

Role of Human Chorionic Gonadotropin Level After Molar Suction Curettage in Anticipating Post-molar Trophoblastic Neoplasia in Vietnam

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ABSTRACT

Objective: The objective of the study was to determine the trophoblastic neoplasia (TN) anticipating the value of beta-human chorionic gonadotropin (β -hCG) concentration 2 weeks after molar suction curettage and its concentration ratio at pre-removal versus 2-week post-removal. **Materials and Methods:** A nested case-control study in hydatidiform mole patients admitted to Tu Du Hospital from July 2016 to December 2017 was conducted. Patients were divided into two groups with all 123 cases of TN (case group) and 247 random cases of spontaneous molar remission (control group). Receiver operating curve was applied to find the β -hCG factors of the most predictive value. **Results:** The average length of time for TN diagnosis was 6.2 weeks as per the Federation of Gynecology and Obstetrics 2002. The ideal cutoff points of β -hCG concentration 2 weeks and 4 weeks after molar suction curettage for anticipating TN were 700 mIU/mL (sensitivity: 79% and specificity: 69%) and 148 mIU/mL (sensitivity: 83% and specificity: 84%), respectively. The ideal cutoff points of β -hCG ratio at pre-removal versus 2-week and 4-week post-removal for anticipating TN were 340 (sensitivity: 77% and specificity: 64%) and 1345 (sensitivity: 79% and specificity: 84%), respectively. **Conclusion:** β -hCG concentration 2 weeks after molar removal is a good factor to early anticipate the risk of TN switch in hydatidiform mole patients.

Key words: Gestational trophoblastic neoplasia, hydatidiform mole, spontaneous remission

INTRODUCTION

Hydatidiform mole is a type of trophoblastic disease related to pregnancy.^[1] The incidence rate varies with territories, eating habit, socio-economic conditions,^[2] etc., low rate in Europe and North America (1.2/1000 pregnancies)^[3] and high in Asia (Vietnam: 1.52/500 pregnancies).^[4] The main therapy of molar pregnancy is uterine cavity suction and curettage and then monitoring beta-human chorionic gonadotropin (β -hCG) progress together with abnormal symptoms. In the complication monitoring course, trophoblastic neoplasia (TN) is the most concerning issue with a notable incidence rate of 15–28%^[5] for complete hydatidiform mole and 1–5% for

partial hydatidiform mole.^[6] This is a malignant, dangerous, and metastatic complication and requires long-term and costly therapy. A few studies have tried to find out the factors that can help to anticipate post-molar TN or remission to better counsel patients and to help clinicians to pay attention to those risks to reduce the length of time between molar pregnancy diagnosis and TN.^[7] The factors such as maternal age, theca lutein cyst size of >6 cm, and history of molar pregnancy have a “low” predictive value for post-molar TN. Recently, there have been international studies on TN detection possibility based on the post-removal β -hCG concentration, and it was noted that the pattern of β -hCG concentration change in TN was different from that in hydatidiform mole remission.^[8,9]

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Tu Du is an Obstetrics and Gynecology specialized hospital (with 2500 patient beds) of the central level providing treatment, training, and research services. The hospital is appointed by the Ministry of Health as the highest level of referral for 32 provinces/towns in Southern Vietnam. At Tu Du Hospital in 2016, there were 1100 molar pregnancies of which 228 cases turned into TN. We were managing quite a huge number of hydatidiform mole patients, but we did not have a study to early anticipate TN yet. From pilot studies in the world and actual situations at Tu Du Hospital, we decided to conduct the study of “Role of β -hCG concentrations 2 weeks after molar suction curettage in anticipating post-molar TN” with a research question: Are β -hCG concentrations 2 weeks after molar removal predictive of post-molar TN?

Objective

The objective of the study was to determine the anticipating values of β -hCG concentration 2 weeks after molar suction curettage and its ratio of pre-molar removal versus 2-week post-molar removal.

MATERIALS AND METHODS

We conducted a nested case-control study on 370 hydatidiform mole patients admitted in Tu Du Hospital Department of Gynecologic Oncology in the period between July 2016 and December 2017. All those patients had full data in their medical records, especially β -hCG results before and after suction curettage, to ensure the correctness of data analysis and assessment for maximal bias elimination in the retrospective study of medical records.

