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**Original Research Article**

# Incidence and risk factors of post-molar gestational trophoblastic neoplasia: a prospective study

**Shana Rahman K. P., Sudhamani C.***

Department of Obstetrics and Gynecology, Institute of Maternal and Child Health (IMCH), Government Medical College, Kozhikode, Kerala, India

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***Correspondence:**
Dr. Sudhamani C.,
E-mail: sudhamen@gmail.com



## ABSTRACT

**Background:** Gestational trophoblastic disease (GTD) is a group of disorders arising from abnormal trophoblastic cells. Gestational trophoblastic neoplasia (GTN) is a malignant counterpart of GTD. In the earlier era, morbidity and mortality associated with GTD was very high, 90-95% presenting with metastatic GTN in 1980's.
**Methods:** This is a prospective study to analyze the incidence and to identify the risk factors of post-molar GTN and to evaluate the role of Beta-hCG level as a predictive factor of post-molar GTN, conducted in the department of Obstetrics and Gynecology, Institute of Maternal and Child Health (IMCH), Government Medical College, Kozhikode, on patients attending the vesicular mole(VM) clinic. Group A (remission group - was diagnosed after 6 months of follow-up with undetectable Beta-hCG values) and Group B (post-molar GTN). The two groups were compared for identifying risk factors.
**Results:** There were 79 cases of molar pregnancy registered in VM clinic with an incidence of 4.87/1000 deliveries. Of the 79 patients with GTD, 17 were diagnosed to have GTN during follow-up with an incidence of 21.51% of GTD. Incidence of post-molar GTN were significantly more among patients with history of previous molar pregnancy. The median Beta-hCG level at 2 weeks post-evacuation and the ratio of Beta-hCG levels at 1week to 2 weeks post-evacuation was found to be highly predictive of post-molar GTN.
**Conclusions:** Incidence of GTD was higher compared to international studies. The ratio of post-evacuation Beta-hCG at 1 week to Beta-hCG at 2 weeks is the most reliable predictor of post-molar GTN.

**Keywords:** Beta-hCG, Gestational trophoblastic disease, Gestational trophoblastic neoplasia, IMCH, Vesicular mole

## INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of disorders arising from abnormal placental trophoblast cells. It includes: hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, placental-site trophoblastic tumor (PSTT) and epitheloid trophoblastic tumor

The term gestational trophoblastic neoplasia (GTN) has been applied collectively to the latter 4 conditions, which can progress, invade, metastasize, and lead to death if left untreated. In Europe the incidence ranges from 0.5-1/1000 pregnancies and 2.5/1000 deliveries in North America while in Asia it stands at 1-2/1000 pregnancies.[1,2] Incidence in our institution is 4.87/1000 deliveries and 22% of all molar pregnancies progressed to GTN.[3] Highest incidence of 12.1/1000 deliveries were reported in Turkey by Harma et al.[4] This disease has a higher prevalence amongst the Asian population. This has been attributed to various factors such as racial disparity, dietary habits, genetics etc. According to Seckl et al, 16% of complete moles and 4% partial moles undergo locally invasive disease and 4% of complete mole grow into malignancy.[1]

Post-hydatidiform mole GTN is diagnosed by rising beta-hCG levels and abnormal radiology suggesting the presence of molar tissue. Histological confirmation is not needed unless placental site trophoblastic tumor is suspected.

Studies by Berkowitz et al have shown that 15% of patients with molar pregnancy develop locally invasive tumor and 4% develop metastatic tumor.[5] Choriocarcinoma was found in 6.45% patients with trophoblastic neoplasia. Almost similar incidence was reported by Khairuneesa et al.[6]

Post-molar GTN is defined by the following criteria: beta-hCG level plateau of four values ±10% over 3 weeks (days 1, 7, 14, 21), beta-hCG level increase of more than 10% among three values recorded over a 2-week period (day 1, 7, 14), persistence of detectable beta-hCG for more than 6 months after molar evacuation, histopathological diagnosis of choriocarcinoma and presence of metastatic disease.

The risk factors for malignant disease were studied and WHO proposed a scoring system which was adopted by FIGO in stratifying patients into high-risk and low-risk categories for propensity to progress to malignancy. Extremes of age are known risk factors of GTN.[7] Teenagers and women over 40 years old have higher incidence. Women with pre-evacuation beta-hCG more than 1 lakh, excessive uterine enlargement and theca lutein cysts more than 6 cm diameter are particularly at high risk.

