CLINICAL-PATHOLOGICAL CHARACTERISTICS AND FACTORSASSOCIATED WITH MORTALITY IN PATIENTS MANAGED FORGESTATIONAL TROPHOBLASTIC NEOPLASIA IN KENYATTA NATIONALHOSPITAL,2012 – 2020. A CROSS-SECTIONALSTUDY.

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2021

DECLARATION

This is to declare that this research report is my original work and has not been presented inanyinstitution leadingtothe award of adegreeoranyother award.

Signature:  **.....Date:**8/11/21.....

Prof.Eunice Jeptoo Cheserem

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DEDICATION

To my loving daughters: Beverly, Winnie, Eva and Karen who have been my source ofencouragement and support during the period of my Fellowship in Gynaecology OncologyProgramme.

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SUPERVISORS'DISSERTATIONAPPROVAL

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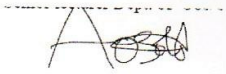

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LISTOFABBREVIATIONS

CHM-Complete hydatidiform mole

CCM-Choriocarcinoma

CT-Computedtomography

EMACO–Etoposide,methotrexate,actinomycin D,cyclophosphamide,andvincristine

ETT-Epithelioidtrophoblastictumour

FAEV– Floxuridine,dactinomycin,etoposideandvincristine

HMs–Hydatidiformmoles

FIGO-InternationalFederationofGynaecologists andObstetricians

GTD - Gestational trophoblastic

disease**GTN** - Gestational trophoblastic

neoplasia**hCG**-

Humanchorionicgonadotropin

IM–Invasivemole

KNH-KenyattaNationalHospital

KNH/UoN ERC – Kenyatta National Hospital/University of Nairobi Ethics and ResearchCommittee

MRI-MagneticResonanceImaging

PHM-Partialhydatidiformmolar

PSTT -Placentalsitetrophoblastic tumour

OPERATIONALDEFINITIONS

RecurrentGTN: RecurrentGTNisatumourthatrecurs aftertreatment.

Ultra-high riskGTN:GTNwithWHO riskcategory>13.

Salvagetherapy: Istherapygivenafteranailmentdoesnotrespondtostandardtherapy.

Abnormalpelvicultrasound: Presenceofamass/vesicles/oranytissuein theuteru

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ABSTRACT

Background: Gestational trophoblastic neoplasia (GTN) comprises of invasive mole (IM),choriocarcinoma(CCM),placentalsitetrophoblastictumour(PSTT)andepithelioidtrophoblastic tumour (ETT). Choriocarcinoma is the most common tumour in this categoryand more fatal than the rest. Little is known about GTN in the developing countries includingthe East African region. This study aims to determine the spectrum of GTN affecting thepopulationseekingmanagementinatertiaryhospitalinKenyaandthemortalityratesassociatedwith the disease.

Objective: Todeterminetheclinical-pathologicalcharacteristics,themortalityrateandfactors associated with mortality in patients managed for GTN in Kenyatta National Hospital(KNH).

Methodsandmaterials

Studydesign andsite: This wasadescriptivecross-sectionalstudyconductedinKNH.

Participants and methods: The study population consisted of women with a documenteddiagnosis of GTN, fully or partly managed at KNH in the period 2012 to 2020. Datawerecollectedbyreviewingpatients'files.Thepatientswithundocumentedoutcomeswereexcluded from the study. Clinic and admission registerswere used to generate a list ofpatientsdiagnosedwithGTNforparticipationinthestudy.Patients'chartswerereviewedand data abstracted into a structured pre-designed data collection tool. Data on the socio-demographic characteristics, clinical-pathological features, GTN management given and theoutcomesas per their last review were collected.

Data management: Data was entered and analysed in SPSS version 23.0 statistical software.Thepopulationwasdescribedby summarizingvariablesintopercentagesandmeansormediansforcategoricalandcontinuousdata,respectively.Clinical-pathologicalcharacteristicsandmortalitywerepresentedasproportions.Thefactorsassociatedwithmortalityweretestedusingchisquaretestandoddsratios.Pointestimatesand95%confidence limits were reported. Findings were considered statistically significant at a p-value<0.05.

Results: Two hundred and fifty (250) charts of patients managed for GTN were reviewed.Theirpointsof entry were mainly asgynaecology admissions(59.6%)andreferralsfromother hospital services (30.8%). The mean age of the women was 32.8 years and their paritywas a median of 2.0. In the study group the reported previous history of molar pregnancieswere in 23.6%, term pregnancies in 82.4% while abortions were in 62% of the women. Theinitial hCG level was a median of 31000 IU/mL which declined in 90% of the patients afterchemotherapy. Most patients (97.6%) presented with per vaginal bleeding and 89.6% had anabnormalultrasound.Themeanhaemoglobinwas9.1g/dland40%wereanaemic.Choriocarcinoma was diagnosed in 77.2% of the patients while 18.8% were complete moles.The type of surgery given was mainly D&C in 63.2%. The mean WHO risk score was 7.4with FIGO stage I in 86% of the cases. The second line chemotherapy was administered to30.8%ofthepatientswhile6.4%receivedsalvagetherapy.ThemedianhCGlevelattheend

of treatment was 0.9 IU/mL. Mortality rate among the women was 19.2% with the risk higherin those with previous mole (p=0.036), those with higher median initial hCG levels (p<0.001)andthe patients with higher median WHOriskscore(p<0.001).

Conclusion: ChoriocarcinomaisthecommonesttypeofGTNinthisstudy population,occurring in young women in their reproductive period with a high proportion of them inFIGO stage I disease. Patients with previous history of molar pregnancy, higher levels ofinitialhCGandhighermedianWHOriskscoreareatahigherriskofdeath.

CHAPTER1:INTRODUCTION ANDLITERATUREREVIEW

INTRODUCTION

Gestationaltrophoblasticdisease(GTD)isasetoftumourscharacterizedbyabnormaltrophoblasticgrowthleadingtohumanchorionicgonadotropin(hCG)production(1,2).Malignant GTD is known as gestational trophoblastic neoplasia (GTN) (1). About 50% ofGTNcasesresultfromhydatidiformmolarpregnancy,25%frommiscarriageortubalpregnancywhile 25%are from term pregnancy(2).

GTNisamalignantcancerarisingfromplacentaltissuethatoccursafteranytypeofpregnancy with long-term survival rate lower than 80% (3). It mostly includes epithelioidtrophoblastictumour(ETT),placentalsitetrophoblastictumour(PSTT),choriocarcinomaand invasive mole (3). Invasive mole and choriocarcinoma occurs in around 15% of females.The incidence of choriocarcinoma is approximately one in 40,000 pregnancies. Placental sitetrophoblastictumourand ETTcontributes to0.2%of GTD cases(4).

Choriocarcinoma is the most common GTN and can be diagnosed through tissue necrosis,acute bleeding and chorionic villi absence which may cover the uterine wall and spreadfurther to the lungs, vagina, intestines, adnexa, kidney, liver and spleen (3). Placental sitetrophoblastic tumour, arare form of GTN, is described as having a slow growth resultingmostly inlowhCGlevelsandconfinedtotheuterusandisresistanttochemotherapy(2,3,5,6). Placental site trophoblastic tumour does not invade much of the blood or lymphvessel therefore there is less bleeding and necrosis in comparison with choriocarcinoma (3).Epithelioid trophoblastic tumour (ETT) resulting from intermediate trophoblasts is anotherkindofGTN(7).

Correct diagnosis is important in the management of GTN because it isusually treatable (3).In a molar pregnancy risk factors for getting GTN are: a complete mole that has trophoblasticincreasedgrowthsigns; ovarianthecaluteincystsofasize>6 cm;andages35-40 (1).

Surgicaluterineevacuationistheusualmanagementforcompleteorpartialmoles.Hysterectomy as an alternative is available when one does not want more children. Afterevacuation of a complete or partial molar pregnancy, if hCG levels increase or stay at highlevels over a duration of weeks, the patient is presumed to have GTN. Managing GTN inmedicalsettingsiscontroversialandnotmanystudieshavebeenundertaken(1).Earlydiagnosis and suitable treatment prevents maternal death, thus allowing women to heal andtheirreproductivepotentialmaintained(8).ThereislittledataonGTNindevelopingcountries including Kenya (5). This study will lay the foundation to understand the magnitudeof occurrence of GTN cases presenting in a tertiary hospital in Kenya and the availablemanagementpracticesaswell as themortalityrates.

LITERATUREREVIEW

Choriocarcinoma is one of the most common GTN worldwide (3). In the United States itoccurs in 1 in 20,000 to 40,000 pregnancies, and the Southeast Asia and Japan in 3-9 per40,000 pregnancies (1). A large number of choriocarcinoma cases occur following non-molarpregnancy(3).PlacentalsitetrophoblastictumourisararevariantofGTN(2,4).However,thelymphaticspreadofPSTTishigherthanforchoriocarcinoma(2,5).Epithelioidtrophoblastictumour, atypeof GTN,accounts forless than 2%of all GTN(7).

