Evaluation of a routine second curettage for hydatidiform mole: a cohort study

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Abstract

Objective. The aim of this study was to evaluate routine second curettage for hydatidiform mole (HM) by comparing the characteristics and outcomes of developing gestational trophoblastic neoplasia (GTN).

Study Design. This was a cohort study including 173 patients diagnosed with HM between January 2002 and August 2019 who were followed-up at Nagoya University Hospital, Japan. After an evacuation, 105 and 68 patients were managed with the routine method (routine group) and elective method (elective group) for a second curettage, respectively. The routine second curettage was performed around seven days after the first evacuation. Patients in the elective group underwent a second curettage if there was ultrasonographic evidence of molar remnants in the uterine cavity. Socio-clinical factors were retrospectively compared between the routine and elective groups and between patients showing regression and those who developed GTN.

Results. The incidence of GTN was 15.2% in the routine group and 20.6% in the elective group, and the difference was not significant (*P*=0.364). The median GTN risk score was significantly higher in the routine group than in the elective group (*P*=0.033). Presence of a complete HM, gestational age, and a pre-treatment human chorionic gonadotropin level of ≥200,000 mIU/mL were independent risk factors for GTN in molar patients.

Conclusion. The incidence of GTN was unchanged but the risk score of GTN was higher in the routine group than in the elective group. Routine second curettage may not be necessary, but further study will be needed to confirm this.

curettage.

Introduction

Gestational trophoblastic diseases (GTDs) are a group of diseases characterized by proliferation of atypical

trophoblastic cells. GTDs can be divided into two groups: hydatidiform mole (HM), which is an abnormal

pregnancy, and gestational trophoblastic neoplasia (GTN), such as invasive mole, choriocarcinoma, placental site

trophoblastic tumor, and epithelial trophoblastic tumor. HMs are pathologically classified into complete

hydatidiform mole (CHM) and partial hydatidiform mole (PHM). Cytogenetically, a CHM is an androgenetic

diploid and PHM is a triploid with one maternal and two paternal genes [1,2]. GTN can occur within 6 months

after the HM mostly as an invasive mole. The incidence of GTN after HM (post-molar GTN) is reported to be 15–

24% and 0.5–5% among patients with CHM and PHM, respectively [3-9]. Previously reported predictive factors

for post-molar GTN other than histology are having an uterine size larger than that required for the gestational age,

theca lutein ovarian cysts >6 cm, pre-treatment human chorionic gonadotropin (hCG) levels of ≥100,000 and

≥200,000 mIU/mL, and a declining ratio of hCG level between pre-treatment and two weeks after evacuation

[5,6,10,11]. Invasive moles can be cured almost 100% of the time, but chemotherapy is necessary because it can

metastasize to the lung, adnexa and vagina. Furthermore, 1–2% of invasive moles develop into choriocarcinomas

with an associated mortality of approximately 15–20% with multidisciplinary therapy [12,13].

Treatment of HM requires evacuation and follow-up using hCG measurements to ensure no residual molar tissues

in the uterine cavity. A second curettage approximately one week after the first evacuation was advocated in the

1980s [14] and used as the standard therapy for HM in some countries, such as Japan, Vietnam, and Hong Kong

[14-16]. However, in most countries, a second curettage is not performed routinely but is performed electively

when retention of molar tissue in the uterus has been suggested by ultrasonography [1,3,7,17]. Therefore, most previous clinical studies on HM included patients who were managed with the elective second curettage. There are some studies on the efficacy of a second curettage for low-risk GTN patients as an initial surgical treatment [18,19], but the aim of curettage for GTN is different from that of HM. Studies regarding molar patients having a routine second curettage are limited and the authors of these studies suggest that a routine second curettage approximately one week after the first evacuation was effective for removing remnant molar tissues and was not associated with any changes in the incidence of GTN after HM. To the best of our knowledge, no previous study has compared the outcomes of HM between routine and elective second curettage. Therefore, in this study, we compared clinical factors, especially the incidence of GTN, between routine and elective second curettage and identified risk factors for developing post-molar GTN.

