PREGNANCY OUTCOMES AFTER SINGLE AGENT VERSUS MULTIAGENT CHEMOTHERAPY FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This is to certfy that this study is my original work and has not been presented for a degree oran award in any other university.

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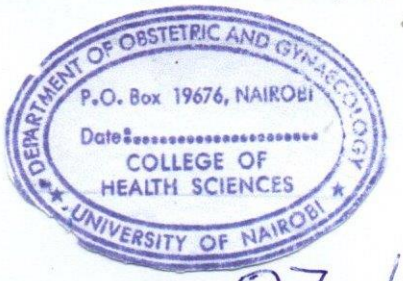

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DEDICATION

This is dedicated to my late mother Rosemary Mbabazi Wekesa the legacy you left behind will always be my guiding light, till we meet again

LIST OF ABBREVIATIONS AND ACRONYMS

BHCG:	Beta Human Chorionic Gonadotropin
EMACO:	Etoposide Methotrexate Actinomycin D Cyclophosphamide Vincristine/Oncovin
EMAEP:	Etoposide Methotrexate Actinomycin D Etoposide Paclitaxel
ETT:	Epithelioid Trophoblastic Tumour
GTN:	Gestational Trophoblastic Neoplasia
HM:	Hydatidiform Mole
PSTT:	Placental Site Trophoblastic Tumour
KNH:	Kenyatta National Hospital
SPSS:	Statistical Package for Social Scientists
WHO:	World Health Organisation
HC:	Hormonal Contraception
KOGS:	Kenya Obstetrics and Gynaecology Society
MOH:	Ministry of Health
ACOG:	American College of Obstetrics and Gynaecology
CHM:	Complete Hydatidiform Mole
COC:	Combined Oral Contraceptives
PHQ-2:	Patient Health Questionnaire-2

DEFINITION OF OPERATIONAL TERMS

Chemotherapy: Therapeutic use of a chemical agent or cytotoxic drugs to inhibit the replication of cancerous cells or destroy them.

Gestational trophoblastic

Neoplasms:Include placental site trophoblastic tumour (PSTT)choriocarcinoma, and invasive moles diagnose by a histopathologic analysis of tissues or the elevation of the human chorionic gonadotropin (hCG) after antecedent pregnancy or evacuation of a molar pregnancy.

Non-molar pregnancy: These histological lesions have some features of partial moles such asmild trophoblastic proliferation or hydropic villi but not sufficient enough to make a diagnosis of a partial mole. The lesions have a varied origins and include digynic triploid conceptions,,chromosomal abnormalities and placental mesenchymal dysplasia.

Incidence: The frequency or rate of occurrence of new cases of a disease

Pregnancy outcome: Results of conception and ensuing pregnancy, which included the stillbirth, preterm delivery, term/ post term delivery spontaneous abortion, and ectopic pregnancy

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ABSTRACT

Background:Gestational Trophoblastic Neoplasia (GTN) is a rare and treatable cancer for women reported in about 2.4/1000 and 4.6/1000 live births in two separate studies in Africa. It occurs because of abnormal proliferation of trophoblastic tissues. To prevent spontaneous abortion and lower the risk of adverse maternal outcomes such as stillbirth, the World Health Organisation (WHO) recommends oral contraceptionpostchemotherapy for GTN and delaying pregnancy by 12 months,if low risk, and 18 months if high-risk. However, it is not clear to what extent these proposals are followed in Kenya. The pregnancy outcomes of women after single agent chemotherapy versus multi agent therapy have likewisenever been explored.

Objective: To evaluate the pregnancyoutcomes of women who hadsingle agent chemotherapy versus multi agent chemotherapy for GTNs at KNH between 2013 and 2017.

Methodology: A classicalcohort studywas done at the health information department at the Kenyatta National Hospital (KNH).Files were checked for completeness and patients who qualified for the study contacted on phone. Oral consent was administered using a telephone transcript, 55 patients who were treated with single agent chemotherapy and 55 who were treated with multi agentchemotherapy for GTNsrecruited, and data on the sociodemographic and medical characteristics of cases captured on a questionnaire. Reproductive outcomes such as the desire for pregnancy, eventual pregnancy, and birth outcomes wasalso be recorded during phone interviews and filled on a questionnaire. The chi square test for categorical data and the t test for continuousdata was used to analyse study's data. The comparability of study groups wasestablished at baseline and confounders controlled using a logistic regression model. Tests for statistical significance was interpreted at the 95% confidence ($P<0.05$ was significant).Version 21 of the statistical package for social scientists (SPSS) was used for data analysis.

Results: The data of 55 patients who received monotherapy and 55 multi therapy was analysed. Patients who mono therapy were younger than those who received multi therapy ($p=0.01$) and had a significantly higher level of education ($p=0.04$). A majority of patients who received multi therapy had a higher risk status ($p<0.01$) and were likelier to have metastasised cancer than those on monotherapy ($p=0.02$). The incidence of pregnancy was significantly higher among patients who received mono therapy (47.3%) than multi therapy (20.5%), $p<0.01$. The desire for pregnancy was also significantly higher among patients who received monotherapy (60.0%) than multi therapy (38.3%). Contraceptive use (63.6% versus 58.2%) and the live birth rate of women who achieved a pregnancy (73.1% versus 72.7%) were comparable ($p>0.05$).

Conclusion: pregnancy outcomes after single or multi-agent chemotherapy are reassuring.

CHAPTER ONE

1 INTRODUCTION

1.1 Background

Gestational Trophoblastic Neoplasia (GTN) is a gynaecological condition that occurs when there is abnormal proliferation of trophoblastic tissues(1). Hydatiform mole is the commonest form of GTN. However, it can occur in nonmolar pregnancy and increases risk of spontaneous abortion (2). Worldwide, 1.67 cases of GTN are reported every year per 1000 live births(3) with a variation in its incidence in different regions reported. In Japan, for instance, 2/1000 live births are complicated by GTNs(4), which is slightly higher than the 1/1000 and 1.5/1000 rates reported in the United States (US) andUnited Kingdom (UK) every year (5,6). Recent evidence indicates that the incidence of GTN in Africa might be higher than previously thought. In a study by Mbamara *et al*. in Southwest Nigeria (7),the frequency of GTN among African women of a reproductive age was found to be 4.6 per 1000 deliveries in 2009. This translated to an incidence of 0.46%, which wasfour times the incidence of GTNs in the US (6). In 2012 Yakasai *et al*. (8) reported a drop in incidence to 2.4/1000 live births, but which was 1.6 times higher than in the UK (5). Regrettably, even withincreasingreports of its higher incidence in Africa, GTN has not attracted sufficient scientific interest in the continent, evenin East Africa.

GTN is commonest among women of childbearing age (16-46 years). However, a difference in the occurrence of GTNbased on the ethnicity, dietary deficiencies, ABO blood group, prior spontaneous abortions,and interpregnancy Interval (IPI) of women has also been reportedin several developed countries(9,10), with adverse pathological outcomes such as placental site Trophoblastic Tumours (PSTT), epithelioid trophoblastic tumours (ETT), and choriocarcinoma(11,12). Unfortunately, in developing countries, the epidemiology of GTNamid black African women is poorly defined. Inadequate information on women who are at risk of GTN in Africa and who have undergone chemotherapy for the treatment of histologically diagnosedGTN has hampered analysis of such epidemiological data, which is essential for public health planning.In Kenya, for instance, data on reproductive outcomes of women who undergo chemotherapy for GTN that include theirpregnancy rate, the duration to next pregnancy after treatment, and neonatal outcomes of subsequent pregnancies after chemotherapy are not defined sufficiently. To contribute to the growing knowledge in this research subject, these gaps need to be filled.

CHAPTER TWO

2 LITERATURE REVIEW

2.1 Clinical Presentation of GTN

GTN refers to a group of neoplasms associated with the proliferation of trophoblastic tissues following a molar pregnancy or because of an aberrant fertilisation process that leads to the development of a complete or partial hydatiform mole(13). In most cases, complete moles are the commonest and often arise when a chromosomally empty ovum is fertilised by one haploid sperm (23X), forming a zygote with duplicated chromosomal material.The development of a partial hydatiform involves two sperms fertilising a normal egg, and therefore a zygote with a triploid chromosomal pattern(14–16). Although moles are the commonest epithelioidtumours, placental site trophoblastic tumours, or choriocarcinomas have also been reported (1). As such, the clinical presentation of GTN is complex and differs between patients. Metastasis to the genital tract (lower), for instance, is a common outcome. These appear as vascularised blue-black and or purple papules that are prone to bleeding profusely when they are biopsied (17).

Whenever gastrointestinal metastasis occurs and a hemoperitoneum forms because of excessive bleeding, women areprone to havingrebound tenderness, abdominal guarding, or signs of haemorrhagic shocksuch as no or low urine output, profuse sweating, and blue fingernails or lips (18,19).Choriocarcinomas have been reported within and along organs with adenocarcinomas being the common (46) than pure primary choriocarcinomas. Primary extragonadal choriocarcinomas are not very common, and are somewhat very hard to diagnose due to their unusual presentations. Their pathogenesis is also poorly understood. Extragonadal sites such as the liver, lung, urinary bladder, breast, nose, and prostate are not common (47). Whenever liver and brain metastasis are present, patients can present with jaundice, if biliary obstruction occurs, and neurologicchangessuch as chronic seizures and or headaches(20,21).

