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The management of hydatidiform mole using prophylactic chemotherapy and hysterectomy for high-risk patients decreased the incidence of gestational trophoblastic neoplasia in Vietnam: a retrospective observational study

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ABSTRACT

The management of hydatidiform mole (HM) and the incidence of post-molar gestational trophoblastic neoplasia (GTN) in Vietnam has not been reported to date. This study aimed to study the incidence of HM and post-molar GTN and identify factors associated with post-molar GTN at a tertiary hospital in Vietnam. Five hundred and eighty-four patients who were treated for HM at Tu Du Hospital between January and December 2010 were included in this study. The mean age and gestational age at the first evacuation were 28.8 years old and 11.0 weeks, respectively. After the initial evacuation and pathological examination, 87 patients who were older than 40 or did not wish to have children underwent a hysterectomy, while the others underwent second curettage. All 472 patients who had human chorionic gonadotropin (hCG) ≥ 100,000 IU/L before treatment received one cycle of methotrexate with folinic acid as prophylactic chemotherapy. The incidence of HM was 11.1 per 1,000 deliveries; 47 patients (8.0%) developed post-molar GTN. Gestational week, hCG level at one week after the first evacuation, and pathological remnants were significantly associated with the development of post-molar GTN. The results of this study suggest that prophylactic chemotherapy and hysterectomy may be useful for high-risk HM patients to reduce post-molar GTN in settings in which the risk of post-molar GTN and loss to follow-up after HM are greater and hCG measurements and appropriate GTN treatments are unavailable. However, future studies on the long-term outcomes and side effects of prophylactic therapies on HM are required.

Keywords: post-molar gestational trophoblastic neoplasia, hydatidiform mole, hysterectomy, prophylactic chemotherapy, Vietnam

Abbreviations:
CHM: complete hydatidiform mole
GTN: gestational trophoblastic neoplasia
hCG: human chorionic gonadotropin
HM: hydatidiform mole

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MTX: methotrexate
PHM: partial hydatidiform mole

INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of diseases characterized by proliferation of atypical placental trophoblasts. GTD consists of hydatidiform mole (HM) and gestational trophoblastic neoplasia (GTN), which includes invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelial trophoblastic tumor (ETT).[1] GTN is the comprehensive name for four diseases as well as a clinical diagnosis when a pathological examination is unavailable. HM is an abnormal conceptus caused by genetic fertilization disorders that is classified into complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) depending on histopathology and karyotype. GTN that occurs within six months after HM is called "post-molar GTN," which is mostly invasive mole pathologically.[2] The incidence of post-molar GTN is 15–24% and 0.5–5% after CHM and PHM, respectively.[3-10] Predictive factors for post-molar GTN are reportedly CHM, age, pretreatment human chorionic gonadotropin (hCG) level, uterine size, lutein ovarian cysts, history of mole, and declining hCG ratio two weeks after evacuation.[3,10,11] Molar patients with at least one of the following criteria are considered as high-risk HM patients: age ≥ 40 years old, pretreatment hCG level ≥ 100,000 IU/L, lutein cyst diameter > 6 cm, and uterine size greater than the number of gestational weeks.[12] High-risk HM patients have a higher chance of developing post-molar GTN (30–50%) than other patients (4%).[1,11,13,14]

The incidence of GTD is higher in Asia than that in Europe and the USA.[1,5,15,16] The incidence of HM is 0.66–1.21 per 1,000 pregnancies in Europe, North America, and Oceania,[5] which is the lowest in the world. The incidence per live births or pregnancies in Asia is higher than that in other regions but varies among countries and studies: 1.5–3 in Japan,[17] 1.6–4.4 in South Korea,[18] 0.81 in China,[19] 2.8 in Malaysia,[20] 1.2 in Singapore,[21] 2.8 in Malaysia,[22] 2.4 in the Philippine,[23] and 1.70 in Thailand.[24]

The common management for HM involves performing a uterine evacuation and following the hCG levels to detect GTN. However, second curettage, hysterectomy, and prophylactic chemotherapy are reported as treatments for molar patients to reduce the incidence of post-molar GTN. Second curettage is performed when retention of the molar tissue in the uterus is detected using ultrasonography in most countries,[3-5,11,12] but it is routinely performed for all cases of HM in some reports.[2,10,25] Recent systematic review studies on prophylactic hysterectomy and prophylactic chemotherapy reported that these methods effectively reduce the incidence of post-molar GTN.[14,26]

The incidence of HM in Vietnam was reported to be 1.5 per 1,000 pregnancies in 1998,[27] but methods of diagnosing and managing HM in Vietnam have not been reported. This study aimed to determine the incidence of HM and post-molar GTN, and identify factors associated with post-molar GTN at a tertiary hospital in Ho Chi Minh, Vietnam.

