

Serum β -hCG Regression Pattern and Time to Normalization in High-Risk Complete Hydatidiform Mole Treated with Prophylactic Chemotherapy

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Abstract

Background: There is a significant risk of progression to gestational trophoblastic neoplasia in complete hydatidiform mole, and many South Asian centers use prophylactic chemotherapy to minimize this risk. The pattern of serial serum β -hCG regression in this practice, however, is not well described.

Objectives: This study aimed to describe the pattern of regression and the time to normalization of serum β -hCG levels in women with high-risk complete hydatidiform mole (CHM) who received prophylactic chemotherapy.

Methods: This prospective observational study of 41 women with ultrasonographically or histopathologically confirmed high-risk complete hydatidiform mole who were conducted at Mugda Medical College & Hospital, Dhaka, Bangladesh from January 2025 to December 2025. Serum β -hCG was determined at baseline, around 48 hours after evacuation, and at serial follow-up visits until normalization. Data were entered and analyzed on SPSS version 26.

Results: The mean age was 25.02 ± 7.08 years, and 56.1% of patients were multigravida. Baseline β -hCG was $\geq 100,000$ mIU/mL in 90.2% of patients (median 170,250 mIU/mL). In 75.6% of cases, prophylactic chemotherapy was used, and none of the patients had toxicity related to the treatment. All 41 patients (100%) had a progressive decline in serum β -hCG levels and reached normalization, with a mean time to normalization of 105.71 ± 38.16 days (median, 97; IQR, 90–119). The time to normalization was significantly shorter in those with histopathologically confirmed complete mole than in those with unspecified/unavailable histopathology (84 days vs 98 days, $p=0.043$), but was not significantly associated with receipt of chemotherapy or baseline β -hCG category.

Conclusion: Prophylactic chemotherapy in high-risk complete hydatidiform mole was found to be associated with complete normalization of β -hCG in all patients without any toxicity, thus suggesting that serial β -hCG monitoring is a reliable, inexpensive method for monitoring regression and follow-up in resource-limited areas.

Keywords: Hydatidiform mole; β -hCG regression; Prophylactic chemotherapy; Gestational trophoblastic neoplasia.

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Introduction:

Gestational trophoblastic disease (GTD) is a group of disorders that result from abnormal growth of the trophoblastic tissue of the placenta, from the non-cancerous hydatidiform mole to the cancerous gestational trophoblastic neoplasia (GTN)¹. Complete hydatidiform mole (CHM) is associated with diffuse trophoblastic hyperplasia and an androgenetic diploid karyotype, and is significantly more likely to develop into GTN than partial mole, with up to 15-20% of cases progressing to GTN². The

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disease is more prevalent in women in South Asia, and there is still a significant burden of molar pregnancy in the country, despite limited population-level epidemiological data in the region, particularly in Bangladesh, in tertiary referral hospitals³. Certain clinical and laboratory characteristics define a “high risk” group for the development of malignant sequelae after molar pregnancy, such as markedly elevated levels of pre-evacuation serum β -human chorionic gonadotropin (β -hCG), excessive uterine enlargement, theca-lutein cysts, and advanced maternal age⁴. In these patients, the use of prophylactic chemotherapy after or at the time of uterine evacuation has been suggested to decrease the risk of GTN by destroying any remaining trophoblastic tissue before it can grow⁵. There is some evidence that the use of prophylactic chemotherapy can reduce the progression of high-risk complete moles to GTN, but the quality of supporting studies is inconsistent, and there are concerns about the potential for unnecessary toxicity, delayed detection of resistant disease, and drug resistance⁶. The mainstay of the treatment of hydatidiform mole, regardless of chemoprophylaxis, is serial measurement of serum β -hCG as a highly sensitive tumor marker that reflects the presence of residual trophoblastic activity⁷. The progressive decrease of β -hCG following evacuation is reassuring, while a plateau or secondary rise indicates the possibility of malignant transformation and should be treated with therapeutic chemotherapy⁸. The shape and time course of the regression curve for β -hCG, not just reaching a normal level, therefore have significant clinical relevance, especially in certain patient subsets where the regression curve may vary⁹. Although the use of prophylactic chemotherapy and β -hCG surveillance is well established, few studies from South Asian tertiary care centers have specifically described the pattern of serial β -hCG regression and the time needed for normalization in high-risk complete mole patients receiving prophylactic chemotherapy¹⁰. This trajectory is especially important in resource-limited environments where the length or irregularity of follow-up care can be a significant burden for patients and health systems. Therefore, this study was designed to describe the sociodemographic and clinical profile, the serial serum β -hCG regression pattern, and the time to normalization of women with high-risk complete hydatidiform mole who received prophylactic chemotherapy in a tertiary care hospital in Bangladesh and

