A 10-Year Clinical Experience of Gestational Trophoblastic Disease at Rajavithi Hospital, 2001-2010

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Background: *Gestational trophoblastic disease (GTD) develops from abnormal cellular proliferation of trophoblasts following fertilization and is categorized as either an hydatidiform mole (HM) or a gestational trophoblastic neoplasia (GTN).*
Objective: *To analyze the clinical characteristics, incidence and treatment outcomes of GTD at Rajavithi Hospital.*
Material and Method: *Medical records of women diagnosed with GTD at Rajavithi Hospital from January 1, 2001 to December 31, 2010 were retrospectively reviewed. Disease diagnosis, treatment and follow-up data were analyzed.*
Results: *A total of 329 cases of GTD were reviewed. HM was diagnosed in 167 patients (incidence 2.32 per 1,000 deliveries); 26 patients were lost to follow-up; and 49 of the remaining 141 patients (34.8%) developed post-molar GTN. In multivariable analysis, uterus >16 week size and pre-treatment human chorionic gonadotropin (hCG) level >250,000 mIU/mL were the significant risk factors for developing post-molar GTN. Of 162 patients with GTN (incidence 2.25 per 1,000 deliveries), 15 patients were lost to follow-up, and 116 patients, 29 patients and 2 patients were classified as having low-risk GTN, high-risk GTN and placental site trophoblastic disease respectively. The overall survival rate in the low-risk group was 100% whereas in the high-risk group it was 86.2%. A modified WHO prognostic score of more than five was the significant risk factor for developing resistant GTN.*
Conclusion: *GTD treatment at Rajavithi Hospital showed excellent clinical outcomes. Uterus >16 weeks size and pre-treatment hCG >250,000 mIU/mL were the significant risk factors for developing post-molar GTN in HM patients. Classifying GTN patients into low- and high-risk groups was useful in planning treatment and counseling.*

Keywords: *Gestational trophoblastic disease, Hydatidiform mole, Gestational trophoblastic neoplasia*

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Gestational trophoblastic disease (GTD) comprises a diverse spectrum of entities of abnormal cellular proliferations originating in placental trophoblasts after fertilization. Clinically, GTD is classified into two categories, molar pregnancy or hydatidiform mole (complete and partial) and gestational trophoblastic neoplasia (GTN). The term GTN has been applied to three pathologic conditions: invasive mole; choriocarcinoma; and intermediate trophoblastic tumors such as placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT).

Epidemiologic studies have reported wide regional and ethnic variations in the incidence of GTD. It is generally accepted that the highest GTD incidence rates are in Hispanics, American Indians and Eskimos, and Asians[1].

Although women diagnosed with GTD used to be associated with significant morbidity and mortality, their clinical prognosis has improved with the availability of the sensitivity and specificity of a human chorionic gonadotropin (hCG) test and the advent of chemotherapy. Currently, the majority of patients can be cured with the preservation of reproductive function even in the presence of widespread metastasis.

Rajavithi Hospital is the largest hospital in Thailand's Ministry of Public Health and is a super-tertiary medical center, which provides treatment in varied specialties and healthcare dimensions. Women with complicated pregnancies and difficult gynecologic problems, especially gynecologic cancers, are referred to this hospital. The aim of this study was to analyze the incidence, clinical characteristics and treatment

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outcomes of GTD at Rajavithi Hospital in the 10-year period from 2001 to 2010.

Material and Method

After obtaining Institutional Review Board approval (No. 55098), the medical records of all GTD patients diagnosed at Rajavithi Hospital from January 2001 to December 2010 were retrospectively reviewed. Patients were excluded in cases of incomplete treatments and loss to follow-up. Measurement of serum quantitative hCG levels was performed by chemiluminescent enzyme immunoassay of Roche Elecsys system. Normal level of serum hCG was defined as lower than 5 mIU/mL.

For patients with molar pregnancy, clinical information was identified including age, gravidity, symptoms, gestational age and uterine size at diagnosis, pre-treatment serum hCG level, pathologic diagnosis, treatment and follow-up data. Suction curettage was the recommended method of molar pregnancy treatment for most patients who were then monitored with weekly serum hCG measurements until the levels were normal for 3 consecutive weeks, and then with monthly measurements for at least 6 months. Contraception was recommended, preferably with a combined oral contraceptivepills. Post-molar GTN was diagnosed using the following criteria: (1) rise of serum hCG levels of 10% or greater for 3 values over 2 consecutive weeks; (2) plateau of serum hCG levels (rise or decline of less than 10%) for 4 values over 3 consecutive weeks; (3) histological diagnosis of choriocarcinoma; (4) presence of metastatic disease; and (5) persistence of serum hCG level in the 6 months after termination of pregnancy[2].

