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GYNAECOLOGY

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## Effects of Prophylactic Chemotherapy on Persistent Trophoblastic Diseases and Post-evacuation Serum Human Chorionic Gonadotrophic Hormone Regression in the Patients with Complete Hydatidiform Mole

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### ABSTRACT

**Objective** To ascertain basic clinical information, the benefit and pitfall of Actinomycin D prophylactic chemotherapy in high risk complete hydatidiform mole with pre-evacuation serum beta hCG (human chorionic gonadotrophic hormone) over 200,000 mIU/mL, and the effect of prophylactic chemotherapy on post-evacuation serum beta hCG regression.

**Design** Prospective study.

**Setting** Department of Obstetrics and Gynaecology, Rajavithi Hospital, Bangkok.

**Subjects** An analysis of 156 patients with complete hydatidiform mole admitted to Rajavithi Hospital between 1990-1995.

**Results** Around fifty-four percent of patients who sought medical services at Rajavithi Hospital domiciled in distant provinces. Fifty-two percent had complete their compulsory education ; 40 percent had received education beyond the compulsory level, 2.8 percent were illiterate. Records were not complete for the remaining 5.2 percent. Eighty-one patients who had regular post-evacuation follow up were recruited for evaluation. Actinomycin D was administered to thirty-one patients who had pre-evacuation serum beta hCG over 200,000 mIU/mL (treated group). The other group of twenty-two patients with serum beta hCG over 200,000 mIU/mL served as the control (untreated group). Nineteen percent of the treated group (6 out of 31) developed GTT compared with 31.8 percent (7 out of 22) in the untreated group, which was not statistically significant ( $P = 0.3446$ , 2-tail Fisher's exact). Neither severe drug toxicity nor death occurred in this study. Only 2 out of 28 or 7.1 percent of the group with serum beta hCG less than 200,000 mIU/mL had persistent disease.

**Conclusion** If selective Actinomycin D prophylaxis was given to the patients with complete hydatidiform mole at Rajavithi Hospital with the condition of serum beta hCG over 200,000 mIU/mL, the incidence of GTT would be 13.6 percent. If no chemoprophylaxis was administered to this group of patients, the incidence of GTT could be expected to be 18 percent. Actinomycin D prophylaxis, while not

trophoblastic disease and significantly reduced the incidence of non metastatic trophoblastic disease. Actinomycin D at a dose level of 12 µgm/kg/day was the drug of choice. Toxic side effects were minimal. The use of methotrexate was associated with significant hepatotoxicity.

In order to avoid the unnecessary exposed patients to prophylactic chemotherapy, high risk moles were identified. The review on current management of complete molar pregnancy based on clinical experience at the NETDC in 1987 had demonstrated the benefit of using actinomycin D prophylaxis at the time of evacuation in high risk hydatidiform moles. The development of persistent disease had decreased from 31% to 11% and had recommended prophylactic chemotherapy in the management of molar pregnancy, especially when hormonal follow up was either unavailable or unreliable. However, all patients must be followed with serial human chorionic gonadotrophin levels to ensure the remission had occurred. The factors associated with an increased risk of post molar tumour were identified at NETDC : pre-evacuation hCG >100,000 mIU/mL, uterine size > gestational age, theca luteal cysts > 6 cm in diameter, associated medical factors (pre-eclampsia, hyperthyroidism, trophoblastic embolization), maternal age over 40 years and previous molar pregnancy.<sup>(3)</sup>

On the contrary, Bagshawe reported the effectiveness of follow-up system in 1969. When persistent tumour had been treated by chemotherapy, in conjunction with other methods of treatment within two to six months of the antecedent mole, serious drug resistance was not encountered, drug toxicity was slight, the duration of treatment was comparatively short and sustained remissions were obtained in 57 of 60 patients. When the start of chemotherapy was delayed beyond six months drug resistance

occurred in many instances, toxicity was often severe, the duration of treatment was much longer and sustained remissions were obtained in 22 out of 40 patients. It is suggested that to supplement local arrangements some form of centralized or regionalized follow-up service based on notification of patients with hydatidiform mole, and making use of radioimmunoassays for chorionic gonadotrophin, could reduce deaths attributable to late diagnosis.<sup>(6)</sup> According to the effectiveness of follow-up system and diagnostic Gestational Trophoblastic Tumour (GTT) criteria, 7.6 percent of molar pregnancy during 1979-1989 required chemotherapy, only 0.2 percent required multiple chemotherapy.<sup>(7)</sup>

It is well accepted that the strict follow-up through sensitive beta-hCG assays is the keystone in the management of GTT<sup>(8,9)</sup> and prophylactic chemotherapy should not be looked as an alternative. Whether the chemoprophylaxis may have its role in patients with high risk complete mole when hormonal follow-up is not possible are rest with the clinician who cares for patient with molar pregnancy and can only be answered by carefully weighing the potential toxic hazards of the therapeutic agents against the advantage to be gained by preventing trophoblastic complications.<sup>(3)</sup>