Patients and methods

Patients

Patients who were pathologically diagnosed with HM after an evacuation between January 2002 and August 2019 and followed up at Nagoya University Hospital, Japan, were included in this study. Patients who were referred to the hospital for follow-up after the first evacuation at other hospitals were included but those who were referred due to suspicion of GTN were excluded. A routine second curettage performed approximately one week after the first evacuation was the standard treatment at the hospital from January 2002 to May 2014 according to the Japanese guideline for management of HM [20,21]. In June 2014, an elective method of second curettage, which

is performed when there is ultrasonographic evidence of molar remnants in the uterine cavity during follow-up,

was introduced as a clinical study involving 70 patients. All 70 patients participated after providing informed

consent. Written informed consent was waived for the patients who were diagnosed with HM between January

2002 and May 2014 because their data were used as the historical control.

Diagnosis and treatment for HM and post-molar GTN

Before treatment, the serum hCG level was measured by enzyme immunoassay using an αhCG monoclonal

antibody (mAb) and a βhCG-CTP mAb (SRL Inc., Tokyo, Japan). The first evacuation was performed using

placental forceps and sharp curettage before 2017, and manual vacuum aspiration (MVA) was introduced in 2017.

Mechanical vacuum was used for patients with a large uterus or massive molar tissues. Vaginal gemeprost was

used for patients who were clinically diagnosed with HM with a co-existing fetus at 12 weeks of gestation or later.

Abdominal ultrasonography was used for monitoring for uterine wall perforations and molar tissue remnants

during evacuations. The routine second curettage was performed using a sharp curettage at approximately the 7th

day after the first evacuation. For patients being managed with the elective method, a second curettage was

performed when there was ultrasonographic evidence of remnant molar tissue in the uterine cavity, namely vesicles

and a thick endometrium, resulting in bleeding, but without blood flow into the myometrium, or maintenance of

the hCG level. Power or color Doppler mode was used to detect blood flow. Pathologists reviewed surgical

specimens after the first evacuation for diagnosis of CHM or PHM. Immunohistochemistry using an antibody

against P57[kip2] was used to differentiate between CHM and PHM diagnoses since January 2016. Curettage

specimens after the second curettage were reviewed for the existence of molar trophoblasts. When HM with a co-existing fetus was suspected by ultrasonography, short tandem repeat (STR) analysis was performed to identify CHM or PHM using DNA extracted from molar tissues and cells from patients and their partners after obtaining informed consent [2,22]. The serum hCG level was measured weekly or biweekly using a cut-off value (0.5 mIU/mL). Remission was defined as a decrease in the hCG level to ≤0.5 mIU/mL. GTN was diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria for GTN [23], except for persistence of the hCG level for six months after mole evacuation. When the hCG level was not normalized at the 6th month after the first evacuation but decreased continuously, observation with measurement of the hCG level was continued [24]. Transvaginal ultrasonography with color Doppler and computed tomography scans were used for detecting lesions in the pelvis and metastases in the lung, respectively. Patients were allowed to become pregnant when their hCG level was ≤0.5 mIU/mL for six months after remission.

All post-molar GTN patients in this study were diagnosed as having a clinically invasive mole according to The Japanese Choriocarcinoma Diagnostic Score authorized by The Japan Society of Obstetrics & Gynecology [15]. Chemotherapy for invasive moles was provided to all GTN patients. The first and second regimens were methotrexate and actinomycin-D (MA) and etoposide and actinomycin-D (EA), respectively, from 2002 to 2010. After 2011, the first, second, and third regimens were methotrexate, actinomycin-D, and etoposide (ETP), respectively. When the hCG level did not reach the cut-off value by EA or ETP, patients received 4 days of methotrexate, etoposide, and actinomycin-D (MEA) [12]. After the hCG level normalized, 1–3 additional courses were provided.

