COMPARISON OF THE TREATMENT OUTCOMES OF METHOTREXATE AND ADRIAMYCIN D IN THE TREATMENT OF LOW RISK GESTATIONAL TROPHOBLASTIC DISEASE AT THE KENYATTA NATIONAL HOSPITAL

(A Retrospective Cohort Study)

A Dissertation Submitted for the Award of Master of Medicine in Obstetrics and Gynecology, College of Health Sciences, University of Nairobi.

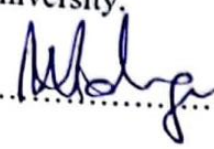**PRINCIPAL INVESTIGATOR**

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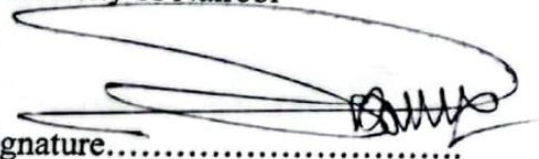Department of Obstetrics and Gynecology

DECLARATION

This research was undertaken in part fulfillment of the Masters of Medicine in Obstetrics and Gynaecology and is my original work and has not been undertaken and presented for a degree in any other University.

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CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of Dr Moses Njoroge, under the guidance and supervision of Dr Felix Odawa and Dr. Orora Maranga. This is to confirm that this dissertation has not been presented in the University for the award of any other degree.

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LIST OF ABBREVIATIONS

Act-D   Actinomycin D

B hcg   Beta Human Chorionic Gonadotropic Hormone

CR   Cure Rate

ESMO   European Society of Medical Oncology

ETT   Epitheloid Trophoblastic Tumor

FIGO   International Federation of Gynecology and Obstetrics

GOG   Gynecology Oncology Group

GTD   Gestational Trophoblastic Diseases

GTN   Gestational Trophoblastic Neoplasm

HM   Hydatid Mole

KNH   Kenyatta National Hospital

MTX   Methotrexate

PSTT   Placental Site Trophoblastic Tumor

WHO   World Health Organization

OPERATIONAL DEFINITIONS

Disease relapse: Defined as an increase in β-hCG concentrations more than six weeks after treatment completion

Complete Response or Remission: This is where three consecutive weekly levels of HCG are in the normal range (less than 5 mIU/mL) and continued remission is where the level of HCG remained at a constant level for whole year

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ABSTRACT

Introduction: Gestational Trophoblastic Disease explains an infrequent and heavily treatable cohort of growths that are caused by placental tissue and by an abnormal conception resulting from abnormal fertilization. The management of these disorders as per the world health organization entails risk scoring; low risk gestational neoplasms (LRGTNs) have been managed using single chemotherapeutic agents with variable outcome. The treatment protocol and outcomes however depend on institutional experience with lack of consensus about the most appropriate treatment regimen.

Objective: To determine the treatment outcomes and side effects of using methotrexate in comparison to Actinomycin D in the management of patient with low-Risk Gestational Trophoblastic Neoplasms at the Kenyatta National Hospital

Methodology: The study was a retrospective cohort study comparing the treatment outcomes for methotrexate and Actinomycin D among patient with low risk gestational neoplasm. A sample of 105 records (70 for methotrexate and 35 on Actinomycin D) was included in the study. Following Ethical approval, data was extracted from the patient records and uploaded to the SPSS version 23 software for cleaning and coding before analysis. Characteristics of the patient and the disease, such as age, parity and serum human chorionic gonadotropic (HCG) levels, FIGO 2002 anatomic stage and risk scores assessed. The Pearson $\mu2$ test was utilized in comparing and identifying possible associations between quantitative variables. In the case of continuous variables with a lop-sided distribution, the Mann Whitney test was utilized in comparing means between two independent classes. The level of significance for each test is fixed at $p<0.05$.

Results:

The patients on actD regimen had significantly better average remision rate (91.4%) than those in MTX regimen (72.9%) (p=0.028). The average number of chemotherapy sessions attended by patients was comparable across both groups, 6 for the ACT-D and 7 for the MTX (P=0.140). Adjusted associations between treatment outcome and potential predictors showed that only the treatment group and the modified WHO scoring before chemotherapy were significant predictors of treatment outcomes.

In our study, hair loss was more common among patients with MTX (57.1%) compared to ACT-D (37.1%), Mouth sores more in patiens on ACT-D (25.7%) compared to MTX (7.1%); The other side effects (nausea, anemia, and thrombocytopenia) were less common and similar across both groups

Conclusion:

Our findings add to the literature that has demonstrated that single-agent chemotherapy can be very effective in treating low-risk GTN. Compared with MTX, ACT-D may be the better option as a first-line single chemotherapy.

Study utility: The outcomes of this study will be incorporated into the KNH treatment protocols for the LR GTNs management using the most effective, safest and easy to follow treatment protocol.

Key words: Gestational Trophoblastic Neoplasm, Low Risk, Methotrexate, Actinomycin D

1.0 INTRODUCTION

1.1 Background and Epidemiology

Gestational Trophoblastic Diseases (GTD) characterizes a rare group of highly curable tumors that are caused by the placental tissues and an abnormal conception of disordered fertilization (1). Most GTD cases consist of two hydatidiform moles (HM) types, with an intrinsic capability to advance towards rare disease known as Gestational Trophoblastic Neoplasia (GTN) (2). The occurrence of GTN is hard to ascertain with conviction, given the lack of data concerning the incidence of pregnancy and following trophoblastic events in most countries. However, roughly 50 percent of GTN cases come from either of the two types of molar pregnancies, 25% from miscarriage or tubal pregnancies and 25percent from term and preterm pregnancies (3). The overall GTN incidence is estimated at 1 in 40,000 pregnancies after all types of pregnancies (3).

Gestational Trophoblastic Neoplasms might have histology of both choriocarcinoma or molar tissue, and sometimes though rare of placental trophoblastic tumor (PSTT) or trophoblastic epithelioid tumor (ETT), if GTN develops after a molar pregnancy. Gestational Trophoblastic Neoplasia, usually non-metastatic, happens in 1 to 4% of patients after partial HM (1). In Europe and North America after a non-molar pregnancy, gestational trophoblastic neoplasia usually occurs in about 2 to 7 per 100000 pregnancies and the incidence is higher in Southeastern Asian and Japan with 5 to 200 per 100 000 pregnancies (4). The GTN incidence is approximated to be 1 in 15,000 pregnancies after a spontaneous miscarriage, while the incidence is estimated at 1 in 150,000 pregnancies following a pregnancy that has reached term (4).

1.2 Pathophysiology of Gestational Trophoblastic Neoplasms

Molar pregnancies result primarily as an imbalance or excess of paternal versus maternal genetic material: complete moles are developed by loss of oocyte genetic material, then fertilized by two or one sperm duplicating their chromosomes. Thus, complete moles have only paternal DNA and are most commonly diploid with a 46XX karyotype (46XY also occurs). Partial moles grow due to oocyte fertilization by two sperms, leading into triploidy with 2:1 paternal to maternal DNA content. Gestational Trophoblastic Neoplasm may have contributions from both paternal and maternal genomes.

It is known that embossing has a role in the molar pregnancies and GT development; with excess paternal genes, there is excessive placental or trophoblastic proliferation. Several studies have described interesting molecular path-ways that might add to the development of GTD (4). Somatic point mutations and instability of mitochondrial DNA were found in samples of hydatidiform moles and choriocarcinoma (5). Amplification and overexpression of various oncogene products, such as c-erbB-2, c-myc, c-fms, and mdm-2, Epidermal Growth Factor and metallo-proteinases have been shown to be linked to a higher proliferation index, more hostile behavior, and malignancy development in GTD (5).

1.3 Classification and Staging of Gestational Trophoblastic Neoplasms

The International Federation of Gynecology and Obstetrics (FIGO) adopted HCG criteria used to diagnose postmolar GTN is as follows: 1) a plateau of hcg values or +/- 10percent of the baseline documented over a period of three weeks (day 1 , 7 , 14 , 21); 2) the level of hCG increased more than 10% over the baseline documented for a period of 14 days (day 1, 7, 14) and 3) hCG persistence over a period of six months following molar evacuation (6).

Gestational trophoblastic neoplasias have an extensive range and could be subdivided into 4 clusters: 1. Invasive moles, 2. Choriocarcinoma, 3. Placenta Site Trophoblastics Tumor, 4. Epitheloid Trophoblastic Tumor (ETT). Patients are categorized as Low risks (LR, stage I–III, score less than 7) and high risks (HR, stage 2-4, scores more than 7) groups. This prognostic system projected by the World Health Organization foretells the potential for chemical resistance (2) as illustrated in Figure 1. FIGO anatomic staging for Gestational Trophoblastic Neoplasia

- **Stage I:** Diseases exists in the uterus.
- **Stage II:** GTD reaches outside the uterus though is confined to genital organs.
- **Stage III:** GTD reaches to the lungs and can involve or not the genital structures.
- **Stage IV:** GTD has protracted to other distant structures.

