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Beta-human chorionic gonadotropin levels as early predictor for progression to Gestational Trophoblastic Neoplasia after molar pregnancy evacuation at a Philippine tertiary hospital

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Abstract:

OBJECTIVE: This study aimed to determine if the beta-human chorionic gonadotropin (hCG) levels during the first 5 weeks after a molar evacuation predict progression to gestational trophoblastic neoplasia (GTN).

MATERIALS AND METHODS: This was a retrospective cohort study of complete mole cases managed at a Philippine tertiary hospital from January 2009 to December 2018. Extracted data were analyzed using applicable statistical tools. The level of significance was set at a $P < 0.05$ using two-tailed comparisons.

RESULTS: One hundred and fifty-five complete patient records were available for review. Disease progression in 15.48% of cases while regression in 84.52% were noted. Uterine size was larger in those who eventually had postmolar GTN (*t*: −3.12, df: 32.64, *P*: 0.01). Analysis of the receiver operating characteristic curve showed that optimum cut-off levels for predicting GTN at 1, 3, and 5 weeks after evacuation were 4,152 mIU/ml (sensitivity: 50%, specificity: 94.7%, area under the curve [AUC]: 0.75), 804 mIU/ml (sensitivity: 62.5, specificity: 96.9%, AUC: 0.94), and 541 mIU/ml (70.8%, specificity: 97.7%, AUC: 0.96), respectively.

CONCLUSION: The level of hCG within the first 5 weeks after molar pregnancy evacuation is predictive of progression to GTN.

Keywords:

Gestational trophoblastic diseases, hydatidiform mole, beta-human chorionic gonadotropin

Introduction

Gestational trophoblastic disease has broad variations in distribution worldwide, with higher frequencies in some parts of Asia, Middle East, and Africa.[1-6] These may be attributed in part to difficulties in methodically obtaining accurate data. Locally, the Philippines has a national prevalence rate of hydatidiform mole (H. mole) of 2.4 per 1000 pregnancies,[7] and in a tertiary hospital where the only trophoblastic disease center of the country is found, the incidence is even higher at 13 per 1000 pregnancies.[8]

Molar pregnancies are typically managed by uterine evacuation. For those who have their desired family size, hysterectomy is an option.[9-12] Trophoblastic disease centers have different postevacuation

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human chorionic gonadotropin (hCG) monitoring schedules. In the Philippines, a preevacuation hCG is determined, followed by hCG determination taken 1 week after evacuation. It is then serially monitored every 2 weeks until two consecutive normal levels of <5 mIU/ml. Monitoring is continued monthly for another 6 months. Postmolar gestational trophoblastic neoplasia (GTN) is diagnosed based on the revised FIGO guidelines: (1) a plateauing hCG over a period of at least 3 weeks (e.g., days 0, 7, 14, 21); (2) rising hCG levels for 3 weekly consecutive measurements or longer, over at least a period of 2 weeks (e.g., days 0, 7, 14); or (3); or a histologic diagnosis choriocarcinoma.[13] The plateauing or rising values to satisfy the criteria for the diagnosis of postmolar GTN do not necessarily occur immediately after evacuation as implied by a local study, but it showed that 94.3% were diagnosed within the first 6 months of HCG monitoring.[14] In Latin America, follow-up consists of weekly clinical evaluation and hCG determination until three consecutive negative values are taken; then monthly for 6–12 months, then annually for life, until the woman has a new pregnancy.[15] In the United Kingdom, serum hCG surveillance is done every 2 weeks until normal, then urine hCG levels every 4 weeks for 6 months after evacuation if the first normal hCG is taken within 56 days after evacuation; or if hCG becomes normal more than 56-day postevacuation, weekly urine hCG determination is done for 6 months of normal values.[16]

Not all patients progress to a spontaneous recovery as seen by the regression of their β-HCG levels. Some will progress to develop GTN and would require chemotherapy. Several studies tried to establish relationship between levels of HCG during the early part of monitoring and GTN.[17-24] In the Philippines, literature review showed paucity of local studies on HCG regression as an early indicator for postmolar GTN. Results of this study will help in early identification of patients who will likely have GTN during the monitoring period. The results may provide additional basis for strongly advising patients to comply with HCG surveillance, especially those who already have risk factors in developing GTN and are at risk of being lost to follow-up.

