Profiling Gestational Trophoblastic Disease in a Tertiary Hospital in South-East Nigeria

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Abstract
Background: Gestational trophoblastic disease (GTD) comprises a spectrum of interrelated tumours including complete and partial hydatidiform mole, placental site trophoblastic tumours and choriocarcinoma.
Objective: To evaluate the clinical presentation, management and treatment outcomes of gestational trophoblastic diseases in a tertiary health institution.
Methodology: This was a descriptive study of all cases of gestational trophoblastic diseases managed at Ebonyi State University Teaching Hospital, Abakaliki over a five-year period.
Results: The incidence of GTD was 3.58 per 1000 deliveries. The age range was 19-55 years and the mean age was 33.4±7.4 years. The mean gravidity was 6 and women who are gravida 5 and above accounted for 63.3% of those that presented with GTD. Gestational trophoblastic disease was commonly found in women with blood group O (60%) and 46.7% of cases of gestational trophoblastic disease occured in age group 30-39 while 23.3% of gestational trophoblastic diseases occured in women 40 years and above. The commonest clinical presentation was recurrent vaginal bleeding 96.7%. Suction curettage (66.7%) was the commonest form of treatment offered to those with GTD in EBSUTH. Total Abdominal hysterectomy and chemotherapy was performed only in 10% of the patients. The commonest complication was haemorrhage (40%). Maternal death attributable to GTD was 10%. About 60% of the patients did not turn up for follow up.
Conclusion: Early presentation and proper treatment of this condition is emphasized. There is need for adequate follow-up of these patients.
Key Words: Molar Pregnancy, Trophoblastic, Mortality, Chemotherapy

Introduction
Gestational trophoblastic disease (GTD) comprises a spectrum of interrelated tumours, including complete and partial hydatidiform mole, placental site trophoblastic tumours (PSTT) and choriocarcinoma[1]. Hydatidiform mole is the benign form of trophoblastic disease, which as a potentially malignant condition may progress to the frankly malignant disorders of choriocarcinoma[2]. Despite the rarity of GTD, patients generally have very successful outcomes with overall cure rates in excess of 95%[3].

Complete or classical hydatidiform mole is described as a generalized swelling of the villous tissue, diffuse trophoblastic hyperplasia with variable degrees of cellular atypia[4], with no embryonic or fetal tissue affecting both the syncytiotrophoblast and cytotrophoblast while partial hydatidiform mole is characterized by

Focal swelling of villous tissue, focal trophoblastic hyperplasia and embryonic or fetal tissue affecting only the syncytiotrophoblast[5, 6]. In the majority of complete moles, all of the genetic material is male in origin and results from the fertilization of an empty oocyte lacking maternal DNA. The chromosome count in complete mole is most commonly 46XX and few have 46XY karyotype which results from one sperm that duplicates its DNA, or less frequently from dispermy[7].

Partial hydatidiform mole is often associated with one haploid maternal and two haploid

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paternal sets of chromosomes as a result of dispermic fertilization of a haploid ovum, or a fertilization of haploid ovum with diploid spermatozoa[6]. Partial mole is usually a triploid containing 69XXX or 69XXY Chromosome[7].

Worldwide, there is marked temporal, regional and ethnic variations in the incidence of hydatidiform mole[4, 8]. High incidence of molar pregnancy is reported in China, Malaysia, Singapore, Hong Kong, Indonesia, Philippines, South East Asia, Northern Europe, Middle East, Eastern and Central Africa[1]. The often cited worldwide incidence is between 0.5-2.5 per 1000 deliveries[9]. The frequency of molar pregnancy in western countries is about 1in 1000-1200 pregnancies[10]. In Nigeria, the incidence among Igbo women is 0.82 per 1000 deliveries[11] and generally ranges between 0.8 and 4.88 per 1000 deliveries in Nigeria[12]. The estimated incidence of complete mole is 1 per 1000-2000 pregnancies whereas the incidence of partial mole is around 1 per 700 pregnancies[5] globally.

The incidence of gestational trophoblastic disesae is higher in women younger than 20 years and older than 40 years of age, nulliparous women, patients of low socio- economic status, and in women whose diets are deficient in protein, folic acid, and carotene[13]. The most remarkable findings are that blood group A women impregnated by group O men have an almost 10-fold greater risk of developing choriocarcinoma than group A women impregnated by group A partners. Furthermore, women with blood group AB tend to have a relatively worse prognosis[13]. There is an increased risk of GTD in a woman with spontaneous abortion, the risk being three times higher after two spontaneous abortions[14].

