Gestational Trophoblastic Disease and Gestational Trophoblastic Neoplasm - An Experience at Tertiary Care Hospital

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Abstract

Objective: To determine the frequency of gestational trophoblastic diseases and gestational trophoblastic neoplasm, its risk factors and prognosis.

Methods: This was a descriptive, cross-sectional study conducted at Civil Hospital, Karachi from March 2015 to September 2015. All cases of gestational trophoblastic disease after necessary investigations like tumour marker β-hCG, ultrasound with classical picture of "bunch of grapes" or "snow storm" pattern and X-ray chest (for lung metastases) under went suction evacuation. In all cases specimen was sent for histopathology to confirm gestational trophoblastic disease. After primary treatment, cases were followed with β-hCG till complete remission was achieved. During follow-up, cases were labelled as gestational trophoblastic neoplasm on the basis of International Federation of Gynecology and Obstetrics (FIGO) criteria. After risk scoring on World Health Organization (WHO) criteria, chemotherapy was given.

Results: Out of 497 pregnant ladies, 40 were cases of gestational trophoblastic disease (8.05%). Frequency/obstetric case was 1.7% and frequency/delivery was 2.1%. Out of 40 cases 13 (32.5%) were cases of gestational trophoblastic neoplasm. Out of 13 cases of gestational trophoblastic neoplasm 9 (69.23%) were labelled as low-risk and 4 (30.76%) as high-risk cases. All cases achieved complete remission. One case of high-risk group expired.

Conclusion: All women with gestational trophoblastic disease must be followed as per recommendation with serum β human chorionic gonadotropin measurement until the levels are undetectable, for early diagnosis and optimum treatment of gestational trophoblastic neoplasm.

Keywords: Gestational trophoblastic disease, neoplasm, choriocarcinoma, suction evacuation.

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Introduction

Gestational trophoblastic diseases are benign or malignant. Benign entity includes hydatidiform mole (complete and partial mole) and gestational trophoblastic neoplasm including invasive mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid tumour. However, these diseases have different pathological features, management and prognosis. They have β-hCG as tumour marker. Gestational trophoblastic disease accounts for <1% of female reproductive cancers.

Gestational trophoblastic disease (GTD) represents a group of abnormalities of trophoblastic tissue development[1]. All of them arise from the placental trophoblastic epithelium so they all have human chorionic gonadotropin (HCG) β-sub unit as tumour marker[2]. They can be divided into distinct group on the basis of their histology; the abnormalities of chorionic villi development, named hydatidi-

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form mole (HM), complete HM or partial HM which may be persistent or invasive (complete HM infiltrating myometrium); and malignant tumours arising from different components of the trophoblastic tissue, namely choriocarcinoma (in contrast to an invasive mole choriocarcinoma does not shows chorionic villi), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT)[1,3]. Gestational trophoblastic neoplasm (GTN) denominates the group of malignant entities, either invasive or malignant tumours. GTD accounts for <1% of female reproductive system cancers[4]. The incidence of GTD varies considerably worldwide with relatively high frequency in South-East Asia compare to the west. The prevalence of this disease is 1-3:1000 pregnancies and about 90% of these are non-invasive HM[3,5]. Malignant potential is also higher in this region i.e. 10-15% as compared to 2-4% in the western world[6]. The main differential diagnosis is incomplete or missed abortion and ectopic pregnancy[5].

GTD is suspected when the serum HCG levels are elevated frequently higher than 100,000 and characteristic ultrasound images are seen. GTN usually presents as a central heterogeneous mass with various anechoic spaces (hydatidiform swelling of the hydropic chorionic villi) classically called "bunch of grapes" or "snowstorm" pattern associated with ovarian the calutien cysts, but with no embryo, foetus or amniotic fluid. The confirmation of diagnosis requires histological examination and microscopy reveals abnormal villous or extra villous trophoblast[1,5,7,8]. Partial hydatidiform mole (PHM) presents as focal anechoic spaces and increased echogenicity of the chorionic villi, classically named the "swiss cheese pattern", usually with a foetus and amniotic fluid but rarely presenting theca lutein cysts[7].

