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Original Research Article

Evaluation of β-hCG regression after evacuation of molar pregnancy as a predictive factor for malignant GTN

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ABSTRACT

Background: Gestational trophoblastic disease (GTD) is a group of disorders identified by abnormal proliferation of trophoblastic tissue. The general term GTN is used to describe a wide range of trophoblastic diseases including invasive mole, choriocarcinoma, epithelioid trophoblastic tumor, and placental site trophoblastic tumor. The persistence of GTN post-molar pregnancy can be efficiently detected with serial measures of the β subunit of hCG, or β-hCG. Therefore, this study aimed to evaluate the β-hCG regression after evacuation of molar pregnancy as a predictive factor for malignant GTN.
Methods: This was a prospective analytical study conducted in the Gynaecological Oncology Unit and Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh during the period from January 2022 to December 2022. In our study, we included 50 patients with molar pregnancies attending the Gynaecological Oncology Unit and Department of Obstetrics & Gynecology of DMCH.
Result: The mean age of participants was 23.5 years. The GTN was diagnosed among 24% of patients. In 2nd week, the mean B-hCG was found 91027.50±24430.53 miU/ml in the persistent GTN group and 19339.68±13978.59 miU/ml in the remission group. The mean B-hCG significantly decreased to 64399.33±23404.81 and 4.47±2.57miU/ml in the persistent GTN and remission group respectively in the 15th week ($p<0.05$).
Conclusion: This study found that serum β-hCG levels in the 2nd, 3rd, and 4th weeks following molar evacuation can predict over 24% of patients who developed GTN after molar evacuation. The decline in serum β-hCG levels during weeks was statistically linked to the development of GTN.

Keywords: Hydatidiform mole, Post evacuation, Serum β-hCG, Gestational trophoblastic neoplasia

INTRODUCTION

Gestational Trophoblastic Disease (GTD) includes a group of pregnancy-related disorders: premalignant disorders of complete and partial hydatidiform mole. Malignant disorders like invasive mole, choriocarcinoma, and the rare placental-site trophoblastic tumor. Gestational trophoblastic neoplasia (GTN) is used to describe these malignant forms and it was recommended by the International Federation of Obstetrics and Gynecology (FIGO) for patients, whose serum beta-Human Chorionic Gonadotropin (Beta-hCG) level failed to regress in the absence of a normal pregnancy.[1] GTN is a collective term that refers to gestational trophoblastic diseases such as

placental site trophoblastic tumors, invasive moles, and choriocarcinoma. GTN originates from the abnormal multiplication of trophoblast after any gestation, especially molar pregnancy.[2]

The human chorionic gonadotropin (hCG) hormone is divided into two components, beta, and alpha, and is generated by trophoblastic tissue. The persistence of GTN post-molar pregnancy can be efficiently detected with serial measures of the β subunit of hCG, or β-hCG.[3] Most of the previous studies used a general linear model, survival model, or longitudinal ROC analysis.[1,4,5]

This study will indicate that the three-week β-hCG concentration (longitudinal classifier) in weeks 2, 3, and 4 can predict over 80% of patients who develop GTN after molar evacuation. Besides, over 90% of advanced patients getting GTN can be correctly identified if we apply all their measurements in the model (48 hours, days 7, 14, 21, and 28). Therefore, monitoring the three-week trend of this marker is recommended for the early detection of this malignancy in women with molar pregnancy.[1]

In the study done in 1989 by Curry et al, the first titer of β-hCG hormone was measured and documented 48 hours after the molar pregnancy evacuation. The follow-up process for patients was a way that their titer of β-hCG hormone was measured weekly until 3 consecutive normal titers were attained and it continued monthly for 6 months.[6] The repeated measures of log-transformed β-hCG concentrations at 5 consecutive time points (48 hrs., days 7, 14, 21, and 28) were considered the predictor of GTN in women with molar pregnancy.[7]

Persistent GTN is a curable disease but can develop into a life-threatening malignancy.[8] Suction evacuation and chemotherapy are suitable treatments for low-risk GTN.[9] Post-molar GTN is defined by clinical and laboratory criteria. Persistent GTN specifically refers to GTNs with the potential for tissue invasion and metastasis.