MATERIALS AND METHODS

Patients and treatment

A total of 654 molar patients visited Tu Du Hospital for treatment from January to December 2010; finally, 584 patients were included in this study because the records of 70 patients were missing some data for analysis. All 584 patients underwent evacuation after cervical dilation

and diagnoses were made postoperatively by the pathological review of obtained specimens. To confirm a lack of remnant molar tissues, 497 patients (85.1%) underwent a second curettage around the 7th day after the first evacuation. A hysterectomy was recommended to patients who were 40 years old or had no desire for future pregnancies, while 87 (14.9%) patients underwent hysterectomy instead of second curettage. Pathologists reviewed the curettage and hysterectomy specimens for the existence of molar trophoblasts. When the pretreatment hCG level was 100,000 IU/L or greater, one cycle of methotrexate (MTX) and folinic acid (FA) (intramuscular MTX 50 mg on days 1, 3, 5, and 7 and oral FA 15 mg on days 2, 4, 6, and 8)[28] was provided to the patients after agreement was obtained.

Serum hCG level was measured before treatment, one week after the first evacuation, and every two weeks until the hCG level decreased to the cut-off value (≤ 5 IU/L). When the hCG level was ≤ 5 IU/L, regression was diagnosed. According to the International Federation of Gynecology and Obstetrics criteria, GTN was diagnosed when the hCG level was stable or increased over at least three weeks, or when hCG level had not reached to 5 IU/L by six months after the first evacuation.[29] Pelvic ultrasonography and chest X-ray were conducted to detect GTN lesions. MTX-FA therapy was administered as treatment for GTN and two additional cycles were administered after hCG levels reached the cut-off value. Age, gravida, para, histology, gestational weeks, hCG level before treatment and one week after the first evacuation, methods of the second operation, pathological remnants, provision of prophylactic chemotherapy, and outcomes (regression or post-molar GTN) were collected from the patients' records. This study was approved by the Ethics Committees of Nagoya University (approval number: 2015–0153) and Tu Du Hospital (approval number: HNVP2016).

Statistical analysis

Logarithmic transformation with reduced skewness was used to analyze the hCG concentrations. The statistical analysis was performed using a chi-square test for the independence test or Student's t-test. Logistic regression analysis with the stepwise entry method was used for multivariate analyses to test the significance of prognostic factors on the development of GTN. Statistical Package for the Social Sciences version 24.0 (IBM SPSS Inc., New York, USA) was used for statistical analyses, and P-values < 0.05 were considered significant.

RESULTS

There were 58,614 deliveries and 654 HM patients in 2010; the incidence of HM at Tu Du Hospital was 11.1 per 1,000 deliveries. Of the 584 included molar patients, the mean age and gestational weeks were 28.8 years (range, 15–56 years); 104 patients were 40 years or older. The mean gestational age at the first evacuation was 11.0 weeks (range, 4–27 weeks). Two hundred and sixty-eight patients (45.9%) were nulligravida, while 309 (52.9%) were nulliparous. Histologically, 473 patients (81.0%) were diagnosed with CHM. A hysterectomy was performed in 87 patients (14.9%), including 85 patients ≥ 40 years old and two patients who were younger than 40 years and had two children. Prophylactic MTX-FA therapy was provided to all 472 patients (80.8%) whose pretreatment hCG level was ≥ 100,000 IU/L. The number of patients who met at least one of high-risk criteria, namely age ≥ 40 years old and pretreatment hCG level ≥ 100,000 IU/L, was 490 (83.9%). Of the 490 patients, 483 patients had either hysterectomy or prophylactic thermotherapy. A total of 47 patients (8.0%) developed post-molar GTN, while 537 patients (92.0%) achieved remission (Table 1).

The 584 patients were divided into the remission group (n = 537) and the post-molar GTN

Table 1 Correlation of post-molar gestational trophoblastic neoplasia with clinical factors in hydatidiform mole

Characteristics		All (N=584)	Remission (N=537)	Post-molar GTN (N=47)	*P*
Age (years)[1]		28.8±9.7	28.6±9.6	31.7±10.0	0.040
Gravida					
	Null	268 (45.9%)	252 (94.0%)	16 (6.0%)	0.089
	≥1	316 (54.1%)	285 (90.2%)	31 (9.8%)	
Para					
	Null	309 (52.9%)	292 (94.5%)	17 (5.5%)	0.016
	≥1	275 (47.1%)	245 (89.1%)	30 (10.9%)	
Histology					
	CHM	473 (81.0%)	434 (91.8%)	39 (8.2%)	0.717
	PHM	111 (19.0%)	103 (92.8%)	8 (7.2%)	
Gestational age at the first evacuation (weeks)[1]		11.0±3.6	10.8±3.5	13.0±4.6	0.003
hCG before treatment (IU/L)[2]		254,688.5 (150-4,547,476)	240,945.6 (150-4,547,476)	480,015.5 (4,468-1,388,469)	<0.001
hCG at 1 week after the initial evacuation (IU/L)[2]		348.0 (5-737,007)	301.9 (5-737,007)	1,589.6 (5-143,199)	<0.001
Second operation					
	Evacuation	497 (85.1%)	465 (93.6%)	32 (6.4)	0.001
	Hysterectomy	87 (14.9%)	72 (82.8%)	15 (17.2%)	
Pathological Remnant					
	No	500 (85.6%)	472 (94.4%)	28 (5.6%)	<0.001
	Yes	84 (14.4%)	65 (77.4%)	19 (22.6%)	
Prophylactic chemotherapy					
	No	112 (19.2%)	109 (97.3%)	3 (2.7%)	0.019
	Yes	472 (80.8%)	428 (90.7%)	44 (9.3%)	