Clinicalstagingof GTN

GTN is staged based on the anatomic staging by International Federation of GynaecologistsandObstetricians(FIGO).StageIreferstoGTNsthatarefullylimitedtouterinecorpuswhile in stage II the tumour has spread to the vagina but is limited to genital structures. StageIII GTNs are those which have metastasized to the lungs and may involve the genital tractwhile stage IV have metastasized to all other sites (3). Furthermore, GTN may be groupedinto low or high risk based on the stage. Stage-I GTN disease is non-metastatic, stages II andIII GTN diseases are low-risk metastatic while stage IV GTN is high-risk metastatic disease(2,7). Using WHO prognostic scoring system, each prognostic factor is assigned a score from0 to 4 and all the scores are summed up to give the WHO risk score. Prognostic factorsconsidered are: age, type of previous pregnancy, months since last pregnancy, site of spread,pre-treatment hCG, largest tumour size, numbers metastatic tumours and previous failedchemotherapy regime.LowriskGTN hasascoreof 6orlessandhasgoodtreatmentoutcomes even if the cancer has spread while high risk GTN has risk score ≥ 7 and mayrequireextreme treatmenteven ifthetumouris in earlystages(8).

Diagnosisof GTN

ThefrequenttypesofGTDsuchascompletehydatidiformmoles(CHM)andpartialhydatidiform moles (PHM) can present during first trimester with acute vaginal bleeding. Thepathologicalexaminationofproductsofconceptionenableshistopathologicaldiagnosis.Around 15% CHMs result in local tumour invasion with 5% metastasizing usually to thevagina or lungs. In the case of PHM, local tumour progresses in around 5% patients andmetastaticdiseaseoccurrenceisuncommon.Elevatedlevelsofgonadotropin-releasinghormone (GnRH) are used to diagnose postmolar GTN after HM elimination. As a result ofthis, chemotherapy can be administered in the absence of diagnostic histopathology with theexception of antecedent pregnancy (2,5). In molar pregnancies, their immediate diagnosis isenabledby ultrasonography diagnosticimagingtechniqueduringpregnancy.Theuseoftransvaginalultrasoundgivesthe first andimmediate diagnosisof HMin uniquecases(3).

Standardized guidelines for a more precise diagnosis of post molar GTN includes histologicdiagnosis of choriocarcinoma; hCG persistence for 6 months following molar pregnancy;plateauing of hCG at 21 days; and an increase in the level of hCG by 10% or more forleastthreevaluesduring14days(8).ThemostfrequentGTNseenduringhistopathologicevaluation is choriocarcinoma. Choriocarcinomamay presentwith non-specific symptomsandsignsmakingexactdiagnosisdifficultandhenceresultingindelayeddiagnosis.Thusthe

need for hCG examination for all women of reproductive age who show abnormal uterinebleedingorrelated unknown metastaticdisease(3).

Managementof patientsdiagnosedwithGTN

Diagnosing GTN enables its management because these tumours are usually treatable andfertility is maintained in a majority of cases. The exact diagnosis of GTN is necessary henceadministrationoflifesavingchemotherapyleadingtotherightmanagementofthismalignancy (3).

Following diagnosis, staging and FIGO/WHO prognostic risk score is a necessity as it allowsthe commencement of the chosen treatment leading to high cure rates (8).The treatment forGTN patients is conventional surgical therapies and chemotherapy. Although sensitive hCGassays and chemotherapy advancement have become primarily important in the managementof GTN, surgery is paramount in the wholesome care of these patients (9). However, in somepatients with resistant disease, these therapies may not be effective and patients may die.Therefore new remedial agents are needed to decrease toxicity levels caused by conventionalchemotherapyand also treatingthosewhohaverefractoryor resistantdisease(3).

Treatment for patients in GTN stages I, II and III low risk score category can begin withsingle agent chemotherapy with remedial success rising up to 85%. At stage IV, multi-agentchemotherapy has to be administered with adjuvant surgery or/and radiation to increase thecurerates(3).

Though it is recommended that chemotherapy should begin immediately for patients withmetastaticchoriocarcinoma,therearecaseswherepatientsareseenwithhistologicaldiagnosis of choriocarcinoma and hCG is normal or lessening and no evidence of metastaticdisease (8).For example, in a Brazilian retrospective cohort study, only 44.7% of suchpatients received chemotherapy. In this case when both groups were compared, the prognosisof those who did not receive immediate chemotherapy did not worsen with no relapses ordeaths (8). In a Peking Hospital study 143 patients were at first assessed on medical history,physicalexamination,chestX-rayorcomputedtomography(CT),transvaginalortransabdominal sonography, serum biochemistry and serum β-hCG levels, blood routine testwith brain Magnetic Resonance Imaging or CT for patients with neurological symptomsbeforetreatmentbegan.Allthepatientswerediagnosedwithchoriocarcinomaandchemotherapywas administered(10).

Placental site trophoblastic tumour diagnosis is more difficult which may be because of thelack of specific and sensitive tumour markers. This type of GTN is more common in youngwomen (11). The two treatment strategies after a patient is evaluated are simple hysterectomyand systemic therapy. In a long-term clinical trial of PSTT, all patients had surgery and theirrecurrence rate wasabout 50% (11). This gave some evidence that surgery is an importantpartofPSTTtreatment.Multidrugplatinum/etoposide-chemotherapyisimportantinmetastatic disease cases and amongst those with non-metastatic disease but have high-riskcharacteristics(6).

In the case of ETT management, a review by Zhang (7) reported extra uterine ETT in 27patients using pathological tests.In the immunohistochemistry there was a positive Ki-67with a staining index of 8.7 to 80%. In 15 cases a hCG positive result occurred. Surgicalmanagement was also done for these ETT patients and included video-assisted thoracoscopicsurgery (14 cases), a hysterectomy without or plus a bilateral salpingo-oophorectomy (2cases) concurrently, dilation and curettage (1 case) for diagnosis, surgical resection of thetumour(6cases),resectedbypulmonarysurgerybecauseoflungmetastasis(1case),Hartmann'sprocedureresection(1 case)andabiopsyonlygiven fordiagnosis(3cases)(7).

Characteristicsof patientswithGTN fromotherregions

A study done in Peking Hospital, Beijing, reported on the clinical characteristics of patientsdiagnosed with choriocarcinoma. Of 143 patients with ultra-high risk GTN and diagnosedwith choriocarcinoma, those older than forty years were 21.0% and had a median serum β-hCG of 43,049 IU/L. Antecedent pregnancy included a mole in 19.6%, an abortion in 39.9%,andtermpregnancyin40.5%.Ittooktwelvemonthsormorebetweentheantecedentpregnancy and chemotherapy in 88.1%. The clinical characteristics were liver metastases(14.0%), brainmetastases(40.6%), or both(5.6%).Kidney,spleen,intestine,bone,andadrenal gland were other sites with metastases. Previous chemotherapy did not work on 102patients. This included multi-agent resistance in 98 cases and single-agent resistance in fourcases. When the cases were classified into the FIGO clinical stage system, 2.8% were at stageI, 2.1% were at stage II, 40.6% at stage III and 54.5% at stage IV. Those at low risk (score ofsix and below) were 26, high risk (score 7-12) were 77 and ultra-high-risk (score of 13 andabove)were15(10).

In a review of 22 clinical studies from Asia, North America, Oceania, Europe and SouthAmerica, 27 cases of ETT were identified with 14.87% located in the lungs, 11.11% in theovaries, 7.41% in the vagina and 29.63% had other primary lesions (7). There were no studiesfrom Africa. Full-term pregnancy was the most common antecedent pregnancy followed byabortion then hydatidiform mole and lastly invasive mole. From the time of pregnancy towhen extra-uterine ETT was diagnosed, it took a median interval of four years. Other resultsshowedthemediangravidityatthreetimesandparityattwotimes.Infiveand14patients,themedianhCGtiterwas14,374mIU/mLandmeanβ-HCGtiter3,724,805mIU/mLrespectively(7).

A few developing countries have documented the frequency of GTN. In Tunisia one in 918deliveries had GTN and the cases of metastases were reported at 43%. Lungs (30%) andvagina(13%)weretheusualsitesformetastases(12).InthecaseofastudyinIndia,where70 GTN patients were treated, 68% were low risk. The most common site of metastasis wasthelungs at 21%(13).

MortalityinpatientsdiagnosedwithGTN

Long-term survival rate is less for high risk GTN patients. Due to the advanced nature of thedisease in the high-risk group, some die before effective treatments are administered whileothersdevelopdrug-resistantdiseases(3).Astudyof143ultra-highriskGTNcases46

patients died giving a mortality rate of 30%including four cases who died before or duringthefirstcycleofchemotherapyandnineafterreceivingtreatmentwithetoposide,methotrexate ,actinomycinD,cyclophosphamide,andvincristine(EMA/CO)becauseofhistory of failed floxuridine, dactinomycin, etoposide and vincristine (FAEV) chemotherapy(10). Proper patient management in GTN is a challenge for clinicians due to the limitedcapability to predict malignant hydatidiform moles (HMs). It is also noted that PSTT tumoursdo not readilyrespond to chemotherapy hence resulting in higher mortality rates than that ofchoriocarcinoma(3).

The survival rate in patients suffering from low risk GTN disease is 95% while that of highrisk is 80% thoughtheoutcomes worsenin patients exhibiting drug-resistance (3).InanAsian study that reviewed GTN patients with FIGO score ≥ 12 between 2002 and 2015,65.7% achieved complete remission while 15.9% relapsed and 67.9% had 5-year survival rate(10).

