Human chorionic gonadotropin surveillance in hydatidiform mole: A need for reevaluation*

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ABSTRACT

Introduction: Serial beta human chorionic gonadotropin (βhCG) monitoring after molar evacuation is advised for early detection of persistent trophoblastic disease. The aim of this study was to determine the percentage of patients who developed post-molar gestational trophoblastic neoplasia during a 6-month follow up period after normalization of βhCG titers to that during a 12-month follow up period in order to ascertain the appropriate period of βhCG surveillance for patients who underwent treatment for molar pregnancy.

Methods: Data was analyzed from the Section of Trophoblastic Diseases at the Philippine General Hospital - Department of Obstetrics and Gynecology to estimate the incidence of persistent trophoblastic disease among 258 women with molar pregnancy from 2000-2011.

Results: Among the 258 registered hydatidiform mole patients, 205 patients (79.5%) attained normal βhCG titers titer levels after evacuation of molar products. There was no occurrence of postmolar gestational trophoblastic neoplasia among patients who achieved normalization of βhCG titers after treatment. βhCG levels did not attain normalization following evacuation in 53 patients (20.5%). Out of the 53 patients, 50 patients (94.3%) were detected to have gestational trophoblastic neoplasia within the first six months post-treatment. Only 3 patients (5.7%) were determined to have disease progression after six months during the one-year follow-up period.

Conclusion: The follow-up period after a molar pregnancy may be reduced for patients whose serum βhCG levels spontaneously decline to normal levels after evacuation. The results of this study showed that the median time to obtaining normal βhCG levels is 88 days for those who received chemoprophylaxis and 85 days for those with lower initial βhCG values (less than 100, 000 mIU/ml).

Keywords: human chorionic gonadotropin, hydatidiform mole, surveillance

INTRODUCTION

Hydatidiform moles are abnormal conceptions with excessive placental proliferation, and little or no fetal development. Its incidence varies worldwide. In North America, the incidence is 0.6 to 1.1 per 1000 pregnancies. This value is three times higher in Asia.[2] In the Philippines, the prevalence rate is 2.4 per 1000 pregnancies. At the Philippine General Hospital, the prevalence increases to 14 per 1000 pregnancies.[3]

The risk of persistent trophoblastic disease (PTD) or gestational trophoblastic neoplasia (GTN) after a complete mole is 15-25 percent while the risk is lower for partial mole which is 0.5 to 4 percent.[4] Due to these numbers, patients are advised to have serial beta human chorionic gonadotropin (βhCG) monitoring after molar evacuation for early detection of PTD. To guide us in recognizing patients with persistence of disease after molar pregnancy, the International Federation of Gynecology and Obstetrics has established the following guidelines for the diagnosis of persistent tumor after molar pregnancy: high levels of βhCG more than 4 weeks post-evacuation (serum level of 20, 000 mIU/ml, urine level of 30, 000 mIU/ml), a rise in βhCG of 10% or greater (2 consecutive weekly determination), plateauing βhCG values (<10% rise or decline) at any time after evacuation (minimum of 3 consecutive weekly determinations), clinical or histologic evidence of metastasis at any site, persistently elevated βhCG titer at 14 weeks post-evacuation, and elevation of a previously normal βhCG titer after evacuation provided the diagnosis of pregnancy is excluded.[5]

Differences in recommendations for βhCG surveillance following molar evacuations have prompted investigators to determine the appropriate frequency and duration of monitoring. The American College of Obstetricians and Gynecologists recommends serum βhCG levels to be determined every 1 to 2 weeks in all patients while the levels are elevated and then at monthly intervals

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for an additional 6 months once the levels become undetectable (<5 mIU per milliliter).[6] In the study by Kerkmeijer and colleagues, weekly βhCG measurements are recommended for all patients until normal levels are achieved. For patients who achieved normal βhCG levels within 2 months after evacuation, it was deemed safe to discontinue monitoring.[7]

