THE PREVALENCE, RISK FACTORS, AND MANAGEMENT OF RESIDUAL CIN FOLLOWING PRIMARY LEEP AT KENYATTA NATIONAL HOSPITAL,A CROSS-SECTIONAL STUDY.

A research proposal submitted in partial fulfillment of the requirements for the award of a Masters of Medicine degree in Obstetrics and Gynecology, at the University of Nairobi

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DECLARATION

I hereby declare that this research is my original workand has not been accepted for the award of any other degree or diploma at the University of Nairobi or any other educational institution and has been supervised by senior members of the Department of Obstetrics and Gynecology, University of Nairobi.

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LIST OF TABLES AND FIGURES.

THE PREVALENCE, RISK FACTORS AND MANAGEMENT OF RESIDUAL CIN FOLLOWING PRIMARY LEEP AT KENYATTA NATIONAL HOSPITAL.

LIST OF ABBREVIATIONS.

LEEP	Loop Electrosurgical Excision Procedure.
LLETZ	Large Loop Excision of Transformation Zone.
HSIL	High Grade Squamous Intraepithelial Lesion.
LSIL	Low Grade Squamous Intraepithelial Lesion.
CIN	Cervical Intraepithelial Neoplasia.
TAH	Total Abdominal Hysterectomy.
VIA	Visual Inspection under Acetic Acid.
VILI	Visual Inspection under Lugols Iodine.
HPV	Human Papilloma Virus.
DNA	Deoxyribonucleic Acid.
HIV	Human Immunodeficiency Virus.
RH	Reproductive Health.
ECC	Endocervical Curettage.
ASCCP	American Society of Colposcopy and Cervical Pathology.
KNH	Kenyatta National Hospital.
UoN	University of Nairobi.
WHO	World Health Organisation.
HAART	Highly Active Anti-Retroviral Therapy.

RLU	Relative Light Units.
ICC	Invasive Cervical Cancer.
RNA	RiboNucleic Acid.
LMIC	Low and Middle Income Countries.

DEFINITION OF TERMS.

Cervical Intraepithelial Neoplasia: Cervical intraepithelial neoplasia is a precancerous lesion affecting the cervical epithelium. It is both a cytological and histological diagnosis following cervical biopsy. It is graded CIN 1 to CIN 3. It is also termed as cervical cancer stage 0.

Positive Surgical margin: A positive margin after LEEP (defined as a histopathological finding of CIN along the specimen margin regardless of the CIN grade).

Residual disease refers to as histopathological HSIL, which was diagnosed from a biopsy or a subsequent surgical (including hysterectomy and LEEP) specimen at any time after the initial LEEP was performed.

Endocervical curettage/sampling includes obtaining a specimen for either histological evaluation using an endocervical curette or a cytobrush or for cytologic evaluation using a cytobrush.

Primary LEEP refers to the first LEEP procedure performed on a patient.

Parity refers to the number of pregnancies reaching 20 weeks and 0 days of gestation or beyond, regardless of the number of fetuses or outcomes. (ACOG).

Invasive Cervical Cancer (ICC). This implies a lesion that has spread beyond the basement membrane of the cervix.

Nulliparity refers to condition of a woman with a parity of zero.

THE PREVALENCE, RISK FACTORS AND MANAGEMENT OF RESIDUAL CERVICAL INTRAEPITHELIAL NEOPLASIA FOLLOWING PRIMARY LEEP AT KENYATTA NATIONAL HOSPITAL,A CROSS-SECTIONAL STUDY.

Abstract

Introduction. Cervical cancer is the second most common cancer in women in developing countries. Cervical cancer screening is the principal preventive measure in detection of cervical intraepithelial lesions. Colposcopy and conservative treatment of intraepithelial lesions detected on screening, has gained prominence due to few complications, good tolerance from patients and the preservation of fertility. Loop Electrosurgical Excision Procedure (LEEP) is one of the conservative treatment options, one of cervical cone biopsy procedures. Its expected outcome is complete excision of lesions, with free surgical margins as the indicator. The presence of positive margins after excision and histological analysis is an indicator of residual disease. Reviewed studies had shown a prevalence of positive margins of between 10-45%. HIV status, reproductive health parameters of patients have been associated positively with residual disease. Subsequent management of these patients with residual disease vary form one center to another.

Objective.To determine the prevalence, socio-demographic, clinical characteristics and management of patients with residual HSIL on histology following primary LEEP at KNH.

Methodology. This was a retrospective cross-sectional study of patients who had undergone colposcopy and primary LEEP in clinic 66 of Kenyatta National Hospital between October 2014 and December 2017. Records of 191 patients who had undergone LEEP during the period under review were retrieved and analyzed.

Results. The prevalence of residual disease among women with CIN post primary LEEP at KNH was 19.6%. No associations were found between residual disease and age, HIV status, parity, years since last delivery and contraception. The follow up review rate after six months was 70.8%. Total Abdominal Hysterectomy was the commonest subsequent management modality upon review of these patients at 70.5%. Other review modalities were Pap smear and EUA. No patients underwent ECC or Repeat LEEP.

Conclusion. The prevalence of residual disease among women with CIN post primary LEEP at KNH was 19.6%. No associations were found between HIV status, reproductive health characteristics and residual disease.

CHAPTER ONE.

1.0. INTRODUCTION

1.1.Background

Cervical cancer remains the fourth commonest cancer in women globally, in the developing world, it is the second after breast cancer. According to data from American Cancer Society, global new cases of cervical cancer stood at 527,600in 2013, with deaths the same year standing at 265,700. Furthermore in the developing world, new cases stood at 444,500 with deaths at 230,200. This implies that > 90% of cervical cancer deaths occur in the developing countries. (1).

According to the data, the geographic variations in cervical cancer deaths was due to differences in availability of screening, detection and removal of precancerous lesions, prevalence of HPV, and co infection with HIV.In several high-income countrieswith available screening,cervical cancer incidence rates have decreased by as much as 80% over the past four decades. (2).

Screening is the principal preventive measure to reduce the burden of cervical cancer in thesewomen.Screening tests offered include HPV test, Pap smear and visual inspection of the cervix with acetic acid and Lugols Iodine. Identified lesions are then visualized via colposcopy and biopsies taken. Themain target of cervical cancerscreening is to identify cervicalintraepithelial neoplasia (CIN), apremalignant lesion that canprogress to cervical cancer if left untreated. Based on the severity of dysplasia, CIN is categorized as CIN1(low-grade), CIN2, and CIN3.It has been estimated that every year approximately1–2%of women globally haveCIN2+lesions; this rate could be substantially higher in women with HIV infection (3).

According to WHO, screening for cervical cancer in women remains the mainstay in reduction of morbidity and mortality associated with the disease. The usual approach of the standard practice is to screen women using cytology (Pap smear), and when cytology results are positive the diagnosis of CIN is based on subsequent colposcopy, biopsy of suspicious lesions,and then treatment only when CIN2+ has been histologically confirmed. In developing countries, WHO recommends the screen and treat approach VIA VILI then colposcopy, biopsy and either cryotherapy or LEEP. Screen-positive women are eligible for cryotherapy if the entire lesion is visible, and the lesion does not cover more than 75%of the ectocervix. If the lesion extends beyond the cyroprobe being used,or into the endocervical canal, the patient is not eligible for cryotherapy and LEEP is the alternative option.

Due to the detection of precancerous lesions duringreproductive ages, conservative treatment has come intoprominence. Loop Electrosurgical Excision Procedure (LEEP), which can be applied in outpatient settings, is welltolerated by patients and causes few complications and is preferred in the treatment of high-grade cervical intraepitheliallesions since it provides diverse materials for histologicalevaluation.(6),(14),(35)

Loop Electrosurgical Excision Procedure also called Large Loop Excision of Transformation Zone (LLETZ), is one of the procedures of performing cone biopsy in CIN of the cervix. The other one being cold knife conization (20).

LEEP involves excision of a cone biopsy using laser/electro surgery. In certain situations(pregnancy, extension of the lesion into the vaginal fornices, or high in the endocervical canal), however, the entire lesion is not obtained by this method. In addition, LEEP excision procedures minimize blood loss by thermal cautery during excision but may cause thermal artifact that impairs the interpretability of a specimen (14).

The LEEP margin status following histological analysis of cone biopsy remains key in evaluating the success of the LEEP procedure, it will further determine the need for a repeat procedure, necessitate follow up and the expected outcome of disease, whether cure, residual or recurrent in the patient (14).

Close observation following excisional treatment is of great importance in the detection of the residualor recurrent disease in the early stages. Incomplete excision is associated with an increased riskof residual disease. 7–85% of patients with positive margins later present with residual disease, recurrence, or invasive disease (4). However, even when the margins are free ofdisease, recurrences may occur (5).

The treatment options for patients with HSIL and positive margins depend on different factors. The ASCCP updated its consensus guidelines in 2013, as follows: “If CIN2, 3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4–6 month is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible” (1).

