

A REVIEW OF GESTATIONAL TROPHOBLASTIC DISEASES IN A TERTIARY HOSPITAL.

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ABSTRACT

BACKGROUND: Gestational trophoblastic diseases (GTD) result from abnormal proliferation of trophoblastic tissue and although rare, are a recognizable cause of maternal morbidity and mortality worldwide. However, prognosis is good when diagnosed and treated early.

OBJECTIVES: To describe the prevalence, pattern of presentation, management practices and outcome of Gestational Trophoblastic Diseases at the University of Abuja Teaching Hospital, Abuja, Nigeria.

MATERIALS AND METHODS: Case notes of women with a diagnosis of Gestational Trophoblastic Disease from 1st January 2009 and 31st December 2016 were retrospectively reviewed. Relevant information was extracted and entered into structured proformas. The data processing and analysis was done with the aid of SPSS for windows version 20.0. Results were expressed as percentages, means and range.

RESULTS: A total of 51 cases of Gestational Trophoblastic Diseases were reviewed, giving a prevalence rate of 4.4/1000 deliveries. The prevalence of molar pregnancy and choriocarcinoma were 2.4 and 1.6 per thousand deliveries respectively. The age group with the highest frequency of occurrence was the 25-29 years {18(35.3%)} and 25(49%) were para 1-4. The commonest antecedent pregnancy event was a miscarriage in 74.5% of cases while the commonest symptoms were amenorrhoea 46(90.2%) and vaginal bleeding 45(88.2%). These were complicated by anaemia in 18(35.5%) of cases. Thirty (58.8%) women had suction evacuation, 16(31.4%) had chemotherapy and 3(5.9%) had hysterectomy. Loss to follow up was 33(64.7%) and case fatality rate was 19.6%.

CONCLUSION: Morbidity and mortality resulting from Gestational Trophoblastic Diseases is still high in University of Abuja Teaching Hospital, Abuja. Significant contributing factors were late presentation and poor compliance. Efforts have to be made to reeducate patients and health workers so as to address challenges related to early diagnosis and compliance.

KEY WORDS: Gestational Trophoblastic diseases, Hydatidiform mole, choriocarcinoma, Abuja, Nigeria.
Short Title: Gestational trophoblastic diseases in Abuja.

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INTRODUCTION

Gestational trophoblastic diseases (GTDs) refer to a wide spectrum of benign and malignant disorders resulting from abnormal proliferation of trophoblastic tissue and although rare, they are a recognizable cause of maternal morbidity and mortality world wide¹. One characteristic however that makes them unique is their significant response to chemotherapy and a cure rate exceeding 90%. This allows affected women who are within child bearing age to achieve their reproductive potential.²

The World Health Organization (WHO) classified gestational trophoblastic diseases into benign

conditions like hydatidiform mole (HM) (partial, complete, and invasive mole), tumours (gestational choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour) and tumour-like conditions (exaggerated placental site, placental site nodule or plaque). Also, hydatidiform mole is further classified as villous or non-villous GTD based on pathology^{1,3} and the tumours or malignant forms of the disease are also referred to as Gestational Trophoblastic Neoplasia (GTN). These tumours, depending on the stage have effects on local tissues or on distant organs.^{3,4,5}

Gestational Trophoblastic Neoplasia most commonly are a complication of molar pregnancy, however they may also follow other pregnancy events like miscarriages, ectopic pregnancy or term pregnancy.⁴ Therefore, by virtue of their origin, they are able to produce

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significant amounts of human chorionic gonadotropin (hCG) which is a reliable tumour marker for diagnosis and monitoring of response to treatment.^{1,2,4,5,6}

There seems to be regional variations in the incidence of GTD world-wide. This is exemplified by the low rate of 23 per 100,000 pregnancies reported in Paraguay and the contrasting high rate of 1,299 per 100,000 pregnancies in Indonesia.⁷ Other rates include 66 per 100 000 pregnancies in Italy, 122 per 100 000 pregnancies in the United States and 23 -265 cases per 100 000 pregnancies in South America.⁸ A study to determine the incidence and pattern of GTD among Asians residing in Northern England and North Wales⁹ reported that the Asian population had an incidence rate 1.95 times higher than in the non Asian population (1 per 387 live births and 1 per 752 live births respectively). Also, in Africa, a study carried out in Ethiopia¹⁰ reported an incidence rate of 2.8 per 1000 deliveries while various studies in Nigeria had rates ranging from 2.3 to 7.2/1000 deliveries.^{6,11-14} Overall, about two-third of these cases are attributed to molar pregnancy while the remaining third are due to malignant forms of the disease.^{1,4} These differences in the prevalence rates of gestational trophoblastic disease have been attributed to use of different criteria for classification of GTDs, clinical diagnosis and research methods.^{8,9}

