

# Early Detection of Gestational Trophoblastic Neoplasia Based on Serial Measurement of Human Chorionic Gonadotrophin Hormone in Women with Molar Pregnancy

## Abstract

**Background:** The majority of studies which investigate the predicted power of Human chorionic gonadotropin (hCG) levels to the occurrence of Gestational trophoblastic neoplasia (GTN) considered the effect of a single measurement of hCG or used classical statistical methods without considering the endogenous marker. The aim of this study is to investigate the association between weekly measurements of  $\beta$ -hCG with time to GTN occurring, using a robust Bayesian joint modeling. **Methods:** Data of 201 women with a molar pregnancy were considered for this retrospective cohort study. After the first measurement of  $\beta$ -hCG in 48 hours post evacuation of mole, the other titration was performed on a weekly basis until three consecutive normal titers. The association between serial measurements of  $\beta$ -hCG and risk of GTN occurring were assessed by the classic and Bayesian joint modeling and in separate analysis the mixed linear effect and Cox-PH model were used. **Results:** The mean age (SD) of participants was 26.6 (6.55) year. The GTN was occurred among 14.9% of patients. The association parameter using Bayesian approach was estimated as 1.30 (95% CI: 0.44 to 2.20) which showed one unit increase in the log  $\beta$ -hCG corresponds to the 2.80-times increase in the hazard for the occurrence of GTN (Hazard Ratio: 2.80, 95% CI: 1.55 to 8.98). **Conclusions:** Findings of this study revealed that weekly measurements of  $\beta$ -hCG are an important and reliable biomarker to early detection of developing of molar pregnancy to persistent GTN.

**Keywords:** Chorionic gonadotropin, gestational trophoblastic disease, Iran

## Introduction

Gestational Trophoblastic Neoplasia (GTN) is a collective term which refers to gestational trophoblastic diseases such as placental site trophoblastic tumor, invasive moles, and choriocarcinoma.<sup>[1]</sup> GTN originates from abnormal multiplication of trophoblast after any gestation, especially molar pregnancy.<sup>[2]</sup>

Molar pregnancy is a precancerous form of GTN. The incidence of molar pregnancy in Asia (2 per 1000 pregnancy) is three times higher than North America and Europe (0.6-1.1 per 1000 pregnancy).<sup>[1]</sup> In Iran, the incidence was 7 per 1000 pregnancy (0.7%).<sup>[3]</sup> Approximately about 15–20% of complete mole and 5% of the partial mole will continue to develop GTN.<sup>[4,5]</sup> All women with molar pregnancy should be managed with uterine evacuation and chemotherapy due to their high risk of developing GTN.

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Although GTN is a curable disease the diagnosis in early stages is important in preventing the spread of it and choosing the less complex and expensive treatment method.<sup>[6,7]</sup>

Some previous studies have focused on the prediction of GTN based on the measurements of  $\beta$ -hCG level over time and showed that regression pattern for patients who were recovering was different from patients go on to have persistence GTN.<sup>[6-9]</sup>

Human chorionic gonadotropin (hCG) is a hormone produced by trophoblastic tissue and comprised of two subunits the alpha and beta.<sup>[10]</sup> Serial measurements of  $\beta$  subunit of hCG ( $\beta$ -hCG) can effectively detect persistence GTN post-molar pregnancy.<sup>[9,10]</sup> Most of the previous studies used general linear model, survival models,<sup>[11,12]</sup> or longitudinal ROC analysis.<sup>[13,14]</sup> While, the values of

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the  $\beta$ -hCG biomarker at any time point can be affected by disease progression and occurrence of GTN at an earlier time point and this important characteristic of the endogenous biomarker may be ignored in these methods. Therefore, we aimed to investigate the association between longitudinal measurements of  $\beta$ -hCG titration and time to post-molar GTN occurring using the Bayesian joint modeling which takes into accounts the endogenous feature of  $\beta$ -hCG titration over time.

