MANAGEMENT OUTCOMES OF GESTATIONAL TROPHOBLASTIC DISEASE AT MOI TEACHING AND REFERRAL HOSPITAL: AN 8 YEAR REVIEW

BY

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Medicine in Reproductive Health

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DECLARATION

I certify that this research thesis is my original work and has not been presented in any other university for the award of academic credit.

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DEDICATION

This thesis is dedicated to my parents; Kassi Riggah and Mwanajuma N'gatiwi and my lovely wife ;Ulla Boga ,for their never ending support and prayers during   this journey

ACKNOWLEDGEMENT

Foremost, I would like to express my sincere gratitude to my supervisors Dr**. Pallavi Mishra** and **Dr Philiph Tonui** for their continuous support of my masters degree study and research, and for their patience, motivation, enthusiasm, and immense knowledge. Their guidance helped me in all aspects of this research work including the proposal designing and development and overall conduct of the study.

I thank my colleagues in Reproductive Health for the stimulating discussions time we have always had concerning this work.

Last but not the least; I would like to thank my family and friends for supporting me throughout my study.

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ABBREVIATIONS

AIDS	Acquired Immuno-Deficiency Syndrome
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHAMOCA	Cyclophosphamide, Hydroxyurea, Methotrexate, Vincristine, Cyclophosphamide, and Actinomycin
CNS	Cerebral Nervous System
Cr	Creatinine
CT	Computerized Tomography
EMACO	Etoposide, Methotrexate, Actimycin D, Cyclophosphamide, and Vincristine
ETT	Epithelioid Trophoblastic Tumor
FIGO	International Federation of Gynecologist and Obstetrician
GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
Hb	Hemoglobin

HIV	Human Immunodeficiency Virus
hPL	Human Placental Lactogen
HTN	Hypertension
IREC	Institutional Research Ethics Committee
LFTs	Liver Function Tests
LH	Luteinizing Hormone
MAC	Methotrexate, Actinomycin, and Chlorambucil or Cyclophosphamide
MRI	Magnetic resonance imaging
MTRH	Moi Teaching and Referral Hospital
PLAP	Placental Alkaline Phosphatase
PSTT	Placental Site Trophoblastic Tumor
Rh-D	Rhesus- D
SD	Standard Deviation
ß-hCG	ß-Human Chorionic Gonadotropin hormone
TSH	Thyroid Stimulating Hormone
UECs	Urea Electrolyte Creatinine
US	United States

WBC   White Blood Cell

WHO   World Health Organization

DEFINITIONS

Choriocarcinoma: A morphologic term applied to a highly malignant type of trophoblastic neoplasia in which both the cytotrophoblast and syncytiotrophoblast grow in a malignant fashion.

Complete Mole: A molar pregnancy with swelling of all placental villi. Fetal tissues are absent.

Gestational Trophoblastic Disease (GTD): Disease that results from the abnormal proliferation of trophoblast associated with pregnancy. The disease is considered persistent or recurrent if it remains active or returns after therapeutic intervention.

Gestational Trophoblastic Neoplasia(GTN): is a type of gestational trophoblastic disease (GTD) that is almost always malignant.

Hydatidiform Mole: A placental abnormality involving swollen placental villi and trophoblastic hyperplasia with loss of fetal blood vessels. There are two types: partial and complete.

Invasive Mole: A variant of hydatidiform mole in which the hydropic villi invade the myometrium or blood vessels. It may spread to extrauterine sites.

Partial Mole: A molar pregnancy with some normal and some swollen villi plus fetal, cord, and/or amniotic membrane elements.

Placental-Site Trophoblastic Tumor: A rare type of GTD arising in the uterus that secretes human placental lactogen and human chorionic gonadotrophin (HCG).

Outcome: The results or consequences of management and procedures used in combating disease.In our study the outcomes were either cure or mortality.

ABSTRACT

Background: Gestational Trophoblastic Disease (GTD) is a curable heterogeneous group of benign and malignant diseases characterized by abnormal growth and proliferation of the trophoblasts. Benign disease is managed by suction curettage. Malignant disease is managed by either single agent or multiagent chemotherapy depending on the WHO risk score. The treatment outcomes of GTD in developing countries are not well documented.

Objective: The objective of this study was to determine management outcomes of patients treated for GTD at Moi Teaching and Referral Hospital.

Methods: This was a retrospective descriptive hospital-based study carried out at MTRH in Chandaria Cancer and Chronic Disease Centre records department. This was a census survey and the study population included all the medical charts of women managed for GTD from Jan 2010 to Dec 2017. The continuous variables were presented as mean, standard deviation (SD), and categorical as frequency and percentage. Bivariate and multivariate logistic regression was performed to identify the variables associated with GTD treatment outcomes.

Results: A total of 85 patient charts were included in the study. The mean age of patients was 31.9 years with majority 54(63.5%) being 20-35years. Most were multiparous 64(75.3%). The main presentation was abnormal vaginal bleeding in 71(83.5%). A previous history of abortion was present in 22(25.9%), only 3(3.5%) had prior GTD. Malignant disease was present in 70(82.4%) patients, the rest 15(17.6%) had benign disease. Histopathologic diagnosis was made in 27(31.8%) of the patients with choriocarcinoma being the dominant finding in 20 (22.3%) patients. Metastasis was present in 16(18.9%) with lungs as the most frequent metastatic site 10(62.4%). Single agent (Either methotrexate or actinomycinD) was started in 41(58.5%) low risk patients.Thirteen patients 13(31.7%) failed to achieve remission and second line therapy was used. Patients on Actinomycin D achieved higher remission rates compared to those on methotrexate at 90.0% vs. 47.6% respectively. Multiple agent regimen was started in 29 high risk patients and 1 was changed to a salvage therapy. Overall,11 patients died. Complete cure was achieved in 74(87.1%) patients. Bivariate analysis showed an association between prior abortion (P=0.028) ,parity(P=0.003),Bhcg levels(0.001),WHO risk category(p=0.003) and metastases(p=0.001) with cure. Multivariate logistic regression adjusting for confounders showed that the low risk patients have more than four times higher odds of being cured, AOR: 4.44 (95% CL: 2.30, 9.10).

Conclusion: The cure rate of GTD in MTRH is consistent with the high cure rates worldwide. Low WHO risk score is associated with a better prognosis. Single agent Actinomycin D has a higher efficacy compared to methotrexate in achieving remission in low risk GTN. History of prior abortion, multiparity and the typical reproductive age (20-35 years) are risk factors for GTD.

Recommendations: Clinicians should have a high index of suspicion for GTD on a multiparous woman with a prior abortion presenting with vaginal bleeding.Further studies on efficacy and side effect profiles between ActinomycinD and Methotrexate in the management of gestational trophoblastic disease.

CHAPTER ONE

INTRODUCTION

1.1Background

Gestational trophoblastic diseases include hydatidiform mole and non-molar trophoblastic diseases (Niemann et al., 2015). It refers to a spectrum of abnormalities of the trophoblasts (Katz, Lentz, Lobo, & Gershenson, 2007; Schorge et al., 2011). Evidence has shown that gestational trophoblastic diseases most commonly develop after a molar pregnancy; however it may follow any gestation, term pregnancy included (Katz et al., 2007). Literature supports that the hydatiform molar is by far the most common gestational trophoblastic disease (Niemann et al., 2015).This condition is characterized by the secretion of ß-hCG and there is a close relation between serum hCG concentration and the amount of trophoblastic tissue (ibid).

Trophoblastic tissue normally shares certain characteristics with malignancies, such as the ability to divide rapidly, to invade locally, and occasionally to metastasize to distant sites such as the lung (Alan, Decherney, Lauren Nathan, Murphy Goodwin, & NuriLaufer, 2007), yet these activities usually cease at the end of pregnancy (Katz et al., 2007). However, in GTD, abnormal growth and development continue beyond the end of pregnancy.The incidence of GTD globally varies in different region worldwide. However studies have shown constant lower prevalence (1 to 2%) in developed countries(Baergen & Dizon, 2014). while in developing countries, Sub-Sahara included, the incidence is still higher and access to adequate treatment is difficult in limited financial resources area .

Risk factors have been identified; these include maternal age, obstetric history especially prior unsuccessful pregnancies (Schorge et al., 2009) . According to

Schorge and coworkers (2008), the diagnosis of gestational trophoblastic disease is easy in late pregnancy. First-trimester diagnosis of hydatidiform mole is now common because of the routine use of serum ß-hCG measurements and transvaginal sonography, only feasible in areas where ultrasound and hCG measurement are available (Alan et al., 2007; Katz et al., 2007; Schorge et al., 2009). In contrast, there is delay in diagnosis making and managing GTD in developing countries, Sub-Saharan Africa included, due to limited resources and access to quality health care remain a huge challenge in many areas of developing countries. Despite the complexity of health care in many areas of developing countries, there is paucity of data about GTD and outcomes of management of affected pregnancies.

1.2 Problem Statement

Gestational trophoblastic disease is uncommon condition, but not rare in some groups of people. Sub-Saharan Africa is among the regions where the prevalence is higher among women of reproductive age. It is a curable condition, characterized by excellent prognosis even in presence of widespread metastases (Schorge et al., 2009). similarly, preservation of fertility and for successful subsequent pregnancy outcomes has been equally demonstrated (Katz et al., 2007; Schorge et al., 2009)

In many developing countries, characterized by limited resources, and poor access to healthcare, the treatment outcomes of GTD are not well documented.

A database on the management of GTD at MTRH exists but no study has been done to audit the outcomes

1.3 Justification

Gestational trophoblastic disease is known to have good prognosis, even in presence of widespread metastasis. Therefore, effort should not be spared in ensuring optimal outcomes. If not diagnosed early and adequate treatment is not initiated, the disease is significant source of maternal morbidity with an increased risk of mortality from complications. Management of GTD in many areas of developing countries, Sub-Saharan African included is a challenge because of limited resources and difficult access to adequate health care. However, there is paucity of data and few studies have been done to determine the outcomes of management of GTD in Western Kenya.

The findings of this study may identify areas that need adjustments. The study may also identify strengths that can be shared with other GTD treatment centres and potentially inform changes in standard of care.

