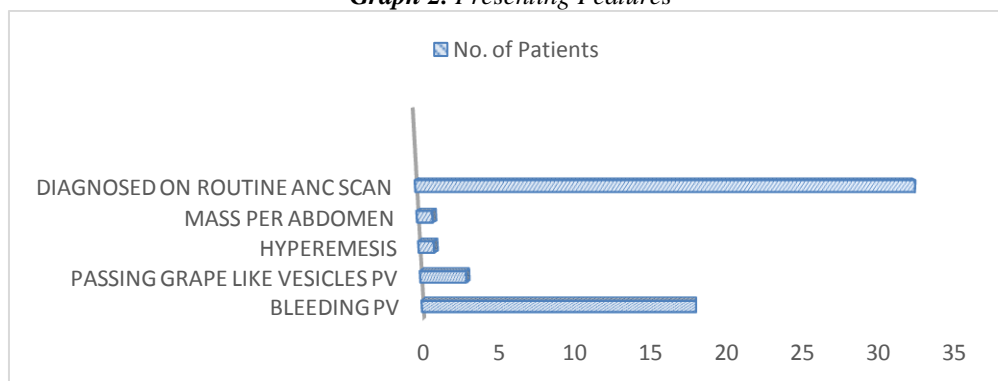
Table 1. Characteristics of the Population

PARAMETER	GROUP	NUMBER OF PATIENTS	MEAN ± SD	RANGE
AGE (in years)	18-20	12	24.76 ± 4.02	18-40
	21-25	21		
	26-30	14		
	>31	8		
PRESENTATION	BLEEDING PV	18		
	PASSING GRAPE LIKE VESICLES PV	3		
	HYPEREMESIS	1		
	MASS PER ABDOMEN	1		
	DIAGNOSED ON ROUTINE ANC SCAN	32		
ANTECEDENT PREGNANCY	PRIMIGRAVIDA	24		
	ABORTION	9		
	LIVE BIRTH	20		
	MOLAR PREGNANCY	2		
GESTATIONAL AGE (in Weeks)	≤ 8	10	13.1 ± 3.83	6-26
	9-12	22		
	13-20	19		
	≥ 20	4		
UTERINE SIZE wrt LMP	SMALLER	8		
	CORRESPONDING	19		
	LARGER	28		

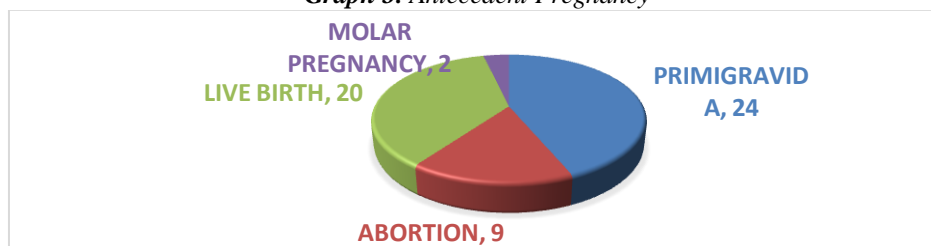
Graph 1. Age of Patients



Graph 2. Presenting Features



Graph 3. Antecedent Pregnancy



Graph 4. Gestational Age (In Weeks)

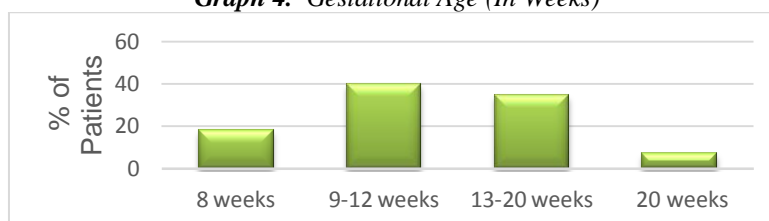


Table 2. shows the pre- and post- evacuation Sr. β -hCG levels. After suction evacuation maximum number of patients had Sr. β -hCG levels below 1 lac. 28 (51%) patients had Sr. β -hCG below 10,000 and 22 (40%) patients had Sr. β -hCG levels between 10,000-1,00,000 post evacuation.

Table 2. Pre and Post Evacuation Sr. β -hCG levels

Sr. β -hCG level (mIU/mL)	Pre-evacuation Sr. β -hCG levels	48 Hour Post-evacuation Sr. β -hCG levels
$\leq 10,000$	0	28
10,000-1,00,000	24	22
1,00,000-10,00,000	27	5
$\geq 10,00,000$	4	0

Table 3. shows statistically significant difference was present in β -hCG levels pre- and post-evacuation.