Data collection

Data regarding the patient's age, gravida, parity, gestational age at first evacuation, history of HM, management method for second curettage (routine or elective), number of operations (evacuation and curettage), presence of an HM with a co-existing fetus, pre-treatment hCG level, histology (CHM or PHM), presence of a pathological remnant at second curettage, outcomes (remission or GTN), and period from the first evacuation to remission or first chemotherapy were collected. For GTN patients, information regarding the FIGO stage and risk score, period from the initial chemotherapy to hCG normalization (≤ 0.5 mIU/mL), number of chemotherapy courses until hCG normalization, and total number of chemotherapy courses were collected. This study was approved by the ethics committee of Nagoya University Graduate School of Medicine (approval number: 2014-009).

Statistical analysis

Statistical analysis was performed using chi-square for the independence test, Student's t-test, or Mann-Whitney U-test. Logarithmic transformation with reduced skewness was used to analyze the hCG level. 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. IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp, Armonk, New York) was used for statistical analyses, and a P-value of <0.05 was considered significant.

Results

Between January 2002 and August 2019, 107 and 73 molar patients were treated with the routine and elective for

second curettage, respectively. Although the routine method was standard at Nagoya University Hospital between

January 2002 and May 2014, eight patients were managed with the elective method based on decisions by the

doctors who performed the first evacuation before referral. Between June 2014 and August 2019, 65 and five

patients agreed with the elective and routine method of second curettage, respectively. Of the 180 patients, four

patients were lost to follow-up and three patients became pregnant before hCG normalization. A total of 173

patients, including 105 patients for the routine method (routine group) and 68 patients for the elective method

(elective group), were registered in this study (Fig. 1). The median follow-up time was 38.6 months (range, 2.8–

189.3 months). Three patients' follow-up time was shorter than 4 months; their hCG levels were normalized at 8-

14 weeks, and they were referred to other hospitals because they relocated at 2.8-3.5 months after the first

evacuation.

The average age of the patients was 31.0 years, and patients were diagnosed with an HM at 9.6 weeks of gestation

on average (Table 1). The hCG level ranged from 432.9 to 1,500,918.5 mIU/mL with an average of 157,709.0

mIU/mL. Three patients had a history of HM and their pathological diagnosis was CHM. Thirteen patients were

clinically diagnosed with HM with a co-existing fetus by ultrasonography and the results of the STR analysis

showed androgenetic CHM in five patients and triploid PHM in four patients. Approximately, 75.7% of patients

were diagnosed with CHM. Of all 173 patients, 143 patients (82.7%) had remission and 30 patients (17.3%)

developed GTN. No patient had uterine perforation during the evacuations or curettages.

There were no differences in patient characteristics between the routine group (n=105) and the elective group

(n=68) except for the number of operations (Table 1). Four patients (5.9%) in the elective group underwent the second curettage 8–55 days after the first evacuation due to the presence of bleeding and the suspicion of molar remnants. In ultrasonography of the four patients, the endometrial thickness ranged from 13.8 to 34.0 mm (median, 26.1 mm); a vesicle pattern was found in three patients (75%), but blood flow was not detected in two patients in whom color Doppler mode was used (Table 2). The pathological findings were molar villi or degenerated villi in all four cases. In 64 patients who did not undergo a second curettage, the median endometrial thickness was 5.3 mm (range, 1.9–16 mm), and only two patients showed vesicles in the endometrium that were cured spontaneously.

There were more HM patients with a co-existing fetus in the routine group (n=11) compared to the elective group (n=2), but the difference was not significant (Table 1). The incidence of GTN was 15.2% and 20.6% in the routine and elective groups, respectively, and there was no significant difference between groups (P=0.253). The routine second curettage was not associated with a shorter period until hCG normalization in 143 remission patients (P=0.487).

Of the 30 patients who developed GTN, 12 patients (40.0%) were FIGO stage I, and 18 patients (60.0%) were stage III (Table 3). The median risk score was 2.0 (range, 0–7). The median period from the first evacuation to initiating chemotherapy was 57.5 days. The routine group had more patients with stage III GTN, a higher risk score, and a longer period from the first evacuation to the first chemotherapy than the elective group. Only the FIGO score was significantly different between the two groups (P=0.033), but all patients were cured by chemotherapy. The period of chemotherapy, number of chemotherapy courses until hCG normalization, and total courses of chemotherapy were not different between the two groups.