In the case of GTN patients, clinical information including age, parity, antecedent pregnancy, symptoms, pre-treatment serum hCG levels, treatment and follow-up data were identified. Extent of disease was evaluated by chest radiography, ultrasonography and/or computed tomography. Planning the management of GTD patients was assigned based on a combination of the 2,000 revised International Federation of Gynecology and Obstetrics (FIGO) anatomic staging system and the modified World Health Organization (WHO) prognostic scoring system[3]. All GTN patients except those with intermediate trophoblastic tumors were categorized as: (1) low-risk disease if stage I or stage II-III, score less than 7; and (2) high-risk disease if stage II-III, score equal or more than 7; or stage IV. Single-agent chemotherapy (methotrexate or actinomycin-D) was the treatment of choice for patients with low-risk disease, whereas combination chemotherapy was considered in patients with high-risk disease. The preferred combination regimen consisted of etoposide, methotrexate, actinomcin-D, cyclophosphamide and viscristine (EMA/CO). During treatment, patients were monitored with weekly serum hCG measurements until normal, after which additional consolidation therapy was utilized (low-risk: 1 cycle; high-risk: 3 cycles). Patients were considered to be in remission when three consecutive weekly serum hCG measurements were at normal levels. Resistant disease was indicated when the following occurred: (1) rising of serum hCG levels over a cycle; (2) plateau of serum hCG levels for two consecutive cycles; or (3) presence of new metastasis[4]. After hCG remission was achieved, the patients were scheduled for monthly serum hCG measurements for at least 12 months in stage I-III and 24 months in stage IV patients. Contraception was also recommended preferably with combined oral contraceptivepills. Relapsed disease was diagnosed when the serum hCG levels rose after achieving an initial remission. Patients with resistant or relapsed disease received second-line chemotherapy. Intermediate trophoblastic tumor (PSTT and ETT) patients were attended to separately and evaluated by the 2000 revised FIGO anatomic staging system. Hysterectomy was the recommended treatment for these patients.

Statistical analysis of the data was carried out using SPSS version 11.5 software for Windows (Chicago, IL). Demographic data were determined using percentage, mean and standard deviation. Comparisons between groups were performed using Student's t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test as appropriate. Multivariable analysis by multiple logistic regression was used in determining independent risk factors, adjusting for potential confounders. Overall survival distributions were calculated by the Kaplan-Meier method and the statistical significance of survival differences was compared by the log-rank test. A probability value (*p*-value) of less than 0.05 was considered statistically significant.

Results

During the 10-year period, three hundred twenty-nine cases of GTD were reviewed, of which 167 cases of molar pregnancy and 162 cases of GTN were identified. The overall incidences of molar pregnancy and GTN were 2.32 per 1,000 deliveries (167/72,086) and 2.25 per 1,000 deliveries (162/72,086) respectively

(Table 1). Twenty-six molar pregnancy patients and fifteen GTN patients were lost to follow-up.

The clinical characteristics of 141 molar pregnancy patients are shown in Table 2. Mean age at diagnosis was 27.5 years (SD, 9.1). Median gestation age was 12 weeks (range, 4-24), and 71 cases (59.9%) were diagnosed in the first trimester. Only one patient had a history of previous molar pregnancy. Abnormal uterine bleeding was the most common presenting symptom (89.4%), while 3.5% of patients were asymptomatic. Mean uterine size at diagnosis was 14.8 weeks (SD, 3.8), uterine size was found to be small, appropriate, and large for gestational age in 7.1%, 48.2% and 44.7% of the patients respectively. Theca-lutein cysts were found in 13.5% of patients and only one patient underwent emergency surgery due to cyst rupture. Pre-treatment serum hCG levels were assessed in 137 cases, with a median level of 210,000 mIU/mL (range 2,400-1,910,000). Pre-treatment thyroid function test was evaluated in 131 cases and found to be abnormal in 25 patients (19.1%), while only eight cases (6.1%) had clinical hyperthyroidism. Most molar pregnancies (98.6%) were terminated by suction curettage, during which the only surgical complication found was massive hemorrhage in 21 cases (14.9%). Histologically, complete and partial molar pregnancies were diagnosed in 128 (90.8%) and 13 (9.2%) cases, respectively.