This study tried to establish the predictive power of β-HCG in postmolar GTN. It determined which values (in mIU/ml) of HCG during the early period of hCG monitoring specifically at 1st, 3rd, and 5th week after the evacuation of complete H. moles were associated or prognostic of postmolar GTN during the monitoring period.

Materials and Methods

Study design

This is a retrospective cohort study and included all patients with a diagnosis of complete H. mole who were admitted and managed at a Philippine tertiary hospital for the period 2009–2018. Sample size computation was based on the risk of a patient with complete H. mole of having malignant sequelae of 15%–25%. The computed sample size is 196 at 15% risk of complete H. moles developing GTN, with a confidence interval of 95%, a Z score of 1.96, and a margin of 5%. The actual sample population that met the inclusion and exclusion criteria was 155.

Description of the procedure

A review of the annual census and reports, admissions and ward reports, OPD census, and the computer database of the section of trophoblastic disease in a Philippine tertiary hospital of diagnosed of H. mole cases was done. Pertinent data such as age, age of gestation, parity and gravidity, history of prior abortion or mole, uterine size, the type of H. mole, mode of evacuation, whether chemoprophylaxis was given, and preevacuation and serial HCG determination following local clinical practice guidelines in postevacuation monitoring were be obtained, recorded, and analyzed. Total number of deliveries per year was also extracted. Anonymity of patients was achieved by assigning a number to each subject.

The conduct of this study commenced after approval of the study protocol from the hospital ethics board.

Description of the outcome measures

The main outcome measures of the study were the cut-off levels of HCG at 1, 3, and 5 weeks after molar evacuation in complete moles most predictive of postmolar GTN. The different sensitivities and specificities of each optimum cut-off values of HCG at 1, 3rd, and 5th week postevacuation were determined.

The gold standard to which these levels were compared to determine the sensitivity and specificity was the diagnosis of postmolar GTN while undergoing serial HCG surveillance after molar evacuation. The incidence of GTN progressing from complete H. mole was determined from the study population.

Data analysis

Data were manually entered into an electronic spreadsheet file and subsequent data processing, and analysis was carried out using Stata 13 (StataCorp LLC, 4905 Lakeway Dr. College Station, TX 77845, USA). Descriptive statistics such as mean and standard deviation for continuous variables were used specifically for the maternal age in years, age of gestation, uterine size, and baseline and subsequent levels of the beta-hCG. The median and interquartile range for the subsequent levels of beta-hCG during the period of observation and frequency (percentage) were used for the categorical

data variables such as disease status (remission or progression to neoplasia). A Pearson's Chi-square test and independent *t*-test with Welch's correction, whichever is applicable, were performed to determine if there is a significant difference in the baseline clinicodemographic variables between the study groups (i.e. remission or progression).

The sensitivity, specificity, positive and negative predictive values, and the area under the curve (AUC) as well as their interval estimates, were also computed based on the 1st, 3rd, and 5th week postevacuation levels of the beta-HCG as predictive values, and the final outcome whether there was regression or progression based on the records as the endpoint for the disease status. The level of significance for all sets of analysis was set at a $P < 0.05$ using two-tailed comparisons.

Results

There were 799 cases of H. mole who were admitted during the period 2009–2018. Ninety-one percent of these had a histopathologic diagnosis of complete mole, 5% were partial mole, and 4% were not classified into either of the two types. The total number of deliveries in the said institution was 46,791 during the said period hence, a prevalence of 15–16 molar pregnancies per 1000 deliveries.

