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Original Articles

Analysis of 401 Cases of Gestational Trophoblastic Disease (GTD) at Bangabandhu Sheikh Mujib Medical University (BSMMU)

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Abstract:

Gestational Trophoblastic Disease (GTD) form a group of early pregnancy related disorders spanning the conditions of complete and partial molar pregnancies, through to the malignant conditions of invasive mole, choriocarcinoma and very rare placental site trophoblastic tumor (PSTT). In the U.K there exists an effective registration and treatment programme for GTD. The programme has achieved impressive results with high cure rate (98-100%) and low (5-8%) chemotherapy rate for the management of GTD. At Bangabandhu Sheikh Mujib Medical University similar type of GTD center run at the Department of Gynaecological Oncology, since 1998.

Objective: *To understand the importance of management of patients with GTD in accordance to the international standard level of care and the importance of establishment of specific center for GTD.*

Method: *Study population were the diagnosed cases of GTD both clinically and radiologically who attended the gynae oncology department of BSMMU. All the cases were managed following an international standard protocol. Total 603 cases were registered in a predesigned "Gestational Trophoblastic Disease Molar Card. Due to incomplete data only 401 cases were statistically analysed by SPSS version 22.*

Results: *Maximum (59.6%) population were at 15-25 years age group. Blood group distribution were almost similar O+ve 27.7%, B+ve 27.7%, A+ve 24.7%. Primigravida were 38.2% cases. Rural women were 67%. Sixty seven percent cases had suction evacuation & curettage at the gynaecological oncology department of BSMMU. Second curettage (check D&C) required in 33. 40% cases, 91% cases had incomplete follow up. Age distribution according to follow-up showed that young women (21-25 years) had maximum follow up. Seventy percent women did not require chemotherapy and 81% women of more than 40 years age required chemotherapy, only 7% women had hysterectomy for molar pregnancy, one of them had cervical cancer with molar pregnancy. Mortality among 603 cases were nil.*

Conclusion: *Outcome of management of molar pregnancy depends on complete evacuation of mole, proper follow-up at regular interval and timely decision regarding hysterectomy and chemotherapy for persistent gestational trophoblastic neoplasia.*

Key wards: *Molar Pregnancy, Complete Evacuation, Follow-up, Chemotherapy, Hysterectomy.*

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Introduction:

Gestational Trophoblastic Disease (GTD) is a spectrum of disease characterized by an autonomous overgrowth of fetal chorionic tissue or trophoblast. Hydatidiform mole (HM) is the most common and benign form of Gestational Trophoblastic Disease.

Incidence of GTD is highest in Asia, with rates ranging from 1 to 2 per 1000 pregnancies in Japan and China[1,2], one to 12 per 1000 pregnancies in Indonesia, India and Turkey[3]. In North America and Europe, the incidence is reported to be lower, at 0.5 to 1 per 1000 pregnancies[4]. The incidence has been reported to vary with race, maternal age, parity, and diet. In Bangabandhu Sheikh Mujib Medical University during 2005 and 2006, the incidence of GTD was 27.82/1000 deliveries. Among them 68 was molar pregnancy, chariocarcinoma 8 and invasive mole were 3 in number. Variations in prevalence may be due to differences in reporting between hospital-based and population-based data or in the availability of central pathology review.

HMs are categorized as partial (PM) or complete moles (CM) based on their gross morphology, histopathology, and karyotype. With complete mole there is no evidence of foetal tissue; however, with PM embryo or fetus frequently dies in early pregnancy and foetal tissue and blood cells may be identified in 20% to 50% of PM specimens, respectively[5]. HMs usually present with vaginal bleeding. Associated features include excessive uterine enlargement, theca lutein cysts, hyperemesis, pre-eclampsia and hyperthyroidism which are more common in CMs; however, these occur less frequently now a days as the routine use of ultrasound has led to earlier diagnosis[5]. For women who want to preserve their fertility, an evacuation of the retained products of conception (ERPC) is performed, ideally by suction curettage, to remove all trophoblastic tissue completely[6]. After suction curettage, around 85% of CMs and more than 98% of PMs will resolve without the need for further treatment[7]. Most women are cured in this way; however, in some women HM persists and becomes malignant gestational trophoblastic neoplasia (GTN), requiring treatment with chemotherapy.