Low mortality rate was reported in a review of ETT studies, in a follow up time of survivorsbetween a fortnight to 24 years. There was disease recurrence in three cases and three diedfrom the disease while one gave birth within 12 months of follow up (7). In an Indian study,overall survival in a low-risk group was 100% and 88.8% in patients with high-risk disease(13).

With PSTT and ETT being the rarest GTN malignant forms, having advanced FIGO stage oran interval ≥48 months from last known pregnancy have poorer outcomes as reported by areview of a United Kingdom database of all cases reported from 1973 to 2014. This wassimilar to earlier workthat showed that an interval of ≥48 months from the antecedentpregnancywas associatedwith100% death rate, independentof the stage(14).

FactorsassociatedwithmortalityinpatientsmanagedforGTN

Identifying causative risk factors for GTN progression is difficult. It may be due to gatheringbias from epidemiologic data and how this is interpreted as well as procedure clarification ofhow the disorders occur. The incidence rate of CHM differs from one part of the world to theother. A previous review showed that CHM is higher among Asians, Hispanics,
AmericanIndians,andAfricanAmericanscomparedtothoseininEurope,NorthAmerica,andAustralia. Pregnancy atan age more than 40yearsand abnormal HM are the commoncausative risk factors of CHM progression. However, because choriocarcinoma is infrequentand also not easy to clinically spot it from a metastatic mole, getting to specify the incidencerateis achallenge (3).

Risk factors for HM include being too young or too old, ethnic background and having hadHM before which may mean there is a genetic basis for its cause. The risk of a complete moleismuchmoreforthose<21and>35years.Itis7.5timesmoreinthoseofagesmorethan
40. Having had a molar pregnancy increases risk of another one at around 1%. This is a ten to20 fold in comparison to the general population. Prior spontaneous abortion may result inwomen having double to triple risk of a molar pregnancy than a woman without. MostreportedincidencesofHMareinSoutheastAsiaandJapanwithfewerintheUnitedStates.

Twentypercentofthemwillresultinmalignancynecessitatingchemotherapyafterthemoleis removed. Choriocarcinoma also occurs at a higher rate in Southeast Asia and Japan than intheUnited States (1).

In a number of studies, some reasons leading to poor PSTT prognosis have been reported andincludeintervalbetweenantecedentpregnancy>2years,deepinfiltration,necrosisandmitotic index >5/10 under high power microscope (11). In a retrospective review at theNorthwestern University among those with PSTT, women usually complained of abnormaluterine bleeding (69%) and a uterine mass was present in 62% of cases. After an endometrialbiopsy or curettage, diagnosis was established 62% of the times. A nonmolar pregnancybefore was reported in 85% of the cases. The serum hCG levels when the diagnosis was madewas 1-2606 mIU/mL. Median time from last pregnancy to diagnosis was 13 months. Afterexamination 23% were reported as having metastatic disease. Thirteen women had surgeriesand nine also received chemotherapy. Overall, the survival rate was 100% at median survivalof65 months (6).

By the time patients are sent to referral centres with high risk GTN and disseminated disease,their survival rate at the beginning is 86%. Deaths are recorded early within the fourth weekusually due to bleeding or metabolic upset from tumour lysis in those in whom the disease iswell progressed or later from those suffering from drug resistant disease (8). This was alsoshown in a Chinese hospital where medical records of those with a FIGO score of 12 andabove were reviewed. Among the 143 patients, 41 were given initial chemotherapy at thehospital. The others had been given referrals from other treatment centres as a result ofchemotherapy that had not worked. Of these patients 65.7% were in complete remission but15.9%relapsed.Five-yearoverallsurvivalratewas67.9%.Amongthe46deaths,25weredue to drug-resistance to initial and salvage chemotherapy, 10 from multiple organ failure,four from cerebral hernia and two subarachnoid haemorrhage, two from respiratory failure;while three were from septic shock due to severe myelosuppression. Of all these mortalities,21.7% occurred within four weeks after treatment initiation and seven of them had brainmetastases(10).

Recurrencealsoplaysaroleinmortality.Between2004and2017,GTNpatientsinaTrophoblasticDis easeCentreatanAsianhospitalwhorecurredaftercompletingchemotherapy were identified. Their 5-year overall survival rate at 80.4%. Those who diedof progressive disease were 19.5%. This included 7 whodied during theirfirstrecurrencesand16 duringsubsequent recurrences (15).

A French study described mortality in GTN cases having a FIGO prognostic score ≥13.ExcludingPSTTandETT,the5-yearmortalitywas2%.High-riskcaseshada5-yearmortalityrateof12% which was 52%ofdeaths ofthe wholegroup (16).

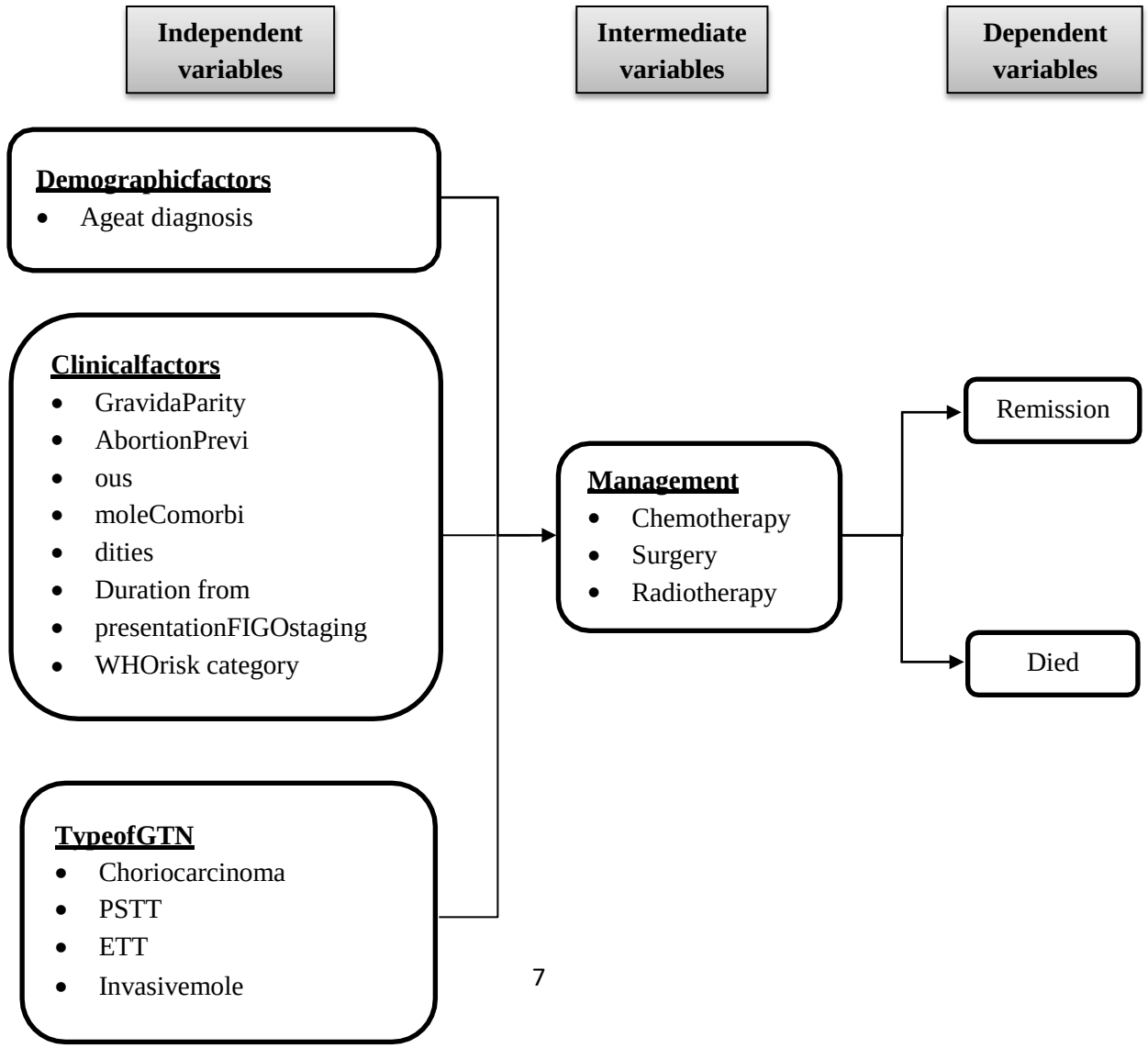
AnotherfactorthataffectsmorbidityandmortalityisthemanagementofGTNbyaspecialist. Brewer reported that morbidity and mortality in those being treated for GTN was 9times less in centres run by experienced doctors. This was the same case in a Brazilianexperiencewherepatientsshowedlessmetastasisrateandalowermediantimeintervalfrom

when the molar was removed and chemotherapy commenced that was quicker than for caseswhobegan treatment in otherplaces thanReferenceCenters (8).