Whereas 92 molar pregnancy patients (65.2%) had spontaneous remission, post-molar GTN developed in 49 women (34.8%). Mean duration from treatment to achievement of remission was 9.5 weeks (SD, 1.3). To determine possible risk factors for developing post-molar GTN, comparisons were made of various variables between these two groups of patients are depicted in Table 3. Post-molar GTN developed more frequently in women who had pathologic diagnosis of complete mole, uterus larger than 16-week size, uterine size larger than gestational age, presence of theca-lutein cyst and pre-treatment hCG levels more than 250,000 mIU/mL. Multivariable analysis with binary logistic regression (Table 4) revealed that the independent risk factors associated with developing post-molar GTN were uterus larger than 16-week size and serum hCG level of more than 250,000 mIU/mL, with adjusted OR of 2.3 (95% CI, 1.1-4.9) and 4.2 (95% CI, 1.9-9.2), respectively. Using these 2 risk factors (uterus larger than 16-week size and/or serum hCG level more than 250,000 mIU/mL), the performance for prediction of developing post-molar GTN showed a sensitivity of 79.6%, specificity of 59.1% and accuracy of 66.4%.

Table 5 displays the clinical characteristics of 147 GTN pregnancy patients. Mean age at diagnosis was 29.3 years (SD, 8.9). Antecedent pregnancy events before diagnosis of GTN were molar pregnancy, abortion and term delivery in 76.9%, 11.6% and 11.6% of cases respectively. Median time interval from pregnancy events to treatment was 2 months (range, 1-240). The majority of GTD patients were found to be asymptomatic (69.4%), while abnormal uterine bleeding was the second common presenting symptom (14.3%). Moreover, twelve women presented with

Table 1. Incidence of gestational trophoblastic disease

Calendar year	Total deliveries	Molar pregnancy		GTN	
		Number of cases	Incidence per 1,000 deliveries	Number of cases	Incidence per 1,000 deliveries
2001	10,129	9	0.89	16	1.58
2002	9,492	13	1.37	17	1.79
2003	9,291	9	0.97	15	1.61
2004	8,981	22	2.45	13	1.45
2005	7,440	16	2.15	9	1.21
2006	4,457	16	3.59	20	4.49
2007	5,566	15	2.70	10	1.80
2008	5,541	26	4.69	18	3.25
2009	5,648	20	3.54	20	3.54
2010	5,514	21	3.80	24	4.35
Total	72,086	167	2.32	162	2.25

GTN = Gestational trophoblastic neoplasia

Table 2. Clinical characteristics of molar pregnancy patients

Characteristics	Total (n = 141)
Age (years), mean (SD)	27.5 (9.1)
GA at diagnosis (weeks), median (range)	12 (4-24)
Gravidity, median (range)	1 (1-7)
Primigravida	83 (58.9)
Multigravida	58 (41.1)
Presenting sign and symptom (%)	
Abnormal uterine bleeding	128 (90.8)
Hyperemesis gravidarum	3 (2.1)
Anemia	3 (2.1)
Severe preeclampsia	1 (0.7)
Pelvic mass	1 (0.7)
Leakage theca-luteal cyst	1 (0.7)
Asymptomatic	5 (3.5)
Uterine size (weeks), mean (SD)	14.8 (3.8)
Uterine size compared with GA (%)	
Small for GA	10 (7.1)
Appropriate for GA	68 (48.2)
Large for GA	63 (44.7)
Theca-lutein cysts (%)	19 (13.5)
Histologic diagnosis	
Complete mole	128 (90.8)
Partial mole	13 (9.2)
Pre-evacuation serum hCG (mIU/mL) (n = 137), median (range)	210,000 (2,400-1,910,000)
Thyroid function (n = 131) (%)	
Laboratory hyperthyroidism	17 (13.0)
Clinical hyperthyroidism	8 (6.1)
Treatment (%)	
Suction and curettage (S&C)	138 (97.9)
Hysterectomy	2 (1.4)
Emergency exploratory laparotomy with S&C	1 (0.7)
Complication of treatment (%)	
Bleeding >1,000 mL	21 (14.9)
Outcome of treatment (%)	
Spontaneous remission	92 (65.2)
Post-molar GTN	49 (34.8)

SD = Standard deviation; GA = Gestational age; hCG = Human chorionic gonadotropin; S&C = Suction and curettage; GTN = Gestational trophoblastic neoplasia

hemoperitoneum, and all underwent emergency surgery. Most GTN patients (73.5%) had serum hCG titer of less than 100,000 mIU/ml. According to the 2,000 FIGO anatomical staging, most GTN patients were assessed as stage I and stage III, at 70.7% and 21.8%, respectively. Common organ metastases were lung (88.1%), vulvovagina (11.9%), liver (11.9%) and brain (7.1%). According to the modified WHO scoring system, median risk score was 3 (range, 0-19).