2.2 Risk Factors for GTN

The maternal and sociodemographic factors that predispose women to hydatiform moles and GTN, in general, have been widely studied worldwide. In a publication by Lurain John (1) in the American Journal of Obstetrics and Gynaecology, the extremities of reproductive age during conception was associated with an increased risk of developing hydatiform moles. For

women who were <21 and >35 years, the risk of GTN was 1.9 times that of women who were pregnant at 21-35 years.On the other hand, women who were >40 years had 7.5 times the risk of GTNs compared to 21-35-year-olds. Lurain alsoreported a correlation between having a prior hydatiform mole and having another molar pregnancy with the risk being10 to 20 times higher among women with a prior hydatiform mole (1). Parazzini*et al*.(22), in a case control study in Italy, reported similar results.The odds of having a partial or complete hydatiform mole were 18 and 12 times high amongpatients with a history of Gestational Trophoblastic Disease (GTD). A history of preceding spontaneous abortions, a long Inter Pregnancy Interval (IPI) between last and index pregnancies, and a history of miscarriages have also been found to increase the risk of hydatiform moles and thus GTN(9). However, mating ABO blood group, contraceptive history, and induced abortions were not linked with a high risk of GTN(9,22).

2.3 Diagnosis of GTN

After a molar pregnancy, an analysis of serial β-hCG titres has been found to be good for diagnosis of GTN (25).βHCGis important for the diagnosis and monitoring the curative effects of drugs. However, because aconclusive diagnosis by histology is difficult in most cases, a persistent or elevated βhCG levels in the serum is required to diagnose persistent and recurrent disease. In women with benign hydatiform moles, HCG levels drop steadily for eight to 12 weeks after an evacuation. However, in patients with malignant transformations, HCG levels plateau or remain the same for over six months even after an evacuation (26,27).

Imaging is the recommended procedure for the diagnosis of high-risk GTN cases. It can detect persistent molar tissue in the lungs (chest radiography), the liver (Magnetic Resonance Imaging (MRI), the uterus (pelvic ultrasonography), and the brain (Computed Tomography)(13,23).Due to its specificity, it can detect the presence of persistent hydatiform moles accurately when GTN is suspected. A histological examination of biopsy and or curettage samples of metastatic lesions canthen be done as confirmation.However, in low-risk women with unsuspected GTN, ultrasound might be an inefficient procedure for the diagnosis of moles because of its inability to differentiate the retained products of conception, nonmolar abortions, and partial hydatiform(24).. Liver enzyme tests and Complete Blood Count (CBC) test can also be used to detect metastasis to the liver or anaemia related to secondary bleeding of a metastatic lesion related to GTN (21). To get a definitive

diagnosis,health facilities should usemultifactorial diagnostic approaches that involve analysis of clinical features, imaging results, and serialβ-hCG titres.

2.4 Management of GTNs

Suction and curettage are essential first steps for the management of hydatiform moles. Preferably, hydatiform moles should be extracted at a gestational age lesser than 16 weeks to prevent the embolization of molar tissue to the lungs or induction of haemorrhage (28).Chemotherapy is the mainstay of treatment of most GTNs with relatively good response butthe effects of chemotherapy on fertility need to be evaluated. In patients with a FIGO score ≥13, Bolze *et al*. (29) reported an overall five year mortality rate of only 2%, which increased to 5% in high-risk patients.In Kenya, Gitau S.M(30) reported an overall remission rate of 65.2% at KNH, which was lower than the 91.8% remission rate reported by Hoekstra *et al*. (31) in the USA; this was largely due to provision of suboptimal care.Chemoprophylaxis during evacuation of a hydatiform mole has also been reported to lower the risk of developing GTN from 50% to 10% with a combo of methotrexate, actinomycin D, and cyclophosphamide chemotherapy regimens found to offer best results (28).Before exposure to chemotherapy, patients should be evaluated for gastrointestinal or peritoneal bleeding, heavy vaginal bleeding, metastatic disease, and serial β-hCG titres after evacuation. The WHO has a prognostic scoring system (Table 1) and a FIGO anatomic scoring system (Table 2) for evaluating risk status.

Table 1. Modified WHO prognostic scoring system as adapted by FIGO

Risk factors	Score			
	0	1	2	4
Age (years)	< 40	≥ 40	–	–
Antecedent pregnancy	Molar	Abortion	Term	–
Interval (months)*	4	4–6	7–12	> 12
Pretreatment serum hCG (mIU/mL)	<1000	1000–10,000	10,000–100,000	> 100,000
Largest tumor (including uterus)	<3cm	3–4cm	≥ 5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases	–	1–4	5–8	> 8
Previous failed chemotherapy	–	–	monotherapy	≥ 2 drugs

Table 2. FIGO anatomic staging for GTN

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is restricted 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

A score of less than 6 or stage I, II, and III is categorized as low risk
A score of ≥ 7 or stage IV is categorized as high risk

2.4.1 Management of Low Risk Women

Irrespective of the uterine size, suction curettage is the most recommended GTN management techniques for those low-risk women who want to preserve fertility. Prostaglandin analogues and oxytocic agents are recommended only when there is significant loss of blood after uterine evacuations (32). However, to contain mole tissues and prevent the induction of metastatic disease, it is advisable that health care providers minimize medical evacuation, sharp curettage, or excessive preparation of the cervix before evacuation. Furthermore, the use of prostaglandin analogues and cytotoxic drugs should be only be considered when there is excessive hemorrhage after a successful evacuation(33).Even though opinions are varied as to which is the best chemotherapy for low-risk women, a combination of methotrexate (MXT), actinomycin-D (ActD), and folinic acid (FA) has yielded positive results.

In a study by Miller *et al*.(34), patients who received multi-day regime of MXT for GTN had a higher remission rate than women who were treated with a single dose of dactinomycin. For premenopausal low-risk women who do not worry about losing their fertility, hysterectomy may be considered. It minimizes the dosage of chemotherapyand therefore its toxic effects.Without salvage chemotherapy, hysterectomy has been found to be effective in 82.4% of women with non-metastatic or low-risk GTN, if used as a first line of treatment, and therefore can be a substitute forsingle-agent chemotherapy. However, hysterectomy is contraindicated in young patients since single-agent chemotherapies are remedialand do maintain fertility (43).

2.4.2 Management of High-Risk disease

In the FIGO scoring system in table 2 above, women with a score ≥7 are considered to have a high risk GTN. Approximately 20-25% of women with this condition relapse after primary treatment. They also have a higher risk of developing drug resistance compared to women with a low risk disease(35). However, with salvage therapies such as paclitaxel/cisplatin

alternating with paclitaxel/etoposide deemed effective, cure of high-risk GTN is still possible. In a study by Wang *et al*. (36), 19% of high-risk GTN and had failed chemotherapy previously had atotal remission after salvage treatment with TP/TE or cisplastin-based chemotherapy, while 31% had a partial remission. TP/TE was well tolerated than cisplastin-based chemotherapy with only one participant developing severe toxic effects. The EMA-EP schedule, which consists of dactinomycin, methotrexate, and etoposide alternating weekly has also yielded good results with a response rate between 75% and 80% reported(37). Moreover, due predictability of its short term toxic events, The EMA-EP schedule is very easy to manage in high risk women(38).

In cases where preservation of fertility is unnecessary, hysterectomy is often the main therapy. For ETT with non-metastatic disease, surgery is recommended. Unfortunately, most women with ETT develop metastatic diseases and terminal diseases with a mortality rate of 10-24%. If patient has uncontrolled uterine bleeding, hysterectomy might be considered, even though uterine artery embolism eliminates its requirement.Laparotomy might also be required to stop bleeding in organs such as kidneys, liver, spleen, and the GIT, while craniotomy is indicated when and increased intracranial pressure is evident because of a brain haemorrhage.If a patient has a drug-resistant tumour (isolated), hysterectomy or the removal of pulmonary and isolated cranial nodules has been found to improve the survival rate.Chemotherapeutic intervention is recommended when a surgical intervention surgical intervention has failed or is inappropriate.

2.5 Follow up

The effect of chemotherapeutic drugs on fertility can be inferred from the prevalence of amenorrhoea, variations in gonadotropins levels, long-term fertility rates and the outcomes of the pregnancies as measures of ovarian function. In this study pregnancy outcome is the focus. Typically, after a chemotherapy the ovaries of most women are mostly normal or have a mild decrease in the number of primordial follicles. The greater decrease reported in the number of larger maturing follicles might indicate that chemotherapy might have lesser effect on oocyte development that it does onfollicular development. This is consistent with most findings of histological exams, which report a high incidence of amenorrhea with high concentrations of serum gonadotropins in women aged 40 years during chemotherapy. However, in some cases, fertility may return after the cessation of the therapy in several months to years (44).