Transformation to GTN is considered to have occurred when trophoblastic activity remains following evacuation, as shown by a) a plateau or rise in serial β-human chorionic gonadotrophin (β-hCG) levels. b) raised β-hCG levels six months after evacuation. c) the histopathological examination indicates choriocarcinoma[8]. However, the presence of raised but falling β-hCG levels six months after evacuation of a molar pregnancy is no longer an absolute indication for chemotherapy: it appears to be safe to continue with active monitoring without detrimental effect[9]. The risk of developing GTN is reported to be 16% to 20% in women with CM and 0.5% to 1% in women with PM[10]. In the UK, this translates to a GTN transformation rate of approximately 8% of all molar pregnancies[10]. Thresholds for treating persistent GTD differ by region with, for example, more than twice as many women in the USA (20%) receiving chemotherapy for persistent GTD than in the UK[11]. In BSMMU 30% received chemotherapy.

HMs may be categorized as being at a low or high risk of malignant transformation based on criteria first introduced by Bagshawe in 1976[12]. Women with high-risk HMs have more than one of the following characteristics:

a) An initial serum β-hCG more than 100,000 mIU/mL;

b) Uterine size larger than gestational age;

c) Theca lutein cysts more than 6 cm in diameter;

d) Maternal age over 40 years; and

e) Other associated medical and epidemiological factors, including previous GTD, hyperthyroidism and trophoblastic embolisation[13]. Approximately 30% to 50% of high-risk HMs will progress to GTN[14]. GTN, which may also follow a 'normal' pregnancy, an ectopic pregnancy or a miscarriage, is classified as low or high risk using a modified World Health Organization (WHO) scoring system adapted by the International Federation of Gynaecology and Obstetrics (FIGO 2009). Low-risk GTN accounts for 95% of cases in the UK and has a cure rate of almost 100%[6]. High-risk GTN has a cure rate of between 80% and 90%; these lesions require combination chemotherapy regimens and frequently develop drug resistance[15].

The use of prophylactic chemotherapy (P-Chem) in women with molar pregnancy was first described in 1966[16]. Since then, studies of Dactinomycin and Methotrexate administered before, during or after evacuation of a molar pregnancy have reported

encouraging results. Since 1968 - 8 case-control and 3 RCT were done on P-Chem. Rate of development of GTN in study group was 2-8%, in control group it was 10-50%. In all the studies - GTN were lower in study group. Several studies have found a significant reduction in GTN for high-risk HMs only[17].

Methotrexate was first reported to be active against trophoblastic tissue in the mid-1950s[18]. Since then, GTN has been shown to be a highly chemosensitive disease, with various chemotherapeutic agents achieving good rates of cure. All women with 'low-risk' GTN and approximately 80% to 90% of women with 'high-risk' GTN will be cured following treatment with one or more chemotherapy regimens[6,15]. Since chemotherapy drugs are associated with various toxic effects, most commonly myelotoxicity, gastrointestinal toxicity, stomatitis and alopecia, the chemotherapeutic aim when treating GTN is to provide the most effective treatment with the least toxicity. Methotrexate is relatively safe agent that is commonly administered as first-line chemotherapy for GTN, alone or in combination with other agents[19]. By use of 8-day cycle (4 doses I/V injections) it may cause mild type of myelosuppression. But we usually use single dose of I/M injection. So, chance of development of myelosuppression is very low. Moreover, if any anaemia develop, it can be treated by blood transfusion, if any infection occurs by myelosuppression it can be treated by injectable antibiotic. They have not been shown any toxicity to be associated with adverse reproductive outcomes, ovarian failure or second tumours[20].

Various dosing schedules have been described, including five-day, eight-day methotrexate-folinic acid and single-dose dactinomycin[14].

Materials & Method:

The objective of this study was to understand the importance of management of patients with GTD by international standard level of care and the importance of establishment of specific center for GTD.

This retrospective analysis was carried out at the Gestational Trophoblastic Disease Registration and Management center of the Department of Gynaecological Oncology at Bangabandhu Sheikh Mujib Medical University during ten years period from 2006 to 2016. Total 603 cases enrolled during this period. Due to loss of data, analysis done on 401 cases only.