In the earlier eras the mortality and morbidity associated with this disease was tremendous. Ranging from 90-95% cases of metastatic GTN in the 1980s. Majority of women would succumb to the disease due to any of the spectrum of complications encountered such as metastases, organ failure, and disease progression. Likewise, malignant potential of the disease is also higher in south-east Asia reaching as high as 10-15% compared to 2-4% in West.

Over the past few decades, there has been great improvement in the prognosis of this disease. This can be attributed to several factors which include the evolution of imaging techniques like ultrasound, CT and MRI, the sensitive radio-immunoassay techniques for estimating beta-hCG as well as the development of effective chemo-therapeutic agents.

Human chorionic gonadotropin (beta-hCG) is a glycoprotein hormone comprising two subunits, alpha and beta, and is an important index for pregnancy and gestational trophoblastic disease. Serial evaluation of beta-hCG can be used for the diagnosis of normal and abnormal pregnancy. According to Mousavi et al the rate of decrease of beta-hCG level at two weeks post-evacuation is the most reliable and strongest predictive factor for the progression of molar pregnancies to neoplasia.[8]

Several studies have attempted to identify factors that would predict persistent GTN or remission to better inform patients and their physicians regarding the risk of developing persistent GTN and to reduce the interval between the diagnosis of molar pregnancy and the diagnosis of persistent disease.[9,10] Other studies have discussed the possibility of identifying persistent GTN based on the level of beta-hCG at a given time point post-evacuation and patients who go on to have persistent GTN have beta-hCG regression patterns that differ from patients who go on to remission.[8,11,12] However, none of the findings have been sufficiently accurate to guide management. According to Kang et al, the decline ratio in beta-hCG level 2 weeks after evacuation in patients with complete molar pregnancies is the most reliable predictor of persistent GTN.[13]

Taking the above findings, this study aimed to evaluate the possibility of finding new predictive factors of post molar GTN based on the levels of beta-hCG following evacuation and to analyse the already established risk factors and incidence of post-molar GTN in our institution.

## METHODS

This prospective observational cohort study consisted of one and half years from January 2018 to July 2019. Study population included patients attending vesicular mole (VM) clinic in IMCH, Government Medical College (GMC), Kozhikode, who underwent evacuation for molar pregnancy.

### *Inclusion criteria*

Patients attending VM clinic for follow-up with history evacuation for molar pregnancy and those with histopathological diagnosis of molar gestation.

### *Exclusion criteria*

Patients who showed non-compliance to the follow-up process and considered dropped cases, who underwent evacuation in view of molar pregnancy but histopathological diagnosis was not suggestive of molar gestation, already diagnosed cases of GTN, and who subsequently became pregnant during the six-month follow-up interval.

### *Sample size*

According to a study conducted in our institution in 2011, 22.03% of gestational trophoblastic disease progressed to GTN, with a precision of 12.

Sample size = $4pq/d^2$

P=22,

Q=100-22=78,

D=12. Therefore, sample size = 47.66 ~ 50.

### *Methodology*

In this prospective study, a total of 73 patients were followed up for a period of 6 months or until they were diagnosed with GTN.

Information on age, gestational age, parity, blood group, clinical findings before evacuation, ultrasonographic features and pre-evacuation beta-hCG were obtained from patient records. Patients were examined clinically and beta-hCG values recorded in each visit. Patients were divided into two groups at the end of study. Group A (remission group) was diagnosed after six months of follow-up, with undetectable beta-hCG values and group B (patients with post-molar GTN). Two groups were compared for identifying the risk factors and analysis was done with appropriate statistical methods.

### *Statistical analysis*

Statistical analysis was done using R software. Qualitative data was expressed as frequency and percentage and quantitative data as mean with standard deviation (SD) or median with range. Comparison between remission group and post molar GTN group was done using Student's t test, Chi square test, Fisher's exact test and Mann Whitney test. Sensitivity and specificity were measured using receiver operating characteristic (ROC) curve. Area under the curve (AUC) was used to find out the diagnostic accuracy of the test. All tests were two sided and a p value <0.05 was considered statistically significant.

### *Ethical aspects*

Study protocol was submitted to the Institutional Research Committee as well as the Institutional Ethics Committee of GMC, Kozhikode and clearance was obtained for conducting the study. Informed consent was obtained from every patient. All information collected were kept strictly confidential.