Folliculogenesis is long in healthy women. According to Gougeon, the growth of Graafian follicles from primordial ones was in the order of 6–12 months (Gougeon, 1996). If anti-cancer drugs affect the development of pre-antral follicles and ovulatory oocytes a short interval after chemotherapy, teratogenic and genetic damages might develop because of the effect of such drugs. Meirow *et al.* found that fertilization shortly after chemotherapy with cyclophosphamideincreased the rate of malformations and pregnancy failure in mice (Meirow *et al*., 2001). Thus, it is vital to define the safety period between cessation of chemotherapy and fertilization.

In a study Braga *et al*. (2), adverse maternal outcomes were reported for women who conceived <6months after chemotherapy for GTN. The incidence of spontaneous abortions, for instance, was higher in the<6 months group compared to 6-12 months group. This underpinned the need for follow-up after chemotherapy for treatment of GTN to improve the reproductive outcomes of women. Pregnancy at this time acts as a smoke screen, which masks the detection of relapse of disease. Even though published data indicate that early pregnancy after GTN chemotherapy,does no compromise the development of foetus, data on the effect of chemotherapy on early pregnancies and subsequent relapse of patients is minimal. In a current retrospective database study, Braga and others found no association between HC use whileβhCG levels are high after a uterine evacuation for complete HM and time toβ hCG regression, development of gestational trophoblastic neoplasia or FIGO risk score.Oral contraceptives do not appear to alter regression patterns ofβ hCG values and recommended by ACOG for contraception during post molarβ hCG monitoring. These tend to lower the LH levels by negative feedbackmechanism and prevent an apparentβ hCG elevation due to similarity in structure with LH.

Frequent monitoring of sera serial β-hCG titres is required weekly for three consecutive weeks during treatment for women with hydatiform moles and weekly for three consecutive weeks for women with GTN. After chemotherapy, β-hCG titres should be checked every monthfor six months in women with hydatiform moles and monthly for 12 months in women with low risk GTN. In women with high risk GTN monthly tests for the first 18 months, every six months for the next two years, and every year for 5 years thereafter are required (26).Use of hormonal contraception does not influence the development of post-molar GTN or delayed time toβ hCG remission. Therefore, HC can safely be used to avert a new

pregnancy following CHM irrespective of theβhCG level after chemotherapy,oral contraception is suggested for women with GTN for 12 months if they have a low risk GTN status or 18 months if high risk (26). Due to paucity of data, it is unknown ifKenyan women adhere to such guidelines.

Regarding psychosocial effects, women with GTN might have mood disturbance, sexual issues, marital difficulties, and anxieties abouttheir fertility in the future. Since GTN is a sequelae of different forms of pregnancy, couples grapple with concerns of malignancy and as well as a loss of pregnancy. Patients also develop worrying levels of anger, financialanxiety, fatigue,confusion, future pregnancy concerns and sexual dysfunction for prolonged time. Among patients with metastatic disease, there is more risk of developing psychological conflictsand therefore require need assessments and interventions during treatment and after achievement of remission (45)

2.6 Conceptual Framework

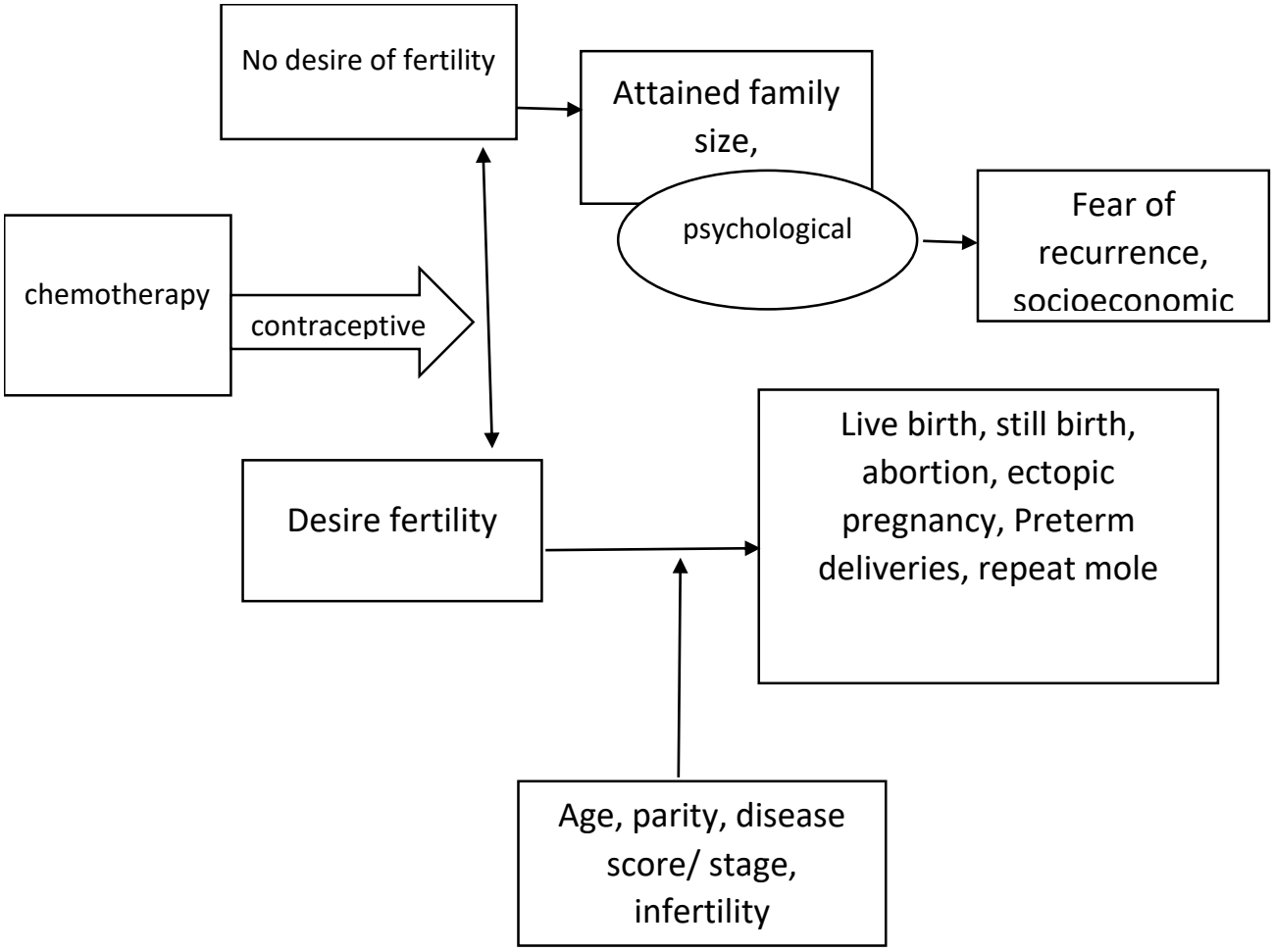

Figure 1. Conceptual framework

2.7 Statement of the Problem

The incidence of GTNs in Africa has been reported to be between 2.4/1000 and 4.6/1000 of all births. To prevent relapse and the development of adverse reproductive outcomes in subsequent pregnancies, the World Health Organisation (WHO) has clinical guidelines that women should follow after chemotherapy for GTN. Oral contraception is recommended in the first six months after treatment. It also recommends that these women should avoid pregnancy for a minimum of 12 months, if low risk and for 18 months, if high risk, to prevent adverse reproductive outcomes after treatment for GTN. However, it is unknown whether women know or adhere to these guidelines. Even though Gitau *et al*. (2015) reported less favourable outcomes for low-risk GTN patients at KNH versus a reference global facility, reproductive outcomes after multi agent versus single agent chemotherapy for treatment of GTN has not been explored. This research gap needs to be filled

2.8 Research Questions

What are the pregnancy outcomes of women after single agent chemotherapy versus multi agent chemotherapy for GTNs at the Kenyatta National Hospital (KNH)?

2.9 Null Hypotheses

Reproductive outcomes were similar for women who received single agent chemotherapy versus multi agent for the treatment of GTNs at KNH.

2.10 Objectives

2.10.1 Broad Objective

To comparethe pregnancy outcomes of women who received single agent chemotherapy versus multi agent chemotherapy forGTNs at KNH between January 2013 and December 2017

2.10.2 Specific Objectives

Among women who received single agent chemotherapy versus multi agent chemotherapy for GTNS at KNH between 2013 and 2017:

a) To compare incidence of pregnancy
b) To compare outcomes of the pregnancies

CHAPTER THREE

3 METHODOLOGY

3.1 Study Design

This was a retrospective classical cohort study at Kenyatta National Hospital.