CONCEPTUAL FRAMEWORKNARRATIVE FRAMEWORK

The clinical management of GTN is geared towards achieving remission. Previous studieshave reported high remission rates in patients with GTN with some achieving completeremission while others recur. Despite the high survival rate, mortality has been reported inother studies which have been linked to various factors with the most important being theFIGO staging and WHO risk category (10). Also, mortality is dependent on the type of GTNwith choriocarcinoma having a higher rate than the other types. The clinical characteristics aswell asthe typeof GTN determinethetypeofmanagement appropriatefor the patient.

SCHEMATICFRAMEWORK



STUDYJUSTIFICATION

GTN is a largely unknown disease to a majority of physicians globally (8).The incidence ofGTN in Africa and in Kenya is poorly documented. There is therefore need for studies tobring this to light. Proper patient management of those suffering from this disorder is also achallenge for clinicians therefore the disease development is still not well known and thecapability of clinicians to predict malignant HMs is limited (3). Choriocarcinoma growsrapidly and may haemorrhage which makes the tumour a gynaecological emergency. There isalso quick metastasis to the lungs, pelvis and vagina and it is common inyoung women.Local mortality and survival rates are unknown. There is also high mortality despite thetumour being chemo-sensitive and with low capacity to manage the condition.Hence theneedforstudies like thisoneto answer someof theunknown statistics.

RESEARCHQUESTION

Whataretheclinical-pathological characteristicsandfactorsassociatedwithmortalityfromGTNamongpatients managedin KenyattaNational Hospital (KNH)?

OBJECTIVES

Broadobjective

Todeterminetheclinical-pathologicalcharacteristicsandthefactorsassociatedwithmortalityin patients managed forGTNin KNH.

Specificobjectives

1. Todescribetheclinical-pathologicalcharacteristicsofpatientswithGTN.
2. Todescribethetypeof managementgiventopatientsdiagnosed withGTN.
3. Todeterminemortalityratein patients diagnosed withGTN.
4. Todeterminethefactorsassociatedwithmortalityin patientsmanagedforGTN.

CHAPTER2:METHODOLOGY

Studydesign

This was a descriptive cross-sectional study, where routinely collected data were used. Areview of outcomes was done based on the information recorded in the patient charts at thefinalvisit.Theclinicalandpathologicalcharacteristicsandthetype(s)ofmanagementreceivedby thepatientsfromthe dateofdiagnosiswereabstractedfrom the patients'charts.

Studysite

This study was conducted at the records department in KNH, the largest referral hospital inKenya. KNH has a bed capacity of more than 2000 and is located in Nairobi County. Thecatchment area is largely from the Nairobi metropolis with referral from all over Kenya andthe East Africa region. The hospital has outpatient specialized clinics that address variousmedical conditions that require specialized treatment. The cancer treatmentcentre managesall types of cancers. The Gynaecology Oncology Unit manages all types of reproductivehealth cancers including GTN averaging 30 cases annually. GTN is a rare condition henceKNH being a referral centre will increase feasibility of the study because of thehighernumber of cases referred from other facilities across the country. The site is also appropriatebecause KNH has the capacity to carry out all the diagnostic and follow-up tests required inthemanagementofGTN.Inaddition,thereisanadequatenumberofqualifiedgynaecologistsandon cologists needed forthe management ofGTN.

Studypopulation

The study populationconsistedof womenwitha documenteddiagnosisofGTNfully orpartly managed at KNH in the period 2012 to 2020. This period was chosen because ofavailabilityof data at therecords department.

Eligibilitycriteria

Inclusion

1. Womenofreproductive age
2. Documented diagnosis of

GTNExclusion

1.Thosewithundocumented outcomes

Samplesizedetermination

Due to the small number of cases of GTN, all cases of GTN that met the study eligibilitycriteriawereincluded inthe study.

SamplingProcedure

Patients who were managed in KNH for GTN in the period 2012 to 2020 were listed fromadmission registers in the gynaecology oncology unit and formed the study population. Thelisted patients' file numbers were handed over to the health information team to retrieve thefilesfrom the records department.

StudyVariables
Thevariables wereas follows:

Independentvariables
- Socio-demographicdata
- Durationtakenfrom firstfacilitytoKNH
- Management given atfirstfacility
- DatefirstseenatKNH
- Durationfromfirst visittostart ofchemotherapy
- Typeofchemotherapygiven
- FigoStage
- Figoriskcategory

Dependentvariables
- Aliveordead
- Recurrence

Datacollectionprocedures
Theretrievedfileswerereviewedbytheinvestigatorassistedbytwotrainedresearchassistants.The researchassistantshadmedicalor nursing degreequalificationandweretrained on the use of the data collection tools and were also given updates on GTN diagnosisand management. The relevant information was abstracted from the files and entered into astructureddatacollectiontool(Appendix1).Thetoolcollecteddataonthesocio-demographic characteristics, clinical-pathological features, GTN management given in thehospitalandtheoutcomesasoftheirlastreviewinthehospital.Theinvestigatorcontinuously reviewed the filled data collection tools to ensure completeness and accuracy.The files werere-checked to completeor clarify any information before data collectionprocesswas completed.

DataManagementandAnalysis
Data was entered and analysed in SPSS version 23.0 statistical software. The population wasdescribed by summarizing the socio-demographic and clinical characteristics into percentagesand means or medians for categorical and continuous data respectively. Type of managementof GTN was presented as proportions out of the total population studied. Similarly, mortalitywas calculated and presented as a percentage. The factors associated with mortality weredetermined using chi square test of associations. Fisher's exact test was used in variableswhere the numbers were small. Where appropriate, comparison of means between groups wasdone using Student's t test while medians were compared using Mann Whitney U test. Oddsratios were reported as estimates of relative risk with 95% confidence intervals. All statisticaltestswereinterpretedat5%levelofsignificance(pvaluelessorequalto0.05wasconsidered significant).

QualityAssuranceProcedures
Researchassistantswere trained on data collection. A pre-test was done and adjustmentsmadeaccordingly.Datawascheckeddailyforinconsistencesandcompletenessandcorrected.

EthicalConsiderations

Ethical approval was sought and obtained from Kenyatta National Hospital/ University ofNairobi Ethics and Research Committee (KNH/UON ERC) to conduct this study. Approvalfrom KNH/UON ERC was submitted to KNH research and programs department to seekclearance to conduct the study and access the patients' records. In addition, permission wassought from the health information department to access the unitand retrieve the files.Individualconsentwasnotrequiredbecausethisstudyreliedonsecondarydata.Confidentiality was upheld at all stages to ensure the retrieved files and the informationcollectedwasnotaccessibletounauthorizedpersons.Patients'identifierswerenotusedo nthe data collection forms but a separate record was kept to link study numbers with patients'identifying information. The findings of the study should help to improve the management ofGTN in KNH and decrease mortality. Study findingswill be provided to KNH and theKNH/UONERC.

CHAPTER3:RESULTS

Twohundred andfifty(250) patients with historyofGTNwerestudied.

Table1:Patients'characteristics

Variable	**Frequency(%) (n=250)**
Placeof firstcontact	
Admitted to hospital as a Gynaecology in-patientSeenin clinic	149(59.6)
ReferredtoGynOncbyotherin-hospitalserviceStartedtreatmentelsewhereandtransferred	10(4.0)
Notdocumented	77(30.8)
	12(4.8)
	2(0.8)
Ageat diagnosis	
Mean(SD)	32.8(7.7)
Min-Max	16.0-58.0
Gravida,median(IQR)	3.0(2.0-4.0)
Parity,median(IQR)	2.0(1.0-3.0)
Abortion,median(IQR)	1.0(1.0-1.0)
Previousmole	
Yes	59(23.6)
No	191(76.4)
Numberofpreviousmoles,median(IQR)	1.0(1.0-1.0)
Deliveries/termination	
TermAb	206(82.4)
ortionM	155(62.0)
olarD&	69(27.6)
C	24(9.6)
Valueofinitialchorionicgonadotropin(**hCG)**(mIU/mL)	
Median(IQR)	31000.0 (10000.0-200000.0)
ClinicalStatus	
Progressionbeforechemotherapy	
Plateau of	60(24.0)
hCGRisinglevelsofh	60(24.0)
CG	1(0.4)
Positive hCG> 6	54(21.6)
monthsDeclininghCG	1(0.4)
levels	74(29.6)
MalignanthistologyduringobservationN	
otdocumented	10(4.0)
Progressionafterchemotherapy	8(3.2)
Plateau of	225(90.0)
hCGRisinglevelsofh	3(1.2)
CG	4(1.6)
DeclininglevelofhCGR	
esistant to	
treatmentNotdocument	
ed	

Presentation	
P.V	244(97.6)
BleedingCou	14(5.6)
ghConfusion	2(0.8)
Pallor	94(37.6)
Abnormalpelvicultrasound	224(89.6)

Theca- luteincystsMiscar riageEnlarged uterusAnaemia Shortnessofbreath(SOB)	105(42.0) 185(74.0) 174(69.6) 94(37.6) 9(3.6)

Majority (59.6%) were admitted to hospital as gynaecology cases while 30.8% were referredto gynaecologybyotherin-hospital service.

The mean age at diagnosis was 32.8 years (SD 7.7 years) with a range of 16 to 58 years. Thewomenhad amediangravidaof3 (IQR 2-4),andmedianparityof 2.

History of previous mole was reported in 23.6% with a median of 1.0. Majority (82.4%) hadever had term pregnancies, 62% had experienced abortion with a median number of 1.0,27.6%had molar pregnancies while9.6%reported historyof D &C.

