

# Prophylactic Chemotherapy In High Risk Complete Hydatidiform Mole

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## Citation

R Sharma, C Gupta. *Prophylactic Chemotherapy In High Risk Complete Hydatidiform Mole*. The Internet Journal of Gynecology and Obstetrics. 2010 Volume 15 Number 2.

## Abstract

The study was done with the aim to find out the effect of prophylactic chemotherapy on regression pattern of serum  $\beta$ -HCG and on the incidence of persistent trophoblastic disease in patients with high risk complete hydatidiform mole. Methods Out of 43 patients of complete hydatidiform mole diagnosed over a period of 1 year, 24 were categorised as high risk on the basis of Curry criteria. After suction and evacuation, 12 out of 24 high risk patients were given prophylactic chemotherapy in the form of low dose oral methotrexate (chemoprophylaxis group) and other 12 high risk patients served as control (control group). Follow up was done clinically and with serum  $\beta$ -HCG levels. Results All 12 patients of chemoprophylaxis group had benign regression of the disease and none of them developed persistent trophoblastic disease. In control group, 4 (33%) out of 12 patients had persistent trophoblastic disease. There was rapid fall of serum  $\beta$ -HCG in chemoprophylaxis group in mean time of 7.3 weeks as against 9.7 weeks in control group. No serious toxicity was observed with chemotherapy. Conclusion Prophylactic chemotherapy reduces the occurrence of persistent trophoblastic disease in high risk hydatidiform mole patients without causing any life threatening toxicity.

## INTRODUCTION

Smellie (1), in 1759, defined hydatidiform mole as a conceptus usually devoid of an intact fetus in which all or many of the chorionic villi show gross nodular swelling culminating in cyst formation with disintegration of blood vessels and variable proliferation of trophoblasts. The trophoblastic cells have a basic neoplastic potential inherent in them. So, hydatidiform mole, invasive mole and choriocarcinoma all form the spectrum of the same disease (2). About 20% of complete hydatidiform moles develop malignant sequelae. Out of these, 70% to 90% are persistent or invasive moles and 10% to 30% are choriocarcinomas (3). The incidence of malignant sequelae is further enhanced to as high as 47% in patients with certain high risk factors (4).

To prevent the morbidity and mortality associated with postmolar malignant sequelae, prophylactic hysterectomy was advocated by some (5), but it could not prevent metastasis in other body parts besides sacrificing the reproductive potential in young patients. Then emerged the concept of prophylactic chemotherapy on the basis of following points - 1. Trophoblastic cells are highly sensitive to certain chemotherapeutic agents particularly methotrexate and actinomycin D.

2. The development of postmolar GTN which occurs in approximately 20% of patients with hydatidiform mole is biologically predetermined.
3. The mechanism for the development of metastatic trophoblastic disease after hydatidiform mole is via hematogenous spread.
4. High blood levels of cytotoxic agents at the time of molar evacuation reduce the incidence of both locally invasive and metastatic GTN (6).

However, the use of prophylactic chemotherapy is still a controversial subject, enthusiastically advocated by some and vehemently opposed by others. The opposition is based on following points -

1. It does not prevent malignant sequelae in all patients of hydatidiform mole.
2. Deaths can occur due to toxic effects.
3. Only 10%-15% of patients of hydatidiform mole will develop malignant sequelae and will require chemotherapy and by current therapy essentially all of these patients will be cured.

## **OBJECTIVES**

The study was conducted with the aim to find out the effect of prophylactic chemotherapy on the regression pattern of serum  $\beta$ -HCG and incidence of persistent GTD in patients with high risk complete hydatidiform mole.

## **MATERIAL AND METHODS**

This study was conducted in the Department of Obstetrics and Gynaecology, SMGS Hospital, Government Medical College, Jammu for a period of 1 year from June 2004 to May 2005. It included 43 patients of complete hydatidiform mole diagnosed on the basis of USG and later confirmed by histopathology. Patients with partial mole were excluded. Detailed history of patients was taken with special reference to age, parity, presenting complaints, period of amenorrhoea, past obstetrical history and socioeconomic status. General physical, systemic and pelvic examination of patients was done. Laboratory investigations performed were complete hemogram, renal function tests, liver function tests, chest X-Ray and pre-evacuation serum  $\beta$ -HCG levels.