1.4 Research question

1. What are the patient characteristics of GTD at MTRH?

2. What are the management outcomes of GTD at MTRH?

3. What factors affect the outcome in management of GTD at MTRH?

1.5 Objectives

1.5.1 Broad objective

To determine outcomes of management of gestational trophoblastic diseases at MTRH

1.5.2 Specific objectives

1. To determine the characteristics of patients diagnosed with GTD at MTRH

2. To determine factors associated with the treatment outcomes of GTD at MTRH

3. To determine the treatment outcomes of patients managed for GTD at MTRH

CONCEPTUAL FRAMEWORK

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│   Gestational Trophoblastic Disease      │
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┌───────────────────────┐   ┌───────────────────────┐
│ **Non- malignant GTD** │   │ **Malignant GTD**)   │
│   │   │   │
│ - Complete mole   │   │ - Invasive mole   │
│ - Partial mole   │   │ - Choriocarcinoma   │
│   │   │ - PSTT   │
└───────────────────────┘   └───────────────────────┘

┌─────────────────────────────────┐
│   **MANAGEMENT OF GTD**   │
└─────────────────────────────────┘

┌──────────────────┐ ┌────────────────────────────┐ ┌──────────────────┐
│   │ │ **Independent Variables**   │ │ Medical Treatment│
│ Surgical Treatment│ │ 1.Sociodemographic   │ │   │
│   │ │ characteristics   │ │ 1. Single agent │
│   │ │ 2.Obstetric characteristics │ │   │
│   │ │ 3.bHCG level   │ │ 2. Combined agent│
│   │ │ 4.Metastasis   │ │   │
│   │ │ 5.WHO risk category   │ │   │
└──────────────────┘ └────────────────────────────┘ └──────────────────┘

┌────────────────────────┐
│ **Dependent Variables** │
│   - **Cure**   │
│   - **Mortality**   │
└────────────────────────┘

Figure 1 Conceptual Framework

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Gestational trophoblastic disease comprises a heterogeneous group of related lesions arising from abnormal proliferation of trophoblast of the placenta. It is comprised of benign, non-neoplastic lesions as well as malignant neoplasms(Alan et al., 2007; Baergen & Dizon, 2014; Katz et al., 2007; Schorge et al., 2009). They are composed of syncytiotrophoblastic and cytotrophoblastic cells, with the exception of placental site trophoblastic tumor (PSTT), which is derived, from intermediate trophoblastic cells(Baergen & Dizon, 2014). While they are rare in incidence and curable with good prognosis, they have the potential to become rapidly fatal diseases if left untreated(Gibbs & Karlan, 2008).

2.1.1 Epidemiology

The incidence of GTD varies widely in different regions of the world. One of the reasons for this variation is that epidemiologic data on GTD are limited by the rarity of the disease and inaccurate ascertainment of the number of cases of gestational events in the population (Kenya national guidelines, 2013). In addition, some of the differences may be due to a variety of selection, detection, and reporting biases and the true extent of difference between developed and developing countries is difficult to decrypt(Berkowitz, Goldstein, Horowitz, Dizon, & Vora, 2015). However, it is thought that throughout the world, the highest rates are often reported in Asia, Africa, and Latin America; while North America, Europe, and Australia have lower rates(Barakat, Markman, & Randall, 2009).

Worldwide, the incidence of GTN is less than 1% of all tumors (Kenya national guidelines,2013), while the incidence of hydatidiform mole ranges from 23 to 1299 cases per 100,000 pregnancies(Chiang, Berek, Goff, & Falk, 2011) . The incidence of GTD in the US varies between 0.6-1.1 per 1,000 conceptions, more frequent in teenagers and women over 40 years (Barakat et al., 2009; Chiang et al., 2011). In Asia and the Far East, the frequency is much higher and may be up to 1 per 120 pregnancies(Eble, Tavassoli, & Devilee, 2003). Sub-Saharan Africa is characterized by paucity of data. A retrospective study done in Rwanda in 2016 to determine treatment outcomes managed to recruit only 35 cases over a 10year period(Nzayisenga et al., 2016). In North-western Nigeria, the incidence of GTD is 7.2 per 1000 pregnancies and constitutes 2.4% of gynecological admissions (Kolawole, Nwajagu, Oguntayo, Zayyan, & Adewuyi, 2016). There is paucity of data in Kenya.

2.1.2 Etiology and pathogenesis

Gestational trophoblastic tumors arise in fetal rather than maternal tissue(Alan et al., 2007). Studies have shown the role of paternal genes in controlling of placental growth during pregnancy as well as the role of maternal genes in controlling fetal growth(Baergen & Dizon, 2014). Cytogenetic studies demonstrated that complete moles are usually euploid, paternal in origin, and sex chromatin-positive 46 XX or 46 XY (Alan et al., 2007) , and result from diandrictriploidy. A complete mole arises when an empty ovum is fertilized by a haploid sperm that duplicates its chromosomes or by two haploid sperm (ibid). It results from diandry (fertilization of an empty ovum)(Eble et al., 2003). Thus, with excess paternal genes, there is excessive placental or trophoblastic proliferation(Baergen & Dizon, 2014). There is also a

difference between the malignant potential of moles that are heterozygous (arising from two sperm) and homozygous (arising from a single sperm with duplication of DNA).

2.1.3 Clinical presentation

The clinical presentation of mole pregnancies has changed considerably over the past few decades. However, vaginal bleeding remains the most common symptom and still occurs in virtually all patients. The patients may present with vaginal bleeding due to the detachment of vesicles from the decidua or expulsion of vesicles through the vagina (complete mole)(Schorge et al., 2009). The latter (expulsion of vesicles) is uncommon clinical presentation in developed, but common in developing countries, sub-Saharan Africa included, due to limited resources of early diagnosis, healthcare seeking behaviour of pregnant women as well as limited access to quality of health care. The bleeding may cause anemia if prolonged or hemorrhagic shock leading to death if delay of seeking healthcare facility or adequate treatment.

Furthermore, the patient may also have uterine sizes in excess of that predicted for their gestational age (ibid). In addition, hyperemesis gravidarum, preeclampsia, and theca-lutein cysts develop in approximately one quarter of women. Currently, these complications typically occur chiefly in patients without early prenatal care who present with a more advanced gestational age and markedly elevated serum ß-hCG levels(Alan et al., 2007; Schorge et al., 2009).

2.1.4 Classification

GTD encompasses several diagnoses, including hydatidiform mole, invasive or persistence mole, placental site trophoblastic tumor (PSTT), epithelial trophoblastic tumor (ETT) and choriocarcinoma(Alan et al., 2007; Baergen & Dizon, 2014; Katz et al., 2007; Schorge et al., 2009).

2.1.5 Hydatidiform mole

Hydatiform mole is the most common GTD(Barakat et al., 2009) and the incidence of hydatidiform mole ranges from 23 to 1299 cases per 100,000 pregnancies(Chiang et al., 2011). In US, hydatidiform moles are observed in approximately 1 in 600 therapeutic abortions and 1 in 1,000 to 2,000 pregnancies (William J. Hoskins et al.2005). Approximately 20% of patients with primary hydatidiform mole develop persistent GTD.

Based on based on gross characteristics, histologic findings, and karyotype, the hydatiform mole is categorized as complete and partial mole.

2.1.6 Complete mole

Typically, it presents with uterine sizes in excess of that predicted for their gestational age (Schorge et al. 2008). Vaginal bleeding is the most common presenting symptom, occurring in 97% of cases, followed by excessive uterine enlargement, in 50% of cases(Schorge et al., 2009). Severe vomiting (hg) and also pregnancy-induced HTN can occur in up to 25% of cases and hyperthyroidism in 7% of cases. Ovarian enlargement caused by theca lutein cysts occurs in 25% to 35% of cases. Levels of ß-hCG and TSH are typically higher. Ultrasonography often, but not always, discloses the diagnosis via the classic a snowstorm appearance(Barakat et al., 2009).

2.1.7 Incomplete or partial mole

Patients with partial moles typically present with signs and symptoms of an incomplete or missed abortion. Uterine size is generally small for gestational date; excessive uterine size is observed in only 4% of patients. Patients present with abnormal uterine bleeding in approximately 75% of cases (William J. Hoskins et al. 2003). A clinical diagnosis of a missed or spontaneous abortion is made in 91% of cases of incomplete molar pregnancy. Serum ß-hCG level is in the normal or low range for gestational age. Pre-eclampsia occurs with lower incidence (2.5%) and presents much later with a partial mole than with complete moles but can be equally(Alan et al., 2007; Barakat et al., 2009; Schorge et al., 2009).

2.1.8 Invasive or persistence mole

It is the most common sequelae or complication of hydatidiform mole, representing 70% to 90% of cases of persistent GTD (William J. Hoskins et al. 2003) and the commonest manifestation of gestational trophoblastic neoplasia. The disorder occurs when hydropic chorionic villi are present within the myometrium, its vascular spaces, or at distant sites. Evidence supports that such moles are locally invasive but generally lack the pronounced tendency to develop widespread metastases typical of choriocarcinoma. Invasive moles originate almost exclusively from complete or partial molar gestations. This lesion has been known as chorioadenoma destruens, penetrating mole, malignant mole, and molar destruens(Barakat et al., 2009; Schorge et al., 2009).

2.1.9 Gestational choriocarcinoma

It is extremely malignant tumor, comprised of sheets of anaplastic cytotrophoblast and syncytiotrophoblast cells with prominent hemorrhage, necrosis, and vascular invasion. Chorionic villi are characteristically absent and gestational choriocarcinoma initially invades the endometrium and myometrium, and tend however, to develop early systemic metastases. Studies have shown that about 25% of gestational choriocarcinomas develop after term pregnancies, 50% after molar gestations, and 25% after abortion or ectopic pregnancies. The commonest sites of metastasis are lungs up to 80%, vagina involvement up to 30%, hepatic metastasis and cerebral nervous system (CNS) 10% (Alan et al., 2007; Baergen & Dizon, 2014; Barakat et al., 2009; Schorge et al., 2009).

2.1.10 Placental site trophoblastic tumor (PSTT)

It is the rarest form of GTD representing approximately 1% of all cases of persistent GTD. PSTT exhibits the tendency to remain confined to the uterus and metastasize late in their course. Approximately 15% metastasize to extra-uterine sites, such as the lungs, liver, abdominal cavity, and brain. These tumors are composed of predominantly intermediate trophoblasts, which produce only small amounts of ß-hCG the tumor is more likely to secrete human placental lactogen and small amount of ß-hCG(Fortner, 2007; Konar, 2016). Serum hPL therefore serves as a marker for disease progression or recurrence (Fortner et al. 2007& Duta et al. 2013). In contrast to other trophoblastic tumors, PSTT is relatively insensitive to chemotherapy, thus surgical treatment is recommended.

2.1.11 Epithelioid trophoblastic tumor (ETT)

This is a rare trophoblastic tumor, distinct from gestational choriocarcinoma and placental site trophoblastic tumor. The preceding pregnancy event may be remote, or in some cases a prior gestation cannot be confirmed. Epithelioid trophoblastic tumor develops from neoplastic transformation of chorionic-type intermediate trophoblast. Grossly, epithelioid trophoblastic tumor grows in a nodular fashion rather than the infiltrative pattern of placental site trophoblastic tumor. Hysterectomy is the primary method of treatment, but approximately 20 to 25 percent of patients will present with metastatic disease. Currently, there are too few reported cases to evaluate the efficacy of chemotherapy(Alan et al., 2007; Konar, 2016; Schorge et al., 2009).

2.2 Risk factors

An increased risk of a complete hydatidiform mole is present at both extremes of reproductive age pregnancies. Women over age 40 have a 5.2-fold increased risk, whereas women less than age 20 have a 1.5-fold increased risk(Alan et al., 2007; Barakat et al., 2009; Schorge et al., 2009). According to Ruth and coworkers, this primarily results from a decline quality of oocyte quality; but changes in hormonal function may also play a role(Fretts & Simpson, 2018).From findings of study done in Nigeria by Kolawole (2016), age appears to be an independent factors as 66.7% of patients with hydatiform mole were 20 to 29 years, however, 60.9% of cases were 30 to 39 years [13]. From the findings of the study done in Rwanda, the mean age of all patients treated for GTN was 32 years(Nzayisenga et al., 2016). Expectedly, in both studies, from Rwanda and Nigeria there should be associated risk factors such as lower socio-economic level or ABO blood group associated with the age of patients.