3.2 Study Site and Setting

The site and setting for the study wasat the Health information department at KNH. Started in 1901, KNH has functioned as the main public level 6 hospital in Nairobi and the largest referral hospital in Kenya and east Africa for decades. It serves as the teaching hospital for the College of Health Sciences of the University of Nairobi (UoN) and is currently the main public hospital in Kenya that offers comprehensive treatment for cancers.About 123 new cancer cases are diagnosed in its cancer facilities daily with 29 of these cases missing or delaying treatment due to lack of money for transport or treatment. In KNH and Kenya in general, breast cancer is the commonest cancer for women of childbearing age. However, rare gynaecological cancers such as GTN are also managed here. Low risk and high-risk cases are treated in the gynaecological wards as follows:

Table 3. Treatment Strategies for Low Risk and High Risk GTN Cases at KNH

Low risk *(GTN score 0-6)*	a)	Methotrexate 1mg/kg (maximum 70mg) on day 1, 3, 5 and 7 with 15mg folinic acid once/day on day 2, 4, 6 and 8 until bHCG levels are negative for three weeks
	b)	Actinomycin D 1.2mg/m^2 IM
High risk *(GTN score ≤ 7 or single drug resistance)*	Day1	Etoposide IV infusion100mg/m^2 in 200ml of normosaline for 30 min
		Methotrexate 300mg/m^2 in 1litre normosaline
		Actinomycin D 0.5 mg im slowly
	Day 2	Etoposide IV infusion100mg/m^2 in 200ml of normosaline for 30 min
		Actinomycin D 0.5mg im slowly
		Folinic acid 15mg IM/orally 12hourly for 2 days
	Day 8	Cyclophosphamide 600mg/m^2 IV bolus
		Vincristine 1mg/m^2 (maximum 2 mg) IV stat

Note:
cycles for high risk patients are repeated every2 weeksuntil bHCG is negative for six weeks
the treatment is continued for 2 to 4 cycles after the first normal bHCG

KNH has a data capture, data archival and patient follow-up system for GTN cancers, which made it a good setting for this study.The data was acquired from the department of Health Information.

3.3 Study Population

Women diagnosed with GTNs at between 16-46 years old,who received chemotherapybetween January 2013 and December 2017at KNH,and met the inclusion criteria.

3.3.1 Inclusion Criteria

a) Had a confirmed dx of GTN using BHCG levels
b) Were treated with chemotherapyfor GTN at KNH from January2013 - December2017
c) Were followed up at KNH

3.3.2 Exclusion Criteria

a) Diagnosed with GTN and treated before January 2013 - December 2017
b) Women who were received chemotherapy for non GTN cancers
c) Women who underwent hysterectomy for treatment for GTN

3.4 Sample Size Calculation

In a study by Cioffi *et al*. (2018), the incidence of amenorrhea after single-agent and multiagent chemotherapy for GTN was 33% and 66.7% respectively. We use these values for calculations.

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

Fleiss, (1981)

Where:

p1, p2 = proportion of groups #1 and #2

Δ = absolute difference between the study proportions (|p2-p1|)

n1 = sample size for single agent chemotherapy group (33%)

n2 = sample size for combination therapy/EMACO (66.7)

α = probability of type I error (0.05)

β = probability of type II error (0.1)

z = standard normal variate for alpha

K = ratio of sample size for multi agent to single agent chemotherapygroup (1)

$$N_1 = \left\{ 1.96 * \sqrt{0.499 * 0.501 * (1 + \frac{1}{1})} + 1.28 * \sqrt{0.33 * 0.67 + (\frac{0.667 * 0.333}{1})} \right\}^2 / 0.337^2$$

$$N_1 = 44$$

$$N_2 = K * N_1 = 44$$

The minimum sample size was 44 in the multi agentchemotherapy group and 44 in the single agent chemotherapy group. A non-response rate of 20% was anticipated. Therefore, after adjusting the sample size by a factor of 0.2 using the formula by Palta *et al*. (1979), effective N = N/ (1-q) was 55 per group (110).

3.5 Sampling Procedure

The files of patients who received chemotherapy for GTNs from January 2013 to December 2017were retrieved from the KNH Health information department and their completeness checked. The files of all women who were aged between 16-46 years old at the time of diagnosis and had a confirmed DX for GTN using BHCG levels wasseparated, contact details, and the telephone transcript in Appendix 2a (English) or 2b (Kiswahili) used to recruit 110 participants (multi agent therapy (55) and single agent chemotherapy (55)) for GTNs. A consecutive sampling technique was used. Patients who offer informed oral consent during interviews was recruited serially until the recommended minimum sample size for study is obtained. Files of patients who decline consent or fail to answer calls on two occasions wasnot be used.

3.6 Data Collection

3.6.1 Data Capture Tool

The study-specific data capture tool in Appendix 1 was used to collect secondary data from files. The tools were organised into sections that capture the following data. Section 1captured the demographic data of participants such as age, marital status, level of education and employment status. Section 2 captured the medical information of patients such as staging (I-IV), risk status using the WHO Figo score, and chemotherapy. Section 3 captured the pregnancy outcomes of women, which included desire for pregnancy after chemotherapy for GTN, contraceptive use, eventual pregnancy, the interval to pregnancy afterchemotherapy

for GTN, andthe outcomes of an eventual pregnancy (live birth, still birth, ectopic or abortion).

3.6.2 Outcome Variables

The data variables for the study are presented in Table 4 below. The main outcome variable was the pregnancy outcomes of women diagnosed with GTN in KNH after chemotherapy and tested the desire of patients to get pregnant after chemotherapy to treat GTN (Table 2).Incidence of pregnancies, IPI, and contraceptive use after chemotherapywas also evaluated.

Table 4. Outcome Variables of the Study

Outcome variables	Outcome of chemotherapy	Remission
		Relapse
		Death
	Desire to get pregnant	Yes
		No
	Eventual pregnancy	Yes
		No
	Duration to pregnancy	≤ 6month >1 year
		≥1 year
	Outcome of pregnancy	Viable preterm or term Nonviable

3.6.3 Independent Variables

The main independent variable wasthe chemotherapy given to the patients.Women ascertained to have a WHO Figo score of 0-6 wasconsidered to have taken single agent chemotherapyand those witha Figo score of 7-10 given multiple therapy.The risk score, stage of infection (I-IV),parity,and age wasintermediate variables (Table 5).

Table 5. Independent and intermediate variables

Independent variable	Chemotherapy	Multi agent
		Single agent
Intermediate variables	Age	16-20
		21-30
		31-40
		>40
	Stage of GTN	I

		II
		III
		IV
	Risk status	Low (0-6)
		High (>6)
	Metastasis	Yes
		No

3.6.4 Reliability and Validity

The reliability of the data capture tools should be ascertained when collecting primary data(39). However, because the data collection procedure was mainly retrospective, the data capture tool was not pretested to ascertain its reliability. The researcher ascertained ifthestudy tool could capture the necessarydata for answering the research questions usingthe face validity technique by Moores *et al*.(40). A data capture tool was printed and shared with lectures and consultant doctors at the department of Obstetrics and Gynaecology of UoN and KNH for their input. The reviewerwas requested to check the capability of the tool answering research questions and provide feedback. Recommendations were implemented before use.

3.7 Data Collection Process

The data collection was in two step, the files of patients were reviewed and medical characteristics such as the parity of women, risk status, and the stage of the disease collected. The data on the education level and marital status of patients was also captured in the tool and the pregnancy outcomes of women obtained and captured during the telephone interviews. These included their desire to get pregnant after chemotherapy (single or multi agent) for GTN and if they had a pregnancy eventually or not. Contraceptive use, interval to next pregnancy, and outcomes of the next pregnancies (viable or non-viable) was also checked. Data collection was moderated by the PI and information recorded on a study questionnaire.

3.8 Data Quality Assurance

To ensure accuracy of data collection, the following measures wasenforced:

a) Astandard data collection toolwas developed, which was validated before use. The toolwas organised into well-defined sections that capture unique sets of data.
b) Before deployment,training of all research assistants on how to extract secondary data from the file of patients and how to conduct follow up interviews using telephone

calls, was done. During trainings, the recommendations of Block and Erskine (41) on how to safeguard the inherent weaknesses of telephone interviews was stressed. Briefly, research assistant was taught how to ask questions accurately, note taking, and how to ask follow up questions. The principle investigator (PI) moderated these trainings.

c) Errors were reported directly to the PI for verification. Research-assistantdated and append their signatures to acknowledge the changes to the questionnaires.
d) All questionnaires were checked for completeness by the PI before data entry
e) Data handling (data entry and cleaning), was done by an experienced statistician.A globally accepted statistics software, SPSS, used for data analysis.

3.9 Data Analysis

The comparability of participants in study arms (sociodemographic and reproductive) was done using the chi-square test and data visualised as proportions or as clustered bar charts. The test for statistical significance was done at 95% confidence interval and interpreted using odds ratios and the p value. The reproductive outcomes between multi-agent and single agent chemotherapy groups was done using the chi-square test at 95% CI. Proportions was computed and the relative risk (RR) interpreted to determine the relationship between treatment options and desire for pregnancy, eventual pregnancy, and the maternal and neonatal outcomes of subsequent births. To control confounding, any difference (sociodemographic and or reproductive) between the study groups established during the first stage of analysis waswas controlled in a logistics regression model. SPSS version 24,was used for the analysis.

