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Analysis of Risk Factors for Postmolar Trophoblastic Disease: Categorization of Risk Factors and Effect of Prophylactic Chemotherapy

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Early identification of high risk molar pregnancy is important in preventing the development of subsequent postmolar trophoblastic disease (PMTD). In the present study, evaluation of risk factors of developing PMTD, and indications for initiating prophylactic chemotherapy, and investigation of the effects of prophylactic chemotherapy were undertaken. One hundred and forty complete molar pregnancies treated at Yonsei University College of Medicine were retrospectively analyzed. Thirty-six cases of PMTD developed in these molar pregnancies during follow-up.

Risk factors for PMTD were ranked according to frequency with which they were associated with PMTD. The patients with no risk factors were classified in the low-risk group, with one or two in the medium-risk group, and with three or more in the high-risk group. Prophylactic chemotherapy was administered to 14 of 52 low-risk, to 21 of 46 medium-risk, and to 17 of 42 high-risk patients. Among the high-risk patients, the time required for remission was significantly shorter in the group with prophylactic chemotherapy (13.5 weeks) than in the group without prophylactic chemotherapy (22.4 weeks). There were no differences in the duration until remission among the low- and medium-risk patients. Of the 52 patients who received prophylactic chemotherapy, 8 (15.4%) developed PMTD. Among the high-risk patients, the occurrence of PMTD was significantly lower in the prophylactic chemotherapy group. Among the low-risk and medium-risk patients, there were no differences in the occurrence of PMTD between the chemoprophylaxis treated and untreated groups.

Our results strongly support the use of prophylactic chemotherapy for patients that were designed under our high risk criteria. Prophylactic chemotherapy helps to prevent or reduce the risk of developing PMTD, and shorten the time required for complete remission in high-risk patients.

Key Words: Hydatidiform mole, postmolar trophoblastic disease, prophylactic chemotherapy

Early identification of high risk molar gestation is important in preventing the development of subsequent trophoblastic sequelae. Clinical and laboratory factors in patients with hydatidiform mole that might correlate with the risk for the development of postmolar trophoblastic disease (PMTD) have been described, such as age, large-for-date uterus, ovarian cysts > 6 cm in diameter, serum β-hCG level over 100,000 mIU /ml, and previous history of molar pregnancy (Curry *et al.* 1975; Morrow *et al.* 1977; Stone and Bagshawe, 1979; Tsukamoto *et al.* 1985; Berkowitz *et al.* 1987; Parazzini *et al.* 1988). The clinical impact of the presence of each of the risk factors in the management of hydatidiform mole is not defined.

The use of prophylactic chemotherapy have been attempted to reduce the incidence of PMTD (Kaku, 1966; Koga and Maeda, 1968; Goldstein, 1974; Kashimura *et al.* 1986; Ayhan

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et al. 1990). However, the practice of prophylactic chemotherapy to prevent PMTD remains controversial. There have been several reports that prophylactic chemotherapy is an effective and safe method to reduce incidence of proliferative trophoblastic sequelae (Kashimura *et al.* 1986; Kim *et al.* 1986; Goldstein and Berkowitz, 1995). There is some argument against the use of prophylactic chemotherapy because most of molar pregnancies can be cured by uterine evacuation alone and none of the chemotherapy regimens described prevent the development of malignancy in all patients treated.

In the present study, further evaluation of the risk factors, and the indications for initiating prophylactic chemotherapy, and investigation of the effects of prophylactic chemotherapy were undertaken.

MATERIALS AND METHODS

We retrospectively analyzed one hundred and forty patients with complete mole treated and followed up at the Department of Obstetrics and Gynecology, Yonsei University College of Medicine from January 1983 to December 1990. Suction curettage was used in 83 (59.3%), sharp curettage in 52 (37.1%), hysterectomy in 4 (2.9%), and hysterotomy in 1 (0.7%) of the patients to treat the molar pregnancy. Each method was chosen on the basis of clinical status of the patient, age, parity, desire for future childbearing, uterine size, existence of preexisting metastases, extent of vaginal bleeding, and available hospital facilities. After the molar evacuation, patients were followed with weekly serum β-hCG titers until they were normal for 3 consecutive weeks and then were followed monthly until the levels were normal for 12 months.