The 145 GTN patients (excluding PSTT patients) were divided into a low-risk and a high-risk group, comprising 80% and 20% of cases, respectively. Treatments and clinical outcomes of GTN patients were compared between the low-risk and high-risk groups and are summarized in Table 6. All GTN patients received chemotherapy, but the high-risk patients received other treatment modalities significantly more frequently than the low-risk patients did. While 84.5% of low-risk patients achieved primary remission and only 15.5% developed resistant disease, the high-risk patients had a 69.0% primary remission rate and 31.0% of patients developed resistant disease. No relapsed disease was reported. Most of the low-risk patients (88.9%) who were resistant to the primary treatment had remission of disease after the second-line chemotherapy treatment, whereas 5 of 9 high-risk patients who were resistant to the primary chemotherapy received third-line chemotherapy. The median follow-up period of surviving patients was 15.2 months. Eventually, the cure rate of the low-risk patients approached 100%, but three cases in the high-risk group died from disease and the cure rate for this group was 89.7%. The estimated 2-year overall survival for the high-risk patients was statistically significantly different from that of the low-risk patients (86.2% vs. 100%; $p = 0.001$). Analyses of risk factors for developing resistant disease in GTN patients are shown in Table 7. Resistant disease developed more frequently in patients who had pre-treatment hCG levels of more than 100,000 mIU/mL and a modified WHO prognostic score of more than 5. However, the only independent risk factor analyzed by multiple logistic regression analysis was risk score more than 5, with adjusted OR of 3.2 (95% CI, 1.4-7.6).

Two PSTT patients were identified at age 32 and 34 years with abnormal uterine bleeding as the presenting symptom, occurring at 15 and 36 months after term deliveries. One patient was in stage I and underwent hysterectomy, while the other was in stage III with lung metastasis and was treated by hysterectomy and combination chemotherapy (EMA-CO regimen). Both were alive at last follow-up.

Discussion

The incidence of GTD varies widely in different regions and ethnicities of the world. The incidence of hydatidiform mole appears to be about 0.5-1 per 1,000 deliveries in most parts of the world[5]. In the present study, the incidence of molar pregnancy

Table 3. Bivariate analysis of risk factors for developing post-molar gestational trophoblastic neoplasia

Variables	Total (n = 141)	Post-molar GTN			
		%	OR	95% CI	*p*-value
Age groups (%)					
≤30 years	95	(33.7)	1.0		
>30 years	46	(37.0)	1.2	0.6-2.4	0.70
Gravidity					
Primigravida	83	(34.9)	1.0		
Multigravida	58	(34.5)	1.0	0.5-2.0	0.96
Uterine size					
≤16 weeks	102	(26.5)	1.0		
>16 weeks	39	(56.4)	3.6	1.7-7.8	0.001*
Uterine size compared with GA					
Small or appropriate for GA	78	(23.1)	1.0		
Large for GA	63	(49.2)	3.2	1.6-6.7	0.01*
Theca-lutein cyst					
Absent	128	(31.3)	1.0		
Present	13	(69.2)	4.9	1.4-17.0	0.01*
Pre-evacuation hCG (n = 137)					
≤$2.5x10^5$ mIU/mL	73	(19.2)	1.0		
>$2.5x10^5$ mIU/mL	64	(54.7)	4.0	2.4-10.9	<0.001*
Thyroid function (n = 131)					
Normal	106	(34.0)	1.0		
Abnormal	25	(52.0)	2.1	0.9-5.1	0.94
Histology					
Partial mole	13	(0.0)			
Complete mole	128	(38.3)			0.003*

GTN = gestational trophoblastic neoplasia; OR = odds ratio; CI = confident interval; GA = gestational age; hCG = human chorionic gonadotropin
* Significant at $p<0.05$

Table 4. Multivariable regression analysis of risk factors for developing post-molar gestational trophoblastic neoplasia

Variables	Coefficient	Crude OR	Adjusted OR	95% CI	*p*-value
Uterine size >16 weeks	0.8	3.6	2.3	1.1-4.9	0.045*
Pre-evacuation hCG >$2.5x10^5$ mIU/mL	1.4	5.1	4.2	1.9-9.2	0.008*

OR = odds ratio; CI = confident interval; hCG = human chorionic gonadotropin
* Significant at $p<0.05$

was 2.32 per 1,000 deliveries, which is comparable with previous studies from Asian countries, which found an incidence of 2.1-2.4 per 1,000 deliveries[6,7]. Data with respect to GTN incidence rates are even more limited. Population-based studies in Europe and North America found that choriocarcinoma affected approximately 1 in 40,000 pregnancies, whereas in Southeast Asia and Japan choriocarcinoma rates have been found to be higher at 9.2 and 3.3 per 40,000 pregnancies, respectively[5]. However, the incidence of GTN patients in the present study (2.25 per 1,000 deliveries) was consistent with the previous hospital-based studies in Asian countries (1.77-2.02 per 1,000 deliveries)[8,9].