Table 1: Clinicodemographic characteristics of the study population (*n*=155)

Characteristics	Regression, *n* (%)	Progression, *n* (%)	*P**
n	131 (84.52)	24 (15.48)	<0.01**
Maternal age (years)			
<20	149 (10.69)	2 (8.33)	0.68
20-40	94 (71.76)	16 (66.67)	
>40	23 (17.56)	6 (25)	
Gravidity			
1	33 (25.19)	4 (16.67)	0.37
≥2	98 (74.81)	20 (83.33)	
Parity			
Nulliparous	36 (27.48)	5 (20.83)	0.78
1	33 (25.19)	7 (29.17)	
≥2	62 (47.33)	12 (50)	
History of abortion	21 (16.03)	4 (16.67)	0.94
Prior molar pregnancy	3 (2.29)	-	0.60
Uterine size (weeks)	17±3.56 (6-26)	19±3.59 (14-30)	0.01**
Age of gestation (weeks)			
<13	46 (35.11)	10 (41.67)	0.54
13-≤26	85 (64.89)	14 (58.33)	
Mode of evacuation			
Suction curettage	106 (80.92)	21 (87.50)	0.44
Hysterectomy	25 (19.08)	3 (12.50)	
Chemoprophylaxis	106 (80.92)	18 (75)	0.51
Follow-up period in weeks	35±4.39 (29-55)	11±10.85 (5-61)	<0.01**
Time-to-event in weeks	9±4.42 (3-29)	11±10.85 (5-61)	0.47

*P<0.05, ** statistically significant

Of the 799 cases, 155 patients had complete record of their serial hCG monitoring. Table 1 shows the clinicodemographic characteristics of the said women. Their average age was 31 years old with more than half of the sample between 20 and 40 years old. The age of gestation of the women ranged from 6 to 27 weeks with an average at 14 weeks. The average uterine size was equivalent to 17 weeks. Less than 2% of the women had a history of molar pregnancy before the current one and 16% reported having a history of abortion. The preevacuation beta hCG levels ranged from 1,105.67 to more than 5 million mIU/mL with an average at 619, 669 units.

Among the women in the disease regression group, 80.92% (106) had suction curettage and 19.08% (25) had hysterectomy. For those who had disease progression, 87.5% (21) underwent suction curettage and 12.5% (3) had hysterectomy. Chemoprophylaxis was given to 80.92% (106) of those in the regression group and 75% (18) in the progression group. Duration of follow-up ranged from 5 weeks to 61 weeks. Those in the disease regression group had a longer average period of follow-up compared to the progression group (35 ± 4.39 [29–55] vs. 11 ± 10.85 [5–61], $p < 0.01$).

Table 2 summarized the series of nonparametric equality of medians test comparing the beta hCG levels during the serial postmolar beta hCG determinations between the two groups of women under study. The values at preevacuation, 1-, 3-, and 5-week postevacuation between the regression and progression groups were 311,331 mIU/ml, 1557 mIU/ml, 118.1 mIU/ml, 21.87 mIU/ml and 1,030,519 mIU/ml, 5,977.43 mIU/ml, 1,079.36 mIU/ml, and 920.52 mIU/ml, respectively. The median hCG values preevacuation ($\chi^{2:}$ 8.53, $P < 0.01$) and 1 week ($\chi^{2:}$ 6.13, $P < 0.01$) after evacuation levels of the beta hCG levels were significantly higher among those women who developed disease progression. Further, the median β-hCG levels were much higher among those women who had disease persistence during the 3rd (χ^{2}: 26.43, $P < 0.01$) and 5th week ($\chi^{2:}$ 26.43, $P < 0.01$) after evacuation of the molar pregnancy.

To obtain optimum cut-off values predictive of postmolar GTN, receiver operating characteristic curve (ROC) was used at 1, 3, and 5 weeks after evacuation. Analysis showed that the AUC when the levels of beta-hCG a week after evacuation is used as a marker for detecting subsequent disease progression was 0.75 [Figure 1]. The optimum cut-off for differentiating progression and regression 1 week after evacuation is 4152 mIU/ml. This

Table 2: Levels of beta-human chorionic gonadotropin at 1, 3, and 5 weeks

Levels	Overall	Regression	Progression	χ^2 (*P**)
Baseline β-hCG	358,000 (784,714)	311,331 (523,107.8) [1105.67-5,070,000]	1,030,519 (718,759.5) [59,386-4,682,000]	8.53 (<0.01**)
1 week after evacuation	1784 (3293.77)	1557 (2,356.6) [27.44-12,729]	5977.43 (6749.92) [45.3138,729]	6.13 (<0.01**)
3 weeks after evacuation	146.1 (303.04)	118.10 (191.99) [1.66-2903]	1079.36 (4491.36) [164.8-26,725]	26.43 (<0.01**)
5 weeks after evacuation	30.98 (184.97)	21.87 (55.53) [0.1-1459]	920.52 (3207.85) [100.9-37,209]	26.43 (<0.01**)