The diagnosis of PMTD was based on the criteria similar to those of Bagshawe *et al.* (1973). (1) two or more consecutive weekly increase in the β-hCG titer; (2) plateauing of the β-hCG titer for three or more consecutive weeks; (3) persistent or recurrent uterine hemorrhage and a persistently detectable β-hCG titers; (4) clinical or histological evidence of metastases with persistently high or rising β-hCG values.

Various risk factors for PMTD reported such as preevacuation β-hCG level, maternal age, gestational age, histologic grade of molar tissue, uterine size, ovarian cysts, presence of medical complication, previous molar pregnancy, ABO blood groups were evaluated. Risk factors for PMTD were ranked according to frequency with which they are associated with PMTD. The patients with no risk factors were classified in the low-risk group, with one or two in the medium-risk group, and with three or more in the high-risk group. Prophylactic chemotherapy was administered to 14 of 52 low-risk, to 21 of 46 medium-risk, and to 17 of 42 high-risk patients. One course of methotrexate with citrovorum factor rescue (MTX-CVF) or actinomycin D was used at the time of molar evacuation. A single course of prophylactic MTX-CVF consisted of 1.0 mg/kg of methotrexate per day (days 1, 3, 5 and 7), followed in 24 hours by citrovorum factor, 0.1 mg /kg (days 2, 4, 6 and 8). Prophylactic actinomycin D was administered intravenously at a dose of 12 μg/kg/day for five consecutive days. No chemotherapy was initiated or continued if the total white blood cell count was under 2500/mm^3, total neutrophil count was under 1500/mm^3, the platelet count under 100,000/mm^3, or if the SGOT level was greater than 50 units. The effects of prophylactic chemotherapy in each risk category were assessed according to the incidence of PMTD and the regression pattern of serum β-hCG.

The statistical tests applied were t-test, chi-square test, and cluster analysis.

RESULTS

Of the 140 patients with complete mole, PMTD developed in 36 (25.7%). Thirty patients (21.4%) had nonmetastatic disease, and 6 patients (4.3%) had metastatic trophoblastic disease (Table 1). Patients who developed PMTD had significantly higher initial β-hCG titers. The frequency of PMTD increased with ute-

Table 1. Postevacuation outcome of complete molar pregnancy

Outcome	No. of patients(%)
Spontaneous remission	104(74.3)
Postmolar trophoblastic disease	36(25.7)
Metastatic	6(4.3)
Nonmetastatic	30(21.4)
Total	140(100.0)

rine size. When molar pregnancies larger than 20 weeks in gestational size are compared to smaller sizes, the frequency of PMTD was significantly higher. Of the 123 patients evaluated, 46(37.4%) had uterus size large-for-date. Among these, 31(67.4%) developed PMTD whereas only 2 of 77(2.6%) developed PMTD in the group with normal or small-for-date uterus. The presence of ovarian cysts influences the occurrence of PMTD. The incidence of PMTD increased with increasing severity of trophoblastic proliferation. PMTD occurred in 5 of 74 (6.8%) patients with mild degree of trophoblastic proliferation. In contrast, 7 of 9 (77.8%) patients with severe degree of trophoblastic proliferation developed PMTD. A preevacuation serum hCG titer reflects the risk of PMTD. A titer greater than 100,000 mIU/ml is indicative of a high risk for developing PMTD. There were no statistically significant differences in gravidity, parity or blood type between patients who did or did not develop PMTD.

Risk factors for PMTD are listed in Table 2 according to frequency with which they were associated with PMTD. Of all the risk factors, large-for-date uterus with ovarian cysts seems to be associated with the highest incidence of PMTD (80%). Table 3 shows the methods of evacuation between patients with and without prophylactic chemotherapy. Suction curettage was the method of choice for evacuation. No specific mode of molar evacuation brought a decrease in the incidence of PMTD to any significant degree. Hysterectomy was carried out in 4 patients. One of these 4 patients (25.0 %) developed PMTD despite removal of the uterus.