Significant risk factors for the development of GTD are the age of the patient and previous history of Hydatidiform Mole(HM). Previous diagnoses with a hydatidiform mole confers a 1% risk of recurrence in subsequent pregnancies. This escalates to approximately 25% with more than one prior HM.¹ Some studies^{11,14,15} reported that 50% or more of cases of GTD had antecedent history of molar pregnancy while about 25% were seen to follow miscarriages or tubal pregnancy, and another 25% term or preterm pregnancy. Also, the risk of GTD appears to be more at the extremes of reproductive age however this association is seen much more with complete mole.^{8,16} Women who are less than 16 years of age are six times more likely to develop the disease than women who fall within the 16-40years age range. Furthermore, there is a 17% risk of molar gestation in women who become pregnant at 50 years or more.^{11, 16} Other factors that have been linked to development of GTD's include low economic status, deficiency of vitamin A, protein, folic acid and carotene^{1,11,13}, use of oral contraceptives, parity,^{13,16} and other unknown environmental factors.⁸

Gestational trophoblastic diseases most commonly present with amenorrhoea and vaginal bleeding. These are considered to be classical symptoms and was a consistent finding in most studies^{6,10,12,13} where they were recorded in up to 90 - 100% of patients. There are also reports of uterine enlargement in about 50% of cases^{6,14}. Other symptoms and signs include, hyperemesis gravidarum, hyperthyroidism, preeclampsia early in pregnancy and anaemia^{1,4,8}. A recent study¹⁷ however revealed that with increasing early diagnosis of complete mole, fewer women now present with these classical symptoms. This early diagnosis however has not been found to modify the risk of development of post molar GTN whose diagnosis is made based on the pattern of serum hCG concentrations measured during post molar follow-up after uterine evacuation. More than half of patients with post molar GTN maybe asymptomatic and those that do, manifest variable symptoms and signs. These clinical features however depend on the histological type and extent of the disease.¹⁸

The treatment of different GTDs depends on the specific type. Options include suction evacuation, chemotherapy, surgery and radiotherapy. Suction evacuation alone is most suited for Hydatidiform mole while cases of choriocarcinoma are amenable to chemotherapy or a combination of the various modalities based on the extent of the disease and associated complications.^{1, 4} Following treatment for GTD, follow up with serial measurements of b-Hcg is important. Unfortunately, this is a problem in resource poor settings where studies conducted reported high rates of loss to follow-up^{10,12}. This is significant and is a major contributing factor to the pattern of presentation and outcome in these areas.

The diagnosis of cancer in our environment is one which is often not accepted by both patients and their relations. This perception may not be unrelated to the fact that many patients present late in the stage of the disease when outcome is not so favourable and reasons for this late presentation may be due to patient and health system factors, including poor health seeking behaviour and unavailability of diagnostic tools in the health system.^{15,19} This situation is different from what is obtainable in advanced settings where cancer management and survival rates have greatly improved. In light of this and the need to improve patient outcome in our environment, the aim of this study was to report the prevalence and describe the pattern of

presentation, management practices and outcome of GTDs at the University of Abuja Teaching Hospital, Abuja, Nigeria. It is hoped that the information obtained will help guide formation of policies and establishment of protocols which are geared towards improving the morbidity and mortality associated with this disorder in our environment.

MATERIALS AND METHODS

This was a retrospective study of all cases of GTD managed over a period of 8 years at the University of Abuja Teaching Hospital, Abuja, Nigeria. The names and hospital numbers of consecutive cases of GTD managed between 1st January 2009 and 31st December 2016 were obtained from registers in the theatre, gynaecological emergency unit, gynaecological clinic and the gynaecological ward. The labour ward and maternity ward registers also provided information on the number of deliveries per year for the same period of time. Information extracted and entered into structured proformas include sociodemographic characteristics, antecedent pregnancy, time period before presentation, symptoms and signs including complications, treatment modalities and follow-up duration. The data processing and analysis was done with the aid of SPSS for windows version 20.0. Results were expressed as percentages, means and standard deviation.

