# Postmolar gestational trophoblastic neoplasia: beyond the traditional risk factors

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**Objective:** To investigate the slope of linear regression of postevacuation serum hCG as an independent risk factor for postmolar gestational trophoblastic neoplasia (GTN).
**Design:** Multicenter retrospective cohort study.
**Setting:** Academic referral health care centers.
**Patient(s):** All subjects with confirmed hydatidiform mole and at least four measurements of $\beta$-hCG titer.
**Intervention(s):** None.
**Main Outcome Measure(s):** Type and magnitude of the relationship between the slope of linear regression of $\beta$-hCG as a new risk factor and GTN using Bayesian logistic regression with penalized log-likelihood estimation.
**Result(s):** Among the high-risk and low-risk molar pregnancy cases, 11 (18.6%) and 19 cases (13.3%) had GTN, respectively. No significant relationship was found between the components of a high-risk pregnancy and GTN. The $\beta$-hCG return slope was higher in the spontaneous cure group. However, the initial level of this hormone in the first measurement was higher in the GTN group compared with in the spontaneous recovery group. The average time for diagnosing GTN in the high-risk molar pregnancy group was 2 weeks less than that of the low-risk molar pregnancy group. In addition to slope of linear regression of $\beta$-hCG (odds ratio [OR], 12.74, confidence interval [CI], 5.42–29.2), abortion history (OR, 2.53; 95% CI, 1.27–5.04) and large uterine height for gestational age (OR, 1.26; CI, 1.04–1.54) had the maximum effects on GTN outcome, respectively.
**Conclusion(s):** The slope of linear regression of $\beta$-hCG was introduced as an independent risk factor, which could be used for clinical decision making based on records of $\beta$-hCG titer and subsequent prevention program. (Fertil Steril® 2015;104:649–54. ©2015 by American Society for Reproductive Medicine.)
**Key Words:** GTN, human chorionic gonadotropin, independent risk factor, penalized logistic regression

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Gestational trophoblastic disease (GTD), a group of disorders identified by abnormal proliferation of trophoblastic tissue, is one of the prognoses of spontaneous recovery, local invasion, and metastasis. The general term of gestational trophoblastic neoplasia (GTN) is used to describe a wide range of malignant trophoblastic diseases including invasive mole, choriocarcinoma, epithelioid trophoblastic tumor, and placental site trophoblastic tumor (1, 2). Although GTN is generally seen in molar pregnancies, it can be seen in any pregnancy.

Although hydatidiform mole is generally diagnosed in the first trimester of pregnancy during routine pregnancy tests, its clinical signs and symptoms are rarely seen at this time (3). According to current available definitions, this neoplasia is confirmed by the following criteria: [1] no decrease in hCG levels over four consecutive measurements, [2] an increase in hCG serum titer measured over 3 consecutive weeks, [3] detectable hCG serum

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titer 6 months after evacuation of molar pregnancy, and [4] histological diagnosis of choriocarcinoma (4–6). Data reveal that about 18%–28% of molar pregnancies lead to a sustainable neoplasia (5). Different designs and populations have been used across the world to study this disorder, with no standard definition for the cases; furthermore, the data used in this field have not generally been collected for research purposes (7). Therefore, reporting the incidence of this neoplasia in a manner by which it can precisely represent the studied populations, whether in Iran or other countries, is a problematic process; this is the reason for the significant differences in the incidence reported from different regions of the world (4, 8, 9). GTN is usually seen after a molar pregnancy, emphasizing the importance of identifying the risk factors of molar pregnancy (10). The traditional risk factors of this malignant disease include professional jobs, abortion history, intervals between pregnancies (11), hormonal changes, early menarche, and contraceptives (12, 13). Studies have reported a significant relationship between uterine height larger for gestational age and prior molar pregnancy and an increased risk for GTN (14). Another study has reported only a relationship associated with serum titer >100,000 mIU/mL as the cutoff (15).

There are very few systematic studies documented that provide a well-elucidated insight into GTN risk factors and introduce newer indicators for it in particular. Attempts to predict this neoplasia are generally based on the hCG indicator (level 2 prevention). In practice, identification of the risk factors and intervention into their mechanisms and biology with the aim of preventing this disease have been overlooked. Using a new and reliable indicator, this study aimed at specifying GTN risk factors to reduce its risk and burden.

