Incidence of Gestational Trophoblastic Neoplasia After Molar Evacuation

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Abstract

Objective: Identify the incidence and related factors of gestational trophoblastic neoplasia (GTN) after molar evacuation. Methods: We designed a retrospective cohort study and selected entire 560 patients with hydatidiform mole treated with molar evacuation from January 2018 to December 2018 at Tu Du Hospital. The Kaplan-Meier survival analysis was performed to determine the incidence of GTN over time. We apply the Cox regression model to identify factors related to GTN. Results: The cumulative incidence of GTN after a 12-month follow-up was 24.71%. Out of 97 cases of GTN, 20 patients were identified after 4 weeks, 52 cases were determined after 8 weeks, 80 cases were identified after 12 weeks, and 92 cases were identified after 16 weeks. There were no cases after 26 weeks from molar evacuation. In patients with an abortion history, the risk of GTN is 1.56 times higher than in patients without a history of abortion (HR = 1.56; CI 1.02 - 2.39, P = 0.039). In addition, in patients 20-39 years old, the risk of GTN is 8.10 times higher than in patients younger than 20 (HR = 8.10; CI 1.0 -53.39, P = 0.041). Conclusions: The overall incidence of GTN is 24.71%, usually within the first 14 weeks after molar evacuation. In our study, abortion history and age of the patients are related to GTN risk.

Keywords: GTN.

Introduction

Gestational trophoblastic disease (GTD) describes a heterogeneous spectrum of aberrant trophoblastic proliferative diseases ranging from benign to malignant, with varying preferences toward local invasion and distant metastasis. GTD is classified according to histopathologic, cytogenetic, and clinical features using the WHO GTD classification. The different histologic categories of GTD include benign forms such as hydatidiform moles (HM), complete hydatidiform moles (CHM) and partial hydatidiform moles (PHM), and gestational trophoblastic neoplasia (GTN), including invasive moles, gestational choriocarcinoma,

epithelioid trophoblastic tumors, and trophoblastic tumors of the placental site.

In recent years, Tu Du Hospital has been managing and monitoring most of the GTN patients in Southern Vietnam, with approximately 1000 cases of molar pregnancy and 200 cases of GTN being treated here yearly [1][2].

After molar evacuation, serum monitoring of human chorionic gonadotropin (hCG) levels is essential to detect GTN progression and initiate chemotherapy. In other words, accurate assessment of disease status with sensitive βhCG assays for early disease detection and effective chemotherapy regimens are crucial factors for making GTD the most curable of all gynecologic malignancies.

In addition, GTN is usually seen after an HM, emphasizing the importance of identifying the risk factors of molar pregnancy. For patients unable to adhere to serial follow-up HCG monitoring, especially in developing countries such as Vietnam, the ability to predict a high risk of persistent disease may justify prophylactic chemotherapy. For this reason, we conducted this study with the question: "What are the incidence and related factors of gestational trophoblastic neoplasia (GTN) after molar evacuation?"

Method

Study design: Retrospective cohort. Population: Patients with hydatidiform mole were treated with molar evacuation from January 2018 to December 2018 at Tu Du Hospital.

Inclusion criteria: Patients with hydatiform mole (complete hydatidiform mole or partial hydatidiform mole), based on histopathology reports. Exclusion criteria:

- Molar evacuation was performed before admission to Tu Du Hospital.

- βhCG increase due to pregnancy during the surveillance period.

- Discontinue βhCG monitoring before complete remission.

Statistical Analysis

Stata version 14.0 was used for statistical analysis.

Kaplan-Meier survival analysis is performed to determine the incidence of GTN after molar evacuation over time. We apply the Cox regression model to identify factors related to GTN after molar evacuation.

The confidence interval of 95% and power of 90% is used in statistical analysis.

Description of essential variables:

Normalization of the βhCG is defined as normal βhCG values below the 5 mIU/mL reference range. Complete remission is confirmed after three consecutive normal βhCG levels, and there was no clinical or radiologic evidence of disease.

Survival time (weeks) is the number of weeks after molar evacuation for hydatidiform mole treatment without any occurrence of GTN or until the patients discontinue βhCG surveillance.

