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Molar Pregnancy: Clinical Analysis of 151 Patients

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ABSTRACT

Objective To analyze the clinical characteristics, treatment, outcome, and risk factors for developing persistent gestational trophoblastic disease (GTD) of patients with molar pregnancy.

Design Cross-sectional study.

Setting Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University.

Subjects One hundred and fifty-one patients with molar pregnancy between January 1993 and December 1997 were identified. Clinical information of the patients, including age, gravidity, symptomatology, gestational age and uterine size at diagnosis, pre-evacuation B-human chorionic gonadotropin (B-hCG) and treatment was collated from the medical records.

Results The incidence of molar pregnancy was 1.67 per 1,000 deliveries. The mean age of the patients was 24.9 ± 6.9 years (range 14- 54 years). About half of the patients (47%) had molar pregnancy diagnosed in their first pregnancy. Mean gestational age at diagnosis was 15.3 ± 5.6 weeks. Vaginal bleeding was the most common presenting symptom (86.1%). The uterine size was larger than gestational age in 41.1% of the patients. Although theca-lutein cysts were found in 17.2% of the patients, only one patient underwent emergency surgery due to rupture of the cyst. Complete and partial molar pregnancies were found histologically in 83.4% and 16.6% of patients, respectively. Suction and sharp curettage was the initial treatment without any serious complications. During follow-up, 17.9% of patients had persistent GTD according to serum B-hCG concentrations. Of 20 evaluated patients, complete remission was achieved in all cases with the administration of sinlgle-agent and combined chemotherapy. Univariate analysis showed that patient's age at diagnosis, gravidity and uterine size might be possible risk factors of developing persistent GTD. However, in multivariate analysis, only patient's age (> 30 years) and uterine size (larger than gestational age) were the independent risk factors of this malignant transformation.

Conclusion The independent risk factors of developing persistent GTD were patient's age (>30 years) and uterine size (larger than gestational age).

Key words: molar pregnancy, persistent gestational trophoblastic disease

Gestational trophoblastic disease (GTD) consists of a spectrum of neoplastic disorders that arise from placental trophoblastic tissue after abnormal fertilization. GTD is classified histologically into four distinct groups: hydatidifrom mole (complete and partial), chorioadenoma destruens (invasive mole), choriocarcinoma, and placental site tumor. These pathologic entities have varying propensities for local invasion and metastasis.[1-3] However, the clinical course, not the pathology determines the management. Most commonly, GTD results in a hydatidiform "molar" pregnancy characterized by the lack of fetus, trophoblastic hyperplasia, edematous chorionic villi, and a loss of normal villous blood vessels.

The present study reviews our experience in the treatment and follow-up of 151 patients with molar pregnancy at Siriaj Hospital, Bangkok, between 1993 and 1997.

Materials and Methods

This study comprises all cases with histologic diagnosis of hydatidiform mole (complete and partial). The series was obtained from the medical records from January 1993 to December 1997 of the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok. Clinical information of the patients, including age, gravidity, symptomatology, gestational age and uterine size at diagnosis, pre-evacuation B-human chorionic gonadotropin (B-hCG) and treatment was identified.

Suction and sharp curettage was the initial treatment method for all of the cases. The patients were then monitored with weekly serum B-hCG measurements until the levels were normal for 3 consecutive weeks and then with monthly measurements for 6 months. Persistent GTD was diagnosed when B-hCG levels were increased or plateaued for at least 3 consecutive weeks. Chest X-ray, ultrasonography and/or computed tomography were performed for patients with persistent GTD to rule out any metastatic lesions.

Single-agent chemotherapy (methotrexate or dactinomycin) was the treatment of choice for patients with persistent disease and metastatic GTD with good prognosis. Patients who did not respond to single-agent therapy or patients with a poor prognosis were treated with combined regimens. Patients were considered to have complete remission when three consecutive weekly B-hCG titers were normal.

Characteristics of all patients were described using means, standard deviation (SD), and percentage. Comparison between groups was made using either Student's t-test or Chi-square test as appropriate. Multiple logistic regression was used in determining independent risk factors, adjusting for potential confounders. The results were considered statistical significance when p value was less than 0.05.

Results

During the year 1993-1997, a total of 151 patients of molar pregnancy were identified. The overall incidence was 1.67 per 1,000 deliveries (151/90629). There was a slightly decline of the incidence after the year 1994 without statistical significance (Table 1). Clinical characteristics of all the patients were shown in Table 2. The ages of patients ranged form 14-54 years with a mean age of 24.9 ± 6.9 years. Molar pregnancy was diagnosed in the first pregnancy in 71 cases (47%) and 10 cases (6.6%) were found in their fourth pregnancy or more. Only one patient had a history of previous molar pregnancy.