Table 1: *Prognostic Scoring for Gestational Trophoblastic Neoplasia (total score < 6 = Low Risk; >7 = High Risk)*

FIGO Scoring	0	1	2	4
Age(years)	< 40	>40		
Antecedent Pregnancy	Mole	Abortion	Term	
Pregnancy to treatment interval (months)	<4	4 to < 7	7 to < 13	> 13
Pretreatment Serum hCG (iu/l)	< 1000	1000–10,000	10,000 – 100,000	> 100,000
Largest tumor size, consisting uterus (cm)	< 3	3 to <5		
Site of metastases	Lung	Spleen & Kidney	Gastro – intestinal	Liver and Brain
Number of metastases		1 – 4	5 – 8	>8
Previous failed chemotherapy			Single Drug	> 2 Drugs

1.4 Management of Low Risk Gestational Trophoblastic Neoplasms

Early detection and treatment of GTNs guarantees excellent cure rates with a total patient survival of 90% grounded on prognostic factors and the International Federation of Gynecology and Obstetrics (FIGO) 2000 scoring system 2000 (7). LRGTN is well-defined as stage 2 or 3 GTN, which also scores below six on the basis of the amended World Health Organization (WHO)

prognostic system as adjusted by FIGO (8) or persistently high HCG and/or uterine-confined tumors (9).

The FIGO in 2002 declared low-risk GTN as being treatable with single-active chemotherapy, which led to a survival rate of about 100percent (10). The European Society of Medical Oncology gave recommendations for the treatment and diagnosis of GTD's in September 2013. They include: (11).

Table 2: *ESMO Guidelines for the Management of Gestational Trophoblastic Neoplasms*

ESMO Recommendations for the Management of Gestational Trophoblastic Neoplasms
• GTN management requires an examination of pathologies, central care and surveillance of human chorionic gonadotropin (hCG)
• Following staging using the FIGO system of scoring, both a single agent methotrexate or a single agent actinomycin D can be used in patients suffering from high-risk disease or multi-agent chemotherapy.
• Low-risk disease needs maintenance therapy for 6 weeks following hCG standardization, whereas high-risks liver or brain metastases require 8 weeks of maintenance dosing.
• In patients with ultra-high risk GTN, low-dose cisplatin and etoposide induction can reduce the risk of premature death
• The management of PSTT/epithelioid trophoblast tumor (PSTT/ETT) differs as per disease stage and risks factors for unfortunate outcomes, that includes intervals since last pregnancy, patients who have had pregnancy over the last four years needing pelvic node sampling + hysterectomy, those who have stayed longer needing a multiagent treatment followed by high-dose chemotherapy.

Subsequently, researchers have used various protocols with Methotrexate (MTX) and Actinomycin D (Act-D) for low-risk GTN treatment (12). Methotrexate has widely been used with actinomycin D being preferred among patients with liver dysfunction.

1.4.1 Methotrexate Therapy

Several treatment and dosage regimens for the single agents have been used in the management of LRGTNs, including the use of sequential therapy. Methotrexate has largely been used because of its effectiveness, convenience, well tolerability and cost effectiveness; folinic acid (FA) is usually administered to protect against bone marrow toxicity. There are several dosing regimens for methotrexate:

1. MTX-FA 1mg/kg (IM/IV) for 8 days on days 1, 3, 5 and 7: FA is administered 24 hours after each dose of MTX

2. MTX 5- day regimen: MTX 0.3 to 0.5mg/kg IM or IV for 5 consecutive days

3. Weekly MTX: Weekly intramuscular injection of MTX: dosage of 30 to 50 mg/m2

4. High dose MTX regimen: high dose MTX infusion (100mg/m2IV) followed by a half day continuous infusion at 200mg/m2; FA is administered orally beginning 24 hours and continued for 6 doses.

At KNH the 8-day regimen is commonly used and only patients who were on this regimen were considered for the study. Nausea, vomiting, hematological toxicity, mucositis and conjunctivitis are among the most known side effects of MTX regimen.

1.4.2 Dactinomycin Therapy

Because of the associated toxicity (hyperemesis, alopecia, tissue injury risk in extravasation case), this is usually administered in 'pulsed' dosing (1.25mg/m2 IV every 14 days). An alternative regimen entails giving an IV push (10 – 12 mcg/kg) daily for five days on weekly basis.

1.5 Follow Up and Prognosis

The levels of serum HCG are observed every week during treatment. After a normal serum HCG level, 6 weeks of maintenance chemotherapy is administered. The levels are monitored on monthly basis for one year after 3-4 normal HCG serum concentrations. The change from methotrexate to Actinomycin D could be considered if the patients getting methotrexate develops higher or plateau levels of serum hCG for non-metastatic or metastatic low-risk GTN. Additionally, consolidation therapy is given after complete remission is attained to prevent relapse; this consists of three courses of the last effective regimen.

The total rates of response for these different treatment regimens range from 60 to 98 percent (Mitra). As main therapy for patients of LRGTN, single-dose actinomycin has generated an outstanding remission percentage, has milder toxicity, and is as well affordable and acceptable. 8–10 Methotrexate as well as actinomycin are both still utilized for LRGTN (10). The risk of LR GTD recurrence is less than 5percent–10percent. If single-agent chemotherapy fails or GTD resets, the patient needs to be re-scored. If they are still at low risk, they can sequentially be given either MTX or Act-D single-agent drugs. However, combination chemotherapy should be used if re-score has led to high risk (16).

2.0 LITERATURE REVIEW

2.1 Introduction

The first MTX study was done in 1956 and was first reported to have been used in conjunction with folinic acid as a rescue in 1971 (10). Act-D was found to be used as a first-line treatment for LR GTD in 1972. Diverse protocols for treating low-risks GTD have so far been observed,

although the best and most economical and minimally toxic protocol has not yet been agreed upon. Nevertheless, each health facility and nation has chosen the appropriate treatment for its patients, based on its circumstances and the conditions of its patient.

Since the rate of success of GTN treatment with either of the known drugs is high, investigators evaluated modified MTX administration protocols to reduce systemic toxicity, reduce overall remission time and costs without hospital admissions (13). As per Osborne and Gerulath, the MTX eight-day Charing Cross modified Bagshawe protocol was the most frequently used in Europe and around the globe, with the exception of Latin and North America: an adjusted dose of MTX 50 mg is repeated every 14- 16 days; reviewing 10 MTX/FA studies in 1238 patients demonstrated 20.3 percent initial resistance) (13).

Act-D is among the two medicines used the most in low-risk GTN therapy. In cases of MTX resistance and/or toxicity, it is usually administered with a 5-day schedule (12)(14). Several researchers assessed the use of the pulsed act-D regimen with a view of reducing toxicities associated with the five-day Act-D schedule (14). In 4 studies, the pulsed Act-D was utilized as the first line chemotherapeutic agent: The mean courses count was 4.9; resistance varied from 8% to 24% and cure rates was 76percent (low risks metastatic GTN) to 86percent (non-metastatic GTN) (15).

2.2 Treatment Outcomes for Single Therapy for Management of Gestational Trophoblastic Neoplasms

In 2011, Gynecologic Oncology Group (GOG) published a phase III randomized trial assesing the effectiveness of weekly MTX and bi-weekly pulse-D Act regimen; remission rate in 216 randomly selected patients suffering from low risk GTN were 58percent and 73percent respectively, on the MTX and Act-D arms (13). The higher reaction rates seen with Actinomycin D was in line with that perceived in other researches that compare Actinomycin D to MTX schemes 5 or 8 days that are widely utilized and give a higher initial remission rate (9).

Corresponding with this, in a Cochrane assessment, Actinomycin D treatments was linked to substantially higher common rates of response than MTX treatments (9). In addition, CR is achieved with less cycles of Act-D chemotherapy (4.8) than for patients on MTX cycles (6.8) (19). In addition, when Act-D is utilized as secondary therapy in Low Risk GTN patients who were previously on MTX, the CR rate was 75percent (12). In a similar survey, Young Jae et al. although the findings showed no statistical significance, the response rates were higher for the Actinomycin D group than for the MTX group (83.3 percent vs. 62.2 percent) (13).

A randomized trial which compared 30 mg/m2 methotrexate per week in GTN patients (with WHO score less than 6) vs 1.25 mg/m^2 of actinomycin D administered weekly revealed a higher rate of response with actinomycin D (16). The distinction is mostly pronounced among WHO patients 5-6 risk stratification (17).

In a similarly conducted study, where the side effects of either MTX or Act-D were compared, there existed no statistically substantial differences in the complications which comprised lesions in the buccal mucosa, elevated liver enzymes, nausea and other conditions between the 2 groups (p=1,0.86,0.46, respectively) (7). The Actinomycin D group got fewer chemotherapy courses to attain remission and was generally more effective.

The outcomes for remission rates between the two groups have also been notably different; The full remissions with MTX pulse therapy was 49-53 percent in three clinical trials markedly lower than the 69–90 percent in ACT-D pulse treatment (1820). In one research study, a 5-day Actinomycin regimen compared to an 8-day MTX-FA regimen for treating GTDs without metastasis; total remission was 100 percent in the Actinomycin group and 74 percent in the Methotrexate group (18). In a study by Yarandy et al, an average of 4.8 courses in the Act D group was noted compared to 6.8 in the group receiving MTX and a longer treatment duration in the group of Act-D was observed for full remission (19). In other studies, 4 Actinomycin D courses was the average number of chemotherapy courses for complete remissions (20).