## RESULTS

During study period, there were 16227 deliveries and 79 cases of molar pregnancy registered in the vesicular mole clinic with an incidence of 4.87/1000 deliveries. Of the 79 patients with GTD, 17 were diagnosed to have GTN during follow-up, with an incidence of 21.51% of the trophoblastic diseases. Of the 79 cases, 51 cases had evacuation of hydatidiform mole from our institution and rest had evacuation outside and were referred for follow-up. Out of the 79 cases 3 cases were diagnosed by histopathological examination following dilatation and curettage for missed miscarriage. Six patients lost follow-up and were excluded from the study.

So, study population consisted of 73 patients. There were no cases of choriocarcinoma during the study period.

**Table 1: Mean age.**

| Age (years) | Minimum | Maximum | Mean±SD | P value |
|---|---|---|---|---|
| **Remission** | 18 | 38 | 24.95±4.7 | 0.01 |
| **Post-molar GTN** | 20 | 38 | 28.4±4.9 | |

The mean age of patients in the study was 25.75 years with a SD of ±4.92 years. The mean age in the remission and post molar GTN were 24.95±4.7 years and 28.4±4.9 years respectively.

Post molar GTN patients had significantly higher mean age compared to remission patients (p=0.01).

In post molar GTN group,13 patients belonged to 20-30 years (76.47%) and 4 (23.5) were >30 years but found statistically insignificant (p=0.192).

Obstetric score distribution of the 73 cases analysed, 25 were primigravida and 48 cases were multigravida. Obstetric score was comparable between the two groups.

**Table 2: Previous history of VM.**

| Previous history of VM | Yes | No | P value |
|---|---|---|---|
| **Remission** | 5 (50) | 51 (81) | 0.046 |
| **Post molar GTN** | 5 (50) | 12 (19) | |
| **Total** | 10 (100) | 63 (100) | |

Out of the 10 cases, 9 cases had history of previous one molar pregnancy. There was one case of recurrent molar pregnancy and her genetic analysis showed mutation in NLRP gene. Proportion of post-molar GTN were significantly more among patients with history of previous molar pregnancy (p=0.046).

### *Gestational age*

Gestational age at diagnosis of molar pregnancy was not significantly different between the groups.

Blood group $B^{+ve}$ and $O^{+ve}$ blood groups were more commonly found. But there was no statistical significance in difference of its occurrence between the groups.

### *Histopathology report (HPR)*

As per HPR, 3 patients of partial mole and 14 of the complete moles progressed to GTN (29%). Proportion of post-molar GTN patients were more among patients with complete mole, with a difference statistically insignificant.

### *Beta-hCG values*

The hCG levels pre-evacuation, and 1 and 2 weeks after evacuation, as well as the three ratios derived from these

measurements, were utilized to construct receiver operating characteristic (ROC) curves and to calculate the area under the curve (AUC) for assessment of the diagnostic accuracy of the test. The accuracy of the prediction of persistent GTN was verified by computing the sensitivity, specificity, predictive values, and diagnostic odds ratio (DOR). To predict the risk of persistent GTN, a multivariate logistic regression model adjusted for age and hCG level was used to compare the decline in hCG levels among patients with persistent disease and spontaneous remission.

**Table 3: Comparison of beta-hCG levels.**

| Beta-hCG values (mIU/ml) | Remission* | Post molar GTN* | P value |
|---|---|---|---|
| **Pre evacuation** | 94800 (6835-811500) | 273000 (122800-773200) | <0.0001 |
| **1 week post evacuation** | 860 (2-62000) | 2985 (577-88755) | 0.001 |
| **2 weeks post evacuation** | 165 (1.5-1942) | 4933 (77-100000) | <0.0001 |

*Values expressed as median (range)

**Table 4: Comparison of beta-hCG ratio.**

| Beta-hCG ratio | Remission* | Post molar GTN* | P value |
|---|---|---|---|
| **Pre-evacuation beta-hCG /1 week post-evacuation** | 113.92 (4.26-4556.67) | 96.63 (2.62-540.7) | 0.383 |
| **Pre-evacuation beta-hCG / 2 weeks post-evacuation** | 658.64 (135.04-12900) | 55.26 (4.5-2284.99) | <0.0001 |
| **1week post-evacuation / 2 weeks post- evacuation** | 5.45 (0.32-151.52) | 0.87 (0.25-11.7) | <0.0001 |

*Values are expressed as median (range)

The median beta-hCG level of the persistent group pre-evacuation was 273000 mIU/ml whereas in remission group was 94800 mIU/ml. The median beta-hCG level 1-week post-evacuation was 2985 and 860 mIU/ml in the persistent and remission groups, respectively. The median beta-hCG level 2 weeks post-evacuation in the persistent group was significantly higher than the remission group. At all time, the median beta-hCG values were significantly higher for post-molar GTN patients.