Clinicopathological factors were compared between 142 patients who had remission (remission group) and 31 patients who developed GTN (GTN group; Table 4). The hCG level was categorized into two groups (i.e., <200,000 and ≥200,000 mIU/mL) according to the results of our previous study [5]. A higher percentage of patients in the GTN group were aged ≤20 years (23.1%) and >40 years (26.7%). The gestational age, a pre-treatment hCG level of ≥200,000 mIU/mL, and CHM were associated with developing GTN. Patients who had null gravida, null para, elective method for second curettage, single operation, or an HM with a fetus were more likely to develop GTN, but the difference was not significant. Of the 105 patients who had the routine second curettage, molar remnants were found pathologically in 43 patients (41.0%) with a higher percentage in the GTN group (23.3%) than in the remission group (9.7%).

To identify risk factors of post-molar GTN, we performed multivariate logistic regression analysis on post-molar GTN using age groups, gravida groups, parity groups, gestational age, history of HM, methods for second curettage, the number of operations, HM with a co-existing fetus, pre-treatment of hCG groups, and histology (Table 5). A longer gestational age ($P=0.037$), pre-treatment hCG level ≥200,000 mIU/mL ($P=0.007$), and CHM ($P=0.015$) were significantly associated with developing GTN.

We then analyzed the data of only CHM patients because the incidence of developing GTN is completely different in CHM compared to PHM. In the 131 patients with CHM, the incidence of post-molar GTN was 22.1% (n=29). In the multivariate logistic regression analysis, the gestational age and a pre-treatment hCG level ≥200,000 mIU/mL were associated with developing GTN among CHM patients (Table 6).

Discussion

To the best of our knowledge, this is the first study in which the association between the management methods of second curettage for HM and the incidence of post-molar GTN has been examined. In this study, the incidence of post-molar GTN was 17.3% in all patients, 15.2% in the routine group and 22.1% in the elective group. There was no significant difference in the incidence of GTN between the two groups. It was thought that the role of routine second curettage was to confirm and remove the molar remnants in the uterine cavity. In this study, molar remnants were pathologically found in 41.0% of patients in the routine group at second curettage. However, in the elective group, only 5.9% of patients (n=4) needed the second curettage, which was performed when remnants were present during ultrasonography. The period from the first evacuation to remission was shorter in the elective group compared to the routine group, which suggests that the remnants can be removed spontaneously from the uterine cavity in most patients. Previous researchers have suggested that routine second curettage approximately one week after the first evacuation may not be necessary or cost-effective to confirm molar remnants [5,14]. However, these studies included only patients who had a routine second curettage. In this study, we included both patients who underwent second curettage routinely and electively and showed that a routine second curettage may not reduce the incidence of GTN after HM.

In the multivariate analysis using all molar patients, a longer gestational age at first evacuation, a pre-treatment hCG level of ≥200,000 mIU/mL, and CHM were independent risk factors for developing post-molar GTN. Furthermore, gestational age and pre-treatment hCG level were risk factors for GTN among CHM patients. There is no doubt that CHM is a strong predictive factor for developing GTN after HM, but there is no evidence that

patients with PHM never develop GTN [25]. Although the hCG level is assumed to be higher in those with a longer gestational age, both the hCG level and gestational age were independent risk factors for developing post-molar GTN.

GTN patients in the routine group showed a significantly higher FIGO risk score than those in the elective group, although all patients in both groups were cured by 7.6 courses of chemotherapy on average. The reason for the difference in risk scores between groups may be because the routine group had more patients with stage III GTN, lung metastases, and a longer period from the first evacuation to chemotherapy for GTN than the elective group. The FIGO score consists of eight factors, including age, hCG level, interval months from index pregnancy, and the number of metastases. There was no significant difference in age and hCG level at diagnosis of GTN.