Moles appear in women during their reproductive period, so the women's desire to preserve fertility is a question of major concern. Molar pregnancies are treated with suction curettage (regular curettage is avoided due to risk of uterine perforation)[5]. Hysterectomy is an option when child bearing is complete with conservation of adnexa even in the presence of the calutein cysts[1].

Most cases of complete or partial mole resolve completely after therapy, but about 15% and 5% of the cases respectively are persistent or malignant[1].

Post molar GTN usually diagnosed during follow up by HCG surveillance as patients are generally symptom free. About 50% of GTN follows molar pregnancy, the rest can occur after a spontaneous abortion, ectopic pregnancy or a term pregnancy where HCG monitoring is not routine[9]. At the 2000 FIGO Gynaecology Oncology Committee meeting the definition of post molar GTN based on HCG levels changes, histology and specific investigation was agreed upon[10]. FIGO criteria are used for diagnosis of post molar GTN. Chemotherapy is recommended treatment of GTN due to its unique genetic origin for highly sensitive to chemotherapy. About 15% of the patients with trophoblastic neoplasm will have metastatic disease, especially to the lungs and vagina. Choriocarcinoma usually spreads to the lungs, brain, liver and pelvic organs after vascular invasion. Placental site trophoblastic tumour may metastasize to the lungs, peritoneum, liver and brain, although it is associated with less vascular invasion and usually presents with lymphatic metastasis[1]. The decision regarding best regimen of chemotherapy depends on stage and classification[9]. In different parts of the world there is decline in frequency of GTN and survival has improved due to early diagnosis and treatment as chemotherapy is highly effective in most patients with GTN[11]. After treatment with chemotherapy of GTN, frequent monitoring of HCG and reliable and safe method of contraception is very necessary for early diagnosis of relapse. There is no evidence that the patients with GTN after chemotherapy have an adverse pregnancy outcome. Its recommended an early ultrasound in order to exclude a new molar pregnancy[12].

In Pakistan, GTD is a challenging problem as most of patients seek medical help very late and follow the treatment poorly. Since this group of disorders is now one of highly curable neoplasm, therefore early diagnosis and prompt treatment is

mandatory. Proper follow up can diagnose post molar GTN and cure rate of GTN is also very attractive. The objective of this study was to find out the frequency of GTD and GTN, risk factors and prognosis of GTN.

Patients and Methods

A descriptive, cross-sectional study carried out at Civil Hospital, Karachi, Gynaecology department from March 2015 to September 2015. During the 6-month period, 40 cases of GTD were evaluated on age, number of deliveries, number of previous abortions or molar pregnancy, the treatment received and response of treatment during follow up. After general physical examination and detailed investigations like β-hCG, ultrasound pelvis and chest X-ray, suction evacuation under general anaesthesia was done. In all cases specimen was sent for histopathology and histopathological findings were considered gold standard for confirmation of diagnosis. The cases were followed as per recommendation of the FIGO (International Federation of Gynaecology and Obstetrics) with weekly measurement of serum β-hCG to evaluate the cure or persistence of reminiscent disease. When complete remission is achieved (defined as 2 negative results) then monthly measurements for 3-6 months in partial mole and 1 year in complete mole. Those cases which had spontaneous HCG return to normal contraception of 6 months were advised to enable conclusive follow-up process. We followed FIGO criteria for the diagnosis of post molar GTN[10]. Parameters of FIGO criteria are: Plateau of HCG lasts for four measurements over a period of three weeks or longer that i.e. day 1, 7, 14 and 21; there is a rise in HCG for three consecutive weekly measurements over at least a period of two weeks or more; day 1, 7 and 14; when the HCG level remains elevated for six months or more; or there is histological diagnosis of choriocarcinoma[10].