Enrollment criteria- Patients reporting at the outpatient department of Gynaecological Oncology with the complain of short period of ammenorrhoea and irregular per vaginal bleeding were advised for serum β-hCG and transvaginal sonography for any molar tissue in the uterus. Some of the patients came with the diagnosis of molar pregnancy, some of the cases reported after incomplete suction evacuation and heavy irregular per vaginal bleeding. Some of the cases reported after suction evacuation and incomplete follow-up.

All types of cases were enrolled in the Gestational Trophoblastic Disease Molar Card which has been used in the center since 1998. According to the presentation, the patients were managed following our protocol. Patients diagnosed molar pregnancy for the first time at BSMMU were evaluated for anesthesia fitness and suction/evacuation done as early as possible. Serum β-hCG done 48 hours after evacuation and a TVS done after 1 week of evacuation. Patients diagnosed as incomplete evacuation were managed by check D&C under anesthesia. Completely evacuated patients were followed by serum β-hCG weekly up to 3 negatives, then monthly for 6 months. During follow-up, all the values of serum β-hCG were recorded in the Gestational Trophoblastic Disease Card in graphical form. When any deviation in normal regression of serum β-hCG were found or the regression criteria fulfilled the diagnosis of GTN the patients were scored to low risk or high risk according to the WHO prognostic criteria and were referred to clinical oncology department for the management of the specific type of GTN.

All the cases were followed after treatment and follow-up criteria were recorded in the Molar card.

Aim of use of Molar Card are:

- To formulate the treatment of molar pregnancy.
- To simplify the follow-up of the patients.
- To keep record of all the GTD cases in a specific center, so, make easy to follow-up of all the GTN cases.

Results:

This was a cross sectional retrospective analysis of the GTD cases attending Gynaecological Oncology Department of Bangabandhu Sheikh Mujib Medical University during the period January 2006 to December 2016. Data were collected in the card for all the cases. Total 603 cases were enrolled in the Gestational Trophoblastic Disease Card but due to incomplete data gathering analysis was possible in 401 cases. Results are expressed in number and percentage and also, in graphical form.

Table-I

Distribution of age & Blood group of study population.

Total case - 401	
Age	Percentage
15 – 25 years	59.6%
> 40 years	7%
Blood group	
O +ve	27.7%
B +ve	27.7%
A +ve	24.7%
AB +ve	10%

Table I shows age and blood group distribution of the patients. About 60% were in the age range of 15-25 years. Only 7% were more than 40 years age. Regarding blood group distribution all the blood group except AB +ve had similar type of distribution.

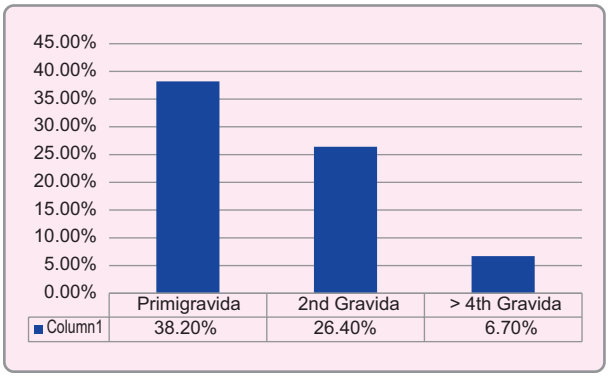

Figure 1: *Distribution of gravidity of the patients*

Figure 1 shows gravida distribution of the patients. Almost half (38.2%) of the patients were primi gravida, (26.4%) were 2nd gravida and (6.7%) were more than 4th gravida.

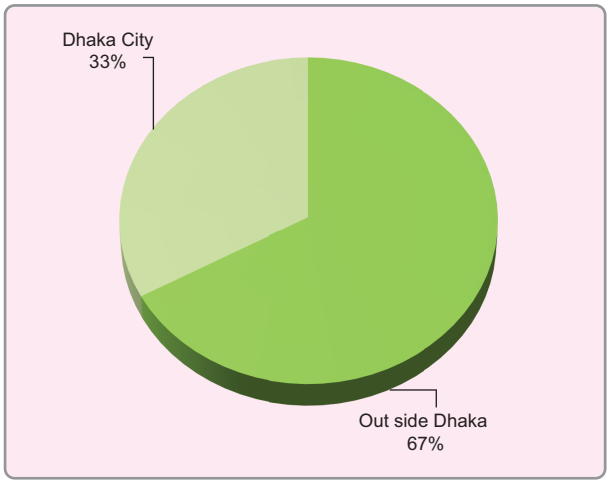

Figure 2: *Distribution of residence of the patients*

Figure 2 shows the residence distribution of the patients. About two thirds (67%) patients came from outside Dhaka city. Only (33%) resided in Dhaka city.