## Methods

The data for this retrospective cohort study were collected from Imam Hossain, Shohada, Mahdih, and Taleghani hospitals in Tehran provenience, from 2003 to 2013. All pregnant women with molar pregnancy were eligible for this study. Therefore, out of a total of 98,658 deliveries in the hospitals, 221 cases of molar pregnancy were identified; of these 20 cases were excluded owing to receiving coprophlaxi drugs, having had initial hysterectomy treatments, or having incomplete files with irrelevant information, respectively. Finally, data from 201 documents of women with molar pregnancy were considered for this study.

The longitudinal outcome was  $\beta$ -hCG titration at four different visiting times during to one-year follow-up post molar pregnancy. The first titer of  $\beta$ -hCG was measured at most 48 hours after evacuation of mole and other titrations were performed on a weekly basis until three consecutive normal titers in all patients. The sensitive and specific RIAs procedure was used to measurements  $\beta$ -hCG. The details of this procedure were described elsewhere.<sup>[15]</sup> The survival outcome was time to occurrence of GTN which was measured as the number of days between molar pregnancy evacuating and occurrence of GTN. Time to occurrence of GTN was censored for pregnant women who were lost to follow-up or experienced hysterectomy surgery during follow-up or did not the event at the end of the study. Demographic and general characteristics including age (year), race, gestational age (week), vaginal bleeding (VB) (yes/no), parity, gravidity, history of abortion (yes/no), uterine height (week), and theca lutein cyst (yes/no) were considered as covariate for the separate survival and longitudinal model as well as joint model.

### Statistical analysis and model specification

Categorical variables were presented as frequency (percent) and continuous variables as mean (standard deviation). All parameters were considered significant if corresponding 95% confidence interval (CI) did not include zero. The backward elimination method was used for selecting the best set of covariates for longitudinal and survival sub-models ( $P$  value higher than 0.10 were considered for dropped). All analysis was conducted using R software (version 3.5.0) packages (JM and JM-Bayes packages) which are free software.

The Linear Mixed effect Model (LMM) was used to investigate the effects of study covariates on the log transform of  $\beta$ -hCG titration over time.<sup>[16]</sup>

The semi-parametric survival model was used to explain how the risk of GTN occurring at a given time is affected by the study covariates. In addition to Cox-PH regression, Weibull parametric model is also considered for this study. We used Akaike's Information Criteria (AIC) and Bayesian Information Criterion to choose the best survival model.<sup>[17]</sup> The covariates in the survival model may or may not to be the same covariates in the LMM.

The main goal of our study investigates the association between longitudinally measured of the  $\beta$ -hCG biomarker with time to GTN occurring. After determining the appropriate longitudinal and survival sub-models separately, these sub-models joined using shared parameter association. This shared parameter associates longitudinally measured of  $\beta$ -hCG random-effects with time to GTN occurring. We used a Bayesian estimation process and a Markov chain Monte Carlo (MCMC) algorithm to parameters estimation and fit the joint modeling. In the Bayesian process, standard prior distribution was considered for all parameters. This procedure provides robust results when compared to the maximum likelihood approach. In addition, specifying a prior distribution for the parameters gives the investigator an opportunity to accommodate any existing information into the model. The DIC score was used to determine the appropriate joint model.<sup>[18,19]</sup>

## Results

The demographic and general characteristics of patients are shown in Table 1. The mean (SD) age of patients was 26.6 (6.55) years and 6% of them were Afghan who living in Iran. Among 201 women with a molar pregnancy, the GTN was occurred in 30 patients (14.9%) during the one-year follow-up.

Based on the values of AIC and BIC we considered LMM model with random intercept and a random slope for this analysis [Table 2]. As shown in Table 2 using backward elimination method the best set of effective covariates on log  $\beta$ -hCG titration was including race, vaginal bleeding, gestational age, and theca lutein cyst ( $P$  value < 0.10). In the final LMM model, log B-HCG had a significant positive association with gestational age (coefficient: 0.018, 95% CI: 0.004 to 0.040). Also, the mean of log  $\beta$ -hCG in women with theca lutein cyst was significantly different from women without theca lutein cyst (coefficient: 0.858, 95% CI: 0.509 to 1.21) [Table 3].