These 13 cases of GTN or persistent trophoblastic neoplasm (PTN) were scored high risk or low risk on FIGO WHO scoring system based on prognostic factors[13] depending upon these prognostic risks factors staging of disease was done. Prognostic risk factors are 8 in number in FIGO WHO scoring system age, antecedent pregnancy, and interval from index pregnancy in months, serum levels of β-hCG, diameter of tumour, number and location of metastasis and previous chemotherapy result. As per recommendation patients with low risk (score</=6) were given single agent chemotherapy methotrexate (MTX) or actinomycin D (ACT-D) protocols and treatment protocol was MTX 1 mg/kg IM (intramuscular) or IV (intravascular) on day 1,3,5,7 and folinic acid 0.1 mg/kg per oral on days 2,4,6,8 or ACT-D 12 mcg/kg IV push for 5 days and remission was considered to be achieved with the HCG level undetected for 3 consecutive weeks. These cases followed with monthly HCG for 12 months. Patients with high risk (score>/=7) received multiple agent chemotherapy (EMA-CO= etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) and protocol was as follows. Day 1: ACT-D 0.5 mg IV bolus, etoposide 100 mg/m^2 IV in 500 mL normal saline over 30 minutes. MTX 100 mg/m^2 IV pushed slowly and MTX 200 mg/m^2 IV in 500 mL 5% dextrose over 12 hours. Day 2: ACT-D 0.5 mg IV bolus. Etoposide 100 mg/m^2 IV in 500 mL normal saline over 30 minutes, folinic acid 15 mg IM 12 hourly ×4 doses starting 30 hours after commencing MTX. Day 8: Vincristin 1 mg/m^2 IV bolus (max 2 mg), cyclophosphamide 600 mg/m^2 IV in 500 mL normal saline over 30 min. The criteria for remission was same except these cases had to be followed for 24 months by monthly HCG. During follow up affective contraception for 2 years was considered mandatory. Follow up of these cases with HCG is still going on.

Incidence of GTD is 3/1000 pregnancies (0.3%)[14], margin of error is 1.5%, with 95% confidence interval. Estimated sample size is at least 497 using WHO sample size calculator[7]. Non-probability consecutive sampling technique was used.

Frequency and percentage was calculated for age, parity, GTD in previous pregnancy, gestational age and need of chemotherapy. Stratification with respect to age, parity, GTD in previous pregnancy

and gestational age was done. Post stratification, chi-square test was applied. p-value less than, equal to 0.05 was considered significant.

The collected data was analysed by using SPSS version 16. Mean and standard deviation was calculated for age and gestational age.

Results

We retrieved and analysed 40 cases of GTD. Out of 497 pregnant women, its frequency was 8.05%. Out of obstetrics cases during study period, 1.7% cases were of GTD. Total deliveries during study period were 1884 and cases of GTD were 40 so frequency was 21/1000 (2.1%). Majority of cases were >25 years and 7 (17.5 %) were >35 years. Average age was 27.36 ± 6.26 years. Regarding parity 29 cases were multiparous and 10 were grand multiparous, 10 cases were 0-1 parity. Two cases (5%) had previous history of GTD, gestational age in majority of cases, 31 (77.5%) was >16 weeks of gestation (Table 1).

Stratification analysis was performed with respect to age parity, gestational age and previous history of GTD. It was found that rate of GTD was significantly high above 35 years of age (p=0.009), rate was also very high with gestational age more than 16 weeks (p=0.007), multiparous women had high risk to develop GTN (p=0.0005) and those with previous history of GTD were also at great risk to develop GTN (p=0.0006).

Out of 40 cases of GTD 13 developed GTN. Frequency of cases of post molar GTN was 13/40 (32.5%). Frequency of post molar cases per delivery was 6.9/1000 deliveries (0.69%). Stratification analysis of cases of GTD developing into GTN for age, parity, previous history of GTD and gestation was performed. It was found that age was an insignificant factor (p-value 0.125%) for cases to develop into GTN. Multiparity and gestational age greater than 16 weeks were significant risk factors (p-value 0.001 and 0.002, respectively) to develop into GTN. On WHO scoring, out of 13 cases of GTN, 9 cases were scored below 6 (low-risk) and received single agent therapy and 4 cases were scored above 7 (high-risk) and received multi agent therapy. All survived cases achieved complete remission in 1-4 cycles of chemotherapy but 3 consolidation cycles were given to them as per protocol after remission to see and prevent relapse. One case of high-risk group expired due to brain metastases.

