OUTCOMES AND CHALLENGES IN THE MANAGEMENT OF GESTATIONAL TROPHOBLASTIC DISEASE IN A TERTIARY INSTITUTION IN NIGERIA

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ABSTRACT

Context Gestational Trophoblastic Diseases are a spectrum of interrelated diseases disorders that arise from abnormal pregnancy and are characterized by excessive elevation of Human Chorionic Gonadotrophins. They include both benign and malignant forms; hydatidiform mole, Invasive mole, Placental Site Trophoblastic (PSTT) tumour and Choriocarcinoma.

Objective: The objective of this study was to present the outcomes and challenges encountered in the management of GTDs in a tertiary centre in South-western part of Nigeria.

Study Design, Setting and Subjects: This was a retrospective study of the cases of gestational trophoblastic disease managed at Obafemi Awolowo University Teaching hospitals complex, Ile Ife between 2009 and 2013. Data were retrieved from the case records and telephone calls were put across the patients to enquire about the state of health of the patients. Data was analysed using SPSS version 20.

Main Outcome Measures: The main outcome measures were the incidence of GTDs, outcomes and challenges encountered in the management of patients with gestational trophoblastic disease.

Results: A total of 27 women were managed for GTDs; 22 had hydatidiform moles and 5 were managed for choriocarcinoma. The mean age of the patients was 31.9 years SD 6.94, mean parity 2 SD 1.53; mean duration of amenorrhoea was 15.7 weeks SD 4.92. The most common presenting symptom was vaginal bleeding in 81.5% of cases. Non-adherence to prescribed treatment was high as over half of the patients with molar pregnancy was lost to follow up after molar evacuation. Mortality was also high among patients with GTDs as 60% of the patients with choriocarcinoma died during treatment.

INTRODUCTION

Gestational Trophoblastic Diseases are a spectrum of interrelated disorders that arise from abnormal pregnancy and are characterized by excessive elevation of Human Chorionic Gonadotrophins. They include both benign and malignant forms; hydatidiform mole, Invasive mole, Placental Site

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Trophoblastic (PSTT) tumour and Choriocarcinoma. Hydatidiform mole or molar pregnancy is divided into two; complete and partial moles. Complete moles have diploid karyotype because they commonly arise by arise as a results of fertilization of an enucleated ovum by a haploid spermatozoon which subsequently duplicates it's chromosomal. They lack maternal genetic contents. Partial moles on the other hand are triploid because they contain an extra chromosome which is obtained from the father. Though considered benign form of GTDs, molar pregnancies could at the same time be considered premalignant because of the propensity to transform into the malignant form which is choriocarcinoma. The risk of malignant transformation is greater with complete moles[1].

The incidence of GTDs has been reported to show racial and geographical variations in many several epidemiological studies. [2,3] with higher incidences being reported from Asian and African countries compared with European and North American countries.[4-7] Even migrants to European countries where the incidence is low have been shown to have higher incidence than the indigenous populations.[8] In addition to racial factors, reproductive factors have been implicated in the risk of developing GTDs. Extreme of reproductive age and history of previous molar pregnancy have been shown to be associated with increased risk of developing GTDs.[9-12]

Due to early diagnosis, most patients with molar pregnancy presents with symptoms of missed abortion such as vaginal bleeding. Other clinical features include exaggerated symptoms of pregnancy probably due to the excessive HCG production, rare presentations may include signs of hyperthyroidism and pre eclampsia.

In the past GTDs were invariably fatal due to late diagnosis but with the advent of ultrasonography early diagnosis is common. Prompt management with suction evacuation for molar pregnancies and early institution of chemotherapy for choriocarcinoma with careful follow up with serum beta HCG monitoring have transformed what used to be a highly fatal disease to one that is curable with preservation of reproductive functions. GTDs have a higher cure rate relative to other gynaecological malignancies. However, achieving this requires long term follow up monitoring with serum β HcG. Patients must also adhere to the treatment plan by coming for regular check for early detection of recurrences in addition to avoid getting pregnant during the follow up period.This is best achieved in specialized centres dedicated to the management of this condition. Oncological services are poorly developed in many developing countries and as such specialized centres are virtually non-existent.

MATERIALS AND METHODS

The medical records of patients who managed for GTDs between January 2009 and December 2013 were retrieved from the medical records department of the hospital. The socio-demographic factors such as age, parity, contraceptive usage and marital status and clinical factors and results of laboratory investigations including pathological results such as presenting symptoms, period of amenorrhoea, uterine size at presentation, duration of symptoms before presenting to the hospital, administration of chemotherapy, duration of follow up and outcome of management were retrieved from the case files. Telephone calls were made to patients and relations to enquire about the state of health of patients and to remind them to come for their chemotherapy. The retrieved data was entered into a proforma designed for the study. Analysis was done by SPSS version 20.

