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RESEARCH

Gestational trophoblastic disease managed at Grey's Tertiary Hospital: a five-year descriptive study

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Background: A study was undertaken to describe the outcomes of gestational trophoblastic disease (GTD) and to determine the influence of antecedent pregnancy, the distance travelled by patients to Grey's Hospital (GH), and HIV status on the disease and clinical outcomes.
Methods: The files of all patients admitted to GH with a diagnosis of GTD from January 2013 to December 2017 were retrospectively reviewed.
Results: Sixty-three files were analysed. Thirty-six (57.1%) patients travelled < 80.5 km and 27 (42.9%) travelled ≥ 80.5km to GH. Eighteen (29%) patients were HIV positive with CD4 count ≥ 200 cells/mm^3. Twenty-six (41.3%) patients had antecedent term pregnancies, 12 (19.1%) and 11 (17.5%) had antecedent hydatidiform molar pregnancy (HMP) and spontaneous miscarriage respectively. Fifty (79.4%) patients presented with vaginal bleeding. Thirty (47.6%) patients were diagnosed with molar pregnancy and 33 (52.4%) patients had gestational trophoblastic neoplasia (GTN). Fourteen (42.4%) patients received single-drug chemotherapy while 19 (57.6%) received multidrug chemotherapy with a remission rate of 90.9%. The final outcome of the study patients was 41 (65.1%) alive without disease, 2 (3.2%) alive with disease, 3 (4.8%) who died and 17 (27%) lost to follow-up. Antecedent term pregnancy was associated with delayed diagnosis, while HMP was associated with early diagnosis of GTN. Long distance travelled by patients was associated with statistically significant levels of poor compliance and final outcomes. HIV-positive status was associated with higher FIGO staging.
Conclusions: The study showed that antecedent pregnancy, HIV status and distance travelled by the patients have an influence on the diagnosis, staging and treatment outcomes of GTN respectively. However, more prospective research is needed to further substantiate these findings.

Keywords: antecedent pregnancy, distance, gestational trophoblastic disease, HIV status

Introduction

GTD mainly affects women of reproductive age and has a wide range of treatment guidelines with varying outcomes. It represents a group of tumours arising from the trophoblastic tissue of the placenta ranging from benign hydatidiform molar pregnancy (HMP) to malignant gestational trophoblastic neoplasia (GTN). GTN includes invasive mole, choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). While histologic confirmation is desirable, it is not essential for the currently used clinical classification.[1]

The incidence of GTD has been reported to be higher in Asian countries than in European countries. Most countries do not have GTD registry and data are being compiled mainly from hospital reports and case series, which makes it difficult to determine the incidence denominators.[2] A study from a single referral institution in South Africa estimated the incidence of 1.2/1 000 deliveries for molar pregnancy and 0.5/1 000 deliveries for GTN.[3]

A study by Clark *et al*. in the United States found that long distance (≥ 50 miles equivalent to ≥ 80.5 km) travelled by patients for GTN treatment was associated with an increased risk of presenting with high-risk disease and longer period between antecedent pregnancy and GTN diagnosis.[4] Our aim was to explore the impact of the distance travelled by patients in our study population.

Some 60% of GTN follows HMP, while 30% and 10% follow spontaneous miscarriage and normal/ectopic pregnancies respectively.[1] The median gestational age at diagnosis of complete mole has decreased from 12 to 9 weeks and vaginal bleeding declined as a presenting symptom from 84% to 46% in high-income countries.[5] However, the typical vesicular appearance of complete mole may not be seen on ultrasound in the early first trimester, resulting in molar pregnancies being frequently misdiagnosed as incomplete miscarriages.[6] The Royal College of Obstetricians and Gynaecologists recommends that tissue obtained at the time of managing spontaneous miscarriage should be examined histologically to confirm pregnancy and to exclude missed ectopic pregnancy and unsuspected gestational trophoblastic disease.[7] However, this recommendation is expensive and not practical for low-income countries. A study by Seckl *et al*. recommended the measurement of the urine or serum human chorionic gonadotropin (hCG) levels between three and four weeks post-termination of pregnancy to screen for possible GTD and institute early interventions as necessary.[8] This approach is more practical and cost-effective. Choriocarcinoma, PSTT and ETT can develop months to years after antecedent pregnancy and the presenting symptoms vary according to

the extent of the disease. Atypical presentations of the disease may pose a diagnostic dilemma to the unsuspecting clinician.[9]

Two local studies found that human immunodeficiency virus (HIV) is associated with more advanced disease at presentation, and patients with CD4 count < 200 cells/mm^3 have a significantly worse prognosis than women without HIV infection.[10,11] We wished to investigate this issue in our study in view of the progress that has been made by the country in the treatment of HIV in the past decade.