The aim of this study is to evaluate the prevalence of positive surgical margins post primary LEEP, to identify patient characteristics associated with positive surgical margins and to evaluate the subsequent management of patients with positive surgical margins at the colposcopy clinic at Kenyatta National Hospital.

CHAPTER TWO.

2.0. LITERATURE REVIEW.

2.1. Introduction. Cervical Intraepithelial Neoplasia.

Cervical intraepithelial neoplasia is a precancerous lesion affecting the cervical epithelium.It is both a cytological and histological diagnosis following cervical biopsy.

The cytology diagnosis is based on the Papanicolaou smear (Papsmear). Collection of the Papanicolaou test currently involves sampling the cervix at the transformation zone using a spatula or brush. The transformation zone is where the ectocervix and endocervix meet and dysplasia is most likely to be identified (7), (32).

Papanicolaou test results are routinely reported according to the Bethesda system (6), (36). Part of the most recent revised Bethseda system of 2014 classifies the epithelial abnormalities as follows:

EPITHELIAL CELL ABNORMALITIES

- SQUAMOUS CELL
    - Atypical squamous cells
        - of undetermined significance (ASC-US)
        - cannot exclude HSIL (ASC-H)
    - Low-grade squamous intraepithelial lesion (LSIL) (encompassing: HPV/mild dysplasia/CIN 1)
    - High-grade squamous intraepithelial lesion (HSIL) (encompassing: moderate and severe dysplasia, CIS; CIN 2 and CIN 3)

- with features suspicious for invasion (if invasion is suspected)

- Squamous cell carcinoma.

Table 1.Correlation between Dysplasia/Carcinoma In-Situ, Cervical Intraepithelial Neoplasia (CIN) and the Bethseda Terminology.

Dysplasia Terminology.	**Original CIN Terminology**	**Modified CIN Terminology**	**Bethseda System Terminology**
Normal	Normal	Normal	Within normal limits, benign cellular changes (infection or repair).
Atypia.	Koilocytic atypia, flat condyloma, without epithelial changes.	Low grade CIN	ASCUS,AGUS LSIL
Mild dysplasia or mild dyskaryosis	CIN 1	Low grade CIN	LSIL
Moderate dysplasia or moderate dyskaryosis	CIN 2	High grade CIN	HSIL
Severe dysplasia or severe dyskaryosis	CIN 3	High grade CIN	HSIL
Carcinoma in-situ	CIN 3	High Grade CIN	HSIL
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

On the basis of histology, it is broadly subdivided into three.

- Cervical Intraepithelial Neoplasia 1 (CIN 1).
- Cervical Intraepithelial Neoplasia 2 (CIN 2).
- Cervical Intraepithelial Neoplasia 3 (CIN 3).

On histology, the changes that indicate intraepithelial neoplasia include enlarged nuclei, increased nuclear-cytoplasmic ratio, increased hyperchromasia, increased nuclear polymorphism, and increased anisokaryosis. As the severity of CIN increases, the number and abnormal configurations of mitotic figures also increase (8) (30).

The lesions are defined by the amount of the squamous epithelium that is dysplastic.

- Low-grade CIN, or CIN-1, displays dysplastic changes in approximately one third of the thickness of the epithelium.
- CIN-2 involves one half to two thirds of the thickness.
- CIN-3 can show full-thickness involvement.

Rates of progression depend on the stage of the lesion.

Low-grade squamous intraepithelial lesions (LSILs) are suggestive of mild dysplasia or expected CIN-1 on histology and HPV infections with high-risk types. Studies looking at the natural progression of this finding suggest that approximately 50% of these lesions will regress in 24 months, 20% will progress to HSILs, and about 0.2% will progress to cancer in the same time period (16).

HSILs are lesions consistent with moderate and severe dysplasia, corresponding with CIN-2, CIN-3, and carcinoma in situ on histology. This cytology result indicates a high suspicion for an

underlying high-grade lesion. These lesions have a lower likelihood of regression within 24 months, with only 35% regressing, 23.4% persisting, and 1.4% progressing to invasive cancer (16).

2.2. Residual disease.

Residual disease was defined as histopathological HSIL, which was diagnosed from a biopsy or a subsequent surgical (including hysterectomy and LEEP) specimen at any time after the primary LEEP was performed (2). In the study "Factors that influence persistence or recurrence of high-grade squamous intraepithelial lesion with positive margins after the loop electrosurgical excision procedure: a retrospective study" by Menghan Zhu et al, of all patients with HSIL who underwent primary LEEP for lesion excision, 6.34% had positive margins on histological analysis. The study also found that age was a strong independent predictor of persistence/recurrence of HSIL (4).

In another study, "Long-Term Clinical Outcome after Treatment for High-Grade Cervical Lesions: A Retrospective Monoinstitutional Cohort Study", by Annarosa Del Mistro et al, positive margins post index LEEP was found at 16.6%. The study also reported high risk CIN2+ and increasing age as positive predictors of disease persistence and recurrence (5).

Andrea S O'Shea et al in the study "The impact of LEEP margin status on subsequent abnormal cervical cytology", found positive margins in 47% of histological samples analyzed post LEEP. However, they did not report any factors or risks associated with persistence/recurrence of disease in the sample they analyzed (7).

In yet another study, "Residual and Recurrence Disease Rates following LEEP treatment in High Grade cervical intraepithelial lesions", by Ali Baloglu et al, the findings were positive margins in 9.5% of samples post index LEEP. They also found age as a risk factor of persistence/ recurrence

of disease. Moreover, they compared the specificity and sensitivity of Positive HPV DNA and Positive Margins in predicting recurrence and persistence of disease. They found HPV DNA to have sensitivity and specificity of 100% and 15.78% respectively, while the sensitivity and specificity of positive margins was 75% and 94.78% respectively. They concluded that the most sensitive factor in prediction of residual disease was surgical margin positivity (4).

In another study by Yunfeng Fu et al, "Residual disease and risk factors in patients with high-grade cervical intraepithelial neoplasia and positive margins after initial conization", it was found that 32.4% of patients who had high-grade CIN with margin involvement after initial conization had residual disease on subsequent surgical treatment. They further reported that age >35 years, major abnormal cytology, and pre-cone high-risk HPV load >300 RLU were predictive of post-cone residual disease for women who had margin involvement with high-grade CIN (3).

High gravidity and parity was reported to be positively associated with microinvasive disease in patients with positive surgical margins. This was in the study, "Repeat LEEP conisation in patients with CIN 3 and positive ectocervical margins", by Ali Ayhan et al (5).

In the study "Predictive factors for persistent and recurrent cervical dysplasia after loop electrosurgical excision procedure in postmenopausal women," by Calina Dragosloveanu et al, positive surgical margins were found in 25% of patients post LEEP. Age, glandular involvement and smoking were significantly associated with residual disease/persistence/recurrence while no association was found with parity, age at first intercourse and use of oral contraceptives (8).

Chen Y et al in the study "Factors associated with positive margins in patients with cervical intraepithelial neoplasia grade 3 and postconization management", had the findings that positive margins were associated with postmenopausal period, LEEP (as opposed to cold knife cone

biopsy), carcinoma in situ and large area of lesion. Positive surgical margins were found in 24.1 % of women after LEEP (3).

In the meta analysis, "Risk of persistent high-grade squamous intraepithelial lesion after electrosurgical excisional treatment with positive margins: a meta-analysis," by Caroline Alves de Oliveira et al, they found a range of positive margins between 17-47%, and the risk of residual disease /recurrence with positive margins to be 24.4 % (9).

2.3. HIV and Cervical Intraepithelial Neoplasia.

Human Papillomavirus (HPV) infection must be present for cervical cancer to occur. HPV infection occurs in a high percentage of sexually active women. However, approximately 90% of HPV infections clear on their own within months to a few years and with no sequelae, although cytology reports in the 2 years following infection may show a low-grade squamous intraepithelial lesion (19),(22).

HIV-infected women are significantly more likely than HIV-uninfected women to have incidental and persistent HPV cervical infections, and to develop incidental pre-cancers such as squamous intraepithelial lesions (SIL) 1–4, including high-grade SIL (HSIL) (12). Among HIV-infected women, the incidence of HPV infection and SIL increases with lower CD4+ T-cell count (CD4). These collective findings strongly support a dose-response relationship between host immune status and the risk of early and intermediate stages of HPV-related tumorgenesis (13).

In a prospective study, HIV-infected women had a significantly higher risk of incidental ICC than HIV-uninfected women, and the risk of ICC increased significantly with diminishing immune status as measured by CD4 count. HIV-infected women with baseline CD4+ T-cells of

≥ 350, 200–349 and <200 cells/ uL had a 2.3-times, 3.0-times and 7.7-times increase in ICC incidence, respectively, compared with HIV-uninfected women. The increased burden of ICC may persist in HIV-infected women even at higher CD4 counts, as HIV-infected women with CD4 counts ≥ 350 cells/uL still experienced significantly higher rates of ICC than the general population or HIV-uninfected women in these cohorts. Nevertheless, these results suggest that the use of ART to maintain CD4 above 350 cells/uL may reduce ICC risk (14), (16).