The clinical picture of molar pregnancy at presentation has significantly changed in the last two

Table 5. Clinical characteristics of gestational trophoblastic neoplasia patients

Characteristics	Total (n = 147)
Age (years), mean (SD)	29.3 (8.9)
Parity, median (range)	1 (1-6)
Antecedent pregnancy (%)	
Molar pregnancy	113 (76.9)
Abortion	17 (11.6)
Term delivery	17 (11.6)
Pregnancy event to treatment interval (months), median (range)	2 (1-240)
Presenting sign and symptom (%)	
Asymptomatic	102 (69.4)
Abnormal uterine bleeding	21 (14.3)
Hemoperitoneum	12 (8.3)
Dyspnea/hemoptysis	4 (2.8)
Bowel ileus	3 (2.1)
Vulvovaginal mass	2 (1.4)
Pelvic pain	2 (1.4)
Pelvic mass	1 (0.7)
Hemiparesis	1 (0.7)
Histologic diagnosis (n = 35) (%)	
Invasive mole	10 (28.6)
Choriocarcinoma	23 (65.7)
Placental site trophoblastic tumor	2 (5.7)
Pre (treatment serum hCG (mIU/mL), median (range)	23,190 (36.4-2,020,000)
FIGO stage (%)	
I	104 (70.7)
II	1 (0.7)
III	32 (21.8)
IV	10 (6.8)
Organs of metastasis (n = 42, %)	
Lung	37 (88.1)
Vulvovagina	5 (11.9)
Liver	5 (11.9)
Brain	3 (7.1)
Bowel	2 (4.8)
Kidney	1 (2.4)
Urinary bladder	1 (2.4)
Omentum	1 (2.4)
Risk score (n = 145), median (range)	3 (0-19)
Risk group (n = 145) (%)	
Low risk	116 (80.0)
High risk	29 (20.0)

SD = standard deviation; GA = gestational age; hCG = human chorionic gonadotropin; FIGO = International federation of Gynecologist and Obstetricians

decades, and most patients are now diagnosed during the early first trimester. The median gestational age at diagnosis of molar pregnancy of 12 weeks found in the present study was consistent with other studies in centers with routine first trimester ultrasound, the method by which the majority of molar pregnancies are diagnosed by 8-12 weeks gestation[10-12]. In the present study, abnormal uterine bleeding was the most common presenting symptom (89%) of molar pregnancy, and it was higher than found in previous studies in which the rates were 51-75%[11-13]; on the other hand, identification of asymptomatic patients was only 3.5% lower than in previous studies (29-41%)[12,13]. The frequency of theca-lutein cysts (13.5%) in this study was lower than that found in other studies in which the rates were 20-46%[14,15]. These cysts usually regress spontaneously and seldom cause acute surgical complications. Montz et al[14] noted a 3% rate of emergency surgery for the cysts, but in the present study, only 0.7% of the patients underwent surgical intervention. Although laboratory evidence of hyperthyroidism is common in molar pregnancy, clinical hyperthyroidism was observed in only 0-7% of patients[16,17], while 5.7% of molar pregnancy patients had clinical hyperthyroidism and required treatment in this study.

Molar pregnancy is well known to have a risk of malignant transformation or post-molar GTN. The incidence of post-molar GTN after molar pregnancy has been reported as varying from 19-34[10,18]. The present study found that 34.8% of molar pregnancy patients developed post-molar GTN. Goldstein et al reported that patients were considered at high risk of developing post-molar GTN[19] if they displayed any one of the following signs: pre-treatment hCG level more than 100,000 mIU/ml; uterine size larger than gestational age; or theca-lutein cysts more than 6 cm in diameter. However, the independent risk factors for developing post-molar GTN in the present study using multivariate analysis were uterine size larger than 16-week size and pre-treatment hCG level of more than 250,000 mIU/mL.