to explore the factors associated with the time to normalization.

Methods:

This prospective observational study was carried out at Mugda Medical College & Hospital, Dhaka, Bangladesh from January 2025 to December 2025, and included 41 women with high-risk complete hydatidiform mole confirmed by ultrasonography and, if available, by histopathological examination of the evacuated products of conception. High-risk status was determined by the presence of clinical and laboratory risk factors, such as a pre-evacuation serum β -hCG level of $\geq 100,000$ mIU/mL, excessive uterine size for gestational age, theca-lutein cysts, and/or maternal age at extremes of reproductive life. Patients who had partial hydatidiform mole, incomplete follow-up records, pre-existing gestational trophoblastic neoplasia at presentation or any other concurrent gynecological malignancy were excluded, as were those who refused consent to participate. Eligible patients received suction evacuation and, if clinically indicated, received a single-agent methotrexate-based chemotherapy as per departmental protocol. Baseline (pre-evacuation) and serial (at about 48 hours post-evacuation) serum β -hCG levels were measured until three consecutive normal readings were achieved, and a subset of patients were followed up thereafter. The variables studied included sociodemographic and obstetric characteristics (age, occupation, gravidity, duration of amenorrhea, and vaginal bleeding), diagnostic and treatment profile (ultrasonographic and histopathological findings, baseline β -hCG category, receipt of prophylactic chemotherapy, and treatment-related toxicity), the serial β -hCG regression pattern across follow-up visits, time to β -hCG normalization and associated follow-up outcomes, characteristics of the regression trajectory (monotonic versus non-monotonic decline), and exploratory factors associated with time to normalization. Data were retrieved from hospital records on a structured proforma and analyzed descriptively using SPSS version 26; continuous variables were presented as mean $\pm$ SD or median with interquartile range, as appropriate, and associations between exploratory factors and time to normalization were assessed using the Mann-Whitney U test, with $p < 0.05$ considered statistically significant.

Results:

Table 1: Sociodemographic and obstetric characteristics of the patients, (n=41)

Variable	Category	n (%) or value
Age, years	Mean $\pm$ SD	25.02 $\pm$ 7.08
Age group	<20 years	10 (24.4)
	20-29 years	19 (46.3)
	30-39 years	10 (24.4)
	$\geq$ 40 years	2 (4.9)
Occupation	Homemaker	36 (87.8)
	Service holder	2 (4.9)
	Operating -theatre staff	2 (4.9)
	Information unavailable	1 (2.4)
Gravidity	Primigravida	18 (43.9)
	Multigravida	23 (56.1)
Duration of amenorrhea, weeks	Median, IQR	10, 8 -12
P/V bleeding or discharge, days	Median, IQR	10, 7 -25

The study population consisted of 41 women aged 25.02 $\pm$ 7.08 years, with almost half (46.3%) aged 20-29 years and only 4.9% $\geq$ 40 years. Most of them were homemakers (87.8%), and multigravida women were slightly more in number than the primigravidae (56.1% vs

43.9%). The median duration of amenorrhea at presentation was 10 weeks (IQR 8-12), and per-vaginal bleeding or discharge had a median duration of 10 days (IQR 7-25 days) with variable time to presentation [Table 1].