Although HIV infected women were at high risk of abnormal cytology, high-grade changes were uncommon. HIV status, HPV detection, CD4 lymphocyte count, and HIV RNA level predicted the incidence of cervical cytologic abnormalities. Progression was significantly increased only among the most immunosuppressed women, while regression was significantly reduced in all HIV seropositive women except those with the best controlled HIV disease (15).

The influence of HAART on the progression of cervical intraepithelial neoplasia has been studied. The reduction in viral load and improvement in immunological response associated with strict adherence and use of HAART has been postulated to halt or slow the progression of cervical intraepithelial neoplasia. HAART can partially restore immune competence. Host immune status is strongly associated with the incident detection and persistence of oncogenic HPV, as well as with precancerous cervical neoplasia, in HIV-positive women (18).

In another study, HAART use was associated with increased regression of SIL among HIV-infected women, and among women who used HAART, increased CD4+ T-cell counts were associated with a greater likelihood of regression (19). In a large prospective cohort study, results suggest that the burden of HPV and SIL is primarily decreased when patients are adherent with their HAART regimen, or there is strong evidence that the HAART is effective against HIV. Specifically, HAART initiation amongst adherent women was associated with a significant

reduction in the prevalent and incident detection of oncogenic HPV, as well as decreased prevalence and more rapid clearance of oncogenic HPV+ SIL (17).

2.4. Treatment of residual disease.

The American Society for Colposcopy and Cervical Pathology recommends reassessment using cytology with endocervical sampling at 4–6 months after treatment as the preferred option if high-grade CIN is identified at the margins of conization. Repeat conization can be done. Hysterectomy can be undertaken if repeat conization is not possible or if the patient has achieved desired family size (1).

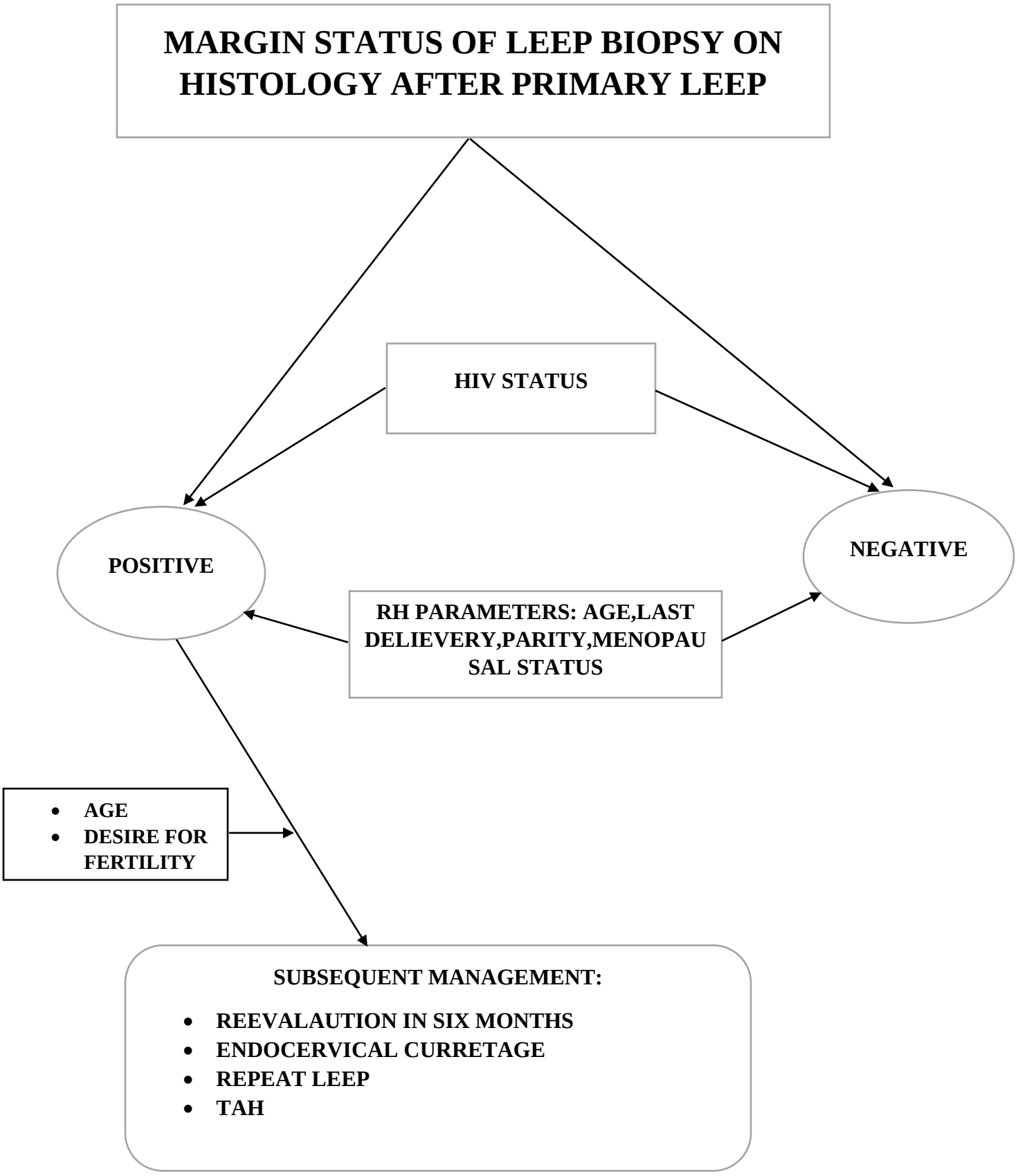
2.5. Conceptual framework narrative.

LEEP biopsy is one of the interventions undertaken in treatment of CIN. The expectations after LEEP intervention is complete excision of the lesion, with free margins as the indicator of complete excision. Finding positive margins indicates residual disease and subsequently the need for further management.

The factors associated with residual disease from literature review are reproductive health parameters: - (age,parity,years since last delivery,menopausal status) and HIV status. Age has been shown to have a positive association with positive histology margins after primary LEEP biopsy, with increasing parity, years since last delivery and menopausal status also shown to have an association. HIV status has also been shown to have an association with positive margins after primary LEEP biopsy. There is also evidence of the histological type being glandular for residual disease.

This study aimed to show the prevalence of positive margin histology after primary LEEP biopsy, and investigated the association between reproductive health parameters, HIV status and residual disease as evidenced by positive histology margins. Further, it aimed to evaluate the subsequent management of patients with positive margins on primary LEEP biopsy.

Fig.1.Conceptual framework Schematic.



From the conceptual framework

Independent variables.

Age.

HIV Status.

Parity.

Years since last delivery.

Histological staging.

Histological type (squamous or adenorcacinoma)

Dependent variables.

Status of histological margins.

Further management of patients with positive margins.

2.6. Problem statement

Cervical intraepithelial neoplasia remains a significant cause of morbidity and mortality due to its risk of progression to invasive cervical cancer. With fertility sparing methods of treatment gaining popularity, the need for the assessment of their clinical success is paramount to evaluate and justify their continued use as a mode of intervention. The reproductive health parameters and their association, if any, with the outcomes of these interventions are also critical. As an independent variable, HIV still poses a big burden responsible for opportunistic infections with HPV and premalignant and malignant states of the cervix. The potential risk of having positive margins on histology after LEEP will increase the morbidity that is associated with progression of the residual disease to invasive cancer, and further increase the cost of treatment.

2.7. Justification of the study.

The increase in screening programs and their availability has meant that more and more women are being screened and consequently increases the incidence of detection of cervical intraepithelial neoplasia. The number of women in reproductive age forms a significant percentage of this population. Treatment thus has to take into consideration the need to retain fertility. Colposcopy and subsequent cryotherapy and LEEP remains the treatment of choice for such patients in the see and treat program which averts delays or missed opportunities towards cure.

There is need to assess outcomes locally associated with primary LEEP in treatment of cervical intraepithelial neoplasia.Currently, the existing protocol of standard of care does not take into consideration other ways of intervention after positive margins on histology. It recommends repeat follow up Pap smear or VIA VILLI after 6 months. Figure 2.. This study will seek to

advise on policy and protocols that are contextualized to LMIC settings, challenged additionally by the cost of services and lost to follow up.

Moreover, the association, if any, of reproductive parameters and HIV status with residual disease will act as a guide in determining the initial approach of such patients found to have HSIL.