Persistent GTD also occurs more frequently in older patients. In sub-Saharan Africa where there are limited resources in many areas, this may be due to lack of proper follow-up and lack of adequate treatment as well as delay in diagnosis making. An obstetric history of spontaneous abortion is more common in patients with GTD than in women without such a history. Similarly, Kolawole and coworkers noted history of abortion in 29.3% of cases. A history of previous hydatidiform mole increases the risk of a subsequent hydatidiform mole by 10- to 20-fold(Alan et al., 2007; Barakat et al., 2009; Kolawole et al., 2016; Schorge et al., 2009). Thus, Kolawole and coworkers noted history of previous mole in 31.7% of cases. With two previous hydatidiform molar pregnancies, the risk is increased by 40-fold. Conversely, term pregnancies and live births have a protective effect(Barakat et al., 2009). This evidence is also supported by the findings from Nigeria where GTD occurred following term pregnancy in 2.4%. Evidence supports that African American women appear to have a decreased risk of GTD when compared to their Caucasian counterparts. In contrast, Asian women may have an increased risk of GTD (Fattaneh A. et al. 2003). An association has been reported between ABO blood group and choriocarcinoma but not hydatidiformmole . Blood group A is most prevalent (William J. Hoskins et al.2003). In contrast, blood group O is least prevalent. Low socioeconomic conditions or dietary factors may contribute to the development of GTD.

In addition, several studies have found an increased risk of trophoblastic diseases associated with long-term use of oral contraceptives. In one study, the association is considerably stronger for partial than complete. Similarly, others have suggested that oral contraceptives may increase the risk of malignant sequelae after mole evacuation through a tumor-stimulating effect. This effect however, has been restricted to users

of high-dose estrogens, although in others, there are no effects of the pill on post-molar complications(Barakat et al., 2009; Katz et al., 2007; Schorge et al., 2009).

Cigarette smoking has also been linked with the occurrence of trophoblastic disease and to date, some evidence suggested that low carotene intake affected the risk of hydatidiform mole, but no specific dietary associations has been observed for other researchers.

Gestational trophoblastic neoplasia is staged anatomically based on a system adopted by the International Federation of Gynecology and Obstetrics (FIGO). However, patients at low risk for therapeutic failure are distinguished from those at high risk using the modified prognostic scoring system of the World Health Organization (WHO). Patients with WHO scores of 0 to 6 are considered to have low-risk disease, whereas those with a score of 7 or higher are assigned to the high-risk GTN group. Moreover, for the most accurate description of these patients, the Roman numeral corresponding to FIGO stage is separated by a colon from the sum of all the actual risk factor scores–for example, stage II:4 or stage IV:9. Molar pregnancy is not a part of this staging.

Table 2.1:Figo Anatomic Staging

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites (brain, liver)

Table 2.2:WHO risk scoring

Prognostic Factor	0	1	2	4
Age	Younger than 40	40 or older	—	—
Previous pregnancy	Hydatidiform mole	Abortion	Full-term pregnancy	—
Months since last pregnancy	Less than 4	4 to 6	7 to 12	More than 12
Pretreatment hCG (IU/mL)	Less than 10^3	10^3 to 10^4	Greater than 10^4 to 10^5	10^5 or more
Largest tumor size, including uterus	Less than 3 centimeters (cm)	3 to less than 5 cm	5 cm or more	—
Site of spread	Lung	Spleen or kidney	Gastrointestinal tract	Brain, liver
Number of tumors that have spread*	Zero	1 to 4	5 to 8	More than 8
Number of drugs used to treat the tumor that have not worked	None	None	1 drug	2 or more drugs

2.3 Diagnosis of gestational trophoblastic disease

The pathologic diagnosis of a hydatidiform mole is made from dilation and curettage (D&C) performed for an incomplete abortion or because of suspicion of hydatidiform mole based on clinical findings (physical examination, ß-hCG levels, imaging and histopathology). Early diagnosis of hydatidiform mole (first-trimester) is now common because of the routine use of serum ß-hCG measurements and transvaginal sonography. However, the following tests should be performed as initial management: Quantitative serum ß-hCGlevel;Complete blood count (CBC); Prothrombin time, partial thromboplastin time; Comprehensive metabolic panel with renal and liver function tests; Blood type and screen; chest radiograph(Barakat et al., 2009; Katz et al., 2007; Schorge et al., 2009).

2.4 Laboratory findings

It is important to remember that the characteristic of molar pregnancy is its tendency to produce excess serum ß-hCG due to trophoblastic proliferation. As a result, serum ß-hCG levels commonly are greater than that expected for the gestational. However, the measurement of serum ß-hCG is an integral part of the diagnosis and evaluation of the patient suspected of having GTD.

The levels in normal pregnancy reach a peak at approximately 10 to 14 weeks and rarely exceed levels of 40.000 mIU/mL. However, a level in excess of 100,000 mIU/mL suggests GTD. The ß- hCG levels tend to be elevated above normal pregnancy values in a complete mole, whereas a partial mole tends to produce lower levels.

The usefulness of a serum gonadotropin assay depends on the level of the patient's ß-hCG titer and the sensitivity of the test. Today, sensitive and specific immunoassays are available to differentiate ß-hCG from luteinizing hormone (LH) by measuring the beta chain of ß-hCG. It is recommended to monitor serial ß-hCG levels in the same laboratory using the same immunoassay technique (Schorge et al. 2008).

In addition, the rate of the decline in ß-hCG titers is also important. Using the serum ß-hCG radioimmunoassay, a normal post-molar pregnancy ß-hCG regression curve highlighting the weekly ß-hCG levels in patients undergoing spontaneous remission has been constructed (Schorge et al. 2008). This provides a reference for the comparison of serial values. In most instances, the ß-hCG values exhibit a progressive decline to non-detectable levels within 14 weeks following evacuation of a molar pregnancy (Schorge et al. 2008). If the ß-hCG titer rises or plateaus, it must be concluded that viable tumor continues to persist (Schorge et al. 2008; Kartz Lenz et al 2007& Alan H. Descherney et al. 2007). If the levels of ß-hCG are very low and not responsive to treatment, a false-positive ß-hCG result caused by cross-reaction of heterophilic antibodies with the ß-hCG test should be considered(Alan et al., 2007).

In many areas of resources-limited countries however, the diagnosis and follow up of patients with GTD by using serum ß-hCG titer is still a challenge because many centres in the healthcare settings are not able to measure the ß-hCG titers. This makes the management difficult.

2.5 Ultrasonography findings

Ultrasound is today the diagnostic method of choice for evaluating patients with suspected molar pregnancy (Gibbs & Karlan, 2008)

In a complete molar pregnancy, the characteristic ultrasound pattern consists of multiple hypoechoic areas corresponding to hydropic villi, at times described as a "snowstorm" pattern. A normal gestational sac or fetus is not present. Theca lutein cysts may also be seen(Katz et al., 2007; Schorge et al., 2009).

In a partial mole, focal areas of trophoblastic changes and fetal tissue may be noted (William J. Hoskins et al.2003). An ultrasonogram of a choriocarcinoma reveals an enlarged uterus with a necrotic and hemorrhagic pattern, whereas that of PSTT can show an intrauterine mass(Alan et al., 2007).

Ideally, an ultrasonography should be obtained in any patient who presents with bleeding in the first half of pregnancy and has a uterus greater than 12 weeks gestational size. Even when the uterus is appropriate for gestational age, ultrasonography can be key in differentiating between a normal pregnancy and a hydatidiform mole. However, in resources limited areas in Sub-Saharan Africa, it is still not easy to get ultrasound for these patients. For complete mole, patients are seen in advanced stage of disease and clinical diagnosis is made by the presence of vesicles throughout the vagina. In incomplete/partial molar pregnancy however, the diagnosis is made at time of expulsion of the product of conception.

2.6 Histopathology features of GTD

2.6.1 Molar pregnancy

Complete moles characteristically have two prominent features: (1) trophoblastic proliferation and (2) hydropic villi. Gross findings include massively enlarged, edematous villi that give the classic grape-like appearance to the placenta and lack embryonic tissue (William J. Hoskins et al.2003). Pathologic features include hydropic swelling in the majority of villi, accompanied by a variable degree of trophoblastic proliferation. Complete moles have widespread, diffuse immunostaining for ß-hCG; moderately diffuse staining for hPL; and focal staining for placental alkaline phosphatase (PLAP) (Alan H. Descherney et al. 2007). In early gestations, hydropic villi may not be apparent, and molar stroma still may be vascular. This therefore, can result in their misclassification as partial moles or non-molar spontaneous abortions(Barakat et al., 2009; Schorge et al., 2009).

Partial moles are reliably diagnosed when three or four major diagnostic criteria are demonstrated: (a) two populations of villi, (b) enlarged, irregular, dysmorphic villi (with trophoblast inclusions), (c) enlarged, cavitated villi (3 to 4 mm), and (d) syncytiotrophoblast hyperplasia/atypia (Schorge et al. 2008). Good diagnostic reproducibility still can be achieved in most circumstances using these histologic distinctions of complete and partial mole.

2.6.2 Invasive molar

Grossly, invasive moles present as an erosive, hemorrhagic lesion extending from the uterine cavity into the myometrium. Invasion can range from superficial penetration to extension through the wall, with uterine perforation and life-threatening

hemorrhage. Molar vesicles are often grossly apparent. The diagnostic feature of invasive mole is the presence of molar villi and trophoblast within the myometrium or at an extrauterine site. Lesions at distant sites are usually composed of molar villi confined within blood vessels, without invasion into adjacent tissue(Alan et al., 2007; Katz et al., 2007).

2.6.3 Choriocarcinoma

On gross examination, uterine choriocarcinoma is generally a dark red, hemorrhagic mass with a shaggy, irregular surface. Rarely, a lesion may lack significant hemorrhage and appear as a fleshy, tan-gray mass with necrosis. Metastases outside the uterus appear to be well circumscribed and hemorrhagic. Ill-defined infiltrative growth is unusual because of the rapid proliferation with hemorrhage and necrosis. On microscopic examination, choriocarcinoma is characterized by masses and sheets of trophoblastic cells without chorionic villi that invade surrounding tissue and permeate vascular spaces(Barakat et al., 2009).

2.6.4 Placental site trophoblastic tumor (PSTT)

Gross lesions can at times be barely visible or may result in diffuse nodular enlargement of the myometrium. Most tumors are well circumscribed, but they can be poorly defined. A PSTT may be polypoid, projecting into the uterine cavity, or may predominantly involve the myometrium. Invasion frequently extends to the uterine serosa and, in rare instances, extends to adnexal structures. The predominant cells of PSTT are intermediate trophoblasts with rare villi(Barakat et al., 2009).

2.6.5 Epithelioid trophoblastic tumor

Microscopically, this tumor resembles placental site trophoblastic tumor, but the cells are smaller and display less nuclear pleomorphism.

2.8 Management of Gestational Trophoblastic Tumor
2.8.1 Medical management
2.8.1.1 Hydatiform moles

Management of GTD starts with basic investigation. Evidence supports that suction curettage as the preferred method of evacuation regardless of uterine size in patients who wish to remain fertile. This is applied for molar pregnancies. Other surgical procedures, however, may be employed for specific indications. For example, hysterectomy may be performed with preservation of the ovaries if a woman wishes surgical sterilization. In addition, theca-lutein ovarian cysts regress after delivery but may be aspirated if symptomatic. According to Schorge and coworkers (2008), oophorectomy, however, should not be performed except for rare circumstances when torsion of an ovary enlarged by theca-lutein cysts leads to extensive ovarian infarction(Alan et al., 2007; Schorge et al., 2009).