The ultra-high-risk group (a subgroup with a risk score ≥ 12, patients with liver/brain or extensive metastases) tends to respond poorly when treated with a standard first-line multidrug chemotherapy due to severe marrow suppression leading to bleeding, septicaemia and multiple organ failure. Starting with a lower dose and a less intensive regimen approach for 1–3 weeks before embarking on the usual chemotherapy regimen may prevent this undesirable outcome.[12]

The primary objective of the study was to describe the outcomes of gestational trophoblastic disease in patients treated at Grey's Hospital per stage and treatment received. The secondary objectives were to determine the influence of antecedent pregnancy, the distance travelled by patient to Grey's Hospital and HIV status on the stage of the disease and clinical outcomes.

Methods

Following ethical approval by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, Ethics Reference number 368/2018, Grey's Hospital granted its permission for the study to be conducted. Grey's Hospital is in the Midlands of KwaZulu-Natal province, providing tertiary services to approximately 4.5 million people that attend second-level regional, first-level district hospitals and primary health care clinics in Area 2. Eighty files of patients who were admitted with the diagnosis of GTD from January 2013 to December 2017 were retrieved from the hospital registry and reviewed.

Data on patients' demographic characteristics, HIV status, past and current obstetrics and gynaecological history, GTD management were collected for analysis. Ten files were excluded from the study after ruling out the admission diagnosis of GTD and seven files with confirmed GTD were excluded due to inadequate information to contribute to the objectives of the study.

The area of residence was categorised into rural, township and urban areas based on the physical address in the patient's file. To estimate the distance travelled by the patients referred to Grey's Hospital, the referring hospital was used as the point of reference. The Google Maps app was used to calculate the distance using Grey's Hospital as the current position and referring institution as the destination point. The distance of ≥ 80.5 km was considered significantly long as per reference from the study that was conducted in the United States of America.[4]

GTN staging was based on the 2000 FIGO staging and classification of GTN as well as FIGO/WHO scoring system based on prognostic factors.[13] Patients with a score ≥ 12 as well as patients with FIGO stage 4 were classified under 'ultra-high risk disease'.[12]

Data were entered on a Microsoft Excel spreadsheet (Microsoft Corp, Redmond, WA, USA), and exported to Stata 13 software for statistical analysis (StataCorp, College Station, TX, USA). Descriptive summary measures included proportions and percentages, means with standard deviations and medians with ranges. Fisher's exact test was used to analyse categorical data. A p-value < 0.05 was regarded as indicating statistical significance.

Results

Sixty-three files of patients with the diagnosis of GTD met the study inclusion criteria for analysis. The mean age of the patients was 25.6 years with a range of 15–53 years. Seventeen (27%) were < 20 years of age while 38 (60.3%) and 8 (12.7%) were in the age category of 20–35 and ≥ 36 years respectively. Thirty-nine (61.9%) patients came from the rural areas, followed by 20 (31.8%) from the township and four (6.4%) from the urban areas.

District hospitals were the first point of healthcare contact for 38 (60.3%) patients, while 17 (27%) and 8 (12.7%) patients visited primary health care and regional institutions respectively. Grey's Hospital received 40 (63.5%) patients referred from the district hospitals and 23 (36.5%) from the regional hospitals. Thirty-six (57.1%) patients travelled < 80.5 km and 27 (42.8%) travelled ≥ 80.5 km from their referring hospitals to Grey's Hospital.

Forty-five (71%) patients were HIV-negative and 18 (29%) were HIV-positive. All 18 HIV-positive patients had CD4 count ≥ 200 cells/mm^3. Twelve (66.7%) patients were on antiretroviral (ARV) treatment for more than six months while four (22.2%) and two (11.1%) were on treatment for less than six months and not on treatment, respectively. Nine (50%) of the HIV-positive patients had unknown viral load and only two (11.1%) had unsuppressed viral load.