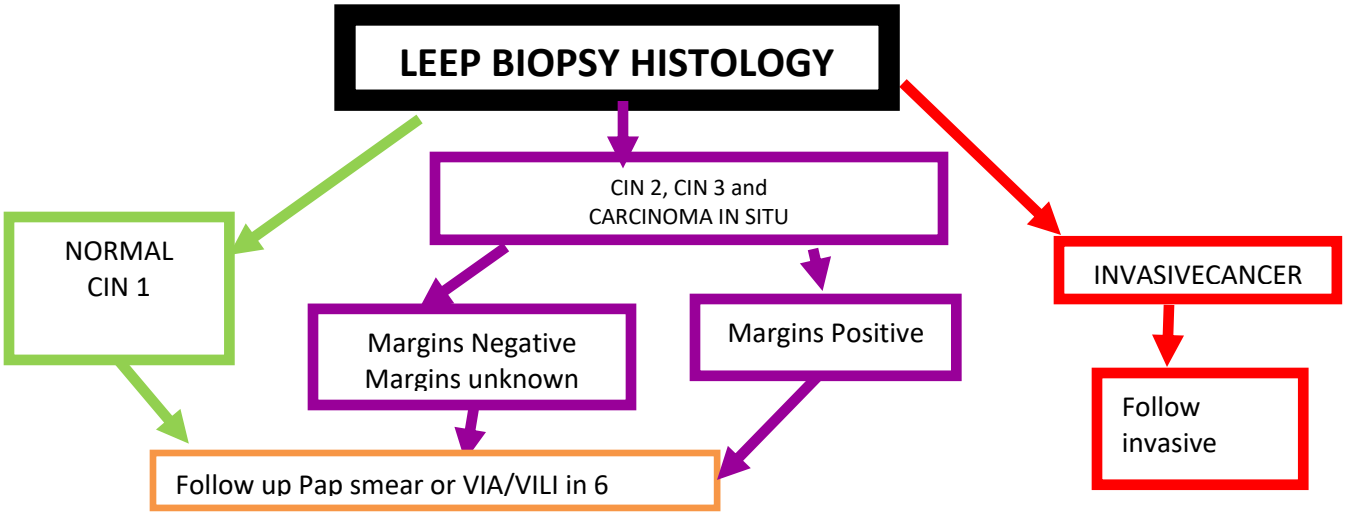


Fig 2: KNH LEEP biopsy result protocol.

2.8. Research question

What is the prevalence, socio-demographics, clinical characteristics and management of patients with residual CIN following primary LEEP at Kenyatta National Hospital?

2.9. Broad objective

To determine the prevalence, socio-demographics, clinical characteristics and management of patients with residual CINfollowing the primary LEEP at KNH.

2.10. Specific objectives.

Among patients who have undergone primary LEEP at KNH:

1) To determine the prevalenceof residual Cervical Intraepithelial Neoplasia (CIN).
2) To describe socio-demographics, HIV, reproductive health and clinical characteristics of patients with, versus those without residual CIN.
3) To describe the follow up and subsequent management of patients with residual CIN.

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CHAPTER 3

3.0 METHODOLOGY

3.1. Study Design.

This was a retrospective cross-sectional study. The records available at KNH's clinic 18 and 66 were used to identify file numbers of all women who had primary LEEP from October 2014toDecember 2017. The respective files wereretrieved from the records department andreviewed by the investigator. All files of the cases that met the inclusion criteria were set aside for extraction of socio-demographic, clinical, cytological and histological data usinga developed data capture sheet [Appendix 1]. The corresponding histology results after primary LEEP, patient follow up plan at 6 months and the subsequent management of those with residual disease (positive histological margins) werealso recorded.

3.2. Study site and setting.

The study was based at the Kenyatta National Hospital (KNH) clinics 18 and 66. KNH is Kenya's largest referral hospital, located in the capital city Nairobi. The hospital attends to referral patients and also acts as a primary hospital serving many inhabitants of Nairobi mainly of poor socioeconomic background. It is one of the few public institutions providing tertiary delivery services in the country.

The KNH Gynaecology department's clinic 18 and 66 provide services for cervical cancer screening using Papanicolau (Pap) cytology smears. Patients from Comprehensive Care Clinic (that follows up HIV positive patients within KNH) are also referred for further follow up. Follow up of abnormal cytology undergo colposcopic examination with VIA VILLI

directedbiopsy. Those confirmed CIN 2 and CIN 3 undergo LEEP treatment on outpatient basis at a nominal fee. Follow up of LEEP histology results is made at a review visit six weeks later. After a Pap smear screening test, cytology results are dispatched and filed within a six weeks period. Upon collection of the results appropriate advice is usually given on the course of action. Clients whose cytology result turns out to be high grade lesions are referred for colposcopic biopsy in clinic 66. At the clinic, their demographic data and clinical information is usually captured using the standard encounter form. (Appendix2 and Appendix 3). Upon receipt of colposcopic biopsy results, clients withCIN2 and CIN3 lesions are counseled on the need for LEEP, informed consent taken and booked accordingly.

Prior to the actual LEEP procedure, informed consent is affirmed and clients are taken through the steps involved. This include having to empty the bladder upfront, then lying on an examination coach in lithotomy position. Subsequently, insertion of a non-conducting speculum, use of a colposcopic light source to visualize the cervix, painting of the cervix with 3% acetic acid and/or iodine solution, application of local anesthesia, the expected sound of a smoke evacuator and the humming of the electrosurgical generator to be used. Possible side effects including cramps, bleeding and foul discharge are addressed.Post procedure advice includes avoidance of coitus and what to do in case of bleeding.A telephone hotline number is given. Finally the procedure is done by excision of the transformation zone using a fine wire loop which is attached to a high frequency electrical generator allowing precise removal of the targeted cervical tissue. Hemostasis is achieved by electro-fulguration of the excised base or by application of a hemostatic solution usually ferric sulphate or both. As a precaution, all patients are observed for one hour to rule out any immediate bleeding that may occur. The specimen is submitted for histological evaluation.

The specimen is put in a sterile container, preserved in 5%formalin, labelled (patients name, age, patient`s number, date, specimen type and test requested.) and dispatched to histopathology laboratory. In the laboratory, the specimen is received and recorded, processed into a tissue block, cut into slides and stained with Hematoxyphillic and Eosinophillic (H&E). Reporting is done by two independent pathologists for quality assurance. If both agree on the status of margins, the report is typed, recorded and dispatched. If they disagree, they call in a third consultant, who gives an opinion on the status of the margins, they hold discussions and consultations,and a final decision is then made. The report is typed and dispatched to the patient`s file.

With the exception of invasive carcinoma on the LEEP specimen, all the other cases are routinely advised to do a 6 months follow up cytology. The entire process from colposcopy to return visits is largely patient driven as each of these processes has cost implications. No active call up program is in place to trace patients whose results require immediate action nor are reminders sent for routine follow up visits. Clients who do not voluntarily return to clinic are therefore not actively followed up for treatment of pre-malignant cervicallesions and are lost to follow up. Patients with residual disease as indicated by positive margins on the histological analysis are booked for re-evaluation in six months, where endocervical curettage, repeat LEEP or hysterectomy is done. Patients with histological diagnosis of invasive cancer of the cervix oncolposcopic biopsy or on LEEP specimens are sent for Examination Under Anaesthesia and Staging and referredeither forWertheim’shysterectomy or radiotherapy based on the staging of the cancer of the cervix.

3.3. Study Population.

Patients who had colposcopy and primary LEEP between October 2014 and December 2017 were recruited into the study. This is the period under review when complete records were available. The HIV status and reproductive health characteristics were followed up retrospectively for the outcome of interest namely, residual disease after histological analysis. Those with disease werere-evaluated at six months on their subsequent management.

3.4. Inclusion criteria.

Patients who underwent primary LEEP for HSIL on cytology in Kenyatta National Hospital between October 2014 and December 2017.

3.5. Exclusion criteria

Patients undergoing repeat LEEP.

Patients with a diagnosis of invasive cervical cancer.

Patients with cytological/histological results from a different facility.

3.6. Sampling method

All patients who underwent primary LEEP at the KNH colposcopy clinic and met the inclusion criteria were sampled until the target sample size was achieved. The patients who would have attended the clinic between the years October 2014 to December 2017.

Patients undergoing LEEP are on average 5 per month hence 5 patients* 12 months*4 years = **240 Patients.**

3.7. Sample size calculation

N = $\frac{z^2_{1-\alpha/2} \times p\,(1-p)}{d^2}$ **(Fisher's** et al., 1998)

α=Level of significance (0.05)

$\mathbf{Z_{1-\alpha/2}}$= Standard normal deviate at 95% confidence interval (1.96)

p= Proportion of patients with a positive surgical margins after LEEP biopsy = 30.6% (using the study by Baloglu et al(4). (The choice of this study is a study done in a LMIC, with a similar sample size 200).

d=margin of error allowed= 0.08

Therefore **N =**231

10% adjustment N=254.

The study was to be a time frame, all patients who underwent primary LEEP at the clinic from October 2014 to December 2017 were to be recruited.