The comparison of survival models is presented in Table 2. Using AIC Cox-PH survival model had a smaller value and therefore we used this model for analysis. After the backward elimination method, the best set of effective covariates on time to occurrence of GTN was including abortion, gestational age, and cervix

**Table 1: The demographic characteristics of the study population**

Variables	Mean $\pm$ SD
Age (year)	26.60 $\pm$ 6.55
Gravidity	1.88 $\pm$ 0.93
Parity	0.69 $\pm$ 0.84
Gestational age (week)	10.0 $\pm$ 2.66
Uterine height (week)	10.3 $\pm$ 3.43
Log $\beta$ -hCG after evacuation mole	4.39 $\pm$ 0.64
Log $\beta$ -hCG <sub>(first week)</sub>	4.00 $\pm$ 0.65
Log $\beta$ -hCG <sub>(second week)</sub>	3.25 $\pm$ 0.62
Log $\beta$ -hCG <sub>(third week)</sub>	3.00 $\pm$ 0.64
Time to cancer (day)	43.20 $\pm$ 10.6
Frequency (%)	
Vaginal bleeding (yes)	24.00 (11.80%)
Abortion (yes)	36.00 (17.70%)
Theca lutein cysts (yes)	10.00 (4.90%)
GTN (yes)	30.00 (14.70%)

GTN: gestational trophoblastic neoplasia

**Table 2: Linear mixed-effect model (LMM) and Cox-regression model selection**

Random effect	AIC	BIC
Random intercept	1200.56	1261.35
Random intercept and linear slope	1149.76	1219.90
Fixed effect (backward elimination)		
Model with all covariates	1149.76	1219.90
Model after cervix height elimination	1141.53	1207.01
Model after parity elimination	1137.86	1198.68
Model after gravidity elimination	1131.88	1188.04
Model after abortion elimination	1127.51	1179.00
Model after age elimination	1118.50	1165.32
<b>Survival models</b>	<b>AIC</b>	
	<b>Cox PH model</b>	<b>Weibull model</b>
Model with all covariates	305.13	397.40
Model after age elimination	303.13	395.43
Model after gravidity elimination	301.13	393.47
Model after vaginal bleeding elimination	299.49	391.78
Model after theca lutein cyst elimination	298.12	390.19
Model after parity elimination	296.89	389.14
Model after race elimination	295.51	387.48

height ( $P$  value < 0.10). As shown in Table 3, in the final Cox-PH model one unit increase in the uterine height of the patient 17% decreases the risk of GTN occurring (HR: 0.829, 95% CI: 0.68 to 0.98) [Table 3].

The joint modeling of log  $\beta$ -hCG titration and time to GTN occurring is shown in Table 4. Results are presented as the parameter's estimation with corresponding 95% CI. Regarding the importance of the effect of age on GTN

occurring, we considered it in two longitudinal and survival sub-model. The estimation of association parameter (95% CI) in classic and Bayesian joint modeling was as 0.580 (0.148 to 1.01) and 1.30 (0.44 to 2.20) respectively, which showed a positive significant association between the serial measurement of  $\beta$ -hCG titration with hazard for the occurrence of GTN. The Bayesian estimation showed a stronger association than the classic models. As shown in Table 4 the history of abortion in survival sub-model were significantly associated with a higher hazard for GTN occurring (HR: 2.06, 95% CI: 1.001 to 4.71), while this association in Bayesian model was not significant. In longitudinal sub-model, the theca lutein cyst was positively associated with log  $\beta$ -hCG titration in two classic and Bayesian models (classic estimation: 0.849, 95% CI: 0.501 to 1.20 and Bayesian estimation: 0.779, 95% CI: 0.413 to 1.15, respectively).