Table 2. Ranking of various risk factors for postmolar trophoblastic disease

Risk factor	No. of patients developing PMTD(%)
Large for dates uterus with ovarian cysts	8/10(80)
Severe trophoblastic proliferation	7/9(78)
Gestational size(wk)>20	24/34(71)
Uterus large for dates	31/46(67)
Previous molar gestation	2/3(67)
Ovarian cysts	10/16(63)
hCG(mIU/ml)>100,000	27/45(60)
Gestational size(wk)>16	26/43(60)
Medical complications	7/12(58)
Maternal age(yr)>40	10/19(53)

PMTD: postmolar trophoblastic disease

Table 3. Method of uterine evacuation in the chemoprophylaxis treated and untreated patients with hydatidiform mole

	Chemoprophylaxis	
	Yes	No
Suction curettage	34	49
D & C	16	36
Hysterectomy	1	3
Hysterotomy	1	

The percentage of high-risk patients who received prophylactic chemotherapy was 40.5% (17/42) while 26.9% (14/52) for low-risk patients underwent prophylactic chemotherapy. In the prophylactic chemotherapy group, 15.4% (8/52) developed PMTD. This percentage is not significantly lower than that in the group without prophylactic chemotherapy, where 31.8% (28/88) developed PMTD. Among the high-risk patients, the occurrence of PMTD was significantly lower in the prophylactic chemotherapy group. Among the low-risk and medium-risk patients, there were no differences in the occurrence of PMTD between the chemoprophylaxis treated and untreated groups. The incidence of metastatic trophoblastic disease was not significantly lower in the prophylactic chemotherapy group. Among

Table 4. Results of chemoprophylaxis treated and untreated patients with hydatidiform mole according to risk category

	PMTD		Spontaneous remission
	Nonmetastatic	Metastatic	
Treated group			
Low risk			14
Medium risk	1		20
High risk*	6	1	10
Untreated group			
Low risk	1		37
Medium risk	3	2	20
High risk*	19	3	3

*: $P<0.01$

Table 5. Time needed to achieve remission according to risk category in chemoprophylaxis treated and untreated patients with hydatidiform mole

Risk category	Time interval(weeks)+	
	Treated group	Untreated group
Low risk	8.5±5.7	7.4±3.2
Medium risk	12.8±6.1	12.1±5.0
High risk*	13.5±7.3	22.4±8.3

+: Mean±SD, *: $P<0.05$

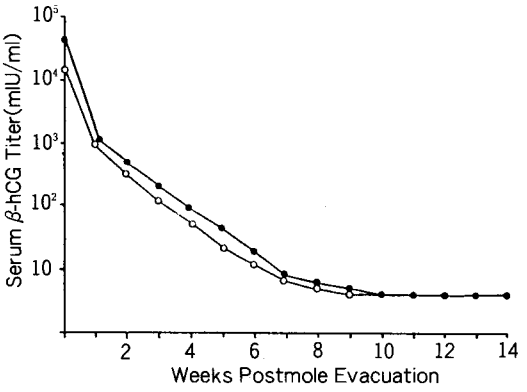

Fig. 1. *Postmolar serum β-hCG regression curves in the low-risk patients with prophylactic chemotherapy (closed circle) and without prophylactic chemotherapy (open circle).*

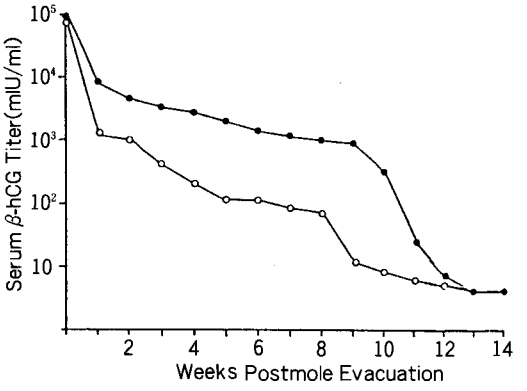

Fig. 2. *Postmolar serum β-hCG regression curves in the medium-risk patients with prophylactic chemotherapy (closed circle) and without prophylactic chemotherapy (open circle).*

the patients with PMTD, 1 of 52 patients with prophylactic chemotherapy and 5 of 88 patients without prophylactic chemotherapy had metastatic trophoblastic disease (Table 4).