The greater proportion of Ebonyi State is made of the low socio-economic group with tendency towards high parity which favours the occurrence of gestational trophoblastic disease. Moreover, the epidemiology of gestational trophoblastic disease among gynaecological admissions has not been studied and documented in EBSUTH which serves as one of the major referral centres for these low income and high parity groups. This study therefore, aims to describe the epidemiology of gestational trophoblastic disease among gynaecological admissions in EBSUTH which is hoped to reflect the prevalence of the disease in this part of Nigeria.

Methodology
Study Background
Ebonyi State University Teaching Hospital, Abakaliki (EBSUTH) is one of the two tertiary health facilities in Ebonyi State located at Abakaliki, the state capital and receives referrals from all parts of the state and the neighbouring states of Benue, Enugu, Cross-River and Abia. Consultants' gynaecologists with resident doctors run the gynaecological clinics every day of the week. Diagnosis of gestational trophoblastic diseases was made mainly on clinical history, physical examination, ultrasonography, serum â hCG and histopathological examination of obtained specimen where possible. All cases of diagnosed gestational trophoblastic disease are admitted and managed in the gynaecological ward of EBSUTH' Their management is individualized depending on the clinical stage of the disease and the assessed risk level.

Study Design
This was a retrospective study of all cases of gestational trophoblastic disease admitted and managed in the gynaecological ward of EBSUTH over a 5 year period (January 1, 2003 to December 31, 2007). There were a total of 8,383 deliveries and 1,352 gynaecological admissions in the period under review. After obtaining permission from the Ethical Research Committee of the hospital, the case notes of all gestational trophoblastic disease were retrieved from the medical records department and relevant data were extracted. Information collected are related to socio-biological variables(age, parity, gravidity, educational level, blood group and history of antecedent pregnancy) uterine size at presentation, clinical presentation, investigations and treatment options employed, outcome of the treatment options were obtained and analyzed using Epi Info (2005) 3.3.2 version.

Table 1: Trend of Gestational Trophoblastic Disease from 2003 -2007 in EBSUTH, Abakaliki

Years	Number of cases	Number of Deliveries	Prevalence per 1000 deliveries
2003	7	1713	4.09
2004	4	2251	1.78
2005	3	1872	1.6
2006	6	1339	4.48
2007	10	1208	8.28
TOTAL	30	8383	3.58

Results

From January 1, 2003 to December 31, 2007 a total of 8383 deliveries were conducted at Ebonyi State University teaching hospital, Abakaliki and a total of 30 cases of gestational trophoblastic disease were treated and histologically confirmed in the period under review giving a prevalence of 3.58 per 1000 deliveries. A total of 1352 gynaecological cases were admitted into the gynaecological ward and GTD accounted for 2.2% of all gynaecological admissions in EBSUTH in the period under review. The mean age of women that presented with GTD in EBSUTH was 33.4 years ± 7.4 (2SD) and the age range was 19-55 years. The mean gravidity was 6.

Table 1 shows the trend of GTD by year from 2003 to 2007 in EBSUTH. The year 2007 had the highest prevalence of 8.3 per 1000 deliveries followed by 2006 with a prevalence of 4.5 per 1000 deliveries. Table 2 shows the socio-demographic characteristics and reproductive history of patients with gestational trophoblastic disease from 2003 to 2007. One patient (3.3%) was below 20 years and eight patients (26.7%) were in the age bracket of 20-29 years, while 14 patients (46.7%) were between 30-39 years. Seven patients (23.3%) were 40 years and above. Seventy-percent of the patients that presented with GTD in EBSUTH were above 30 years. Nulliparas accounted for 10% of the women that presented with GTD while grandmultiparous women were 46.7%. Para 1-4 women accounted for 43.3% of women with GTD in EBSUTH.

In this study, 15 patients (50%) had abortion in the antecedent pregnancy while 12 patients (40%) had live birth in the antecedent pregnancy. Considering the educational status of the patients, 19 patients (63.3%) of women that presented with GTD had no formal education. Eighteen patients (60%) were of blood group O. Women with blood group A and blood group B accounted for 13.3% and 26.7% of cases of GTD treated in EBSUTH respectively. Table 3 shows the clinical features of GTD in patients that presented at the centre. Twenty nine patients (96.7%) presented with vaginal bleeding while 11 patients (36.7%) presented in the hospital with passage of vesicles. Fundal height was greater than gestational age in 17 patients (56.7%). The presence of theca lutein cyst was found in 26.7% of the cases that were treated while ultrasonography aided in the diagnosis of GTD in 73.3% (95% CI 54.1-87.7) of all the cases seen. Pre-eclampsia and hyperemesis gravidarum complicated 16.7% and 13.3% of all the cases of GTD managed in EBSUTH respectively during the study period.