Hydatidiform mole is more prevalent in certain global regions such as Asia and Africa where medical follow-up is less available according to the lack of fund and poor patient compliance. Unfortunately, Thailand is among these countries. The follow-up after complete mole is problematic. During 1990 to 1995, patients whom were confirmed molar pregnancy by pathology report at Rajavithi Hospital would be offered serum hCG test at the clinic every one or two weeks until normal and then monthly for at least one year. Only 69, 56 and 23% of the

patients were presented at the end of third, six and twelve months respectively and selective chemoprophylaxis in patients who had pre-evacuation hCG titers > 200,000 mIU/mL by actinomycin D had not revealed the benefit. The interesting finding observed in this study was the very high percentage of patients had high serum hCG. If NETDC high risk criteria was applied, 89% of patients who had pre-evacuation hCG over 100,000 mIU/mL would be categorized as high risk moles. According to the report from NETDC,<sup>(3)</sup> only 41% of the patients who had the following signs of marked trophoblastic proliferation (hCG > 100,000 mIU/mL, uterine size > gestational age, and theca luteal cyst > 6 cm.) were high risk. In this report, the patients with pre-evacuation hCG > 200,000 mIU/mL were selected to give prophylactic chemotherapy and patients who had serum hCG at this level were usually accompanied other high risk criteria such as uterine size larger for date and/or large luteal cyst. The estimated uterine sizes were varied between examiners and were not possible to obtain in patients who did not know their last menstrual periods or had irregular menstrual cycles. Luteal cysts were clinically palpated only 6 of 153. If the uterus was larger than 12 weeks, the chance to identify the cysts was limited. The uncertainty of the uterine and luteal cyst size provided the imprecision of statistical analysis.

Goldstein also reported that patients who had developed persistent trophoblastic disease despite chemoprophylaxis had a higher pre-evacuation hCG level (mean = 381,000 mIU/mL) than did patients who did not develop persistent tumour (mean = 191,000 mIU/mL).<sup>(3)</sup> The selection of higher hCG titer (> 200,000 mIU/mL) as the high risk criteria for analysis may be the reason for statistical insignificance in this study.

In conclusion, prophylactic chemotherapy

could not prevent the occurrence of trophoblastic tumours and too many patients would be exposed to cytotoxic drug to obtain few disease-free patients even when the high risk criteria was being applied. Moreover, the main purpose of the prophylactic chemotherapy is to eliminate the occurrence of choriocarcinoma after the molar evacuation. Kashimura et al conducted the long term follow-up study (5 to 15 years). The occurrence rate of choriocarcinoma was 0.7% in prophylactic chemotherapy group and 1.6% in control group. Prophylactic chemotherapy did not eliminate the occurrence of choriocarcinoma for a long time after the molar pregnancy evacuation.<sup>(10)</sup>

The percentage of patients treated for progressive trophoblastic disease following complete hydatidiform mole evacuation ranges from 5.7% to 36%. The differences in the number of the patients treated are largely due to variations in the exact indications for therapy.<sup>(11)</sup> Bagshawe and associates treated only 5.8%. Patients with vaginal and pulmonary metastases were not treated unless the hCG titer was rising or there were haemorrhage from the lesion. They also did not treat patients with plateauing hCG titers.<sup>(12)</sup> Hatch and associates treated most of patients with elevated hCG titers 12 weeks after evacuation and reported a persistent disease rate of 32%.<sup>(13)</sup> Morrow and associates treated 26% of their patients for post molar trophoblastic disease on the basis of elevated hCG titers at 8 weeks after evacuation.<sup>(14)</sup> Schlaerth and associates reported on the results using hCG regression curve with 95% confidence limits to aid in the early recognition of persistent trophoblastic disease and ending with 36% of patients were treated.<sup>(15)</sup> In this study, patients with plateau hCG titers at low level were not treated until the end of fourth months and 18% of patients required treatment (no chemoprophylaxis).

The conclusions obtained from the study of post-evacuation hCG titer regression were summarized. Eight weeks after evacuation of hydatidiform mole, 59.7% of patients had elevated hCG titers ; 5.3% had hCG elevated at the end of twelve weeks and none had elevated hCG beyond fifteen weeks. There were no differences in post-evacuation hCG regression between high and low pre-evacuation hCG titers, with or without chemoprophylaxis.

The author is aware of the incompleteness of data mainly due to low follow-up rate. However, this report has confirmed that the improvement of follow-up rate is the only way to control the GTT preceding hydatidiform mole. Local arrangements and some form of centralized follow-up service based on notification of patients with hydatidiform mole as suggested by Bagshawe may provide patient convenience and may be the only way that could reduce deaths attributable to late diagnosis and improve the quality of the research works of such a rare disease.

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