In this study, 370 patients were selected from 1110 molar cases during the same period of whom all 123 post-molar TN cases meeting inclusion criteria were taken in and 57 TN cases were ruled out due to unmet inclusion criteria, and 247 molar cases meeting inclusion criteria were randomly selected from 764 molar cases which did not progress to TN and were not administered preventive chemotherapy (166 cases with preventive chemotherapy were initially excluded from the non-TN group).

We separated patients into two groups of case versus control on 1:2 ratio in which case group TN was diagnosed as per the International Federation of Gynecology and Obstetrics (FIGO) (FIGO 2002)^[10] on such criteria as β -hCG plateau in four consecutive measurements during 3 weeks (e.g., days 1, 7, 14, 21); β -hCG increase in three consecutive measurements during 2 weeks (e.g., days 1, 7, 14), β -hCG existence after 6 months; choriocarcinoma by histopathology testing. The control group (spontaneous remission) was defined as post-molar patients without progression into TN, β -hCG negative remained negative after 6 months' suction curettage. Of course, all patients of the two groups

who were not on chemotherapy had full information and made return visits as scheduled would fully meet sampling criteria. β -hCG test was made with an immuno-chemo-fluorescent method on Architect machine at the maximum threshold of 1,500,000 mIU/mL and the minimum threshold of 5 mIU/mL.

Ethics approval for the study was obtained from the Institutional Review Board of University of Medicine and Pharmacy at Ho Chi Minh City on October 12, 2017 (N_o. 357/DHYD-HD).

Data processing and analysis

Student *t*-test was used to compare the means of quantitative variables of the two groups. β -hCG concentrations 2 weeks and 4 weeks after molar removal as well as their ratios as compared with those of pre-removal were used to draw curve receiver operating curve (ROC), area under the curve (AUC) would represent the TN anticipating value. The ideal cutoff point was built on Youden indicator, then from that point, the indicators of a complete anticipating method were determined on cutoff point, sensitivity, specificity, positive, and NPVs. Multivariate analysis was also applied to assess the true correlation between β -hCG of 2-week post-molar removal and TN after ruling confounders out.

RESULTS

In the period of study, there were 180 over 1110 (16.2%) molar patients who were diagnosed TN by FIGO 2002. There were 57 TN cases excluded for two main reasons for preventive chemotherapy and unscheduled return visits, the remaining 123 cases were analyzed showing: one case was diagnosed TN 1 week after molar removal, one case after 2 weeks, nine cases after 3 weeks (7.3%), 43 cases after 4 weeks (35%), 31 cases after 6 weeks (25.2%), 13 cases after 8 weeks (10.6%), and the remaining 25 cases (19.5%) after 10, 12, and 14 weeks. The mean time of TN diagnosis was 6.2 weeks. Some characteristics of the patient groups were described in Table 1. TN patients had a higher mean age than those with spontaneous remission (31.3 vs. 28.3, $P < 0.05$). The two groups were also compared on age group, history of pregnancy, and uterine size versus gestational age matching. The factors of previous molar pregnancies, pre-eclampsia, hyperthyroidism, and trophoblastic embolism were not present in the study groups; there was one case only with a theca-lutein cyst of >6 cm in TN group. β -hCG mean concentration before suction curettage in case group was 403678 mIU/mL, ranging from 4689 to 1,500,000 mIU/mL; whereas control group's β -hCG mean concentration before suction curettage was 239,998 mIU/mL, ranging from 32 to 1,500,000 mIU/mL ($P < 0.5$). β -hCG mean concentration 2 weeks after molar removal in case group was 12,616 mIU/mL (70–497,403 mIU/mL) which was significantly different from β -hCG mean concentration of 1154 mIU/mL

Table 1: Comparison of baseline characteristics of the patients, and β -hCG levels at pre-evacuation and after two and 4 weeks in the two groups