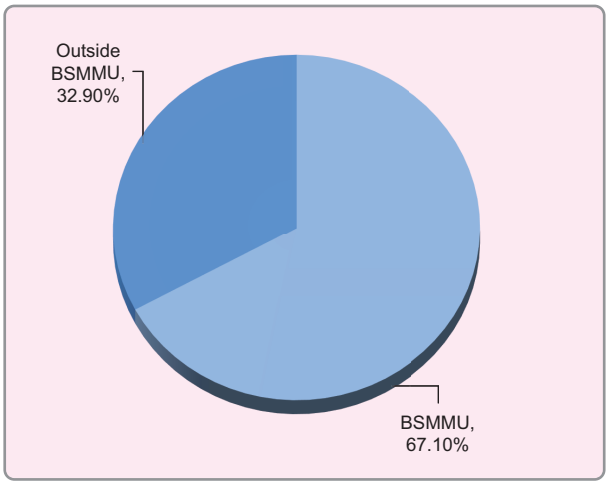

Figure 3: *Distribution of hospital where suction evacuation was performed.*

Figure 3 shows the distribution of hospital where suction, evacuation and curettage procedure was performed. Sixty seven percent patients had suction evacuation in Bangabandhu Sheikh Mujib Medical University. Rest of the patients came with the history of suction/evacuation and due to abnormal and excessive per vaginal bleeding.

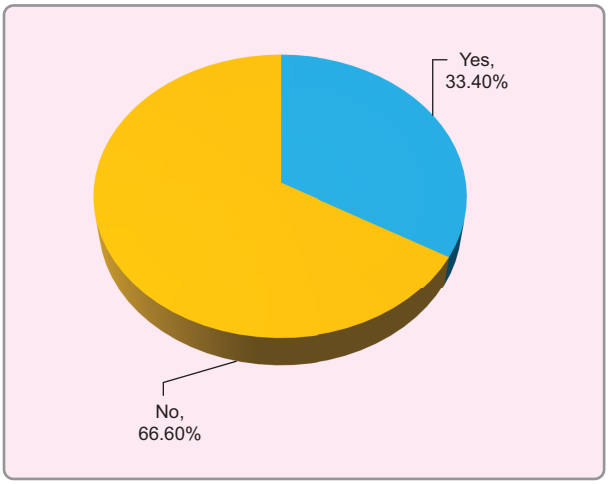

Figure 4: *Distribution of patients by second curettage (check D&C)*

Figure 4 shows the distribution of patients by second curettage. About (67%) patients did not require any second curettage (check D&C). Only 33.40% patients needed second cure of curettage.

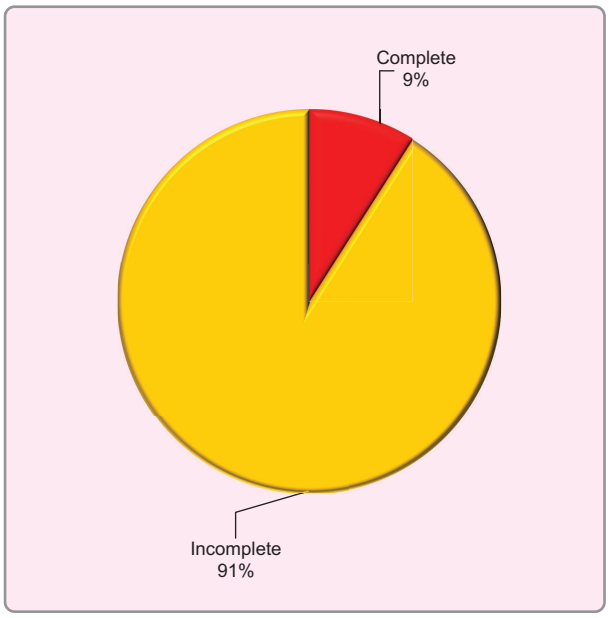

Figure 5: *Rate of follow-up*

Figure 5 shows the rate of follow-up of the patients. Ninety one percent patients had incomplete follow-up. Only (9%) completed their follow-up schedule.