*P<0.05. ** stistically significant; β-hCG=Beta-human chorionic gonadotropin

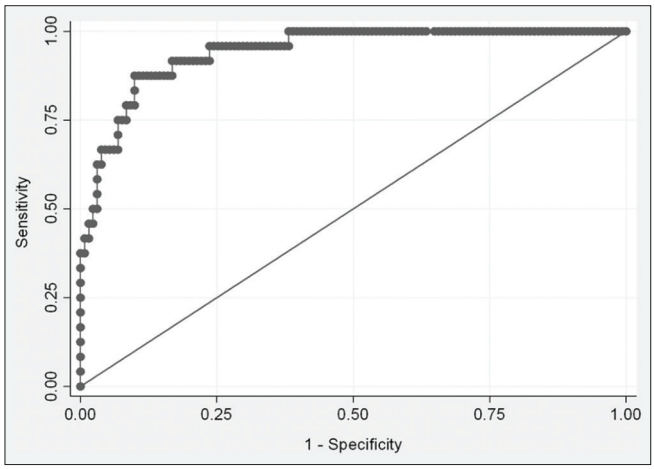

Figure 1: Receiver operating characteristic curve for beta-hCG Levels 1 week after evacuation

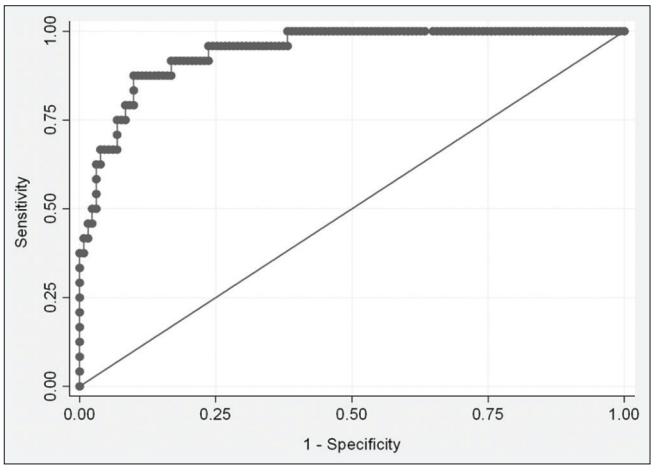

Figure 2: Receiver operating characteristic curve for beta-human chorionic gonadotropin levels 3 weeks after evacuation

cut-off correctly classified 81.29% of the cases with an associated sensitivity of 66.67% and specificity of 83.97% who later disease progression.

Further analysis of the ROC showed that the AUC when the levels of beta-hCG after 3 weeks from molar evacuation is used as a marker for detecting subsequent disease progression was 0.94 [Figure 2]. The optimum cut-off for prognosticating disease progression at 3 weeks after evacuation is 804 mIU/mL. This cut-off correctly classified 91.61% of the cases with sensitivity of 62.50% and specificity of 96.95% who later had disease progression.

Moreover, it can be shown that the AUC when the optimum cut-off levels of beta-hCG after 5 weeks from molar evacuation is used as a marker for detecting subsequent disease progression was 0.96 [Figure 3]. The optimum cut-off 5 weeks after evacuation is 512 mIU/ml for later prognostic outcomes. This cut-off correctly classified 93.55% of the cases who were later diagnosed of disease progression with a sensitivity of 70.83% and specificity of 97.71%.

In Table 3, the hCG values in predicting progression to GTN were summarized. The cut-off levels of hCG at 5-week postevacuation showed the highest sensitivity, specificity, and positive and negative predictive values as compared to levels at 1 and 3-week postevacuation. The optimum cut-off hCG level at 5-week postevacuation was 541 mIU/ml with a 70.8%, 97.7%, and 93.55% sensitivity, specificity, and accuracy rate.