Table 4 shows the various management options employed in the treatment of gestational trophoblastic disease from 2003-2007. Twenty patients (66.7%) had suction curettage alone with no further treatment while four patients (13.3%) had both suction curettage and chemotherapy. Chemotherapy alone was the method of choice in three patients (10%) while total abdominal hysterectomy and

Table 2: Social-Demographic Characteristics and Reproductive History of Patients With Gestational Trophoblastic Diseases in EBSUTH from 2003-2007.

Characteristics	Number	%	95% CI
Ages (Years)			
<20	1	3.3	0.1-17.2
20-29	8	26.7	12.3-45.9
30-39	14	46.7	28.3-65.7
=40	7	23.3	9.9-42.3
Educational Level			
None	19	63.3	43.9-80.1
Primary	2	6.7	0.8-22.1
Secondary	7	23.3	9.9-42.3
Tertiary	2	6.7	0.8-22.1
Parity			
Nullipara	3	10	2.1-26.56
1-4	13	43.3	25.5-62.6
=5	14	46.7	28.3-65.7
Antecedent pregnancy			
Abortion	15	50	31.3-68.
Live birth	12	40	22.7-59.4
Molar Pregnancy	2	6.7	0.8-22.1
Ectopic Pregnancy	1	3.3	0.1-17.2
Blood group			
O	18	60	40.6-77.3
A	4	13.3	3.8-30.7
B	8	26.7	12.3-45.9
AB	-	-	-

chemotherapy was the treatment of choice in 10% of the patients. Table 5 shows the complications associated with GTD. Twelve patients (40%) had severe haemorrhage defined as blood loss above 1000ml in this study. Twenty percent of the patients that presented with GTD had choriocarcinoma while 6.7% of the cases of GTD seen were complicated by sepsis. Three patients (10%) died from complications of GTD. From this study, sixty three point three percent (63.3%) of women that presented with GTD were gravida 5 and above while gravida 2-4 and primigravidas accounted for 30% and 6.7% of all the cases of GTD seen in EBSUTH in this study respectively. This study shows that hydatidiform mole accounted for 80% of GTD seen in EBSUTH with complete mole accounting for 60 % while partial mole was seen in 20% of the cases. Six patients (20%) were histologically confirmed to have choriocarcinoma.

Table 6 shows that 60% of the patients did not come back for any sort of follow-up after their discharge from the hospital, while only a patient (3.3%) was followed up for over a year.

Discussion

Gestational trophoblastic disease refers to a spectrum of proliferative disorders of the

Table 3: Clinical Features of Gestational Trophoblastic Diseases in Patients at EBSUTH from 2003-2007.

Characteristics	Number	%	95% CI
Passage of vesicles	11	36.7	19.9-56.1
Vaginal bleeding	29	96.7	82.8-99.9
Theca lutein cyst	8	26.7	12.3-45.9
USS confirmation of GTD	22	73.3	54.1-87.7
Hyperemesis gravidarum	4	13.3	3.8-30.7
Haemoptysis	2	6.7	0.8-22.1
Cough	6	20	7.7-38.6
Pre-eclampsia	5	16.7	5.6-34.7
Fundal height > GA	17	56.7	37.4-74.5

USS= Ultrasound scan; GA= Gestational age; GTD= Gestational trophoblastic disease.

Table 4: Management Options Employed in the Treatment of GTD At EBSUTH from 2003-2007.

Treatment modalities	Number	%	95% CI
Suction Curettage alone	20	66.7	47.2-82.7
Suction Curettage/ Chemotherapy	4	13.3	3.8-30.7
Chemotherapy alone	3	10.0	2.1-26.5
TAH/ Chemotherapy	3	10.0	2.1-26.5
TAH alone	-	-	-

TAH= Total Abdominal hysterectomy.

placental trophoblast, with a wide range of histologic appearances and clinical behaviours[15]. The incidence of gestational trophoblastic disease recorded in this study was 3.58 per 1000 deliveries, which is higher than the often cited world wide incidence of 0.5 to 2.5 per 1000 deliveries [2] and also higher than 0.82 per 1000 deliveries reported by Egwuatu and colleagues in women from the same geopolitical zone as ours [11]. However, the incidence of gestational trophoblastic disease reported in Nigeria 0.87-4.88 per 1000 deliveries[12] is comparable with the findings in this study.