ThemedianinitialhCGwas31000mIU/mL.Priortochemotherapyobservation,hCGplateaued in 24% of the women while another 24% had rising levels; declining levels werereportedin21.6%ofthepatients.Progressionafterchemotherapywasdocumentedinmajority of the patients and 90% had declining levels of hCG. The clinical presentation wasmainly per vaginal bleeding (97.6%), abnormal ultrasound (89.6%), miscarriage (74%) andenlargeduterus (68.6%).

Table3:ResultsofLaboratoryinvestigations

Variable	**Frequency(%) (n=250)**
Totalbloodcount(TBC)done **Haemoglobin (Hb)(g/dl)** Mean(SD) Min-Max	249(99.6) 9.1(3.1) 2.3-15.4
Anaemia Yes No	 100(40.0) 150(60.0)
hCGleveltakenPriortoDandC **hCG(mIU/mL)** Median(IQR) Min-Max	90(36.0) 50000(10000-198322.3) 1.6-817642.0
hCGlevel priorto hysterectomy **hCGValue(mIU/mL)** Median(IQR) Min-Max	15(6.0) 59721.5 (3745.0-116212.0) 2.2-285437.0
IfTheca-lutein cystsyes,sizeof largestcyst(cm)	

Median(IQR) Min-Max	4.0(3.0-5.0) 1.0-15.0
Ifuterusenlargedfordates:Sizeof uterus(equivalenceof gestation) (n=197) 8–10weeks 12–14weeks 16–18weeks >18weeks	 142(72.1) 41(20.8) 7(3.6) 7(3.6)

The total blood count (TBC) was documented in 99.6% of the patients with a mean Hb of 9.1g/dl and 40% had anaemia. hCG was recorded prior to D and C in 36% of the patients and themedian level was 50000 mIU/mL. hCG level was monitored prior to hysterectomy among 15patients (6%) and the median was 59721.5 mIU/mL. The median size of largest cyst amongthose with theca-lutein cysts was 4 cm. The size of uterus equivalence of gestation was 8-10weeksin 72.1%of thepatients.

Table4:Histologicaltypes andinitialsurgicalmanagement

Variable	**Frequency(%)**
PathologyPartial MoleComplete MoleInvasive MoleChoriocarci nomaPSTT Notdocumented	 2(0.8) 47(18.8) 1(0.4) 193(77.2) 1(0.4) 6(2.4)
Type of surgeryD&CHy sterectomy Exploratorylaparotomy	 158(63.2) 15(6.0) 7(2.8)

The pathology wasmainly choriocarcinoma in77.2% of thepatientswhile complete molewas diagnosed in 18.8% of the patients. The initial surgical management received was mainlyD&Cas reportedin 63.2%of thepatients. Hysterectomywasdonein6%ofthe patients.

Table5:WHO/FIGO risk Score

Variable	Frequency(%)
Age(Years)	
<40	197(78.8)
>=40	53(21.2)
PretreatmenthCGlevel	
<1000	25(10.0)
1,000– 10,000	61(24.4)
10,000– 100,000	77(30.8)
>100,000	87(34.8)
AntecedentPregnancy	
Complete	38(15.2)
MolePartial	9(3.6)
MoleAbortion	113(45.2)
TermPregnancy	87(34.8)
Primigravida(nopreviouspregnancy)	1(0.4)
IntervalIndexfromPregnancy(months)	
<4 months	69(27.6)
4 –6 months	25(10.0)
6 –12 months	31(12.4)
>12months	124(49.6)
Notdocumented	1(0.4)
Largesttumoursizeincludingthoseintheuterus	
<3 cm	149(59.6)
3– 4 cm	41(16.4)
>=5cm	50(20.0)
Notdocumented	10(4.0)
Siteofmetastases	
LungBrain/	29(11.6)
LiverNone	2(0.8)
	219(87.6)
Numberof metastasesidentified	
0	204(81.6)
1 – 4	35(14.0)
Notdocumented	11(4.4)
Previousfailedchemotherapy	
None	211(84.4)
1drug	30(12.0)
Morethan2drugsN	6(2.4)
otdocumented	3(1.2)
Risk	
scoreMean	7.4(3.4)
(SD)Median(I	7.0(5.0-9.0)
QR)Min-	1.0-20.0
MaxHighrisk	
Lowrisk	
FIGO	
StageStageI	215(86.0)
Stage II	7 (2.8)
StageIII	26(10.4)

StageIV	2(0.8)

Majority of the patients (78.8%) were less than 40 years and pre-treatment hCG level wasmore than 100000 mIU/mL in 34.8% of the patients and between 10000 to 100000 in 30.8%.The antecedent pregnancy was abortion in 45.2% and term pregnancy in 34.8%; completemole was documented in 15.2% of the patients. About a half (49.6%) of the patients hadinterval of more than 12 months from the index pregnancy. Majority of the patients (59.6%)had the largest tumour size including those in the uterus being less than 3 cm in size. Therewere no metastases in 87.6% of the patients while 11.6% had lung and 0.8% had brain/livermetastases.

Majority (84.4%) of the patients had no previous failed chemotherapy while those with failedchemotherapy had failed 1 drug (12%) and 2.4% had failed more than 2 drugs. The medianrisk score was 7.0 (IQR 5-9). The FIGO stage was stage I in 84.8% of the patients while stageIIandIVwas 10.4%and0.8%respectively.

Table6:ResultsofRadiologicalinvestigations

Variable	**Positive n (%)**	**Negative n (%)**	**Not donen (%)**
Ultrasoundpelvis	229(91.6)	18(7.2)	3(1.2)
UltrasoundAbdomen	165(66.0)	67(26.8)	18(7.2)
ChestX-ray	30(12.0)	188(75.2)	32(12.8)
PelvisX-ray	1(0.4)	46(18.4)	203(81.2)
CTScanChest	6(2.4)	39(15.6)	205(82.0)
CTScanAbdomen	-	9(3.6)	241(96.4)
CTScanPelvis	-	9(3.6)	241(96.4)
CTScanBrain	1(0.4)	8(3.2)	241(96.4)
MRIAbdomen	3(1.2)	18(7.2)	239(91.6)
MRIPelvis	2(0.8)	4(1.6)	244(97.6)
MRIBrain	3(1.2)	7 (2.8)	240(96.0)

Pelvic ultrasound was positive for 91.6% of the patients while positive abdominal ultrasoundrecorded in 66%. Chest x-ray was positive in 12% of the patients while 1 patient had positivepelvis x-ray. Chest CT scan was positive in 2.4% and 1 patient had a positive brain CT scan.MRI was positive for abdomen, pelvis and brain in 1.2%, 0.8% and 1.2% of the patientsrespectively.

Table7:Treatment

Variable	Frequency(%)
Patientstartedtreatmentelsewhere	
Yes	24(9.6)
No	226(90.4)
Initialtreatmentplan	
Followup	2(0.8)
Single agent	47(18.8)
chemotherapyCombination	194(77.6)
chemotherapyHysterectom	7(2.8)
y	
Reasonforhysterectomy	7(100.0)
Bleeding	
hCGLevelpriortofirst chemotherapytreatment(mIU/mL)	
Median(IQR)	33660(10000-200000)
Min-Max	0.5-2250230
Numberof cyclestonormalizehCG	
Median(IQR)	6.0(5.0-8.0)
Min-Max	2.0-14.0
ChemoRegimen	
Methotrexate	35(14.0)
Act-D	7(2.8)
EMA-	179(71.6)
COEMA-	23(9.2)
EP	6(2.4)
Missing	
Secondlinetreatmentplan(n=77)	
Combinationchemotherapy	61(79.2)
ChangetoanothercombinationchemoH	7(9.1)
ysterectomy	8(10.4)
Stopchemo	1(1.3)
Reasonforhysterectomy(n=8)	
BleedingPersiste	6(75.0)
ntdiseaseNotindi	1(12.5)
cated	1(12.5)
hCGlevelpriortosecondchemotherapytreatment(mIU/mL)	
Median(IQR)	10000(1120.6-79640.5)
Min-Max	5.6-443442.0
Numberof cyclestonormalizehCG	
Median(IQR)	5.0(4.0-7.0)
Min-Max	2.0-9.0
ChemoRegimen	
EMA-	44(57.1)
COEMA-	19(24.7)
EP	

SalvageTreatmentPlan(n=16)	
Followup	1(6.3)
Combinationchemotherapy	4(25.0)
Change to another combination	3(18.8)
chemoStopchemo	2(12.5)
Hysterectomy	6(37.5)
Reasonforhysterectomy(n=6)	
Bleeding	4(66.7)

Recurrentdisease Notindicated	1(16.7) 1(16.7)
hCGlevelpriortosalvagechemotherapytreatment(m IU/mL) Median(IQR)	 30(7.8-3740.5)
Numberof cyclestonormalizehCG Median(IQR)	 5.0(5.0-7.0)
Numberof singleagentcyclestotal Median(IQR)	 5.5(5.0-7.0)
Numberofcombinationcyclestotal Median(IQR)	 6.0(5.0-8.0)
Numberof salvagecyclestotal Median(IQR)	 5.0(3.3-5.0)

A small proportion (9.6%) started treatment elsewhere while majority (90.4%) started inKNH.Theinitialtreatmentplanwasmainlycombinationchemotherapy(77.6%).Hysterectomy was done in 7 patients (2.8%) and most of them were due to bleeding. Themedian hCG level prior to first chemotherapy was 33,660 mIU/mL and the median number ofcyclestonormalizehCGwas6.ThefirstchemoregimenusedwasmainlyEMA-CO(71.6%).