Table 3. Comparison of Mean Pre-evacuation and 48 hours Post-evacuation Sr. β -hCG levels.

Variable	Statistics/Category	Pre evacuation	48 Hour Post evacuation
Sr. β -hCG level	N	55	55
	Mean \pm SD	262422.66 \pm 204512.20	24686 \pm 24658
	Min-Max	(18562 - 14,45,821)	(1008 - 1,38,930)
	Paired t test (to find difference between pre- and post- evacuation β -HCG level)		
	P value	<0.0001*	Statistically significant

Table 4. indicates that majority of the patients (69.08%) had taken 7-10 weeks before β -hCG became normal and the mean time was 8.31 ± 1.96 weeks. 2 (3.63%) patients had persistently high Sr. β -hCG levels even after 12 weeks and 6 patients were lost to follow up before first normal Sr. β -hCG.

Suction evacuation was done in 53 (96.36%) patients. Hysterectomy was done in 2 (3.63%) patients as both patients had features suggestive of invasive mole on USG and completed their family. Complications were uncommon, only few patients had hemorrhage and fever.

Table 4. Time for normalization of Sr. β -hCG

Time taken for Sr. β -hCG to become normal	Number of patients	Percentage
Within 8 weeks	26	47.27
8-12 weeks	21	38.18
Not returned to normal after 12 weeks	2	3.63
LFU Before 1 st normal Sr. β -hCG	6	10.90

Graph 5. Time for Sr. β -hCG normalization

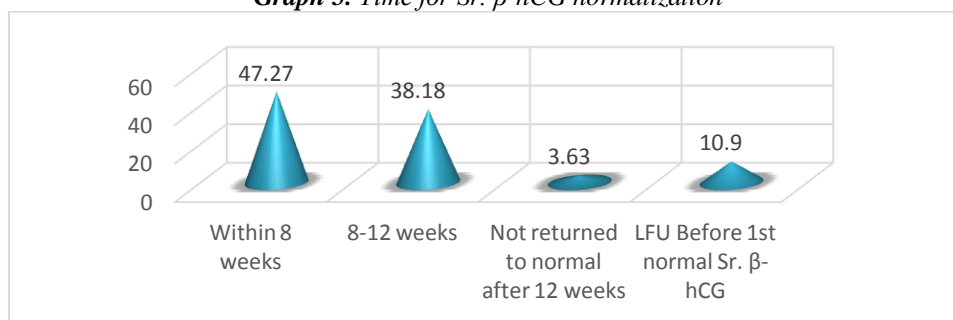
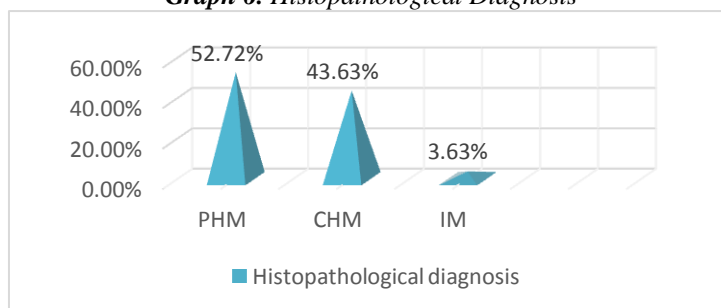


Table 5. shows on histopathological examination 96.35% of the patients had hydatidiform mole of which 52.72% patients had partial hydatidiform mole, 43.63% patients had complete hydatidiform mole. 2 patients had invasive mole. 2 patients with post molar GTN and one patient with invasive mole were given single agent chemotherapy and attained remission and completed follow up. The other patient with invasive mole was referred for multiagent chemotherapy.

Table 5. Histopathological Features

Histopathological feature	Number of patients	Percentage
Partial hydatidiform mole	29	52.72
Complete hydatidiform mole	24	43.63
Invasive mole	2	3.63

Graph 6. Histopathological Diagnosis



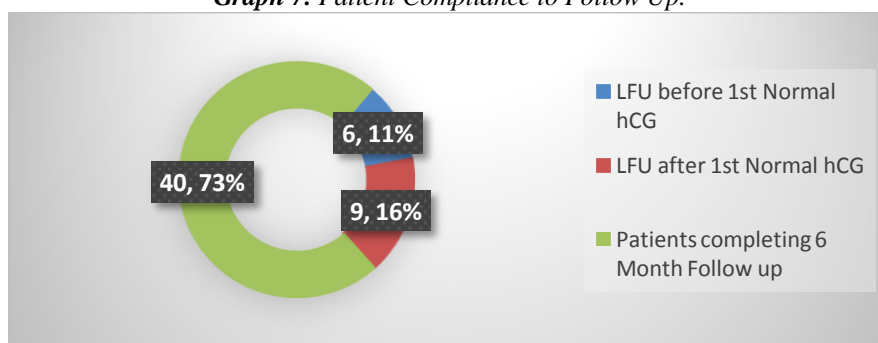
10.09% patients lost to follow up (LFU) before first normal β -hCG, but 72% patients completed the recommended follow up as seen in Table 6.