Table 1. Demographic features of Gestational Troph)oblastic Disease (GTD) cases n=40/497

Characteristics	Cases of GTD n= 40	Cases without GTD n= 457	p-value	Test value
Age in years				
<25	11 (27.5)	231 (50.54)		
26-35	22 (55)	190 (41.57)	0.009	
>35	7 (17.5)	36 (7.8)		9.50
Parity				
Nulliparous	6 (15)	9 (1.96)		
Primiparous	4 (10)	70 (15.3)		
Multiparous	20 (50)	305 (66.7)	0.0005	24.76
Grandmultiparous	10 (25)	73 (15.97)		
Previous GTD	2 (5)	0 (0)	0.006	
Gestational age				
<16	9 (22.5)	211 (46)		10.21
16-20	17 (42.5)	160 (35)	0.007	
>20	14 (35)	86 (18.81)		

Table 2. Stratification analysis of cases of GTD n= 40 developing post molar GTN n= 13

Characteristics	Yes GTN n= 13 (%)	No GTN n= 27 (%)	p-value	Test value
Age in years				
<25	4 (30.7)	7 (25.9)		
26-35	9 (69.23)	13 (48.1)	0.125	4.15
>35	0 (0)	7 (25.9)		
Parity				
nulliparous	0 (0)	6 (22.22)		
primiparous	4 (30.7)	0 (0)	0.001	17.48
multiparous	3 (23.07)	17 (62.92)		
grandmultiparous	6 (46.15)	4 (14.81)		
Previous GTD	2 (15.38)	0 (0)	0.037	4.37
Gestational Age				
<16	6 (46.15)	3 (11.11)		
16-22	7 (53.8)	10 (37.03)	0.002	12.11
>22	0 (0)	14 (51.85)		

Discussion

GTD is a rarer complication of pregnancy caused by defective differentiation of the trophoblast. Trophoblastic tissue does not underlie common regulatory mechanism avoiding neoplastic growth. As a result, GTD and GTN can develop due to insufficient control mechanism[3]. Frequency of GTD in this study is 21/1000 live births or 1/50 live births. Frequency in two local studies is 28/1000 or 1/38 live birth[15] and 1/45 live births[16]. These frequencies are almost similar to our study. Worldwide, GTD is reported to be highest in Asian countries with a relatively higher risk for blacks[17]. In the Asian population it is 1.95 times higher than non-Asian population (1 per 387 live births versus 1 per 752 live births)[1]. This frequency is also higher within our country if compared in hospital-based studies from Sindh[16] and Hyderabad[14]. One study conducted by Thame stated that low socioeconomic status and malnutrition are attributed to high incidence in Asian countries[17]. Our centre is major referral centre and we cater larger number of cases. As molar pregnancy appears during reproductive life of women, therefore women's desire to preserve fertility is a question of major concern. Being highest frequency in Asian countries our threshold for investigating cases with features in favour of GTD should be low and all diagnostic tools carried out early to start managementas early as possible. Suction curettage is non-invasive and definite treatment to conserve uterus, so to achieve successful results early diagnosis is key to manage this disease. In this study majority of cases were 26-35 (35%) and 7 cases (17.5%) were more than 35 years. One local study reported cases seen either before 20 years or after 40 years of age[16]. We did not find extremes of age as risk factor and mean age of this study 27.36 ± 6.26 is almost similar to one study in Hyderabad and one study from Africa[14,19]. Majority of our cases were multi and grand multipara while many studies found in 0-1 parity[14-16]. Previous history of GTD is also a risk factor reported in literature[1,7]. We found that 2 cases (5%) had previous history of GTD but a very significant factor we observed was that these two cases this time developed GTN. Clinical presentation is similar to other studies i.e. period of amenorrhea and vaginal bleeding[19]. All cases had suction evacuation. None had hysterectomy as suction evacuation is a safe procedure to avoid perforation[5]. Hysterectomy is an option when desire for child bearing has been completed[20]. In few studies reasons of hysterectomy were invasive mole and persistent vaginal bleeding not settled on evacuation and chemotherapy[16]. Around 77.5% cases presented after 16 weeks. Berkowitz et al. and others reported that majority of cases presented within 1st trimester of pregnancy[14].

