Thai Journal of Obstetrics and Gynaecology
March 1999, Vol. 11, pp. 17-22

OBSTETRICS

A 14-Year Retrospective Study of Molar Pregnancy in Maharaj Nakorn Chiang Mai Hospital : High Incidence of Persistent Disease

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ABSTRACT

Objective To determine the clinical characteristics and outcomes of patients with histologically diagnosed hydatidiform mole.

Design Retrospective study.

Setting Department of Obstetrics and Gynecology, Maharaj Nakorn Chiang Mai Hospital.

Subjects One hundred and sixty nine patients with histologically diagnosed hydatidiform mole between January 1984 to December 1997 Main outcome measures : Clinical characteristics, remission, and the incidence of persistent gestational trophoblastic disease (PGTD).

Results : The incidence is 1.96:1,000 deliveries. The mean maternal age was 27.8 years (range 14-54). Forty two percent of patients were primigravida. The mean gestational age at diagnosis was 14.4 weeks (range 6-28). The average uterine size at surgical evacuation was 17.4 weeks (range 8-32). The most common presenting symptoms was vaginal bleeding. About 90 % of patients were classified as high risk for PGTD. The incidence of PGTD was 53.3 % in patients undergoing suction curettage without chemoprophylaxis. When separately analyzed, PGTD occurred in 59 % and 16.7 % of high-risk and low-risk patients, respectively. The incidence of PGTD remained high at 43.8 % despite receiving chemoprophylaxis during suction evacuation. PGTD also occurred in 12.5 % of patients undergoing hysterectomy with chemoprophylaxis. Loss of follow-up rate was relatively high at 28 %.

Conclusion Due to high incidence of PGTD, regular follow-up with sensitive hCG assays must be emphasized to all patients following termination of molar pregnancy.

Key word : molar pregnancy, hydatidiform mole, gestational trophoblastic disease

Molar pregnancy or hydatidiform mole is an abnormal pregnancy characterized histologically by abnormalities of chorionic villi, consisting varying degrees of trophoblastic proliferation and edema of villous stroma. The chorionic villi are transformed to a mass of clear vesicles varying in size from barely visible to a few centimeters in diameter occupied in the uterine cavity. Data derived from both hospital-based and population-based studies showed that the incidence of molar pregnancy was highest in parts of Asia.[1,2] In Thailand, such incidence, based on hospital studies, was relatively high and varied between 1.61 to 2.86 per 1000 deliveries and 1.5 to 9.5 per 1000 pregnancies.[3] Management principles of patient with molar pregnancy include : (a) detection and correction of complications, i.e. anemia, hypertension and hyperthyroidism until hemodynamically stable; (b) surgical evacuation of molar tissues; (c) close monitoring of postevacuation hCG levels for possible malignant sequelae. The risk of malignant sequelae or persistent gestational trophoblastic disease (PGTD) requiring further treatment is approximately 20-30 %.[4-8]

The purpose of this study is to present the clinical characteristics and outcomes of molar pregnancy in Maharaj Nakorn Chiang Mai Hospital, a tertiary health care center in the northern region of Thailand.

Subjects and Methods

From January 1984 to December 1997, 169 patients with histological diagnosis of complete hydatidiform mole were admitted to the Department of Obstetrics and Gynecology, Maharaj Nakorn Chiang Mai Hospital. Patients who were not primarily managed at our hospital were excluded. Prior to evacuation, the following clinical features were evaluated from the medical records in all patients : maternal age at diagnosis, gravidity, parity, history of previous molar pregnancy, estimated gestational age at evacuation, vaginal bleeding, mole expulsion, excessive uterine enlargement (larger than gestational age by 4 weeks), anemia (hemoglobin level < 10 g/dl), hyperemesis, clinical hyperthyroidism, preeclampsia, respiratory insufficiency, sonographic data and hCG level.

The patients were classified as high risk for PGTD when one or more of the following criteria was present : 1) pre-evacuation hCG level > 100,000 mIU/ml, 2) excessive uterine enlargement, 3) theca-lutein cysts larger than 6 cm in diameter, 4) age > 40 years, 5) previous molar pregnancy, and 6) associated medical problems (preeclampsia,hyperthyroidism, trophoblastic embolization).[4] Prophylactic chemotherapy with either intravenous actinomycin D 13 ug per kg per day for 5 days or intramuscular methotrexate 1.0 mg per kg on days 1,3,5, and 7 alternating with intramuscular folinic acid 0.1 mg per kg on days 2,4,6, and 8 were administered to a subset of patients identified as being at high risk for PGTD. Surgical evacuation of hydatidiform mole was carried out on the third day of chemoprophylaxis.