However, following curettage, because of the possibility of partial mole and its attendant fetal tissue, Rh immune globulin should be given to non-sensitized RhD-negative women. Rh immune globulin, however, may be withheld if the diagnosis of complete mole is certain. Medical induction of labor with prostaglandin, oxytocin, intra-amniotic instillation of prostaglandin or hypertonic solutions (eg, saline, glucose, urea) are no longer acceptable methods for evacuation of a molar pregnancy(Alan et al., 2007; Schorge et al., 2009).

2.8.1.2 Follow-up after evacuation of molar pregnancy

After the surgical evacuation of a hydatidiform mole, all patients should be monitored as follows: serum ß- hCG level should be measured 48 hours after evacuation; then ß-hCG level should be determined weekly until results are normal for 3 consecutive weeks, then monthly until results are normal for 6 to 12 consecutive months. However, Pelvic examinations should be performed to monitor the involution of pelvic structures (e.g., ovaries, uterus) and to aid in early detection of metastasis symptomatic. If ß-hCG titer is plateaus or rises, chest X-ray is recommended(Alan et al., 2007; Barakat et al., 2009; Schorge et al., 2009).

In addition, effective contraception is recommended for the entire interval of ß-hCG follow-up testing, namely 6 to 12 months. Preventing pregnancy is important, because a rising ß-hCG titer due to a normal pregnancy cannot be distinguished from that of persistent GTD. During surveillance, oral contraceptive pills, contraceptive patches, and injectable progestins are typically recommended as safe and reliable birth control method. Although barrier methods decrease the risk of transmission of sexually transmitted diseases, in practice the potential for contraceptive failure is greater with diaphragms and condoms than with hormonal methods. Barrier methods are therefore not the first choice for contraception (Schorge et al. 2008). An intrauterine device should not be inserted until the patient achieves normal gonadotropin levels because of the risk of uterine perforation. Finally, all future pregnancies should be evaluated by ultrasonography early in their course because of increased risk of a second mole in subsequent pregnancies. The magnitude of the risk of recurrent partial moles is approximately 2% to 4%(Konar, 2016).

2.8.1.3 Gestational trophoblastic neoplasia (GTN)

Malignant gestational trophoblastic neoplasia may be diagnosed in the setting of invasive mole, choriocarcinomas, placental-site trophoblastic tumors, and plateauing or rising post-molar ß-hCG values (a plateau of 4 values ± 10% over a period of 3 weeks, a rise in ß-hCG of > 10% of 3 values over a period of 2 weeks, or persistence of detectable ß-hCG> 6 months after evacuation).

Once the diagnosis of malignant trophoblastic disease is established, an accurate history and physical examination are crucial. A chest radiograph can diagnose lung metastases, whereas liver metastases may be diagnosed with ultrasonography or computerized tomography (CT) scan. Brain metastases are best evaluated with a CT scan or magnetic resonance imaging (MRI). The ratio of serum ß-hCG values to the concentration of ß-hCG in cerebrospinal fluid (normal > 60:1) may prove helpful (Alan H. Descherney et al. 2007). Baseline hematologic counts, coagulation studies, and hepatic and renal function tests are critical in assessing the risk for drug toxicity(Alan et al., 2007).

After all sites of metastases have been identified and the patient's desires for preservation of reproductive function are determined, specific therapy should be initiated after staging (Schorge et al. 2008; Alan H. Descherney et al. 2007; Kartz Lenz et al.2007 & William J. Hoskins et al.2003). In low risk (with no metastases) patients, the following agents are recommended.

Table 2.3: Drug and dosage

Drug/dosage:
Methotrexate 30–60 mg/m^2 IM once a week.[1]
Methotrexate 0.4 mg/kg/d IV or IM for 5 days, repeat every 14 days
Methotrexate 1 mg/kg IM on days 1, 3, 5, and 7 and folinic acid 0.1 mg/kg IM on days 2, 4, 6, and 8, repeat every 15–18 days
Dactinomycin 1.25 mg/m^2 IV every 14 days
Dactinomycin 10–12 µg/kg/d IV for 5 days, repeat every 14 days

In high risk patients with metastatic gestational trophoblastic, treatment uses either single-agent chemotherapy or multiple agent chemotherapy (Schorge et al. 2008 ; Alan H. Descherney et al. 2007; Katz Lenz et al.2007 & William J. Hoskins et al.2003). However, multiple-agent chemotherapy is used in cases where resistance to a single agent is anticipated (Schorge et al. 2008 ; Alan H. Descherney et al. 2007)

2.8.1.4 Follow-up of GTN

Follow-up of gestational trophoblastic is summarized in the following table

Table 2.4: Follow-up of GTN

Follow ß-hCG titer weekly. Switch to alternative drug if ß-hCG titer rises 10-fold or more, titer plateaus at an elevated level, or new metastasis appears.

Obtain labs daily during treatment cycle or weekly as indicated. Hold chemotherapy for WBC count < 3000 (absolute neutrophil count < 1500); platelets < 100,000; significantly elevated BUN, Cr, AST, ALT, or bilirubin; or for significant side effects (severe stomatitis, gastrointestinal ulceration, or febrile course).

Oral contraceptive agents or other form of birth control should be taken concurrently, and continued for at least 1 year following remission.

Chemotherapy continued for one course after negative ß-hCG titer.

Follow-up program: ß-hCG titer weekly until 3 consecutive normal titers; monthly ß-hCG titer for 12 months thereafter; ß-hCG titer every 2 months for 1 additional year or every titer for 6 months indefinitely.

Physical examination including pelvic examination and chest radiography monthly until remission is induced; at 3-month intervals for 1 year thereafter; then at 6-month intervals indefinitely.

2.9 Prognosis of gestational trophoblastic disease

As described previously, the GTD has good prognosis, even in the setting of widespread metastases; unless untreated. However, based on the clinical classification of malignant gestational trophoblastic disease, patient age and obstetrical history, WHO established a prognostic scoring system as adopted by FIGO(Eble et al., 2003). Adding of prognostic scoring system to anatomic staging established by FIGO, it's though show best reflect of the disease behavior (Schorge et al. 2008). Thus, women with high risk scores (>7) are more likely to have tumors that are resistant to single-agent chemotherapy (Schorge et al. 2008 ; Alan H. Descherney et al. 2007; Katz Lenz et al.2007 & William J. Hoskins et al.2003). They are therefore treated initially with combination chemotherapy (Schorge et al. 2008). Although patients with stage I disease infrequently have a high risk score, those with stage IV disease invariably have a high risk score (Fattaneh A. et al.2003).

The modified WHO prognostic scoring system is summarized in the following table.

Table 2.5 Modified WHO Prognostic Scoring System as Adapted by FIGO

Scores	0	1	2	4
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4-<7	7-<13	≥13
Pretreatment serum hCG (IU/mL)	$<10^3$	10^3-<104	104-<105	≥105
Largest tumor size (including uterus)	-	3-<5cm	≥5cm	-
Site of metastases	Lung	Spleen, kidney	GI	Liver, brain
Number of metastases	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

The clinical classification of malignant gestational trophoblastic disease is used to determine good or poor prognosis in response to single-agent chemotherapy. This classification is summarized as following.

Table 2.6 prognosis

Good-prognosis metastatic disease	Poor-prognosis metastatic disease
a. Short duration (< 4 months).	a. Long duration (> 4 months).
b. Serum ß-hCG < 40,000 mlU/mL.	b. Serum ß-hCG> 40,000 mlU/mL.
c. No metastasis to brain or liver.	c. Metastasis to brain or liver.
d. No significant prior chemotherapy	d. Unsuccessful prior chemotherapy.
	e. Gestational trophoblastic neoplasia following term pregnancy

Generally, these patients of poor prognosis require prolonged hospitalization and multiple courses of chemotherapy (Alan H. Descherney et al. 2007). They often need specialized care and other life-support measures, including hyperalimentation, antibiotics, and transfusions, to correct the effects of marrow depression (Schorge et al. 2008 ; Alan H. Descherney et al. 2007; Katz Lenz et al.2007 & William J. Hoskins et al.2003). The treatment regimens for high risk gestational trophoblastic disease are summarized in the following table.

Table 2.7: drug/dose

Day	Drug	Dose
1	Etoposide	100 mg/m^2 IV (infused over 30 min)
	Actinomycin D	0.5 mg IV bolus
	Methotrexate[2]	100 mg/m^2 IV bolus
		200 mg/m^2 IV (infused over 12 h)
2	Etoposide	100 mg/m^2 IV (infused over 30 min)
	Actinomycin D	0.5 mg IV bolus
	Folinic acid	15 mg IM infusion or orally every 12 hours for 4 doses beginning 24 hours after start of methotrexate
8	Cyclophosphamide	600 mg/m^2 IV infusion
	Vincristine	1 mg/m^2 IV bolus

Treatment of malignant trophoblastic disease must be continued with repeated courses of combination chemotherapy until ß-hCG titers return to non-detectable levels (Schorge et al. 2008). However, complete remission is documented only after three consecutive weekly normal ß-hCG titers have been achieved (Schorge et al. 2008; Alan H. Descherney et al. 2007; Katz Lenz et al.2007 & William J. Hoskins et al.2003). In addition, it is recommended that all high-risk patients receive at least three courses of triple-agent chemotherapy after ß-hCG titers have returned to normal (Alan H. Descherney et al. 2007& Rebecca N. Baergenet al.2013). After remission is achieved, follow-up is the same as for hydatidiform mole and non-metastatic or good-prognosis disease (Rebecca N. Baergenet al.2013).

2.10 Surgical management

Most patients diagnosed with post-molar GTN have persistent tumor confined to the endometrial cavity and are treated primarily with chemotherapeutic agents (Alan H. Descherney et al. 2007). Repeat dilatation and curettage generally are avoided to prevent morbidity and mortality caused by uterine perforation, hemorrhage, infection, uterine adhesions, and anesthetic complications (Schorge et al. 2008). This approach is most applied in United States (Schorge et al. 2008). In Europe however, repeat

uterine curettage is a much more standard part of the management of post-molar GTN and has been shown to reduce significantly both the number of patients needing any further treatment and the number of courses in those who do require chemotherapy (National guideline, Irland 2001).

Hysterectomy may play several roles in the treatment of GTD. First, it may be performed primarily to treat placental site trophoblastic tumors, epithelioid trophoblastic tumors, or chemotherapy-resistant disease (Schorge et al. 2008). In addition, severe uncontrollable vaginal or intra-abdominal bleeding may necessitate hysterectomy as an emergency procedure (Schorge et al. 2008; Alan H. Descherney et al. 2007; Kartz Lenz et al.2007). Studies have shown that in the context of extreme indications, most women undergoing hysterectomy have higher mortality (Schorge et al. 2008). Finally, adjuvant hysterectomy decreases the total dose of chemotherapy needed to achieve clinical remission in low-risk GTD (Schorge et al. 2008; Alan H. Descherney et al. 2007; Katz Lenz et al.2007 & William J. Hoskins et al.2003). Patients with disease apparently confined to the uterus who do not desire future fertility should be counseled about this option (Schorge et al. 2008).