Thirty-nine (61.9%) patients were multigravidas while 24 (38.1%) were primigravidas. Fourteen of the 24 primigravidas were symptomatic for the first time when the diagnosis of GTD was made, therefore no antecedent pregnancy event could be allocated to them (Table 1).

Fifty (79.4%) patients presented with vaginal bleeding while 10 (15.9%), 10 (15.9%), 6 (9.5%) and 4 (6.35%) patients presented with amenorrhoea, rising β-HCG, thyroid symptoms and hyperemesis gravidarum, respectively. Three other patients presented with low abdominal pain and two with cardiovascular symptoms. There was overlapping of presenting symptoms in other patients.

Twenty-eight (93.3%) of the 30 hydatidiform molar pregnancies were surgically managed with suction curettage and 2 (6.7%) had primary hysterectomies.

Fourteen (42.4%) patients with GTN were treated with single-drug chemotherapy, methotrexate, while 19 (57.6%) received multidrug chemotherapy. The multidrug regimen consisted of etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMACO). No treatment modification was done for all 11 ultra-high-risk GTN patients. No secondary chemotherapy was required in 27 (81.8%) patients, while 3 (9.1%) patients required second- and third-line chemotherapy. Twenty-seven (81.8%) patients received two consolidation cycles while two (6.1%) and one (3%) received three cycles and one cycle, respectively.

One patient with WHO stage 1 disease in the GTN group was offered a primary hysterectomy and two (6.1%) had hysterectomies as secondary treatment. Two (10.5%) of the 19 GTN patients with distant metastasis had surgery for metastatic disease. Uterine artery embolisation was done in four (12.1%)

Table 1: Antecedent pregnancy and index pregnancy characteristics

Variable	Frequency	Percentage
Antecedent pregnancy:		
HMP	12	19.0
Spontaneous miscarriage	11	17.5
Term pregnancy	26	41.3
None	14	22.2
n	63	
Type of GTD:		
Complete HMP	28	44.4
Partial HMP	2	3.2
Post-molar GTN	11	17.5
Clinical/imaging based GTN	15	23.8
Choriocarcinoma on histology	7	11.1
n	63	
β-HCG at diagnosis of GTD:		
$< 10^3$	3	4.7
10^3–10^4	4	6.3
10^4–10^5	17	27.0
$> 10^5$	39	62.0
n	63	
Interval between antecedent pregnancy and diagnosis of GTN (weeks):		
< 8	9	27.3
8–12	8	24.2
13–16	6	18.2
> 16	10	30.3
n	33	
GTN FIGO stage:		
I	14	42.4
II	0	
III	12	36.4
IV	7	21.2
n	33	
WHO risk score:		
≤ 6	13	39.4
7–11	11	33.3
≥ 12	9	27.3
n	33	

GTD = gestational trophoblastic disease; HMP = hydatidiform molar pregnancy; GTN = gestational trophoblastic neoplasia; β-HCG = beta-human chorionic gonadotropin; FIGO = International Federation of Gynaecology and Obstetrics; WHO = World Health Organization.

of the GTN group and two (6.1%) chemotherapy central lines were inserted by the interventional radiology department.

The remission rate was 90.9% in the GTN group. Three (9.1%) out of 33 patients defaulted treatment before remission was achieved.

The overall outcome of 63 patients with GTD after first-line treatment was 47(74.6%) remission, two (3.2%) patients were resistant to treatment and 14 (22.2%) patients defaulted. Forty-two (68.8%) patients were followed up for ≤ 12 months, one required > 12 months' follow-up and 18 (29.5%) failed to attend post-treatment remission follow-up. Four (6.6%) patients relapsed, with two (3.3%) relapsing in < 6 months. The final outcome of the study patients was 41 (65.08%) alive without disease, 2 (3.17%) alive with disease, 3 (4.8%) who had died from the disease and 17 (27%) lost to follow-up (Table 2).

Thirty (90.9%) chemotherapy-related haematological adverse events were documented in the study. Other documented complications included 28 (84.8%) bleeding complications, 4 (12.1%) dermatological and 5 (15.2%) other complications. ECOG toxicity grade 2 and 3 was equally documented in 27 (81.8%) complications, followed by 11 (33.3%) grade 4 toxicity and 5 (15.2%) grade 1 toxicity. Most ECOG grade 3–4 toxicities were related to the haematological system. HIV status of the patients who received a single-drug versus multidrug regimen did not show statistical significance in relation to the ECOG grade of toxicity with Fisher's exact test p-value = 0.381, $p = 0.333$ and $p = 0.475$ for grades 2, 3 and 4, respectively (Table 2).