After the complications had been corrected, appropriate method of mole evacuation was considered. If preservation of fertility was not desired, hysterectomy might be performed with the mole in situ. In patients who wished to retain fertility, suction curettage was the preferred method of evacuation. Postevacuation surveillance included baseline physical examination, pelvic examination, chest radiographs and serum hCG levels. Serial hCG levels were determined every 1 to 2 weeks until normal, then monthly for 6 months, every other month for 6 months and at 6-month intervals indefinitely thereafter, when possible. Adequate contraception, usually oral pills was advised to avoid an intercurrent pregnancy.

Remission was diagnosed after three consecutive weekly hCG levels were within the normal range. Complete remission was defined as undetectable hCG on multiple repeat assays during the first six months after remission and there was no clinical or radiologic evidence of residual disease. The diagnosis of PGTD was made primarily on the basis of the hCG titer including the presence of a re-elevation (> 10 %) or persistent plateau (< 10 %) in hCG for at

least 3 consecutive weeks, persistent hCG level at 4-month after evacuation, and evidence of metastases such as a positive chest film, presence of a vaginal implant with persistent high hCG titers.

Results

During January 1984 to December 1997, there were 169 molar pregnancy patients and 86,282 deliveries at Maharaj Nakorn Chiang Mai Hospital. The estimated incidence of molar pregnancy was 1:510 deliveries or 1.96:1000 deliveries. The mean maternal age was 27.8 years (range 14-54). Two patients aged 14 years were hilltribe people. Primigravida and secundigravida were observed in 42% and 31% of patients, respectively. The maximum gravidity was 15. No patient had prior history of molar pregnancy. The mean gestational age at diagnosis was 14.4 weeks (range 6-28). The average uterine size at surgical evacuation was 17.4 weeks (range 8-32). Only 27 of 136 patients (19.8%) had pre-evacuation hCG titer < 100,000 mIU/ml.

Table 1 presents the clinical features prior to uterine evacuation in patients with molar pregnancies. Vaginal bleeding was the most common presenting symptom, occurring in 86.6 % of 164 patients. Excessive uterine enlargement and anemia were found in 45.7% and 28% of patients respectively. Approximately one-fifth of patients had mole expulsion prior to admission.

Of the 154 patients available for risk assessment, 16 (10.4%) and 138 (89.6%) were classified as low-risk and high-risk molar pregnancies respectively. Of the 162 patients evaluated for method of uterine evacuation, 130 (80.2%) were terminated by suction curettage, 9 (5.5%) by cervical dilatation and endometrial curettage, and 21 (13%) by abdominal hysterectomy. One patient underwent vaginal hysterectomy for uterine prolapse. The final pathology revealed hydatidiform mole and elongation of the cervix. The remaining one patient underwent emergency hysterotomy for severe antepartum hemorrhage and clinical diagnosis of placenta previa. The operative finding was complete hydatidiform mole. Loss of follow-up rate in our patients was relatively high at 28.0% or 46 in 164 patients.

Among 90 patients undergone suction curettage without prophylactic chemotherapy, 48 (53.3%) developed PGTD. The incidence of PGTD was much higher in the high-risk patients (59%) than that of the low-risk (16.7%) as shown in Table 2. The incidence of PGTD remained high at 43.8% despite receiving prophylactic chemotherapy either methotrexate or actinomycin D at the time of suction curettage as displayed in Table 3.

Table 1. Clinical features of molar pregnancy*

Clinical features	Number	(%)
Vaginal bleeding	142	(86.6)
Excessive uterine size	75	(45.7)
Anemia	46	(28.0)
Mole expulsion	32	(19.5)
Theca-lutein cysts	31	(18.9)
Hyperemesis	31	(18.9)
Preeclampsia	19	(11.6)
Hyperthyroidism	15	(9.1)
Respiratory distress	10	(6.1)

* Several patients had more than one clinical feature
* Data were available in 164 patients

Table 2. Results after suction curettage without chemoprophylaxis in low-and high-risk molar pregnancy

Outcomes	Number of patients (%)		
	Low risk	High risk	Total
Remission	10 (83.3)	32 (41)	42 (46.7)
Persistent GTD	2 (16.7)	46 (59)	48 (53.3)
Total	12 (100)	78 (100)	90 (100)

Data are presented as number (%)

Table 3. Results after suction curettage with chemoprophylaxis in high-risk molar pregnancy

Outcomes	Number (%)
Remission	9 (56.2)
Persistent GTD	7 (43.8)

Data are presented as number (%)

Neither severe toxicity nor death occurred in patients receiving chemopro phylaxis. Among 8 patients undergone abdominal hysterectomy with chemoprophy laxis, 1 (12.5%) still developed PGTD. However, no PGTD occurred in 3 patients who underwent abdominal hysterectomy without chemoprophylaxis.

Fourty patients experienced subsequent pregnancies that resulted in 34 full-term livebirths (85%), one preterm livebirth (2.5%), 4 abortions (10%) and one repeated molar pregnancy (2.5%).