Patients categorized as having low-risk GTN can usually be treated successfully with primary chemotherapy. In the present study, 15.5% of low-risk GTN patients needed second-line chemotherapy with or without surgery, but eventually all patients were cured. These clinical outcomes were comparable with those of the study by the Brewer Trophoblastic Disease Center[20] which reported that 21% of low-risk patients developed resistance to the initial chemotherapeutic agent, and that the cure rate approached 100%.

Patients with high-risk metastatic GTN should be treated initially with combination chemotherapy, with or without adjuvant surgery, or radiation therapy. Half

Table 6. Treatments and clinical outcomes of gestational trophoblastic neoplasia patients

Treatments and clinical outcomes	Low-risk group (n = 116)	High-risk group (n = 29)	*p*-value
Primary treatment (%)			
Chemotherapy	116 (100.0)	29 (100.0)	
Methrotrexate-Folinic acid	89	1	
Actinomycin D	5	-	
EMA	2	-	
EMA-CO	20	27	
BEP	-	1	
Others	11 (9.5)	15 (51.7)	<0.001*
Hysterectomy	11	8	
Salpingooophorectomy	-	1	
Whole brain irradiation	-	3	
Arterial embolization	-	1	
Ligation of internal iliac artery	-	2	
Response to primary treatment (%)			0.055
Remission	98 (84.5)	20 (69.0)	
Resistant	18 (15.5)	9 (31.0)	
Treatment of resistant GTN (%)			
Second-line chemotherapy	18 (15.5)	9 (31.1)	0.055
Methrotrexate-Folinic acid	1	-	
Actinomycin	9	1	
EMA-CO	6	1	
EMA-EP	1	6	
BEP	1	1	
Third-line chemotherapy	2 (1.7)	5 (17.2)	<0.001*
EMA-CO	2	1	
BEP	-	2	
VIP	-	1	
Carboplatin-paclitaxel	-	1	
Hysterectomy	1 (1.0)	3 (7.1)	
Whole brain irradiation	1 (1.0)	-	
Vital status (%)			
Alive	116 (100.0)	26 (89.7)	< 0.001*
Death	0 (0.0)	3 (10.3)	
Overall survival rate[#]			0.001*
1-year overall survival rate (%)	100	92.4	
2-year overall survival rate (%)	100	86.2	

EMA = Etoposide methotrexate actinomycin; EMA-CO = Etoposide methotrexate actinomycin cyclophosphamide vincristine; EMA-EP = Etoposide methotrexate actinomycin cisplatin; BEP = Bleomycin etoposide cisplatin; VIP = Vincristine ifosphamide cisplatin; GTN = Gestational trophoblastic neoplasia
* Significant at $p<0.05$, [#] Log-rank test

of the high-risk patients in the present study underwent surgical procedures during the course of treatment, and this was in keeping with treatment delivered in previous studies[21-23]. Despite the use of multimodality of primary therapy in high-risk GTN cases, 20-30% of these had an incomplete response to first-line chemotherapy[18,20,24]. These outcomes were consistent with the present study in which 31% of high-risk patients developed disease resistance to primary chemotherapy. Lurain et al[25] reported that 61.5% of high-risk GTN patients who received secondary chemotherapy had complete response. However, of the 9 high-risk GTN patients in this study who failed primary treatment and received second-line chemotherapy, four patients (44.4%) had complete response to second-line chemotherapy and five patients (55.6%) had incomplete response and received third-line chemotherapy. Overall, the cure rate for high-risk GTN

Table 7. Risk factors of resistant gestational trophoblastic neoplasia

Variables	Total (n = 147)	Resistant/relapsed GTN			
		%	OR	95% CI	*p*-value
Age groups (%)					
≤40 years	126	19.0	1.0		
>40 years	21	14.3	0.7	0.2-2.6	0.766
Parity					
1	84	19.0	1.0		
>1	63	17.5	0.9	0.4-2.0	0.806
Antecedent pregnancy					
Molar pregnancy	113	16.8	1.0		
Abortion	17	11.8	0.7	0.1-3.1	
Term delivery	17	35.3	2.7	0.9-8.2	0.189
Pregnancy event to treatment interval					
0-12 months	126	16.7	1.0		
>12 months	21	28.6	2.0	0.7-5.8	0.192
Largest tumor size					
<5 cm	106	17.0	1.0		
≥5 cm	41	22.0	1.4	0.6-3.4	0.485
Number of metastasis					
<5	126	18.3	1.0		
≥5	21	19.9	1.1	0.3-3.4	0.931
Pre-treatment hCG level					
$\leq 10^5$ mIU/mL	108	13.9	1.0		
$>10^5$ mIU/mL	39	30.8	2.8	1.2-6.6	0.020*
Stage					
I-II	105	15.2	1.0		
III-IV	42	26.2	2.0	0.8-4.7	0.121
Risk score (n = 145)**					
0-5	97	12.4	1.0		
>5	48	31.3	3.2	1.4-7.6	0.006*
Risk groups (n = 145)					
Low risk	116	15.5	1.0		
High risk	29	31.0	2.5	1.0-6.2	0.055
Brain and liver metastasis					
No	141	17.0	1.0		
Yes	6	50.0	4.9	0.9-25.6	0.076
Histologic diagnosis (n = 35)					
Invasive mole	10	10.0	1.0		
Choriocarcinoma/PSTT	25	32.0	5.0	0.5-39.4	0.235
Hysterectomy					
No	126	19.1	1.0		
Yes	21	14.3	0.7	1.2-2.7	0.602