Median regression ratio after 1week of evacuation was not significantly different between the two groups. The median regression ratio after 2 weeks and ratio between 1 week and 2 weeks post evacuation were statistically significant.

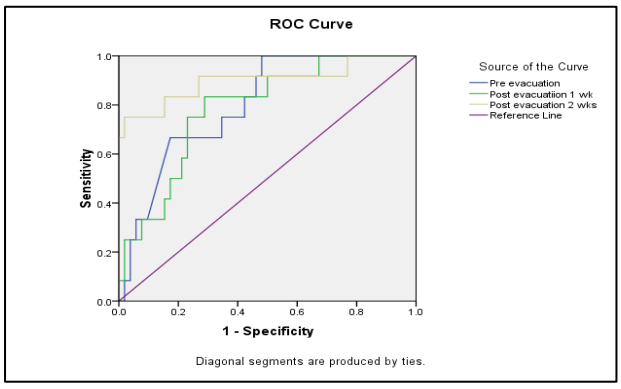


**Figure 1: Determination of cut-off beta-hCG values.**

The AUC was more for ROC curve plotted for beta-hCG 2 weeks post-evacuation followed by 1-week post-evacuation.

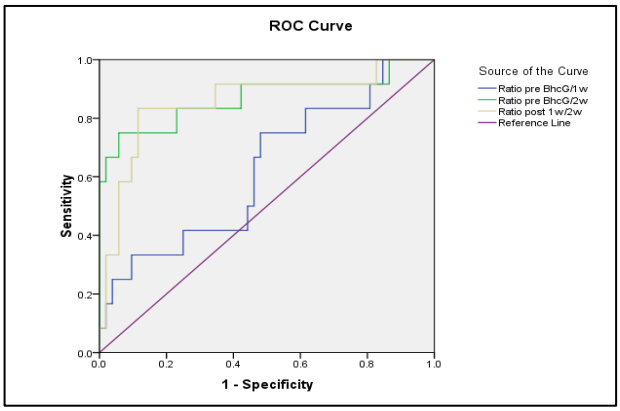


**Figure 2: Median beta-hCG regression ratio.**

The optimal cut-off points for the beta-hCG level 1- and 2-weeks post-evacuation were 1400 mIU/ml (AUC, 0.773; sensitivity, 81.8%; specificity, 71.2%) and 400 mIU/ml (AUC, 0.890; sensitivity, 90.9%; specificity, 73.1%).

The AUC was more for ROC curve plotted for median beta-hCG regression ratio 1-week post-evacuation to 2-weeks post-evacuation followed by pre-evacuation to 2-weeks post-evacuation. The optimal cut-off points for the ratio of pre-evacuation beta-hCG to beta-hCG after 1 and 2 weeks, and beta-hCG after 1 week to beta-hCG after 2 weeks were 100 (AUC, 0.623; sensitivity, 61.5%; specificity, 50%), 350 (AUC, 0.867sensitivity, 84.6%; specificity, 76.9%), and 2 (AUC, 0.856; sensitivity, 66.7%; specificity, 95.8%).

Based on the multivariate logistic regression model, the odd ratio (OR) was adjusted for covariates. The risk of

persistent GTN was higher for the ratio of beta-hCG after 1 week to beta-hCG after 2 week <2 [OR=46; 95% confidence interval (CI), 8.22-257.35; p<0.0001], beta-hCG level 2 weeks after evacuation >400 mIU/ml (OR=38; 95% CI, 4.57-316.35; p<0.0001), the ratio of pre-evacuation beta-hCG to beta-hCG after 2 weeks <350 (OR=18.33; 95% CI, 3.56-94.41; p<0.0001), and the beta-hCG after 1 week ≥1400 (OR=10.4; 95% CI, 2.57-42.10; p<0.0001).