More than 60% of patients, molar pregnancies were diagnosed prior to evacuation. Mean gestational age at diagnosis was 15.3 ± 5.6 weeks and 88.1% of cases were first diagnosed before 20 weeks of gestation. Vaginal bleeding was the most common presenting symptom (86.1%). Uterine size was found to be small, appropriate, and large for gestational age in 26.5%, 32.5%, and 41% of the patients, respectively. Theca-lutein cysts were found in 17.2% of patients and only one patient underwent emergency surgery due to rupture of the cyst.

Pre-evacuation serum B-hCG was determined in 103 cases and revealed that majority of cases (70.9%) had hCG titer $>10^5$ mIU/ml. Anemia (hemoglobin < 10 g%) was found in 22.5% of cases at

the time of diagnosis. Pre-evacuation thyroid function test was evaluated in 128 cases and found to be abnormal in 29 cases (22.7%) and only 7 cases (5.5%) had clinical hyperthyroidism. Pre-eclampsia and hyperemesis gravidarum was diagnosed in 9 (6%) and 5 (3.3%) cases, respectively. All molar pregnancies were terminated by suction and sharp curettage without any serious complications. However, 30 patients (19.9%) received blood transfusion during the procedure. Complete and partial molar pregnancies were diagnosed histologically in 126 (83.4%) and 25 (16.6%) cases, respectively.

While 124 (82.1%) patients had spontaneous remission, persistent GTD developed in 27 cases (17.9%). Seven patients had been lost to follow-up before complete evaluation could be achieved. Of 20 evaluated patients, 18 received single-agent chemotherapy while 2 patients had combined regimens. Complete remission was achieved with the administration of 2-14 courses of single agent in 18 cases and 6-11 courses of combined chemotherapy in 2 cases.

To determine possible risk factors of developing persistent disease, we compared various characteristics between these 2 groups of patients, as shown in Table 3. Mean age was significantly higher in persistent GTD cases than those with spontaneous remission ($p = 0.014$). Persistent GTD developed more common in patients who were older than 30 years (OR 7.3, 95% CI 2.6-20.8), in their fourth pregnancy or more (OR 5.41, 95% CI 1.22-24.08), and in those who had uterine size larger than gestational age (OR 2.98, 95% CI 1.17-7.73). It should be noted that , although higher proportion of persistent GTD cases had serum B-hCG level > 105 mIU/ml compared with spontaneous remission cases (76.5% and 69.8%), the difference was not statistically significant.

Multiple logistic regression analysis was used to identify independent risk factors associated with the development of persistent GTD. The results are shown in Table 4. The only risk factors found were patient's age more than 30 years and uterine size larger than gestational age, with adjusted OR of 6.3 (95% CI 2.2-17.9) and 2.9 (95% CI 1.2-7.6) respectively. The results show that the risk of developing persistent GTD is about 6 times if the patient's age at diagnosis is more than 30 years old, and almost 3 times if the uterine size is larger than gestational age.

Table 1. Incidence of molar pregnancy

Calendar years	Number of cases	Total deliveries	Incidence per 1,000 deliveries
1993	37	18,516	2.00
1994	38	18,531	2.05
1995	24	19,493	1.23
1996	24	18,627	1.29
1997	28	15,462	1.81
Total	**151**	**90,629**	**1.67**

Table 2. Clinical characteristics of patients

Characteristics	Number (%)
Mean age (± SD) years	24.9 ± 6.9
Mean GA (± SD) at diagnosis (weeks)	15.3 ± 5.6
Gravidity	
1	71 (47.0)
2-3	70 (46.4)
≥ 4	10 (6.6)
Presenting symptoms	
Vaginal bleeding	130 (86.1)
Others	21 (13.9)
Uterine size	
Small for gestational age	40 (26.5)
Appropriate for gestational age	49 (32.5)
Large for gestational age	62 (41.0)
Theca lutein cyst	26 (17.2)
Histologic diagnosis	
Complete mole	126 (83.4)
Partial mole	25 (16.6)
Pre-evacuation hCG (n = 103)	
$< 10^5$ mIU/ml	30 (29.1)
$> 10^5$ mIU/ml	73 (70.9)
Thyroid function (n = 128)	
Abnormal laboratory test	29 (22.7)
Clinical hyperthyroidism	7 (5.5)
Other medical complications	
Preeclampsia	9 (6.0)
Hyperemesis gravidarum	5 (3.3)