3.10 Results Dissemination Plan

The results were formulated as reports and manuscripts, which will be used to disseminate data to practicing doctors, KNH, UON, the scientific community, the Ministry of Health (MoH) The results of this study was presented in the department of Obstetrics and Gynaecology organised by UoN College of Health Sciences. To guide formulation of policies that could improve service delivery to patients, a final report will be shared with the department of obstetrics and gynaecology- UON and MoH in Kenya.

3.11 Limitations of the Study

Aretrospective descriptive approach wasusedduring data collection. Therefore, there might be adifficulty finding patients' files and or find files with missing data. To lower bias related with missing files or data, the minimum sample size was adjusted by a factor of 20%. Second, locating patients from far-flung regions of Kenya might be a challenge during data collection. To solve this, contacts participants and their next of kin was extracted from files and follow-ups made. Bilingual interviewers were trained whenever there were language barriers.

3.12 Strengths of the Study

Since KNH is the main public referral hospital, the sample was expecting women from all geographical areas of the country thus was generally representative. Unlike some studies that rely solely on retrospective data, primary data was collected by performing telephone interviews. Data collection enabled efficient saving of time and funds,thus, many cases were analyzed.

3.13 Ethical Considerations

Ethical approval was sought afterfrom the KNH/UoN ethical review board.Waiver of written consent was obtained thus oral consent sought from participants using a telephone script,whichwas read verbatim(appendix 2a and 2b) and the confidentiality of patients upheld by omitting personal information during data collection and dissemination.Authorisation to conduct the study was sought from KNH, as the custodian of patient's files.Third, becausethe line of questions might evoke the feeling of grief or anxiety in participants, the psychological wellness of all subjects was evaluated after interviews and referrals to a counsellordone. Finally, because this was a retrospective in nature, written informed consent was not be sought from participants. An application for waiver of written informed consent from participants was made to the ERC during the application for approval stage.

3.14 Funding

This was a self-sponsored study.

CHAPTER FOUR

4 RESULTS

4.1 Flow chart

A review of patient files was done and yielded 171who satisfied our criteria for inclusion. Seventy nine (79) were treated with single agent chemotherapy, of which 24 were excluded for not availing the primary data(no consent or not reachable on telephone). Ninety two patients were treated with multi agent chemotherapy, of which 37 were excluded for lack of primary data. As such, 55 patients were recruited in both groups, primary and secondary data collected, and analysed (Figure 1).

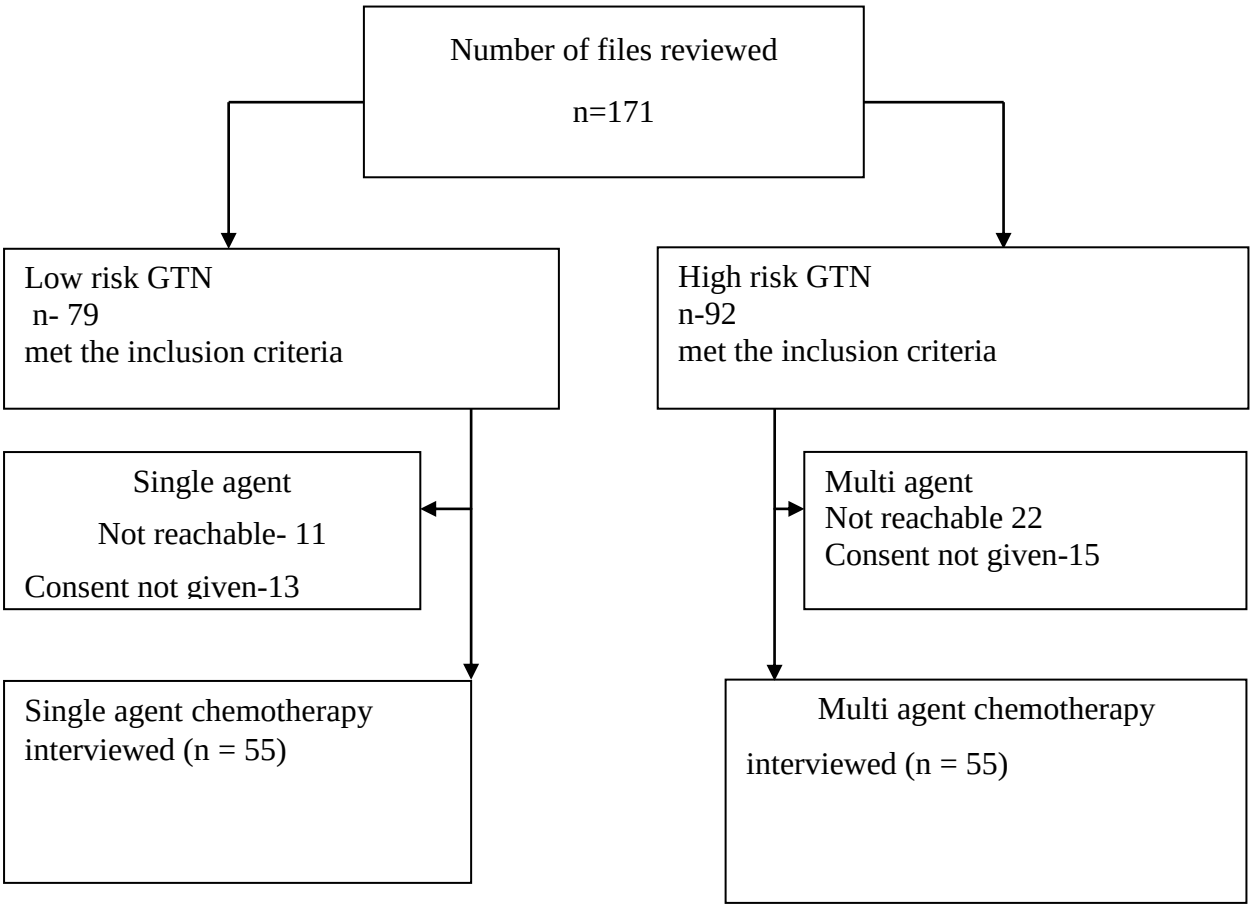

Figure 2. Study flow chart

4.2 Demographic Characteristics

The age of patients on single and multi-agent chemotherapy varied statistically significantly (-=0.01). About 25.5% more patients in age group 21-35 had single agent chemotherapy,

while 20.0% more patients in age group 36+ years had multi agent chemotherapy. The gravidity and marital status of patients was comparable (>0.05), while significantly more patients who had single agent chemotherapy (23.6%) than multi agent chemotherapy (9.1%) has a primary level of education (P=0.04). Patients who had multi-agent than single-agent chemotherapy were more likely to have a high-risk status (92.7% vs 7.3%) and metastasises cancer (16.4% vs 3.6%). Among the 55 patients who were treated with multi-agent chemotherapy, EMACO (98.2%) followed by EMA-EP (1.8%) were the commonest treatment modalities. Among the 55 who received single agent chemotherapy, Methotrexate (MXT) was the commonest (70.9%) then Actinomicin D (29.1%).

Table 6. Demographic characteristic of women who received single agent and multiagent chemotherapy for gestational trophoblastic neoplasia at KNH

	Single	Multi	P
Age			0.01
<21	2 (3.6)	5 (9.1)	
21-35	44 (80.0)	30 (54.5)	
36	9 (16.4)	20 (36.4)	
Gravidity			1.00
1 to 4	49 (89.1)	48 (89.1)	
5+	6 (10.9)	6 (10.9)	
Marital status			0.51
Married	32 (58.2)	31 (56.4)	
Separated	15 (27.3)	16 (29.1)	
after GTN	8 (14.5)	5 (9.1)	
Single	8 (14.5)	6 (10.9)	
Widowed	0 (0.0)	2 (3.6)	
Education			0.04
Primary	20 (36.4)	25 (45.5)	
Secondary	22 (40.0)	21 (38.2)	
Tertiary	13 (23.6)	5 (9.1)	
Employment			0.47
Formal employment	8 (14.5)	4 (7.3)	
Self-employment	17 (30.9)	18 (32.7)	
Unemployed	30 (54.5)	33 (60.0)	
Religion			0.41
Christian	46 (83.6)	49 (89.1)	
Muslim	9 (16.4)	6 (10.9)	
Risk status			<0.01
High	4 (7.3)	52 (92.7)	
Low	51 (92.7)	3 (7.3)	
Metastasis			0.02
Yes	2 (3.6)	9 (16.4)	

No	53 (96.4)	46 (83.6)	
Treatment modalities			
Actinomicin D	16 (29.1)	0 (0.0)	
MTX	39 (70.9)	0 (0.0)	
EMACO	0 (0.0)	54 (98.2)	
EMA-EP	0 (0.0)	1 (1.8)	
Outcomes of treatment			0.09
Relapse	6 (10.9)	12 (21.8)	
Remission	49 (89.1)	41 (74.5)	

4.3 Incidence of Pregnancy among Patients on Single and Multi-agent Chemotherapy

Twenty-six patients on single agent chemotherapy and eleven on multiagent chemotherapy conceived. This translated to a crude incidence rate of 47.3% and 20% respectively, which was statistically significantly different [RR (95% CI) = 1.76 (1.24-2.51), p<0.01]. After controlling for the age, risk status of patients, and metastasis of cancer, the pregnancy rate of women on multi agent versus single agent chemotherapy was similar [ARR (95% CI) = 0.72 (0.12-4.31), p=0.71)].