Figure 6 shows the pattern of follow-up according to their age group. Complete follow up was done in 14.5% of patient who were in the age group of 26-30 years. This was the largest group of patients who completed their follow-up.

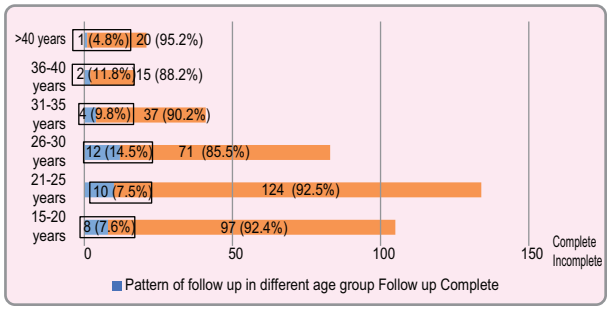

Figure 6: Pattern of follow up among different age group

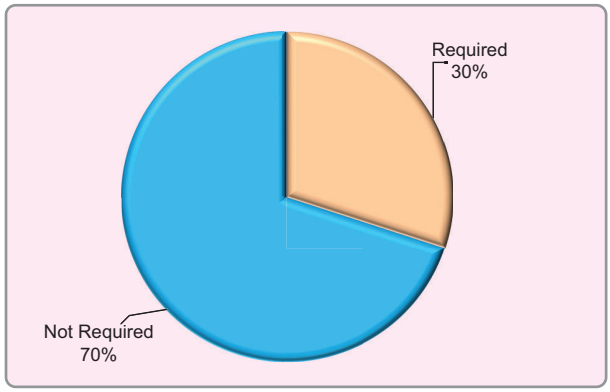

Figure 7: *Distribution of study population by requirement for chemotherapy (n=401)*

Figure 7 shows distribution of study population by requirement of chemotherapy. Maximum number of patients (70.1%) did not require any chemotherapy.

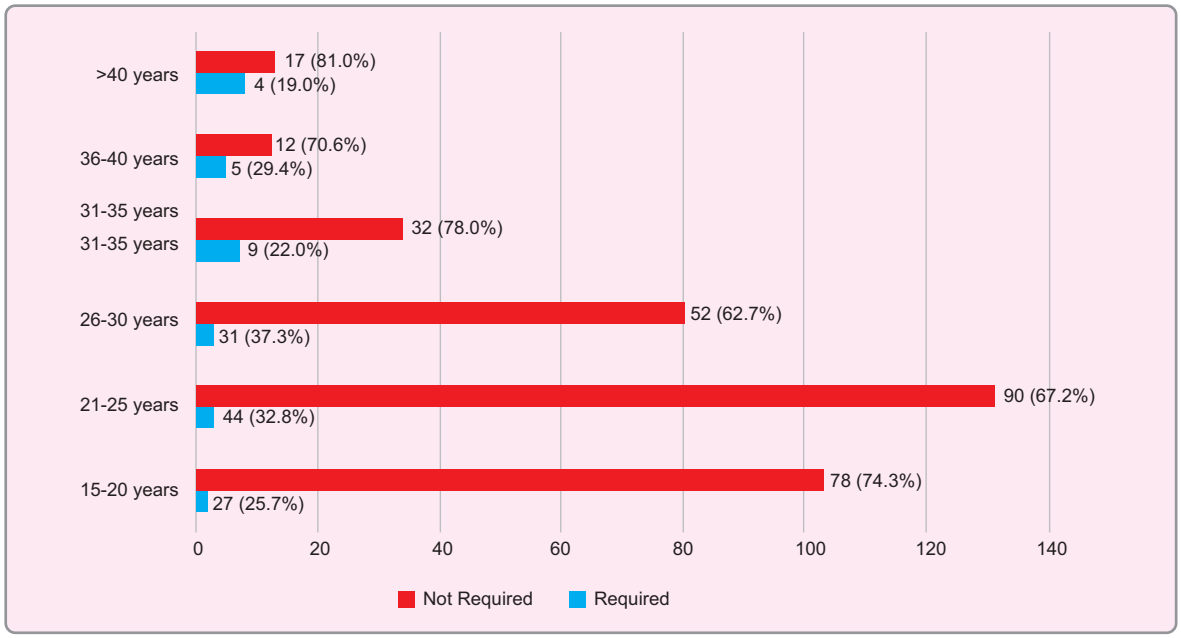

Figure 8: *Distribution of requirements of chemotherapy with age ranges (n = 401)*