In the study by Sebire, et al., the policy of extended (2 years) follow up was evaluated. Three women developed postmolar gestational trophoblastic disease at 402, 677 and 1267 days after evacuation following spontaneous normalization of βhCG levels. Only one woman was detected by routine extended follow up. The protocol in United Kingdom was then revised to recommend a follow up of 6 months after spontaneous return of βhCG levels to normal for all women.[10] In another study by Pisal, et al., a less intensive follow up was recommended for patients with normal βhCG titers, however, a definite period was not stated.[11]

Currently, there are varying recommendations for the monitoring of βhCG following evacuation of a molar pregnancy. Worldwide, follow-up of βhCG levels for gestational trophoblastic disease is increasingly individualized. The follow-up period can be as short as 56 days and can even extend to 2 years. Follow-up continues indefinitely because it is unclear when it is safe to cease monitoring.[4] In our country, the Philippine Society for the Study of Trophoblastic Diseases, Inc. recommends measurement of the βhCG titer one week after molar evacuation then every two weeks until the level becomes normal for three determinations. Normal βhCG is defined as less than 5 mIU/mL. The monitoring is then decreased to every month for six months followed by every 2 months for 6 months. This equates to a period of one year after three normal βhCG titers.[3]

This study was therefore undertaken to determine the appropriate period of βhCG surveillance for patients who underwent treatment for molar pregnancy. Given the current follow up of one year in the Philippines, the question arises whether this period may be reduced to six months. Once the period is decreased to six months, this will provide several advantages for the patients in terms of cost reduction and decreased anxiety associated with anticipating the development of malignancy. This will also solidify the practice that patients with molar pregnancy are allowed to be pregnant six months after treatment.

OBJECTIVES

General Objective

To compare the percentage of patients who developed post-molar gestational trophoblastic neoplasia during the 6-month follow up period following normalization of βhCG titers to that during the 12-month follow up period

Specific Objectives:

1. To determine the incidence of postmolar GTN during the period of January 2000 to December 2010
2. To determine the difference in the incidence of gestational trophoblastic neoplasia after a complete and partial hydatidiform mole
3. To determine the interval from evacuation of molar products to development of gestational trophoblastic neoplasia
4. To determine the interval from evacuation of molar products to achieving three normal βhCG titers

METHODOLOGY

Study Design

This is a retrospective cohort study of all patients with hydatidiform mole who were managed at the Section of Trophoblastic Diseases at the Department of Obstetrics and Gynecology of the Philippine General Hospital from January 2000 to December 2010. The protocol for this investigation was approved by the University of the Philippines Manila Research Ethics Board (UPMREB) PGH Review Panel. No informed consent was necessary because there was no actual interaction with the participants of the study. Nevertheless, personal information and research data that were collected from the patient records were kept confidential, and their names did not appear in the analysis or in the reporting of the study.

Subject Selection

This study included all patients who were diagnosed and managed as cases of hydatidiform mole at the Philippine General Hospital from January 2000 to December 2010. The patients should have histopathological confirmation of hydatidiform mole, completed the prescribed 1-year follow up period, and had complete patient data that included all serum βhCG titers during the 1-year follow up period. Excluded in this study were patients who had accompanying gynecologic malignancy.

Study Procedure

The study aimed to compare the percentage of patients who developed post-molar gestational trophoblastic neoplasia during a 6-month follow up period to that during a 12-month follow up period.

Data for all patients with hydatidiform mole who were admitted and managed at the Section of Trophoblastic Diseases at the Department of Obstetrics and Gynecology of the Philippine General Hospital between the dates of January 1, 2000 to December 31, 2010 was gathered from the case registries of the Section of Trophoblastic

Diseases. A detailed review of each patient's hospital record was conducted. For each patient included in the study, the following data was extracted and recorded in a patient data form:age, gravidity and parity, βhCG titers taken upon admission and during the follow-up period, procedure for molar evacuation, type of hydatidiform mole, chemoprophylaxis, outcome (development of GTN, achievement of normal βhCG titer), and number of days to progression to GTN or attainment of normal βhCG titer.

