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ORIGINAL ARTICLE

Prophylactic Chemotherapy for the Prevention of Gestational Trophoblastic Neoplasia - A descriptive study at a tertiary care hospital

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ABSTRACT

Background: Gestational trophoblastic neoplasia develops from the trophoblastic cells which later form the placenta. It ranges from the relatively benign partial and complete hydatidiform mole while choriocarcinoma and the rare placental site trophoblastic tumor are its malignant variants. The risk of developing gestational trophoblastic neoplasia (GTN) is 15-17% after complete mole and 3.5-4% after partial mole[1,2]. This risk is more in patients with high-risk molar pregnancy[1,2].
Aim: To evaluate the role of prophylactic chemotherapy in prevention of gestational trophoblastic neoplasia in patients who fall in high-risk molar category.
Place and duration of study: Ghurki Trust Teaching Hospital and Surgimed Hospital, 2016-2020 (4 years duration)
Study design: Descriptive case series
Methodology: Twenty three patients who presented with high-risk molar pregnancy in the study period were included in this study after takinginformed consent.These patients were divided into two groups. Group A included those patients who underwent suction evacuation followed by prophylactic chemotherapy; they were 13 in number, while group B had 10 patients and they underwent suction and evacuation only. Single dose of methotrexate 1mg/kg body weight was given to the patients in group A. Patients were asked about the history of excessive vaginal bleeding and serial beta hcg levels were carried out on follow up.
Results: The patients average age was 32 years with the range between 25-42 years**.**14 patients (61%) were more than 40 years old while 9 patients (39%) were less than 40 years old. Three patients had beta hcg levels above 100,000 IU/ml. Patients were followed up withserial beta hcg levels till they became negative.No patient (0%) in group A developed gestational trophoblastic neoplasia while two patients (15.3%) in group B developed persistent vaginal bleeding and 1 patient (7%) developed choriocarcinoma involving the brain.
Conclusion: Prophylactic chemotherapy reduces the risk of development of gestational trophoblastic neoplasia as concluded by thisstudy. However, only 16% of patients in high-risk molar category develop gestational trophoblastic neoplasia[2] which means this will expose 84% patients to unnecessary chemotherapy. This will increase the cost of treatment also.
Keywords: Molar pregnancy, Prophylactic chemotherapy, Gestational trophoblastic neoplasia

INTRODUCTION

Gestational trophoblastic disease arises from the abnormal proliferation of trophoblastic tissue containing sheets of syncitiotrophoblasts and cytotrophoblasts with hydropic degeneration[1,2]. It ranges from the relatively benign partial and complete hydatidiform mole while choriocarcinoma and the rare placental site trophoblastic tumor are its malignant variants[2]. They have potential for local invasion and metastasis[3,4]. Although they are rare tumors but 95% cure rates are expected in even those patients with molar pregnancies whoget additional treatment after evacuation[3,6,7].

The genetic constitution of partial moles is triploid having 69 chromosomes, comprising of two sets of paternal and one set of maternal chromosomes. In such pregnancies, there is a viable embryo on early pregnancy ultrasound scan, which later becomes non-viable by 10-12 weeks. In complete moles, there is fertilization of an empty oocyte and hence the genetic makeup is completely male in origin. The chromosome complement is mostly 46XX,because the sperm which carries X chromosome duplicates its DNA[1,2]. Although the mainstay of treatment is suction and evacuation but, in some patients, the growth persists causing the formation of Gestational Trophoblastic Neoplasm (GTN) which have varying potential of local invasion and metastasis[6]. However, these tumors are unique because they can be cured even in the presence of metastasis[4,5].

Gestational trophoblastic neoplasms usually followa molar pregnancy, risk being 15-17% after complete mole and 3.5-4% after partial mole.[1,2] However, it can develop after any pregnancy event including induced or spontaneous miscarriage, ectopic pregnancy or a term pregnancy. Among the patients with molar pregnancy, the risk is more if the patient falls in high-risk molar category[5,6]. New England Trophoblastic Disease Center (NETDC)

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revealed that if two of the following signs and symptoms are found in the patients with complete mole, they are labelled as having high risk molar pregnancY[9,10].

1. Age more than 40 years or very young (teenage pregnancy)
2. Serum beta hcg level greater than 100,000 IU/mL / urinary beta hcg level more than 30,000
3. Uterine size greater than duration of gestation
4. Bilateral theca lutein cysts 6cm in diameter or larger (unilateral theca lutein cyst greater than 6cm in size along with other features is also labelled as high-risk molar pregnancy)
5. Thyroid disease
6. Coagulopathy
7. Pre-eclampsia

Among these patients, there is increased risk of local uterine invasion and metastasis as compared to low-risk patients[9,10]. This increased risk of developing GTN can be prevented by the judicious use of prophylactic chemotherapy. However, whether routine prophylactic chemotherapy in all high-risk patients should be given or not is still not clear.This is because approximately 80% of molar pregnancies resolve following evacuation (as shown by the declining levels of b-hcg on post evacuation follow up) and only 20% patients develop GTN. However, if follow-up is not possible for a patient which is usually prolonged[11], it is better to give prophylactic chemotherapy.

Prophylactic chemotherapy can be given using any of the following regimens;

Actinomycin D IV 12 microgram/kg daily for 3 days prior to evacuation and 2 days after evacuation

- Methotrexate 50 mg orally for 3 days prior to planned evacuation and 2 days after evacuation
- During evacuation, 50 mg MTX IV drip lasting for 3-4 hours
- Methotrexate 1mg/kg alternating with 0.1 mg/kg folinic acid on alternate day with MTX being administered on day 1 and 3[12].