## MATERIALS AND METHODS

### Study Population

This multicenter retrospective cohort study evaluated all documents of patients with hydatidiform mole who were referred to educational and treatment centers between 2003 and 2013 (10 years) and whose illness was confirmed by pathological tests carried out during hospitalization and follow-up. Data of partial and complete hydatidiform mole with at least four measurements of $\beta$-hCG titer were included in the study. After identifying the prevalence of different GTDs, the study excluded [1] patients with no useful data owing to having inappropriate follow-ups or test result records, [2] patients whose hCG level was not measured at most within 48 hours after evacuation, [3] patients who received prophylactic chemotherapy before mole evacuation, and [4] patients who had undergone hysterectomy.

To this end, the files of 98,658 births from 2003 to 2013 were studied and 221 cases of molar pregnancy were identified; of these nine, three, and eight cases were excluded owing to receiving coprophlaxi drugs, having had initial hysterectomy treatments, or having incomplete files with irrelevant information, respectively. Among the qualified patients (n = 201), 31 had GTN, and the serum hormone level in the remaining cases had spontaneously returned to normal values during follow-up practices. In the present study, high-risk molar pregnancy was defined according to the following criteria: [1] initial titer of $\beta$-hCG hormone >100,000 mIU/mL, [2] uterine height larger than 2 weeks for gestational age, and [3] theca lutein cyst bigger than 6 cm.

### Evaluation and Immunoassays

According to current literature, in all treatment centers, the first titer of $\beta$-hCG was measured and recorded at most 48 hours after evacuation of molar pregnancy (16). The follow-up procedure was as follows: in all cases with molar pregnancy, titration was perfomed on a weekly basis until three consecutive normal titers were obtained. After normalization of titers, the procedure was performed on a monthly basis for 6 months.

All measurements of $\beta$-hCG in serum were performed with sensitive and specific RIAs, developed in our laboratories based on polyclonal antibodies raised in rabbits; the RIAs of $\beta$-hCG have been described elsewhere (17). In the RIA for $\beta$-hCG, a highly purified hCG $\beta$-subunit preparation labeled with iodine-125 ($NaI^{125}$, Amersham plc) was used as a tracer. The RIAs were calibrated with the third International Standard (IS) preparations for intact hCG or the hCG $\alpha$- or hCG $\beta$-subunits (WHO third IS hCG 75/537, hCG$\alpha$ 75/569, or hCG $\beta$ 75/551, respectively).

### Statistical Analysis

Basic demographic and clinical continuous data are shown as mean and SD, while grouped data are shown in the form of frequency and percentage. Chi-square or Fisher's exact tests were used to show whether the two categorical variables are independent. Since the distribution of $\beta$-hCG concentration was not normal in the beginning, it was normalized by transforming the scale to a natural logarithm. The main variable studied for determining GTN risks was the $\beta$-hCG concentration regression line slope. Therefore, the data were reshaped from wide to long, after which the $\beta$-hCG concentration regression line slope was calculated by Stata, using four recorded measurements for each case. The Fracpoly model was also used to determine the type of relationship between the main variable, that is, $\beta$-hCG concentration logarithm slope, and outcome; this model was used owing to the continuous nature of $\beta$-hCG in serum as well as the disadvantages of converting continuous to categorical data. The relevant details of the model have been published elsewhere (18–20). For estimation of GTN-associated risk factors odds ratio (ORs), Bayesian logistic regression with penalized likelihood estimation was used to control for confounding variables. Confounding variables were selected in accordance with the backward method, by studying to what extent the addition or elimination of the variables changes ORs between risk factor and outcome. Application of the models in discrete data with low population size has been discussed before (21, 22). The method of Kaplan–Meier was used to show the time of GTN diagnosis in high- and low-risk molar pregnancies. All analyses were performed by Stata 12. The proposal of this project was approved by the Institutional Review Board of Shahid Beheshti University of Medical Sciences.