Secondlinetreatmentwasdocumentedin30.8%ofthepatientswith79.2%beingoncombination chemotherapy. Hysterectomy was done in 8 patients (10.4%) with 75% due tobleeding. The median hCG level prior to second line chemotherapy treatment was 10000mIU/mL and median number of cycles to normalize hCG was 5. The second line chemoregimenwas mainlyEMA-CO (57.1%).

Salvage therapy was given to 16 patients (6.4%) with 37.5% being hysterectomy. The mainreason of hysterectomy was bleeding. The median hCG level prior to salvage therapy was 30mIU/mLand thenumber ofcycles to normalizewas 5.

Table8:WeeklyhCGlevel duringtreatment

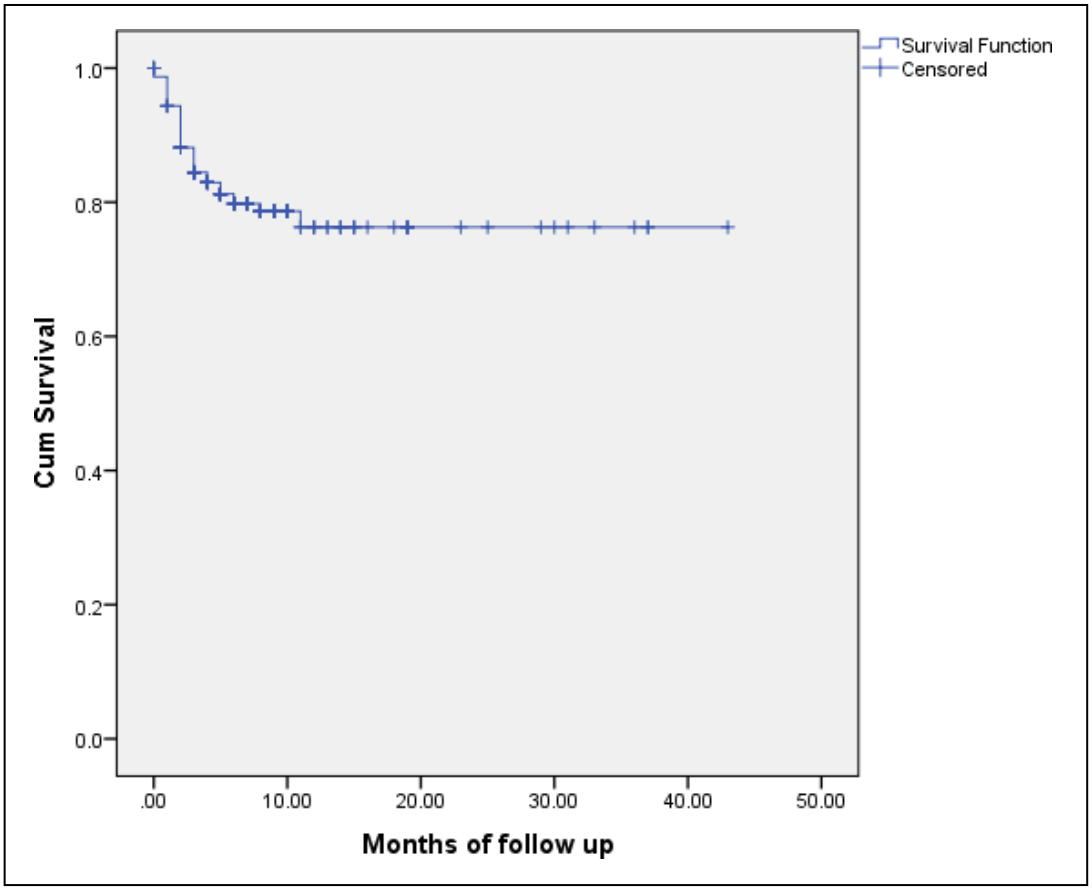
Variable	**Frequency (%)(n=250)**
Pre-treatmenthCGLevel(mIU/mL)	
Median(IQR)	35320(10000-200000)
Pre-treatmentTrend	
Increasing	114(45.6)
Decreasing	105(42.0)
Plateau	25(10.0)
Missing	6(2.4)
1st treatment cyclehCGLevel (mIU/mL)	
Median(IQR)	10000(2552-31381.8)
1st treatmentcycleTrend	
Increasing	21(8.4)
Decreasing	206(82.4)
Plateau	19(7.6)
Missing	4(1.6)
2nd treatmentcyclehCGLevel(mIU/mL)	
Median(IQR)	1755(382.6-9913)
2nd treatmentcycleTrend	
Increasing	21(8.4)
Decreasing	214(85.6)
Plateau	6(2.4)
Missing	9(3.6)
3rd treatmentcyclehCGLevel (mIU/mL)	
Median(IQR)	190(26.9-1400)
3rd treatmentcycleTrend	
Increasing	20(8.0)
Decreasing	203(81.2)
Plateau	6 (2.4)
Missing	21(8.4)
4th treatment cyclehCGLevel(mIU/mL)	
Median(IQR)	24.6(7.3-158.4)
4th treatment cycleTrend	
Increasing	7(2.8)
Decreasing	205(82.0)
Plateau	1(0.4)
Missing	37(14.8)
5th treatment cyclehCGLevel(mIU/mL)	
Median(IQR)	5.2(2.1-16.1)
5th treatment cycleTrend	
Increasing	6(2.4)
Decreasing	180(72.0)
Plateau	2(0.8)
Missing	62(24.8)
6th treatment cyclehCGLevel(mIU/mL)	
Median(IQR)	1.7(0.6-4.2)
6th treatment cycleTrend	

Increasing Decreasing Plateau Missing	3(1.2) 154(61.6) 3(1.2) 90(36.0)
Numberof cyclesgiven afterhCGreturnedtonormal Median(IQR)	 2.0(2.0-3.0)
hCGlevelat endoftreatment Median(IQR)	 0.9(0.2-1.6)
LasthCG Median(IQR)	 0.2(0.1-1.0)

ThemedianhCGlevelwas35320mIU/mLatpre-treatmentperiodandthetrendwasincreasingin45.6%whiledecreasingin42%ofthepatients.ThehCGlevelsdecreasedfroma median of 10000 mIU/mL at 1st treatment cycle to a median of 1.7 mIU/mL at the 6thtreatment cycle. The median number of cycles given after hCG returned to normal was 2 andthe median hCG level at the end of treatment was 0.9 mIU/mL while the final hCG level wasamedian of 0.2 mIU/mL.

Mortalityrate

Figure1:Kaplan-Meier (KM)curveshowingoverallsurvivaltime



As showninFigure1,the overallmortalityrate was19.2%.The meansurvivaltimewas33.7 months (95% CI 30.9 – 36.4 months). Death occurred in a median duration of 2 months fromthefirstencounterdatewiththelongestsurvivaltimetaking11months.Thecharacteristicsofthe patients who diedwere as shownin Table9below.

Table9:Characteristics of patientswhodied

Variable	**Frequency(%) (n=48)**
Ageat diagnosis	
Mean(SD)	34.5(7.8)
Min-Max	20.0-47.0
Previousmole	17(35.4)
Presentation	
P.V	48(100.0)
BleedingCou	6(12.5)
ghConfusion	2(4.2)
Pallor	39(81.3)
Abnormal pelvic	46(95.8)
ultrasoundTheca-lutein	33(68.8)
cystsMiscarriage	41(85.4)
Enlarged	40(83.3)
uterusAnaemia	38(79.2)
Shortnessofbreath(SOB)	7(14.6)

FIGO **Stage**StageI Stage IIStage III StageIV	 37(77.1) - 10(20.8) 1(2.1)
PathologyComp lete MoleChoriocarci noma Notdocumented	 3(6.3) 44(91.7) 1(2.1)

As indicated in Table 9, the mean age of the patients was 34.5 years and 35.4% had history ofprevious mole. PV bleeding was reported in all the patients with other common presentationsbeing abnormal pelvic ultrasound, pallor, miscarriage, enlarged uterus and anaemia. Morethanthree-quarters(77.1%)ofthepatientshadFIGOstageIand91.7%werechoriocarcinoma.