RESULTS

During this study period, 27 women were managed for GTD; 22 patients with molar pregnancies and 5

with choriocarcinoma. Majority of the molar pregnancies were partial moles (51%) (Table 1). There was a total of 6347 deliveries in the hospital during the study period. The mean age of the patients was 31.9 years SD 6.94, mean parity 2 SD 1.53; mean duration of amenorrhoea was 15.7 weeks SD 4.92. Most of the patients (60%) were within the age group 25 to 34 years. Patients with molar pregnancies were younger compared with those with choriocarcinoma with a mean age of 30.6 years against 34 years, however, this was not significant (p=0.84). The mean number of pregnancy per woman was 3.3 and the mean number of delivery was 2. The most common presenting symptom was vaginal bleeding in 81.5% of cases (Table 2). Late presentation was common as the mean duration of symptoms before presenting to the hospital was 21.5 days.

Uterine size was larger than the period of amenorrhoea in 14/27 (51.9%), small for date in 1 (3.7%) and appropriate for date in 12 (44%) patients. Only one (3.7%) patient with complete mole had pre-eclampsia.

Of the 22 patients managed for molar pregnancy with suction evacuation during this study period,17 (77.3) had normalization of serum βHCG following suction evacuation while 5patients (22.7%) had persistent trophoblastic diseases. A total of nine (33%) of the patients received chemotherapy; 4 patients with persistent trophoblastic diseases following molar evacuation and 5 patients with choriocarcinoma. The patients with persistent trophoblastic disease received single agent chemotherapy; (3 MTX, one Actinomycin D). The patients with choriocarcinoma received combination chemotherapy in the form of EMACO (Table 3)

Non adherence to prescribed treatment and follow up was high as 45% of patients with molar pregnancy were never seen again at the hospital following evacuation. Of the remaining patients 59% defaulted during the period of follow up (Table 4). The average number of visit was 3.6 and the mean duration of follow up was 148 days (1 to 1095 days)

There was a high mortality associated with the management of GTDs in our centre as 4 patients were known to have died of the disease while on admission; 3 of these patients had choriocarcinoma patients (60%) and one patient with molar pregnancy (6%). Pre eclampsia, a known complication of molar pregnancy was found in only one patient (3.7%).

Preservation of reproductive function was high among the patients who adhered to the follow up plan with prompt return of menstrual functions; though one patient had Asherman's syndrome and was managed with hysteroscopic adhesiolysis. Of the 5 patients that were followed up for more than one year following molar evacuation, four of them (80%)had normal intrauterine pregnancy with three delivering at term.

DISCUSSION

Hydatidiform mole was the most common GTD managed in our centre.[13] In our centre, partial mole was the most common molar pregnancy unlike the study in Iraq in which the complete mole comprised 80% of the molar pregnancy managed in one centre[14]. In this study the majority of the GTDs (82%) managed in this study was molar pregnancy while choriocarcinoma comprises only 18% of the total number of GTD.There was no invasive mole or placental site trophoblastic tumour.The incidence of gestational trophoblastic diseases in this study was 4.3 per 1000 deliveries, while the incidence of molar pregnancy was 3.5 per 1000 deliveries. The incidence of choriocarcinoma was 0.78 per 1000 deliveries. Though this is an institutional study, the figures are higher than the ones reported from Caucasian countries, they are

however lower than the reported figures from Asian countries of 1 in 100 to 300 deliveries [1].

In a 5-year study by Mbamara et al[7] in Eastern part of Nigeria, the majority of GTDs (66%) was choriocarcinoma.[7]Findings similar to our study was seen in Istanbul, Turkey, where the majority of GTDs managed (97%) was hydatidiform moles.[15]In another part of Turkey, Tokat province, 73 cases of GTDs managed over a period of 8 years were all were hydatidiform moles.[16]

Incidence of GTD vary across countries and even within the same geographic zone, different incidences were reported.[15]Results from several centres in Nigeria also confirms that the incidence of GTD varies in different parts of countries. In an 8-year review done by Jimoh et al, in North-central Nigeria, an incidence of 4.1 per 1000 deliveries which was similar to the findings from this study. [17] The incidence from this study was also similar to the study carried out by Mbamara et al[7] in Eastern Nigeriabut lower than the incidence in Northern central part of Nigeria by Amaka.[7,18]The different incidences reported may be due to different case definitions and use of hospital data instead of population-based data.

The most common presentation in this study was vaginal bleeding (85%). This is not surprising as most patients with molar pregnancy presented as complications of early pregnancy. This mode of presentation was also the findings of studies done in other parts of Nigeria.[17, 20]In Malaysia, in a study by Audu et al,[21]vaginal bleeding was the most common presenting symptom in 95% of 102 women studied.