Diagnosis of postmolar gestational trophoblastic disease was based on the following parameters:

1. High level of hCG more than 4 weeks post-evacuation (serum level of 20,000mIU/ml)
2. Progressively increasing or plateauing hCG values at any time after evacuation (minimum of 3 weekly determinations)
3. Clinical or histologic evidence of metastasis at any site
4. Persistently elevated hCG titer at 14 weeks post-evacuation
5. Elevation of a previously normal hCG titer after evacuation provided the diagnosis of pregnancy is excluded.

The data extracted by the investigator from the charts and all the information were manually entered into a spreadsheet and processed using Microsoft Excel computer software.

Statistical Analysis

Data processing and analysis were carried out using the CDC Epi Info 7. Summary data were reported as means with standard deviations for continuous variables, survival-computed median weeks to events and hazard ratios with 95% confidence intervals, and proportions (percentages) for categorical data, which were compared with contingency table ($\chi 2$) or Fisher's exact test (p). Statistical tests of hypotheses were two-sided, at $\alpha = p \leq 0.05$.

Kaplan-Meier survival analyses determined median weeks to start of a first recurrence with 95% confidence intervals (CIs), with unadjusted univariate Mantel-Cox log-rank tests to compare survival times between groups. Cox multivariate proportional hazards modeling estimated the hazard ratio and 95% CI for median time to persistence between the groups, with adjustment for predictors of persistence suggested by preliminary univariate analyses. Logistic regression modeling was also used to evaluate risk factors for significant and independent association with persistence. Also, the number of patients who developed GTN over a 6 month period and over a 12 month period following molar evacuation were determined.

RESULTS

During the period of January 1, 2000 to December 31, 2010, there were 258 patients diagnosed with hydatidiform mole and were subsequently managed by the Section of Trophoblastic Diseases at the Philippine General Hospital. Table 1 presents the baseline demographic factors of patients. The age of patients diagnosed with hydatidiform mole ranged from 16 years to 52 years with a mean of 30.81 years. The gravidity ranged from 1-7 with a mean of 3.22, and the parity ranged from 0-6 with a mean of 1.96. There were 196 patients (75.97%) who underwent the more conservative form of evacuation of hydatidiform mole which is suction curettage while 62 patients (24.03%) underwent total hysterectomy with mole-in-situ. On histopathology, 215 patients (83.3%) had findings consistent with complete mole while 43 patients (16.6%) had partial mole. After evacuation, a majority of patients (202 patients out of 258 or 78.29%) received chemoprophylaxis in the form of Methotrexate.

Normalization group

There were 205 patients (79.45%) who were able to achieve normal βhCG titer levels after treatment. More than half of the patients were younger than 35 years, and only 66 patients (25.58%) were greater than 35 years of age. In terms of baseline βhCG titer levels, 84 patients (40.98%) had values greater than or equal to 100, 000 mIU/ml. There were 168 patients (81.95%) who had histopathologically

Table 1. Distribution of Characteristics among Sample Population

	All Subjects (n=258)	
Demographic	N	%
Age >35 years old	76	29.46
First pregnancy	78	30.23
Gravida >4	94	36.43
Baseline β-HCG≥100,000	110	42.64
Complete molar pregnancy	215	83.33
Partial molar pregnancy	43	16.67
Treatment		
Suction curettage	196	75.97
Surgical management	62	24.03
Chemoprophylaxis	202	78.29

confirmed results of complete hydatidiform mole while 37 patients (18.05%) had partial hydatidiform mole. Majority of patients underwent suction curettage (n=147; 71.71%) while 58 patients (28.29%) underwent total hysterectomy with mole-in-situ. After evacuation, 171 patients (83.41%) received methotrexate chemoprophylaxis (Table 2).