Primary treatment was done as suction and evacuation in operation theatre with wide bore suction cannula (12-14mm). Intravenous oxytocin (10 units in 500ml of normal saline) was started simultaneously. Uterine fundus was massaged to assist in involution and to reduce the risk of perforation. Gross appearance of products was noticed and they were sent for histopathology. USG was done after 1 week and if it showed retained products in uterine cavity, check curettage was performed.

Out of these 43 patients of hydatidiform mole, 24 were categorised as high risk and 19 as low risk on the basis of high risk factors (Curry criteria<sup>(7)</sup>). These high risk factors were –

Serum  $\beta$ -HCG levels more than 100,000 IU/ml ,

Large for dates uterus ,

Theca –lutein cysts > 6cm in diameter,

Maternal age > 40 years and

Associated preeclampsia, coagulopathy, trophoblastic embolisation and /or hyperthyroidism.

24 high risk patients were then randomly divided into 2 groups –chemoprophylaxis group and control group .Chemoprophylaxis group (n=12) received prophylactic chemotherapy while Control group (n=12) was not given

prophylactic chemotherapy.

Prophylactic chemotherapy was given orally as methotrexate 0.4mg /kg /day not exceeding 25mg/day in 3 divided doses for 5 days .Second course was repeated after 2 weeks, if required on the basis of regression of Serum  $\beta$ -HCG levels. Oral methotrexate is available as tablet Neotrexate 2.5mg (Galaxo smithkline) and tablet Biotrexate 2.5mg (Biochem).

On day 1 and day 5 of chemotherapy, complete hemogram, RFTs and LFTs were obtained .Therapy was discontinued if

TLC was < 2500/mm<sup>3</sup>

Neutrophil count (TLC x % Neutrophils) was < 1500/mm<sup>3</sup>

Platelet count was < 100,000/mm<sup>3</sup>

SGOT > 50 IU/ml

Follow up of all the patients was done by Serum  $\beta$ -HCG every 2 weeks till levels became negative and thereafter monthly for 6 months. Serum  $\beta$ -HCG was measured by Radioimmunoassay technique with sensitivity of 3 IU/ml. At each visit, history was taken and general physical and pelvic examination was done. Chest X-ray was repeated in case of respiratory signs and symptoms.

Persistent GTD was diagnosed if

Serum  $\beta$ -HCG rose or plateau for 2 values ,

Irregular uterine or vaginal bleeding , uterine sub involution or theca-lutein cysts were present with persistent serum  $\beta$ -HCG ,

Metastasis was detected.

Statistical analysis was performed with computer software Microsoft excel for windows and Epi info version 6.2. t-test and Fischer Exact test were applied wherever required. p value of < 0.05 was considered statistically significant.

## **RESULTS**

In our study conducted over a period of 1 year, 43 patients of complete hydatidiform mole were found out of 15355 pregnancies with an incidence of 1 in 357 pregnancies. The mean age of patients was 27.1 years ( $\pm$  6.6 years) and majority of them (70%) were from Para 0 to Para 2 group. None of the patients had previous history of molar pregnancy. The mean period of amenorrhoea at the time of diagnosis was 13.7 weeks ( $\pm$  3.2 weeks) and mean height of uterus was 15.3 weeks ( $\pm$  4.1 weeks). (Table 1)

**Figure 1**

Table 1 Baseline characteristics of hydatidiform mole patients

Baseline characteristic	Value
Mean age (years)	27.1(±6.6)
Mean parity	2.0
Mean period of amenorrhoea (weeks)	13.7(±3.2)
Mean height of uterus(weeks)	15.3(±4.1)

Patients presented with multiple signs and symptoms. Vaginal bleeding was the most common symptom seen in 86% cases while anaemia was seen in 70% cases. 9% patients were asymptomatic and were diagnosed on USG. (Table 2)