Results

Patient characteristics:

From January 2018 to December 2018, 1143 patients were diagnosed with hydatidiform moles and underwent treatment at Tu Du Hospital. 583 patients were excluded from the study. Among the remaining 560 patients, 262 had a complete hydatidiform mole, and 298 had a partial one. Overall, after monitoring serum hCG titers of these patients for 12 months, 97 patients developed gestational trophoblastic neoplasia (GTN) before the first normal βhCG value, and 463 patients were in complete remission. No patients developed GTN after βhCG normalization. The clinical characteristics of the participants are shown in Table 1**.**

Table 1: Patient characteristics

Variable	Frequency (N = 560)	Percentage (%)
Age		
< 20	31	5.5
20 – 39	425	75.9
≥ 40	104	18.6
BMI (kg/m²)		
<18,5	101	18.0
18,5 – 23	358	64.0
>23	101	18.0
History of cesarean section or myomectomy	459	82.0
History of gestational trophoblastic disease	0	0.0
Enlarged uterus for gestational age	207	37.0

Variable	Frequency (N = 560)	Percentage (%)
Theca lutein cyst > 6 cm	22	3.9
Preeclampsia	3	0.5
Hyperthyroidism	12	2.1
Trophoblastic embolism	0	0.0
Hyperemesis gravidarum	12	2.1
Anemia	220	39.3
Blood type		
A	121	21.6
B	195	34.8
AB	28	5.0
O	216	38.6
βhCG concentration before molar evacuation		
< 100,000 mUI/mL	164	29.3
≥100,000 mUI/mL	394	70.7
Pathology report of intrauterine tissue		
Complete hydatidiform mole	262	46.8
Partial hydatidiform mole	298	53.2
Prophylactic chemotherapy	49	8.8
Hysterectomy	83	14.8
High-risk for post molar GTN according to WHO 1983	133	23.8
High-risk for post-molar GTN, according to Goldstein	430	76.8

The mean age of our participants was 30.9 (+/- 8.6), ranging from 18 to 55, with about a fifth who are older than 40 years old. Most were of Kinh ethnicity and worked as housewives or in the service industry.

One-third of them had a history of abortion, and about a fifth had uterine scars due to cesarean section or myomectomy. None of them had a previous history of gestational trophoblastic disease.

The participants' mean BMI was 20.9 (3.0) kg/m2; 39.3% had anemia. Hyperemesis gravidarum was present in 12 women (2.1%). The prevalence of preeclampsia and hyperthyroidism was 0.5% and 2.1%, respectively. None of our women had a trophoblastic embolism. The most prevalent blood types were O (38.6%) and B (34.8%); type AB was 5%.

About a third had an enlarged uterus for gestational age. Theca lutein cysts larger than 6 cm were present in 22 women (3.9%). The mean βhCG concentration (SD) before molar evacuation was 271 947.8 (284 493.3) mUI/mL, and the prevalence of βhCG > 100 000 was around two-thirds.

Of the pathology reports, approximately half (46.8%) had complete hydatiform moles, 8.8% had prophylactic chemotherapy, and 14.8% underwent hysterectomy because of the high risk of GTN.

According to Goldstein's standard, the high-risk hydatidiform mole was present in nearly a quarter, but according to WHO's standard, this was present in three quarters.

After 12 months of follow-up, out of the 560 cohort patients, 97 developed GTN, accounting for 17.32% of the total patients. The remaining 463 patients had three consecutive hCG normalizations, but 306 discontinued hCG surveillance.

Among 97 GTN patients, 50 had a complete hydatidiform mole, and 47 had a partial one.