Factors	TN (n=123) (%)	Remissions (n=247) (%)	P Value
Age			
≥ 40	28 (8.9)	20 (9.7)	0.017
21-39	84 (68.3)	203 (82.3)	
≤ 20	11 (22.8)	24 (8.1)	
Parity			
0	22 (17.9)	70 (28.3)	0.07
1	32 (26.0)	76 (30.8)	
≥ 2	69 (56.1)	101 (40.9)	
Large-for-date uterus			
No	94 (76.4)	236 (95.6)	0.000
Yes	29 (23.6)	11 (4.4)	
Pre-evacuation β -hCG (mIU/mL)			
Median	403,678	239,998	0.000
Range	4689-1,500,000	32-1,500,000	
β -hCG after 2 weeks (mIU/mL)			
Median	12619	1154	0.000
Range	70-497403	5-75247	
β -hCG after 4 weeks (mIU/mL)			
Median	6555	214	0.000
Range	10-170451	5-12150	

β -hCG: Beta-human chorionic gonadotropin, TN: Trophoblastic neoplasia

Table 2: Cutoff point using a receiver operating characteristic curve

Factors	Cutoff point	AUC	95% CI
Pre-evacuation β -hCG (mIU/mL)	NA	0.69	0.62-0.74
β -hCG after 2 weeks (mIU/mL)	700	0.80	0.75-0.84
β -hCG after 4 weeks (mIU/mL)	148	0.89	0.86-0.93
Ratio of pre-evacuation β -hCG to β -hCG after 2 weeks	340	0.75	0.69-0.80
Ratio of pre-evacuation β -hCG to β -hCG after 4 weeks	1345	0.86	0.82-0.90

CI: Confident interval, AUC: Area under the curve, β -hCG: Beta-human chorionic gonadotropin

(5–7,5247 mIU/mL), ($P < 0.05$) in control group 2 weeks after molar removal. β -hCG mean concentrations at 4-week post-molar removal in case group and control group were 6555 mIU/mL and 214 mIU/mL, respectively, with concentration ranges of 10–170, 451 mIU/mL and 5–12, 150 mIU/mL ($P < 0.05$), respectively.

ROC curve was constructed with our data (Figure 1). The ideal cutoff point and area under ROC of β -hCG concentrations at 2-week and 4-week post-molar removal as well as their ratios comparing with those of pre-molar removal are presented in Table 2. The ideal cutoff points of β -hCG at 2-week and 4-week post-molar removal were 700 mIU (AUC, 0.80; sensitivity 0.79 and specificity

0.69) and 148 mIU/mL (AUC, 0.89; sensitivity 0.83 and specificity 0.84), respectively. The ideal cutoff points of β -hCG concentration ratio at pre-removal versus 2-week and 4-week post-molar removal were 340 mIU (AUC, 0.75; sensitivity 0.77 and specificity 0.64) and 148 mIU/mL (AUC, 0.86; sensitivity 0.79 and specificity 0.84), respectively [Table 3].

Risk ratios were adjusted with multivariate analysis. The risk of TN switch was higher when β -hCG concentration at 2-week post-removal was >700 mIU/mL (Odd ratio [OR] = 3.95, $P < 0.05$) or β -hCG concentration ratio of pre-removal versus 2-week post-removal <340 (OR = 5.1, $P < 0.05$) [Table 4].