The type of antecedent pregnancy did not have a statistically significant influence on the FIGO stage and WHO risk score. Antecedent HMP was associated with early diagnosis of GTN < 8 weeks in 8 out of 12 patients and previous term pregnancy was associated with delayed diagnosis > 16 weeks in 6 out of 8 patients ($p = 0.001$). There was no statistically significant association between antecedent pregnancy and the number of chemotherapy cycles received to remission, outcome after first-line treatment and the final outcome (Table 3).

The overall outcome after first line of treatment was statistically significant in 31 (86.1%) of 36 patients who travelled < 80.5 km achieving remission compared with 14 (51.8%) of 27 patients in the > 80.5 km group. The default rates were 11.1% in the group that travelled < 80.5 km vs. 37% for patients who travelled > 80.5 km ($p = 0.036$). The same trend was observed on the final outcome where 40.7% of patients in the > 80.5 km group were lost to follow-up compared with 16.7% in the < 80.5 km group ($p = 0.014$).

Twelve out of 24 (50%) HIV-negative patients were staged to FIGO stage 1 and 5 (55.6%) out of 9 HIV-positive patients were assessed and allocated to FIGO stage 4 disease, which was statistically significant ($p = 0.023$).

Discussion

Our retrospective study involved 63 patients with GTD. The mean age was 25.6 years, which was in line with a local study that documented a mean age of 28.5 years.[3] Although the literature documented extremes of age as the risk factors for GTD,[14] only 12.7% and 27% of the study patients were in the category of > 35 years and < 20 years, respectively. The majority of the patients (60.3%) presented to the district hospitals as their first point of contact, while only 27% went to the primary health care institutions. This indirectly highlighted the underutilisation of primary health care institutions, which are meant to be the first point of contact of the community for health services.

Our study did not find a statistically significant association between the distance travelled by patients and the FIGO stage, WHO risk score, the interval between antecedent pregnancy and the diagnosis of GTN, as well as the number of chemotherapy cycles to remission. However, long distance (≥ 80.5 km) was associated with statistically significant default trends by patients. The overall outcome after first line of treatment was associated with high default rates in the long-distance travelling group ($p = 0.036$). Although none of the three deaths occurred in the long-distance travelling group, 40.7% of patients in this group were lost to follow up ($p = 0.014$). Our results

Table 2: Treatment modalities and outcomes of gestational trophoblastic disease

Variable	Frequency	Percentage
Primary chemotherapy:		
Single drug	14	42.4
Multidrug	19	57.6
n	33	
Secondary chemotherapy:		
None	27	81.8
Second line	3	9.1
Third line	3	9.1
n	33	
Primary surgical treatment:		
None	32	50.8
Abdominal hysterectomy	3	4.8
Suction curettage	28	44.4
Other	0	
n	63	
Secondary surgical treatment:		
None	61	96.8
Abdominal hysterectomy	2	3.2
n	63	
Interventional radiology procedure:		
None	27	81.8
Uterine artery embolisation	4	12.1
Other	2	6.1
n	33	
Number of chemotherapy cycles to remission:		
≤ 6	10	30.3
7–10	14	42.4
> 10	6	18.2
Defaulted treatment	3	9.1
n	33	
Outcome after first-line treatment:		
Remission	47	74.6
Resistant	2	3.2
Lost to follow-up	14	22.2
n	63	
Follow up post-remission:		
≤ 12 months	42	68.9
> 12 months	1	1.6
Lost to follow-up	18	29.5
n	61	
Final outcome:		
Alive without disease	41	65.1
Alive with disease	2	3.2
Died from disease	3	4.8
Lost to follow-up	17	27.0
n	63	

differed from the study by Clark *et al*., which found that the long distance travelled by patients to receive treatment for GTN was associated with delay in presentation and high-risk disease, with no difference in recurrence risk.[4] The fact that 27% of patients were lost to follow-up precludes recurrence rate analysis in