The median time to normal βhCG levels from the time of evacuation of molar products was 85 days (95% CI: 74-96 days) among those who have an initial βhCG of less than 100,000 mIU/mL (n=148), and 107 days (95% CI: 89-125 days) among those who have an initial βhCG greater than or equal to 100,000 mIU/mL (n=110; $\chi 2 \geq 3.06$, df=1,p-value>0.05), a 1.26-fold difference (Figure 1).

The median time to achieving normal βhCG levels from the time of evacuation of molar products was 126 days (95% CI: 99-153 days) among those who did not receive chemoprophylaxis (n=56) and 88 days (95% CI: 80-96 days) among those who received chemoprophylaxis (n=202; $\chi 2 \geq 10.59$, df=1,p-value<0.01). There was a 1.43-fold difference (Figure 2).

There was no occurrence of postmolar gestational trophoblastic neoplasia among the patients who achieved normalization of βhCG titers after treatment.

Persistent trophoblastic disease

Among the population, 53 patients (20.5%) developed gestational trophoblastic neoplasia. For these patients whose disease progressed, the age ranged from 16-51 years. About 10 patients (18.87%) were greater than 35 years old and 13 (24.53%) of them had a gravidity greater than 4.

The initial βhCG titer levels varied from as low as 10.6 mIU/ml up to a value of greater than one million. Forty nine of them (92.4%) underwent suction curettage while total hysterectomy was performed on four patients (7.5%). Only thirty one patients (58.5%) received methotrexate chemoprophylaxis. For the results of the histopathology, 47 patients (88.7%) had complete hydatidiform mole while 6 patients (11.3%) had partial hydatidiform mole. Most of the patients with persistent GTN had a higher rate of suction curettage (92%, p=0.001), and a lower rate of

Table 2. Distribution of Characteristics comparing the normalization group and persistent trophoblastic disease group

	Normalization (n=205)		**Progression (n=53)**		**p[a]**
Demographic	N	%	N	%	
Age >35 years old	66	32.20	10	18.87	.08
First pregnancy	60	29.27	18	33.96	.62
Gravida >4	81	39.51	13	24.53	.06
Baseline β-HCG≥100,000	84	40.98	26	49.06	.37
Complete molar pregnancy	168	81.95	47	88.68	.33
Partial molar pregnancy	37	18.05	6	11.32	.33
Treatment					
Suction curettage	**147**	**71.71**	**49**	**92.45**	**.01****
Surgical management	**58**	**28.29**	**4**	**7.55**	**.01****
Chemoprophylaxis	**171**	**83.41**	**31**	**58.49**	**.01****

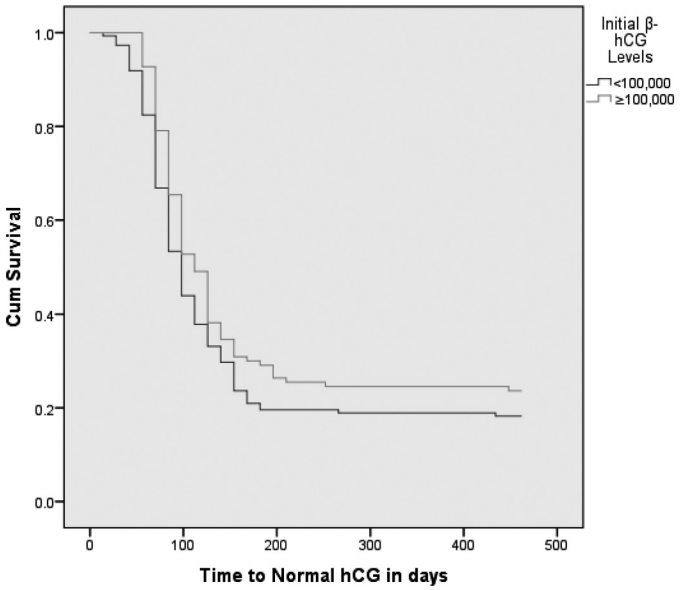

Figure 1. Kaplan-Meier Survival Functions for Gestational Trophoblastic Disease Patients controlling for Initial hCG Levels