2.11 Outcomes of management of gestational trophoblastic disease

The outcome for more than 98% of women with GTD is excellent, however a small number of women will die from the disease, mainly due to late presentation and diagnosis or drug resistance (Ruth C Frett et al.2013). Findings from several studies have shown the prognosis of patients with low risk disease very closed to 100% survival, whilst patients with high risk disease have a survival of 85-95% (Fattaneh A. et al.2003). Even in developing countries with resources limited, few studies have shown good outcomes. In Nigeria for example, the mortality rate due to GTD was

estimated to 2.4%. Careful follow-up is critical after evacuation of a molar pregnancy, to identify those at risk of developing malignant sequelae (A.H. Gerulathet al.2002).

Long term outcomes however, are early menopause, increased risk of developing secondary cancer as well as infertility. Evidence has shown that the age of menopause for women who receive single-agent chemotherapy is advanced by 1 year and by 3 years if they receive multi-agent chemotherapy. A study of 1377 women treated between 1958 and 1990 showed a 16.6 relative risk of developing acute myeloid leukemia. There were also a 4.6 relative risk for developing colon cancer, 3.4 relative risks for melanoma and 5.79 relative risks for breast cancer in women surviving for more than 25 years. In contrast, if combination chemotherapy is limited to less than 6 months there appears to be no increased risk of secondary cancers (RCOG, 2010).

CHAPTER THREE

METHODOLOGY

3.1 Study design

This was a retrospective descriptive study carried out between January 2010 to December 2017 to determine the outcomes of gestational trophoblastic disease at Moi Teaching and Referral Hospital.

3.2 Study setting

This study was carried out at Moi Teaching and Referral Hospital, The largest referral and teaching hospital in Western Kenya. MTRH is the Second National referral hospital in Kenya located in Eldoret Town of Uasin Gishu County. It serves as a Teaching Hospital for Moi University's school of medicine, Kenya Medical Training College and Baraton University. It has a catchment population of 13 million people located in Western Kenya, parts of North-Rift and some parts of Eastern Uganda. It has several wards and outpatient clinics including the Gyno-oncology clinic which manages all patients with gyno-oncological malignancies including GTD.Gynaecological malignancies are managed by 3 Gynae-oncologists as well as fellows undertaking gynaeoncology sub-specialization in the facility.

3.3 Study population

The study included all medical charts of patients managed for GTD at Moi Teaching and Referral hospital for the period under review: January 2010 to December 2017.

3.4 Eligibility criteria

3.4.1 Inclusion criteria
1. All medical charts of patients diagnosed with gestational trophoblastic disease based on clinical findings (Physical examination-HCG levels, Imaging and Histopathology) and managed as documented in the patient file.

3.4.2 Exclusion criteria

1. All patients who were still undergoing treatment during the study period

2.All patients who did not complete treatment or were lost to follow up.

3.5 Sample size determination

This study was a census survey due to the small number of study population.

3.6 Sampling procedures

A consecutive sampling procedure was used for all medical charts of patients managed for gestational trophoblastic disease who met the eligibility criteria as described. .The files were retrieved from the hospital's Records Department. An electronic database at the gynae-oncology clinic for GTD was used to guide the retrieval of the relevant files for review.

3.7 Study period

This study was carried out from January 2010 to December 2017.

3.8 Data collection and recruitment

Data collection was done through a review of patients' medical charts by the principal investigator and a trained research assistant. Upon obtaining records in the electronic database of the patients diagnosed with GTD from January 2010 to December 2017, the relevant patient files were retrieved from the records department for review.

Clinical notes from the Gynae-oncology ward and clinic at the Cancer Centre provided the required information on the patients with GTD seen during study period. Exposure and variables as outlined in the data collection form were collected retrospectively to determine the outcomes of management of GTD at MTRH. A questionnaire was used for data collection. Information from patients' charts followed up for malignant GTD was stratified as low and high-risk patients according to the modified WHO prognostic scoring system as adopted by FIGO.Information from files of patients followed for non-malignant GTD was collected without stratification. The outcomes of treatment were determined as our main objective.

3.9 Study variables

From patient charts and database, this review considered following variables to determine retrospectively the outcomes of management of gestational trophoblastic disease: Demographic data including maternal age, education level, profession, marital status, residence. Obstetrical history included parity, history of miscarriage or abortion, history of molar pregnancy, use of oral contraceptives or other family planning methods, history of ectopic pregnancy, history of term pregnancy within six, twelve or more than twelve months. Medical history was focused on chronic diseases such hypertension, diabetes mellitus, HIV/AIDS, systemic diseases and life style such as alcohol taking, smoking. Blood works determined HIV status, blood group and rhesus factors, and serum ß-hCG titers. Information on imaging finding, histopathology findings, staging and clinical classification, treatment regimens, surgical treatment and follow-up was also collected.

3.10 Data Management and Analysis

Data was collected using a questionnaire. A descriptive analysis was performed to determine the outcomes of management of GTD at MTRH. The continuous variables were presented as mean with corresponding standard deviation (SD), and categorical as frequency and percentage. In addition, bivariate and multivariate logistic regression was performed to identify the variables associated with GTD outcomes. The data processing and analysis was carried out using the Statistical Package for the Social Sciences software version 16 (SPSS Inc. Released 2007, SPSS for Windows, Version 16.0. Chicago, SPSS Inc). Missing data was handled using Multiple Imputation. Each multiple imputed data set produced was then be analyzed to improve the quality of estimation.

Filled questionnaires will be destroyed by shredding after successful defense of the study findings or publication of study results, whichever comes first and computer databases and USBs will be deleted after 10years.

3.11 Ethical Considerations

1. Approval from IREC and management of MTRH was sought before data collection.

2. Data management was maintained strictly confidential; locking questionnaires in lock and keys cabinets, pass wording the databases

3. There were no conflicts of interest in this study

Study Flow chart

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┌─────────────────────────┐
│                         │
│  103 Patients           │
│                         │
└─────────────────────────┘
            │
            │────────────────────────────►┌────────────────────────────────┐
            │                             │ EXCLUSIONS:13 patients did not   │
            │                             │ meet the inclusion criteria      │
            │                             │                                  │
            ▼                             └────────────────────────────────┘
┌─────────────────────────┐
│                         │
│  90 patients included   │
│                         │
└─────────────────────────┘
            │
            │────────────────────────────►┌────────────────────────────────┐
            │                             │ 5 patients got pregnant during   │
            │                             │ follow up. Excluded from         │
            │                             │ analysis due to difficult in     │
            │                             │ determining whether GTD after    │
            │                             │ pregnancy was Persistence of     │
            ▼                             │ previous disease or Recurrence   │
┌─────────────────────────┐              └────────────────────────────────┘
│ 85 Patients Analysed    │
│ (70 patients with       │
│ GTN,15 with h.mole)     │
│                         │
│ -15 patients with H.mole│
└─────────────────────────┘
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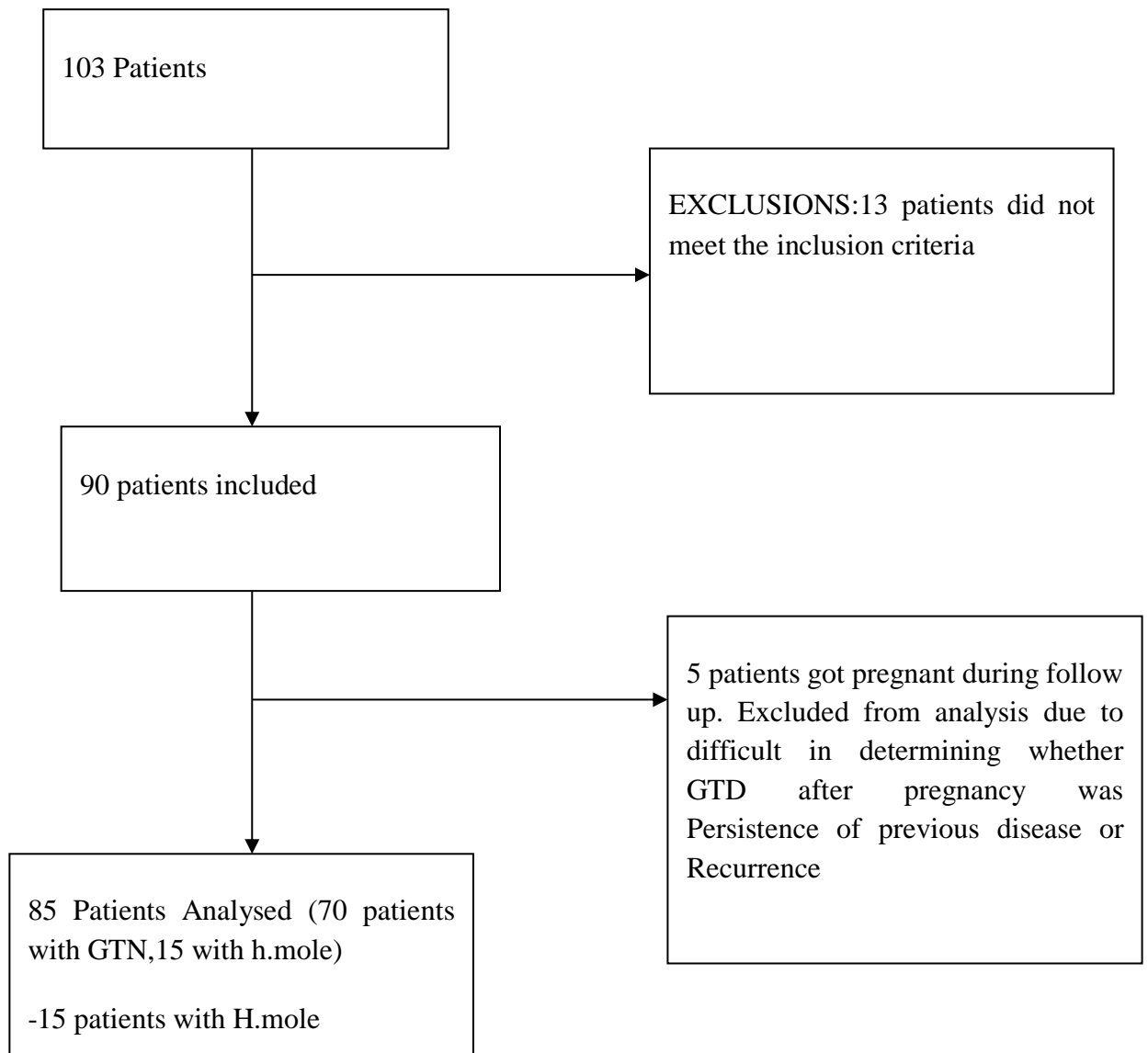
103 medical charts were retrieved from the records department. Thirteen (13) patients did not meet the inclusion criteria and were excluded from the study. Ninety (90) patients were included in the study. Five(5) patients got pregnant during follow up and were excluded from analysis. Eighty five(85) patients were analyzed.