[1]Mean ± standard deviation
[2]Geometric mean computed on the log-transformed variable and converted to the original scale of measurement, and range in parenthesis
GTN: gestational trophoblastic neoplasia, CHM: complete hydatidiform mole, PHM: partial hydatidiform mole.
Age, gestational age at the first evacuation and hCG were analyzed by a chi-square test and gravida, para, histology, second operation, pathological remnant and prophylactic chemotherapy were analyzed by Student's t-test.

group (n = 47). We compared age, gravid, para, histology, gestational weeks, hCG levels before treatment and one week after the first evacuation, and pathological remnant of molar trophoblasts in the specimens from the second operation between the two groups (Table 1). The mean age and gestational weeks were significantly higher in the post-molar GTN group than in the remission group. A higher proportion of patients in the post-molar GTN group than the remission group had gravida status or para of one or more, but the difference was significant only for para. The mean hCG level before treatment was significantly higher in the post-molar GTN group than in the remission group (480,015.5 IU/L vs. 240,945.6 IU/L, $P < 0.001$). The mean hCG level at one week after the first evacuation was 1,589.6 IU/L in the post-molar GTN group, significantly higher than that in the remission group (301.9 IU/L, $P < 0.001$). Patients who underwent a hysterectomy, in whom pathological remnants were found at the second operation, or who received prophylactic chemotherapy had a significantly higher incidence of post-molar GTN than the others. CHM patients were more likely to develop GTN than PHM (8.2% v.s. 7.2%), but the difference was not significant.

To identify risk factors for post-molar GTN, multiple logistic regression analysis with the stepwise method was performed using all variables. The results showed that gestational weeks, log-transformed hCG at one week after the initial evacuation, and pathological remnant were significantly associated with post-molar GTN (Table 2). Patients in whom remnant molar trophoblasts in the uterus were noted in the second operation were 3.22 times more likely to develop GTN than those without remnants ($P = 0.001$).

DISCUSSION

This study showed that the incidence of HM at Tu Du Hospital was 11.1 per 1,000 deliveries, higher than that in previous studies conducted in Asian countries. This value was calculated using the number of patients who had deliveries and who received treatment for HM at Tu Du Hospital, but these patients were not related to the same population. Because Tu Du Hospital is the largest obstetrics and gynecology hospital in the South Vietnam, molar patients were more likely than normal pregnant patients to visit the hospital for treatment. In the Vietnamese health system, people can visit any health facilities; a referral from lower-level health facilities is not absolutely necessary to visit tertiary hospitals.[30,31] The addresses of molar patients included Ho Chi Minh City, Kan Tho City, and 35 provinces, and patients from Ho Chi Minh City accounted for only 17.0% of our population. In contrast, it is assumed that most patients who experienced childbirth was from Ho Chi Minh City. If the incidence of HM is calculated using the total

Table 2 Multivariate analysis of post-molar gestational trophoblastic neoplasia

Variables	Odds Ratio	95% CI	*P*
Gestational age at the first evacuation (weeks)	1.14	1.03–1.20	0.006
Log-transformed hCG at 1 week after the initial evacuation	1.37	1.18–1.60	<0.001
Pathological remnant			
Negative	1	Reference	
Positive	3.22	1.61–6.47	0.001

CI: confidence interval.

number of deliveries and molar patients from Ho Chi Minh, the incidence would be 1.9 per 1,000 deliveries, close to the incidence in other Asian countries as well as the previous report in Vietnam.[27]

Second, the incidence of post-molar GTN was 8.0%, which was much lower than that reported in previous studies.[3-8,10] The prophylactic chemotherapy and hysterectomy undergone by high-risk HM patients may be the reason for the lower incidence. The meta-analysis of the data of six studies reported that the incidence of post-molar GTN was significantly lower in patients who underwent hysterectomy than that in patients who underwent evacuation (odds ratio 0.19, $P < 0.0004$).[26] The significant advantage of hysterectomy in reducing the incidence of post-molar GTN over evacuation was also found in the subgroup analyses of the study region (East Asia and Western countries), patient age (≥ 40 years old and ≥ 50 years old), and diagnosis (CHM and HM). However, complications during or after hysterectomy and anesthesia may occur more often and be more severe than curettage and the surgical procedure may promote vascular dissemination of trophoblastic cells and tissues. Furthermore, post-molar GTN or choriocarcinoma can occur in metastatic lesions after hysterectomy.[32]