In a study carried out by the Gynecology Oncology Group (GOG), a 73 percent remission rate with Act-D pulse regime, administered once in every 2 weeks, was observed. The MTX group achieved a 58 percent remission rate. When compared, two weekly intravenous Act-D pulse regimens were therefore seen to be superior to intramuscular MTX given weekly(20). In a research by Nadri et al, the response in Act-D group was higher than in MTX (86.6 percent compared to 53.3 percent). In research conducted in Thailand, the two drugs were administered as 5-day doses and ACT-D again showed greater efficiency than MTX (20).

In the research by Yarandi et al., the key treatment response predictor was levels of β-hCG prior to treatment ((9). However, in a Nadri study, the treatment response was more acute in the ACT-D Group, despite equal serum βhCG levels in both groups (6). Regardless of the regimen, CR was achieved for all patients with β-hCG less than 500 IU/L pretreatment. A lower β-hCG title might merely reflect a smaller amount of tumor, thereby increasing the probability of response to either of the first line agents.

In the study conducted by Mitra etal, 89 percent of patients in the Act-D group attained a CR with first-line chemotherapy, in comparison to the 94 percent response in a research conducted by Pettrilli and coworkers (15). Pretreatment βhCG and the drugs administered were the major important prognostic factors for firstline chemotherapy failure. These findings support Kwon et al., that revealed that a high value of pre-treatment β-hCG was the principal determinant of failure of methotrexate therapy (21). Overall, given the findings from several studies, Act-D is a better therapy for low-risks GTD. In addition, Actinomycin D has a reduced toxicity profile and can therefore provide the best way to treat low-risk GTD patients.

3.0 THEORETICAL FRAMEWORK

The management of GTNs is based on the principle of rapid multiplicity of the cells as shown in figure 2. The choice of the medications to use in the management of low grade GTNs is multifactorial and based on the staging of the disease, the toxicity profile of the drug, the patient's condition, cost and ability to monitor follow up regimens. Methotrexate's mechanism of action is due to its inhibition of enzymes responsible for nucleotide synthesis including dihydrofolate reductase, thymidylate synthase, aminoimidazole carboxamide ribonucleotide transformylase

(AICART), and amido phosphoribosyl transferase thus preventing cell division. Actinomycin D, binds to DNA and inhibits RNA synthesis (transcription), with chain elongation more sensitive than initiation, termination, or release. As a result of impaired mRNA production, protein synthesis also declines after dactinomycin therapy.
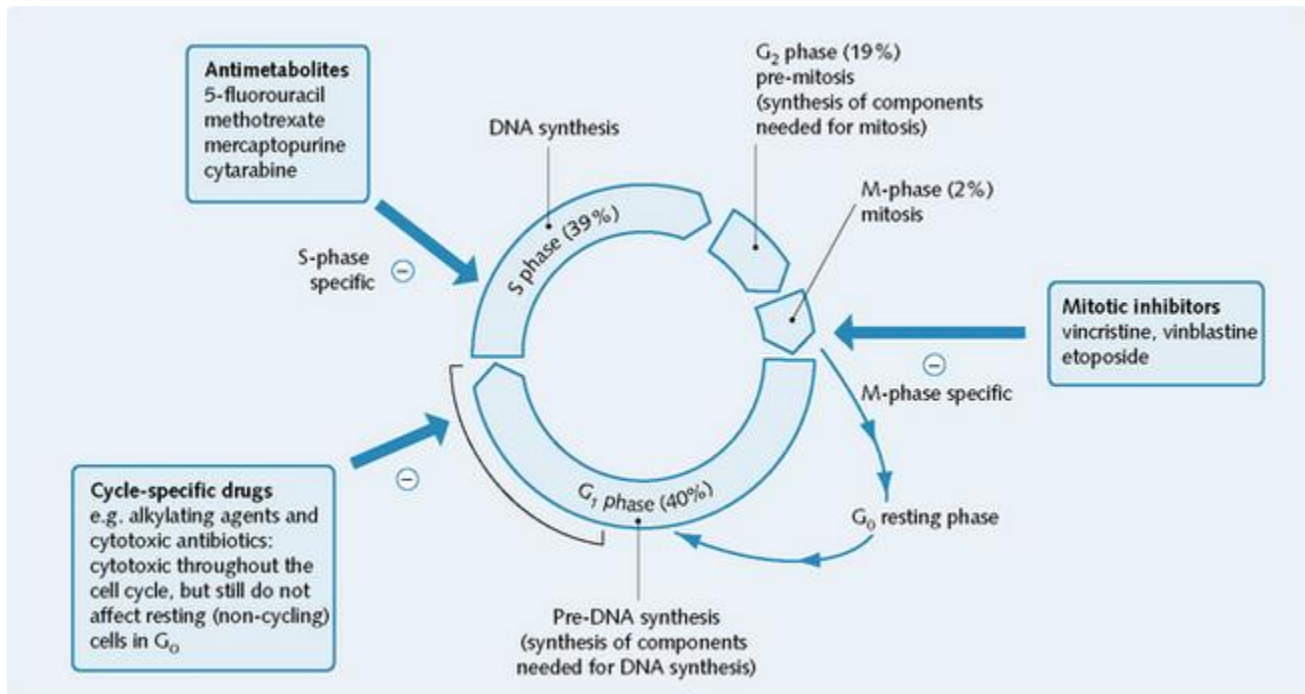
Figure 2: *Cell cycle and point of action anti-cancer medications (adapted from basicmedical.org)*

4.0 CONCEPTUAL FRAMEWORK

4.1 Conceptual Framework: Narrative

The management of patients with LR GTN, has over time, been using single drug agents with MTX and Act-D used with variable results. Treatment outcomes and side effects for these treatment regimens could be affected by several factors like patient's age, the level of bhcg and the dosage regimen. The choice of the type of regimen to use can also be influenced by the cost and availability of the different drugs.

4.2 Conceptual Framework: Diagrammatic Representation

Independent variable	Intermediate variables	Dependent variables

Health System Factors:
Availability of Drugs

Treatment Monitoring and Follow up Mechanism

Chemotherapy for Low Risk Gestational Trophoblastic Neoplasm (MTX, ACT – D)

Patient Level Factors:
Age

Pre-Treatment b HCG levels

Organ Function (Liver, Bone Marrow)

Treatment Outcomes
Success

Side Effects

Figure 3: *Conceptual Framework*

5.0 JUSTIFICATION

There are numerous effective single-drug chemotherapy regimens, but the decision on which drug or regimen varies depending on the institution. Although effectiveness is the most significant goal of treatment among the young women of reproductive ages, other issues like cost effectiveness,

administration ease, toxicity, avoidance of exposure to second line multidrug options, patients' preferences and adherence to treatment are also significant factors.
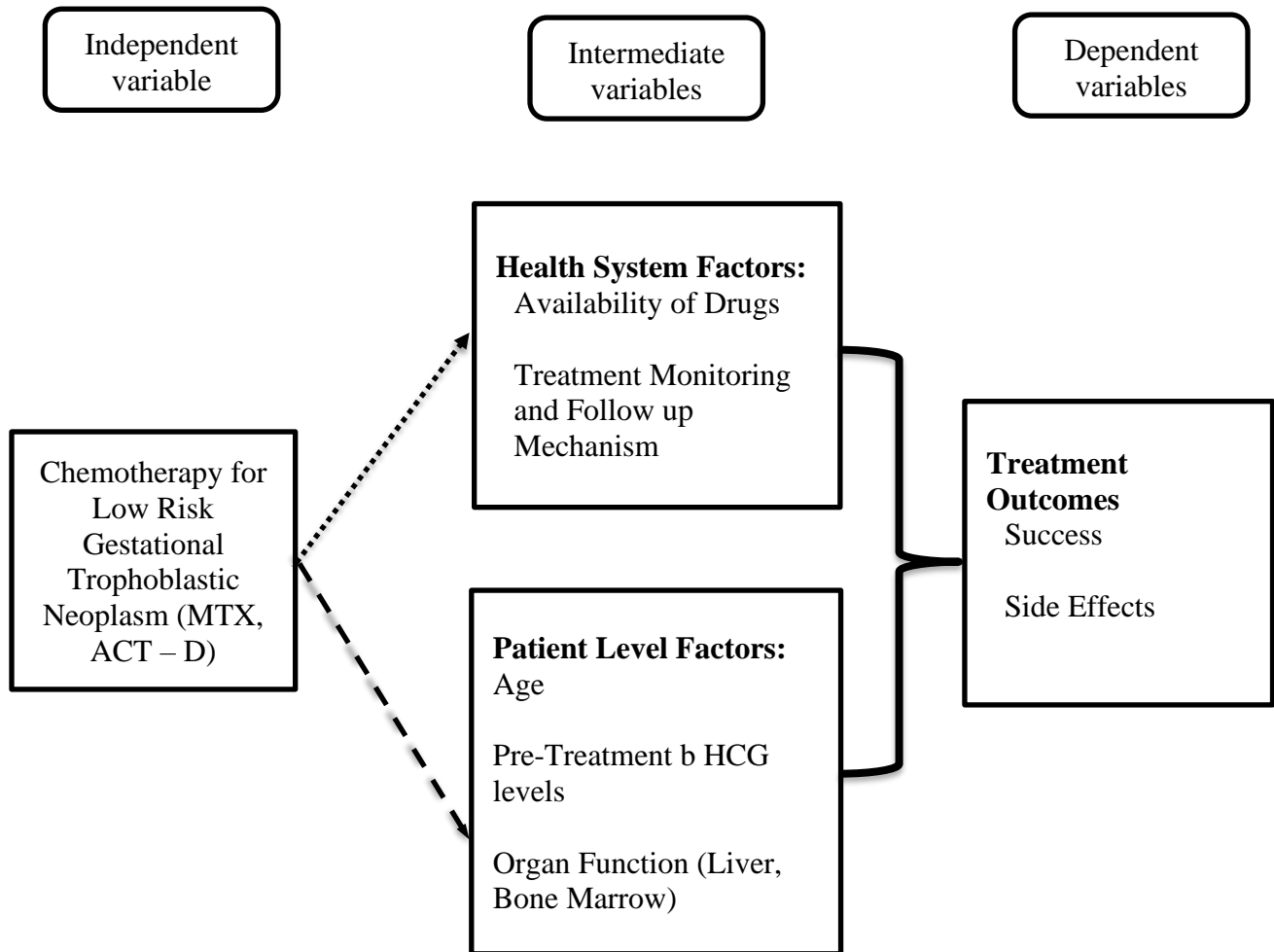
There has been no agreement regarding the optimal single drug agent for LR GTD treatment. The choice largely relies more on the medical practitioners' own experiences or preferences for a specific treatment rather than on any proof of clinical effectiveness, safety or convenience. There is no data comparing the treatments of LR GTNs using MTX or Act-D in the Sub Saharan Countries. The study aim therefore is to compare the treatment outcomes and side effects for patients with LR GTN who were managed either using MTX or Act-D at the KNH. The outcomes of this study will be incorporated into the KNH treatment protocols for the management of LR GTNs using the most effective, safest and easy to follow treatment protocol.