**Table 5: DOR of the cut off value to predict GTN (1).**

| Beta-hCG values (mIU/ml) | DOR (95% CI) | P value |
|---|---|---|
| **Pre-evacuation ≥205650 versus <205650** | 7.74 (1.92-31.21) | 0.002 |
| **1-week post-evacuation ≥1400 versus <1400** | 10.4 (2.57-42.10) | <0.0001 |
| **2-weeks post-evacuation ≥400 versus <400** | 38 (4.57-316.35) | <0.0001 |

**Table 6: DOR of the cut-off value to predict GTN (II).**

| Ratio | DOR (95% CI) | P value |
|---|---|---|
| **Pre-evacuation Beta-hCG /1-week post evacuation <100 versus ≥100** | 1.6 (0.46-5.52) | 0.455 |
| **Pre-evacuation Beta-hCG /2-weeks post evacuation <350 versus ≥350** | 18.33 (3.56-94.41) | <0.0001 |
| **1-week post evacuation / 2-weeks post evacuation <2 versus ≥2** | 46 (8.22-257.35) | <0.0001 |

**Table 7: Median hCG level comparison (study).**

| Beta-hCG values (mIU/ml) | Remission* | Post molar GTN* | P value |
|---|---|---|---|
| **Pre-evacuation** | 94800 | 273000 | <0.0001 |
| **1-week post-evacuation** | 860 | 2985 | 0.001 |
| **2-weeks post-evacuation** | 165 | 4933 | <0.0001 |

Follow-up remission was between 4 weeks to16 weeks with mean 8.25 weeks and SD 3.07 weeks. Out of 17 cases of post-molar GTN only one post-molar GTN patient had plateau, rest had elevated beta beta-hCG. The minimum time gap between diagnosis of VM and GTN was 2 weeks. and maximum 9 weeks. The mean time gap was 4.8 weeks. All the post-molar GTN patients belonged to the low-risk category.

## DISCUSSION

The incidence of molar pregnancies in our institution during the study period was 4.87/1000 deliveries which was comparable to study conducted in the same institution by D'Couth et al for a period of 5 years from 2006 to 2010.[3] Incidence at that time was 4.8/1000 deliveries. This was higher compared to the 1 in 1000 pregnancies in Europe reported by Seckl et al and 2.5/1000 deliveries in North America as reported by Lara et al.[1,2] Of the 79 patients with GTD, 17 were diagnosed to have GTN during follow-up, with an incidence of 21.51% of the trophoblastic diseases. Our institution caters a wide range of population from Northern districts of Kerala. Moreover, most of the GTDs after suction evacuation are followed up and managed over here. This could be the reason for the higher incidence in our study.

Maternal age has been reported as a significant risk factor for molar pregnancy in many countries including the United States, Asia, Europe and middle East. According to Soares et al, women <16 or >40 years of age have a 4-10 times higher risk of developing GTD than those aged 20-30.[14] At the extremes of the reproductive age range, the risk of HM for girls having pregnancy at the age of 13 is 1:208, and 1:8 for women aged ≥50 years. Age of the patients in our study were between 18-38 years with a mean age 25.75 with SD±4.92. D'Couth et al reported mean age of 25.6 years.[3] Lurain et al reported a higher incidence of molar pregnancies in women <25 years.[15] Extremes of age are known risk factors of GTN.[3] In our study post-molar GTN group had significantly high mean age compared to remission group (28.4±4.9 years). Majority of patients with post-molar GTN were in the age group of 20-30 years (76%), maximum age of 38 years. Chabra et al cite that 24.4% of GTN patients were more than 25 years of age with 47.47% falling between 20-25 years.[16] But other authors have reported age specific incidence to reveal a J shaped curve; teenagers and women over 40 years have higher incidence.

Of the 73 cases analyzed, 25 cases were primigravida whereas 48 cases were multigravida. A similar trend of gravidity was noted between the two groups (p=0.1), this corroborates with the evidence stated by Ngan et al.[17]

The incidence of repeat moles was 13.69% during the period of study of which 50% cases progressed to GTN, but Eagles et al noticed an incidence of 1% following previous VM.[18] Proportion of post-molar GTN were significantly more among patients with a history of previous molar pregnancy compared to patients without same (p=0.046). Previous history of molar pregnancy increases the risk of recurrent molar pregnancy to 1.8%, around 20 times higher than the background risk. Recent genetic studies also showed that mutation in NLRP7 gene-

a CATERPILLER protein family involved in pathogen-induced inflammation and apoptosis- on chromosome 19q13.4 was associated with familial and recurrent HM.[15,19] In our study there was one case of recurrent molar pregnancy with NLRP7 gene mutation, who developed post-molar GTN for a second time and was managed with 6 cycles of actinomycin D.

