Correlates of Post Loop Electrosurgical Excision Procedure (LEEP) Recurrence of Cervical Intra epithelial Neoplasia

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A research dissertation, submitted to the University of Nairobi, department of Obstetrics and Gynaecology in partial fulfilment of the requirements for the award of Master of Medicine in Obstetrics and Gynaecology.

DECLARATION

This dissertation is my original work and has not been presented elsewhere.

Signature..... Date..1/07/2011

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DEDICATION

To my late mother Florence, for the challenges you met to earn me a place in school.

CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of Dr Muruka Kays,

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LIST OF ABBREVIATIONS

ACOG – American College of Obstetrics and Gynaecology

AGUS – Atypical Glandular Cells of Undetermined Significance

ASCCP – American Society for Colposcopy and Cervical Pathology

ASCUS - Atypical Squamous Cells of Undetermined Significance

ICC - Invasive Cervical Cancer

CAP - College of American Pathologists

CIN- Cervical Intra epithelial Neoplasia

DNA - Deoxyribonucleic acid

DRH – Division of Reproductive Health

HAART – Highly Active Antiretroviral Therapy

HIV - Human Immunodeficiency Virus

HPV - Human Papilloma Virus

HSIL - High grade Squamous Intra epithelial Lesion

IREC - Institutional Research and Ethics Committee

KNH - Kenyatta National Hospital

LEEP - Loop Electrosurgical Excision Procedure

LSIL - Low grade Squamous Intraepithelial Lesion

RR – Relative Risk

SPSS - Statistical Package for Social Sciences

WHO - World Health Organization

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ABSTRACT

Background: Cervical cancer is the commonest gynaecological malignancy worldwide, with an increased burden of disease in developing countries. Effective cytological screening and follow up intervention programs have been credited for the sharp decline in its prevalence in Europe and North America. This has not been the case in the developing world where resources and infrastructure have proved insufficient to offer quality screening and appropriate follow-up. Real gains will require sustainable effective treatment of pre-malignant lesions and early management of disease recurrences. Adequate knowledge on factors associated with disease recurrence after treatment is essential in identifying high risk clients and their management. Outpatient therapy employing methods such as Loop Electrosurgical Excision Procedure (LEEP) combined with proper follow up is appropriate for dealing with colposcopy aided visible lesions on the ectocervix when invasive cancer and endocervical involvement have been ruled out.

Objectives:

1) To determine the post LEEP recurrence rate of lesions ≥CIN2 at KNH
2) To determine factors associated with recurrence of ≥CIN2 disease post LEEP at KNH.
3) To describe early post LEEP complications at KNH.
4) To determine the rate of return visits post LEEP at KNH gynaecology clinic between January 2008 and December 2010.

Methods

This was a retrospective cohort study. Case records for all women who had LEEP between January 1st 2008 and December 31st 2010 at KNH's clinic 18 and 66 were retrieved and reviewed. By these criteria, 124 file records were eligible and therefore included. The socio-demographic, clinical, cytological and histological data were extracted using a structured questionnaire. The post LEEP return visits and dysplasia surveillance findings were recorded and analysis done to identify recurrence of ≥CIN2 lesions, associated risk factors, complications and follow up rates.

Results:

A total of 124 cases were recruited, out of this (90)72.6% returned for their LEEP histopathology results; (52) 41.9% had at least one post LEEP Pap smear cytology done, (21)16.9% had two post LEEP Pap smear cytology tests done and 7(5.6%) had three Pap smear tests done. A recurrence rate of ≥CIN2 lesions among women who were followed up with at least a single pap smear cytology reporting a HSIL and confirmed on colposcopy was 21.2% . Recurrence was strongly associated with HIV infection (p value 0.014) and a histological diagnosis of CIN3 on both colposcopic biopsy and LEEP (p value 0.017 RR 4.533), No major short term complications were reported after LEEP. Pap smear cytology results indicating High grade lesions were in 86.8% of cases confirmed to be ≥CIN2 on histopathology.

Conclusion

The recurrence rate for ≥CIN2 lesions among women who were followed up with Pap smear cytology after LEEP treatment for ≥CIN2 is higher than the average regional and international findings; the return rate for post LEEP Pap smear screening was low. A higher recurrence rate was noted in women with HIV infection and CIN3 lesions on colposcopic biopsy or LEEP histopathology results. The procedure was associated with minimal complication.

Recommendation

A standard post LEEP follow up protocol that identifies the risk factors for recurrence of High grade Lesions in its scheme and incorporates an active client re-call component should be developed and adopted by KNH. This will achieve early diagnosis and management of recurrences, promote uniformity in follow up plans among clinicians and improve patient return rates.