6.0 RESEARCH QUESTION

What are the treatment outcomes and side effects of using methotrexate in comparison to Actinomycin D in the management of patients with Low Risk Gestational Trophoblastic Neoplasms?

6.0 STUDY OBJECTIVES

6.1 Broad Objective

To determine the treatment outcomes and side effects of using methotrexate in comparison to Actinomycin D in the management of patients with Low Risk Gestational Trophoblastic Neoplasms at the Kenyatta National Hospital

6.2 Specific Objectives

a. To describe the treatment protocols for Methotrexate and Actinomycin D used in the management of gestational trophoblastic neoplasms at the Kenyatta National Hospital

b. Determine the side effects profile and remission rates among patients on Methotrexate and Actinomycin D regimens for the management of gestational trophoblastic neoplasms

c. To compare the side effect profile and remission rates of methotrexate Actinomycin D as used in the management of gestational trophoblastic neoplasms

7.0 METHODOLOGY

7.1 Study Design

The design adopted a retrospective cohort study design where the treatment outcomes and side effects of the patients with LR GTN treated using MTX at the KNH between 2012 to 2018 were compared to those treated using Act-D. A retrospective cohort study design was therefore an appropriate design where the outcomes for the two treatment regimens were compared at the end of the treatment period.

7.2 Study Site

The study was conducted in the Kenyatta National Hospital (KNH). The KNH is a public teaching and referral hospital serving patients from a broad socio – cultural divide not only in Kenya but in East and Central Africa. The oncology unit is managed by a multi-disciplinary team of professionals from different departments including oncologists, nurses trained in oncology, nutritionists, social workers, laboratory, pharmacy, radiology and hematology. On average, 150 to 200 patients are reviewed in the oncology clinic in a month.

7.3 Study Population

The study population comprised of patients who were treated for LRGTD at the Kenyatta National Hospital. The study population was generated from records of patients who were managed for LRGTD at the KNH from January 2012 to December 2020. The period was settled on as it provided the study team with an appropriate sample size for analysis.

7.3.1 Inclusion Criteria

1. Patients with a diagnosis of and treated for low risks gestational trophoblastic disease at the Kenyatta National Hospital between January 2012 to December 2020

2. Patients having treatment with either Methotrexate or Actinomycin D monotherapy.

7.3.2 Exclusion Criteria

1. Incomplete records that may not allow for data collection

2. Patients who did not complete the treatment as per the treatment protocol for either methotrexate or Actinomycin D

3. Patients with histologically confirmed invasive PSTT

4.. Patients who had to get sequential treatment with MTX and Act-D or EMACO

7.4 Sample Size Determination and Formula

The size of the sample was computed utilizing the proportions differences - Fleiss JL formula (Statcalc epi-info[TM]) for comparative cross-sectional studies as shown below. The following presumptions derived from the same research by Young Jae et al (16) where 59.5% of patients on

methotrexate weekly regimen and 80.0% of patients with Actinomycin D 5-day regimen had complete response to treatment:

$$n = (\frac{r+1}{r})\frac{(\bar{p})(1-\bar{p})(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

n = sample size per arm

r = ratio of methotrexate to actinomycin D group 2:1

P_1= proportion of patients with complete remission following treatment with actinomycin D 5-day regimen (80%)

P_2= proportion of patients with complete remission following treatment with methotrexate 8-day regimen (59.5%)

Ṕ =measure of variability, taken as 80+59.5/2

Z_β=Value equivalent to the study power, in this case 80 percent = 0.84

Zα = Value equivalent to the normal standard deviation at 95% C.I in this case =1.96, with 0.05 significance level

P_1- P_2 = effect size (proportions differences = 80-59.5)

Odds ratio to be detected of 4.0

Applying this in the Statcalc epi info software gives a value of 105:

 70 from the methotrexate group and 35 from the Act-D groups (ratio of 2:1)

7.5 Sampling Procedure

All the records were retrieved from the Records department at the KNH after seeking a written authorization from the hospital Records officer. Data extraction was done by the principal researcher and two other research assistants and entered into a structured data extraction tool. For

the 105 participants, proportionate sampling was applied to arrive at the number to be sampled from each of the years based on the patient numbers.

7.8 Selection of Study Participants

Once the patient records were identified and separated per year, consecutive sampling using random tables was used to arrive at the appropriate files for data extraction. Files that did not have relevant data as per the data extraction tool were replaced by the next eligible file from the same year. This was done until the appropriate sample size was attained for each group. Data was then extracted on to the specially designed data collection tool. This was done by the PI with the help of research assistants.

7.5 Ethical Considerations

The study proposal was submitted to the KNH/UON ERC for approval, through the chairman, **Prof M.L. Chindia** before the commencement of the study. In addition, permission was sort from the department of obstetrics and gynecology UON and the KNH administration to carry out the study. Since the study was retrospective patients' consent was not required but a request for waiver for consent for the study from the ethics committee was made. Patients' data was de-identified to maintain confidentiality.

7.6 Study Procedures

Normally once GTN diagnosis is arrived at, an evaluation with clinical, laboratory and radiological data is done. Patients with GTN are subsequently characterized into either low or high-risk groups

for treatment. The low risk group were treated with a single chemotherapy agent according to the KNH treatment guidelines for LRGTN.

The MTX regimen is either an 8-day (intra-muscular [IM] MTX, 1 mg/kg, days 1, 3, 5 and 7) with a rescue of folinic acid of 0.1/kg to 15mg (days 2, 4, 6 and 8). This is given every 14 days until remission of hCG. Post-remission, after one normal hCG value (<5 mUI/mL), a 6-week maintenance treatment is given. In the Act-D group, intravenous Act - D (1.25 mg/m2; maximum dose of 2.0 mg) is administered and recycled every 2 weeks until a normal hCG value, Similarly, therapy is retained for 6 weeks more after remission.

GTN treatment monitoring would include two-weekly hCG measurements taken at the start of each treatment course. If the β-hCG levels continues to increase (a more than 20%) or plateau decrease (<10 percent), therapy is changed with either a switch to another single agent or combination therapy started to try and avoid resistance. A relapse is diagnosed where there is an elevation in values of β-hCG 6 weeks or more after treatment was completed.

Toxicities are evaluated as per the Common Terminology Criteria for Adverse Events of the National Cancer Institute for Complications. Vomiting, bone marrow toxicity, hepatotoxicity, mucosal ulcer and skin necrosis are normally assessed. Irrespective of the degree of Hcg in serum, patients received other single-agent ChT regimens when resistance or toxicity evidence is identified to the First Single-agent ChT.

Every patient is given advice on prevention of pregnancies and usually receives contraceptive pills on monthly basis. After the very first hCG value that is normal, patients undergo treatment

consolidation of 2-3 cycles of the last ChT regimen 18,20. Patient received medical assessment and hCG observations as recommended after completion of ChT. A year after ChT, the patients are allowed to be pregnant if they desired. When the third-line GTN therapy is required, patients are treated with EMA/CO multi-agent ChT regime (etoposide + MTX/FA + Actinomycin D + vincristine + cyclophosphamide). The complete response (CR) or remission is diagnosed where for 3 weeks consecutively the hcg levels remain less than <5 mIU/mL and sustained remission is whereby the values of hCG remain at this level for a whole year.