3.8.Data management and collection methods

The data comprising of socio-demographic characteristics, clinical information,histological diagnosis and follow up visits were extracted from each file by the principal investigator. Patients` personal details were de-identified and filled in a coded structured data capture sheet (Appendix 2). Thecompleted forms were kept in locked cabinets accessible to the researcher only. All databases were password protected in order to guarantee confidentiality of the patients` details. Hard copies of the questionnaires werethoroughly checked for missing entries and inconsistent data before entry into the data base.Upon entry, a line listing was done to compare the hard copy forms with the entered data for accuracy and corrections made appropriately.

3.9. Data Analysis and Presentation of Results

Data analysis was conducted using IBM Statistics Version 21(formerly SPSS) and begun with exploratory data analysis were summaries of demographic characteristics,parity, marital status, years since last delivery and HIV status.

Univariate analysis.

Descriptive statistics were carried out and discrete variables were summarized with frequencies and percentages while continuous variables were summarized using measures of central tendency and dispersion such as mean, median, mode, standard deviation and inter-quartile ranges.

Bivariate analysis.

Factors associated with residual HSIL were determined by estimating the relationship between it and individual socio-demographic characteristics, medical history, sexual and reproductive history. Categorical-categorical comparisons were determined through chi-square test, categorical-continuous relationships were determined using T-Tests while continuous-continuous relationships were determined through correlation coefficients. Significant relationships formed the basis for further multivariate analysis

3.10. Study limitations

The retrospective nature of the studypredisposed it to missing data. To mitigate for this, thestudy recruited all eligible women in the time frame under investigation. If a file being sampled was found to have incomplete data, file registers in clinic 18, 66 and theatre were reviewed. If missing, purposive sampling of the next case was undertaken until the targeted sample size was achieved. Missinghistology and cytology reports were minimized by checking with the backup records atthe department of pathology.

3.11. Ethical considerations and approval.

The research protocol was approved by the Department of Obstetrics and Gynaecology, University of Nairobi and subsequently by the Kenyatta National Hospital Ethics andResearch Committee. Informed consent from patients was not sought because of the retrospective natureof the study. Confidentiality was observed by the researchers: all participant records didnot leave the hospital premises and were kept in locked cabinets. Patient names and identifiers were removed from all data tables and records prior to data analysis. All theelectronic records within

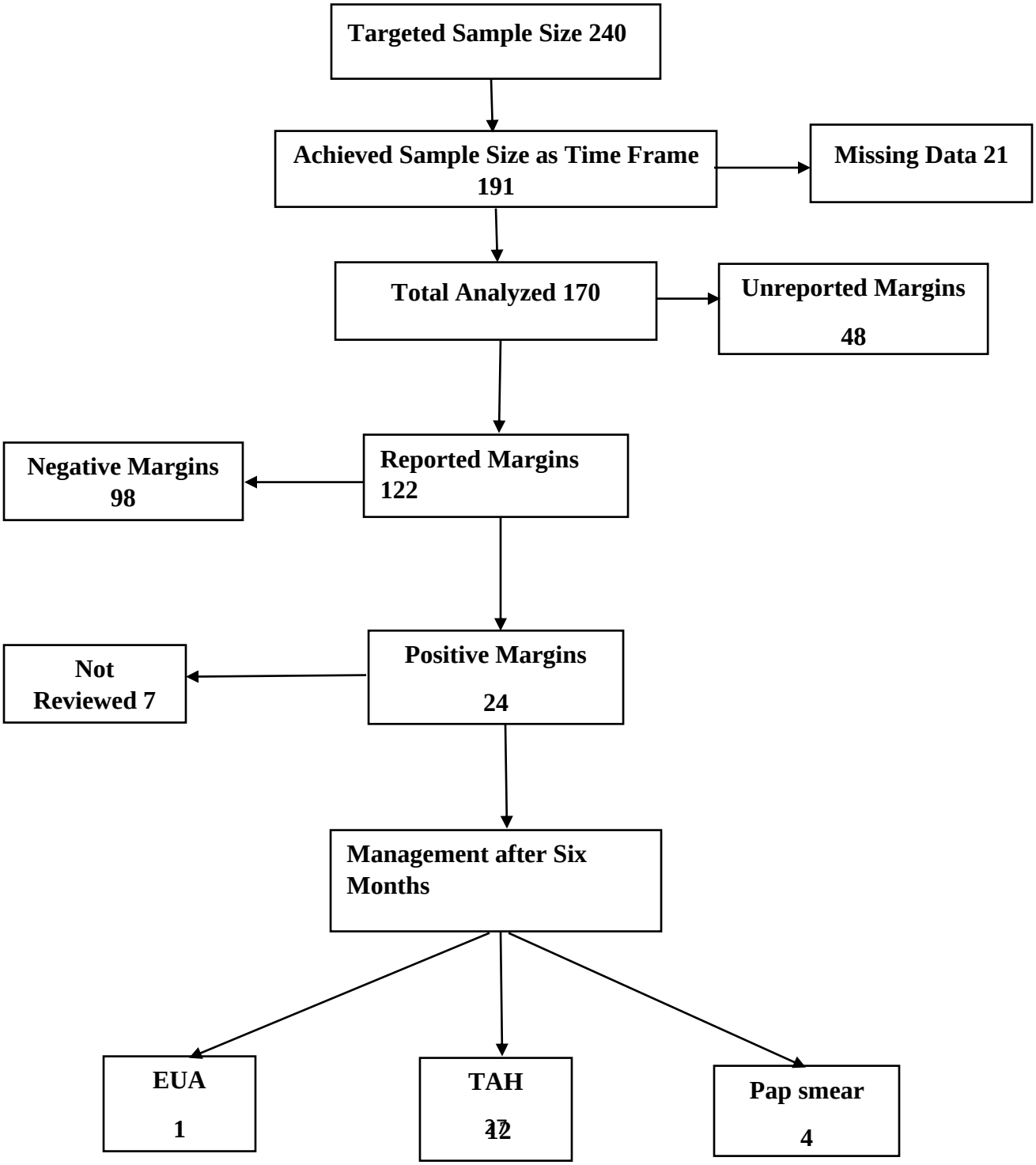
the database were password protected. Only data entrypersonnel, clinicians overseeing the database, and researchers involved on this project had access. Results from thisstudy will be useful in informing of guidelines used in the managementof patients with cervical premalignant lesions and offered primary LEEP with positive histological margins at their subsequent follow up. It will also provide pilot data addressing effectiveness of treatment options contextualized to LMIC where financial constraints and loss to follow up is a problem.

CHAPTER FOUR

RESULTS

4.1. Results flow.

Figure 3. Results Flow Diagram.



A total of 191 files were sampled as a time frame, which included all files between October 2014 and December 2017, of all patients who had undergone LEEP at clinic 66. Data for patients from October 2014 backwards were missing, occasioned by the shifting of the colposcopy clinic from its earlier site under GOPC in clinic 18 to its current clinic 66 location. The patient registers were missing from the registry. Of the 191 files, 21 files were found to have incomplete data, hence were not analyzed. Subsequently, a total of 170 files were analyzed, with 122 of them having margins reported, while 48 files had margins not reported.

170filesrepresented 70.8% of the expected sample size.

4.2 Patient Demographics.

The mean age of our patients was 40 years.Two (1.2%), fell in category of 20 years and below while 3(1.8%) were 70 years and above, while 65 (38.2%) were aged 31-40 years, 53 (31.2%) were aged 41-50 years, 21 (12.4%) were aged 51-60 years and 20 (11.5%) were aged 21-30 years. An analysis of the marital status revealed that majority of our patients, 117 (68.8%) were married, 42 (24.7%) were single, 9 (5.3%) were widows, 2 (1.2%) were separated. No patients were reported as divorced.

Two (1.2%) of the patients were reported as having received no education at all, 49 (28.8) had received education up to primary level, 95 (55.9%) had received upto secondary education, with 24 (14.1%) having received tertiary education. Eighty (47.1%) were reported as housewives, with 64 (37.6%) in business and 26 (15.3%) in formal employment.

Table 2. Demographics.

Variable		N (%)
Age group	up to 20 years	2 (1.2)
	21-30 years	20 (11.5)
	31-40 years	65 (38.2)
	41-50 years	53 (31.2)
	51-60 years	21 (12.4)
	61-70 years	6 (3.5)
	Over 70 years	3 (1.8)
Marital status	Single	42 (24.7)
	Married	117 (68.8)
	Separated	2 (1.2)
	Divorced	0 (0.0)
	Widowed	9 (5.3)
Education level	Illiterate	2 (1.2)
	Primary	49 (28.8)
	Secondary	95 (55.9)
	Tertiary	24 (14.1)
Occupation	Employed	26 (15.3)
	Business	64 (37.6)
	Housewife	80 (47.1)

4.3. Patient Reproductive Health Parameters

The mean parity was 4, with mean number of years since last delivery reported as 11 years. Three (1.8%) were reported as nulliparous, with 10 (5.9%) reported as grand multiparous. Majority, 130 (76.6%) of patients had between 1-4 pregnancies. Fifty-seven (33.3%) of patients reported not using any form of contraception. Eighty four (49.4%) were using hormonal contraception, while 29 (17.3%) were using non hormonal contraception.