The incidence of hydatidiform mole in this study was 2.86 per 1000 or 1 in 349 deliveries which is comparable with 2.4 per thousand (or 1 in 416) deliveries recorded by Eniola and colleagues[16] in Ife and the 1 in 332 deliveries reported by Obiechina and colleagues[17] in women at Onitsha , Nigeria but higher than 1 in 676 deliveries reported for Saudi Arabia[18]. The incidence of complete hydatidiform mole in this study was 2.15 per 1000 deliveries lower than 3.42 per 1000 deliveries reported by Dan in Uganda[19], while that of partial hydatidiform mole was 0.72 per 1000 deliveries. The incidence of Choriocarcinoma of 0.72 per 1000 deliveries, found in this review compares favourably with the 0.5 per 1000 deliveries reported by Moodley and colleagues in South Africa[20] and earlier studies in Ogbomoso, Nigeria (0.99 per 1000 deliveries)[21] but lower than those reported from of Lagos[22] and Ibadan[23].

The differences in the incidence of gestational trophoblastic disease reported in this study compared to similar studies done elsewhere could be explained by the significant variations in geographic spread of the disease as well as factors of race, socio-economic status, nutritional variations among people studied and the concept of variable host resistance[1,24-27]. Maternal age is the most consistent risk factor for gestational trophoblastic disease in every region and ethnic group in which it has been studied with most studies showing a significant incidence in risk in women delivering above age 35 years and a further 10 fold increase beyond age 40 years[28]. In this study, 14 patients (46.7%) were between ages 30-39 years while 23.3% were 40 years and above.

Increasing parity and gravidity were confirmed in this study as risk factors for the development of gestational trophoblastic disease. Majority of the cases (90%) in this study occurred in parous women. However, it is difficult to separate the influence of gravidity/parity from that of age on gestational trophoblastic disease. These findings were consistent with other studies[1,29]. Vaginal bleeding of varying severity is the commonest feature of gestational trophoblastic disease[4, 8]. In this study, 96.7% of the patients that presented with gestational trophoblastic disease in EBSUTH had vaginal bleeding. This is consistent with 80%

Table 5: Complications in Patients Managed for GTD in EBSUTH from 2003-2007.

Complications	Number	Percentage
Severe haemorrhage (EBL=1000ml)	12	40
Sepsis	2	6.7
Mortality	3	10

EBL= Estimated blood loss.

Table 6: Pattern of Follow-up for GTD in EBSUTH.

Follow-up	Number	%	95% CI
No follow-up	18	60	40.6-77.3
Follow-up < 1 month	3	10	2.1-26.5
Follow-up 1-6 months	6	20	7.7-38.6
Follow-up 7-12 months	2	6.7	0.8-22.1
Follow-up 1-2 Years	1	3.3	0.1-17.2

to 98.63% reported in other studies[24,25,30]. Abdominal pain, vomiting, increased blood pressure and anaemia were other important presenting symptoms, thus showing the importance of these symptoms in the diagnosis of hydatidiform mole. These clinical signs and symptoms are particularly relevant for those patients presenting late.Theca lutein cysts, which are due to stimulation of the ovaries by high level of hCG is one of the clinical features of gestational trophoblastic disease [1]. In this study, eight patients (26.7%) were found to have theca lutein cysts and three patients had bilateral theca lutein cyst. This was comparable with 32.7% reported by Dan in a hospital based study in Uganda[19].

Ultrasonography is the diagnostic method of choice in some centres because of its reliability, sensitivity and safety [1]. However, histopathological examination of products of conception remains the current gold standard for the identification of GTD[31]. Ultrasonography contributed in the diagnosis of gestational trophoblastic disease in 88.5 to 95% of the cases of GTD in other studies[24, 25]. In this study ultrasonography contributed in the diagnosis of GTD in 73.3% of women that presented with GTD in EBSUTH. The serum level of â-hCG is markedly elevated in GTD and when combined with urine hCG both in neat and dilute has proved useful in the diagnosis and follow up of GTD. However, hCG estimations cannot be dependent upon alone for absolute diagnosis of GTD, although they usually add strong supporting evidence [1]. In this study, serum hCG was found to be elevated in all the patients that presented with GTD and about 10% of the patients had serum hCG greater than 100,000 miu/ml.