RESULTS

There was a total of 55 cases of Gestational Trophoblastic Diseases managed within this time period however, only 51 case files were retrieved and analysed. This gave a retrieval rate of 92.7%. During the study period, the total number of deliveries was 12,517. There were 30(58.8%) cases of molar pregnancy (26 complete moles and 4 partial mole) and 21(41.2%) cases of choriocarcinoma. This therefore puts the prevalence of GTDs at 0.44% or 4.4 per 1000 deliveries while the prevalence of molar pregnancy and choriocarcinoma were 2.4 and 1.6 per thousand deliveries [(1 in 416) and (1 in 625)] respectively.

Sociodemographic characteristics:

The mean age of the patients was 32.2 ± 8.5 years with a range of 20-50 years. Most of the patients with GTD were within the age group 25-29 years {18(35.3%)}. This was followed by 12(23.5%) patients who were aged 40 years and above. The lowest number of cases {5(9.8%)} were in the 30-34year age group. The highest number of patients

(36.7%) with molar pregnancy were in the 25-29year age group while the highest number with choriocarcinoma (38.1%) were in the age group of 40 years and above. This is shown in table 1.

Table 1: Age distribution of patients with GTD in UATH, Abuja.

Age range(years)	Molar pregnancy n(%)	Choriocarcinoma n(%)	Total n(%)
20-24	8(26.7)	1(4.8)	9(17.6)
25-29	11(36.7)	7(33.3)	18(35.3)
30-34	4(13.3)	1(4.8)	5(9.8)
35-39	3(10.0)	4(19.0)	7(13.7)
≥40	4(13.3)	8(38.1)	12(23.5)
Total	30(100)	21(100)	51(100)

Table 2 shows the parity distribution of the Most (49%) of cases were para 1-4, followed by nulliparous women which constituted 33.3% of cases.

Table 2: Parity distribution of patients with GTD.

Parity	Molar pregnancy n(%)	Choriocarcinoma n(%)	Total n(%)
0	12(40.0)	5(23.8)	17(33.3)
1-4	15(50.0)	10(47.6)	25(49.0)
≥5	3(10.0)	6(28.6)	9(17.6)
Total	30(100)	21(100)	51(100)

Table 3 highlights the other sociodemographic characteristics of the patients. Most of them were Christians (64.7%), married (90.2%) and housewives (37.3%). Although most (41.2%) of them were from a mixture of other tribes, the single most common ethnic group were the Igbos who made up 33.3% of the population.

Table 3: Sociodemographic characteristics of patients with GTD.

Characteristic	Frequency	Percent(%)
Tribe		
Hausa	4	7.8
Igbo	17	33.3
Yoruba	9	17.6
Others	21	31.2
Religion		
Islam	18	35.3
Christianity	33	64.7
Occupation		
Civil servant	2	3.9
Student	4	7.8
House Wife	19	37.3
Trading	13	25.4
Teaching	7	13.7
Artisan	6	11.7
Marital Status		
Married	46	90.2
Single	5	9.8

Clinical Presentation:

The antecedent pregnancy events reported include miscarriage, live birth and molar pregnancy, seen in 38(74.5%), 12(23.5%) and 1(2%) of patients respectively. The most common symptom at presentation was amenorrhoea 46(90.2%), followed by vaginal bleeding 45(88.2%), lower abdominal pain 21(41.2%) and passage of vesicles 9(17.65). Convulsion was seen in 2(3.9%) cases. The commonest sign was a large for gestational age uterus, seen in 27(52.9%) patients (See Table 4). Also, following laboratory investigations, 3(5.9%) of cases had metastases to the chest, 2(3.9%) to the brain and 6(11.8%) had metastases to more than one distant site.

Eighteen (35.5%) patients had anaemia (PCV less than 30%) at presentation and other complications recorded were shock and preeclampsia in 1(2%) case each.

Table 4: Clinical features of patients with GTD at UATH, Abuja.