7.8 Quality Assurance Procedures

The following measures were taken for quality assurance through all the stages of the study.

1. Data obtained from the records and files were counterchecked by the data manager/ principal investigator to ensure it is correctly filled. This was done on a daily basis

2. Data was stored in password protected computers, hard drives and flash drives that was accessible to only the principal investigator, supervisors and statistician to ensure confidentiality was maintained.

3. Two research assistants, clinical officers by training, were taken through a one-day training on data collection processes, coding and quality assurance measures during the data collection process

4. Pre-testing of the data abstraction tool was done to a sample of 10 records randomly selected from the records department to inform the data collection and management processes

7.9 Data Collection Procedures

We conducted a retrospective review of medical records to find patients receiving chemotherapy for confirmed GTD at the KNH in Kenya between 2012 and 2020. From the records the following information was sought: clinical history, physical exam results, laboratory test results (full blood count, β-hCG, test results for liver functions and test results for renal functions), histological results, chest X-ray and CT findings, the tumor size assessed by existing imaging tools, such as sonography or Computed tomography.

8.0 RESULTS

A total of 105 patient files (n=35 actinomycin D group and n=70 methotrexate group) with complete records in the variables of interest were retrieved and data extracted. These data included patients' socio-demographic characteristics, clinical profile, treatment protocols, toxicity profile, and treatment outcomes.

Socio-Demographics and Clinical Profile

The median (IQR) age of patients in the methotrexate group was 28 years (IQR, 23-32) was significantly higher than that of patients in the actinomycin D group (24 years, IQR 21-31) (p=0.016). The patients in both groups had comparable modified WHO scoring before chemotherapy (p=0.068). Regarding parity, a significantly higher percentage of patients in the actinomycin D group (45.7%) than those in the methotrexate group (21.4%) were primigravida (p=0.10). See Table 1.

Table 1: Socio-demographics and clinical profile for the participants who underwent treatment for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 to 2020

Variable	Actinomycin D	Methotrexate	Total	p-value
	N=35	N=70	N=105	
	n (%)/median (IQR)	n (%)/median (IQR)	n (%)/median (IQR)	
Age in yrs (Median (IQR)	24.0 (21.0-32.0)	29.0 (25.0-32.0)	28.0 (23.0-32.0)	**0.016**
Education level: Primary	10 (28.6)	33 (47.1)	43 (41.0)	0.068
Secondary+	25 (71.4)	37 (52.9)	62 (59.0)	
Pre-Chemotherapy WHO scoring (Median – IQR)	4.0 (2.0-4.0)	4.0 (3.0-4.5)	4.0 (3.0-4.5)	0.068
Gravidity Median (IQR)	22.0 (17.0-33.0)	24.0 (16.0-37.0)	24.0 (16.0-34.0)	0.800
Parity: Primigravida	16 (45.7)	15 (21.4)	31 (29.5)	**0.010**
Multigravida	19 (54.3)	55 (78.6)	74 (70.5)	
Serostatus: Negative	13 (37.1)	20 (28.6)	33 (31.4)	0.373
Positive	5 (14.3)	8 (11.4)	13 (12.4)	0.675
Unknown	17 (48.6)	42 (60.0)	59 (56.2)	0.266

Laboratory Profile by Treatment Group

The patients in both treatment groups were comparable across most lab measurements before treatment except creatinine, sodium and Hb (Table 2). The actD group (median (IQR) = 92 (74-116)) had significantly higher median of creatinine than the MTX group (median (IQR) = 82 (67-91)) (p=0.018). Similarly, patients in the actD group (median (IQR) = 142 (139-145)) had significantly higher median of sodium than those in the MTX group (median (IQR) = 137 (135-142)) (p<0.001). The median Hb level was significantly higher on the MTX group (12) than the actD group (11) (p=0.021). The measurements in Table 2 are illustrated graphically in Figure 1.

Table 2: Laboratory profile by treatment group for the patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Variable	Actinomycin D	Methotrexate	Total	p-value
	N=35	N=70	N=105	
	Median (IQR)	Median (IQR)	Median (IQR)	
BHCG	10,000.0 (4,280.0-10,000.0)	10,000.0 (3500.0-10,000.0)	10,000.0 (3,640.0-10,000.0)	0.980
Creatinine	92.0 (74.0-116.0)	81.7 (67.0-91.0)	83.0 (69.0-97.0)	0.018
Albumin	40.0 (38.1-47.8)	41.1 (34.0-44.0)	41.0 (35.0-44.4)	0.180
Sodium	142.0 (139.0-144.7)	137.4 (135.0-142.0)	139.0 (136.0-143.0)	<0.001
Hb	11.0 (10.2-12.1)	12.0 (10.7-12.6)	11.6 (10.5-12.5)	0.021
PLT	258.0 (189.0-330.0)	304.5 (220.0-362.0)	281.0 (205.0-349.0)	0.056
WBC	7.5 (3.7-12.3)	7.6 (5.7-11.8)	7.5 (5.4-12.3)	0.270
ALT	25.0 (12.0-38.0)	22.5 (12.0-36.0)	23.0 (12.0-38.0)	0.460
AST	25.0 (13.0-37.0)	22.1 (16.0-36.0)	24.0 (16.0-36.0)	0.870
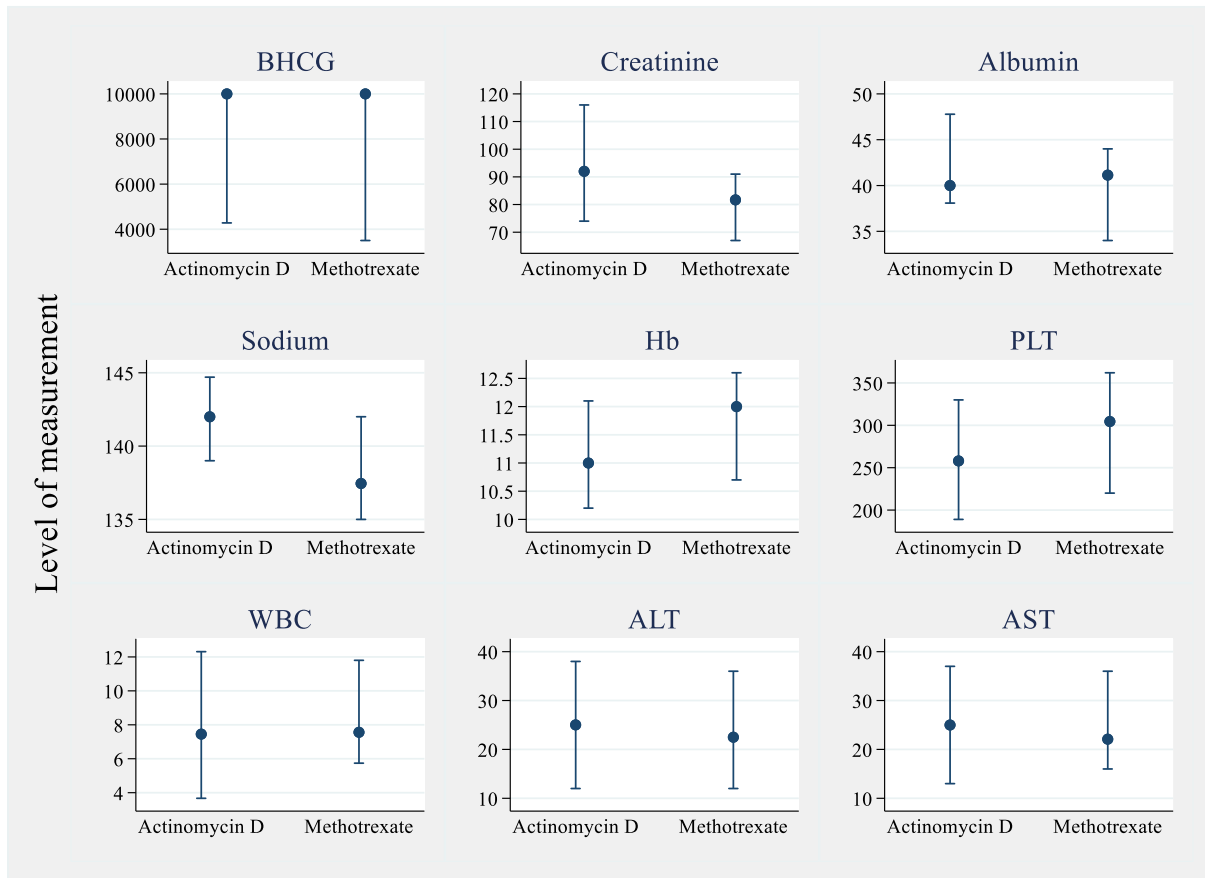
Figure 4: Illustration of laboratory profiles (measurements) of patients by treatment group (median (IQR) of the measurements)

Laboratory Profiles of Patients by Treatment Outcomes

When the laboratory measurements were summarized by treatment outcome, only creatinine was significantly different between the groups (Table 3). The baseline median creatinine measurement for the patients who had complete remission (median 81, IQR 65-97) was significantly lower than that of those who experiences drug resistance (median 90, IQR 82-100, p, 0.042). The laboratory measurements in Table 3 are illustrated in Figure 5.