Discussion

The incidence of molar pregnancy in our hospital-based study, 1.96:1000 deliveries is much higher than those reported from North America and Europe which are 0.5-0.8:1000 deliveries.[9] However, it is comparable to those reported in Thailand.[3] It has been recognized for a long time that the incidence of molar pregnancy varies between different countries, with the highest rates in parts of Asia. Although large differences in the incidence of molar pregnancy have been reported, this variation may be mainly attributable to methodological problems, i.e over-reporting in hospital-based studies which have more abnormal pregnancies receiving hospital care and under-reporting in region where medical attention is suboptimal. Even in developed countries with formal responsibility to report cases of molar pregnancy, the incidence of under-reporting is high at 25%[10]

Vaginal bleeding is the most common presenting symptom of molar pregnancy patients in our study, accounts for 86.6%. Goldstein et al. and Curry et al. also noted a high incidence of vaginal bleeding in 97% and 89% of patients with molar pregnancy, respectively.[4,5] Molar chorionic villi may disrupt maternal blood vessels by separating from the decidua causing profuse bleeding into the endometrial cavity. Bleeding may be prolonged, considerable and occult resulting in anemia in 25% of our patients.

Uterine size larger than dates by 4 weeks occurred in 45.7% of our patients comparable to those reported by Goldstein et al. (51%),[4] Curry et al (46%),[5] and Kohorn (38%).[11] The uterus is distended from retained blood and large amount of chorionic tissue. Excessive uterine size is often associated with markedly increased levels of hCG from trophoblastic proliferation.

The proportion of our patients with high-risk molar pregnancy is much higher than that of Goldstein's series,[4] accounts for 90% and 41% respectively. This may be, in part why the incidence of PGTD in our study is higher than those in other reports.[4-8] A high rate of lost to follow-up in our patients is possibly the cause of such high incidence. Following molar evacuation, PGTD occurred in 16.7% and 59% of low-risk and high-risk patients, respectively. In contrast, such incidences occurred only 4% and 40% respectively in a report of Goldstein et al.[4] In general, molar pregnancy that presents with signs of marked trophoblastic proliferation, such as markedly elevated hCG titers, excessive uterine size and prominent theca lutein cysts are at increased risk of developing PGTD.[8] The risk of PGTD was greatly decreased in patients who did not present with signs of trophoblastic overgrowth.

Despite receiving chemoprophylaxis during suction evacuation, 43.8% of our high-risk patients still developed PGTD which is incompatible with the previous reports.[4,12,13] In 1982, Goldstein and Berowitz had reported the efficacy of chemoprophylaxis in reducing the likelihood of developing PGTD in patients with molar pregnancy. Only 10 in 247 patients (0.4%) receiving dactinomycin prophylaxis developed nonmetastatic disease, while in the control group of 858 patients evacuated without chemoprophylaxis, 14.6% developed nonmetastatic and 4% developed metastatic trophoblastic disease which required treatment.[4] Later, in 1986 Kashimura et al confirmed from a retro-spective study that chemoprophylaxis decreased the frequency of PGTD form 18% to 7% in patients with complete hydatidiform mole.[12] Kim et al. conducted an important prospective randomized study of the use of chemoprophylaxis, methotrexate and folinic acid in patients with low-risk and high-risk complete molar pregnancies. Among high-risk patients, prophylactic chemotherapy reduced the incidence of PGTD from 47% to 14%. Among low-risk patients, prophylactic chemotherapy did not influence the incidence of persistent disease (7.7% versus 5.6%).[13] However, patients who developed PGTD after prophylactic methotrexate, subsequently required more courses of methotrexate to achieve remission.

The administration of chemotherapy either concurrent or subsequent to molar evacuation to prevent PGTD is highly controversial. The controversy concerns the risk of exposing all patients to potentially toxic agents while only about 20-30% develop persistent disease. Furthermore, none of the chemotherapeutic regimens could prevent the development of PGTD in all patients. Such practice may yield a false sense of security resulting in inadequate hCG surveillance. Although the long-term effects of chemotherapeutic agents is possibly minimal, the use of such toxic and hazardous agents in young reproductive women seems unjustifiable. Chemoprophylaxis may be particularly beneficial in patients with high-risk molar pregnancy, especially when hCG surveillance is either unreliable or unavailable. Since nearly all patients developing PGTD, can be successfully treated with chemotherapy, the high-risk factor appears to be only patient compliance with follow-up schedule.

After surgical evacuation of molar pregnancy either with or without chemoprophylaxis, regular follow-up based primarily on serial, sensitive hCG assays is of most importance. The patient should be advised that although the molar tissue has been already evacuated, the treatment has not yet finished. She remains at risk for developing PGTD. Regular follow-up is necessary to early detect and treat persistent disease. Hysterectomy also does not preclude the need for careful follow-up. PGTD can occur as shown in our study.

In conclusion, this study presents a high incidence of persistent GTD following surgical evacuation of molar pregnancy either with or without

chemoprophylaxis. Regular follow-up with sensitive hCG assays must be emphasized in all patients after termination of molar pregnancy.

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