Age is an important reproductive factor influencing the risk of GTD. According to Parazzini et al,[9]extreme of reproductive age has been linked with development of molar pregnancy. [19] In a 10-year review by Audu at al, the peak age of incidence of molar pregnancy was 17.5 years.[21] However, in this study, none of the patient was less than 20 years,the peak incidence was in women within the 25 – 29 age group and this group constitutes 50% of the women in this study. The next major age group was 30 to 34 years (25%). All patients were within the reproductive age group with exception of one patient (5%)who was above 50 years. In Malaysia, the mean age of women with molar was 32.0 ± 7.9 years.[22]We found no statistical significant difference between the ages of the women with molar pregnancy and choriocarcinoma.

Large for date uterus is one of the risk factors for persistent trophoblastic disease.[23, 24]In the study by Nirmala et al,[22] only 17.6% of the patients had large for date uterus while in this study 51% of patients had large for date uterus. [22] The higher incidence of persistent trophoblastic disease seen in this study may not be unconnected with the higher number of patients with large for date uterus (51%) observed in this study. In the study by Nirmala et al[22], 17.6% of the patients had large for date uterus and the incidence of persistent trophoblastic disease was 3.9%.[22]

One of the problems associated with the management of malignancy in many developing countries is late presentation and poor compliance with management plan.[25] Patients present late due to ignorance, poverty, myths and superstitions associated with malignancies. In the absence of universal health insurance, the most common mode of payment in both public and private hospitals in Nigeria is out of pocket which limits access and affordability. With increasing poverty, most women cannot afford the high cost of investigations and payment associated with malignancies. Moreover, cancer is almost synonymous with death in many developing countries.Late presentation is associated with higher incidence of complications and poor outcomes in patients with GTDs. For successful outcomes of molar pregnancy and to prevent complications, early diagnosis is essential

in the management of patients with GTDS. Despite the fact that majority of the patients had vagina bleeding after periods of amenorrhoea, late presentation was common.The mean duration of presentation was 21.5 days after the onset of symptoms.

The incidence of pre eclampsia in this study was low as only one patient had this complication. Unlike the study by Egwuata et al[26] in which preeclampsia occurred in 27% .GTD is one of the few human malignancies that are curable.[27] Irrespective of the type of GTDs, long time monitoring is required even after the patient had attained remissionbecause most recurrences occur within the first six months.[28]During the period of follow up, patients and the partners are counseled to avoid pregnancy. In order to achieve this, effective contraception is offered. In this study, adherence to treatment plan was poor. Majority of the patients especially with hydatidiform moles defaulted after molar evacuation while the patients with choriocarcinoma did not complete the full course of prescribed chemotherapy due to inability to afford the drugs. Poor compliance with chemotherapy was also high as two of the patients with choriocarcinoma did not received any chemotherapy, one had one cycle, one also had two cycles while only one patient with choriocarcinoma had 4 cycles of chemotherapy. Many of them also could not appreciate the importance of prolonged follow up despite counselling and explanation. In the absence of symptoms such as vaginal bleeding with which many of them presented with, they had the illusion that 'all was well'. The combination of poverty and illiteracy contributed to the high mortality seen in this study. The reproductive outcome was good for patients that complied with the follow up regimen. Four of the women were able to get pregnant with three of them having term deliveries.

In conclusion, though GTD are a group of disease with high cure rate in Western countries, sadly this type of success cannot be replicated in our environment due to a combination of ignorance and poverty which makes compliance with treatment difficult. Specialized centres should be established as this is the case in more advanced countries to manage GTD. This will enable health care providers to acquire the expertise due to accumulation of experience. In addition, public education and subsidizing cost of managing malignancies by the government will no doubt encourage many patients to present early and to comply with management plan.

Table 1: Types Of Gtd

Types	Frequency	Percentage
Partial mole	11	40.74
Complete mole	6	22.22
Persistent GTD	5	18.52
Choriocarcinoma	5	18.52
Total	27	100.00

Table 2: Presenting Complaints

	Frequency	percentage
Vaginal bleeding	22	81.5
Abdominal pain	1	3.7
Amenorrhoea	3	11.1
Absence of fetal movement	1	3.7
Total	27	100.0

Table 3: Antecedent Pregnancy

Types Of Pregnancy	Frequency	Percentage
Abortion	7	25.9
Ectopic pregnancy	6	22.2
Term pregnancy	11	40.7
Molar pregnancy	3	11.1
Total	27	100.00

Table 4: Management Options Of Hydatidiform Mole

Management Options	Frequency	Percentage
Suction evacuation alone	18	66.7
Single agent MTX	3	11.1
Single agent Act-D	1	3.7

Table 5: Outcome Of Management

Outcome	Frequency	Percentage
Defaulted	15	55.6
Dead with disease	4	14.8
Alive with no disease	6	22.2
Alive with disease	2	7.4
Total	27	100

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