The mean gestational age at diagnosis for remission group was 10.2±1.4 weeks. The mean gestational age at diagnosis of molar gestation in post-molar GTN group was 10.6±1.5 weeks. Gestational age at diagnosis of molar pregnancy was not significantly different between the groups (p=0.272).

Amongst the study population, $B^{+ve}$ and $O^{+ve}$ blood groups were commonly found. This was comparable to inference of D'Couth et al.[3] There was no statistical significance in difference of its occurrence between the two groups. According to Goldstein et al, $A^{+ve}$ and $O^{+ve}$ were commonly found.[20]

The histopathology report (HPR) of the study population consisted of 48 complete moles (65.7%) and 25 (34.2%) partial moles. Of the complete moles 14 progressed to GTN (29%). Out of 25 partial moles 3 progressed to GTN (12%). Proportion of post-molar GTN patients were more among patients with complete mole, but the difference was not statistically significant (p=0.631). According to Lurain et al, 15-20% of complete mole and less than 5% of partial mole progress to post-molar GTN.[15]

***Changes in beta-hCG values and GTN prediction***

Our objective was to evaluate the role of beta-hCG level as a predictive factor of post-molar GTN. The hCG levels pre-evacuation, and 1- and 2-weeks post-evacuation, as well as the three ratios derived from these measurements, were utilized to construct receiver operating characteristic (ROC) curves and to calculate the area under the curve (AUC) for assessment of the diagnostic accuracy of the test. The accuracy of prediction of persistent GTN was verified by computing the sensitivity, specificity, predictive values, and diagnostic odds ratio (DOR).

According to Kang et al, only the median hCG level 2 weeks after evacuation in the persistent group [4962 mIU/ml (range, 30-2,150,000 mIU/ml)] was significantly higher than the remission group [720 mIU/ml (range, 10-38,400 mIU/ml)].[13]

According to Mousavi et al, the only predictors of persistent GTN were hCG levels at one- and two-weeks post-evacuation.[8] Other factors were not related to persistent GTN.

In our study, median regression ratio after 1week of evacuation was not significantly different between the groups. The median regression ratio after 2 weeks and ratio between 1- and 2 weeks post-evacuation were statistically significant.

The cut-off points for pre-evacuation hCG levels, and hCG levels 1 and 2 weeks post-evacuation, as well as for the three ratios derived from these measurements. The risk of persistent GTN was higher for the ratio of hCG after 1 week to hCG after 2 week <2 [OR=46; 95% confidence interval (CI), 8.22-257.35; p<0.0001], hCG level 2 weeks after evacuation >400 mIU/ml (OR=38; 95% CI, 4.57-316.35; p<0.0001), the ratio of pre-evacuation hCG to hCG after 2 weeks <350 (OR=18.33; 95% CI, 3.56-94.41; p<0.0001), and the hCG after 1 week ≥1400 (OR=10.4; 95% CI, 2.57-42.10; p<0.0001).

According to Kang et al, the decline ratio in the hCG level 2 weeks post-evacuation in patients with complete molar pregnancies is the most reliable predictor of persistent GTN among early predictive factors.[13] In their study patients with partial molar pregnancies were excluded because regression of the hCG level was more rapid in patients with partial moles than with complete moles.

Feltmate et al reported that the mean time to achieve the first undetectable beta-hCG was 8.4 weeks in uneventful complete mole, comparable to 8.25 weeks in our study.[21] According to Kang et al, average time to achieve remission was 9 weeks.[13] Considering this mean time and further follow-up period, most patients will undergo beta-hCG tests for 8-9 months. So, an easier and more rapid method to predict post-molar GTN would be helpful to both patients and clinicians.

The mean time gap between diagnosis of VM and GTN was 4.8 weeks in our study. According to Kang et al, median time to diagnose post-molar GTN was 5.8 weeks.[13] So, we can conclude that beta-hCG values at 2-weeks post evacuation and their ratios are significant and based on that, high risk patients need close follow-up and better surveillance.

## CONCLUSION

Incidence of GTD was higher compared to international studies. Proportion of post-molar GTN was significantly more among patients with history of prior molar pregnancy. The ratio of post-evacuation beta-hCG of 1-week to 2-weeks is the better predictor for development of post-molar GTN. Post-molar GTN has got good prognosis with single agent chemotherapy, hence continued patient awareness and strict surveillance is required so that neoplasia developing after molar pregnancy can be detected as early as possible, thereby reducing complications and mortality and preserving future fertility.

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