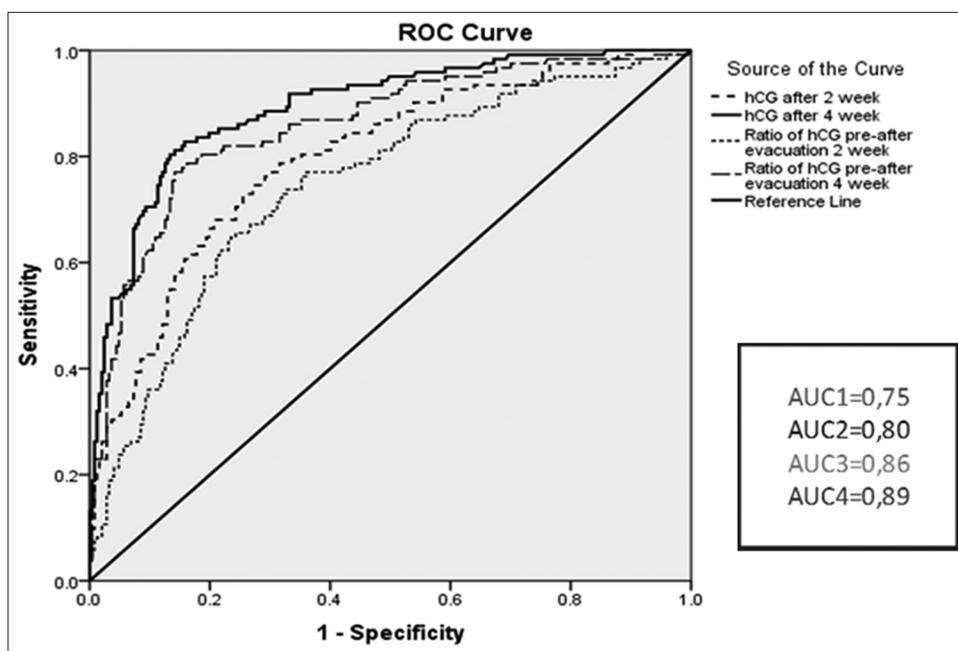


Figure 1: ROC curve presenting correlation between Trophoblastic Neoplasia and β -hCG after molar removal

Table 3: Sensitivity, specificity, predictive value to predict TN

Factors	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
β -hCG after 2 weeks (mIU/mL) ≥ 700 versus <700	78.86 (70.6-85.7)	68.52 (62.2-74.2)	55.43 (50.3-60.4)	86.67 (82.1-90.2)
Ratio of pre-evacuation β -hCG to β -hCG after 2 weeks: ≤ 340 versus <340	77.24 (68.8-86.4)	63.97 (57.6-69.9)	51.63 (65.9-77.9)	84.95 (86.9-93.6)
β -hCG after 4 weeks (mIU/mL) ≥ 148 versus <148	82.79 (75.1-89.1)	84.21 (79.1-88.2)	72.34 (68.1-80.5)	90.83 (85.7-92.4)
Ratio of pre-evacuation β -hCG to β -hCG after 4 weeks: ≤ 1345 versus <1345	78.69 (70.6-85.7)	83.81 (78.6-88.2)	70.80 (64.3-76.6)	88.84 (85.3-92.3)

CI: Confident interval, β -hCG: Beta-human chorionic gonadotropin, PPV: Positive predictive value, TN: Trophoblastic neoplasia, NPV: Negative predictive value

Table 4: Multivariate logistic regression for TN

Factors	Odds ratio	P Value
Risk hydatidiform mole by the WHO (1983)		
High	1	0.002
Low	4.22 (1.7-10.1)	
β -hCG after 2 weeks		
≥ 700 mIU/mL	1	0.044
<700 mIU/mL	3.95 (2.1-6.9)	
Ratio of pre-evacuation β -hCG to β -hCG after 2 weeks		
≤ 340	1	0.000
>340	5.1 (2.5-10.0)	

β -hCG: Beta-human chorionic gonadotropin, TN: Trophoblastic neoplasia, WHO: World Health Organization

DISCUSSION

The main purpose of this study is to determine whether β -hCG concentration and ratio 2 weeks after molar removal can help to early predict the possibility of TN switch for post-molar patients (based on FIGO criteria).

β -hCG concentration increase reflects the disease existence whereas β -hCG concentration reduction is the evidence of remission. To diagnose TN, patients must be monitored every week or every 2 weeks after molar removal until β -hCG is negative for 3 consecutive times, and then the monitoring is made every month for 6 months.^[11] The average time for β -hCG return to the first negative in our study was 6.2 weeks, nearly equivalent to Genest's *et al.*^[11] (9 weeks). We also collected the same results as other studies including maternal age ≥ 40 related to TN.^[12] We did not find other

TN-related factors such as theca-lutein cyst ≥ 6 cm, history of molar pregnancy, pre-eclampsia, hyperthyroidism, and trophoblastic embolism. β -hCG concentrations before molar removal $>100,000$ mIU/mL were considered a TN predictive factor and applied to a predictive score ladder.^[10] However, there were also some studies demonstrating no correlation ($P = 0.08$) (Kang *et al.*^[13] and Wolfberg *et al.*^[13]). We found β -hCG before molar removal had a predictive meaning of TN ($P < 0.05$), an average AUC of 0.69, and hence, its TN predictive value was low.