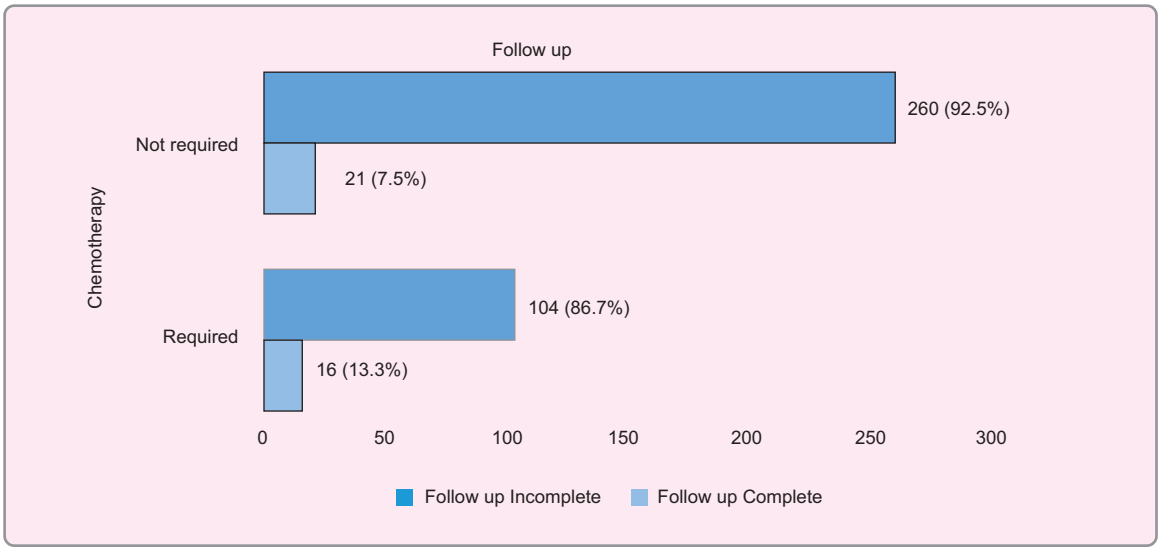

Figure 9: *Pattern of follow up among chemotherapy group and among no chemotherapy group (n = 401)*