Table 2: Baseline diagnostic, laboratory, and treatment profile, (n=41)

Variable	Category	n (%) or value
Ultrasonographic diagnosis	Molar pregnancy or hydatidiform mole	37 (90.2)
	Snowstorm appearance	2 (4.9)
	Molar pregnancy with ovarian hyperstimulation features	2 (4.9)
Histopathological diagnosis	Complete hydatidiform mole	11 (26.8)
	Hydatidiform mole, unspecified	24 (58.5)
	Molar pregnancy, unspecified	2 (4.9)
	Histopathology unavailable	4 (9.8)
Baseline serum β -hCG, mIU/mL	Median, IQR	170,250, 100,000 - 316,550
	Range	22,500 -842,700
Baseline β -hCG category	<100,000 mIU/mL	4 (9.8)
	$\geq$ 100,000 mIU/mL	37 (90.2)
Prophylactic chemotherapy	Received	31 (75.6)
	Not received	8 (19.5)
	Information unavailable	2 (4.9)
Treatment -related toxicity	Developed	0 (0.0)
	Not developed	41 (100.0)

The diagnosis of molar pregnancy or hydatidiform mole was made by ultrasonography in 90.2% of patients, and ovarian hyperstimulation features were observed in 4.9% of patients. In 26.8% of cases, the diagnosis of complete hydatidiform mole was confirmed histopathologically, and in 58.5% the diagnosis was hydatidiform mole,

unspecified. Baseline β -hCG was significantly elevated, with 90.2% of patients having a level $\geq$ 100,000 mIU/mL (median 170,250 mIU/mL). Prophylactic chemotherapy was given in 75.6% of patients, and no toxicity was seen in any patient due to the chemotherapy [Table 2].

Table 3: Serial serum β -hCG regression pattern during follow-up (n=41)

Assessment	Patients assessed, n	Median day from admission	Median β -hCG, mIU/mL	IQR, mIU/mL
Baseline	41	0	170,250.00	100,000.00 - 316,550.00
Approximately 48 hours	41	2	45,000.00	20,728.18 -62,650.00
Follow -up 2	41	9	7,380.20	2,454.42 -12,420.00
Follow -up 3	41	28	2,580.31	1,459.24 -6,320.00
Follow -up 4	41	44	872.60	343.60 -1,980.20
Follow -up 5	41	57	423.00	113.23 -945.20
Follow -up 6	41	73	81.34	25.00 -285.00
Follow -up 7	41	90	25.00	5.00 -84.20
Follow -up 8	41	106	5.00	5.00 -15.02
Follow -up 9	41	121	5.00	5.00 -5.00
Follow -up 10	31	137	5.00	5.00 -5.00

All 41 patients showed a steady decline in serial β -hCG levels from a median of 170,250 mIU/mL to 45,000 mIU/mL at 48 hours and 7,380.20 mIU/mL at day 9. Levels decreased further with each subsequent follow-up visit, to a

median of 25.0 mIU/mL at day 90 and 5.0 mIU/mL, the lower limit of detection of the assay, at day 121, and remained at this lower limit with subsequent visits in the subset of 31 patients who were followed [Table 3].

Table 4: Time to serum β -hCG normalization and follow-up outcomes, (n=41)

Outcome	Category	n (%) or value
Time to β -hCG normalization, days	Mean $\pm$ SD	105.71 $\pm$ 38.16
	Median, IQR	97, 90 -119
	Range	42-227
Time category	≤ 90 days	15 (36.6)
	91 –120 days	16 (39.0)
	121 –180 days	8 (19.5)
	>180 days	2 (4.9)
Achieved β -hCG normalization	Yes	41 (100.0)
	No	0 (0.0)
Number of follow -up measurements	Median, IQR	11, 9 -12
Last recorded follow -up, days	Median, IQR	164, 131 -223
Follow -up status	Further surveillance after normalization	31 (75.6)
	Follow -up ended after normalization	10 (24.4)

All 41 patients (100%) achieved serum β -hCG normalization, with a mean time to normalization of 105.71 $\pm$ 38.16 days (median 97 days, IQR 90–119; range 42-227). Normalization was achieved in 36.6% of patients within 90 days, in 39.0% within 91-120 days, and in 4.9%

more than 180 days. The median number of follow-ups β -hCG measurements was 11 (IQR 9-12); 75.6% of patients did not stop follow-up after documented normalization [Table 4].