## RESULTS

This study used information from 201 patients with molar pregnancy, of which, based on pathology reports, 18 had partial mole and the remaining 183 cases (91%), had complete mole; the mean age of the patients was 26.7 ± 6.7 years. According to the high-risk molar pregnancy definition, 59 patients (29%) had high-risk molar pregnancy, while 142 patients had low-risk molar pregnancy. Among 201 cases with molar pregnancy referred to health centers from 2003 to 2013, pathological tests confirmed 30 patients with GTN. Among patients with high-risk and low-risk molar pregnancy, 11 (18.6%) and 19 patients (13.3%) had GTN, respectively. However, eight patients (26.7%) needed multidrug chemotherapy. According to $\chi^2$ test results, there was no significant relationship between the components of a high-risk pregnancy and GTN ($P$=.34). Table 1 shows basic and demographic information, where the continuous variables are shown as mean and SD and the grouped variables are shown in number and percentage. Since hCG was not distributed normally, it was transformed to natural logarithmic scale to normalize the distribution.

According to Table 1, there was no significant difference in chemotherapy, abortion history, and vaginal bleeding between the low-risk and high-risk molar pregnancy groups, while the difference was seen in other variables at a significance level of <.01. Since this field of study deals with the mechanism by which a hormone returns to a normal level, the regression line slope was estimated in the next step for each case on the basis of four measurements, and the related graphs were drawn for the GTN and spontaneous recovery groups. In linear regression relation of ($y = ax+b$), $y$ is the logarithm of hormone concentration, $x$ is time in days, $a$ is the line's slope, and $b$ is the model's intercept. The linearity of four measurements over time was tested via the Fracpoly regression method (coefficient: −0.16; 95% confidence interval [95% CI], −0.15 to −0.17.5).

According to Figure 1, the β-hCG return slope is higher in the spontaneous group. However, the initial level of this hormone in the first measurement is higher in the GTN group, compared with in the spontaneous recovery group. According to Cox analysis, the average time for diagnosing GTN in the high-risk molar pregnancy group was about 2 weeks less than that of the low-risk pregnancy group, as shown in Figure 2.

To study the risk factors for GTN, initially univariate analysis and then penalized logistic regression were used. The backward stepwise method was used to determine the best model with respect to the penalized log likelihood; however, profile likelihood was used to obtain more accurate estimations. The results of the finalized model with the maximum penalized log likelihood, compared with other models, showed that the introduction of hCG logarithmic concentration slope, as a variable independent of traditional risk factors of GTN, was clinically justifiable (Table 2).

The results of the final model indicated that, as a risk factor independent of traditional ones, a concentration of hCG with a ratio of 12.7 can help in the prediction and classification of patients with GTN risk. The OR of 12.7 implies that every 0.1 increase in β-hCG logarithmic slope increases the odds of GTN 13-fold. Another important finding was that elimination of influential variables on outcomes in three consecutive models did not change the estimated OR for other