Table 3: Laboratory Profiles of Patients by Treatment Outcomes for patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

| Variable	Resistance	Complete remission	Total	p-value
	N=22	N=83	N=105	
	Median (IQR)	Median (IQR)	Median (IQR)	
BHCG	10,000.0 (2,492.0-10,000.0)	10,000.0 (3,640.0-10,000.0)	10,000.0 (3,640.0-10,000.0)	0.942
Creatinine	90.0 (82.0-99.7)	81.4 (65.0-97.0)	83.0 (69.0-97.0)	**0.042**
Albumin	40.6 (33.0-49.2)	41.3 (35.6-44.0)	41.0 (35.0-44.4)	0.710
Sodium	138.4 (135.0-144.0)	139.0 (136.2-143.0)	139.0 (136.0-143.0)	0.680
Hb	11.9 (10.7-13.3)	11.5 (10.5-12.5)	11.6 (10.5-12.5)	0.202
PLT	267.0 (189.0-345.0)	285.0 (208.0-350.0)	281.0 (205.0-349.0)	0.491
WBC	7.6 (6.5-11.4)	7.5 (5.2-12.4)	7.5 (5.4-12.3)	0.730
ALT	20.1 (12.0-28.0)	23.0 (12.0-38.0)	23.0 (12.0-38.0)	0.313
AST	21.0 (15.0-32.0)	25.0 (16.0-37.0)	24.0 (16.0-36.0)	0.192
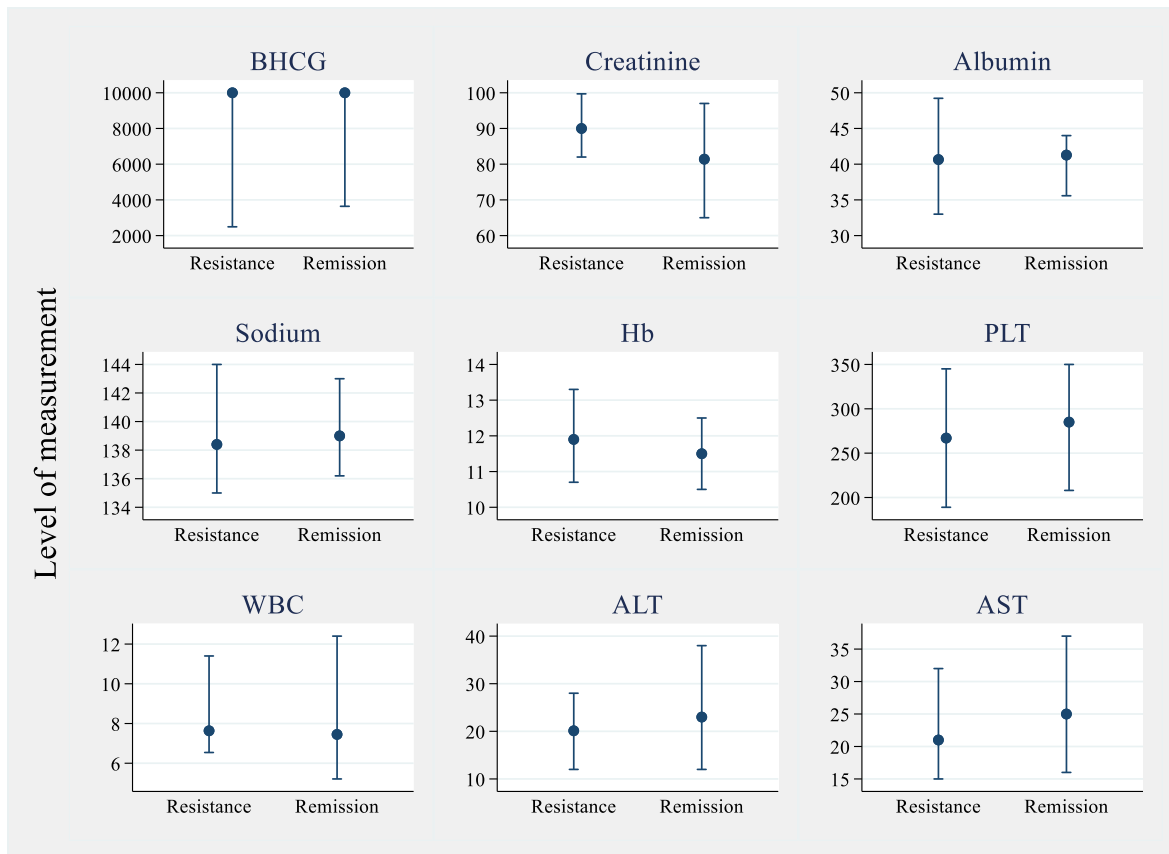
Figure 5: Graphical illustration of laboratory profiles of patients by treatment outcome (median, IQR) for patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Treatment protocols for Methotrexate and Actinomycin D regimens

There was no significant difference between the treatment groups with regards to the type of imaging done at diagnosis (91% and 95% of act D and MTX respectively were subjected to ultrasound). Similarly, the average number of chemotherapy sessions attended by patients was comparable across both groups (P=0.140). Four (anemia, thrombocytopenia, hair loss, and nausea/vomiting) out of the five side effects recorded were not significantly different across the two treatment groups. A significantly higher percentage of the actD group (25.7%) experienced mouth sores compared to the MTX group (7.1%) (p=0.008). Regarding treatment outcomes,

patients in the actD group had a significantly higher remission rate (91.4%) than those in the MTX group (72.9%) (p=0.028). See table 4.

Table 4: Treatment protocols for Methotrexate and Actinomycin D regimens among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Variable	Actinomycin D	Methotrexate	Total	p-value
	N=35	N=70	N=105	
	n (%)/median (IQR)	n (%)/median (IQR)	n (%)/median (IQR)	
Imaging: Ultrasound	32 (91)	42 (95)	74 (94)	0.067
Ultrasound + CT	3 (9)	2 (5)	2 (3)	
No. of chemorx. sessions attended (median – IQR)	6.0 (4.0-8.0)	7.0 (5.0-8.0)	7.0 (5.0-8.0)	0.142
Period of time in months followed up (median – IQR)	7.0 (5.0-9.0)	7.0 (4.0-13.0)	7.0 (5.0-13.0)	0.841
Toxicity profile: Anemia	5 (14.3)	10 (14.3)	15 (14.3)	1.000
Thrombocytopenia	4 (11.4)	5 (7.1)	9 (8.6)	0.459
Hair loss	13 (37.1)	40 (57.1)	53 (50.5)	0.053
Nausea/vomiting	4 (11.4)	10 (14.3)	14 (13.3)	0.685
Mouth sores	9 (25.7)	5 (7.1)	14 (13.3)	**0.008**
Treatment outcomes				
Resistance	3 (8.6)	19 (27.1)	22 (21.0)	**0.028**
Complete remission	32 (91.4)	51 (72.9)	83 (79.0)	

Assessment of the toxicity profile for patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

In both treatment groups, hair loss was the most common side effect recorded (37.1% in actD and 57.1% in MTX group). However, there was no significant difference in the proportions (p=0.053). Mouth sores were more common in actD group (25.7%) than MTX group (7.1%) (p=0.008). The other side effects (nausea, anemia, and thrombocytopenia) were less common and similar across both groups (Figure 6).
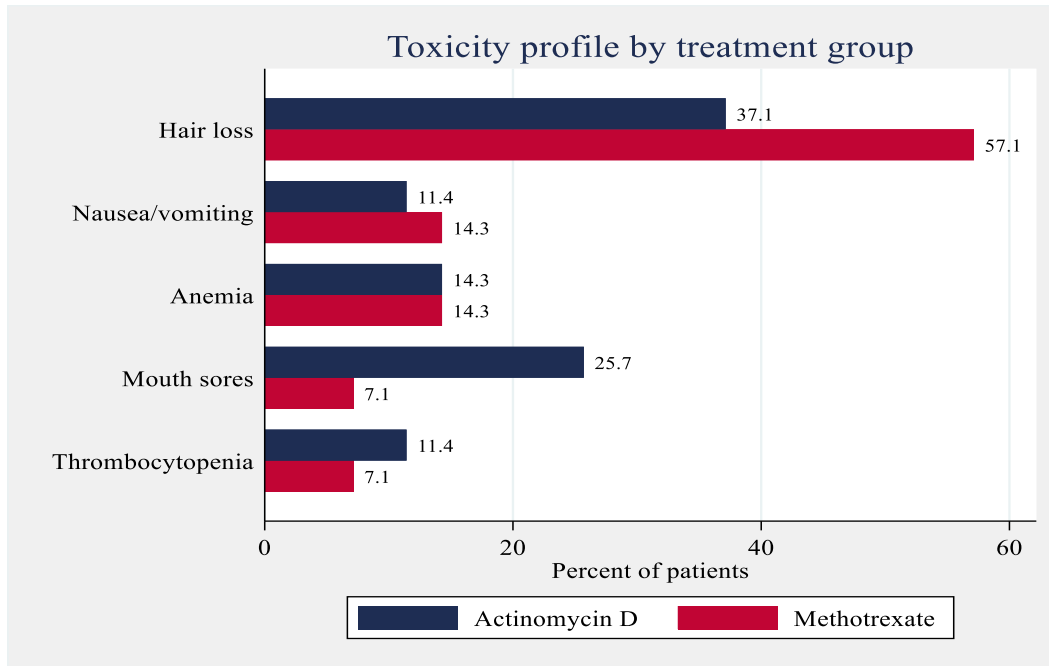
Figure 6: Side effects profile by treatment group among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Treatment outcomes among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