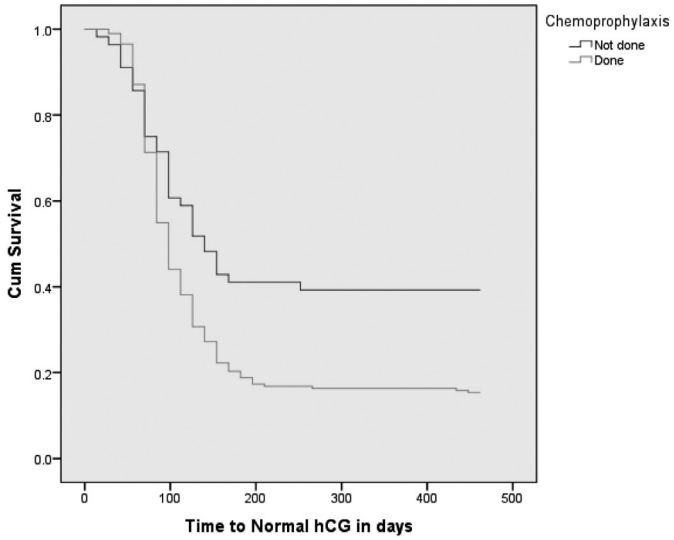

Figure 2. Kaplan-Meier Survival Functions for Gestational Trophoblastic Disease Patients controlling for Treatment

chemoprophylaxis (58%, p<0.001).

During the one-year follow-up period, 50 patients (94.3%) were detected to have gestational trophoblastic neoplasia within the first six months post-treatment while only 3 patients (5.7%) were determined to have the disease progression after six months. As early as 36 days after treatment, gestational trophoblastic neoplasia was already identified in seven patients among the population of this study. The period of detection of disease progression ranged from 36 to 246 days. For the 50 patients identified during the first six months after treatment, the period of development of gestational trophoblastic neoplasia ranged from 36 to 159 days with a mean of 65 days. For the three patients who developed gestational trophoblastic neoplasia beyond the 6 months from molar evacuation, the period of detection ranged from 195-246 days.

Majority of the patients who progressed to postmolar gestational trophoblastic neoplasia were diagnosed due to rising βhCG levels (n=44, 83%) while 9 patients (16.9%)had plateauing βhCG values.

DISCUSSION

The purpose of this study was to compare the percentage of patients who developed post-molar gestational trophoblastic neoplasia during the 6-month follow up period following normalization of βhCG titers to that during the 12-month follow up period in order to determine the appropriate period of βhCG surveillance for patients who underwent treatment for molar pregnancy. Information including demographics, baseline βhCG levels, treatment, and subsequent βhCG levels during the follow-up period of patients diagnosed with hydatidiform mole during the period of January 1, 2000 to December 31, 2010 at the institution were obtained for data analysis.

Table 3. Distribution of Characteristics comparing the patients with progression during the 6 month follow-up period and 12 month follow-up period

	Progression during 6 month follow-up period (n=50)		**Progression during 12 month follow-up period (n=3)**	
Demographic	N	%	N	%
Age >35 years old	10	20	0	0
First pregnancy	17	34	1	33.3
Gravida >4	13	26	0	0
Baseline β-HCG≥100,000	25	50	2	66.7
Complete molar pregnancy	45	90	2	66.7
Partial molar pregnancy	5	10	1	33.3
Treatment				
Suction curettage	46	92	3	100
Chemoprophylaxis	29	58	2	66.7