Among the patients with prophylactic chemotherapy, the mean time taken to reach remission after molar evacuation was 13.5 weeks for high-risk patients, 12.8 weeks for medium-risk patients, and 8.5 weeks for low-risk patients. There was no significant difference in the time needed to achieve remission between the three patients groups. In the high-risk patients, the time required for remission was significantly shorter in the prophylactic chemotherapy group, however, there were no differences in the time needed to achieve remission among the low- and medium-risk patients regardless of prophylactic chemotherapy (Table 5).

Fig. 1, 2, and 3 demonstrated the comparison of the regression curves of the prophylactic chemotherapy and untreated groups in each of the low-, medium-, and high-risk categories. Fig. 1 shows the patterns in the low-risk patients. Fig. 2 shows the patterns of the medium-risk patients. The patterns of regression

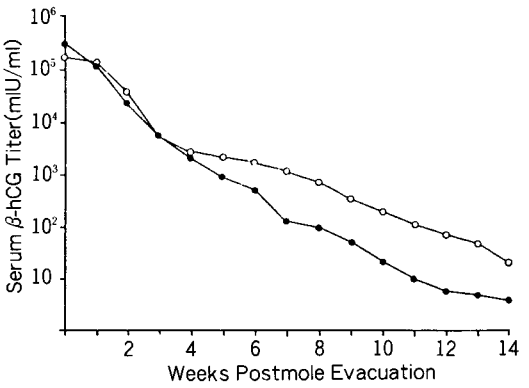

Fig. 3. *Postmolar serum β-hCG regression curves in the high-risk patients with prophylactic chemotherapy (closed circle) and without prophylactic chemotherapy (open circle).*

Table 6. Toxicity of prophylactic chemotherapy

Toxicity	MTX-CVF (N=18)	Actinomycin D (N=34)
Hematologic		
Leukopenia	2	4
Thrombocytopenia		1
Hepatic		
SGOT elevation	3	1
Gastrointestinal		
Nausea, vomiting	2	15
Epithelial		
Skin eruption		8
Stomatitis	1	4
Alopecia		3

MTX-CVF: methotrexate with citrovorum factor rescue

curve in these two risk groups remained similar despite prophylactic chemotherapy. In Fig. 3, the curves reveal that the regression in the high-risk patients after prophylactic chemotherapy was somewhat hastened as weeks progressed after treatment shortening the time needed for normalization of serum beta-hCG.

Several complications associated with prophylactic chemotherapy were observed (Table 6). No serious toxic effects were observed. Hepatotoxicity was observed frequently with MTX-CVF regimen, as indicated by a significant rise in the SGOT level. Gastrointestinal symptoms, mainly nausea and vomiting, occurred frequently when actinomycin D was given. Hematologic toxicity was transient and mild. Alopecia was minimal and reversible. Stomatitis was also mild and transitory.

DISCUSSION

The risk of PMTD after a hydatidiform mole is reported as 5.7% to 36% (Bagshawe *et al.* 1973; Curry *et al.* 1975; Morrow *et al.* 1977; Lurain *et al.* 1983). In this series PMTD developed in 25.7% (36/140). In these 36 patients, the disease was metastatic in 4.3% (6/140) of the patients, and in 21.4% (30/140) the disease remained nonmetastatic. The incidence of PMTD obtained in our study is somewhat higher than what several previous reports have documented (Bagshawe *et al.* 1973; Curry *et al.* 1975; Lurain *et al.* 1983).