**Figure 2**

Table 2 Clinical presentation of hydatidiform mole patients

Symptom/sign	Number of patients (%)
Vaginal bleeding	37(86%)
Anaemia	30(70%)
Preeclampsia	2(5%)
Hyper emesis	3(7%)
Hyperthyroidism	1(2%)
Respiratory distress	0(0%)
Asymptomatic	4(9%)

On the basis of Curry criteria, 24 (56%) patients belonged to high risk group while 19 (44%) were in low risk group. Among high risk group, most common high risk factor was large for date uterus seen in 19 (44%) patients. (Table 3)

**Figure 3**

Table 3 Frequency of high risk factors in hydatidiform mole patients

Risk Factor	Number of patients (%)
Serum β-HCG >100,000IU/ml	15(35%)
Large for dates uterus	19(44%)
Ovarian enlargement >6cm	7(16%)
Maternal age >40 years	3(7%)
Previous h/o molar pregnancy	0(0%)
Associated –preeclampsia	2(5%)
- coagulopathy	0(0%)
-trophoblastic embolisation	0(0%)
-hyperthyroidism	1(2%)

The group of high risk patients who received prophylactic chemotherapy (chemoprophylaxis group) and control group who did not receive chemoprophylaxis were both comparable with respect to age, mean period of amenorrhoea, size of uterus and mean serum β-HCG levels at the time of diagnosis. (Table 4)

**Figure 4**

Table 4 Characteristics of high risk hydatidiform mole patients

Characteristics	Chemoprophylaxis group n=12	Control group n=12	p value
Mean age (years)	27.9(±7.5)	28.8(±7.9)	>0.77
Mean period of amenorrhoea(weeks)	13.0(±4.0)	14(±3.1)	0.52
Mean height of uterus (weeks)	16.6(±4.6)	17.5(±4.1)	0.64
Mean serum β-HCG levels at the time of diagnosis (IU/ml)	189282	132247	0.24

In our study, all those 12 high risk patients, who received prophylactic chemotherapy (chemoprophylaxis group), had benign regression of the disease and none of them developed persistent trophoblastic disease. On the other hand, in the control group, 4 (33%) out of 12 patients developed persistent trophoblastic disease. This difference in the occurrence of PTD in chemoprophylaxis group is significantly less (p value 0.04) than control group. (Table 5)

**Figure 5**

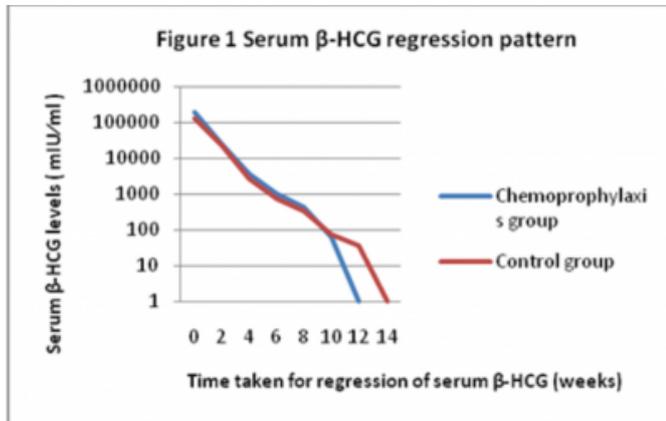
Table 5 Results of prophylactic chemotherapy

Outcome	Chemoprophylaxis group n=12	Control group n=12
Benign regression	12(100%)	8(67%)
Persistent trophoblastic disease	0(0%)	4(33%)

During follow up, serum β-HCG levels had fallen

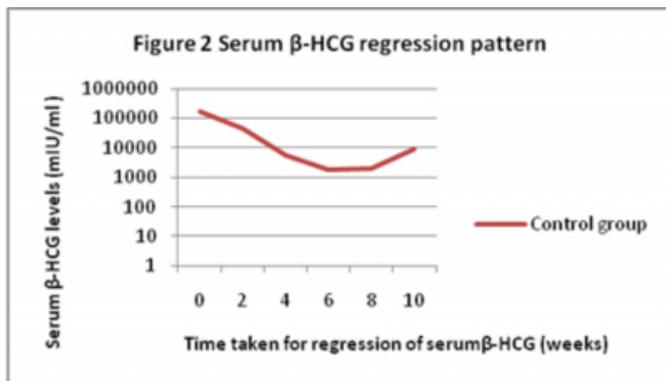
sequentially in logarithmic fashion to undetectable in all 12 patients of chemoprophylaxis group and 8 patients of control group, who had benign regression of the disease (Figure 1).