## TABLE 1

**Comparison of basic and demographic data between the spontaneous recovery and the GTN groups.**

| | High-risk molar pregnancy | | Low-risk molar pregnancy | | |
|---|---|---|---|---|---|
| **Variable** | **Spontaneous cure** | **GTN** | **Spontaneous cure** | **GTN** | ***P* value** |
| Age, y | 30.8 ± 8.5 | 25.6 ± 7.8 | 25.2 ± 5.5 | 26.9 ± 4.2 | >.001 |
| Gestational age, wk | 10.1 ± 3.3 | 11.2 ± 3.4 | 9.8 ± 2.3 | 8.7 ± 1.6 | >.0005 |
| β-hCG$_0$, mIU/mL | 165,715 ± 27,289 | 178,840 ± 22,564 | 26,545 ± 2,897 | 34,999 ± 2,876 | >.001 |
| β-hCG$_7$, mIU/mL | 62,846 ± 7,192 | 84,731 ± 13,877 | 15,382 ± 3,176 | 18,013 ± 1,624 | >.001 |
| β-hCG$_{14}$, mIU/mL | 4,484 ± 938 | 42,710 ± 6,208 | 3,054 ± 899 | 9,999 ± 19.64 | .005 |
| β-hCG$_{21}$, mIU/mL | 2,196 ± 688 | 43,628 ± 7,134 | 1,180 ± 453 | 7,286 ± 345 | .003 |
| Gravidity | 2.1 ± 1.05 | 2.18 ± 1.16 | 1.76 ± 0.8 | 1.7 ± 0.9 | .002 |
| Parity | 1.02 ± 0.5 | 0.82 ± 0.3 | 0.6 ± 0.2 | 0.48 ± 0.12 | >.001 |
| Uterine height, wk | 12.6 ± 3.6 | 13.6 ± 4.8 | 9.26 ± 2.1 | 9.05 ± 1.54 | >.001 |
| Abortion history | | | | | |
| Yes | 8 (16.7) | 3 (27.3) | 19 (15.4) | 6 (31.6) | .86 |
| No | 40 (83.3) | 8 (72.8) | 119 (84.6) | 13 (68.4) | |
| Vaginal bleeding | | | | | |
| Yes | 45 (93.8) | 10 (90.9) | 104 (84.6) | 18 (94.7) | .14 |
| No | 3 (6.3) | 1 (9.1) | 19 (15.4) | 1 (5.3) | |
| Theca lutein cyst | | | | | |
| Yes | 7 (14.6) | 3 (27.3) | 0 (0) | 0 (0) | >.001 |
| No | 41 (85.4) | 8 (72.7) | 123 (100) | 19 (100) | |
| Chemotherapy required | | | | | |
| Yes | 1 (2.1) | 0 (0) | 1 (0.8) | 0 (0) | .51 |
| No | 47 (97.9) | 11 (100) | 122 (99.2) | 19 (100) | |

*Note:* Values presented as mean ± standard deviation or N (%). Independent *t* test and $\chi^2$ test were used to assess differences in grouped and quantitative variables between high- and low-risk molar pregnancies.

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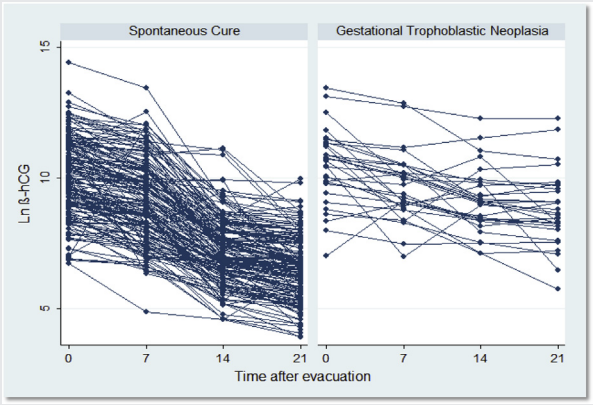
## FIGURE 1




Natural logarithmic regression line slope of hCG in two groups after evacuation (day): GTN and spontaneous recovery.

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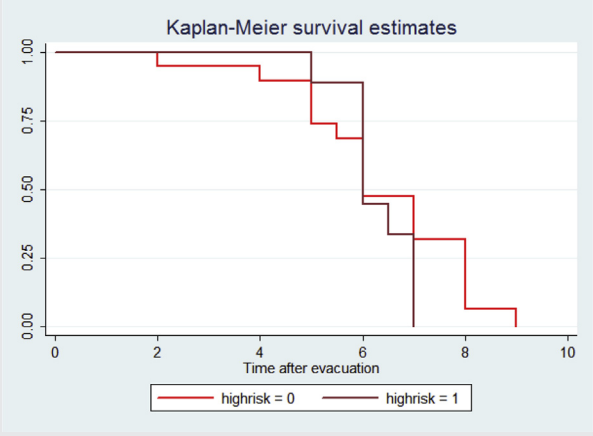
variables, implying that the relation was not disturbed by other variables.

As mentioned earlier, this study used the penalized logistic regression model instead of other classic models, which resulted in more accurate estimations, adjustment of the effects of discrete data to a large extent, and adjustment of sample size effect on estimation accuracy. The higher change of the logarithmic regression line slope of $\beta$-hCG concentration justifies the use of this risk factor as an appropriate and economic variable for predicting GTN risk. With an area under curve (AUC) of 0.9079 corresponding with the C-index in binary response variables and considering no censured cases, this model demonstrates a high discrimination between patients and spontaneously recovered cases.