Table 3. Reproductive Health Parameters.

Variable		N (%)
Parity group	No prior pregnancy	3 (1.8)
	1-4 prior pregnancies	130 (76.5)
	5-9 prior pregnancies	27 (15.9)
	More than 9 prior pregnancies	10 (5.9)
Last delivery in years	Up to 5 years	37 (21.8)
	6-10 years	47 (27.6)
	11-20 years	55 (32.4)
	More than 20 years	31 (18.2)
Family planning	None	57 (33.3)
	Non Hormonal	29 (17.3)
	Hormonal	84 (49.4)

4.4. HIV Parameters.

Analysis of HIV status revealed that 61 (35.8%) were positive, 89 (52.4%) were negative, with 20 (11.8%) having their status unknown.

The mean CD 4 Count among the positive patients was 540 cells per ml, with the CD4 range being 391 to 620.

Of the HIV positive patients, 57 (93.4%) were compliant on HAART, while 4 (6.6%) were reported as non-compliant.

Table 4. HIV Parameters

Variable		N (%)	CD4 Count (Median [IQR]
HIV Status	Positive	61 (35.8)	538 [391 – 620]
	Negative	89 (52.4)	-
	Unknown	20 (11.8)	-

4.5. Cancer Screening History.

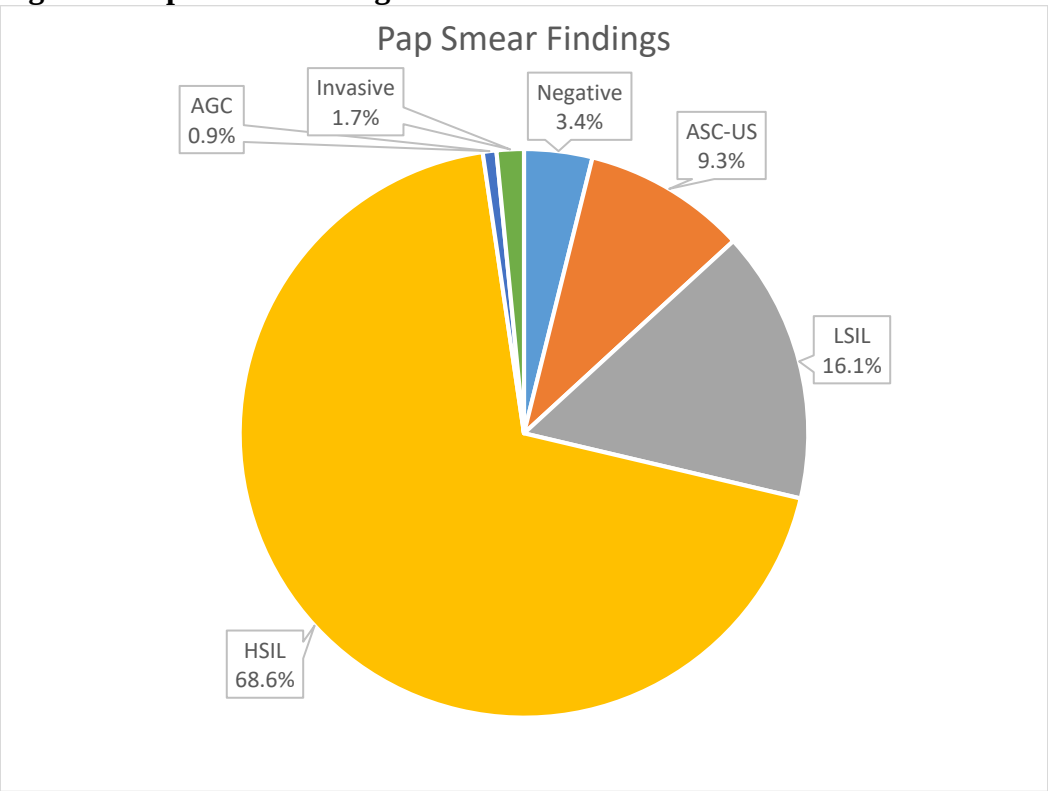
Majority of the patients, 118 (69.4%) had had a Pap smear, with 52 patients (30.6%) having had none. The findings on Pap smear were 81 (68.6%) had HSIL, 11 (9.3%) had ASC-US, 19 (16.1%) had LSIL, 4 patients (3.4%) had their pap smear reported as negative, 2 patients (1.7%) had invasive cancer on Pap smear, and 1 patient (0.9%) had AGC.

Eighty-eightpatients (51.5%) had VIA VILLI screening, with 82(49.5%) having had no screening. Of the screened patients, 85 (96.6%) had VIA positive, while 84 (97.7%) had VILLI positive.

Table 5. Cancer Screening History.

Screening		**N (%)**
Pap smear screening history	Yes	118 (69.4)
	No	52 (30.6)
Pap smear findings	Negative	4(3.4)
	ASC-US	11 (9.3)
	LSIL	19 (16.1)
	HSIL	81 (68.6)
	AGC	1 (0.9)
	Invasive	2 (1.7)
VIA VILI screening history	Yes	88 (51.5)
	No	82 (48.5)
VIA	Positive	85 (96.6)
	Negative	3 (3.4)
VILI	Positive	84 (97.7)
	Negative	2 (2.3)

Figure 4. Pap smear Findings.



4.6. Colposcopy Findings.

Most patients, 168 (98.8%) underwent colposcopy punch biopsy, and histology revealed 13 (7.7%) had CIN 1,74 (44.0%) had CIN 2, 69(41.1%) had CIN 3, with 5 (3.0%) having invasive cancer. Seven (4.2%) were reported as negative.

Also most patients, 156 (92.9%) had satisfactory colposcopy, with entire transformation zone seen.

Table 6. Colposcopy Findings

Variable		**N (%)**
Colposcopy punch biopsy done	Yes	168 (98.8)
	No	2 (1.2)
Number of lesions seen	1	35 (20.8)
	2	80 (47.6)
	3	47 (28.0)
	>3	6 (3.6)
Transformation zone	Entire TZ seen	156 (92.9)
	Entire TZ not seen	12 (7.1)
Extension of lesion into endocervical canal	Yes	9 (5.4)
	No	159 (94.6)
Biopsy findings	Negative	7 (4.2)
	CIN 1	13 (7.7)
	CIN 2	74 (44.0)
	CIN 3	69 (41.1)
	Invasive Cancer	5 (3.0)

4.7. LEEP

LEEP analysis was done 170 patients with the session being primary. Complications were reported on 3 (1.8%) patients.

Analysis of histological findings revealed that 74 (43.5%) had CIN 3, 52 (30.6%) had CIN 2, 24 (14.1%) had CIN 1, while 9 (5.3%) patients had invasive cancer. 11 (6.5%) patients had negative findings on tissue histology.

Almost three-quarters, 122 (71.7%) of patients had the status of their margins reported, with 24 (19.6%) reported as positive margins.

Table 7. LEEP Findings.

Variable		**N (%)**
Session	Primary	170 (100)
	Repeat	0(.0)
Specimen collected	Yes	170 (100.0)
	No	0 (.0)
Complications	Excessive bleeding	1(0.6)
	Other	2 (1.2)
	None reported	167 (98.2)
If Primary LEEP, histological findings	Negative	11 (6.5)
	CIN 1	24 (14.1)
	CIN 2	52 (30.6)
	CIN 3	74 (43.5)
	Invasive Cancer	9 (5.3)
Status of margins	Reported	122 (71.7)
	Not reported	48 (28.3)
	Positive	24 (19.6)
	Negative	98 (80.4)

4.8. Comparison of Margin Status with Socio-demographics, HIV and Reproductive Health Parameters.

No significant association was found between status of margin and socio-demographics, HIV status or reproductive health parameters.

Table 8. Factors associated with margin result.