In our study, the risk of developing PMTD is high with a large-for-date uterus, hCG > 100,000 mIU/ml, ovarian cysts > 6 cm in diameter, gestational size > 16 weeks, maternal age > 40 years, severe trophoblastic proliferation, a history of molar pregnancy, and medical complications. These findings are in general agreement with published studies (Morrow *et al.* 1977; Goldstein *et al.* 1981; Berkowitz *et al.* 1987). However, contrary to results reported by Parazzini *et al.* (1988), ABO blood group had no value in defining the risk of PMTD in this study. Our data show that the combination of ovarian cysts and a large-for-date uterus characterized a subgroup of which 80.0 percent (8 of 10) developed PMTD. The report of Morrow *et al.* (1977) also indicated that the risk of PMTD was greatest in the patients with theca lutein cysts and a large-for-date uterus.

The use of prophylactic chemotherapy in molar pregnancy has been the subject of controversy. The main objections in the use of prophylactic chemotherapy appear to be that

(1) unnecessary exposure to potent chemotherapy agents in the majority of patients; (2) incomplete protection against PMTD; (3) serious toxicity; and (4) tumor resistance to chemotherapy. Thus, proper application of prophylactic chemotherapy needs to select a subgroup of patients who could benefit most from chemoprophylaxis.

Most studies that have been reported categorized patients with molar pregnancy as low-risk or high-risk using Curry's criteria (1975). In the present study, we further subdivided the category into low-, medium- and high-risk group according to the number of associated risk factors. The patients with 3 or more risk factors were categorized as high-risk patients, the patients with one or two as having medium-risk, and the patients with no risk factors as having low-risk factors. Parazzini *et al.* (1988) classified patients with molar pregnancy into low-risk (defined as with no risk factors), intermediate-risk (presence of one or two risk factors), and high-risk group (presence of three or four risk factors) similar to our criteria. However, risk factors used to define the risk groups (40 or more years old, previous mole, bleeding in pregnancy, large-for-date uterus at evacuation) were somewhat different from those of our study.

Variability in the methods of sampling, drug protocol, and differing criteria for using prophylactic chemotherapy made it difficult to compare data from different series.

In the present study, the selection of the drug for prophylactic chemotherapy does not seem to be a major problem because both methotrexate and actinomycin D have been reported to be the optimal regimen with regard to effectiveness and toxicity (Goldstein, 1974; Osathanondh *et al.* 1975; Kim *et al.* 1986; Berkowitz *et al.* 1987; Goldstein and Berkowitz, 1995). Goldstein (1971) reported that the effectiveness of prophylactic chemotherapy in reducing the incidence of nonmetastatic trophoblastic disease might be dose-related. The optimal dose or dosage schedule, however, has never been well defined. Most of the studies reported to date use standard treatment protocols.

Prophylactic chemotherapy reduced the risk of PMTD in a retrospective study (Berkowitz *et al.* 1987) and in prospective studies (Goldstein, 1971; Goldstein, 1974; Kashimura *et al.* 1986; Kim *et al.* 1986). Kashimura *et al.* (1986) reported that the use of prophylactic chemotherapy reduced the incidence of PMTD from 18% to 7% in patients with complete mole. Kim *et al.* (1986) found that prophylactic chemotherapy decreased the incidence of PMTD from 47% to 14% in high-risk patients based on the criteria described by Curry *et al.* (1975). In their prospective study, the patients were selected at random for the prophylactic chemotherapy. This study confirmed that there is a significant decrease in the incidence of PMTD among high-risk patients in the chemoprophylaxis group. On the contrary, there are several reports describing that prophylactic chemotherapy did not lead to any significant reduction of neoplastic sequelae after molar pregnancies (Kaku, 1966; Ratnam *et al.* 1971; Ayhan *et al.* 1990). Ayhan *et al.* (1990) reported that the difference in the incidence of PMTD between prophylactically untreated and treated groups of either low-risk (13.9% versus 5.3%) or high-risk (26.2% versus 25.0%) patients was found to be insignificant. These investigators divided 233 patients with complete mole into low- and high-risk categories based on the criteria described by Curry *et al.* (1975) and used single agent methotrexate for prophylactic chemotherapy.