Serial HCG testing can be used to diagnose both normal and abnormal pregnancies.[10,11] A comprehensive investigation was conducted to discover predictive indicators in the progression from normal pregnancy, molar pregnancy, and invasive mole to malignant illness. The following risk variables cannot substantially predict persistent GTN: age, gestational age of pregnancy, positive past medical history of molar pregnancy, HCG titer greater than 100,000, and theca lutein cyst larger than 6 cm.[12]

Various risk factors for post-molar trophoblastic disease have been reported such as pre-evacuation β hCG level, maternal age, gestational age, uterine size, ovarian cyst, presence of medical complication, previous molar pregnancy, and ABO blood groups were evaluated. Gestational trophoblastic illness can develop after any sort of previous pregnancy. The most common antecedent pregnancy is when a patient presents with a hydatidiform mole. Nearly 45% of choriocarcinomas occur following the evacuation of a hydatidiform mole, 25% after a full-term normal pregnancy, 25% after spontaneous abortion, and 5% after an ectopic pregnancy.

The primary symptom of chronic trophoblastic illness is irregular uterine bleeding, which occurs sooner or later following the expulsion of a mole or a normal pregnancy.

Often the disease presents by way of its metastasis, such as haemothorax, dyspnoea, or hemoptysis, or the emergence of neurological signs and symptoms such as headache, visual abnormalities, or focal neurological impairments. Therefore, in this study, we aimed to evaluate the β-hCG regression after evacuation of molar pregnancy as a predictive factor for malignant GTN.

METHODS

Study place

This was a prospective analytical study conducted in the Gynaecological Oncology Unit and Department of Obstetrics & Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh.

Study duration

The study was done during the period from January 2022 to December 2022.

Sample size

In our study, we included 50 patients with molar pregnancies attending the Gynaecological Oncology Unit and Department of Obstetrics & Gynecology of DMCH.

Inclusion criteria

These are the criteria to be eligible for enrolment as our study participants. Patients aged more than 40 years. Patients diagnosed with molar pregnancies clinically and radiologically and patients who were willing to participate were included in the study.

Exclusion criteria

Patients who received chemoprophylaxis, patients with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD etc.), and patients who showed noncompliance to the follow-up process were excluded from our study.

Data collection procedures

Information on age, gestational age, gravida, para, and history of prophylactic chemotherapy before molar evacuation were obtained from the patients. Serum level of β-hCG was measured in all patients before and after the evacuation of a mole in the same institute.

It was measured first after 48 hours of evacuation then weekly at 2nd, 3rd, 4th, 8th, and 15th week. Spontaneous remission was diagnosed in patients with β-hCG level <5 mIU/ml for two consecutive weeks after evacuation. Thereafter monthly serum β-hCG was measured for 6 months.

Statistical analysis

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. The chi-square test with Yates correction was used to analyze the categorical variables, shown with cross-tabulation. Student t-test was used for continuous variables. A p-value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 23 (Statistical Package for Social Sciences) for Windows version 10. The study was approved by the Ethical Review Committee of Dhaka Medical College Hospital.

RESULTS

Table 1 shows that 35 (70.0%) patients belonged to age 21-25 years. The mean age was found 23.5±3.2 years with a range from 18 to 32 years. The majority (58.0%) of patients were primi para and 21 (42.0%) were multi para.

Table 1: Distribution of the study subjects by baseline characteristics (n=50).

Baseline characteristics	Number of patients	%
Age (in years)		
≤20	4	8
21-25	35	70
26-30	8	16
>30	3	6
Mean±SD	23.5±3.2	
Range (min-max)	18.0-32.0	
Parity		
Primi	29	58
Multi	21	42
Present complaints		
History of amenorrhea	50	100
History of irregular bleeding per vagina	49	98
Passage of moles	16	32
History of hyperemesis gravida, vomiting, weakness, nausea, giddiness	15	30
Abdominal pain	14	28
Cough	1	2
Haemoptysis	1	2
Headache	1	2

All (100.0%) patients had a history of amenorrhea followed by 49 (98.0%) had a history of irregular bleeding per vagina and 16 (32.0%) had a history of the passage of moles. Another result is depicted in Table 1.