CHAPTER FOUR

RESULTS

4.1 Socio-demographic characteristics

4.1.1 Age distribution

During the time period under review, a total of 85 patients who met the eligibility criteria were managed at MTRH and the Medical Charts of these patients were retrieved and reviewed. The median age of the participants was 29 years with a range of 16 – 57 years. Most women were aged between 18 and 30 years, while the least group was aged below 18 years.
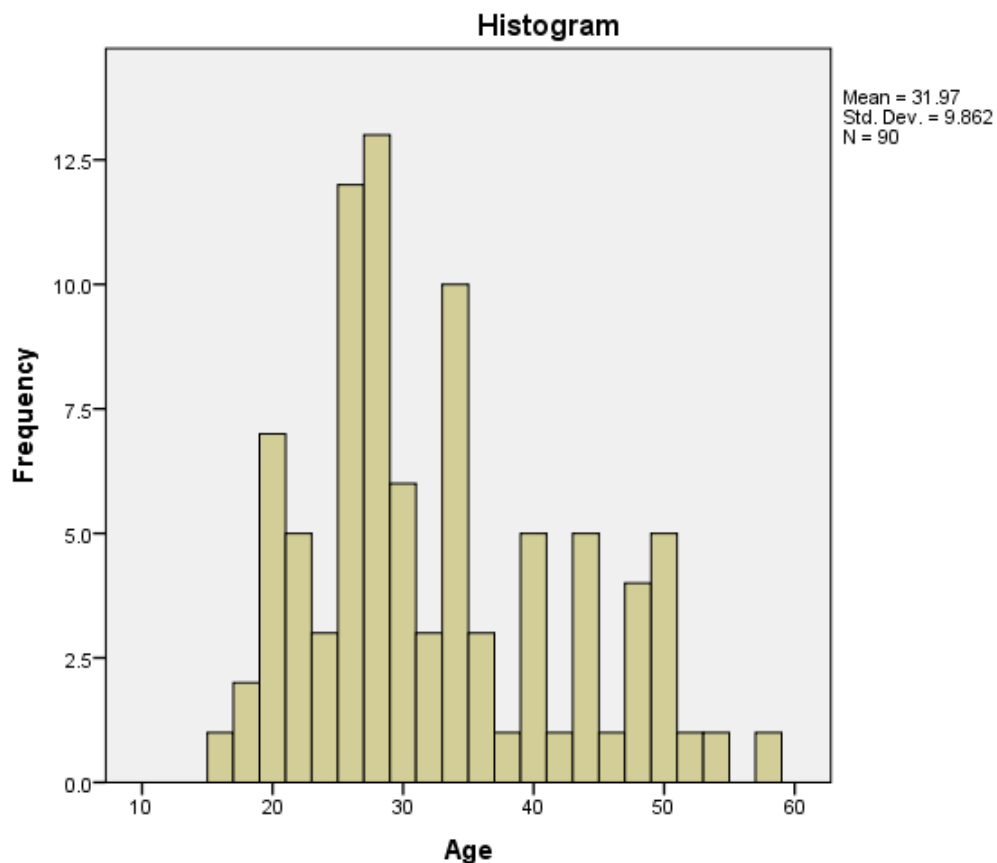

Figure 2: Age distribution N=85

Table 4.1: Socio-demographic characteristics

Variable	Categories	Frequency	Percent
Age	13-19 Years	5	5.9
	20-35Years	54	63.5
	>35 Years	26	30.6
Marital status	Married	50	58.8
	Single	35	41.2
Education level	None/Primary	39	45.9
	Secondary	27	31.8
	Tertiary/University	19	22.3
Occupation	Unemployed	46	54.2
	Employed	39	45.8
NHIF Covered	Yes	29	34.1
	No	58	65.9
Residence	Uasin Gishu	23	27.1
	Outside Uasin Gishu	62	72.9
Total		**85**	**100**

Majority of the women, 50 (58.8%) were married and 35(41.2%) were single. Most of the respondents, 39(45.9 %) had attained only primary level of education or none and 27(31.8%), secondary level. Majority of respondents, 46(54.2%), were unemployed. Majority of the women 58 (65.9%) had no Health insurance and most of them 62 (72.9%) came from outside Uasin Gishu County meaning they were referred to Moi teaching and Referral Hospital.
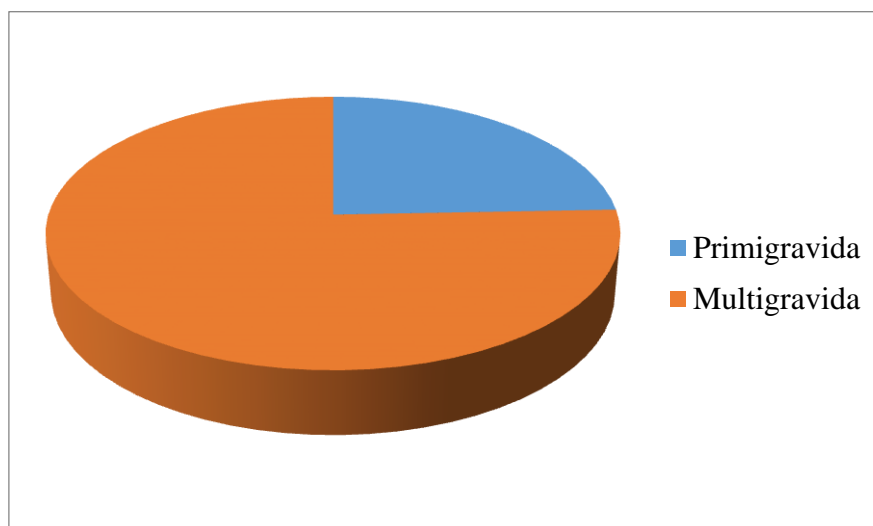
Figure 3: Parity of participants

Of the 85 women, three quarters 64 (75.3%) were multigravida, while 21 (24.7%) were primigravida.

Table 4.2 Other Obstetric Characteristics

Variable	Categories	Frequency N=90	Percent
Family Planning	Yes	21	24.7
	No	64	75.3
Pregnancy Interval	< 6 Months	31	36.5
	6-12 Months	28	32.9
	Above 12 months	26	30.6
Prior Abortion	Yes	22	25.9
	No	63	74.1
Prior GTD	Yes	3	3.5
	No	82	96.5
Partners	1	79	92.9
	More than 1	6	7.1
Total		**85**	**100**

Majority of the women 64 (75.3%) were not using any form of family planning with a larger percentage 31 (36.5%) having a birth spacing of less than 6 months. Twenty six percent of the women had had previous spontaneous abortion with only 3.5 % having had prior GTD. Majority of them 79 (92.9%) had one partner in all their pregnancies.

Table 4.3: Presentation

Variable	Categories	Frequency	Percent
Vaginal Bleeding	Yes	71	83.5
	No	14	16.5
Passage of vesicles	Yes	4	4.7
	No	71	95.3
Total		**85**	**100**

Majority of the women 71 (83.5%) had vaginal bleeding with a mere 4 (4.7%) with vesicles.

Table 4.4: Symptoms

Variable	Frequency	Percent
Vomiting	24	28.3
Blurred Vision	2	2.4
Headache	9	10.5
Epigastric Pain	3	3.5
Abdominal Pain	19	22.4
None	28	32.9
Total	**85**	**100%**

Vomiting and abdominal pains seemed to be the most common symptoms amongst the women studied at 28.3% and 22.4% respectively blurred vision and epigastric pain fell in the minority group at 2.4% and 3.5% respectively.

Table 4.5: Types of GTD

Variable	Frequency N=85	Percent
Hydatidiform Mole	15	17.7
GestationalTrophoblastic Neoplasia	70	82.3
Total	85	100

Majority of the patients seen were categorized as having GTN, at 82.3%, the rest were diagnosed as H. mole

Table 4.6: Histopathology Results

Variable	Frequency	Percent
None	58	68.2
Invasive mole	4	4.7
H mole	4	4.7
Choriocarcinoma	19	22.4
Total	**85**	**100%**

Majority of the patients did not have documented histopathology results 58(68.2%). Histopathological findings showed that most of the patients 19 (22.4%) were diagnosed with choriocarcinoma followed by invasive mole and H Mole at 4 (4.7%) each.

Table 4.7: Serum β-HCG levels at admission

Variable	Frequency	Percent
< 100000	52	61.2
≥100000	33	38.37
Total	**85**	**100%**

Majority of the patients 32(37.7%) had BHCG levels above 100000 at admission.

Table 4.9: Metastatic sites (N=16)

Variable	Frequency n=16	Percent
Lungs	10	62.4
Vaginal	4	25.0
Bladder	1	6.3
Brain	1	6.3
Total	16	100

The most common site for metastasis was the lungs at 10(62.4%) followed by vaginal at 4(25.0%). Bladder and brain were the least frequent sites of metastasis with 1(6.3%) each.

Table 4.14 :WHO risk category

Variable=Risk category	Frequency N=85	Percent
High risk>7	28	27.0
Low risk<7	42	49.4
N/A=h.mole	15	17.6
Total	85	100

Majority of the patients were categorized as low-risk (42/85). High-risk patients were (28/85). The rest 15/85 patients were H. mole patients therefore not categorized per risk level.

Table 4.11: Chemotherapy Regimen Used

Variable		Frequency n=70	Percent
Single Agent Chemotherapy	Dactinomycin/ Actinomycin	18	25.7
	Methotrexate	10	11.4
Combined Agent Chemotherapy	EMACO	28	40.0
Sequential Regimen	Methotrexate then EMACO	8	14.3
	Methotrexate then Actinomycin	3	4.3
	Actinomycin then EMACO	1	1.4
	Actinomycin then EMACO then PT/PE	1	1.4
	Emaco then PT/PE	1	1.4
Total		70	100

Table 4.12: Chemotherapy efficacy

	Frequency n= 70	Change of regimen	Death	Complete remission (%)
Methotrexate	21	11	1	10(47.6 %)
Actinomycin D	20	2	1	18(90.0 %)
EMACO	29	1	8	20(68.9%)

Of the patients treated with methotrexate 47.6% achieved remission, with 11 requiring a change of regimen and 1 death, compared to 90.0% of those treated with actinomycinD achieving remission,2 requiring change of regimen and 1 death.

Only 1 patient started on EMACO was changed to a salvage therapy, with 8 deaths reported, achieving complete remission in 65,6%.

Table 4.13: Surgical complications after suction currettage

Variable	Frequency (n=67)	Percent
Yes	7	10.4
No	60	89.6
Total	67	100

Severe vaginal bleeding was the only reported surgical complication at 7(10.4%).1 patient had hysterectomy done due to hemorrhage.

Table 4.14 :Cure Rate

Variable	**Frequency (N=85)**	**Percent (%)**
Cured	74	87.1
Died	11	12.9
Total	85	100

74(87.1%) patients achieved remission/cure while 11(12.9%) patients died. Cure was defined as 6 months of normal BHCG levels post-treatment.

4.2 Bivariate analysis between independent variables and GTD outcomes.

Table 4.16: Bivariate association between Socio demographic characteristics and outcome

Variable	Categories	Cured n=85	Died	P value
Age	13-19 years	4	1	
	19-35 years	46	8	
	>35 Years	24	2	**0.003**
Marital status	Married	43	7	
	Single	31	4	**0.004**
Education level	None/Primary	30	9	
	Secondary	25	2	
	Tertiary/University	19	0	0.898
Occupation	Unemployed	31	10	
	Employed	34	1	0.954
NHIF	Yes	21	3	
	No	53	8	0.400
Residence	Uasin Gishu	19	4	
	Outside Uasin Gishu	55	7	0.711
Total		**85**	**100**	

A bivariate association between socio demographics and GTD outcomes showed age and marital status to be associated statistically significant with GTD outcomes at p value of 0.003 and 0.004 respectively. The rest of the variables i.e. age education level, occupation, insurance cover and residence showed no association with p values of over 0.05.