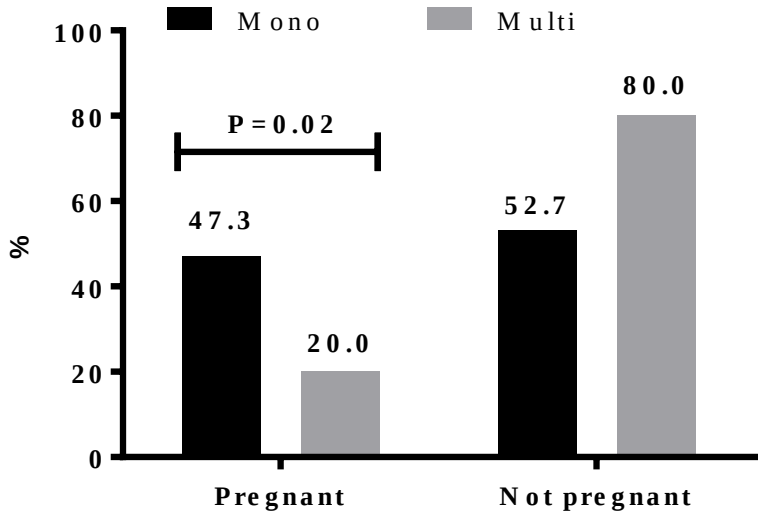

Figure 3. Incidence on pregnancy by the chemotherapy type of GTN patients

4.3.1 Incidence of pregnancy by the demographics of patients

Patients who conceived after single agent chemotherapy for GTN were more likely to be age <21 years old than age 21-25 or 36+ years (p<0.01). However, among women who conceived after multi-agent chemotherapy, age of patients did not influence the incidence of conception statistically significantly (P=0.35). The gravidity, marital status, and education level of patients did not influence the incidence of conception after treatment (p>0.05). Moreover,

employment status, religion, risk status of patients, and the presence of metastasised cancer did not influence incidence of pregnancy among women who had single or multi-agent chemotherapy (Table 7).

Table 7. Eventual pregnancy and the demographics of patients

	Single			Multi		
	Pregnant	No pregnant	P	Pregnant	Not pregnant	
Age			<0.01			0.35
<21	2 (100)	0 (0.0)		1 (20.0)	4 (80.0)	
21-35	24 (54.5)	20 (45.5)		8 (26.7)	22 (73.3)	
36+	0 (0.0)	9 (100)		2 (10.0)	18 (90.0)	
Gravidity			0.38			0.24
1 to 4	24 (49.0)	25 (51.0)		11 (22.4)	38 (77.6)	
5+	2 (33.3)	4 (66.7)		0 (0.0)	6 (100)	
Marital Status			0.76			0.49
Married	15 (46.9)	17 (53.1)		7 (22.6)	24 (77.4)	
Separated	8 (53.3)	7 (46.7)		4 (25.0)	12.0)	
Single	3 (37.5)	5 (62.5)		0 (0.0)	6 (100.0)	
Widowed	0 (0.0)	0 (0.0)		0 (0.0)	2 (100)	
Education			0.96			0.66
Primary	10 (50.0)	10 (50.0)		4 (16.0)	21 (84.0)	
Secondary	7 (31.8)	15 (68.2)		4 (19.0)	17 (81.0)	
Tertiary	9 (69.2)	4 (30.8)		2 (40.0)	3 (60.0)	
None	0 (0.0)	0 (0.0)		1 (25.0)	3 (75.0)	
Employment			0.17			0.51
Formal employment	6 (75.0)	2 (25.0)		1 (25.0)	3 (75.0)	
Self-employment	6 (35.3)	11 (64.7)		2 (11.1)	16 (88.9)	
Unemployed	14 (46.7)	16 (53.3)		8 (24.2)	25 (75.8)	
Religion			0.57			0.34
Christian	22 (47.8)	24 (52.2)		9 (18.4)	40 (81.6)	
Muslim	4 (44.4)	5 (55.6)		2 (33.3)	4 (66.7)	
Risk status			0.34			0.6
High	1 (25.0)	3 (75.0)		10 (19.6)	41 (80.4)	
Low	25 (49.0)	26 (51.0)		1 (25.0)	3 (75.0)	
Metastasis			0.27			0.41
Yes	0 (0.0)	2 (100)		11.10%	88.90%	
No	26 (49.1)	27 (50.9)		10 (21.7)	36 (78.3)	

4.4 Pregnancy Outcomes after Single and Multi-Agent Chemotherapy

Desire for a pregnancy was significantly higher among patients on single agent chemotherapy (60.0%) than multi agent chemotherapy (38.2). However, after controlling for age, risk status of patients, and metastasis, the desire for pregnancy was comparable [ARR (95%) =1.48 (0.25-8.6), p=0.51)]. Eight more patients on multi agent chemotherapy cited the psychological trauma of illness as a hindrance for pregnancy. About 52.5% of patients on multi agent chemotherapy and 64.3% single agent chemotherapy were on contraceptives, with IUCD and oral pills being the most preferred respectively. The preference for condoms,

depo injections, and DMPA were low and comparable (p>0.05). Of the 20 and 11 who conceived after single agent and multi-agent chemotherapy, 73.1 and 72.7% had a live birth. Miscarriages were five (19.2%) and two among women who had single agent and multi-agent chemotherapy respectively, while ectopic pregnancy (tuboovarian) was reported in one patient on single agent chemotherapy. Three women on multi-agent chemotherapy (5.5%) and five single agent chemotherapy (9.1%) had eventual pregnancies with H-mole, recurrent GTN, and HTN being commonest eventualities (Table 8).

Table 8. Pregnancy outcomes of patients on multi and single agent chemotherapy for GTN

			Univariate		Multivariate	
	Single	Multi	OR	P	OR	P
Desire for pregnancy	33 (60.0)	21 (38.2)	1.55(1.05-2.29)	0.03	1.48 (0.25-8.6)	0.66
No desire for pregnancy	22 (40.0)	34 (61.8)		Ref		
Reasons						
Desired family size	11 (50.0)	12 (35.4)	1.54 (0.77-3.07)	0.25		
No reason	9 (40.9)	20 (58.8)		ref		
Psychological trauma	5 (9.1)	13 (23.6)	0.89 (0.35-2.25)	1.00		
On contraceptives	35 (63.6)	32 (58.2)	1.123 (0.75-1.66)	0.69	3.67 (0.58-22.87)	0.16
Type						
Condoms	2 (3.6)	1 (1.8)	1.20 (0.48-2.95)	1		
Depo	5 (9.1)	8 (14.5)	0.69 (0.31-1.54)	0.47		
DMPA	1 (1.8)	0 (0.0)				
E-pills	2 (3.6)	3 (5.5)	0.72 (0.22-2.27)	0.64		
E-pills/condoms	9 (14.6)	2 (3.6)	1.47 (0.89-2.42)	0.23		
IUCD	7 (12.7)	11 (20.0)	0.70 (0.34-1.42)	0.5		
Pills	10 (18.2)	8 (14.5)		ref		
Not on contraceptives	20 (36.4)	23 (41.8)		ref		
Reasons						
Breastfeeding	1 (1.8)	0 (0.0)				
No reason	5 (9.1)	6 (10.9)		ref		
Not sexually active	8 (14.5)	7 (12.7)	1.17 (0.52-2.61)	1.00		
Unknown	7	10				
pregnancy	26 (47.3)	11 (20.0)	1.76 (1.24-2.51)	<0.01	0.72 (0.12-4.31)	0.71
Outcome						
Live birth	19 (73.1)	8 (72.7)		ref		
Miscarriage	5 (19.2)	2 (18.2)	1.01 (0.59-1.72)	1.00		
1st trimester	2 (40)	0 (0.0)				
2nd trimester	3 (60)	2 (100)	0.85 (0.40-1.81)	0.63		
Ectopic	1 (3.8)	0 (0.0)				
Repeat mole	1 (3.8)	1 (9.1)	0.71 (0.17-2.90)	1.00		
Eventful pregnancy	5 (9.1)	3 (5.5)	0.91 (0.49-1.68)	1.00		
H Mole	2 (40.0)	0 (0.0)				
HTN	1 (20.0)	1 (20.0)				
Miscarriage	0 (0.0)	1 (20.0)				
Recurrent UTI	1 (20.0)	0 (0.0)				
Recurrent GTN	1 (20.0)	1 (20.0)				
Uneventful pregnancy	15 (27.3)	7 (12.7)		ref		

CHAPTER FIVE

5 DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Discussion

To investigate the incidence of pregnancy among women who underwent chemotherapy for GTN and the outcomes in eventual pregnancies, the files of 110 patients were reviewed and primary data collected through phone interviews. Fifty-five patients who underwent single agent chemotherapy and 55 multi agent chemotherapy were reviewed and the incidence of pregnancy computed. The data showed that the desire for pregnancy did not vary significantly by the agent of chemotherapy administered, but the crude incidence of pregnancy was significantly higher among women on single agent chemotherapy (47.3%) than multi-agent chemotherapy (20%). However, after controlling confounding, the type of chemotherapy was not identified as a predictor for eventual pregnancy.