In this study, PMTD developed in 15.4% of patients with prophylactic chemotherapy and 31.8% of those without prophylactic chemotherapy. In the high-risk patients, the occurrence of PMTD was 41.2% in the prophylactic chemotherapy group. The high risk patients without prophylactic therapy, however, showed a higher occurrence rate (88.0%). The difference between the two groups was statistically significant. No difference in the occurrence of PMTD was seen in the low- and medium-risk patients regardless of prophylactic therapy.

Koga and Maeda (1968) reported that choriocarcinoma did not develop in the patients who received prophylactic chemotherapy with a short-term follow-up. On the contrary, Kashimura *et al.* (1986) concluded that prophylactic chemotherapy did not eliminate the occur-

rence of choriocarcinoma for a long time after the molar evacuation. In this study, the incidence of metastatic trophoblastic disease in the high-risk patients was not significantly different despite the prophylactic chemotherapy. In 1987, Berkowitz *et al.* performed the use of prophylactic actinomycin D in 93 patients with high-risk complete molar pregnancy. They found a significant relationship between the pre-evacuation hCG level and the risk of developing PMTD despite chemoprophylaxis.

In this study, prophylactic chemotherapy influenced the time needed for remission. In the high-risk patients, the time required for remission was significantly shorter in the prophylactic chemotherapy group than in the untreated group. No difference in time for remission was noted between the low- and medium-risk patient groups regardless of prophylactic chemotherapy. The study reported by Kim *et al.* (1986) found that there were no differences in the time interval to reach negative conversion of hCG between the prophylactic chemotherapy group and the control. Kashimura *et al.* (1986) reported that the urinary hCG regression after molar evacuation showed a similar regression pattern between the prophylactic chemotherapy group and the control.

The toxicity of prophylactic chemotherapy has been reported to occur in 16.9% to 70.2% of the cases (Bagshawe *et al.* 1969; Chun *et al.* 1970; Ratnam *et al.* 1971; Kim *et al.* 1986; Ayhan *et al.* 1990). Some deaths due to drug toxicity have been reported (Bagshawe *et al.* 1969; Chun *et al.* 1970; Ratnam *et al.* 1971; Ayhan *et al.* 1990). The toxicity increased according to the amount of the drug. In this study, prophylactic chemotherapy was well tolerated without serious toxicities.

Bagshawe *et al.* (1973) reported that ineffective prophylactic chemotherapy might favor the development of drug resistance. Kim *et al.* (1986) and Ayhan *et al.* (1990) observed that patients who developed PMTD after prophylactic methotrexate subsequently required more courses of therapeutic methotrexate to achieve remission. In order to avoid problems with drug resistance, Berkowitz *et al.* (1987) suggested to use a different cytotoxic agent for therapy following failed chemoprophylaxis. In a recent Gynecologic Oncologic Group (GOG) study it was suggested that another agent, such as actinomycin D, should be used to manage methotrexate failure (Homesley, 1994). However, resistance to prophylactic chemotherapy was not observed in other studies (Ratnam *et al.* 1971; Kashimura *et al.* 1986). In this study, several treatments were performed in the cases of PMTD and we were unable to compare the data in term of drug resistance.

Goldstein and Berkowitz (1995) recently suggested the use of prophylactic chemotherapy in patients with high-risk complete moles (characterized by large-for-date uterus, hCG titer more than 100,000 mIU/ml, ovarian cysts greater than 6 cm in diameter, and medical complications) where a patient may be noncompliant or where quantitative gonadotropin testing may not be available.

This study suggests the use of prophylactic chemotherapy in high-risk patients according to our criteria. Prophylactic chemotherapy may help prevent or reduce the risk of PMTD, and shorten the time required for complete remission in high-risk patients.

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