Table 4.18 :Bivariate association between obstetric characteristics and outcomes

Variable	Categories	Cured	Died	P value
Family Planning	Yes	14	7	
	No	60	4	0.221
Pregnancy Interval	< 6 Months	30	3	
	6-12 Months	42	8	0.198
Prior Abortion	Yes	15	7	
	No	59	4	**0.028**
Prior GTD	Yes	1	2	
	No	73	9	0.603
Parity	Primipara	18	3	
	Multipara	56	**8**	**0.003**

A bivariate association between selected obstetric characteristics and GTD outcomes showed a significant association between prior abortion and parity at P value of 0.028 and 0.003 respectively with mortality from the disease.

An in-depth analysis done to assess obstetric characteristics and GTD outcomes showed that most of the women who died were multiparous (8/11). History of prior abortion was present in 7 of the mortalities.

Table 4.19: Bivariate association between risk level and GTD outcomes

| Variables | Categories | Outcome | | p-values |
		Cured n (%)	Died n (%)	
Risk category	Low Risk<7	40(47)	2(2.4)	
	High Risk>7	20(23.5)	8(10.6)	
	Not Applicable	14(16.5)	1(0)	
	Total	**74**	**11**	**0.003**

[c] Chi Square, N=85

One(1) patient with H.mole (Benign disease) died at a peripheral facility due to severe hemorrhage during follow up.

A bivariate association between risk category of the disease and outcome showed low-risk disease was associated with higher chances of cure at p value=0.003

Table 4.20: Bivariate association between metastases and GTD outcomes

| Variables | Categories | Outcome | | p-values |
		Cured n (%)	Died n (%)	
Metastases	Present	10(62.5%)	6(37.5%)	
	Absent	64(92.8%)	5(7.2%)	
	Total	**74**	**11**	**0.001**

The most common type of metastases was lungs 10/16 followed by vaginal at 4/16 then bladder and brain each at 1/16.

A bivariate analysis showed that presence of metastasis was associated with higher mortality at P value of 0.001.

Table 4.21: Bivariate association between HCG levels and GTD outcomes

Variables	Categories	Cured n (%)	Died n (%)	p-values
		Outcome		
Bhcg levels	<100000	53(71.6)	0	
	≥100000	21(28.4%)	11(100%)	
	Total	**74**	**11**	**0.001**

A bivariate analysis between bHCG levels and GTD outcomes showed a statistically significant association between bHCG levels>100,000 and mortality at p<0.001

Table 4.22: Multivariate logistic regression association between significant variables and GTD outcome

Variable	N	Unadjusted OR (95% CL)	AOR (95% CL)
Risk category (low risk)	85	**5.16 (2.60, 11.80)**	4.44 (2.30, 9.10)
Metastases	85	**0.34(0.18, 0.78)**	0.19 (0.04, 0.72)
bHCG levels > 100,000	85	**0.89 (0.07,0.90)**	0.77(0.61,0.98)
Prior abortion	85	**0.70 (065,087)**	0.89 (0.64,0.92)
Parity	85	**0.66 (0.44,0.71)**	0.69 (0.55,0.85)

Adjusted estimate for risk level the results show that the low risk patients have more than four times higher odds of being cured, AOR: 4.44 (95% CL: 2.30, 9.10). Presence of metastasis, bHCG levels more than 100,000, multiparity and prior abortion have lower odds of being cured.

CHAPTER FIVE: DISCUSSION

In this study 85 cases of GTD were reviewed. The median age of the participants was 29 years with a range of 16 – 57 years. This coincides with a study done in Nigeria by SU Odenwai and his colleague (Odenwai, 2015) in which the median age was 31 years, It is also close to a study by Lockert and his colleagues in South Africa who found the mean age of patients to be 28.5 years (Lockert et al 2009). In the study of Razieh Mohammed and her colleagues the mean age in Iran was 27.6 years.

Majority of GTD cases occurred in multiparous women. Primiparas were the less affected group. Studies by Sajjanshetty Shalini and Tariq Kashoggi in India also found GTD commonly occurred in multiparous women. This study however differs from the findings in a study by Razieh Mohammed and her colleagues in Iran, who found primiparas as the most common affected group.

This study also showed that in (25.9%) of the cases there was a previous history of abortion and the number of abortions ranged from 1-3. This is consistent with the findings of Moodley M & his colleagues in South Africa where 26% of the cases had history of abortion. Sana & Razieh Mohammed in Iran found 28% of GTD cases had a history of previous abortion.

Clinically most cases presented by vaginal bleeding 71(83.5%), in 4(4.7%) the vaginal bleeding was associated with passage of vesicles. These findings are similar to a study by Sana, where vaginal bleeding was the major presenting feature (78%), passage of vesicles occurred in 5% of cases, which is similar to our study (4.4%). This is in contrast to studies by BM, IU Takai and co-workers in Nigeria & Sajjanshetty Shalini in India where abnormal vaginal bleeding occured in (100%) of the cases.

This could possibly be due to the fact that the study focused on H. mole, whereas most of the patients in our study had GTN.

Review of histopathogical findings showed that 58(68.2%) of the patients did not have histopathology results. This was mainly attributed to the fact that the diagnosis of GTD is mostly made by clinical, biochemical and radiological findings. However, samples collected after suction currettage may not have been processed for histopathology at the referring centre. Choriocarcinorma was the dominant histopathological diagnosis (22.4%), followed by invasive mole and H. mole at 4.7% each. The higher frequency of choriocarcinoma may have been be due to the fact that MTRH is a tertiary facility and the patients seen at the MTRH cancer centre were mainly referrals which could not be managed in the peripheral facilities. The same pattern is seen in studies done by Moodley M and his colleagues in South Africa, Razieh Mohammed and her colleagues in Iran, Dr. Sajjanshetty Shalini in India and Aligbe J.u. and colleagues from Nigeria which showed higher prevalence of choriocarcinorma but with little variations in percentages. Exceptionally this study differs from a study done in Nigeria by Maram and her colleagues, which showed higher prevalence of molar pregnancy (66.7%) followed by choriocarcinorma (33.3%). It also differs from Nizam K & his colleagues' study in Pakistan in which choriocarcinoma was the least common pathology.Most patients with benign disease(H.Mole) are not routinely seen at the cancer centre but are seen in general gynaecology clinic.These patients were not included in the study.

A total of 85 medical charts were reviewed during the study period. Complete cure was achieved in 74(87.1%) of the patients, 11(12.9%) patients died. This is almost similar to 89% cure rate in a study by Moodley M in South Africa. Findings from

several studies have shown the prognosis of patients with low risk disease very close to 100% survival, whilst patients with high risk disease have a survival of 85-95% (Fattaneh A. et al.2003). It is also consistent with high cure rates for GTD worldwide. Even with faster growing GTN,cure rates are as high as 80-90% with intensive treatment(*American cancer society, 2017*).This in contrast to a remission rate of 65.2% in KNH(Gitau S.M 2016),who attributed the low remission rate to non-adherence to established management protocols.

67 patients had surgical intervention and 7(10.4%) suffered persistent vaginal bleeding after evacuation with 1 necessitating a hysterectomy. No other surgical complication was found. This is slightly higher than a study by Khaskheli M et al which found a complication rate of 8.69% in patients who underwent surgical management.

One(1) patient with H.mole (Benign disease) died at a peripheral facility due to severe hemorrhage during follow up.The patient had been seen at MTRH cancer centre and sent for investigations as an outpatient.

Single agent chemotherapy was started in 41(58.6%) patients,13(31.7%) failed to achieve remission and salvage therapy was used. EMACO was the preferred second line therapy in 10(76.9%) of the patients. ActinomycinD was found to be superior to methotrexate in achieving remission at 90.0% vs. 47.6% respectively. Several studies have shown Actinomycin to be superior. Shahbazian et al (2014) found complete remission of 53.3% and 86.7% in patients treated with methotrexate and actinomycinD respectively. Gitau S.M (2016) at KNH found 48.21% remission with methotrexate.

EMACO for high risk disease was started in 29(41.4%) patients and only 1(3.4%) needed second line therapy.

In our study patients with low risk disease had more than four times higher odds of being cured, AOR: 4.44 (95% CL: 2.30, 9.10) this was consistent to a study done by Allazam et al which found that low risk patients were more likely to be cured when put under methotrexate and sufficiently followed up (Allazam,2014). A study done by Musay in Philippines which showed that low risk patients had a 6 time fold odds of getting cured than high risk patients (Musay, 2016).

Our results were also consistent with Goldstein who also found out that low risk patient on combined therapy EMACO were more likely to get cured after a 12 month follow up (Goldstein,2015). However, this is in contrast with Lurain who found no association with risk level and GTD outcomes (Lurain, 2005).

However, a study done in Hong Kong did not find any association between low risk and high-risk patients with a p value of P 0.876. Similarly, another study done in Singapore also found the same results where there was no association between risk levels and GTD outcomes which is not in agreement to what our study found.

Our study also found out that all of the women who died had a bHCG level of over 100,000 this conforms with a study done by Cheng who found the similar results from his prospective study which found out that all the deceased women had a bHCG level of over 100,000.However due to our small sample size statistical significance of bHCG levels and outcomes could be elucidated.

Study Limitations

- The study used data that was derived from routine care; not from a specifically designed study that would have measured predictive factors with greater accuracy.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusions

- In this study the GTD was higher in the 20- 35 years compared to in above 35 years age group, so reproductive age extremities may not be a risk factor for GTD as it is in the literature.

- Increased parity and a history of prior abortion may increase the risk of GTD.

- Patients started on Actinomycin D achieved higher remission rates compared to those started on Methotrexate.

- Cure rate for GTD in MTRH is comparable to the rates worldwide.

- Low risk patients have higher chances of getting cured

6.2 Recommendations

- GTD should be suspected in any multiparous lady in her second/ third decade of life, with a previous history of abortion presenting with vaginal bleeding in her current pregnancy.

- A further study on efficacy and side effect profiles between ActinomycinD and Methotrexate in the treatment of GTD.

- Studies on the outcomes of benign disease patients followed up at general gynaecology clinic as well as studies long-term treatment outcomes of GTD.

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William J Krause & his colleagues. Krause essential Human Histology for Students.

APPENDICES

Appendix A: Questionnaire and Data Collection Tool on Outcomes Of Management Of Gestational Trophoblastic Disease At Moi Teaching And Referral Hospital, Eldoret- Kenya

A. DEMOGRAPHIC INFORMATION	
1. Identification Study ID number[ ][ ][ ][ ][ ][ ] [ ] [ ] IP/OP number [ ][ ][ ][ ][ ][ ][ ][ ][ ] Date of birth: [ ][ ][ ][ ][ ][ ][ ][ ][ ] Age at time of admission: [ ] years old **2. Family and social information** **Marital status: Tick ONE**	**3. Level of education (completed)** **Please tick ONE** Primary school [ ] Secondary [ ] Tertiary(college/University) [ ] Other [ ] None [ ] **4. Life style** **Please tick ONE or more** Alcohol taking [ ] Smoking [ ] Drug abuse [ ] Other [ ], Please specify………………………………… ……

Married [ ] Single [ ] Divorce [ ] Widowed [ ] If married number of living child [ ] **Health insurance**: Yes [ ] No [ ] **Profession: Tick ONE** Student [ ] Health provider [ ] Teacher [ ] Business women [ ] other [ ], please specify………………………………………… **Residence (please fill accordingly):** County…………………Estate………………………..	**5. Contacts** Mobile number………………………………... Partner mobile number……………………….. Other………………………………………… ……. (Precise the relationship with the user)…………………………………… ………

B. OBSTETRIC BASELINE EVALUATION

1.Maternal age

Please tick the interval age

13-19years [ ]

20-29 years [ ]

30- 40 years [ ]

>40 years   [ ]

1. Related to pregnancy

Fill all, please

Parity(delivery beyond 28 weeks   [   ]

Spontaneous abortion (Before 28w)   [   ]

Induced abortion (Medical or not)   [   ]

Gravida (no of preg. Including current) [   ]

4. Related to prior abortion (medical or not)

Please, tick ONE

One previous abortion   [   ]

Two previous abortion   [   ]

Three previous abortion   [   ]

More than three abortion   [   ]

5. Related to the partner

Please, tick ONE

One partner for one pregnancy   [   ]

Different partner for all pregnancies   [   ]

6. Related to use of family planning

Please, tick ONE

Progestins pill   [ ]

Combined oral contraception   [ ]

IUCD   [ ]

Jadelle   [ ]

Implanon   [ ]

Depo-medroxyprogesterone acetate [ ]

2. Related to the interval of last term pregnancy

Please, tick ONE

<6 months   [   ]

Between 6 to 12 month   [   ]

Above 12 months   [   ]

3. Related to abortion (spontaneous abortion)

Please, tick ONE

One previous abortion   [   ]

Two previous abortion   [   ]

Three previous abortion   [   ]

More than three abortion   [   ]

Barrier methods   [   ]

None   [   ]

7. Related to current pregnancy

Please, fill all if known

LMP : ………./………/……

EDD:…………/………/…….