**Figure 6**



In 4 patients of control group, levels plateau and started rising after sometime and they developed persistent trophoblastic disease (Figure 2).

**Figure 7**



There was speedy regression of serum  $\beta$ -HCG levels to undetectable in chemoprophylaxis group in a mean time of 7.3 weeks ( $\pm 1.9$  weeks) as against 9.7 weeks ( $\pm 3.1$  weeks) (Table 6)

**Figure 8**

Table 6 Time taken for regression of serum  $\beta$ -HCG

Group	Mean time taken for regression of serum $\beta$ -HCG (weeks)
Chemoprophylaxis group	7.3( $\pm 1.9$ )
Control group	9.7( $\pm 3.1$ )

p value 0.04

No serious side effect was associated with prophylactic chemotherapy. 2 cases had alopecia, 1 had nausea and

vomiting and 1 had hepatic toxicity. No death due to toxicity occurred. (Table 7)

**Figure 9**

Table 7 Toxicity with prophylactic chemotherapy

Type of toxicity	Number of patients (%)
Nausea & vomiting	1(8%)
Stomatitis	0(0%)
Hepatic	1(8%)
Haematological	0(0%)
Neuromuscular	0(0%)
Alopecia	2(17%)

**DISCUSSION**

The incidence of persistent trophoblastic disease after hydatidiform mole has been reported between 5.7% to 29.1%<sup>(8, 9, 10, 11)</sup>. Several attempts were made to reduce this risk including prophylactic hysterectomy and prophylactic chemotherapy. Prophylactic hysterectomy sacrifices the reproductive potential and also cannot prevent metastasis at other sites. Many studies investigated the role of prophylactic chemotherapy in reducing the risk of postmolar GTD. Significant decrease in the incidence of postmolar GTD in prophylactic chemotherapy group as compared to control group was noticed by Fasoli et al (3% versus 9%)<sup>(12)</sup>, Goldstein (8% versus 20%)<sup>(13)</sup>, Kim et al (14.3% versus 47.4%)<sup>(4)</sup> and Kashimura et al (7.5% versus 18.1%)<sup>(14)</sup>. In our study, the incidence of PTD in chemoprophylaxis group of high risk patients is also significantly less than control group (0% versus 33.3% ,p value 0.04) . On the other hand, Ratnam et al<sup>(15)</sup> and Ayhan et al<sup>(16)</sup> found no significant decrease in incidence of postmolar GTD after chemoprophylaxis.

In present study ,prophylactic chemotherapy also led to rapid fall of serum  $\beta$ -HCG to undetectable .Other studies ,too, observed that the time taken for regression of serum  $\beta$ -HCG to normal was significantly less in chemoprophylaxis group than control group .<sup>(4,9,17)</sup>

The toxicity of prophylactic chemotherapy has been reported to occur in 20% to 60% cases.<sup>(15, 18, 19)</sup> Deaths due to toxicity have also been reported. It depends upon the dose of chemotherapeutic agent used .In present study; low dose oral methotrexate has been used. With this regime, toxicity was seen in 33% cases, which was not life threatening. No death due to toxicity occurred.

## CONCLUSION

To conclude, prophylactic chemotherapy in the form of low dose oral methotrexate could reduce the incidence of PTD in high risk hydatidiform mole patients without causing life threatening toxicity. It may prove especially helpful in those high risk patients who are non complaint and are lost to follow-up. But still the gold standard is careful follow up of each and every patient of hydatidiform mole clinically and estimation of serial serum  $\beta$ -HCG levels.

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