## Discussion

Findings of this study revealed that serial measurements of  $\beta$ -hCG titration post molar pregnancy were positively associated with a hazard rate of time to GTN occurring. According to the Bayesian joint estimation, one unit increase in the log  $\beta$ -hCG corresponds to the 2.80-times increase in the hazard for the occurrence of GTN. Consistent with our finding previous studies showed that  $\beta$ -hCG measurement after treated a molar pregnancy is a good marker to differentiate patients who will get spontaneous recovery from patients developing GTN.<sup>[7,20-22]</sup> A study on 3926 women with partial or complete mole showed that risk of GTN was clearly different based on the levels of  $\beta$ -hCG and rising with  $\beta$ -hCG level.<sup>[2]</sup> In another study more than 50% of patients who will really develop GTN can be predicted using the slope of the regression line of  $\beta$ -hCG with 97.5% specificity.<sup>[23]</sup> Similarly, Kim *et al.* reported that using comparing regression rate in two weeks after molar evacuation the occurrence of GTN can be estimated with 48.0% sensitivity and 89.5% specificity and post 2<sup>nd</sup> week both specificity and sensitivity continue to increase.<sup>[8]</sup>

The  $\beta$ -hCG produced by the placenta during pregnancy. In addition to pregnancy,  $\beta$ -hCG can be secreted by abnormal embryonic tissues and gestational trophoblastic disease such as GTN.<sup>[24]</sup> After the surgical evacuation of molar pregnancy, the level of  $\beta$ -hCG falls rapidly in patients who have trophoblastic tissue limited to the endometrial cavity, while in patients whose trophoblastic tissue has been trespassed the uterine wall or metastasized in other organs  $\beta$ -hCG level decrease slowly due to the presence of the residual  $\beta$ -hCG producing trophoblastic tissue. Indeed, a slow decrease in  $\beta$ -hCG levels post-molar evacuation can predict the presence of invasive trophoblastic tissue.<sup>[7,25]</sup>

We used Bayesian joint modeling to investigate the link between longitudinal  $\beta$ -hCG titration and risk of GTN. This model is a powerful approach that takes into account

the dependency and association between longitudinal biomarker and time to a specific event.<sup>[26]</sup> While, in the majority of previous studies in this field the classical models such as simple regression model, linear mixed model, extended cox model, and ROC analysis were used which cannot consider dependencies between two different type of data.<sup>[2,6,23]</sup> Furthermore, we used the Bayesian approach to estimate the parameter due to the low frequency of the event (GTN).<sup>[27]</sup> This approach was the major difference between our study and other studies.<sup>[13,28]</sup> Therefore, it is expected that the models were used in this study by taking into account more information lead to more reliable and accurate estimation than other studies.

**Table 3: Linear mixed-effect model (LMM) and Cox-regression model parameter's estimation separately**

Fixed effects	Parameters estimation	95% CI	
Intercept	4.00	(3.70, 4.30)*	
Visit time	-0.07	(-0.08, -0.07)	
Race	0.29	(-0.03, 0.61)	
Vaginal bleeding	0.18	(-0.04, 0.39)	
Gestational age (week)	0.02	(0.004, 0.04)*	
Theca lutein cyst	0.86	(0.51, 1.21)*	
Random effects			
$\sigma_{intercept}$	0.51	(0.44, 0.55)	
$\sigma_{slop (time)}$	0.02	(0.02, 0.03)	
$\sigma_{between\ subject\ error}$	0.32	(-0.53, -0.17)	
Cox-PH model	Parameters estimation	HR	95% CI
Abortion (yes/no)	0.68	1.98	(0.90, 4.36)
Gestational age (week)	0.11	1.11	(0.98, 1.26)
Cervix height (cm)	-0.19	0.83	(0.68, 0.98)*

\*Indicates covariates are significant at 5% level. CI: Confidence interval. HR: Hazard ratio