Since the first report of prophylactic chemotherapy for HM in 1966,[33] several retrospective studies have reported that prophylactic chemotherapy was highly effective in reducing the incidence of post-molar GTN in high-risk HM patients.[14,34-36] The meta-analysis of three randomized controlled trials in Japan, South Korea, and Thailand[34,37,38] showed that prophylactic chemotherapy reduced the risk of post-molar GTN among CHM patients with the risk ratio of 0.37 but increased the duration to the diagnosis of GTN.[14] Prophylactic chemotherapy may cause drug-related side effects and toxicity-related deaths depending on the patient's condition and treatment regimen.[34,38,39] However, loss to follow-up, low access to healthcare, and limited health services at health facilities in rural areas are problems in low- or middle-income countries. Treatment for HM in early gestational weeks and subsequently regular hCG monitoring are needed to prevent development choriocarcinoma, a life-threatening malignant GTN. Although most studies of prophylactic chemotherapy were published before 2000, some reported that prophylactic chemotherapy and hysterectomy were provided to high-risk patients until 2009–2013 in China and Brazil and were cost-effective.[40,41] These results suggest that prophylactic chemotherapy and hysterectomy for high-risk HM patients may be useful but should be limited to areas or situations in which the risk of post-molar GTN and loss to follow-up after HM are greater, and when hCG measurements and the appropriate treatment for GTN are unavailable.

The independent risk factors for post-molar GTN were gestational weeks, hCG level at one week after the first evacuation, and pathological remnant. The incidence of post-molar GTN in CHM did not differ from that in PHM patients. Factors associated with post-molar GTN in this study were different from those in previous studies. In this study, all 472 patients whose pretreatment hCG level was ≥ 100,000 IU/L had prophylactic chemotherapy; 81.7% of 104 patients who were 40 years old or older underwent hysterectomy. A total of 484 patients (82.9%) received either prophylactic treatment; 75 patients received both therapies. A higher proportion of patients in the CHM group versus PHM group received prophylactic chemotherapy (86.2% v.s. 13.8%, $P < 0.001$). In this study, most patients who met the high-risk criteria received prophylactic therapies; therefore, the independent risk factors in this study did not include age, initial hCG level, or CHM.

There are some limitations to this study. First, it did not include side effects of prophylactic chemotherapy and hysterectomy. Kashimura et al reported that 27.3% of patients who received one cycle of prophylactic methotrexate therapy experienced several mild or moderate complications such as stomatitis (10.2%), nausea/vomiting (6.8%), leukopenia (4.4%), and elevated glutamic oxaloacetic transaminase (3.3%).[38] The toxicity of methotrexate is milder and occurs

less often than that of dactinomycin.[42] Despite one cycle of chemotherapy, the effectiveness of the prophylactic therapies should be evaluated by comparison of the side effects. Second, this study included only the short-term outcomes within six months after HM treatment but not the long-term outcomes, namely choriocarcinoma, developed after the remission of HM or post-molar GTN. Post-molar GTN is curable, but 1–2% of patients experience recurrence in the form of choriocarcinoma. Choriocarcinoma may also occur after HM remission is achieved. The incidence of choriocarcinoma after HM, including that after post-molar GTN, was reportedly 2–3%.[10,32] Choriocarcinoma requires multi-agent chemotherapy, and the 5-year survival rate is 75–90%.[43] Prophylactic chemotherapy reportedly did not reduce the incidence of choriocarcinoma after HM,[38] but the long-term outcome and side effects of HM patients who had prophylactic therapies require further study.

In conclusion, the incidence of HM at Tu Du Hospital was 11.1 per 1,000 deliveries; 83.9% of patients were categorized as having high-risk HM. A hysterectomy was performed in 87 patients who were 40 years or older or had no desire for future pregnancies. Prophylactic chemotherapy with MTX-FA was provided to 472 patients whose pretreatment hCG level was ≥ 100,000 IU/L. The incidence of post-molar GTN was 8.0%, and factors associated with post-molar GTN were gestational weeks, hCG level at one week after the first evacuation, and pathological remnant at the second operation. Prophylactic chemotherapy and hysterectomy may be useful for high-risk HM patients in settings in which the risk of post-molar GTN and loss to follow-up after HM are greater, and when hCG measurements and the appropriate treatment for GTN are unavailable. However, further studies on the long-term outcomes and side effects of prophylactic therapies in patients with HM are required.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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