GBD:…………/………/………

Number of ANC visit   [   ]

C. BASELINE OF MEDICAL AND PHYSICAL EVALUATION

1. Medical hx current pregnancy

Please, tick one or all

Hypertension   [ ]

Diabetes mellitus   [ ]

Thyroxicosis   [ ]

HIV /AIDS   [ ]

Cardiac disease   [ ]

DVT   [ ]

Renal disease   [ ]

Hepatitis   [ ]

3. Physical exam

Estimation of fundal height. Please, tick ONE

12/40 [ ] 16/40 [ ] 18/40 [ ] 20/40 [ ]

22/40 [ ] 23/40 [ ] 24/40 [ ] 25/40 [ ]

26/40 [ ] 28/40 [ ] 30/40 [ ] >32/40 [ ]

Vaginal examination

Vaginal bleeding: Yes [ ] No [ ]

Os dilated: Yes [ ] No [ ]

Presence of vesicles: Yes [ ] No [ ]

4. Related to symptoms or signs

Please, tick all

Coercive vomiting   [ ]

Blurred vision   [ ]

Headache   [ ]

Gynecologic cancers   [   ]

Epigastric pain   [   ]

Anemia   [   ]

STDS   [   ]   Abdominal pain   [   ]

Other   conditions(please,   specify   )   [   ]……

Other (please, specify) ………..[   ]

2. Vitals

Please, fill all

[   ] BPs (in mmHg)

[   ] Pulse rate (bpm)

[   ] SPO2 (in percentage)

[   ] Respiratory rate (bpm)

[   ] Weight (Kg)

[   ] Height (cm)

[   ] BMI

D. BASELINE OF LABORATORY EVALUATION

1. Blood work up

[   ] Blood group and Rhesus (e.g A+)

[   ] Hemoglobin level (Hb)

[   ] VDRL (please put 'N' if negative and 'P' if positive)

[   ] HIV (please put 'N' if negative and 'P' if positive). If positive please specify the year of positivity

[   ] RBS or FBS

[   ] Partner blood group

Renal function

[   ] Creatinine

[   ] Urea

[   ] Electrolyte

Liver function

[   ] AST

2. Urine

[   ] Pregnancy test, if positive put "+" , if negative put "- "

[   ] Proteinuria (please put 'N' if negative and '+ or ++' if positive)

3.

4. Serum ß-hCG

Please, tick ONE

[   ] Undetectable

[   ] 5-10

[   ] 10-100

[   ] 100-1,000

[   ] 1,000- 10. 000

[   ] 10.000- 20.000

[   ] 20.000-40.000

[ ] ALT	
[ ] Bilirubin	[ ] 40. 000-50.000
Thyroid function test	
	[ ] 50.000- 100.000
[ ] T3	
	[ ] ≥100.000
[ ] T4	
[ ] TSH	
Other tests	
[ ] BUN	
[ ] CBC, specify abnormal values…………	
…………………………………………….	

E. BASELINE OF IMAGING AND HISTOPATHOLOGY EVALUATION

1. Ultrasonography findings

Please, tick all

[   ] Multiple hypoechoic area (hydropic villi)

[   ] Absent fetus

[   ] Focal hypoechoic area plus fetal tissue

[   ] Ovarian cysts (theca cysts)

[   ] enlarged uterus with a necrotic and hemorrhagic pattern

[   ] Intrauterine mass

[   ] Other findings, please specify……………..

………………………………………

………………………………………

4. X-ray

Done: Yes [   ] No [   ]

If yes, please specify findings………………...

………………………………………
……

………………………………………
……..

………………………………………
……..

………………………………………
……..

5. Related to metastases

Metastasis presents : Yes [   ]   No [   ]

If yes, please specify extension or affected
organs………………………………
………

6. Histopathology features

Please, tick all

……. **2. MRI** Done: Yes [ ] No [ ] If yes, please specify findings…………………. ………………………………………… …	[ ] hydropic swelling trophoblastic proliferation [ ] Enlarged, irregular, dysmorphic villi (with trophoblast inclusions),
	[ ] Enlarged, cavitated villi (3 to 4 mm),
3. CT- Scan Done: Yes [ ] No [ ]	[ ]Syncytiotrophoblast hyperplasia/atypia
If yes, please specify findings…………………. ………………………………………… ……. ………………………………………… ……	[ ] Presence of molar villi and trophoblast within the myometrium or at an extrauterine site
	[ ] Sheets of trophoblastic cells without chorionic villi
	[ ] Presence of intermediate trophoblasts with rare villi

F. BASELINE OF TREATMENT

1. Surgical treatment

Please, tick all

[   ] Suction curettage

[   ] Subtotal hysterectomy

[   ] Total abdominal hysterectomy

[   ] radical hysterectomy

[   ] Cystectomy

[   ] oophorectomy

Related to complications:

Please, tick all

[   ] Perforation

[   ] Profuse bleeding

[   ] Respiratory distress (pulmonary embolism)

[   ] Heart failure

2. Medical treatment

Given: Yes [   ] No [   ]

Before starting treatment, the patient is classify as (Please, tick ONE)

[   ] Low risk

[   ] High risk

Patient received (please, tick ONE)

[   ] Single- agent chemotherapy

[   ] Combined –agent chemotherapy

Related to the drugs regimens, tick ONE or more that patient received

[   ] Methotrexate

[   ] Dactinomycin/ Actinomycin

[   ] MAC

[   ] CHAMOCA

[ ] None	[ ] EMACO
Transfusion during procedures:Yes[ ] No[ ]	
	[ ] EP-EMA
Related to family planning after evacuation	[ ] Other,specify
Please, tick ONE	[ ]SEQUENTIAL REGIMENS,describe the sequence of regimens used
[ ] Combined oral contraception (pills)	
[ ] IUCD	
[ ] Jadelle	
[ ] Implanon	
[ ] Condoms	
[ ] Other methods, please specify…………….	

G.FOLLOW-UP AND OUTCOMES

(WITHIN 12 MONTHS)

Related to follow-up post surgical treatment	Related to the cycles of chemotherapy
	Please, tick ONE in each session
What surgical method was done	[ ] First session
Evacuation/suction curretage[ ]	[ ] Second session
Hysterectomy [ ]	
	[ ] Third session
Date:……../……./………(Date of suction evacuation/hysterectomy)	[ ] Fourth session
Please, tick ONE	[ ] More sessions-specify cycle number
[ ] Weekly follow-up	
	1. **Related to outcomes**

[　] Monthly follow-up	**Pleased, tick ONE**
If it is a weekly follow-up, please specify how many weekly follow-ups **[　　].**	[　] Patient improved
If it is a monthly follow-up, please specify how many months of follow-up [　　].	[　] Patient cured
	[　] Patient needs further intervention
Serum ß-hCG level	[　] Patients got complications, please specify
Please, tick ONE,and indicate week or month of follow up	…………………………………………… ……………………………………………
[　] Undetectable [ ]week [ ]month	[　] Patient got pregnancy during follow-up
[　] 5-10　　　　[ ]week [ ]month	[　] Patient died during treatment or follow-up
[　] 10-100　　　[ ]week [ ]month	[　] Other outcomes, please specify

[ ] 100-1,000 [ ]week [ ]month [ ] 1,000- 10. 000 [ ]week [ ]month [ ] 10.000- 20.000 [ ]week [ ]month [ ] 20.000-40.000 [ ]week [ ]month [ ] 40. 000-50.000 [ ]week [ ]month [ ] 50.000- 100.000 [ ]week [ ]month [ ] ≥100.000 [ ]week [ ]month	

Appendix B: Work Plan

Month& year	January to May	June to July	July	Aug2016	Sept to	January To June	April to June	Aug to
Proposal Development and Approval	▓							
IREC Submission and IREC approval		▓						
Training of research assistants			▓					
Data collection and Follow up				▓				
Data analysis& Thesis writing					▓			
Extern review						▓		
Dissemination and feedback							▓	

Appendix C: Study Estimated Budget

ITEMS	QUANTITY	UNIT PRIZE	TOTAL COST
Biro pens	10	20	200
Printing Paper	10	1000	10000
Box Files	10	500	5000
Staple Pins	5	200	1000
Stick Notes Pad	2	250	500
internet charges			5000
typing proposal			-
printing proposal			5000
photocopying Data Collection Forms			5000
Research assistant allowance and communication fees	2	25000	50000
TOTAL			81,700

Appendix D:IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/1/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2017/176
Approval Number: 0002072

1st March, 2018

Dr. Riggah Hamadi Mwariggah,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH &
ETHICS COMMITTEE
0 1 MAR 2018
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Riggah,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-
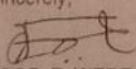
"Management Outcomes of Gestational Trophoblastic Disease at Moi Teaching and Referral Hospital: A 7 Year Review".

Your proposal has been granted a Formal Approval Number: FAN: IREC 2072 on 1st March, 2018. You are therefore permitted to begin your investigations.
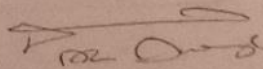
Note that this approval is for 1 year; it will thus expire on 28th February, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc   CEO   -   MTRH   Dean   -   SOP   Dean   -   SOM
     Principal   -   CHS   Dean   -   SON   Dean   -   SOD

Appendix E:Hospital Approval

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone:(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

7ᵗʰ March, 2018

Dr. Riggah Hamadi Mwariggah
Moi University,
School of Medicine,
P.O. Box 4606-30100,
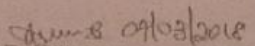ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Management Outcomes of Gestational Trophoblastic Disease at Moi Teaching and Referral Hospital: A 7 Year Review".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
C E O
APPROVED
0 7 MAR 2018
SIGN................................ - 30100, ELDORET

09/03/2018
DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc   -   DCEO, (CS)
      -    Director of Nursing Services (DNS)
      -    HOD, HRISM

All correspondence should be addressed to the Chief Executive Officer
Visit our Website: www.mtrh.go.ke
A WORLD CLASS TEACHING AND REFERRAL HOSPITAL