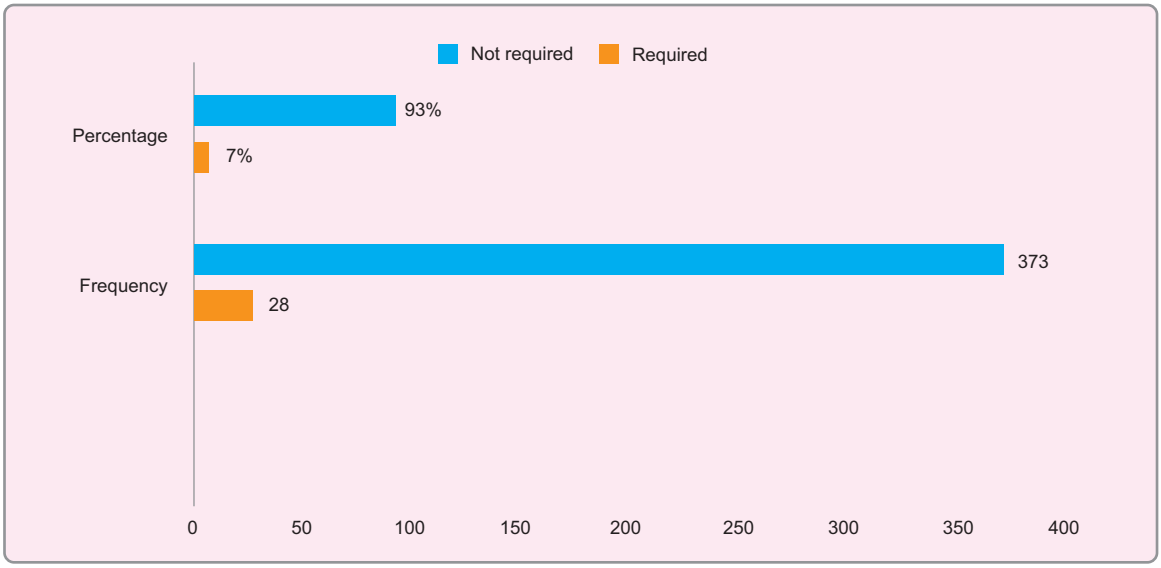

Figure 10: *Distribution of study population by the requirements for hysterectomy (n = 401)*

Figure 8 shows requirement of chemotherapy with age distribution. Chemotherapy requirement were much higher in the age group of 36 – 40 years.

Figure 9 shows the pattern of follow-up among chemotherapy and no chemotherapy group. Rate of follow-up among chemotherapy group were higher (13.3%) than among no chemotherapy group (7.5%).

Figure 10 shows the distribution of patients by hysterectomy done. Here we can find that only 28 (7%) patients required hysterectomy.

Figure 11 shows the distribution of indications of hysterectomy. Majority 17 (60.7%) patients had prophylactic hysterectomy due to their higher age and completed family. Only 4 (14.2%) patients had hysterectomy due to invasive mole. Other two cases had hysterectomy due to choriocarcinoma, two cases due to intractable hemorrhage and in two cases due to associated adenomyosis. One case of cervical cancer with molar pregnancy and one case of fibroid uterus with molar pregnancy also had hysterectomy.