The patients on actD regimen had significantly better average remision rate (91.4%) than those in MTX regimen (72.9%) (p=0.028). See Figure 4.
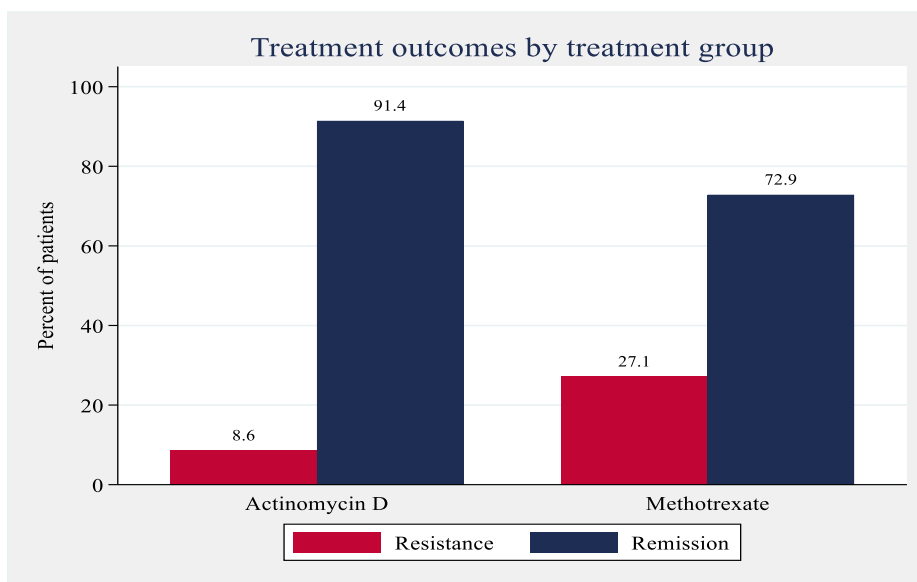

Figure 7: Treatment outcomes by treatment group among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Crude associations between treatment outcomes and potential predictors among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

To determine the potential predictors of treatment outcomes, the medians (for numeric variables) or the proportions (binary variables) were compared between two groups: those who experienced drug resistance (resistance group) vs those who had complete remission (remission group). Among all the potential predictors, only the treatment regimen had a significant difference between the two groups, that is, there was a significantly higher percentage of patients in the actD regimen (91%) who experienced complete remission compared to the MTX regimen (73%) ($p=0.028$). See Table 5 for more details.

Table 5: Crude associations between treatment outcome and potential predictors among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Variable	Resistance	Complete remission	Total	p-value
	N=22	N=83	N=105	
	n (%)/median (IQR)	n (%)/median (IQR)	n (%)/median (IQR)	
Age in yrs Median (IQR)	29.0 (26.0-33.0)	28.0 (22.0-32.0)	28.0 (23.0-32.0)	0.173
Education level: Primary	10 (23)	33 (77)	43 (100)	0.631
Secondary+	12 (19)	50 (81)	62 (100)	
Gravidity in wks: Median (IQR)	24.0 (20.0-35.0)	24.0 (16.0-34.0)	24.0 (16.0-34.0)	0.740
Parity: Primigravida	4 (13)	27 (87)	31 (100)	0.195
Multigravida	18 (24)	56 (76)	74 (100)	
BHCG: Median (IQR)	10,000.0 (2,492.0-10,000.0)	10,000.0 (3,640.0-10,000.0)	10,000.0 (3,640.0-10,000.0)	0.942
Follow up period: Median IQR)	6.0 (4.0-8.0)	8.0 (5.0-13.0)	7.0 (5.0-13.0)	0.080
Treatment group: Actin. D	3 (9)	32 (91)	35 (100)	0.028
Methotrexate	19 (27)	51 (73)	70 (100)	
WHO scoring: Median (IQR)	3 (2-4)	4 (3-4.5)	4 (3-4.5)	0.103
Toxicity profile: Anemia	4 (27)	11 (73)	15 (100)	0.557
Thrombocytopenia	3 (33)	6 (67)	9 (100)	0.340
Hair loss	12 (23)	41 (77)	53 (100)	0.668
Nausea/vomiting	1 (7)	13 (93)	14 (100)	0.173
Mouth sores	2 (14)	12 (86)	14 (100)	0.510

Adjusted associations between treatment outcome and potential predictors among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

To determine the predictors of treatment outcomes, a logistic regression model was fit. In this model, the dependent variable was treatment outcome (resistance=0; complete remission=1) while the independent variables included treatment group, age of patient (years), gravidity (weeks), parity, patient's bHCG level, and the modified WHO scoring before chemotherapy. Treatment group and the modified WHO scoring before chemotherapy were significant predictors of treatment outcomes (Table 6).

Adjusting for other factors in the model, patients in the ActD regimen had four times higher odds of having complete remission than those in the MTX group (aOR=4.14; 95% CI: [1.06, 13.62]). This implies that the ActD regimen conferred higher remission rates than the MTX regimen.

After controlling for other factors in the model, for every unit increase in the modified WHO scoring before chemotherapy, the odds of complete remission was 50% lower. Put another way, the higher the modified WHO score, the lower the chances of a patient having complete remission.

Table 6: Adjusted associations between treatment outcome and potential predictors among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

Factors	Odds Ratio	P-value	[95% CI]
Treatment: Methotrexate	Ref.		
Actinomycin D	4.14	**0.046**	[1.06, 13.62]
Age in years	0.98	0.399	[0.93, 1.03]
Gravidity (in weeks)	1.00	0.978	[0.95, 1.05]
Parity: Primigravida	Ref.		
Multigravida	0.71	0.654	[0.16, 3.15]
BHCG	1.00	0.917	[0.99, 1.00]
Modified WHO scoring before chemotherapy	0.51	**0.030**	[0.04, 0.91]

Predicted probabilities of remission by selected variables in the model among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

The probabilities of remission by treatment regimen, age and WHO scoring were determined post-regression (Figure 5). In both treatment groups, there is a gradual reduction in the probability of complete remission from as patients grew older. Therefore, the older the patient is, the lower the chances of remission. Regarding WHO scoring, the probability of complete remission declined as the score increased. It can be deduced that the higher the modified WHO score before chemotherapy, the lower the chances of remission.
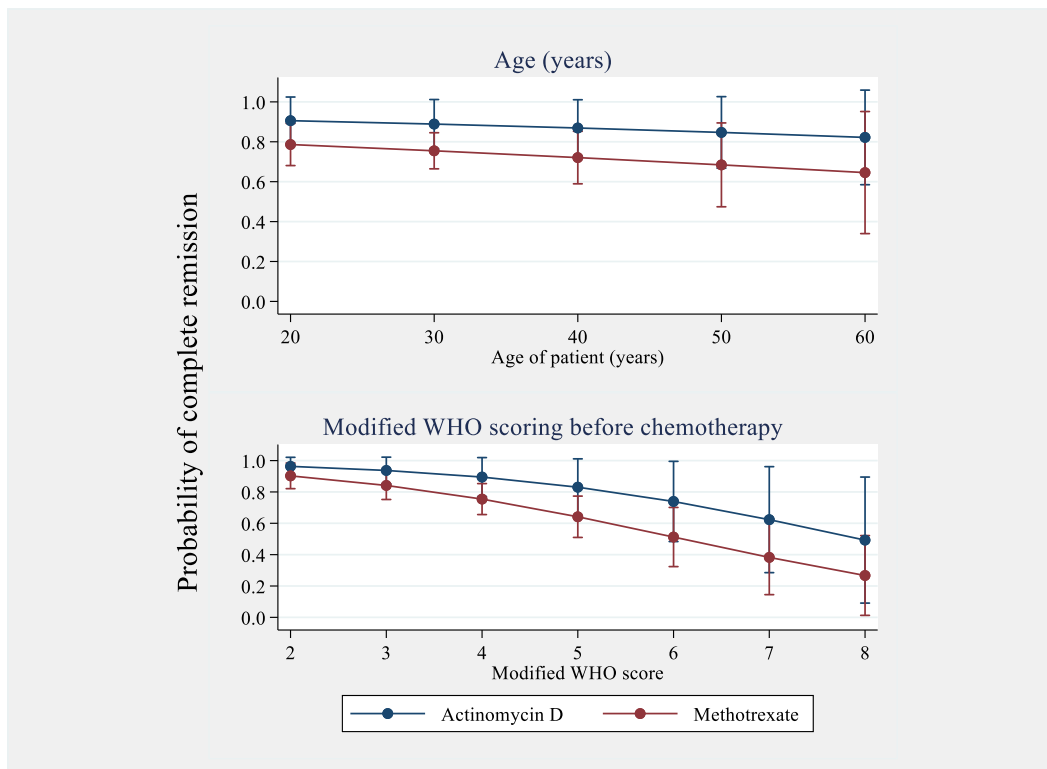

Figure 8: Predicted probabilities of success (remission) by selected predictors among patients who were treated for low risk gestational neoplasms at the Kenyatta National Hospital between 2012 and 2020

9.0 DISCUSSION

Our findings add to the literature that has demonstrated that single-agent chemotherapy can be very effective in treating low-risk GTN (9). Patients with stage I and low-risk stage II and III GTN (FIGO prognostic score of ≤6) generally respond well to single-agent chemotherapy. The most commonly used agents for low-risk GTN are sequential methotrexate (MTX) and actinomycin D (ACT-D) . The results of previous studies have shown that both methotrexate (MTX) and actinomycin D (dactinomycin, ACT-D) are safe, effective, and inexpensive chemotherapy agents for LR GTD (22).