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.1 Background and Literature review

Cervical cancer is the third most common cancer world-wide, with at least 400,000 new cases identified throughout the world each year [1]. It is the commonest gynaecological malignancy world over, with an increased burden of disease in developing countries, where 83% of the cases occur [2]. An estimated 230,000 women die each year from invasive cervical cancer (ICC). In many parts of the developing world, age standardized incidence rates of ICC are ≥ 4-fold higher than what is reported in North America and Western Europe, reaching values in excess of 30-to-50 per 100,000 women in large areas of sub-Saharan Africa [3].The large differences in mortality, with estimates of 11.2 and 4 deaths per 100,000 women-years in less developed and more developed countries respectively point to the persisting major survival differences.

Five of the seven countries with the highest incidence rates of cervical cancer are in Eastern and Southern Africa; while in Northern Africa the incidence is lower [4]. In Kenya the national incidence of cervical cancer is unknown as there is no population based cancer registry; It is estimated that the incidence is between 37 -47 per 100,000 women per year [5]. It is the second commonest malignancy, after breast cancer, as reported in the cancer registry at the department of pathology, Kenyatta National Hospital (KNH) [6]. Kaguta in his review of all Gynaecological malignant tumours in the year 1974 to 1981 showed that malignant tumours of the cervix accounted for 75 percent of all gynaecological tumours in women as seen at KNH [7].

The burden of cervical cancer in industrialized countries has decreased sharply after the wide spread introduction of effective cytological screening programs, these favourable results have not been replicated in the developing world where resources and infrastructure have proved insufficient to offer quality Pap smear screening to more than a small fraction of adult women and high rates of loss to follow-up associated with multi-visit screening protocols [8].

Although precise figures are not available, laboratory surveys from the College of American Pathologists (CAP) indicate that more than 1 million women in the united states are diagnosed with low-grade intraepithelial lesions annually, referred to as Cervical Intraepithelial Neoplasia grade 1(CIN 1), and 500,000 will be found to have high-grade cervical cancer precursor lesions, referred to as CIN-2 and CIN-3[9]. It is estimated that 3-7 million women worldwide may have high-grade dysplasia [5]. Kirima J, in a retrospective study of all cervical smear reports in KNH Nairobi, found the prevalence rate of cervical dysplasia from December 1977 to November 1979 to be 20.4 per thousand (2.04%) among women attending gynaecology outpatient clinic[10].

According to the Bethesda classification system, cervical cytological abnormalities of the squamous cells are uniformly reported as Low grade Squamous Intraepithelial Lesions (LSIL) representing mild cervical dysplasia; High grade Squamous Intraepithelial Lesion(HSIL) representing moderate to severe dysplasia or Atypical Squamous cells of Undetermined Significance (ASCUS) that comprise a category that is suspicious but not conclusive for cellular dysplasia. A further category of glandular cell abnormality named Atypical Glandular cells of Undetermined Significance (AGUS) denotes an inconclusive appearance of glandular cells that are neither normal nor clearly dysplastic. In general terms, a cytological diagnosis of LSIL represents a histological diagnosis of CIN1 whereas a cytological diagnosis of HSIL would represent CIN2 or CIN 3 lesions on histology [9, 18].

The objective of treatment of CIN is the prevention of invasive cancer of the cervix. Limited data are available to calculate the risk of invasive disease in women with untreated CIN [11]. The natural history of untreated CIN1 is characterized by high rates of spontaneous regression and low rates of progression to cancer. In his review, Ostor A,G found that in patients with CIN1, spontaneous regression occurs in 57% cases whereas 11% progress to CIN2 and CIN3 or cancer[12]. Overall, the rate of progression to invasive cervical cancer observed in these studies was 0.3%. Independent recent meta-analysis of the natural history of CIN1 arrived at similar conclusions [13].

Follow-up studies have found that despite marginal relative differences, CIN2 and CIN3 lesions are more likely to persist or progress than to regress. Review of the published natural history literature indicates that 43% of untreated CIN-2 lesions will regress in the absence of treatment, whereas 35% will persist and 22% progress to carcinoma in situ or invasive cervical cancer. For comparison, 32% of CIN-3 lesions spontaneously regress, 56% persist, and 14% progress [14].