Age, risk status, education, and metastasis statistically significantly different between the 2 groups ($P<0.05$) and therefore were potential confounders of outcomes

The age, risk status, and presence of metastasis contributed to the difference in the pregnancy incidence rates reported with significantly more young women (<21) who were on single agent chemotherapy being more likely to be pregnant (100%) than those on multi-agent chemotherapy. This was consistent with Lurain John (1) in the American Journal of Obstetrics and Gynaecology, stating that the extremities of reproductive age during conception was a risk factor and that for women who were <21 the risk of GTN was 1.9 times that of women who were pregnant at 21-35 years.

There were only 2(1.8%) patients with repeat molar pregnancy in this study which was lower than Parazzini *et al*.(22) , in a case control study, showing the odds of having a partial or complete mole 12 times high among patients with a prior history of Gestational Trophoblastic Disease (GTD)

Other factors such as the education level, employment status, gravidity, and religion of patients did not influence the incidence of pregnancy postchemotherapy for GTN statistically significantly. Garcia et al reported comparable results in a systematic review of literature, in which there was no evidence of a reduction in fertility of women after chemotherapy for GTN.

However, because abortion rates were higher when women had an IPI <6 months, Garcia proposed routine clinical surveillance of patients who deliver early postchemotherapy for GTN to prevent pregnancy complication (1). Our patients had a mean IPI of 9 months, which was closer to the WHO recommended IPI postchemotherapy for GTN of 12 months.Braga et al 2008 found that majority of participants delivered between 6-12 months post chemotherapy and there was no variance in adverse perinatal outcomes (stillbirth) in both groups.Williams et al.2014, involving 225 patients in the UK had the following findings; 73.3% of early conceptions (<24 months) after single-agent and multiagent chemotherapy for GTN resulted in live births and a likely favorableoutcomecan be assured among women who become pregnant within 12 months post chemotherapy for GTN. Although the safest option is still to delay pregnancy for a year. This is the ideal recommendation in the Kenyan setting where ample resources are not yet available for close follow up and monitoring of all the patients.

In another study in China, the incidence of pregnancy after single and multi-agent chemotherapy of GTN patients who had not undergone hysterectomy was comparable (2) and not linked with adverse outcomes for mother and child.

Our data indicated that reproductive outcomes of women who underwent single and multi-agent chemotherapy for GTN at KNH was comparable. Live birth rate of women on single agent chemotherapy (73.1%) and multi-agent chemotherapy (72.7%) were high and comparable to the data of other researchers published in literature and there were no congenital anomalies reported among the live births. In China, follow-up of 222 women who underwent chemotherapy for GTN, 24.2% of whom became pregnant reported a live birth rate of 74% for EMA-CO and 76% from methotrexate. In another study in the UK in 2014 on 225 women who underwent chemotherapy for GTN, 73.3% of pregnancies post chemotherapy resulted in a live birth. Overall, even though a majority of women did not meet the threshold of 12 months IPI postchemotherapy for GTN, as recommended by WHO; patients were reassured of favourable pregnancy outcomes (3). Similar results were found in this study.

Devoid of the treatment options women were subjected, the incidence of ectopic pregnancies and repeat moles were low. Moreover, only 9.1% and 5.5 of women who received single agent and multi agent chemotherapy for GTN respectively had eventful pregnancies with hypertension and recurrent UTIs being the commonest complications. Contraceptive use wascomparable (63.6% and 58.2%), which explains the IPI

reported in this study (median 9 months).Unfortunately,whether patients strictly adhered to the WHO recommended contraceptives during the first year of follow up, could not be effectivelyassessed from the patients' files due to missing data and recall bias.

There was an assessment of whether these patients were psychologically affected by the disease burden.The Patient Health Questionaire-2 (PHQ-2)investigated the occurrence of anhedonia and depressed mood over a period of the preceding two weeks. The purpose was to screen for depression in a "first-step" approach and patients who got a positive screening test(score ≥3), needed to be further evaluated. 12 % of the whole group of patient in this study were separated / divorced from their partners after their diagnosis of GTN and 20 patients (18%)of the entire cohort got a score of 3 or more. Out of these, 14 patients(70%) were interested in talking to a counsellor

This emphasized the need for follow up and providing psychological support to these patients during the treatment and monitoring period.

5.2 Conclusions

- The incidence of pregnancy postchemotherapy for GTN was modest [20-47.3%] and does not vary significantly by the agent of treatment
- Favorable maternal and neonatal outcomescan be reassured towomen who become pregnant within 12 months postchemotherapy for GTN.

5.3 Recommendations

Women who conceive after either single or multi-agent chemotherapy regimen for GTN within one year, should be reassured of favourable reproductive outcomes but should adhere to the recommended contraceptive protocol to minimise the risk of unfavourable pregnancy outcomes

Clinicians should adhere to the standard operating procedures for follow up and monitoring as this study showed higher abortion rates in pregnancies conceived less than 6 months post chemotherapy

There is need to establish a registry for patients with GTNs at KNH to enable more rigorous long term follow up and surveillance of the patients and the children born after treatment

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APPENDICES

Appendix 1: Study Questionnaire

PREGNANCY OUTCOMES AFTER CHEMOTHERAPY FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA AT KENYATTA NATIONAL HOSPITAL, KENYA

Study Questionnaire

Fill all sections:

Study number……

Telephone number……next of kin number…….....

SECTION I: DEMOGRAPHIC CHARACTERISTICS

1. Age:……..
2. Parity……....

3. Marital status: ☐Married
☐Single
☐Divorced
☐Widow
☐Separated☐ before GTN
☐After GTN

4. Education level ☐Primary
☐Secondary
☐Tertiary
☐None

5. Employment status ☐ formal employment
☐Self employed
☐Unemployed

6. Religion ☐Christian
☐Muslim
☐Other…….

SECTION II: MEDICAL INFORMATION

7. Risk status ☐Low (0-6)
☐High (>7)

8. Stage of GTN ☐I
☐II
☐III
☐IV

5. Chemotherapy: ☐Single (specify agent ……..……)
☐Multiple (specify agent ……..)

6. Number of cycles specify ……

7. Metastasis ☐Yes
☐No
If Yes, location: …….....

8. Other treatment modalities:☐ Surgery ☐ Adjuvant
☐Neoadjuvant
☐ Radiotherapy specify……

SECTION III: PREGNANCY OUTCOMES

7. Outcome of treatment: ☐Remission
☐Relapse
☐Death

8. Desire to get pregnant: ☐Yes
☐No(reason) ☐attained desired family size
☐Psychological trauma of illness
☐Other……

9. Contraceptive use: ☐Yes (specify type……..…….)
If yes, duration of use in months …….
☐No (reason)……..

10. Eventual pregnancy: ☐Yes
☐No

11. Duration to pregnancy in months ……

12. Outcome of pregnancy: ☐Live birth ☐term≥ 37weeks(number……..)
☐preterm≤ 37weeks(number……...)
☐Any anomaly specify……
☐Miscarriage ☐ 1st trimester (No…….)
☐ 2nd trimester (No……)
☐Stillbirth (No…….)
☐Any anomaly specify……

☐Ectopic☐Tuboovarian
☐Abdominal (explain…….
☐Repeat mole

☐ Recurrent GTN

13. Maternal morbidity during pregnancy ☐uneventful

☐Eventful (explain…….

Comments……
……
……
……
……
……

14. The Patient Health Questionaire-2 (PHQ-2) inquires about the frequency of anhedonia and low mood over the past two weeks.

- A"first-step" approach is employed by the PHQ-2 is to screen for depression.
- Patients who screen positive should be investigated to determine whether the criteria for a depressive disorder is met

a)Over the **last 2 weeks**, how often have you been bothered by the following problems?

☐Not at all

☐Several days

☐More than half the days

☐Nearly every day

b)1. Loss of interest in pleasurable things

- **0**
- **+1**
- **+2**
- **+3**

c). Low mood or hopelessness

- **0**
- **+1**
- **+2**
- **+3**

PHQ-2 score = (total points)

Interpretation:

- The PHQ-2 score ranges from 0-6, with a score of 3 as the cutoff when using it to screen for depression.

- A score of 3 or more, is a likelihood of major depressive disorder .
- A positive screen test should be evaluated further using other diagnostic tools, or direct interview via mental health specialist

Would you be interested in talking to a mental health specialist? ☐ yes

☐ no

If yes……..