In the present study according to the separate analysis of repeated measurements data, the gestational age and theca lutein cyst have a positive effect on log  $\beta$ -hCG titration. Two case studies reported that theca lutein cysts were correlated with elevated  $\beta$ -hCG level and large size cysts were seen in the maximum level of  $\beta$ -hCG.<sup>[29,30]</sup> The theca lutein cyst occurred by an abnormal response of atretic follicles in the ovaries to flowing the  $\beta$ -hCG and typically are not seen in the first trimester of pregnancy due to the low level of  $\beta$ -hCG at this time.<sup>[29]</sup>

Our finding in a separate analysis of time to event data showed that gestational age and history of abortion were positively associated with a high risk of GTN, while gestational age in survival sub-model of joint modeling was not significant. Consistent with our result in the overview by Steigrad the prior abortion was a risk factor for the occurrence of GTN.<sup>[31]</sup> Similarly, other studies reported that the history of abortion is linked with risk of GTD such as hydatidiform and GTN and 25% of all cases of GTN occur post-abortion.<sup>[5,32-34]</sup>

This study has some strengths and limitations. Along with considering the longitudinal endogenous biomarker (GTN), Using Bayesian joint modeling to determine the association between study variables was the main strength of this study. Data for this study were collected by registration, so information error in data classification and incomplete registration of some covariates could occur which is the main limitation of our study.

### Conclusions

The findings of this study using more robust methods reported that  $\beta$ -hCG trajectories post-molar pregnancy is an important marker to predict the occurrence of GTN. This malignancy in early stages has a low risk of metastasis and is more treatable even with single-agent chemotherapy.

**Table 4: The joint modeling of longitudinal and time-to-event data**

Longitudinal sub-model	Classic joint model		Bayesian joint model	
	Parameter's estimation	95% CI	Parameter's estimation	95% CI
Intercept	4.15	3.77, 4.54)	4.17	(3.76, 4.57)
Visit time	-0.07	(-0.07, -0.07)*	-0.07	(-0.07, -0.07)*
Age (year)	-0.01	(-0.02, 0.004)	-0.01	(-0.02, 0.004)
Race	0.31	(0.001, 0.63)*	0.32	(-0.02, 0.68)
Vaginal bleeding	0.19	(-0.03, 0.40)	0.20	(-0.02, 0.43)
Gestational age (week)	0.02	(-0.002, 0.041)	0.02	(-0.003, 0.04)
Theca lutein cyst	0.85	(0.50, 1.20)*	0.78	(0.41, 1.15)*
Survival sub-model	Parameter's estimation	HR (95% CI)	Parameter's estimation	HR (95% CI)
Age (year)	-0.005	0.99 (0.94 1.05)	-0.01	0.99 (0.93 1.05)
Abortion (yes/no)	0.72	2.06 (1.001 4.71)*	0.66	1.93 (0.81 4.35)
Gestational age (week)	0.10	1.10 (0.97 1.25)	0.04	1.04 (0.91 1.19)
Uterine height (cm)	-0.15	0.86 (0.71 1.04)	-0.18	0.84 (0.68 1.00)
Association parameter	0.58	1.79 (1.15 2.75)*	1.30	2.80 (1.55 8.98)*
		AIC: 1530.79	DIC: 1576.94	
		BIC: 1576.46	pD: 212.47	

\*Indicates covariates are significant at 5% level. HR: hazard ratio- CI: confidence interval

Therefore, follow-up with serial measurements of the  $\beta$ -hCG level is very important to early detection of GTN which can reduce cancer's financial impact and enable more effective and less complex treatment. Suggested that the  $\beta$ -hCG levels were monitored on a weekly basis until normal during three consecutive weeks, and then followed by monthly determinations up to six months.<sup>[35]</sup> However, a new study illustrated that daily measurements of  $\beta$ -hCG give a better prediction of post-molar GTN.<sup>[36]</sup> Further studies using robust statistical methods to determine the optimal duration of  $\beta$ -hCG monitoring are recommended.

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### Conflicts of interest

There are no conflicts of interest.

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