Table 2 shows that 27 (54.0%) patients were found gestational age ≤10 weeks. The mean gestational age was found 10.1±2.0 weeks with a range from 5.0 to 13 weeks.

Table 3 shows that the majority (86.0%) of patients were found in larger than the period of amenorrhea, 6 (12.0%) in smaller than the period of amenorrhea and 1 (2.0%) to correspond to the period of amenorrhea.

We found that 48 (96.0%) patients had complete mole and 2 (4.0%) had partial mole evaluation by histopathology findings. Among 50 patients, 12 (24.0%) patients were found persistent GTN, and 38 (76.0%) were in remission of gestational trophoblastic neoplasia.

Table 4 shows that mean β-hCG was found 127340.2±37909.0 miU/ml, 104217.9±33093.0 miU/ml, 65896.9±40248.1 miU/ml, 49308.9±37274.1 miU/ml, 36763.9±33034.6 miU/ml, 24573.9±27969.9 miU/ml, 17535.1±21550.5 miU/ml, 8209.7±11311.5 miU/ml in initially, at 48th hours, at 1st week, at 2nd weeks, at 3rd weeks, at 4th weeks, at 8th weeks and 15th weeks respectively.

Table 2: Distribution of the study subjects according to gestational age (n=50).

Gestational age (in weeks)	Number of patients	%
≤10	27	54
>11	23	46
Mean±SD	10.1±2.0	
Range (min-max)	5.0-13.0	

Table 3: Distribution of the study subjects according to the size of the uterus, histopathology findings and gestational trophoblastic neoplasia (GTN) (n=50).

Size of the uterus	No. of patients	%
Corresponding to the period of amenorrhea	1	2
Larger than a period of amenorrhea	43	86
Smaller than a period of amenorrhea	6	12
Histopathology findings		
Complete mole	48	96
Partial mole	2	4
Gestational trophoblastic neoplasia		
Persistent GTN	12	24
Remission	38	76

Table 4: Mean β-hCG level during the follow-up period (n=50).

β-hCG (miU/ml)	Mean±SD
Initially	127340.2±37909.0
At 48th hours	104217.9±33093.0
At 1st week	65896.9±40248.1
At 2nd weeks	49308.9±37274.1
At 3rd weeks	36763.9±33034.6
At 4th weeks	24573.9±27969.9
At 8th weeks	17535.1±21550.5
At 15th weeks	8209.7±11311.5

In 1st week, mean β-hCG was found 100820.33±28144.77 miU/ml in the persistent GTN group and 39807.37±30349.20 miU/ml in the remission group.

In 2nd week, mean β-hCG was found 91027.50±24430.53 miU/ml in the persistent GTN group and 19339.68±13978.59 miU/ml in the remission group. In 4th week, mean β-hCG significantly decreased to 76602.75±25462.57 and 843.84±842.44 miU/ml in persistent GTN and remission groups respectively.

At 15th weeks, mean β-hCG was found 64399.33±23404.81 miU/ml in the persistent GTN group and 4.47±2.57 miU/ml in the remission group, which were statistically significant ($p<0.05$) between the two groups.

Table 5: Difference in Mean β-hCG level between two groups during follow-up.

β-hCG (miU/ml)	Persistent GTN (n=12)	Remission (n=38)	P value
	Mean±SD	**Mean±SD**	
Initially	123535.00±34997.71	127404.00±38238.05	0.75^{ns}
At 48th hours	111953.50±29604.84	97546.82±31509.45	0.16^{ns}
At 1st week	100820.33±28144.77	39807.37±30349.20	0.001^{s}
At 2nd weeks	91027.50±24430.53	19339.68±13978.59	0.001^{s}
At 3rd weeks	83713.17±24229.55	9086.89±7766.50	0.001^{s}
At 4th weeks	76602.75±25462.57	843.84±842.44	$0.001^{s`}$
At 8th weeks	69871.92±25666.19	17.84±15.13	$0.001^{s`}$
At 15th weeks	64399.33±23404.81	4.47±2.57	$0.001^{s`}$

s= significant; ns= not significant

DISCUSSION

This study observed that 35 (70%) patients belonged to age 21-25 years. The mean age was found 23.5±3.2 years with a range from 18-32 years. Mousavi et al, revealed the mean age of patients was 27.28±8.1 years with a range from 15-54 years.[13]