Preoperative imaging studies such as ultrasound, MRI, arteriography, and positron emission tomography (PET) scans may be helpful in identifying the site of residual tumor and can, therefore, facilitate surgical planning (9). In our study, ultrasound was the commonly used imaging modality. Most of the patients (94%) underwent ultrasound studies in the MTX group compared to the ACT-D group where 91% underwent ultrasound imaging studies.

Similarly, the average number of chemotherapy sessions attended by patients was comparable with the ACT-D group having slightly less courses, 6 for the ACT-D and 7 for the MTX (P=0.140). In a study by Nahid, the mean number of courses of chemotherapy to achieve complete remission in the ACT-D group was 4.33 courses compared to 6.53 courses in the MTX group (6). These numbers are statistically different (p=0.04) and Actinomycin D group received a smaller number of courses of chemotherapy. In a study by Yarandy et al., the mean number of chemotherapy courses to achieve complete remission was 4.8 in ACT-D group and 6.8 in the MTX group and the duration of treatment in the ACT- D group was longer (19). In the study by Tymaa et al, the

number of courses of chemotherapy in patients treated with Actinomycin D was also less than the other group (4.33 versus 6.53) (23). Hence, we can conclude that patients are more likely to be satisfied with ACT-D

One of the determinants of the choice of treatment has been the side effect profile of the patients. In our study, hair loss was more common among patients with MTX (57.1%) compared to ACT-D (37.1%); this was not however significant statistically. This is similar to other studies that have demonstrated common side effects of the MTX regimen to include nausea, vomiting, hematologic toxicities, mucositis, and conjunctivitis, whereas the 5-day ACT-D regimen is associated with a higher prevalence of alopecia and nausea.

Mouth sores: in our studies were more common among patients on ACT-D (25.7%) compared to MTX (7.1%); this was significant statistically. However, a GOG study (15) and a Cochrane review suggested that the bi-weekly pulsed ACT-D regimen had fewer, or at least same toxicities than the MTX regimen. They also found that there was no significant difference in toxicities between the two groups although the data used in the study were too heterogeneous to be conclusive. In a study by Tymaa et al, no severe adverse effects (SAEs) were observed in either group. Most of the side effects in the ACT-D group were mild side effects, such as fatigue or gastrointestinal problems, and there was no incidence of alopecia (9).

In three clinical trials, complete remission with MTX pulse therapy was 49-53%, markedly lower than ACT-D pulse treatment which was 69-90% (18- 20). In one study, a 5-day regimen of ACT-D was compared to an 8-day regimen of methotrexate and Folinic acid (MTX-FA) to treat GTD

without metastases; complete remission was 100% in the ACT-D group and 74% in the MTX group (20).

ActD had better remission rate (91.4%) compared to the MTX (72.9%) (p=0.028; Adj OR 0.046). An important phase III randomized trial examining MTX and ACT-D in the treatment of low-risk GTN was published by the Gynecologic Oncology Group (GOG) in 2011 (25). Two hundred sixteen patients were randomized to receive either biweekly ACT-D 1.25 mg/m2 IV or weekly MTX 30 mg/m2 intramuscularly (IM). The remission rate was 58% in the MTX arm and 73% in the ACT-D arm(13). Complete remission rates of 77%–81% have been previously reported with MTX (12). The superior response rate observed with ACT-D was consistent with that observed in other studies that compared ACT-D treatment with 5- or 8-day MTX regimens, which are more commonly used and offer a higher initial remission rate (9). In a Cochrane review, ACT-D treatment was associated with significantly higher primary response rates than MTX treatment [13]. Furthermore, CR is attained with fewer ACT-D chemotherapy cycles (4.8) than MTX cycles (6.8) (25). Additionally, when pulsed ACT-D was studied as a secondary therapy in MTX-failed LR GTN patients, it showed a CR rate of 75% (12).

Documented predictors of treatment response include pretreatment bHCG, compliance to medications and toxicity profile. In a study by Yarandi et al., the most important predictor of treatment response was β-hCG levels before treatment (25). However, in the study by Tymaa et al, despite equal serum β- hCG levels in both groups, response to treatment was more in the ACT-D group (23). Similarly, in our study, there were no statistically significant differences in pretreatment β-hCG levels, WHO prognostic scores, between the successful and failed treatment groups. These predictors could be affected by different inclusion criteria across the studies and the smaller sample size.

Conclusion

Various chemotherapy regimens are used as first-line treatments in patients with LR GTD. However, there is no worldwide consensus regarding the best initial chemotherapy for patients with LR GTD. Our study showed a better response rate with ACT-D than with MTX in LR GTD. Compared with MTX, ACT-D may be the better option as a first-line single chemotherapy though with more severe side effects.

Recommendations

Concerns regarding the potential significant side effects associated ACT-D can be addressed by using a bi-weekly pulsed ACT-D regimen, which shows minimal toxicity. However, a definitive conclusion cannot be made, due to the lack of strong supporting evidence. Further larger prospective controlled trials will be necessary to establish comprehensive guidelines for GTN treatment.

Strengths and weaknesses

This study reviewed a large number of cases covering a 9-year period; considering the rarity of GTD, this can be considered a particular strength of this study. The However, being retrospective in nature, there is a high probability of selection bias, misclassification or information bias.

10.0 STUDY TIMELINE

Activity	January – December 2020	February – August 2021	September 2021	October 2021	November 2021- May 2022
Proposal Development	███				
Ethical Approval		███			
Data Collection			███		
Data Analysis				███	
Dissertation Writing and Presentation					███

11.0 BUDGET

Item	Unit Cost (Ksh)	Units	Total Cost (Ksh)
Research Assistant Per Diem	21, 000	2	42000
Printing	10,000	1	10,000
Photocopy and Binding	10000	3	10000
Flash Drives and Stationery	5000	2	5000
Communication/ Airtime	1000	2	2000
Statistician/ Data Analysis	40000	1	40000
Miscellaneous	5000	1	5000
Total Cost			**112, 000**

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13.0 ANNEXES

Annex 1: Data Collection Tool

Comparison of Treatment Outcomes for management of low risk gestational trophoblastic neoplasm using methotrexate and actinomycin D

1. Group for the Study

   Methotrexate

   Actinomycin D

2. Socio Demographic data

   Age in years……………………

   Education level

    Primary

    Secondary

    Tertiary

   Serostatus

    Positive

    Negative

    Don't know

3. Clinical Characteristics

   Parity……P……+……………….

   Gravidity (in weeks) ……………..

   Diagnosis

    Imaging…………………………………………

    Histological………………………………….

4. Investigations Done (indicate values)

      Laboratory: UECs

             Hgm

             LFTs

      Imaging: Ultrasound

             Magnetic Resonance Imaging

             Computed Tomography

5. Modified WHO Scoring before chemotherapy

6. Number of chemotherapy sessions attended……………………..

7. Period of time in months followed up

8. Loss to Follow up

    Yes

    No

9. Toxicity profile

    Nausea/Vomiting

    Hair Loss

    Bone Marrow Toxicity

    Peeling of the Skin

10. Treatment Outcomes

    Complete Remission

    Resistance and initiation of second agent

    Death

    Not indicated

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APPROVED
01 SEP 2021
KNH/UoN-ERC

1st September, 2021

Dr. Moses Njoroge Ndung'u
Reg. No.H58/82322/2015
Dept. of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Ndung'u

RESEARCH PROPOSAL: COMPARISON OF THE TREATMENT OUTCOMES OF METHOTREXATE AND ADRIAMYCIN D IN THE TREATMENT OF LOW RISK GESTATIONAL TROPHOBLASTIC DISEASE AT THE KENYATTA NATIONAL HOSPITAL (P289/04/2021)

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 1st September 2021 – 31st August 2022.
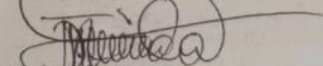
This approval is subject to compliance with the following requirements:

i.   Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. 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.
iv. 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.
v.   Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
vi. 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).
vii. Submission of an executive summary report within 90 days upon completion of the study.

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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
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