Khoo's *et al.*^[14] and Ayhan's *et al.* studies^[15] did not report a significant correlation between β -hCG and TN, but some other authors did the contrary^[16,13] and recently some studies found β -hCG 1 and 2 weeks after molar removal had a TN prognostic meaning (Mousavi *et al.*^[17] and Kang *et al.*^[16]). However, due to economic status and geographic distance, patients, in our study, were monitored every 2 weeks, and thereby, we were not able to do assessment at 1-week post-molar removal, and instead, we examined at two points of 2 and 4 weeks to use β -hCG at 2-week post-molar removal for early prediction and at 4-week post-removal for prediction in cases missing a return visit at 2-week point. The remaining question was between concentration and ratio which one provided a better prediction. Kang's and Mousavi's studies concluded the 2-week point gave better prediction than the 1-week, but there was a difference when comparing predictive values between ratio and concentration, which was demonstrated with areas under ROC curve (Kang: $AUC_{\text{ratio}} = 0.77$, $AUC_{\text{concentration}} = 0.74$; Mousavi: $AUC_{\text{ratio}} = 0.78$, and $AUC_{\text{concentration}} = 0.80$). In our study, β -hCG 4 weeks after molar removal gave better prediction than that at 2-week post-removal with both concentration and ratio indicators. In the meantime, at each point of time, it was noted that β -hCG concentration had a better predictive value of TN than concentration ratio of pre-removal versus post-removal, but the distinction was not big [Table 2]. The ideal cutoff point and under-ROC area of prediction method based on ratio of pre-removal versus 2-week post-removal were 340 and $AUC = 0.77$ (95% confident interval [CI]: 0.69–0.80). At this cutoff point, the β -hCG concentration ratio of pre-removal versus 2-week post-removal for TN prediction had sensitivity 77% and specificity 64%. After such TN-related factors as patient's age, history of pregnancy, history of birth delivery, large-for-date uterus, blood group, etc., were ruled out, β -hCG concentration ratio of pre-removal versus 2-week post-removal was an independent predictor of TN (OR = 5.1, 95% CI: 2.5–10.0, $P < 0.05$).

Although the reduction rate of β -hCG has been a TN prognostic factor of interest in recent years,^[18,19] concentration values after suction curettage are also a factor in place for TN prediction.^[16,17] Our study also showed the similarity when β -hCG concentration 2 weeks after molar removal anticipated TN quite well (AUC = 0.80, 95% CI: 0.75–0.84; equivalent

to Mousavi's *et al.*^[17]). The ideal cutoff point of prediction method based on β -hCG concentration at 2-week post-removal was 700 mIU/mL; at this cutoff point, sensitivity and specificity were 79% and 69%. After such TN-related factors as patient's age, history of pregnancy, history of birth delivery, large-for-date uterus, blood group, etc., were removed, β -hCG concentration 2 weeks after molar removal was an independent predictor of TN (OR = 3.95, 95% CI: 2.1–6.9, $P < 0.05$).

In brief, β -hCG was a TN-related factor, its predictive value gradually increased from the point of pre-suction curettage to the point before the average time of TN diagnosis (as per the FIGO 2002). Therefore, what time can ensure both the value of TN prediction method and early detection is the most appropriate; 1 week is ideally early but Mousavi's and Kang's results had not highly predictive value; 4 weeks are quite late although the predictive value is good, and therefore 2-week point with above-mentioned results is the highest priority for the use of β -hCG to early anticipate TN. As a result, it can be applied to clinical practice for screening post-molar patients with a high risk of TN switch, helping closer monitoring, more careful counseling, and maximum reduction of follow-up loss in those patients.

Although there were limits due to medical records review, we maximally reduced errors in data thanks to specially structured records, careful note-taking, and refinement. Therefore, with obtained results, it is hoped to help clinicians with one more tool of 2-week post-suction-curettage β -hCG factor to early predict TN, and thereby, there will be a strategy to better manage patients.

CONCLUSION

Study data from 123 TN cases and 247 hydatidiform mole cases with spontaneous remission collected from July 2016 to December 2017 showed that the TN anticipating the value of β -hCG concentration 2 weeks after molar suction curettage had AUC = 0.8 with a cutoff point of 700 mIU/mL, sensitivity = 79%, and specificity = 68%. The TN anticipating the value of β -hCG concentration ratio at pre-molar removal versus 2-week post-molar removal had AUC = 0.75, with the cut-off point of 340, sensitivity 77%, and specificity 64%

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