		Margins result				
		Positive		Negative		
		N	%	N	%	p-value
Age group	Up to 20 years	0	.0	2	100.0	0.289
	21-30 years	2	14.2	12	85.7	
	31-40 years	8	16.0	42	84.0	
	41-50 years	12	30.8	27	69.2	
	51-60 years	0	.0	11	100.0	
	61-70 years	1	25.0	3	75.0	
	Over 70 years	1	50.0	1	50.0	
Marital status	Single	7	26.0	20	74.0	0.261
	Married	15	16.9	74	83.1	
	Separated	0	.0	2	100.0	
	Divorced	0	.0	0	.0	
	Widowed	2	50.0	2	50.0	
Education level	Illiterate	0	.0	0	.0	0.260
	Primary	3	11.1	23	88.9	
	Secondary	15	19.0	64	81.0	
	Tertiary	6	35.3	11	64.7	
Occupation	Employed	4	21.1	15	78.9	0.356
	Business	11	25.0	33	75.0	
	Housewife	9	15.0	51	85.0	
Parity group	No prior pregnancy	0	.0	2	100.0	0.792
	1-4 prior pregnancies	21	21.2	78	78.8	
	5-9 prior pregnancies	2	12.5	14	87.5	
	More than 9 prior pregnancies	1	20.0	4	80.0	
Last delivery in years	Up to 5 years	2	8.7	21	91.3	0.213

	6-10 years	11	26.8	30	73.2	
	11-20 years	7	21.2	26	78.8	
	More than 20 years	4	16.0	21	84.0	
Family planning :	None	7	17.1	36	82.9	0.412
	Homonal	10	16.7	50	83.3	
	Non-hormonal	7	36.8	12	63.2	
HIV Status	Positive	13	27.7	34	72.3	0.139
	Negative	8	14.0	49	86.0	
	Unknown	3	16.7	15	83.3	

4.9. Management after six months.

Of the 24 patients with positive margins, 17 (70.8%) were re-evaluated after six months. Half of them had undergone TAH, while 4(16.7%) had undergone a Pap smear. Only one (4.2%) had undergone EUA and staging for advanced cancer of the cervix.

Table 9. Subsequent management

	Positive margins
Re-evaluation after 6 months	**N (%)**
Endo-cervical curettage/sampling	0(.0)
Trachelectomy	0(.0)
Repeat LEEP	0(.0)
TAH	12 (50.0)
Referred for EUA + Staging and biopsy	1 (4.2)
Pap smear	4 (16.7)
None	7 (29.2)

CHAPTER FIVE

5.0. DISCUSSION

5.1. Prevalence

As both a diagnostic and therapeutic procedure, LEEP provides a conservative approach to treat HSIL, particularly for women who are young or who desire to preserve their fertility. However, cervical lesions persist or recur in a certain portion of patients after LEEP. Positive margins have been identified as a predictive factor of disease persistence/recurrence. The review of patients who had undergone index LEEP at KNH revealed a residual CIN prevalence of 19.6%, as shown in Table 7. Reviewed studies had shown a prevalence rate of between 10- 45%. Our prevalence fell within what other similar studies had shown (3), (4), (5), (7).

Published references vary greatly, which may be attributed to the different inclusion criteria, definitions of persistence/recurrence and follow-up times. We compared our study with other publications that contained this information as well as predictive factors for persistence/recurrence.

Of the total analyzed samples, 48 (28.3%) had their margins not reported. Two samples were reported as having their margins burned hence difficult to report, while 3 other samples were reported as fragmented. The rest 43, of the samples no reasons were given.

According to the guidelines ASCCP,

"For excision specimens the status of all surgical excision margins must be recorded (ectocervical, endocervical andradial/deep stromal). For each margin, the status of HSIL, AIS(including SMILE)must be recorded.

If a margin is not involved by HSIL/AIS/SMILE, the distance to the surgical margin should be documented. In occasional cases where tumor involvement of the margin cannot be determined for various reasons (processing artefact, multiple pieces or poor tissue orientation), it should be specified as “indeterminate” and the reason explained.

The distance to the excision margin should be documented if less than 10mm.

Information regarding the margin for AIS influences management.

Close surveillance is indicated if the margin for AIS is close but apparently excised (less than 5 mm).Women with positive margins for HSIL do not necessarily require re-excision.” (2).

Given the importance of margin status as an indicator of either residual disease or recurrent/persistence disease, 28.3% as the unreported margin status is a significant number that should be evaluated further.

5.2. Reproductive, clinical characteristics and HIV.

Whereas our study looked at status of the margin as a predictor of residual disease, many other studies have looked at the status of the margin as a predictor of recurrence/persistence of disease.

From the analysis of our data, we evaluated the associations between age, HIV status and reproductive health parameters with positive margin status.

The mean age of our patients was 40 years, which is comparable to 42 found by Baloglu et al (4), but older than 35 years found by Zhu M et al (5). No associations were found between age and positivity of margins. In other studies, (4), (5), (11), age has been associated with recurrence of disease, with age specifically above 35 being strongly associated with recurrence/persistence.

Worth mentioning though is that in our study, one patient above the age of 70 was evaluated, and her margin status was positive.

The HIV prevalence among the evaluated patients was 35.8% (Table 4). This is higher than in the general population, and correlates with reports from other studies that reported a correlation between HIV status and CIN. (23), (25), (26). This higher prevalence is explained by documented evidence that HIV infection predisposes to HPV co-infection. No association was found though between HIV status and the status of margins.

Reproductive health parameters evaluated were parity, years since last delivery and method of contraception (Table 3). Most patients (76.5%) were found to have had between 1-4 pregnancies, similar to the study by Fu Y et al (38) who found 72.4% of their patients had between 1-4 pregnancies. Years since delivery was evenly distributed between the different years clusters. And like in the study by Fu Y et al, no association was found between parity, years since last delivery and status of margins.

Our findings on contraception revealed that a third, 57 (33.3%) of our patients were not using any form of contraception, with 29 (17.3%) on a non-hormonal contraceptive, while 84 (49.4%) patients were on a hormonal contraceptive. This represents a contraceptive prevalence of 66.7%, higher than the national average of 53%, but similar to Nairobi county of 68% (KDHS 2014). However, no association was found between contraception and status of margins.

5.3. Subsequent management.

According to ASCCP's guidelines: "If CIN2, 3 is identified at the margins of an excisional procedure or post procedure ECC, cytology and ECC at 4–6 month is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible" (1). Of our 24 patients with positive margins, 17 (70.8%) were reevaluated after 6 months. This correlated with reports from different studies that showed a review percentage of between 60 to 100%. (3), (4), (5). Of the reviewed patients, 12 (70.5%) underwent TAH. None underwent ECC or repeat LEEP. In comparison, Zhu m et al (5), found most frequent reevaluation methods as repeat LEEP (31.1%) and Hysterectomy (20.3%).

5.4. Conclusion.

The prevalence of residual disease among women with CIN post primary LEEP at KNH was 19.6%. No associations were found between residual disease and age and reproductive health parameters. The follow up review rate after six months was 70.8%. Total Abdominal Hysterectomy was the commonest subsequent management modality upon review of these patients at 70.5%.

5.5. Strengths and weaknesses.

The strengths of our study are that data was captured as a census (time frame) over a long duration of time (four years), with the patients treated in the same institution by experienced personnel, in a routine setting. Long-term evaluation is particularly important to understand the real risk of residual disease in women treated for CIN with LEEP.

The limitations of our study are mainly represented by the retrospective nature of data analysis, nonetheless, these weaknesses reflect what occurs in the every-day routine clinical setting.

Another limitation of the study was the small sample size, which is as a result of poor record keeping and unavailability of records.

5.6. Recommendations

In conjunction with the pathology department, review the reporting protocols to ensure all LEEP specimen are reported as per the ASCCP guidelines.

To increase the screening rates for HIV of patients undergoing LEEP.

Further prospective study to look at long term outcomes of patients with positive margin status.

Strengthen the current follow up system of patients undergoing LEEP in clinic 66.

Ensure proper record keeping for ease of research.

6.0. References.

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APPENDIX

Appendix 1. Data Extraction Tool.

A) Patientdemographic

Age.☐☐

Residence.

Marital status ☐ Single ☐ Married ☐separated.

☐Divorced ☐ Widowed

Education level ☐Illiterate. ☐ Primary ☐Secondary

☐ Tertiary.

Occupation. ☐Employed ☐Business ☐ Housewife.

B) Patient Reproductive Health parameters

Parity☐ +☐.

Last delivery (years) ☐☐

Family Planning. ☐ None ☐ IUCD ☐ LARC ☐ Depo

☐ COCs ☐ Condom.

C) HIV Parameters

HIV status ☐Positive ☐Negative ☐ Unknown

HAART ☐ None ☐ Compliant.

CD 4 Count ☐ Unknown ☐Known Number_____

Viral load ☐ Unknown ☐ Known

If known ☐ Undetectable ☐ Detectable _____

D) Cancer screening history

Pap smear screening history ☐Yes ☐No

If Yes, Pap smear findings ☐Negative ☐ASC-US ☐LSIL

☐HSIL ☐AGC ☐Invasive

VIA VILI screening history ☐ Yes ☐No

VIA ☐ Positive ☐Negative

VILI ☐ Positive ☐Negative

E) Colposcopy Findings.

Colposcopy punch biopsy done ☐ Yes ☐No

Number of lesions seen 1☐ 2☐ 3☐ >3 ☐

Transformation zone ☐entire TZ seen ☐ Entire TZ not seen

Extension of lesion into endocervical canal ☐ Yes ☐ No

Biopsy findings. ☐ Negative ☐ CIN 1 ☐CIN II

☐ CIN III ☐Invasive Cancer

F) LEEP

Session ☐ Primary ☐ Repeat

Specimen collected ☐ Yes ☐ No

Copmlications. ☐ Excessive Bleeding ☐ Other

If primary LEEP, histological findings

☐ CIN I ☐ CIN II ☐ CIN III

☐ Invasive Cancer

Status of margins ☐ Positive ☐ Negative (Free).