This study found that all (100.0%) patients had amenorrhea, 49 (98.0%) had irregular vaginal bleeding, and 16 (32.0%) had passage of mole. Sultana et al, reported that the case of a complete mole presented with bleeding per vagina and abdominal pain whereas the case of a partial mole presented with only amenorrhoea.[14]

In this study showed that 27(54.0%) patients had gestational age ≤10 weeks. The mean gestational age was found 10.1±2.0 weeks with a range from 5.0 to 13 weeks. Neelakanthi, study observed the mean gestational age at presentation was 12.40±4.12 weeks.[15]

This study observed that the majority of patients (86.0%) had a uterine size larger than the period of amenorrhea, 6(12.0%) had smaller than the period of amenorrhea, and 1(2.0%) corresponding to the period of amenorrhea. In Neelakanthi's study, 52.92% of patients were found to be larger than gestational age.[15]

In this study observed that 48(96.0%) patients had complete mole and 2(4.0%) had partial mole. Sultana et al reported that 75.0% of patients had partial hydatidiform mole and the remaining 25.0% cases had complete hydatidiform mole.[14] Neelakanthi et al, observed histopathology revealed partial moles in 53.8% and complete moles in 44.2% of patients.[15] Bakhtiyari et al, reported that 18 (9%) cases had partial mole and the remaining 183 (91%) cases had complete mole.[16]

In this study, it was reported that 38 patients (76.0%) had gestational trophoblastic neoplasia in remission, while 12 individuals (24.0%) had persistent GTN. According to Mousavi et al, a total of 260 individuals were assessed, and 44.7% of them were identified with persistent GTN.[13] In comparison, Kang et al discovered a rate of 24.2% in another study.[8] GTN was found in 30 patients (14.9%) among 201 women with a molar pregnancy, according to Riahi et al.[2]

In this study, 9 (75%) of the patients in the persistent GTN group were between the ages of 21 and 25, while 26 (68.42%) were in the remission group. We found no significant differences between the two groups. Hoeijmakers et al, reported the mean age was also not statistically significant between the two groups.[17] That consistence with our observation.

In the current study, 9 patients (75.0%) were found to be primipara in the persistent GTN group and 20 patients (52.63%) in the remission group. We found no significant differences between the two groups. Mousavi et al discovered that 24 (22.9%) of patients in group A (remission) and 34 (25.2%) of patients in group B (persistent GTN) were primiparas. We found no significant differences between the two groups.[13]

The current study observed that 6 (50.0%) patients were found gestational age >11 weeks in the persistent GTN group and 21 (55.26%) in the remission group. We found no significant differences between the two groups. A similar observation was found in Hoeijmakers et al and Nahar et al they also found no statistically significant between the two groups.[17,18]

In this study, B-hCG decreased in both groups from the first to the fifteenth weeks however the persistant group serum B-hCG decreased slowly which was less than 10% from the prior value which was statistically significant between the two groups. Mousavi et al observed the median hCG level before evacuation and one and two weeks after evacuation in groups A and B were 89,595 and 29000, 1893 and 6300, and 427 and 2090 mIU/ml respectively.

At one and two weeks of hCG levels were statistically significant ($p<0.05$) between the two groups.[13] According to Hoeijmakers et al patients with post-molar GTN had median serum B-hCG levels of 12000 ng/ml, whereas patients in the spontaneous regression group had much lower levels (5000 ng/ml) before evacuation ($p<0.001$).[17]

Limitations of the study was that it was a single-center study. We took a small sample size due to our short study period. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION

The findings of this study show that serum β-hCG levels in the 2nd, 3rd, and 4th weeks following molar evacuation can predict over 24% of patients who developed GTN after molar evacuation. The decline in serum β-hCG levels during this week was statistically linked to the development of GTN.

This means that for the early detection of GTN in women with molar pregnancy monitoring the three-week declining trend of this marker is recommended. Therefore, follow-up with 2nd, 3rd, and 4th weeks β-hCG level is very important for early detection of GTN which can reduce financial impact and enable more effective and less complex treatment and development of malignancy.

Recommendations

So further study with a prospective and longitudinal study design including a larger sample size needs to be done to validate the findings of our study.

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