The passage of vesicles in the uterine discharge is conclusive evidence but rarely occurs until abortion is eminent[1]. In this study 36.7% of patients with GTD actually confirmed passage of vesicles. One of the striking features of GTD is that of the uterus being too large for the period of amenorrhoea. This sign is present in only 50% of cases; sometimes the uterus is smaller than normal, especially if the mole dies[1]. In this study the uterine size was larger than the gestational age in 56.7% of women that had GTD. It is equally of interest to note that an excess of blood group A or AB has been reported in a series of 219 diseases in Malaysia[32]. There is some evidence that serologic incompatibilities between husbands and wives may be important. Studies have shown excess risks for group A women with group O husbands[33] as well as for group O women with group A husbands [34]. In this study, 60% of patients with GTD were blood group O. This was confirmed by Abdellatif and colleagues who reported an incidence of 62% of women with GTD having blood group O. Similar findings have been reported by other researchers[35].

Socio-economic and nutritional factors have been cited as contributing to the high incidence of gestational trophoblastic disease in some populations[14]. Studies from Italy and United States suggest that the risk for complete molar pregnancy progressively increased with decreasing levels of consumption of dietary carotene and animal fat[36]. In studies in developing countries, cases were found in association with lower socio-economic status. This was consistent with the findings in this study in which 60% of those affected are peasant farmers and 63.3% of women afflicted with GTD had no formal education. Education has been used as a good proxy for the estimation of socio-economic status in any given population[37]. Anaemia, consequent upon prolonged vaginal bleeding was very high in this review. Severe anaemia (PCV< 18%) was found in 53.3% of women with GTD and was indirectly linked with

all the maternal deaths of 10% recorded in this review. The unusually high maternal mortality and morbidity in this study was due to late presentation of the patients in moribund condition.

Complete hydatiform mole and partial hydatidiform mole is both potentially malignant [10]. However, complete hydatidiform mole has higher degree of propensity to become malignant compared to partial mole. The risk of gestational trophoblastic neoplasia from partial hydatidiform mole is less than 5-10% and that of complete mole is 20%[10]. All the choriocarcinoma found in this study occurred denovo after a live birth and one, following an ectopic pregnancy. Transformation from complete mole or partial mole to choriocarcinoma and a repeat hydatidiform mole were not observed in this study apparently because 60% of patients treated for GTD in this study did not have any form of follow-up and only a patient had follow-up for more than one year despite the presence of high risk factors for malignant transformation such as pre-evacuation uterine size larger for gestational period, age more than 40 years, bilateral theca lutein cyst of more than 6cm size and pre-evacuation hCG level more than 100,000 miu/ml[38] which were present in some of the patients in this study.

The method of choice for the treatment of hydatidiform mole is suction curettage[24]. However, certain authors have reported decreased risk for the development of persistent trophoblastic disease 10-15% when suction curettage is followed by prophylactic chemotherapy in high risk patients[24,25]. Hysterectomy may also be performed with the mole in situ for women aged 40 years and over who have completed their families[1]. In this study, 66.7% of patients treated for GTD had suction curettage while 13.3% had both suction curettage and chemotherapy for patient with high risk diseases and 10% of the patients had total abdominal hysterectomy and chemotherapy. Ten percent of the patients treated for GTD had chemotherapy alone. The factors considered for instituting chemotherapy are: high levels of hCG of more than four weeks post evacuation (serum> 20,000 IU/L; urine > 30,000 IU/24 hours), persistent uterine haemorrhage, progressively rising serum beta hCG level at any time post evacuation, any detectable hCG not showing tendency to extinction four to six months post evacuation, evidence of brain, renal, hepatic, gastrointestinal tract or pulmonary metastases with any level of hCG[10]. The use of prophylactic chemotherapy in some of the patients was necessary because majority of the patients with high risk disease do not turn up for or are lost to follow up.

This study shows that gestational trophoblastic disease is still a cause of significant morbidity and mortality in our environment as opposed to what obtains in developed countries where early diagnosis of the disease by ultrasonography and subsequent treatment before major bleeding episodes occur is the norm. The need for early presentation in the hospital and diagnosis of the disease with subsequent initiation of the correct treatment to reduce morbidity and mortality associated with this disease cannot be over emphasized. The fact that more than 60% of the patients with GTD refused to turn up for follow up despite adequate counselling strongly emphasizes the need for the establishment of GTD referral centres and effective follow-up facilities.

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