The above findings gave incidence of partial hydatidiform mole (PHM) of 1.46 PHM / 1000 Pregnancies, of complete hydatidiform mole (CHM) of 1.21 CHM / 1000 Pregnancies and of Invasive mole (IM) of 0.1 IM / 1000 Pregnancies in our institute. There were no cases of choriocarcinoma, PSTT or ETT during our study period.

Table 6. Patient Compliance to Follow Up.

Compliance of Patient	Number of patients	Percentage
Patient lost to follow up before first normal β -HCG	6	10.09
Patient lost to follow up after first normal β -HCG	9	16.36
Patients completing 6 months follow up	40	72.72

Graph 7. Patient Compliance to Follow Up.



IV. Discussion

Table 7. summarizes few findings from other studies in comparison with our study.

Table 7. Comparison of studies

AUTHORS	KUMAR N. et al.(9)	CHANDRAN JR et al.(10)	Al RIYAMI N et al.(11)	CHHABRA S et al(12)	CHINTHALA P et al.(13)	LAKRA P et al.(14)	PRESENT STUDY
INCIDENCE/ 1000 PREGNANCIES	-	-	-	-	-	-	2.77
LIVE BIRTHS	1.31	-	3	2.9	-	-	3.24
DELIVERIES	-	2.36	-	-	2.23	2.3	3.12
AGE in years							
MEAN±SD	24.6±4.4	24.65	31±7.5	-	-	23.02±2.96	24.76±4.02
MAX. Patients in age group	20-25	-	-	20-25	21-35	21-34	21-25
PRIMIGRAVIDAE (%)	21	-	-	21.21	50	47.4	43.63
GEST. AGE at presentation (in weeks)							
In 1 st trimester (%)	-	-	93	33.33	-	-	58.18
Mean ±SD	-	-	11±3.2	-	14-16	13.84±3.24	13.07±3.83
β-hCG > 1 lakh (% of patients)	66.7	50.3	-	63.63	62	18.4	52
HISTOPATH (%)							
CHM	63	≈ 70	43.8	88.08	-	-	43.63
PHM		≈20	54.7		-	-	52.72
IM	37	≈3	1.6	8.08	-	-	3.63

In this study vaginal bleeding was the most common symptom present in 32.72% of the patients. 5.45% patients had complaints of passing grape like vesicle PV. In a study of Chandran et al.(10) the most common presenting symptom was vaginal bleeding (78.1%), hyperemesis (19.4%), thyrotoxicosis (4.1%) and pain abdomen (3.5%). Almost 2/3rd patients (58.18%) were symptomless and diagnosed on routine antenatal USG in our study. The routine use of first trimester USG scans has led to an early detection of GTD and decrease in the severity of the symptoms(15). Above results are consistent with recent studies by Rangwala et al.(4) with 51% patients having USG findings of molar pregnancy. Joneborg et al. reported that patients with vesicular mole were diagnosed before the onset of symptoms in 42.5% of cases(16). The results are not in accordance with studies of Kumar et al. (6.5%)(9) and Shrivastava et al. (10.1%)(17).

Majority of the patients (50.90%) had uterine size larger than the period of gestation, Nirmala CK et al.(7) in Malaysia observed that only 17.6% patients had uterine size larger than the gestational age, while Rangwala et al.(4) observed it in 34% of their patients. In Indian scenarios, studies by Shrivastava S. et al., Lakra P et al. found that 56.75% patients, 54.6 % patients had uterine size larger than the expected gestational age(14,17).