Table 3. Persistent GTD : a univariate analysis of prognostic factors*

Characteristics	Spontaneous remission (n = 124)	Persistent GTD (n = 27)	Odds ratio (95% CI)	P value
Age in years (mean ± SD)	24.1 ± 6.0	28.9 ± 9.2		0.014**
Age group				
≤ 30 years	110 (88.7%)	14 (51.9%)	1.0	
> 30 years	14 (11.3%)	13 (48.1%)	7.3 (2.6 - 20.8)	< 0.001
Gravidity				
< 4	119 (96.0%)	22 (81.5%)	1.0	
≥ 4	5 (4.0%)	5 (18.5%)	5.4 (1.2 - 24.1)	0.021
Presenting symptoms				
Vaginal bleeding	108 (87.1%)	22 (81.5%)	1.0	
Others	16 (12.9%)	5 (18.5%)	1.5 (0.4 - 5.2)	NS
Uterine size				
Small or appropriate for GA	79 (63.7%)	10 (37.0%)	1.0	
Large for GA	45 (36.3%)	17 (63.0%)	2.9 (1.2 - 7.7)	0.011
Theca lutein cyst				
Absent	106 (85.5%)	19 (70.4%)	1.0	
Present	18 (14.5%)	8 (29.6%)	2.5 (0.8 - 7.2)	NS
Histologic diagnosis				
Complete mole	102 (82.3%)	24 (88.9%)	1.0	
Partial mole	22 (17.7%)	3 (11.1%)	0.6 (0.1 - 2.3)	NS
Pre-evacuation hCG (n = 103)				
< 10^5 mIU/ml	26 (30.2%)	4 (23.5%)	1.0	
> 10^5 mIU/ml	60 (69.8%)	13 (76.5%)	1.4 (0.4 - 5.7)	NS
Thyroid function (n = 128)				
Normal	81 (78.6%)	18 (72%)	1.0	
Abnormal	22 (21.4%)	7 (28%)	1.4 (0.5 - 4.2)	NS
Medical complication				
Absent	111 (89.5%)	24 (88.9%)	1.0	
Present	13 (10.5%)	3 (11.1%)	1.1 (0.2 - 4.5)	NS

* CI = confidence interval, NS = not significant (p > 0.05)

** Student's t-test

Table 4. Multivariate analysis of risk factors for developing persistent GTD

Characteristics	Adjusted Odds ratio (95% confidence interval)	P value
Age > 30 years	6.3 (2.2 - 17.9)	0.0006
Uterine size large for GA	2.9 (1.2 - 7.6)	0.02

Discussion

The incidence of molar pregnancy varies widely in different regions of the world. In the United States, a molar pregnancy develops in every 1,000 to 2,000 deliveries, while in Europe, the rates have been reported to be 1.46-1.54 per 1,000 deliveries.[4-6] It should be noted that the incidence is higher in the Far East and Southeast Asia than in the United States and in Europe, with as many as 2.5 per 1,000 deliveries in Japan being molar.[7] However, in the present study, the incidence was 1.67 per 1,000 deliveries, slightly higher than that reported in Europe.

Molar pregnancy was strongly associated with nulliparity.[8,9] Our study confirms this characteristic since molar pregnancy was diagnosed in 47% of our patients during the first pregnancy while only 6.6% had the disease in their fourth pregnancy or more. The incidence of vaginal bleeding as the presenting symptom (86.1%) and larger uterine size (41%) found in the present study are consistent with those reported in the literature.[10,11] The frequency of theca-lutein cysts (17.2%) in this study is slightly lower than that in other reports in which the rates were 20-46%.[11-13] The cysts usually regress spontaneously and seldom cause acute surgical complications. Montz et al.[12] noted a 3% rate of emergency surgeries for the cysts. In our study, only 0.7% of the patients underwent surgical intervention.

Preeclampsia, hyperemesis gravidarum are known to be associated with molar pregnancy. Curry et al.[10] reported preeclampsia in 12% of patients which is higher than the incidence (6%) found in our study. Kohorn et al.[14] noted that 26% of their patients had hyperemesis but only 2% required hospitalization. We found that 3.3% of our patients had hyperemesis and needed hospitalization. Although, laboratory evidence of hyperthyroidism is common in molar pregnancy, clinical hyperthyroidism is observed in only 7% of patients.[15] In the present study , 5.5% of our patients had clinical hyperthyroidism and required treatment.

Molar pregnancy is well recognized to have a risk of developing persistent GTD. The incidence of persistent disease after molar pregnancy has been reported from 8-29%.[10,16-19] The present study demonstrated that 17.9% of our patients developed persistent disease. Goldstein et al.[20] reported that patients with any one of these signs; pre-evacuation B-hCG level $>10^5$ mIU/ml, large uterine size or theca-lutein cysts > 6 cm in diameter were considered at high risk of developing persistent GTD. Comparison of patients with spontaneous remission and patients with persistent disease in our study, patient's age at diagnosis (>30 years), number of pregnancy (4 or more), large uterine size were possible risk factors of developing persistent GTD. However, in multivariate analysis, only patient's age (>30 years) and large uterine size appeared to be independent risk factors of this malignant transformation.

In conclusion, molar pregnancy is the disease of women in their reproductive years. Patients with molar pregnancy have the risks of developing persistent GTD and should be followed after the termination of pregnancy. The independent risk factors of this malignant transformation are patient's age (> 30 years) and uterine size (larger than gestional age).

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