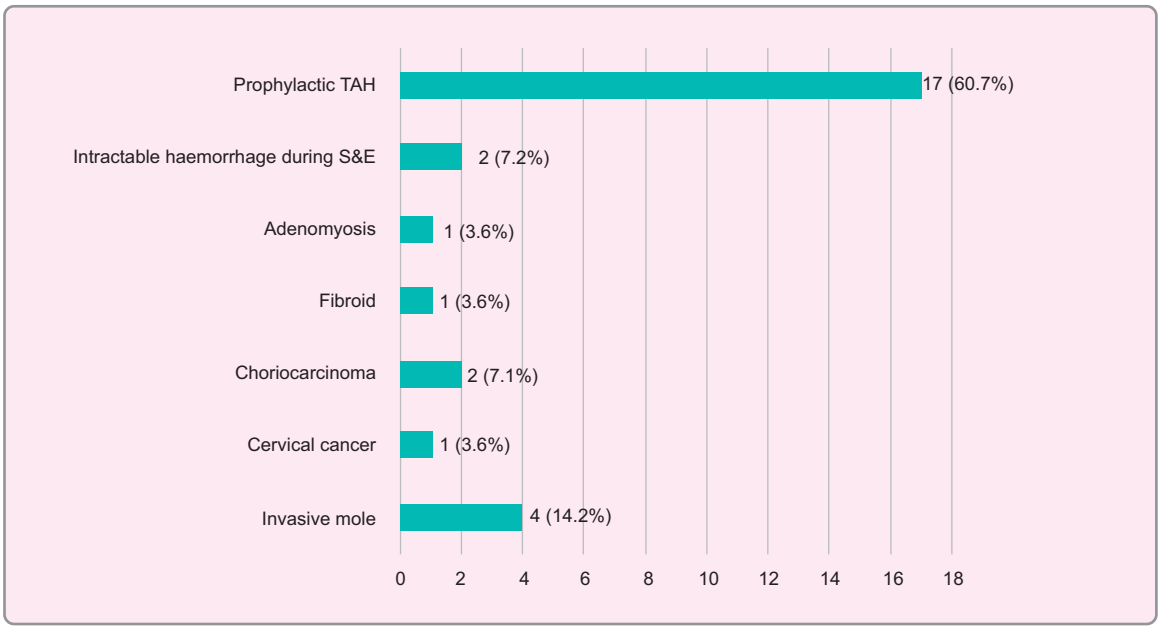

Figure 11: *Distribution of indications of hysterectomy (n = 28)*

Discussion

Gestational Trophoblastic Disease is a group of early pregnancy related complications. Histologically it includes two benign conditions – Complete hydatidiform mole (CM) and Partial hydatidiform mole (PM). The malignant forms of this condition include invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). This malignant forms can arise from any type of pregnancy and collectively known as Gestational Trophoblastic Neoplasia (GTN). Atypical placental site nodules (APSN) are another placenta related complication, which has recently been included in the GTD spectrum as 10% to 15% of APSN may coexist with or develop in to PSTT/ETT[21].

These last three conditions produce human chorionic gonadotropin in less constantly and as a marker for the diagnosis is not unique. On the other hand, all other forms of GTD produce this hormone in constantly rising level. So, hcg is an excellent biomarker of disease progression, treatment response and subsequent post treatment surveillance. The use of this biomarker together with the development of highly effective chemotherapy has transformed survival outcomes so that today nearly all women affected by GTN can expect to be cured provided managed properly[22].

Molar pregnancies are more common at the extremes of reproductive age (<15 and >45 years). The risk increases after age 35 and there is 5-10 times increased risk of complete mole after 45 years. Teenagers have a two-fold risk of molar pregnancy[22]. In this analysis we found 59% patients were between 15 to 25 years age. In the similar type of analysis done among 322 Asian patients with GTD who were registered between January 1991 to 31 December 1999 at the Weston Park Hospital of UK, the youngest patients were 15 years and oldest was 45 years[23].

According to the study done by Collen M and et. al. in 2003 at the New England Trophoblastic Disease Center, a distant of greater than 20 miles from the patient's residence to the center was associated with failure to complete follow up[24]. In our analysis we found 67% patients came from outside Dhaka, only 33% resided in Dhaka city. This is in contrast to their findings.

Among the patients of New England GTD center 63% completed follow-up and 33% did not completed follow-up. The situation is very disappointing in our center, where 91% had incomplete follow-up and only 9% completed their follow-up in our center. This may be due to the fact that, most of our patients came from outside Dhaka and could not attain the center regularly.

Regarding management of molar pregnancy, 67% patients had suction/evacuation at BSMMU and 67% did not require any second curettage. Regarding requirement of chemotherapy, among our patients,

30% and among patients of New England Trophoblastic Disease Center 16.8% developed persistent gestational trophoblastic tumor and required chemotherapy[4].

Eighty one percent of women >40 years age required chemotherapy. Similar type of result found in a prospective observational study done among 2046 consecutive women registered between January, 1994 and December 1998 with a diagnosis of molar pregnancy at the Supraregional tertiary referral center for GTD of Whittington Hospital, London UK. They found that women older than 39 years were more likely to need chemotherapy; although this difference was not statistically significant[25].

It is generally acknowledged that age over 39 years is a predisposing factor for persistent disease[26]. And age is still included in the new FIGO 2000 staging/ scoring system[27]. Hysterectomy with or without chemotherapy is a mode of treatment in some molar pregnancy cases. Advantage of hysterectomy as a source of the disease is removed. So, hysterectomy is not indicated when the disease has been spread outside the uterus. Other advantages of hysterectomy are number of post hysterectomy follow-up is greatly reduced, number of GTN development also greatly reduced- among hysterectomized women. But there should be clean cut indication of hysterectomy. In our study only 28(7%) patients needed hysterectomy among them associated adenomyosis, fibroid and cervical cancer were one for each of the cases.

Every research work face some limitations, similarly we faced the problem of inadequate data gathering, incomplete follow-up, loss to contact, cooperation from the primary attending physician and lastly incomplete evacuation and use of chemotherapy without FIGO staging and WHO prognostic scoring. Due to inadvertent use of chemotherapy by the primary physician, patients develop chemotherapy resistance and need multiagent chemotherapy who could be treated by single agent chemotherapy if proper complete suction/evacuation with proper follow-up could be done.

In this regard value of single or two to three referral centers where registration and treatment of all molar pregnancy cases can be done is tremendous. The responsibility of the primary physician to refer all the molar pregnancy cases to their referral center can improve the outcome of the patients.

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