This study was conducted to evaluate the role of prophylactic chemotherapy in the prevention of gestational trophoblastic neoplasia in patients with high-risk molar pregnancy.

MATERIALS AND METHODS

This descriptive case series was conducted at Ghurki Trust Teaching Hospital and Surgimed Hospital, 2016-2020 (4 years duration)

Inclusion criterion: Patients suffering from high-risk molar pregnancypresenting to out-patientdepartment were included in this study using non probability convenient sampling technique.

Exclusion criterion: All patients with low-risk molar pregnancy and normal pregnancies were excluded.

Methodology: There were 23 patients who presented with high-risk molar pregnancy in the period between 2016-2020. Informed consent was taken and patients were divided into two groups. Group A included those patients who underwent suction evacuation followed by prophylactic chemotherapy; they were 13 in number, while group B had 10 patients but they underwent suction and evacuation only. Single dose of methotrexate 1mg/kg body weight was given to the patients in group A. Patients were inquired about the history of excessive vaginal bleeding and two weekly beta hcg levels were carried out on follow up visits. The data was recorded on a predesigned proforma.

RESULTS

The average age of our patients was 32 with the age range of 25-42. 14 patients out of 23(60%) were more than 40 years old, 9 patients (39%) were less than 40 years old. 8 patients were primigravida, 13 patients were multigravida (gravida 4) and 2 patients were pregnant for the 7th time.

Table 1: Age distribution of patients (n=23)

Age	n
Less than 40 years	14
More than 40 years	9

Table 2- Pretreatment beta hcg levels

b-hcg level	Frequency	%age	Valid%	Cumulative%
1000-10,000	7	30.4	30.4	30.4
10,000-50,000	9	39.1	39.1	69.6
50,000-100000	4	17.4	17.4	87.0
Above 100000	3	13.0	13.0	100.0
Total	23	100.0	100.0	

Patients were followed up with two weekly beta hcg levels till three consecutive levels became negative.Then they were followed up monthly till three consecutive negative levels. Afterwards, beta hcg levels were carried out three monthly till three consecutive negative levels.

No patient (0%) in group A developed gestational trophoblastic neoplasia as shown by falling beta hcg levels while two patients (15.3%) in group B developed persistent vaginal bleeding and one patient (7%) developed choriocarcinoma involving the brain.

DISCUSSION

All patients with molar pregnancy need serial beta hcg levels to ensure the prognosis of the disease. They should be counselled about frequent blood tests and close follow-up to ensure compliance. They should also be informed of the increase risk of another molar pregnancy later in life as well as contraception for two years. The patients with high-risk molar pregnancy, once identified, should not only be emphasized about the importance of prophylactic chemotherapy at the time of suction and evacuation but also the importance of serial beta hcg levels should be stressed upon due to high risk of progression to GTN.

Moreover, the importance of contraception for two years can't be overemphasized.In the current study, the beta hcg levels were followed up fortnightly till three consecutive negative results, then monthly till three consecutive negative results and then three monthly till three consecutive negative levels.Benjamin and colleagues have proposed that long term surveillance should be discouraged as it is not cost effective. Moreover, they found that once hcg levels are normalized, there is a less chance of development of gestational trophoblastic neoplasia[11].

Prophylactic chemotherapy reduced the risk of development of gestational trophoblastic neoplasia in the current study as no patient in group A developed GestationalTrophoblastic Neoplasia. The results of this study are in line with another study carried out on 247 patients with complete molar pregnancy receiving actinomycin D prophylactically at the time of evacuation. Only 10 patients (4%) developed local uterine invasion and no patient developed metastasis. All 10 patients with local uterine invasion required only 1 additional course of chemotherapy to achieve complete remission[13].

Therefore administration of prophylactic chemotherapy not only prevented metastasis but also reduced the chances of developing locally invasive GTN. Duration of treatment in the patients with local invasion was also reduced to one dose of chemotherapy thus reducing the chances of developing side effects and toxicity associated with multiple doses of chemotherapy.

Another study carried out by Kim and colleagues reported a significant reduction in incidence of post-molar GTN (from 47.4%-14.3%) using a single course of methotrexate and folinic acid in patients with high-risk molar pregnancies, although it didn't reduce the incidence in low-risk molar pregnancies[12].

Another study observed the reproductive outcomes after prophylactic chemotherapy and found no reduction in fertility and live birth rates after patients with high-risk molar pregnancy received prophylactic chemotherapy[15].

However, the risk of development of GTN in patients with high-risk molar pregnancy is 16% which means if all patients with high-risk molar pregnancy are given prophylactic chemotherapy, 84% of patients will be exposed to unnecessary chemotherapy[10]. The chemotherapy itself decreases the quality of life, increases the cost of treatment and morbidity. Moreover, the cost of serial beta hcg levels is high.

Pakistan is a developing country and a lot of patients live below the poverty line. They are unable to meet their basic necessities of life. So in compliant patients, after thorough counselling, monitoring the disease and instituting chemotherapy only if post-molar GTN develops may be a suitable alternative.

More studies are needed on larger scale to establish the clear role of prophylactic chemotherapy in patients with high-risk molar pregnancy. Moreover, we need cancer registry in Pakistan. This will help us to know the burden of the disease so that countrywide consensus on proper treatment and follow-up can be developed.

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