OR = odds ratio; CI = confident interval; GTN = gestational trophoblastic neoplasia; hCG = human chorionic gonadotrophin
* Significant at $p<0.05$
** Only risk score >5 has significantly in multivariable regression analysis with adjusted OR 3.2 (95% CI, 1.4-7.6, $p = 0.008$)

of 89.7% was comparable with that of other studies (78-96%)[18,20,24].

Various risk factors for drug resistance to initial chemotherapy in GTN patients have been identified in the literature such as clinicopathologic diagnosis of choriocarcinoma, antecedent non-molar pregnancy, age >35 years, WHO prognostic score >5, pre-treatment hCG level >100,000 mIU/mL, metastatic

site other than the lung or vagina, prior unsuccessful chemotherapy at another institution, and duration of disease >12 months[20,26-29]. Nevertheless, the only independent risk factor for developing resistant disease in this study was a modified WHO prognostic score >5; age, pre-treatment hCG level, organ metastasis and duration of disease were not significant factors.

A combination of the 2,000 revised International Federation of Gynecology and Obstetrics (FIGO) anatomic staging system and the modified World Health Organization (WHO) prognostic scoring system has been used in Rajavithi Hospital as a guide for treatment planning of GTN patients since the 2,000 consensus. While the outcomes of this 10-year period of treatment revealed a 97.9% cure rate, the high-risk patients had significantly lower cure and survival rates than the low-risk patients (89.7 vs. 100%, $p<0.001$ and 86.2 vs. 100%, $p<0.001$, respectively). The main problem in GTD management at Rajavithi Hospital was patients' lack of compliance: 15.6% of molar pregnancy patients and 9.3% of GTN patients were lost to follow-up. This data reflects the quality of surveillance and promotion of GTD knowledge. Since this is a curable disease, it is essential to attain patients' compliance and interdisciplinary management by developing patient monitoring systems and fast track treatment systems in order to achieve successful clinical outcomes.

The limitation of this study is that it was a hospital-based retrospective study from a referral hospital, so that it may not be representative of the whole country. Being a retrospective study renders the results inherently more susceptible to bias, especially on pre-treatment detail; however, the data obtained will be valuable as a basic description of GTD patients at Rajavithi Hospital.

Conclusion

In summary, GTD treatment at Rajavithi Hospital showed good outcomes. Large uterine size and pre-evacuation hCG of higher than 250,000 mIU/mL were the significant risk factors for developing post-molar GTN. Classification of GTN patients into low- and high-risk groups was useful in planning treatment and counseling.

What is already known on this topic ?

The incidence of molar pregnancy was 2.32 per 1,000 deliveries which was comparable the previous studies from Asian countries[6,7]. The incidence of GTN patients in the present study (2.25 per 1,000 deliveries) was consistent with the previous hospital-based studies in Asian countries (1.77-2.02 per 1,000 deliveries)[8,9].

The median gestational age at diagnosis of molar pregnancy of 12 weeks found in the present study was consistent with other studies which the majority of molar pregnancies were diagnosed by 8-12 weeks gestation[10-12].

The incidence of post-molar GTN after molar pregnancy had been reported from 19-34%[10,18]. The present study demonstrated that 34.8% of molar pregnancy patients developed post-molar GTN.

Overall survival rate in low-risk GTN patient was 100%, which was comparable with study from Brewer Trophoblastic Disease Center[20], which reported cure rates approached 100%.

Twenty to thirty percent of high-risk GTN patients had an incomplete response to first-line chemotherapy[18,20,24]. These outcomes were consistent with the present study that 31% of high-risk patients developed resistant disease to primary chemotherapy. The treatment outcomes of high-risk GTN patients were consistent with the present study that 31% of high-risk patients developed resistant disease to primary chemotherapy. Eventually, cure rate for high-risk GTN of 89.7% was comparable with other studies (78-96%)[18,20,24].