## FIGURE 2




Duration (weeks) required for definite diagnosis of GTN in the high- and low-risk molar pregnancy groups.

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## DISCUSSION

The results of this study showed significant differences in all the variables studied (Table 1), except for abortion history, vaginal bleeding, and chemotherapy requirement between the high- and low-risk molar pregnancy cases, after univariate analysis. The investigation of GTN risk factors showed that in addition to other variables like theca lutein cyst, large uterine height for gestational age, and abortion history, the use of $\beta$-hCG concentration logarithmic slope (OR, 12.74; $P<.01$) as an independent risk factor is justifiable as a first-line preventive measure, facilitating early diagnosis. In recent years, considerable attempts have been made to detect new risk factors not only in the field of female diseases but also in all human health-associated fields (23, 24). Important considerations in the event of introducing a new risk factor are how it will be assessed from different aspects and how medical scientists and statisticians can use and apply the knowledge.

Some recommendations, made by D'Agostino, for confirmation of a new risk factor, by which the usefulness/applicability of the factor can be accepted or rejected, are definition of the studied population, definition of outcome(s), the efficiency of employing traditional risk profiles simultaneously, and the selection of a proper model for assessing the discriminative ability of the new factor (25).

The current study showed that there is a natural difference in $\beta$-hCG regression line slope between the GTN and the spontaneous recovery cases. Figure 2 shows that the slope of return to plasma level is lower in cases with GTN outcome and that it requires more time to reach lower levels, a finding confirmed by the Lybol et al. study (26). Kim et al. showed that measuring $\beta$-hCG return to normal level can be used to diagnose GTN (27). The use of all four titers and taking time trend change into account makes it justifiable to use the $\beta$-hCG logarithmic slope as a powerul predictive factor totally independent of other risk factors. According to the final model results (model 3, Table 2), in the presence of other influential factors, GTN odds increased 13-fold for every 0.1 change in $\beta$-hCG regression line slope in the studied cases. However, the odds of GTN in the cases with abortion history was 2.53-fold higher than that of cases with no abortion history. In addition, large uterine height for gestational age and theca lutein cyst increased the odds of GTN 1.26-fold and 4.56-fold, respectively. Generally, studies on the risk factors of GTN have reported the primary levels of hCG, theca lutein cyst, and molar pregnancy history as the major risk factors (28, 29). According to the Kuyumcuoglu et al. study, the variables of age, gravidity, and $\beta$-hCG titer are associated with an increase in the odds of GTN (30).

Khoo et al. showed that when the time for reaching a negative and nondetectable hCG titer was over 12 weeks, the risk for GTN increased 120-fold compared with the control group. However, in cases with a pregnancy interval of more than 12 months, the risk for GTN decreased by 75% (31). In the current study, age, gravidity, parity, and vaginal bleeding had no significant relationship with the outcome. In Parazzini et al.'s study, no significant relationship was found between induced abortion and GTN; this study showed, however,

## TABLE 2

**Penalized logistic regression model results for GTN risk factors in the studied cases.**

| Variable | Model 1 | Model 2 | Final model |
|---|---|---|---|
| Slope of linear regresion | 13.15 (5.4–31.8) | 13.17 (5.5–31.5) | 12.74[a] (5.42–29.2) |
| Age, y | 0.98 (0.9–1.07) | – | – |
| Gestational age, wk | 0.96 (0.78–1.18) | – | – |
| Gravidity | 1.67 (0.66–4.2) | 1.61 (0.64–4.1) | – |
| Parity | 0.57 (0.18–1.8) | 0.57 (0.19–1.72) | – |
| Abortion history | | | |
| Yes | 2.22 (1.06–4.66) | 2.21 (1.6–4.61) | 2.53[a] (1.27–5.04) |
| No | Reference | Reference | Reference |
| Vaginal bleeding | | | |
| Yes | 1.59 (0.25–7.6) | – | – |
| No | Reference | Reference | Reference |
| Large uterine height for gestational age | | | |
| Yes | 1.25 (1.03–1.53) | 1.43 (1.11–1.75) | 1.26[b] (1.04–1.54) |
| No | Reference | Reference | Reference |
| Theca lutein cyst | | | |
| Yes | 4.7 (2.45–9.13) | 4.73 (2.45–9.1) | 4.65[a] (2.43–9.2) |
| No | Reference | Reference | Reference |
| Penalized log likelihood | −69.68 | −62.93 | −58.1 |