(Participant informed that their contact information with be shared with a mental health specialist and they was contacted for further evaluation and counselling)

Appendix 2a: Telephone Transcript for Oral Consent

PREGNANCY OUTCOMES AFTER CHEMOTHERAPY FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA AT KENYATTA NATIONAL HOSPITAL,

Telephone Transcript

Hello, my name is…….., I am research assistant in a study by Dr. Angela Namarome Wekesa, MBCHB, from the University of Nairobi's department of Obstetrics and Gynaecology. Are you free to talk to me for a few minutes?

a) *If yes, continue.*
b) *If interested but not free to talk, schedule a better time for the interview.*
c) *If not interested (no), thank the patient for the corporation and end the interview.*

You are being invited to be a participant in this study because you were once a patient at Kenyatta National Hospital and received treatment for a gynaecological condition called GTN/ choriocarcinoma on……. To accomplish the necessity for the degree of Master of Medicine, Dr. Angela Namarome Wekesa, under the supervision of Dr Marangaand Dr Bosire; is trying to establish whether the treatment that you received worked and your pregnancy outcomes thereafter. Our main aim is to know whether women like you decide to get pregnant after undergoing the treatment, time taken before pregnancy, and the outcomes of the pregnancies for women who eventually get pregnant.

Once youdecide to contribute informationto this study, we will ask you a few questions around the treatment you received for your gynaecological problem and events that ensued thereafter. We want to know whether you were fully treated or whether you underwent more treatment sessions later on because the disease came back. We also want to know whether you were using contraceptives and whether you decided to get pregnant after the treatment. Finally, if you got pregnant, we will ask about the duration it took you to get pregnant and the outcome. We are looking for 110 women to answer these questions, which take you about ten minutes.

We will not pay you money to be a participant in this study nor offer you any favours in kind for your participation. However, we will answer all of your questions until you feel satisfied. Taking part in this study will have no foreseen health risks to you. If you cannot recallsome answers and/ or you feel uneasy answering some questions, you can choose to stop the interview at any time without prejudice. Likewise, you can ask for more time to remember if needed.

Is this something that you might like to participate in?

a) *If yes, continue.*
b) *If no, thank the patient for the cooperation and end the interview.*

Before you agree to be one of our participants, here are other things that you should know:

a) Being a participant in this study is out of your volition. You are free to withdraw your involvementin this studyat any time and for whatever reason you deem fit. We will

not penalise you nor will it affect the provision of all medical services you are entitled to.

b) We will review your medical records at KNH to know the type of treatment that you received for the type and the severity of the disease you were treated for. However, all the personal information we will collect about you will not be shared with anyonewhoelse. Your name and your identification number will not be recorded anywhere.

c) This interview was recorded for easy review when analysing data. However, all audio recordings was destroyed after transcription and analysis of our data.

Do you have any questions for me?

a) If yes, answer questions until the participant is satisfied
b) If no, proceed with consenting

Do you agree to be a participant in this study?

☐ Yes: Document oral consent
☐ No: Proceed to establish wellness.

Do you need the assistance of a psychologist to discuss your situation in detail?

☐ Yes: Schedule appointment
☐ No: Thank the patient for cooperation and end the interview

Name of participant: ……..

Declaration of Person Obtaining Consent

I have read this form as is to the participant. Explanations on the aims of the study, procedures, and the risks and benefits of participation in the study have been given. A concept of voluntary participation has been elucidated and the questions of the participant answered satisfactorily.The subject has demonstrated an understanding of the information and provided oral consent.

…….....
Name and Title (Print)

……. …….....
Signature Day/Date/Time

Appendix 2b: Hati ya Simu (Kiswahili kupeana idhini ya utafiti)

PREGNANCY OUTCOMES AFTER CHEMOTHERAPY FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA AT KENYATTA NATIONAL HOSPITAL, KENYA

Hati ya Simu

Halo, jina langu ni ...., Mimi ni msaidizi wa utafiti katika utafiti na Dk Angela Namarome Wekesa, MBCHB, kutoka Idara ya Chuo Kikuu cha Nairobi ya Obstetrics na Wanawake. Je! Wewe ni huru kuzungumza nami kwa dakika chache?

a) *Akisema ndio, endelea.*
b) *Akiwa na nia lakini hayuko huru kuzungumza, panga wakati bora wa mahojiano.*
c) *Akisema la, mshukuru mshirika kwa ushirika na umalize mahojiano.*

Unakaribishwa kuwa mshiriki katika utafiti huu kwa sababu ulikuwa mgonjwa wa KNH na upokea matibabu kwa hali ya kizazi inayoitwa GTN kwenye ..... Kutimiza mahitaji ya shahada ya wauguuzi, Dk Angela Namarome Wekesa, chini ya usimamizi wa Dk Maranga na Dk Bosire; anajaribu kuthibitisha ikiwa matibabu uliyopata yalifanya kazi na matokeo yako ya uzazi baadaye. Lengo letu kuu ni kujua kama wanawake kama wewe huamua kuambukizwa baada ya kupata matibabu, muda uliochukuliwa kabla ya ujauzito, na matokeo ya uzazi ya wanawake ambao hatimaye hupata mjamzito.

Ikiwa unaamua kushiriki katika somo hili, tutakuuliza maswali tano kuhusu matibabu uliyopata kwa shida yako ya kizazi katika ..... (tarehe) na matukio yaliyothibitishwa baadaye. Tunataka kujua kama ulikuwa unatibiwa kikamilifu au ikiwa ulipata vikao vya matibabu zaidi baadaye kwa sababu ugonjwa ulirudi. Tunataka pia kujua ikiwa unatumia uzazi wa uzazi na kama umeamua kupata mimba baada ya matibabu. Hatimaye, ikiwa una mjamzito, tutauliza kuhusu kipindi ulichochukua kupata mimba na matokeo. Tunatafuta wanawake 157 kujibu maswali haya, ambayo inakuchukua muda wa dakika kumi.

Hatutakulipa pesa kuwa mshiriki katika utafiti huu wala kukupa neema yoyote kwa aina kwa ushiriki wako. Hata hivyo, sisi kujibu maswali yako yote mpaka wewe kujisikia kuridhika. Hakuna hatari ya afya inayotarajiwa kwa kushiriki katika utafiti huu. Ikiwa hukumbuka majibu fulani na ukihisi wasiwasi kujibu maswali fulani, unaweza kuchagua kuacha mahojiano wakati wowote bila chuki. Unaweza pia kuomba muda zaidi wa kukumbuka ikiwa inahitajika.

Je, hili ni utafiti ambacho unaweza kupenda kushiriki?

a) *Akisema ndio, endelea.*
b) *Akisema hapana, mshukuru mshirika kwa ushshirika na umalize mahojiano.*

Kabla ya kukubali kuwa mmoja wa washiriki wetu, haya ni mambo mengine ambayo unapaswa kujua:

a) Wewe unao uhuru wa kuondoa uhusiano wako na kutoka muda wowote na kwa sababu yoyote unaona inafaa, kwa hiari yako. Hatutakusanya pesa wala hatathiri utoaji wa huduma zote za matibabu unazostahili.

b) Tutaangalia kumbukumbu zako za matibabu kwa KNH kujua aina ya matibabu uliyopokea kwa aina na ukali wa ugonjwa uliopatiwa. Hata hivyo, maelezo ya kibinafsi ambayo tutakusanya kuhusu wewe hayatashirikiwa na mtu yeyote mwingine. Jina lako na nambari yako ya kitambulisho hazitarekodi mahali popote.
c) mahojiano haya yatarekebishwa kwa mapitio rahisi wakati wa kuchambua data. Hata hivyo, rekodi zote za redio zitaharibiwa baada ya usajili na uchambuzi wa data zetu.

Una maswali yoyote kwangu?

a) Akisema ndio, jibu maswali mpaka mshiriki huyo ameridhika
b) Akisema la, endelea na idhini

Je!, unakubali kuwa mshiriki katika utafiti huu?

☐Ndio: Jaza idhini ya mdomo
☐Hapana: Asante mgonjwa kwa shirika na kumaliza mahojiano.

Jina la mshiriki: ..... ……..

Azimio la Anyechukua Idhini

Nimemsomea mshiriki fomu hii kama ilivyo. Maelezo juu ya malengo ya utafiti, taratibu, na hatari na faida za kushiriki katika utafiti zimepewa. Dhana ya ushiriki wa hiari imeeleweka na maswali ya mshiriki alijibu kwa kuridhisha. Mshiriki ameonyesha uelewa wa habari hili na kutoa idhini ya mdomo kwa hiari yake.

....
Jina na Cheo

....
Saini siku/Tarehe/saa

Appendix 3: Dummy Tables

Table 1. *Demographic and medical characteristics of patients*

		Single agent chemotherapy	EMACO	OR	P
Age	16-20				
	21-30				
	31-40				
	>40				
Marital Status	Married				
	Single				
	Divorced				
	Widow				
	Separated				
Level of education	Primary				
	Secondary				
	Tertiary				
Religion	Christian				
	Muslim				
	Other				
Employment	Employed				
	Self employed				
	unemployed				
Risk status	Low (0-6)				
	High (>6)				
Stage of GTN	I				
	II				
	III				
	IV				
Chemotherapy	Single				
	Multiple				
Metastasis	Yes				
	No				

Table 2.*Reproductive outcomes by chemotherapy*

		Single	Multi	RR	P
Desire to get pregnant					
Contraceptive use					
Eventual pregnancy					
Duration to pregnancy	>1 year				
	≥1 year				
Outcome of pregnancy	Alive				
	Still Birth				