What this study adds ?

In the present study, abnormal uterine bleeding was the most common presenting symptom (89%) of molar pregnancy and higher than the previous studies in which the rates were 51-75%[11-13], on the other hand asymptomatic patients were identified only 3.5% lower than the previous studies (29-41%)[12,13].

The independent risk factors for developing post-molar GTN were uterus larger than 16 week size and pre-treatment human chorionic hormone (hCG) level higher than 250,000 mIU/mL from multivariate analysis.

The independent risk factor for developing resistant GTN in this study was only a risk score of more than 5; whereas, age, pre-treatment hCG level, organ metastasis and duration of disease were not significant factors.

Potential conflicts of interest

None.

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ประสบการณ์ทางคลินิก 10 ปี ของโรค Gestational trophoblastic disease ที่โรงพยาบาลราชวิถี พ.ศ. 2544-2553

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ภูมิหลัง: *Gestational trophoblastic disease (GTD) เกิดจากการเจริญเติบโตผิดปกติของเซลล์ trophoblasts ซึ่งเกิดตามหลังการปฏิสนธิและแบ่งออกเป็นสองกลุ่มคือ ครรภ์ไข่ปลาอุก และ gestational trophoblastic neoplasia (GTN)*

วัตถุประสงค์: *เพื่อวิเคราะห์ลักษณะทางคลินิก อุบัติการณ์ และผลการรักษาของ GTD ที่โรงพยาบาลราชวิถี*

วัสดุและวิธีการ: *ทบทวนเวชระเบียนย้อนหลังของสตรีที่ได้รับการวินิจฉัยเป็น GTD ที่เข้ารับการรักษาที่โรงพยาบาลราชวิถีตั้งแต่วันที่ 1 มกราคม พ.ศ. 2544 ถึง วันที่ 31 ธันวาคม พ.ศ. 2553 ทำการวิเคราะห์ข้อมูลการวินิจฉัยโรค การรักษา และการตรวจติดตาม*

ผลการศึกษา: *ผู้ป่วย GTD ทั้งหมด 329 รายได้รับการทบทวน ผู้ป่วยครรภ์ไข่ปลาอุก 167 ราย (อุบัติการณ์ 2.32 ต่อ 1,000 การคลอด) โดยผู้ป่วย 26 รายไม่ได้มาตรวจติดตาม ผู้ป่วย 49 รายจาก 141 ราย (ร้อยละ 34.8) กลายเป็น post-molar gestational trophoblastic neoplasia (GTN) ตามมาจากการวิเคราะห์พหุตัวแปร พบว่าขนาดมดลูกใหญ่กว่า 16 สัปดาห์ และระดับซีรัม human chorionic gonadotropin (hCG) ก่อนการรักษาสูงกว่า 250,000 mIU/mL เป็นปัจจัยอิสระต่อการเกิด post-molar GTN ผู้ป่วย GTN 162 ราย (อุบัติการณ์ 2.25 ต่อ 1,000 การคลอด) โดยผู้ป่วย 15 รายไม่ได้มาตรวจติดตาม พบว่าผู้ป่วย 116 ราย เป็น GTN กลุ่มเสี่ยงต่ำ, 29 ราย เป็น GTN กลุ่มเสี่ยงสูง และ 2 ราย เป็น placental site trophoblastic disease อัตราการรอดชีพในกลุ่มเสี่ยงต่ำเท่ากับร้อยละ 100 ในขณะที่กลุ่มเสี่ยงสูงเท่ากับร้อยละ 86.2 คะแนนความเสี่ยง WHO ที่มากกว่าห้าคะแนนเป็นปัจจัยอิสระต่อการเกิด GTN ที่ดื้อยา*

สรุป: *การรักษา GTD ที่โรงพยาบาลราชวิถีให้ผลการรักษาที่ดีมาก ปัจจัยเสี่ยงอิสระสำหรับการเกิด post-molar GTN ในผู้ป่วยครรภ์ไข่ปลาอุกได้แก่ มดลูกขนาดใหญ่กว่า 16 สัปดาห์ และระดับซีรัม hCG ก่อนการรักษามากกว่า 250,000 mIU/mL การแบ่งผู้ป่วย GTN เป็นกลุ่มความเสี่ยงต่ำและกลุ่มความเสี่ยงสูงสามารถนำมาใช้ประโยชน์ในการวางแผนการรักษาและการให้คำปรึกษา*