Table10:FactorsassociatedwithmortalityinGTNcases

Variable	Mortality		OR(95%CI)	Pvalue
	Yes(n=48)	No(n=202)		
Meanage (SD)	34.5(7.8)	32.5(7.6)	-	0.101
Previousmole				
Yes	17(36.2)	42(21.5)	2.1(1.0-4.1)	0.036
No	30(63.8)	153(78.5)	1.0	
Abortion				
Yes	35(72.9)	120(59.7)	1.8(0.9-3.6)	0.090
No	13(27.1)	81(40.3)	1.0	
Molarpregnancy				
Yes	16(33.3)	53(26.4)	1.4(0.7-2.7)	0.333
No	32(66.7)	148(73.6)	1.0	
Cough				
Yes	6(12.5)	8(4.0)	3.5(1.1-10.5)	0.032
No	42(87.5)	194(96.0)	1.0	
Pallor				
Yes	39(81.3)	55(27.4)	11.5(5.2-25.3)	<0.001
No	9(18.8)	146(72.6)	1.0	
Abnormalultrasound				
Yes	46(97.9)	178(88.6)	5.9(0.8-45.2)	0.052
No	1(2.1)	23(11.4)	1.0	
ThecaLuteinCysts				
Yes	33(70.2)	72(35.8)	4.2(2.1-8.4)	<0.001
No	14(29.8)	129(64.2)	1.0	
Miscarriage				
Yes	41(85.4)	144(71.3)	2.4(1.0-5.6)	0.045
No	7(14.6)	58(28.7)	1.0	
Enlargeduterus				
Yes	40(83.3)	134(67.0)	2.5(1.1-5.6)	0.026
No	8(16.7)	66(33.0)	1.0	
Anaemia				
Yes	38(79.2)	56(27.7)	9.9(4.6-21.2)	<0.001
No	10(20.8)	146(72.3)	1.0	
Shortnessof breath				
Yes	7(14.6)	2(1.0)	17.1(3.4-85.2)	<0.001
No	41(85.4)	200(99.0)	1.0	
MedianinitialhCG level(IQR)	138817.5 (35873.5-211000)	22087(10000-150000)	-	<0.001
WHOriskscore, median(IQR)	9(7-12)	7(5-9)	-	<0.001

As shown in Table 10, those with history of previous mole were at a statistically significantlyhigher risk of death compared to those with no such history, OR 2.1 (95% 1.0-4.1). Similarly,patients who presented with cough, confusion, pallor, abnormal ultrasound, theca lutein cysts,miscarriage,enlargeduterus andshortness ofbreath wereat ahigherriskof death.

The initial hCG level was statistically significantly higher (median 138817.5 mIU/mL) inthose who died compared to the ones who survived (median 22087 mIU/mL), $p<0.001$. Also,the WHO risk score wasstatistically significantly higherin thosewho died (median 9)comparedto thosewho survived (median 7),$p<0.001$.

CHAPTER4:DISCUSSION

Choriocarcinoma contributed to more than three quarters of the GTN cases reviewed in thehospital. This type of GTN has been reported in previous studies as the most common canceroccurring with a frequency of 1 in 20,000 to 40,000 pregnancies (1,3). Also, complete molecontributed to a significant proportion of the cases while there was only one case identified asPSTT. Previous studies have shown PSTT as a rare case of GTN responsible for only 0.2% ofcasesofGTN(4).

The GTN cases managed in the hospital were found among a relatively young population ofwomen with a mean age of 32.8 years with the youngest being 16 years and 78.8% aged lessthan 40 years. Age between 35 and 40 years is a known risk factor of developing GTN inwomen with molar pregnancies (1). Most of the women had history of term pregnancies(82.4%) though there was a high prevalence of reported abortions affecting almost a third ofthe women (62%). The antecedent pregnancy was mainly abortion (45.2%) with more than athird reporting term pregnancies while 18.8% had mole pregnancies. A similar trend wasreported in Beijing where the antecedent pregnancy in the study population included moles(19.6%), abortion in 39.9%, and term pregnancies in 40.5%(10). The median WHO riskscorewas7inthisstudywhichindicatedahigh-riskGTNdiseaserequiringintensivetreatment (8). This was the case despite the minimal metastases reported among these caseswith a small proportion of patients (12.4%) reporting spread mostly to the lungs then brain orliver. In other developing countries the lungs were also the common site of metastases,Tunisia at 30% (12) and India at 21% (13), though at a higher percentage. The patients in thestudy in Beijing showed a different distribution in relation to the status of metastasis with ahigher spread to the liver (14.0%) and brain (40.6%) (10). It is also notable that this studyfound a high proportion of patients (86%) having FIGO stage I disease with only 2 cases instage IV. The population studied in Beijing showed a more advanced disease with more than90%ofthe patients in FIGO stage IIIandIV(10).

The radiological investigations were highly positive for pelvic and abdominal ultrasoundwhile CT scan and MRI were not done in majority of the cases. Ultrasonography diagnosticimagingtechniqueisrecommendedfordiagnosisofmolarpregnancieswiththeuseoftransvaginalultrasoundgivingthefirstandimmediatediagnosisofhydatidiformmoles(3).

Chemotherapy as well as surgical interventions are paramount in management of GTN hencetheneedforcorrectandimmediatediagnosis.Therightmanagementofthetumourshave

been shown to have positive results with high cure rates and high potential to maintainingfertility.ThoughtreatmentforGTNstagesItoIIIispossiblewithasingleagentchemotherapy, combination chemotherapy was the most preferred treatment in this setting.ThiswassimilartoaBrazilianandBeijingstudy(8,10).Surgerywhichinvolvedhysterectomy occurred in a few cases and this intervention was administered mainly as aresult of bleeding. There was a high response to first line treatment with only 30.8% of thepatients demanding second line treatment andonly 16 patients needing salvage therapy.Therewas a notabledecreaseof hCG level during thetreatment cycles.

This study showed a lower mortality (19.2%) compared to Beijing (30%) (10). This could beexplained by a lower percent in those in the high risk group. The overall survival rate wasmore than 80%. The deaths occurred within 1 year of diagnosis therefore 2 year and 5 yearsurvival rate was not calculated in this population. This was in line with the expected successrates of chemotherapy that have been reported to be as high as 85% (3). Survival of thepatients is dependent on the risk score of the disease. Study findings from elsewhere reporteda survival rate among low risk GTN disease of 95% while that of high risk group was 80%(3). This study showed some of the patients' characteristics that was associated with a higherrisk of death. Patients with history of previous mole had a two-fold risk of death compared totheir counterparts. The history of previousmole may be an indicator torecurrence butthedata was not conclusive. Those who died all had PV bleeding and high percentages of pallor,abnormal pelvic ultrasound, miscarriage, enlarged uterus, anaemia. In addition they had asignificant higher WHO risk score of 9. Also, the patients who died had a higher level ofinitialhCG levels which maymean amoreseverediseaseat theonset.

STUDYLIMITATIONS

This study relied on the secondary data hence it was expected that there was missing data as aresult of incomplete records. The investigator minimized this by collecting information frommultiple records including the doctor's notes, nursing cadex, laboratory reports and otheravailableinvestigations.

TheresultsofthisstudymaynotbegeneralizabletoGTNmanagedacrossvarioushospitalsin the country. This is because KNH is a referral hospital which apart from having a superiormanagement practice because of availability of appropriate personnel and facilities, receivespatientswhomay havebeenreferredtothefacility whenthedisease ismore severe andhenceincreasedriskofpoorprognosis.However,thefindingswillbeusefulininforming

management of the treatment received by all patients with GTN at KNH and the challengesinvolved. This will assist in establishing protocols on management of GTN at the facility andnationally.

CHAPTER5:CONCLUSIONSANDRECOMMENDATIONS

CONCLUSIONS

a) Choriocarcinoma is the commonest type of GTN in this study population, occurring inyoung women in their reproductive period with a high proportion of them in FIGOstageIdisease.
b) InitialsurgicalmanagementreceivedwasD&Cat63.2%andcombinationchemotherapywas the most preferred treatment.
c) Mortality rate was at 19.2% with a mean survival time of 33.7 months. Thus around afifthof those diagnosedwith GTNdiedin theperiod.
d) Patients with previous history of molar pregnancy, higher levels of initial hCG andhighermedian WHOriskscoreareata higher riskof death.

RECOMMENDATION

1. hCGlevelsshouldbedeterminedinwomenpresentingwithabnormaluterinebleeding.
2. Efforts should be directed at early diagnosis of GTN, by referring patients diagnosedwithGTDtoGynaecologiconcologistforproperfollow-upwithtimelyinterventionattheearliest onsetoffeatures suggestiveofGTN.
3. Considering the mortality rate in a young population as seen in this study, properscreeningis important toreducethenumberof deaths.
4. Advocacy isrequiredtocreateawarenessofGTN,includingriskfactors,inthegeneralpopulationas oneof thecausesofmedical emergency.