Table 5: Characteristics of the serum β -hCG regression trajectory, (n=41)

Regression characteristic	Category	n (%)
Overall β -hCG trajectory	Monotonic decline	31 (75.6)
	Non-monotonic decline	10 (24.4)
Trajectory review flag	Not required	29 (70.7)
	Required	12 (29.3)
β -hCG normalization documented	Yes	41 (100.0)
Additional measurements after normalization	Recorded	31 (75.6)
	Not recorded	10 (24.4)

The majority of patients (75.6%) had a monotonic fall in serum β -hCG without a rise, whereas 24.4% had a non-monotonic pattern, with at least one interval increase followed by normalization; this non-monotonic pattern led to a review of the trajectory in 29.3% of the patients. All

patients had documented normalization, and in 75.6% of patients, further β -hCG levels were obtained after normalization, which is consistent with continued precautionary monitoring in most patients [Table 5].

Table 6: Exploratory factors related to time to serum β -hCG normalization (n=41)

Factor	Group	n (%)	Median time, days, IQR	p-value
Prophylactic chemotherapy	Received	31 (79.5)	98, 87 -114.5	0.931
	Not received	8 (20.5)	105.5, 86.5 -122.3	
Histopathology	Complete hydatidiform mole	11 (26.8)	84, 83 -103	0.043
	Other, unspecified, or unavailable	30 (73.2)	98, 90.8 -124.8	
Baseline β -hCG	<300,000 mIU/mL	29 (70.7)	97, 90 -110	0.785
	$\geq$ 300,000 mIU/mL	12 (29.3)	107.5, 84 -121	
β -hCG trajectory	Monotonic	31 (75.6)	97, 87 -106.5	0.066
	Non-monotonic	10 (24.4)	119, 96 -158	

There was no significant difference between receipt of prophylactic chemotherapy and time to normalization (98 days vs 105.5 days, $p=0.931$) or baseline β -hCG category (<300,000 mIU/mL vs $\geq$ 300,000 mIU/mL; $p=0.785$). Histopathologically confirmed complete hydatidiform mole was significantly associated with faster normalization compared to other or unspecified histopathology (84 days vs 98 days, $p=0.043$). Patients with a monotonic β -hCG decline tended to have a faster normalization than patients with a non-monotonic pattern (97 days vs 119 days, $p=0.066$) [Table 6].

Discussion:

This study aimed to describe the serial serum β -hCG regression pattern and time to normalization in 41 women with high-risk complete hydatidiform mole who received

prophylactic chemotherapy in a tertiary care hospital in Bangladesh. Eventual normalization of β -hCG levels was achieved in all patients, with no documented malignant sequelae or treatment-related toxicity, and the mean time to normalization was about 106 days, which is in line with the generally good results reported for the active monitoring of high-risk molar pregnancies when treatment is indicated¹¹. The predominance of women in their third decade of pregnancy and the almost equal distribution of primigravida and multigravida in this age group is similar to that reported in other regional molar pregnancy series, confirming that complete mole is not limited to any particular reproductive age group¹². Similarly, the high proportion of patients with very high baseline β -hCG levels (more than 90% with levels $\geq$ 100,000 mIU/mL) is similar to that seen in cohorts that were selected specifically for high-risk features,