Characteristic	Frequency	Percent(%)
Symptoms		
Amenorrhoea	46	90.2
Vaginal bleeding	45	88.2
Lower abd. Pain	21	41.2
Passage of vesicles	9	17.6
Dyspnoea	7	13.7
Excessive vomiting	7	13.7
Cough	5	9.8
Convulsion	2	3.9
Signs		
Large for GA uterus	27	52.9
Theca lutein cyst	8	15.7
Sub urethral nodules	5	9.8
Jaundice	1	2.0

Treatment and follow-up:

Treatment comprised of either one or a combination of the following modes of treatment, suction evacuation, hysterectomy(TAH+BSO) and chemotherapy using the MAC, EMACO or EMACE regimen. Thirty (58.8%) patients had suction evacuation, 16(31.4%) had chemotherapy and 3(5.9%) had hysterectomy. Three (5.9%) patients had suction evacuation and chemotherapy while 2(3.9%) had both hysterectomy and chemotherapy. The 3 patients who had hysterectomy were cases of choriocarcinoma

Overall, only 8(15.7%) patients had adequate follow up and were discharged. Outcome in

33(64.7%) patients was unknown as they were lost to follow up (Table 5). Ten patients died in the course of treatment giving a fatality rate of 19.6%. The average duration of symptoms before presentation for these mortality cases was 14months (Range: 5-24 months). Nine had metastasis to one or two organ systems, 3 were on second line chemotherapy with EMACE and death usually occurred shortly after 1st course of chemotherapy.

Table 5: Outcome of patients with GTD in UATH, Abuja.

Treatment outcome	Molar pregnancy n(%)	Choriocarcinoma n(%)	Total
Discharged	8(26.7)	0(0)	8(15.7)
Death	0(0)	10(47.6)	10(19.6)
Not Known	22(73.3)	11(52.4)	33(64.7)
Total	30(100)	21(100)	51(100)

DISCUSSION

The prevalence of Gestational Trophoblastic Diseases (GTDs) in this study was 4.4 per 1000 deliveries. This estimate is lower than 7.2 per 1000 deliveries which was obtained in a study in Zaria (northern Nigeria),⁶ higher than 2.3 per 1000 deliveries reported in Port-harcourt (southern Nigeria)¹² but similar to the 4.7 per 1000 births reported in Nnewi (eastern Nigeria).¹³ These figures when compared to UKs⁹ rate of 1.4 per 1000 live births show that this disorder is still common in our environment.

This study noted a higher percentage of occurrence of molar pregnancy when compared to choriocarcinoma, 58.8% and 41.2% respectively. This report is similar to reports of retrospective studies conducted in other centers in Nigeria.^{12,13} Other retrospective studies in Ethiopia¹⁰ and Pakistan¹⁵ reported significantly higher percentages of occurrence of hydatidiform mole and another prospective observational study carried out in the UK reported that that choriocarcinoma occurred in only 0.9% of GTDs. Conversely, there were other retrospective studies done in Zaria and Nnewi in Nigeria where the percentage occurrence choriocarcinoma was more than that of HM. These comparisons are being made to support the observations made by previous authors,⁹ on the fact that the comparison of incidences between countries can be challenging due to inconsistencies in case

detection by the different hospitals. Reasons for these may include both human and health system challenges and these are most predominant in settings like ours where patients present late or present to primary health centers where there is usually delay in diagnosis. There is also the issue of unavailability or unaffordability of investigative tools. One of the solutions proffered was establishment of regional and/or national registration centers to ensure unbiased and uniform data collection.⁹

The occurrence of GTD's have been reported to have a bimodal distribution of age with the highest risk seen in women under 16 years of age and higher risk also seen in women greater than 40 years of age.^{16, 8,11, 9,13} The findings in this study did not follow this pattern because the highest risk was observed in the 25-29 year age group. This finding is similar to that of a few other studies^{6,10,19} and one possible reason for this finding is that there was no representation of patients 19 years and below in both our own study and theirs. About two thirds of the cases in our study were in women of low parity and this finding was similar to the finding of the study in Pakistan¹⁵ but at variance with that of other studies.^{10, 11, 14} Take for example. The study done in Ethiopia¹⁰ and Ebonyi¹⁴ reported that more than 50% of cases were seen in women who were para 5 and above. These variations in findings may just be supportive of the fact that parity has not been identified as a significant risk factor for GTDs.¹³