Therefore, two evacuations in 7–10 days might increase the potential of metastasis of molar trophoblasts. In this study, a sharp curette was used for the first evacuations and the second curettage in most patients of the routine group, while an MVA was used for most patients in the elective group. Methylergometrine and/or oxytocin was injected during and/or after evacuations or curettages. In a previous study, it was reported that the incidence of GTN was significantly different among modes of evacuation, but sharp curettage was associated with a lower incidence of GTN compared to medical and suction evacuation [26]. Some researchers suggested that an increase of the intrauterine pressure by medical evacuation, using oxytocin or labor pain, might cause trophoblasts particles in venous blood to flow from the uterus leading to trophoblastic embolism in the lung [27,28]. In this study, we administered a normal dose of uterine contraction agents at each evacuation or curettage, but increasing the dosage to double the normal amount or more might increase the risk of lung metastases.

There were some limitations in this study. The number of patients included in the study was only 173. However, we were able to observe some differences in the analyses between the two groups of management methods for second curettage and between patients with remission and GTN. Secondly, the mode of the first evacuation was not collected for all patients because 26 patients underwent the first evacuation at other clinics or hospitals. Dilation and curettage are the major modes for evacuation in Japan but recently MVA has become more popular. Thirdly, the accuracies of diagnosing CHM, PHM, and abortion are not 100% by hematoxylin staining [4,29]. Only STR analysis can be used to make accurate diagnoses, but it is available at only research institutes. P57^{kip2} immunohistochemistry is helpful for making a more accurate diagnosis, and it should be used for diagnosing HM.

In conclusion, this is the first report in which the routine and elective methods for second curettage in HM were compared. Although the incidence of GTN was unchanged, the FIGO risk score of GTN was significantly higher in the routine group than in the elective group. Independent risk factors for post-molar GTN were CHM, longer gestational age, and a pre-treatment hCG level $\geq$200,000 mIU/mL but not the management method for second curettage. Therefore, the routine second curettage may not be needed, because it does not decrease the incidence of GTN and may increase the risk of GTN. However, a further study with a greater number of molar patients will be needed to confirm the association between two times of evacuations with uterine contraction agents and FIGO risk scores.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Figure captions

Fig.1. Flow diagram of recruitment, study groups and outcome of patients with hydatidiform mole from January 2002 to August 2019. Patients had a second curettage routinely approximately one week after the first evacuation or electively if there was ultrasonographic evidence of molar remnants in the uterine cavity. GTN, gestational trophoblast neoplasia.

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Between Pathological Diagnosis and Cytogenetic Diagnosis by Short Tandem Repeat Polymorphism Analysis of

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Table 1. Comparison of characteristics of molar patients in the routine group and the elective group

Characteristics		All	Routine group	Elective group	P
		(N=173)	(n=105)	(n=68)	
Age (years)		31.0 ± 6.9	30.3 ± 7.1	32.2 ± 6.5	0.076[c]
Gravida	null	63 (36.4%)	39 (37.1%)	24 (35.3%)	0.805[d]
	≥1	110 (63.6%)	66 (62.9%)	44 (64.7%)	
Parity	null	88 (50.9%)	54 (51.4%)	34 (50.0%)	0.854[d]
	≥1	85 (49.1%)	51 (48.6%)	34 (50.0%)	
Gestational age (weeks)		9.6 ± 2.5	9.8 ± 2.5	9.4 ± 2.5	0.412[c]
History of HM	No	170 (98.3%)	103 (98.1%)	67 (98.5%)	0.831[d]
	Yes	3 (1.7%)	2 (1.9%)	1 (1.5%)	
Number of operations	1	64 (37.0%)	0 (0%)	64 (94.1%)	< 0.001[d]
	2	109 (63.0%)	105 (100.0%)	4 (5.9%)	
HM with a co-existing fetus					
	No	160 (92.5%)	94 (89.5%)	66 (97.1%)	0.066[d]
	Yes	13 (7.5%)	11 (10.5%)	2 (2.9%)	
Pre-treatment hCG (mIU/mL)[a]		157,709.0 ± 3.3	159,603.9 ± 2.9	154,735.3 ± 4.1	0.873[c]
		[432.9-1,500,918.5]	[6,245.3-1,000,000.0]	[432.9-1,500,918.5]	
Histology	CHM	131 (75.7%)	77 (73.3%)	54 (79.4%)	0.362[d]

	PHM	42 (24.3%)	28 (26.7%)	14 (20.6%)	
Outcome	Remission	143 (82.7%)	89 (84.8%)	54 (79.4%)	0.364[d]
	GTN	30 (17.3%)	16 (15.2%)	14 (20.6%)	
Period from the first evacuation to remission (weeks)[b]					
		13.8 ± 6.4	14.1 ± 6.3	13.3 ± 6.6	0.487[c]
		[3-39]	[7-39]	[3-37]	

Values represent mean ± standard deviation [range] or number (percentage).