In view of reported literature, 15% of CHM and 5% of PHM cases developed into persistent trophoblastic disease[2], serial measurement by β-hCG after suction evacuation was carried out. In one study neither persistence nor recurrences were diagnosed after primary treatment. These case series highlights the importance of an accurate diagnosis and a long term follow-up considering the risk of persistency or malignancy as gestational trophoblastic neoplasia usually has good response to the adequate therapy[2]. In most cases (90%) persistent high levels corresponded to invasive moles, except after non-molar pregnancies, in which persistent levels of β-hCG were always due to choriocarcinoma or placental site trophoblastic tumour[2]. It was observed in one study that during monitoring, out of 40 cases 27 had undetectable β-hCG by 6-8 weeks[1]. Out of those cases with undetectable β-hCG 37.03% discontinued follow up protocol. This loss to follow up protocol 48.8% has been alsoreported in one study[14]. Low socioeconomic status, illiteracy and inability to understand the importance of follow-up were the major contributing factors in our region as well as majority of them were from remote areas and lack of facilities to reach tertiary care hospitals.

Thirteen (32.5%) cases were labelled as post molar GTN during follow up on FIGO criteria for the diagnosis of post molar GTN[2]. GTN represents <1% gynaecological malignancies and have high cure rate if treated early and on well established guide-

lines. Frequency of GTN in other studies is 29.9% and 18%[15,16]. This frequency is almost equal to our study. Risk factors for cases of GTD to develop into GTN were also studied and we found age as an insignificant risk factor (p-value= 0.125) but parity and gestational age are significant risk factors (p-value 0.001 and 0.002, respectively). Multiparity and gestational age greater than 16 weeks are strong risk factors to develop into GTN from GTD. During follow these high risk cases should be strongly counselled regarding importance of follow up. These 13 cases were labelled as low risk and high risk according to WHO scoring to start chemotherapy. Before the advent of chemotherapy, metastatic choriocarcinoma carried mortality close to 100%[13]. Therefore chemotherapy started to achieve remission. Remission observed in 99.99% of low-risk cases almost similar to one study with remission of 92.5%[13]. Remission was observed in 3/4 cases (75%) of high-risk cases and one case of high-risk group was expired due to brain metastases. Remission in high-risk group found inother study was 89.47%[13]. Chemotherapy was highly effective in almost all cases of GTN, and one study found the overall rates of cure of GTN were estimated to be around 98%[21]. In low-risk patients treated with monotherapy the rates of survival are around 100% while high-risk patients after polychemotherapy are 87%[22] but in some variety, role of other therapies such as surgery and radiation therapy should not be overlooked. To achieve best results patients should be treated under the auspices of a multidisciplinary team. One case expired for brain metastasis, one study found 27 cases of brain metastases over 22 year study period. One case resulted from a prior molar pregnancy. The incidence of brain metastases in post molar GTN is extremely low[23]. Brain metastases indicate a poor prognosis in patients with choriocarcinoma[24]. The standard chemotherapy regimen are EMA-CO or EMA-EP with enhanced CNS methotrexate dose combined with intrathecal methotrexate[23]. Our case expired before such therapy can be started, other complications were not serious. Limitation of our study was that it was a single-centre hospital-based study. Large number of cases are required to establish risk of GTN and associated risk factors.

Conclusion

This study highlights the importance of an early and accurate diagnosis of GTD, particularly the importance of follow up, considering the risk of GTN; a group of malignant entities that have good response to chemotherapy. Multiparity, gestational age greater than 16 weeks are strong risk factors to develop GTN from GTD.

Preferred chemotherapy for low risk is single agent therapy and for high risk is multi-agent EMA-CO regimen. There is no evidence that patients with GTN after chemotherapy have an adverse pregnancy outcome. Brain metastases is extremely rare but carries poor prognosis. Intrathecal chemotherapy is recommended. All pregnancies after GTD must be investigated properly to exclude other molar pregnancy due to higher risk for it.

Disclaimer: Abstract has not been previously presented or published in a conference, or other related information.

Conflict of interest

Authors have no conflict of interests and no grant/funding from any organisation.

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