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APPENDICES
APPENDIX1:DATAABSTRACTIONTOOL
PatientDemographics

1. **DateofBirth:**(dd/mm/yyyy)_____
2. **Addressarea: _____**
3. **Dateoffirstcontact:** (dd/mm/yyyy)_____
4. **Placeoffirstcontact:**□AdmittedtohospitalasGynaecology

   ♈ Seeninclinic

   □ReferredtoGynoncbyotherinhospitalservice

   ♈ Startedtreatmentelsewhereandtransferred

5. **Ageat Diagnosis** (____)

ObstetricalHistory

6. **Gravida:**(numeric) _____
7. **Para:**(numeric) _____
8. **Abortion**:(numeric) _____
9. **Previous mole**: Yes□ No □

Ifyeshowmanypreviousmoles?(numeric)_____

10. **Datesof priorpregnancies: (Theyear)1. _____ 2._____3._____ 4._____5._____ 6_____7. _____ 8._____9. _____ 10.----------**
11. Deliveries/termination,e.g.spontaneousabortion, DandC)

_____

Clinicalinformation:

12. **Dateof InitialHCG**(mm/dd/yyyy)_____
13. **Valueof InitialHCG**(IU/mL)_____
14. **ClinicalStatus**:

□Dateoffirstvisit(mm/dd/yyyy)

ϒ Progressionafterobservation

ϒ PlateauofHCG

ϒ Risinglevels ofHCG

[]Positive HCG>6 months

[] Malignanthistologyduringobservation

ϒ Progressionafterchemotherapy

ϒ NoEvidenceofDisease

ϒ Other:Specify _____

15. Presentation:

Presentation	**Yes**	**No**
P.VBleeding		
Cough		
Confusion		
Stroke		
Pallor		
Abnormalultrasound		
Theca-luteincysts		
Miscarriage		
Enlargeduterus		
Anaemia		
Shortnessofbreath(SOB)		

LaboratoryTests

16. **TBC** Yes□No□Hb…….g/dlValue
17. **Anaemia**Yes□ No□
18. **HCGlevel takenPrior toD and C** Yes□No□

If aboveisYes,hCG..... mIU/

19. **HCGlevelpriortohysterectomy**Yes□No□

If aboveisYes hCG Value .....mIU/

20. IfTheca-luteincystsyes,sizeoflargestcyst..... Cm
21. Ifuterusenlargedfordates:Sizeofuterus(equivalenceofgestation)8–10weeks□ 12–14weeks□16–18weeks□>18weeks□
22. **InitialSurgicalmanagement:**

Typeof surgery	**Yes**	**NO**	**If Yes, Indication**	**Date(dd/mm/yyyy)**
D&C				
Hysterectomy				
Lung				
Liver				
Neurosurgery(Brain)				
Exploratory laparotomy				

23. **<u>WHO/FIGOScore</u>**

FIGOScoreinfluencingfactors:

Age(Years):

□<40 □>=40

PretreatmentHCGlevel:

□<1000 □1,000 – 10,000 □10,000–100,000 □>100,000

AntecedentPregnancy:

□HydatidiformMole□Abortion □ TermPregnancy

IntervalIndexfromPregnancy(months):

□<4months □4–6months □6–12months□>12months

LargestTumourSizeIncludingthoseinthe Uterus(cm):

□<3cm □3–4cm □>=5cm

Siteof Metastases:

ϒ Lung □Spleen/Kidney□Gastrointestinal □Brain/Liver

Numberof MetastasesIdentified:

ϒ0 □1–4□5–8 □>8

PreviousFailedChemotherapy:

ϒ N/A□ SingleDrug □TwoorMoreDrugs

24. WHO RISK SCORE CRITERIA (TICK AT THE RIGHT SCORES THENADDTOGETTHE SCOREFOREACH INDIVIDUALPATIENT)

PrognosticFactor	0	1	2	4
Age	Youngerthan40 ☐	40 orolder ☐	—	—
Previouspregnancy	Hydatidiform mole ☐	Abortion ☐	Full-termpregnancy ☐	—
Months since lastpregnancy	Lessthan 4 ☐	4 to 6 ☐	7 to 12 ☐	Morethan 12 ☐
Pretreatment hCG(IU/mL)	Lessthan 10^3 ☐	10^3 to 10^4 ☐	Greaterthan $10^4$to 10^5 ☐	10^5ormore ☐
Largesttumoursize,including uterus	Less than 3centimetres(cm) ☐	3toless than5cm ☐	5cm or more ☐	—
Siteofspread	Lung ☐	Spleenor kidney ☐	Gastrointestinal tract ☐	Brain,liver
Numberoftumoursthathavespread*	Zero ☐	1 to 4 ☐	5 to 8 ☐	Morethan8 ☐
Numberofdrugsusedto treat the tumourthathavenotworked	None ☐	None ☐	1drug ☐	2ormoredrugs ☐

Riskscore ----------**DateofWHOriskScore:**(dd/mm/yyyy)_____

25. <u>Radiology</u>

Imagingtype	**Positive**	**Negative**	**NotDone**
Ultrasoundpelvis			
UltrasoundAbdomen			
ChestX-ray			
PelvisX-ray			
CTScanChest			
CTScanAbdomen			
CTScanPelvis			
CTScanBrain			
MRIAbdomen			
MRIPelvis			
MRIBrain			

26. FIGOStage:□Stage1□Stage2□Stage3□Stage4

27. Pathology:□PartialMole□CompleteMole□InvasiveMole

□Choriocarcinoma□PSTT□ETT□Unknown

28. Patientstartedtreatmentelsewhere Yes □ □

NoIfyes;

ᵞ Singleagent

□Multipleagents

29. InitialTreatmentPlan:

ᵞ Follow

ᵞ SingleagentChemotherapy

ᵞ CombinationChemotherapy

ᵞ ChangeChemo

ᵞ StopChemo

ᵞ Surgery

ᵞ Hysterectomy

Reason: □bleeding □initialtherapy

□persistentdisease

□Discharge Patient□Other----------

30. ChemotherapyTreatmentstartDate:(mm/dd/yyyy): _____

31. hCGLevel priortofirstchemotherapytreatment(mIU/mL): _____

32. Numberof cyclestonormalizehCG _____

33. ChemoRegimen:

ᵞ Methotrexate□Act-D □EMA-CO

ᵞ EMA-EP□EMA(CNS)-CO □EMA(CNS)-EP

ᵞ TE-TP□Lowdose EP□Pembrolizumab

ᵞ Other _____

34. SecondLineTreatmentPlan:

ϒ Follow

ϒ SingleagentChemotherapy

ϒ CombinationChemotherapy

ϒ ChangeChemo

ϒ StopChemo

ϒ Surgery

ϒ Hysterectomy

Reason□bleeding□initialtherapy□persistentdisease□DischargePati

ent□Other----------

35. ChemotherapyTreatmentstartDate:(mm/dd/yyyy): _____

36. hCGLevel priortofirst chemotherapytreatment(IU/mL):_____

37.Numberofcyclestonormalizeh CG----------

38. ChemoRegimen:

ϒ Methotrexate□Act-D □EMA-CO

ϒ EMA-EP□EMA(CNS)-CO □EMA(CNS)-EP

ϒ TE-TP□Lowdose EP□Pembrolizumab

ϒ Other _____

39. SalvageTreatmentPlan:

ϒ Follow

ϒ SingleagentChemotherapy

ϒ CombinationChemotherapy

ϒ ChangeChemo

ϒ StopChemo

ϒ Surgery

ϒHysterectomy

Reason □bleeding □initialtherapy

□Persistentdisease □ DischargePatient

ϒ Other .....

40. ChemotherapyTreatmentstartDate:(mm/dd/yyyy): _____

41. hCGLevel priortofirstchemotherapytreatment (IU/mL):_____

42. Numberof cyclestonormalizehCG:_____

43. ChemoRegimen:

ᛉ Methotrexate□Act-D □EMA-CO

ᛉ EMA-EP□EMA(CNS)-CO □EMA(CNS)-EP

ᛉ TE-TP□Lowdose EP□Pembrolizumab

ᛉ Other _____

44. Numberofsingleagentcyclestotal:----------

45. Numberofcombinationcyclestotal:----------

46.Numberofsalvagecyclestotal:----------

47.WeeklyhCGlevel whileontreatment

Timeof Test	**hCGLevel(mIU/ml)**	**Trend(Increasing/Decreasing/Plateau)**
Pre-treatment		
1st cycle		
2nd cycle		
3rd cycle		
4th cycle		
5th cycle		
6th cycle		

51. DatehCGnormalizes: _____

52. Numberof cyclesgiven afterhCGreturnedtonormal**:----------**

53.Endoftreatmentdate:(dd/mm/yyyy**)----------**

54.hCGlevelatendoftreatment:----------

55.Lastfollow-update:(dd/mm/yyyy)----------

56.DateofDeath:(dd/mm/yyyy)----------

57.LasthCG----------

58.DateofDeath(dd/mm/yyyy) ----------

59.Causeof death:

□ GTD □ Other

APPENDIX2:ETHICSANDRESEARCHCOMMITTEEAPPROVAL

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Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

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Ref: KNH-ERC/A/453

15th December 2020

Prof. Eunice Jeptoo Cheserem
Reg. No.H117/28161/2019
(Fellow in Gynaecology Oncology)
Dept.of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Prof. Cheserem

RESEARCH PROPOSAL – CLINICAL-PATHOLOGICAL CHARACTERISTICS AND FACTORS ASSOCIATED WITH MORTALITY IN PATIENTS MANAGED FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA IN KENYATTA NATIONAL HOSPITAL 2012 – 2020 (P578/10/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 15th December 2020 –14th December 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Obstetrics and Gynaecology, UoN
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Dr. Alfred Osoti, Dept.of Obstetrics and Gynaecology, UoN
Dr. Jackline Chesang, School of Public Health, UoN

Protect to discover

APPENDIX3:PLAGIARISM REPORT

CLINICAL PATHOLOGIAL CHARACTORISTICS AND FACTOR ASSOCIATED WITH MORTALITY IN PATIENTS MANAGED FOR TROPHOBLASTIC NEOPLASIA IN KENYATTA NATIONAL HOSPITAL 2012 - 2020 A CROSS SECTIONAL STUDY.

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