The detection rate for postmolar GTN during the first 5–6 weeks of monitoring was 4.17%. At 12 weeks of postmolar monitoring, disease progression was significantly detected in 22 (91.67%) of the women under study ($\chi^{2:}$ 139.95, $P < 0.01$).

Discussion

This study was done to find out what levels of hCG during the early monitoring period after the evacuation of a molar pregnancy can be used as predictor for postmolar sequalae. Studies show that with the complete molar pregnancy, there is a 15%–25% chance of developing GTN.[25] This was similarly seen in our study. An earlier local study in the same institution reported that 20.5% had disease progression or did not achieve normalization of hCG titers.[14] The difference in the rate from this current study may be attributed to the fact that this study included only those who had complete serial hCG monitoring according to protocol particularly those who had hCG levels at 1, 3, and 5 weeks and went on to do so until they were finally discharged from monitoring.

Except for the uterine size, there were no noted significant differences in terms of baseline clinicodemographic characteristics such as age, antecedent pregnancy,

Table 3: Predictive power of beta-human chorionic gonadotropin postevacuation

Parameters	1 week after evacuation	3 weeks after evacuation	5 weeks after evacuation
Overall			
AUC (SE)	0.75 (0.05)	0.94 (0.02)	0.96 (0.01)
95% CI	0.65-0.85	0.90-0.98	0.93-0.99
Optimal cut-off (IU/ML)	4152	804	541
Sensitivity (%)	50	62.5	70.8
Specificity (%)	94.7	96.9	97.7
Positive predictive value (%)	63.2	78.9	85
Negative predictive value (%)	91.2	93.4	94.8
Accuracy rate (%)	81.29	91.61	93.55

CI=Confidence interval, SE=Standard error, AUC=Area under curve

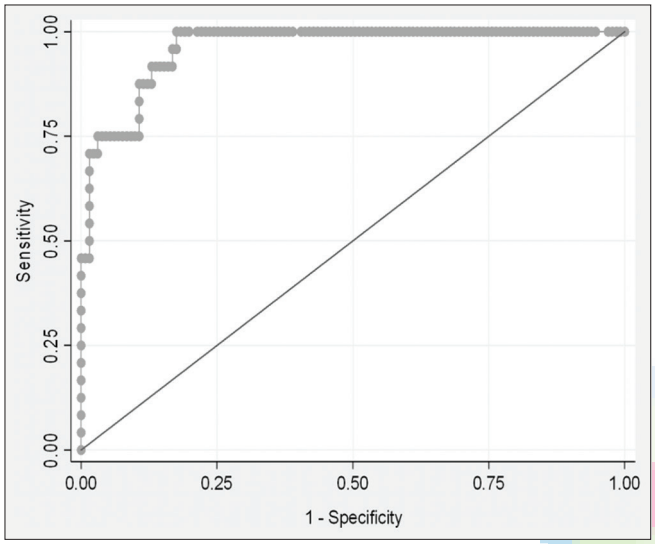

Figure 3: Receiver operating characteristic curve for beta-human chorionic gonadotropin levels 5 weeks after evacuation

age of gestation, mode of evacuation, and use of chemoprophylaxis between those who had disease progression and regression. Women who eventually developed the disease were noted to have larger uterine size by at least 2 weeks than that of those in the regression group (19 ± 3.59 [14–30] vs. 17 ± 3.56 [6–26]) (*t*: −3.12, df: 32.64, *P*: 0.01). In contrast, a study at Sheffield Trophoblastic Disease Center found that the initial urine hCG and antecedent pregnancy were identified as the most significant among the risk factors for possible postmolar GTN.[17]

This study showed that women who had regression had longer follow-up period until discharge from monitoring than those women who had progression (35 ± 4.39 [29–55] weeks vs. 11 ± 10.85 [5–61] weeks) (*t*: 10.80, df: 24.52, $P < 0.01$). In the regression group, the first normal hCG levels were reached as short as 3 weeks to as long as 29 weeks after evacuation. Furthermore, 23 (96%) who developed GTN were diagnosed within 6 months after molar evacuation, and 1 (4%) developed GTN after more than 1 year. This result echoes that done by Mendoza *et al*., wherein 94.3% of those who developed postmolar GTN were detected within the first 6 months after evacuation and only 5.7% were detected after 6 months of monitoring.[14] Similarly, Bakhtiyari *et al*. reported that GTN was diagnosed early after evacuation and the average time it took to diagnose it after molar evacuation is between 7 and 9 weeks. The median time it took for the hCG to be undetectable was a little over 6 weeks or 46 days.[20] Our results showed that those who followed the schedule for serial hCG monitoring were diagnosed early of disease progression and allowed early initiation of intervention.