The reduction in Sr. β -hCG levels 48 hours after evacuation has been proposed by RCOG guidelines. This fall was noted to be around 90% of pre-evacuation values with mean level being 24686 ± 24658 in our study and was found to be statistically significant. A study was published by Kumar et al. in Delhi stating that 60-80% fall can be seen post-evacuation in Sr. β -hCG levels within the first week. (9)

The time taken by 85.45% patients in our study for Sr. β -hCG levels to normalize was less than 12 weeks with the mean time being 8.31 ± 1.96 weeks. 47.27% patients had normal Sr. β -hCG levels within 8 weeks. 2 patients did not attain normal Sr. β -hCG levels and developed Post molar GTN. In a study done by Chhabra et al.(12) β -HCG levels were elevated in all the cases but 12 (12.12%) had high levels after 3 weeks (seven initially diagnosed as hydatidiform mole, three as invasive mole, and two as choriocarcinoma). Only two (2.28%) women out of 89 with hydatidiform mole had persistently elevated β -hCG. In a study of Al Riyami N et al. negative Sr. β -hCG was achieved 70 days after diagnosis in 41 women(11).

In our study suction evacuation was done in 96.36% patients. Hysterectomy was done in 3.63% patients as they had features of invasive mole and fertility was not desired. In a study by Chandran et al. (10) after diagnosis, 84.5% patients underwent suction evacuation, dilatation and evacuation was done in 14.5% and hysterectomy in 0.8%. On histopathological examination 96.35% of the patients had evidence of hydatidiform mole. 52.72% patient had partial hydatidiform mole and 43.63% patient had complete hydatidiform mole. 3.63% patients that is 2 patients had invasive mole for which they had undergone hysterectomy. No cases of choriocarcinoma, PSTT, ETT were seen in this study.

Al Riyami N et al.(11) reported that partial hydatidiform mole was diagnosed in 54.7%, complete hydatidiform mole in 43.8%, and invasive mole in 1.6% of women. Lybol C. et al. observed 30.2% having CHM and 44.5% having PHM(18). In a study done by Chhabra et al. out of 99 women, 88 (88.88%) had hydatidiform mole, eight (8.08%) had invasive mole and three had choriocarcinoma. (12)

In the present study 4 patients had GTN which is about 7.27% of the cases, 2 being invasive mole and 2 developed post molar GTN. The 2 patients having invasive mole had undergone hysterectomy, were confirmed on histopathological examination and started on chemotherapy. One patient had a FIGO score of 6 and was given single drug regimen with Methotrexate + Folinic acid weekly and she had complete remission in 5 months and completed her follow up of 6 months after that. The other patient had a FIGO score of 11 and was referred to another center for chemotherapy and her follow up was still going for 11 months.

The 2 patients with Post molar GTN had persistently elevated Sr. β -hCG levels and had low risk FIGO score of 6 and had remission with single agent chemotherapy (Methotrexate + Folinic acid) within 3 and 4 months and completed their follow up of 6 months, respectively. The remission rate in GTN was 100%. Similar proportions were reported in a Malaysian study(7) where 3.9% patients developed persistent trophoblastic disease while in the study of Kumar et al., persistent GTD was 12.02%.(9)

In our study 10.09% patients were lost to follow up before first normal β -hCG and 16.36% patients lost to follow up after first normal β -hCG. Many patients (73%) in our study completed the recommended follow up of 6 months after normal β -hCG levels. In a study by Nirmala CK et al.(7) 27.5% of women were lost to follow up before completing the protocol. This was in stark contrast with other studies that experienced a high number of women who defaulted at follow up before completion of the protocol. Feltmate et al.(19) observed 33% women who attained undetectable β -hCG but did not complete the protocol.

There were no recurrent molar pregnancies, no mortalities and none of the patients conceived during the follow up.

V. Conclusion

In the present study the prevalence of gestational trophoblastic disease is higher when compared to non-Asian countries but similar to Asian countries. The findings of the present study are consistent with the previous studies. Hence, we can say that Asian women may be at a higher risk for developing GTD. Latest diagnostic imaging and biochemical testing have aided in reducing the time of presentation of GTD and decreased the mortality and morbidity due to GTD. Ultrasonography plays a key role in earlier diagnosis and better management of GTD in first trimester. Majority of the cases are treated by simple suction evacuation. Uncomplicated molar pregnancy should be followed up for 6 months duration or until attaining undetectable serum β -hCG level. Longer follow up do not pose additional benefit but increases financial burdens on health providers and emotional disturbances to the women. The follow up protocols must be individualized on patient-to-patient basis.

VI. Recommendations

Proper counselling and good understanding of the disease and the need for follow up should be told to the patient. A urine pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after any pregnancy event to look for persistent GTN. To determine the actual prevalence and morbidity related to GTD in India, a multi centric study and centralized disease specific registry for GTD should be established.

Declarations

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Conflict of interest: None

Ethical approval: Yes

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