*Note:* Data presented as odds ratio (95% confidence interval). All confidence intervals have been reported by the profile likelihood method.
[a] Significant at $P < .01$.
[b] Significant at $P < .05$.

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that a history of GTN, whether in one member or in the family, has an inverse relationship with a high risk of molar pregnancy in subsequent pregnancies (32). Results of studies may differ depending on the study design, the population studied, and the study location. For example, Kumar et al. showed that there is a relationship among age >30 years, gravidity, abortion history, and the risk for GTN, while our study did not (33).

In recent decades, the use of logistic regression has played a significant role in analyzing epidemiologic data and social studies; these are nonlinear models and, therefore, are analyzed by the maximum-likelihood method as there is no limitation for independent variables (34). Meanwhile, Bayesian analyses have attracted attention as they are used in applications with smaller sample sizes and have more accurate estimations in which previous data are taken into account to replace prior and later probability distribution (35).

The study of Kang et al. introduced the ratio of pre-evacuation hCG of molar pregnancy to hCG 2 weeks after evacuation titer as an independent GTN risk factor with odds of 6.8; the notable point in this study is that the appropriate cutoff point for this ratio (the ratio of pre-evacuation hCG to hCG 2 weeks after evacuation) aimed at predicting GTN was 30, with a sensitivity and specificity of 63% and 86%, respectively (36). In our study, receiver operating characteristic AUC of the independent risk factor up to the point of diagnosing GTN was 90%, with a sensitivity and specificity of 75% and 89%, respectively. Regarding the average time required to diagnose GTN, we found that it varies between 7 and 9 weeks for high-risk and low-risk groups, respectively. Kizaki et al. studied the duration required for hCG serum titer to normalize and found that it varies from 3 to 29 weeks (37). It should be mentioned that the current study measured four consecutive hCG levels and converted them to one unique variable, which facilitated data associated with the time of developing GTN or spontaneous recoveries. However, it applies an integrated strategy for measuring $\beta$-hCG.

It needs to be emphasized that for discrimination of the GTN cases using the slope of the linear regression line of $\beta$-hCG, clinicians have to use user-friendly software like SPSS and be familiar with simple linear regression to determine the slope. Although this concept is basic in the science of statistics, many of the clinicians working in this field prefer to apply rational measures such as traditional risk factors (with lower AUC and sensitivity) in their practice. In addition, accuracy of the prediction of GTN cases based on the slope of the linear regression line of $\beta$-hCG is that it is not based on absolute $\beta$-hCG values but on the gradient of the regression curve. In addition, the prediction model is based on four $\beta$-hCG measurements, providing a reliable reflection of the course of the $\beta$-hCG level.

Our study has strengths and limitations. Generally, our study followed an approach with complete data and a surrogate regression line slope (representative of the four serum titers of $\beta$-hCG), yielding, therefore, more reliable estimations; it also used presumptions confirmed by other studies to determine the magnitude of the effect of every variable introduced into the penalized logistic regression model, considered a proper model for low size discrete data (38).

Regarding limitations, since the data of this study were registered as retrospective and the data were not collected initially for research purposes, there is the possibility of information error in data classification, which is the reason why 20 cases were initially excluded. The limitations regarding coverage of all treatment and health centers answering the study question should also be mentioned.

To conclude, introducing the slope of linear regression of $\beta$-hCG as a strong independent risk factor and comparing it with the traditional ones showed that it could be easily used for clinical decision making based on records of $\beta$-hCG titer

and subsequent prevention programs without any extra imposed cost. The authors recommend that further studies be conducted on appropriate populations, concentrating on the disease etiology and related health-threatening factors, which will ensure more accurate estimations of the prevalence of this disease.

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