because very high levels of β -hCG are one of the criteria used to define a high-risk mole¹³. Three-quarters of patients in this series were treated with prophylactic chemotherapy, which is broadly similar to the proportion of patients receiving chemoprophylaxis to prevent post-molar GTN in high-risk patients as described in other centers that offer chemoprophylaxis¹⁴. Importantly, in our study, receipt of prophylactic chemotherapy was not significantly associated with time to normalization of β -hCG ($p=0.931$), which should be interpreted with caution because of the observational study design and the potential for preferential treatment of patients who were considered to be at higher risk at baseline. Similar regression times have also been observed in other single-center studies and highlight the continued uncertainty regarding the incremental value of prophylaxis after complete evacuation and close β -hCG monitoring¹⁵. One of the important findings of this study was that the normalization period was significantly shorter in patients with histopathologically confirmed complete mole than in those with histopathology reported as unspecified or unavailable (84 days vs 98 days, $p=0.043$). This could be due to differences in trophoblastic tissue burden or diagnostic certainty, rather than a true biological difference, and emphasizes the need for consistent histopathological confirmation in the management of molar pregnancy, which is not always available in all the tertiary centers in the region¹⁶. Although the pretreatment β -hCG level has been shown to have a significant prognostic role as described elsewhere, there was no significant association between baseline β -hCG category and normalization time ($p=0.785$) in this cohort, which may be due to the relatively small range of markedly elevated pretreatment β -hCG levels that were captured after the high-risk selection criteria had been applied¹⁷. About 1/4 of patients had a non-monotonic β -hCG decline, and while this difference in time to normalization was not statistically significant (97 days versus 119 days, $p=0.066$), this finding is consistent with literature that suggests that an irregular regression course, even if not a plateau or rise, may indicate a more indolent course of trophoblastic tissue resolution and warrant closer monitoring¹⁸. This trajectory monitoring, which can be accomplished by regular serial β -hCG testing, provides a practical and inexpensive way to risk stratify the intensity of follow-up in situations where more sophisticated regression-slope modeling is not readily available¹⁹. Three-quarters of patients continued

surveillance beyond documented normalization, consistent with the recommendation to continue follow-up after normalization to identify late recurrence, especially in patients in tertiary referral settings who may have geographic and logistic barriers to follow-up²⁰. The lack of treatment-related toxicity in this group is reassuring and in line with the reports of generally low toxicity of single-agent methotrexate-based prophylaxis²¹. Together, these results confirm that structured, serial β -hCG monitoring remains the mainstay of post-molar surveillance in high-risk complete hydatidiform mole, regardless of the chemoprophylaxis approach used, and are consistent with the worldwide trend of good outcomes for actively monitored and managed trophoblastic disease²².

Limitations of the Study:

The study was conducted at a single center and included a small number of patients and may not be generalizable; definitive causal inferences about the effect of prophylactic chemotherapy on regression of β -hCG were not possible.

Conclusion:

The use of prophylactic chemotherapy with structured serial serum β -hCG monitoring was linked with progressive hormonal regression and normalization in all women with high-risk complete hydatidiform mole, with no evidence of malignant transformation or treatment-related toxicity. The overall pattern of β -hCG fall was mostly monotonic, and those with definitive histopathological confirmation of complete mole had a more rapid normalization than those without definitive histopathological confirmation. There was no statistically significant difference between the time to normalization and receipt of prophylactic chemotherapy or baseline β -hCG category in this cohort. These results justify the use of serial β -hCG as a practical, reliable, and cost-effective method to assess regression and to determine the duration of follow-up in high-risk complete hydatidiform mole treated in a tertiary care center. The observed individual regression patterns suggest that continued extension of follow-up beyond initial normalization, as done in most of this cohort, seems to be a reasonable precaution.

Recommendations:

It is recommended that larger, multicenter, prospective studies be performed to determine the independent role of

chemoprophylaxis in hormonal normalization in high-risk complete hydatidiform mole.

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Author Contribution:

1. Dr. Farhana Rahman: primarily responsible for the drafting of the article.
2. Dr. Mst. Rukshana Pervin: Conceptualization and data analysis
3. Dr. Shamsun Nahar: Review and supervision.
4. Dr. Mohammad Mozammel Huq: Helps in questionnaire preparation and correction of article.
5. Dr. Mohammad Abu Sayeed Talukdar: Providing access to necessary resources and creating figures and tables.
6. Dr. Sarwar Mahboob: Providing access to necessary resources and manuscript drafting.
7. Dr. Md. Kamrul Islam: Helps in data collection.
8. Prof. Dr. Md. Saiful Islam, Providing review and update.

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