HM, hydatidiform mole; hCG, human chorionic gonadotropin; CHM, complete hydatidiform mole; PHM, partial

hydatidiform mole; GTN, gestational trophoblastic neoplasia.

[a]Geometric mean computed on the log-transformed variable and converted to the original scale of measurement.

[b]143 patients including 89 patients of the routine group and 54 patients of the elective group.

[c]Student's *t*-test.

[d]Chi-square test.

Table 2. Comparison of clinical factors of patients in the elective group according to second curettage

Patient	Age (years)	Histology	Evacuation method	Days from evacuation	Ultrasonographic factors			hCG at second curettage (mIU/mL)	Pathological findings at second curettage	GTN
					Endometrium (mm)	Vesicle pattern	Blood flow			
Case 1	37	PHM	DC	40	34.0	Yes	No	68.1	Degenerated villi	No
Case 2	31	CHM	DC	7	13.8	Yes	No	77,088.0	Molar villi	Ye
Case 3	33	PHM	DC	42	20.0	No	NA	518.0	Molar villi	No
Case 4	32	CHM	MVA	14	32.1	Yes	NA	32,697.2	Molar villi	No
No second curettage (n=64)	33.3 ± 2.6	CHM 52 PHM 12 NA 1	DC 37 MVA 26 NA 1	12.2 ± 5.0	5.3 [1.9-16]	Yes 2 No 60 NA 2	Yes 1 No 31 NA 32	-	-	Yes 13 No 51

Case 1-4 are patients who underwent second curettage. Values represent number, mean ± standard deviation, and median [range]. Power or color Doppler mode was used to detect blood flow. hCG, human chorionic gonadotropin; GTN, gestational trophoblastic neoplasia; CHM, complete hydatidiform mole; PHM, partial hydatidiform mole; DC, dilation and curettage; MVA, manual vacuum aspiration; NA, not available.

Table 3. Comparison of clinical factors of patients with gestational trophoblastic neoplasia in the routine group and the elective group

Characteristics		All (N=30)	Routine group (n=16)	Elective group (n=14)	*P*
FIGO stage	I	12 (40.0%)	4 (25.0%)	8 (57.1%)	0.073[a]
	III	18 (60.0%)	12 (75.0%)	6 (42.9%)	
FIGO risk score		2.0 [1.0-4.3]	3.0 [2.0-5.75]	1.5 [1.0-2.5]	0.033[b]
Period from the first evacuation to the first chemotherapy (days)		57.5 [30.3-82.0]	59.5 [33.8-78.8]	44.0 [27.3-110.25]	0.852[b]
Duration of chemotherapy to hCG normalization (days)		85.2 ± 48.9	87.1 ± 51.4	82.9 ± 47.8	0.819[c]
Number of chemotherapy courses until hCG normalization		5.5 ± 2.7	5.6 ± 2.4	5.4 ± 3.2	0.841[c]
Total chemotherapy courses		7.6 ± 2.6	7.6 ± 1.9	7.6 ± 3.3	0.956[c]

Values represent number (percentage), median [interquartile range] and mean ± standard deviation. hCG normalization means that the serum hCG level reaches 0.5 mIU/mL.

hCG, human chorionic gonadotropin.

[a]Chi-square test.

[b]Mann-Whitney *U*-test.