G) Reevaluation after six months.

☐ Endo cervical Curettage/Sampling

☐ Trachelectomy.

☐ Repeat LEEP ☐ TAH

☐ Referred for EUA + Staging and biopsy.

Appendix 2: KNH-CRYOTHERAPY AND LEEP FORM

CRYOTHERAPY AND LEEP FORM

KENYATTA NATIONAL HOSPITAL

NAME	IP NO	DATE ……/…../…..	**Consent** to procedure(patients signature)

REFFERAL CLINIC /FACILITY	PHONE NO	ADDRESS	use **X** to check boxes

LMP ……/……../….	PARA	GRAVIDA (if pregnant)	AGE	DOB	FP use ☐Present ☐Past ……

HIV STATUS:☐ unknown ☐ negative ☐ positive	Latest CD4 count	HAART☐Yes ☐No

PRIOR DYSPLASIA HISTORY RESULT (*result that led to today's LEEP or Cryotherapy)*
VIA :☐ Negative ☐ Positive ☐ Suspicious for cancer Date **……/…../…..**
VILI :☐ Negative ☐ Positive ☐ Suspicious for cancer Date **……/…../…..**
Papsmear:☐ASCUS ☐ASC-H ☐ LSIL ☐HSIL ☐AGC ☐Cancer Date **……/…../…..**
Colposcopic histology results:☐ Normal ☐ CIN 1 ☐ CIN 2☐ CIN 3 (includes CIS)☐ ASCUS ☐ASC-H ☐ AGC ☐AIS ☐ Sq Carcinoma ☐Adeno carcinoma ☐ other Date **……/…../…..**
Other significant prior abnormal results
……
……

PRIOR TREATMENT : ☐None ☐Cryotheraphy Date **……/…../…..**☐LEEP Date **……/…../…..**
☐ Other Date **……/…../…..**

TREATMENT GIVEN TODAY: ☐ Cryotherapy ☐ LEEP☐ None (give reason)……

Cryotherapy (write notes here)	**LEEP** **Excision of cervical lesion:** ☐ Intact ☐ Fragmented ☐ Plus top hat ☐ Plus ECC **Number of bottles submitted to histology:** ☐ 1☐ 2 ☐ other **Complications during procedure:** ☐None ☐Blood loss ……ml ☐ Burns ☐other

OTHER FINDINGS: *(if space small use back of the form)*

RETURN DATE:	**FOR HISTOLOGY RESULT IF LEEP:** _____/_____/_____	**FOR FOLLOW UP IF CRYOTHERAPY** _____/_____/_____

CARE PROVIDER NAME : **SIGN:** **DATE:**

COMPLETE THE FOLLOWING SECTION AFTER HISTOLOGY RESULT FOR LEEP PROCEDURE

LEEP HISTOLOGY:
☐ Normal ☐ CIN 1 ☐ CIN 2☐ CIN 3 (includes CIS)☐ ASCUS ☐ASC-H
☐ AGC ☐AIS ☐ Sq Carcinoma ☐Adeno carcinoma ☐ other

MARGINS
☐Not documented☐Disease Free☐ With disease specify ……

PLAN

FOLLOW UP DATE: **CLINIC:**
CARE PROVIDER NAME : **SIGN:** **DATE:**

Appendix 3: KNH - COLPOSCOPY FORM

COLPOSCOPY FORM

KENYATTA NATIONAL HOSPITAL

NAME	IP NO	DATE …../…../…..	**Consent** to procedure(patients signature)

REFFERAL CLINIC /FACILITY	PHONE NO	ADDRESS	use **X** to check boxes

LMP …../……../….	PARA	GRAVIDA *(if pregnant)*	AGE	DOB	FP use ☐Present ☐Past ……

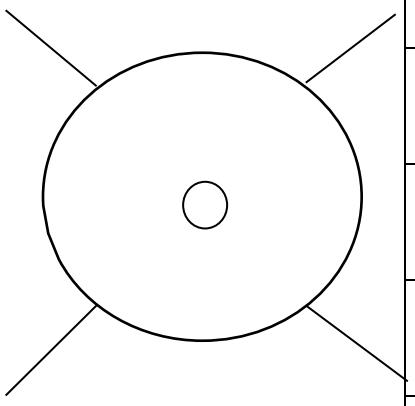
HIV STATUS: ☐ unknown ☐ negative ☐ positive	**Latest Cd4 count**	**HAART**☐Yes ☐No

PRIOR DYSPLASIA HISTORY RESULT (*result that led to today's colposcopic exam)* boxes
VIA :☐ Negative ☐ Positive ☐ Suspicious for cancer Date …../…../…..
VILI : ☐ Negative ☐ Positive ☐ Suspicious for cancer Date …../…../…..
Papsmear:☐ASCUS ☐ASC-H ☐ LSIL ☐HSIL ☐AGC ☐Cancer Date …../…../…..
Colposcopic histology results:☐ Normal ☐ CIN 1 ☐ CIN 2☐ CIN 3 (includes CIS)☐ ASCUS ☐ASC-H ☐ AGC ☐AIS ☐ Sq Carcinoma ☐Adeno carcinoma ☐ other
Date …../…../…..
Other significant prior abnormal results
……
……

PRIOR TREATMENT : ☐None ☐ Cryotherapy (Date …../…../…..) ☐ LEEP (Date …../…../…..)
☐ Other (Date …../…../…..)

COLPOSCOPY FINDINGS:
Satisfactory: ☐ Yes ☐Q tip used
☐ entire SCJ not seen☐ entire lesion not seen
Colour: ☐ No lesion ☐ Leukoplakia ☐ pale-white
☐ bright-white ☐ dull-white
Borders:☐ Faint, indistinct, geographic ☐ smooth, straight outlines ☐ Internal borders
☐ Rolled or peeled edges
Vessels:☐No vessel ☐Branching normal
☐ Fine punctation ☐ Coarse punctation
☐ Fine Mosaic ☐ coarse Mosaic ☐ Atypical Vessels
Size: ☐1 quadrant ☐2 quadrants ☐3 quadrants
☐4 quadrants
Location of Biopsy:
Number of Biopsies:

Cervical cancer colposcopy map



Key

External os (EO)

- - - - Squamo-columnar junction (SCJ)

Acetowhite lesion (AWL)

Suspicious for Cancer (SFC)

X site (s) where biopsy taken

Endocervical Curettage (ECC)

OTHER FINDINGS: *(if space small use back of the form)*

COLPOSCOPY VISUAL IMPRESSION:
☐ Normal ☐ Inflammation ☐ CIN 1 ☐ CIN 2 ☐ CIN 3 ☐ Carcinoma ☐ Other

RETURN DATE FOR HISTOLOGY RESULT

CARE PROVIDER NAME :	**DESIGNATION:**	**SIGN:**

COMPLETE THE FOLLOWING SECTION AFTER HISTOLOGY RESULT

COLPOSCOPY BIOPSY HISTOLOGY **Date** _____/_____/_____

☐ Normal ☐ CIN 1 ☐ CIN 2☐ CIN 3 (includes CIS)☐ ASCUS ☐ASC-H ☐ AGC ☐AIS
☐ Sq Carcinoma ☐Adeno carcinoma ☐ other

ECC RESULT IF DONE: ☐ Normal ☐ CIN 1 ☐ CIN 2,3☐Adeno carcinoma☐ Other

PLAN

PATIENT NOTIFIED OF RESULT:
☐No ☐Yes in person ☐Yes by phone ☐Other

FOLLOW UP DATE:	**CLINIC:**	
CARE PROVIDER NAME :	**DESIGNATION:**	**SIGN:**

Appendix 4. Study Budget.

ITEM	DESCRIPTION	QUANTITY	UNIT PRICE	TOTAL
1	Biro pens	10	20	200
2	Pencils	5	10	50
3	Box files	4	150	600
4	Spring files	4	100	400
5	White out pen	1	150	150
6	Stapler	1	500	500
7	Paper punch	1	600	600
8	Staple remover	1	250	250
9	Notebook	1	150	150
10	Printing	50	10	500
11	Photocopying	3000	3	9000
12	Binding	100	3	300
13	Final proposal booklet	4	1000	4000
14	Final dissertation booklet	4	1000	4000
15	Poster presentation	4	2500	10000

16	**Communication**		**10000**	**10000**
17	**Research assistants**	**4**	**10,000**	**40,000**
18	**Statistician**	**1**	**40,000**	**40,000**
TOTAL				**110,750**

Appendix 5: Study Timelines

GHANT CHART OF STUDY						
Timelines	**Aug - Oct`17**	**Nov`17- Jan`18**	**Feb- Apr`18**	**May- July`18**	**Aug- Oct `18**	**Nov `18- Jan `19**
Proposal development						
Presentation						
Ethical Board review.						
Data collection						
Data analysis						
Thesis writing						