The mean time (SD) to diagnose GTN was 8.6 (4.4) (weeks). The shortest time was 4 weeks, and the longest was 26 weeks. All GTN patients were diagnosed within 6 months of the D&C procedure, 94 of whom were diagnosed based on abnormal hCG progression; the rest were based on pathology reports. No patients developed GTN after hCG normalization.
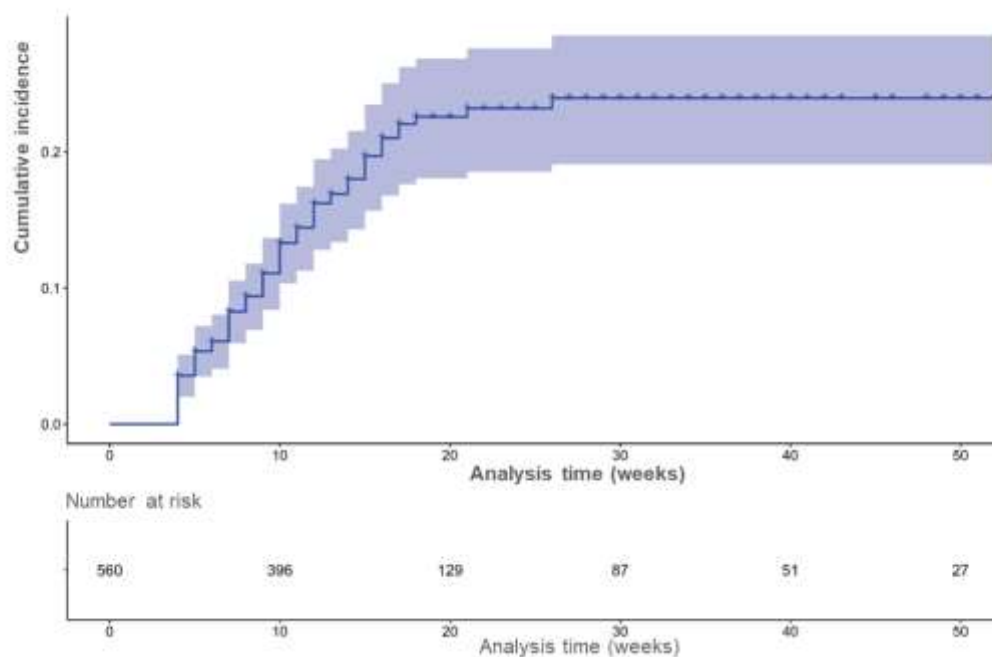
Incidence of GTN after molar evacuation

Figure 1: Cumulative incidence of post-molar gestational trophoblastic neoplasia

Figure 1 shows the cumulative incidence of GTN during a 12-month follow-up in survival analysis. The incidence rises steadily from the 4th week to the 14th week. In the 12th week, the median time to diagnosis, the GTN cumulative incidence was 16.7%. In the 26th week, the cumulative incidence hits the highest point (24.71%) and remains stable until the end (52nd week).

Factors for post-molar gestational trophoblastic neoplasia

Table 2. Univariate logistic regression of factors for post-molar GTN with Cox proportional hazards regression.

Factor		HR	95% CI	P
Age	<20	1		
	20 – 39	6.83	0.95-49.09	0.056
	≥ 40	4.57	0.60-34.60	0.141
BMI (kg/m²)	< 18.5	0.90	0.52-1.56	0.706
	18.5 - 23	1		
	> 23	1.16	0.70-1.92	0.574
Abortion history		1.59	1.07-2.36	**0.023**
History of cesarean section or myomectomy		1.09	0.66-1.80	0.737
Hyperemesis gravidarum		1.06	0.26-4.30	0.935
Enlarged uterus for gestational age		1.64	1.03-2.60	**0.036**
Theca lutein cyst > 6 cm		1.91	0.93-3.95	0.080
Preeclampsia		1.89	0.26-13.62	0.524
Hyperthyroidism		0.87	0.21-3.52	0.841
Anemia		1.52	1.02-2.26	**0.040**
Blood type	O	1		
	B	1.07	0.62-1.83	0.814
	A	1.82	0.83-3.97	0.134
	AB	0.86	0.49-1.49	0.587
βhCG concentration before molar evacuation ≥ 100 000 (mUI/ml)		1.46	0.88-2.41	0.141

Factor		HR	95% CI	P
Pathology report	CHM	1		
	PHM	1.14	0.76-1.69	0.520
Prophylactic chemotherapy		1.33	0.74-2.38	0.342
Hysterectomy		0.89	0.50-1.56	0.680
High risk for post-molar GTN, according to Goldstein		0.94	0.60-1.47	0.782
High risk for post-molar GTN, according to WHO 1983		0.97	0.62-1.53	0.904

HR: Hazard Ratio

Table 2 shows the variables significantly associated with post-molar GTN risk according to the Cox proportional hazards regression. In univariate analyses, three factors were found to have a significant risk effect on the development of GTN. In particular, when compared with patients with no abortion history, the risk increased significantly in subjects who had an abortion history (HR = 1,59, 95% CI: 1,07 - 2,36). Furthermore, an enlarged uterus for gestational age (HR = 1,64, 95% CI: 1,03-2,60) and anemia (HR = 1,52, 95% Cl: 1,02 - 2,26) were independent risk factors for post-molar GTN.