Table 4. Correlation of gestational trophoblastic neoplasia with clinicopathological factors in hydatidiform mole

Characteristics		All (N=173)	Remission group (n=143)	GTN group (n=30)	P
Age (years)		31.0 ± 6.9	30.9 ± 6.3	31.7 ± 9.3	0.664[b]
Age group (years)	15-20	13 (7.5%)	10 (76.9%)	3 (23.1%)	0.692[c]
	21-30	67 (38.7%)	56 (83.6%)	11 (16.4%)	
	31-40	78 (45.2%)	66 (84.6%)	12 (15.4%)	
	41-59	15 (8.7%)	11 (73.3%)	4 (26.7%)	
Gravida	null	63 (36.4%)	51 (81.0%)	12 (19.0%)	0.654[c]
	≥1	110 (63.6%)	92 (83.6%)	18 (16.4%)	
Parity	null	88 (50.9%)	70 (79.5%)	18 (20.5%)	0.271[c]
	≥1	85 (49.1%)	73 (85.9%)	12 (14.1%)	
Gestational age (weeks)		9.6 ± 2.5	9.4 ± 2.2	10.7 ± 3.4	0.006[b]
History of HM	No	170 (98.3%)	140 (82.4%)	30 (17.6%)	0.424[c]
	Yes	3 (1.7%)	3 (100%)	0 (0.0%)	
Second curettage	Routine	105 (60.7%)	89 (84.8%)	16 (15.2%)	0.364[c]
	Elective	68 (39.3%)	54 (79.4%)	14 (20.6%)	
Number of operations	1	64 (37.0%)	51 (79.7%)	13 (20.3%)	0.429[c]
	2	109 (63.0%)	92 (84.4%)	17 (15.6%)	

HM with a co-existing fetus					
	No	160 (92.5%)	133 (83.1%)	27 (16.9%)	0.570[c]
	Yes	13 (7.5%)	10 (76.9%)	3 (23.1%)	
Pre-treatment hCG (mIU/mL)					
	<200,000	105 (60.7%)	96 (91.4%)	9 (8.6%)	< 0.001[c]
	≥200,000	68 (39.3%)	47 (69.1%)	21 (30.9%)	
Histology	CHM	131 (75.7%)	102 (77.9%)	29 (22.1%)	0.003[c]
	PHM	42 (24.3%)	41 (97.6%)	1 (2.4%)	
Pathological molar remnant at the second curettage[a]					
	No	62 (59.0%)	56 (90.3%)	6 (9.7%)	0.057[c]
	Yes	43 (41.0%)	33 (76.7%)	10 (23.3%)	

Values represent mean ± standard deviation [range] or number (percentage).

GTN, gestational trophoblastic neoplasia; HM, hydatidiform mole; hCG, human chorionic gonadotropin; CHM,

complete hydatidiform mole; PHM, partial hydatidiform mole.

[a]105 patients who had the routine second curettage.

[b]Student's *t*-test.

[c]Chi-square test.

Table 5. Multivariate analyses on developing gestational trophoblastic neoplasia in 173 molar patients

		Odds Ratio	95% CI	*P*
Gestational age (weeks)		1.21	1.01-1.44	0.037
Pre-treatment hCG (mIU/mL)	<200,000	1.00		0.007
	≥200,000	3.52	1.41-8.70	
Histology	CHM	1.00		0.015
	PHM	0.08	0.01-0.60	

hCG, human chorionic gonadotropin; CI, confidence interval.

Logistic regression analysis was performed using age groups, gravida groups, parity groups, gestational age, history of hydatifirom mole, methods for second curettage, number of operations, hydatifirom mole with a co-existing fetus, pre-treatment of hCG groups, and histology.

Table 6. Multivariate analyses on the development of gestational trophoblastic neoplasia in 131 patients with

complete hydatidiform mole

		Odds Ratio	95% CI	*P*
Gestational age (weeks)		1.24	1.03-1.50	0.025
Pre-treatment hCG (mIU/mL)	<200,000	1.00		0.018
	≥200,000	3.10	1.21-7.94	

hCG, human chorionic gonadotropin; CI, confidence interval.

Logistic regression analysis was performed using age groups, gravida groups, parity groups, gestational age, history

of hydatifirom mole, methods for second curettage, number of operations, hydatifirom mole with a co-existing fetus,

and pre-treatment of hCG groups.