Based on the results, among the 258 patients managed for molar pregnancy, 53 patients (20.5%) progressed to post-molar gestational trophoblastic neoplasia. This is comparable to the study by Wolfberg, et al, wherein 15% of the population developed gestational trophoblastic neoplasia.[11] It was also noted in that study that the median time required for serum hCG levels to become undetectable among the 238 women with remission was 46 days. In the study by Kerkmeijer on recurrent gestational trophoblastic disease, 355 patients with hydatidiform mole registered at the Dutch Central Registry of hydatidiform mole were serially monitored using βhCG assays. There were ninety patients (25%) whose βhCG levels did not decline to normal (defined as < 2.0 ng/ml in the study). Relapse rates were 8.1% and 6.3% for the low-risk and high-risk groups.[8] Based on the group's analysis, the risk for relapse in hydatidiform mole patients with spontaneous normalization of βhCG levels is extremely low at 1 in 265 patients after two normal βhCG levels were achieved.[8]

Most patients with post-molar gestational trophoblastic neoplasia are diagnosed early due to rising levels of βhCG. Out of the 53 patients with persistent disease, fifty (n=50, 94.3%) patients were detected during the first six months after evacuation of molar products. This is comparable to a retrospective study done at the United Kingdom wherein data on women who were registered for βhCG monitoring following evacuation of molar products were reviewed. Of those patients who developed postmolar gestational trophoblastic neoplasia, 98% of patients presented within the first six months after evacuation.[9] Hence, their protocol for monitoring of βhCG titers after treatment was based on when the hCG reached normal levels. When the hCG concentration became normal within 56 days, urine surveillance continued for a total of 6 months from the evacuation date. However, when the hCG levels became normal after 56 days from the evacuation date, additional 6 months surveillance from the time the levels became normal was required.

In the study by Kerkmeijer, 414 patients with complete hydatidiform mole were studied to determine the number of patients who spontaneously achieved normal βhCG levels but eventually developed gestational trophoblastic neoplasia. The study recommended weekly βhCG measurements for all patients until normal levels are achieved. It was stated in the study that among patients

who attained normal βhCG levels within 2 months after evacuation of molar products, monitoring may be safely discontinued once normal levels are achieved. However, for patients who do not achieve normal βhCG level by 2 months post-evacuation, monthly βhCG titer determination should be done for one year after normalization.[8]

Worldwide, the recommendations regarding the protocol for monitoring patients after a molar pregnancy are not standard. However, most studies have shown that in a large percentage of patients, the βhCG levels reach normal levels within the first six months after evacuation of molar products and the risk of progression or relapse to gestational trophoblastic neoplasia is extremely low.

The results of this study showed that the median time to obtaining normal βhCG levels is 88 days for those who received chemoprophylaxis and 85 days for those with lower initial βhCG level (less than 100, 000 mIU/ml). Furthermore, only three patients were detected to have abnormal βhCG titers after the 6 month follow-up period. A reduction in the surveillance period after normalization of βhCG levels leads to reduction in financial cost, decrease in fertility consequences especially in elderly women attempting to become pregnant after a hydatidiform mole, and spares the patients unnecessary anxiety during the follow-up period.

CONCLUSION

Majority of cases of postmolar gestational trophoblastic neoplasia presents within the first six months after treatment. In this study, there was no occurrence of postmolar gestational trophoblastic neoplasia in the patients who attained normalization of βhCG titers after treatment. Patients who received methotrexate chemoprophylaxis and had lower initial βhCG values (less than 100,000 mIU/ml) had shorter periods of obtaining normal βhCG results from the time of treatment,with period of 88 days and 85 days respectively. Furthermore, ninety-four percent of the patients who had persistent gestational trophoblastic neoplasia were diagnosed within the first six months during follow-up while only three patients were detected after six months.

A period of six months seems to be adequate in monitoring βhCG levels in patients following molar pregnancy. A shorter follow-up period has several advantages such as cost reduction especially in our setting wherein patients often have difficulty completing the proper monitoring due to financial limitations, and diminishing the patient's anxiety associated with her disease. ■

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