ROC analysis to identify optimum cut-off hCG levels showed the following values 4152 mIU/ml, 804 mIU/ml, and 541 mIU/ml at 1, 3, and 5 weeks, respectively. There is a significant correlation between the levels of hCG at 1, 3, and 5 weeks postevacuation and subsequent disease outcome. Areas under the curve as shown in Figures 1-3 when such cut-off levels are used are 0.74, 0.94, and point 0.96, denoting moderate test accuracy when 4152 mIU/ml is used as cut-off at 1-week postevacuation, and an excellent level of accuracy when 804 mIU/ml and 541 mIU/ml is used as optimum cut-offs at 3- and 5-week postevacuation. The cut-off of 804 mIU/ml at 5-week postevacuation showed the highest sensitivity and accuracy, which correctly classified 93.55% of the cases who later developed postmolar GTN with sensitivity of 70.83% and specificity of 97.71%. In a similar study, Kang *et al*. concluded that the cut-off points for HCG levels at 1- and 2-week postevacuation were 6400 mIU/ml (sensitivity: 54.1%, specificity: 65.1%) and 2400 mIU/ml (sensitivity: 64.2%, specificity: 78.3%), respectively. They went further and determined that the cut-off ratio for the decline between the HCG levels preevacuation and 2-week postevacuation was 30 (sensitivity: 63.3%, specificity: 85.5%). Based on multivariate analysis, this <30 ratio was an independent factor for persistent GTN (odds ratio: 6.885; 95% confidence interval, 4.006–11.832; $P < 0.001$).[18]

Mousavi *et al*. also showed similar results to our study. Cut-off point for preevacuation HCG was 6000 mIU/ml (AUC, 0.58; sensitivity, 38.53; specificity:

77.4%) while the cut-off points for the HCG levels at 1 and 2 weeks after evacuation were 6288 mIU/ml (AUC, 0.63; sensitivity, 50.46%; specificity, 77%) and 801 mIU/ml (AUC, 0.8; sensitivity, 79.82%; specificity: 71.64%), respectively. The ratio of the preevacuation HCG and HCG 2-week postevacuation was 250 and was a better predictive factor than the other ratio.[19] In contrast, Khoo *et al*. did not observe a significant relationship between serum hCG levels and postmolar GTN.[23]

Limitation of study

The large fall-out rate of this study resulting to a sample size of 155 was due probably to economic and demographic reasons. In a health system wherein most treatment expenses are out-of-pocket, the cost of hCG determination ranging from PhP 600 to a little over PhP 1000 is admittedly burdensome to a majority of the women who have to undergo serial hCG monitoring. These women also come from far-flung areas to get treatment in the said institution so their geographic location is also a factor in their compliance to monitoring.

Conclusion and Recommendation

The prevalence of complete mole is 15–16/1000, deliveries. The incidence of post-GTN after evacuation of complete mole is 15%. However, there were no significant clinicodemographic characteristics that would significantly influence or improve the predictive properties of the beta-hCG levels in differentiating outcomes.

This study showed that the beta-hCG levels within the first 5 weeks after evacuation is highly predictive of subsequent disease outcomes. Particularly, the optimum cut-off level of 512 mIU/ml at 5-week postevacuation correctly classifies 93.55% of the cases with sensitivity of 70.83% and specificity of 97.71%. These cut-off levels will allow clinicians to identify those patients who need to rigorously follow the scheduled visits.

It is recommended that patients should be properly educated regarding possible malignant sequelae and that early diagnosis may equate to better prognosis to motivate them to comply with serial hCG monitoring. A multicenter study may be of value to get a better representation of the actual women who have molar pregnancy in the country.

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Conflicts of interest

There are no conflicts of interest.

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