Most commonly, GTN develops after a molar pregnancy¹⁶ however this was not the case in this study as the commonest antecedent pregnancy event for both hydatidiform mole and choriocarcinoma was a miscarriage in about 77% and 71% of cases respectively. Only one case of choriocarcinoma was documented to have followed a molar pregnancy. One possible explanation for this might be the fact that our center, being a referral center have most patients presenting after having had some form of treatment from the referring facilities and these hospitals do not routinely send samples for histology following evacuation. So the history at presentation is usually that of an incomplete miscarriage with multiple uterine evacuations. It does not preclude the fact that some of these so called 'miscarriages' may have been even molar

pregnancies from the onset, making this one of the limitations of our study. Also, this scenario forms part of the challenges in the definition and management of GTDs in resource poor settings and may also explain the relatively high occurrence of choriocarcinoma (41.2% of cases) in this study.

The commonest clinical features reported in this study were amenorrhoea, vaginal bleeding and a large for date uterus. These findings are similar to those of other studies where as many as 90-100% of patients presented with amenorrhoea and vaginal bleeding^{13,11,10,6,14} and more than half of the patients had large for date uteruses.^{6, 20} It is interesting to note that contrary to what is observed in these studies which are mainly from developing countries, the clinical presentation of molar pregnancy in developed countries has changed over the past few decades¹⁶ with fewer women presenting with these traditional signs and symptoms. Reason for this is early prenatal care in these climes with early beta human chorionic gonadotrophin (b-hCG) estimation and ultrasound scan (USS). Nonetheless, in the absence of this, it is important for health care practitioners at all levels to consider GTDs as a differential diagnosis early in the management of cases that present with these classical features. The most common complication reported in this study was anaemia and this finding, not surprisingly, is in agreement with the finding in most studies. Possible reasons for this include late presentation following abnormal uterine bleeding as was seen in our study, coupled with delay in making diagnosis and prompt referral. It could also be as a result of bleeding during the process of evacuation or as a result of chemotherapy.^{1,4,16}

The most common mode of treatment in this study was suction evacuation and this is the standard of care especially for patients with molar pregnancy²¹. Chemotherapy use was relatively frequent because of the high proportion of cases with choriocarcinoma and it is also indicated in patients with molar pregnancy with persistent rise or plateau of b-HCG. This was reported in only two cases in this study. Prophylactic use of chemotherapy has remained a controversial issue¹ but in the light of the poor health seeking behaviour and high rate of loss to follow up of

patients as seen in this study, and other studies done in settings like ours^{10,12,14} there may be need to consider this as an option in certain group of patients. Specific factors to be considered should include literacy level of the patient, level of ignorance with regard to health issues, economic ability, ability to communicate and access to standard health care. Hysterectomy is indicated in patients with a diagnosis of choriocarcinoma especially if they are older women who have completed family size or in patients with intractable haemorrhage.⁶ In our study, two of the patients who had hysterectomy were older women who had completed family size and the third was a younger woman with intractable haemorrhage.

In this study, the final outcome of the disease was not known in a significant proportion of the patients and this is a limitation of the study. Similar and even higher figures than ours have been reported in other studies,^{10,12,14,15} especially those done in similar settings and the multifaceted reasons for these have been highlighted previously. It is expected that patients with a diagnosis of molar pregnancy be followed up for a period of 6-12 months and those with choriocarcinoma be followed up for life.^{1,16}

The mortality rate of 19.6% recorded in this study is higher than reports from studies conducted in other parts of Nigeria^{6,11,12,13} and reasons for this may be the fact that our center is a referral center for neighbouring states. A significantly lower mortality rate of 0.84% was reported by a retrospective study conducted in Argentina²² while analysis of survival rates of high-risk gestational trophoblastic neoplasia (GTN) patients treated over a 15-year period at the Charing Cross Gestational Trophoblastic Disease Centre, UK²³ reported an overall mortality rate of 6%, most of which were from drug resistance. These reports highlight the excellent prognosis of the disease in the presence of early diagnosis, adequate treatment and good compliance, especially in the setting of well-established centers.

CONCLUSION

Morbidity and mortality resulting from GTDs is still high in our environment. There was late presentation and poor compliance of patients in this study. It is therefore important to reeducate

health care workers on the disease so as to improve early diagnosis and referral. There is also need to reinforce education and counselling of patients so as to improve compliance. Establishing a system that could ensure a system of recall could also help improve compliance.

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