Table 3. *Multivariate logistic regression of factors for post-molar GTN with Cox proportional hazards regression*

Factor		HR*	95% CI	P(*)
Age	< 20	1		
	20 – 39	8.10	1.0-53.39	**0.041**
	≥ 40	3.38	0.30-20.74	0.256
Abortion history		1.56	1.02-2.39	**0.039**
Enlarged uterus for gestational age		1.59	0.95-2.69	0.079
Theca lutein cyst ≥ 6 cm		1.19	0.55-2.57	0.665
Anemia		1.19	0.77-1.82	0.437
Blood type	O	1		
	B	1.14	0.66-1.95	0.646
	A	2.03	0.91-4.52	0.082
	AB	0.90	0.51-1.57	0.710
βhCG concentration prior D&C ≥ 100000 mUI/ml		1.18	0.68-2.04	0.556

HR*: modified HR

Next, Cox multivariate analyses were performed among the variables with p-value < 0.2 to identify the risk factors for GTN (Table 3). The results of the multivariate analyses indicated that abortion history with a ratio of 1.56 could help predict patients with GTN risk. Besides, the age of patients in the range of 20 to 39 also has a significant risk effect on the development of GTN compared to women under 20.

Discussion

The incidence of GTN occurred most frequently during the first 16 weeks of surveillance, especially after the fourth week. Specifically, the cumulative incidence of GTN was 3.57% after the fourth week, 9.49% after the 8th week, 16.73% after the 12th week, 21.74% after the 16th week, and 24.71% after the 26th week. At 12 weeks was the median time for diagnosis. At week 26, the cumulative incidence hits the highest point (24.71%) and remains stable. All were diagnosed before hCG normalization. Our incidence is much lower than that of Braga et al., 24.14%, reported in 2015 [5]. The differences between study populations can explain these differences in GTN incidence between studies. Three hundred six patients discontinued hCG surveillance, which accounted for 54.54% of total patients. This incidence also correlates with the report from Massad LS and Alen JE et al., which is more than 50% [5][6].

Our study showed a significant difference in GTN incidence based on abortion history. In particular, the HR of GTN in the cases with an abortion history was 1.56-fold higher than that of patients with no abortion history. Cho et al.'s study [8] found a significant relationship between abortion history and GTN. In the current research, the history of cesarean section and hCG concentration >100 000 mUI/ml are strongly associated with GTN risk. In contrast, age, parity, vaginal bleeding, uterine size, and theca lutein cyst had no significant relationship with the outcome. Our finding of the association between the age of 20 to 39 and the risk of GTN compared to the period under 20 was unexpected; the risk increased 8-fold in patients aged 20 – 39 years, while it was not significant in patients 40 years and older. To our knowledge, this risk factor was not the subject of previous analyses. We cannot explain this finding.

Furthermore, Khoo et al. showed that when the time to reach a negative and undetectable hCG titer was greater than 12 weeks, the risk for GTN was increased 120-fold compared with the control group [9] and in the current study, age, gravidity, parity, and vaginal bleeding had no significant relationship with the outcome. In Bakhtyari et al.'s study, no significant association was found between induced abortion and GTN; this study showed, however, that a history of GTN, whether in one member of the family, has an

inverse relationship with a high risk of molar pregnancy in subsequent pregnancies [10]. Results of studies may differ depending on the study location, characteristics of the study cohort, selection or referral bias, and possibly sociodemography and ethnicity.

Our study has limitations. Since the data of this study was registered as retrospective and the data was not collected initially for research purposes, there is the possibility of information errors in data classification.

Conclusion

After conducting a study on 560 patients with a hydatidiform mole who underwent molar evacuation, we found the following: (1) The cumulative incidence of GTN after a 12-month follow-up was 24.71%. The median time to diagnosis was 12 weeks, with the highest was 26 weeks. GTN occurred most frequently during the first 14 weeks. (2) Abortion history and the age of 20-39 significantly correlated with GTN risk after uterine evacuation. Patients with an abortion history had a 1.56-fold increase in the risk of GTN compared to those without a history of abortion. Patients aged 20 to 39 years had an 8.1-fold increased risk of GTN compared with those under 20.

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