Table 3: Impact of distance travelled by patients, HIV status and antecedent pregnancy on gestational trophoblastic disease

Variable	n *(%)*	Distanced travelled	HIV status	Antecedent pregnancy
FIGO GTN stage:		0.128	0.023	0.052
1	14 (42.4)			
2	0			
3	12 (36.4)			
4	7 (21.2)			
n	33			
WHO GTN risk score:		1.000	0.133	0.053
≤ 6	13 (39.4)			
7–11	11 (33.3)			
≥ 12	9 (27.3)			
n	33			
Interval between antecedent pregnancy and diagnosis of GTN:		0.482	0.729	0.001
< 8 weeks	9 (27.3)			
8–12 weeks	8 (24.2)			
13–16 weeks	6 (18.2)			
> 16 weeks	10 (30.3)			
n	33			
Outcome after first-line treatment:		0.036	1.000	0.899
Remission	47 (74.6)			
Resistant	2 (3.2)			
Defaulted	14 (22.2)			
n	63			
Final outcome:		0.014	0.944	0.177
Alive without disease	41 (65.1)			
Alive with disease	2 (3.2)			
Died from disease	3 (4.7)			
Died from other causes	0			
Lost to follow-up	17 (27)			
n	63			

HIV = human immunodeficiency virus; FIGO = International Federation of Obstetrics and Gynaecology; WHO = World Health Organization; GTN = gestational trophoblastic neoplasia.

our study. Most importantly, these findings highlight the unmet need for follow-up programmes best suited to our socioeconomically diverse population.

Our study found that antecedent pregnancy statistically influenced the interval of the diagnosis of GTN ($p = 0.001$). Antecedent HMP was predominantly associated with early diagnosis of GTN compared with other antecedent pregnancies. This was mainly due to close follow-up with β-HCG post-suction curettage. Antecedent term pregnancy in particular was associated with delayed diagnosis of GTN. Fourteen (22.2%) primigravidas were diagnosed with GTD, which was consistent with the previous literature findings of 18.8%.[3] Three of the 33 (9.1%) patients with GTN were primigravidas who presented with metastatic disease. This finding confirmed the FIGO guideline that GTN can be diagnosed on the basis of clinical, biochemical and imaging findings, without histological confirmation.[1] Antecedent pregnancy, however, did not statistically influence FIGO staging, WHO risk scoring and final outcomes of the of the patients in our study.

Altogether, 27% of patients with GTN were HIV-positive and they all had a CD4 count above 200 cells/mm^3. HIV status was found to have a statistically significant influence on the FIGO staging in our study. Only 8.3% of HIV-negative patients were diagnosed with stage IV disease compared with 55.6% of HIV-positive patients ($p = 0.023$). Among HIV-negative patients, 50% presented with FIGO stage I disease. However, HIV status did not show a statistical significance on the WHO risk scoring, interval between antecedent pregnancy and diagnosis of GTN, number of chemotherapy cycles to remission and outcomes of treatment. These findings were consistent with previous local studies with regard to HIV-positive patients with CD4 count $\geq$ 200 cells/mm^3.[10,11] Our study did not find a statistically significant influence of HIV status on ECOG toxicity grade of complications in both groups of patients receiving single-drug and multidrug chemotherapy. However, we observed a clinical trend of higher rates of ECOG toxicity grades in the HIV-negative group compared with the HIV-positive group. These results need to be interpreted with caution given the type of study, sample size and the fact that there was no standardised tool for documenting treatment complications.

The retrospective nature of the study makes it susceptible to bias. The sample size was small, which impacts on statistical significance analysis. However, the study was the first analysis of gestational trophoblastic disease in our institution and highlighted gaps in care to allow improvement in our treatment protocols and surveillance tools. It will also contribute to local literature and may be relevant to other low-income settings.

Conclusion

Vaginal bleeding continues to be the most common presenting symptom of GTD. Healthcare facilities must exclude GTD in all postpartum and post-miscarriage patients who present with persistent vaginal bleeding. Long distance from base hospital is associated with increased rates of loss to follow-up. Clinicians, social work professionals and patient transport departments need to work together to draft flexible protocols to accommodate patients with complex socioeconomic characteristics. More than half of HIV-positive patients present with advanced FIGO stage of the disease. More research is needed on the GTD in HIV-positive patients.

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