Both ablative treatment methods that destroy the affected cervical tissue in vivo and excisional modalities that remove the affected tissue are utilized for treating CIN lesions [15]. Ablative methods include cryotherapy, laser ablation, electro-fulguration, and cold coagulation. Excisional methods that provide a tissue specimen for pathological examination include cold-knife conization, loop electrosurgical excision procedures (LEEP), laser conization, and electrosurgical needle conization. Although various studies show that both ablative and excisional modalities have a similar efficacy in eliminating CIN and reducing a woman's risk of future invasive cervical cancer [16, 17], a diagnostic excisional procedure is recommended for women with recurrent CIN 2 and CIN 3. Ablation is also unacceptable and a diagnostic excisional procedure is recommended for women with a histological diagnosis of CIN 2 and CIN 3 with unsatisfactory Colposcopy [18]. There are no accepted nonsurgical therapies for CIN.

Acceptable post treatment management options for women with CIN 2, 3 include Human Papilloma Virus (HPV) detection by HPV DNA testing at 6-12 months. Follow-up using either cytology alone or a combination of cytology and Colposcopy at 6 month intervals is also acceptable. Colposcopy with endocervical sampling is recommended for women who are HPV DNA positive or have a repeat cytology result of Atypical Squamous cells of Undetermined Significance (ASCUS) or greater. If the HPV DNA test is negative or if 2 consecutive repeat cytology tests are negative for intraepithelial lesion or malignancy, routine screening for at least 20 years commencing at 12 months is recommended. It is therefore unacceptable to offer repeat treatment or hysterectomy based on a positive follow up HPV DNA test alone [18].

Many developing countries face serious obstacles that have hindered establishment of successful cervical cancer control programs. Various countries are now seeking to strengthen cytology services and identify simple low-cost screening strategies; but any real gains in reducing cervical cancer incidence and mortality will also require effective treatment of women with pre-invasive disease. Despite a trend toward conservative outpatient approaches for treating cervical dysplasia in industrialized countries, clinicians in many developing countries still rely primarily on invasive inpatient methods such as cone biopsy and hysterectomy [19]. For women who could be treated with less invasive methods, these procedures tend to pose unnecessary risks and entail high costs that put them beyond the reach of many patients.

Outpatient therapy employing methods such as cryotherapy and LEEP combined with proper follow-up, is appropriate for dealing with visible lesions on the ectocervix when invasive cancer and endocervical involvement have been ruled out. Cryotherapy and LEEP hold out particular promise for developing countries because of their effectiveness, simplicity, minimal side effects and low cost. Cure rates range from 80% to 95%, depending on the method used and the severity of the lesions. However, each method has advantages and disadvantages that demand consideration [19].

LEEP has become an established modality in the diagnosis and treatment of CIN [20]. The procedure can be quickly and safely performed in a clinical setting and is well tolerated by the patient. Relative to cone biopsy, morbidity is lowered by shorter operative times, elimination of general or regional anaesthesia, and reduced blood loss. [21] In addition, a pathologic specimen is provided for histology review and confirmation. Often, this specimen is smaller, yet adequate for evaluation as compared to other conization techniques [21, 22]. Reported success rates in the treatment of dysplasia with LEEP are high, ranging from 63–97% and are comparable with older ablative procedures [22]. Approximately 10% of women having LEEP are reported to have recurrent disease [23]. Incomplete excision of dysplasia has been reported to increase the failure rate; however, controversy exists on the best way to predict residual disease. Although some authors have found that severity of dysplasia or marginal status can be

used to predict persistent disease, others have shown no correlation with residual dysplasia and have found margins difficult to interpret. [22, 24, 25]. Furthermore, no standardized follow-up after LEEP has been established, and protocols vary from institution to institution. Some centres only use cytology, whereas others extensively employ Colposcopy and HPV DNA testing. [24, 25].

Certain factors have been associated with failure of treatment or recurrence of CIN following LEEP. These include the presence of CIN at ectocervical and endocervical margins of resection, involvement of endocervical glands, large CIN lesions, depth of the loop used and a higher grade of CIN at the time of the procedure [25, 26, 27]. Larger lesions of a severe CIN grade and occupying several quadrants represent a significant risk for residual disease and recurrence following the primary excisional procedure. This is attributed to remaining dysplastic cells after apparent excision of the entire lesion. Proper histopathology reports on the state of the resection margins could be an early warning when margins are reported positive for CIN especially for higher grades. Likewise, extremes of ages, a history of smoking and a low socioeconomic status have been associated with higher recurrence.

Human Immuno-deficiency Virus (HIV) infection has also been associated with higher rates of persistence and progression of dysplasia, the increased risk of CIN appears related to the greater prevalence of HPV infection in these women at 64% versus 27% in HIV-uninfected women [28]. Presence of HPV infection represents exposure to a major oncogenic factor in the pathogenesis of CIN and subsequently cervical cancer. Clinical and Laboratory controls using CD4 cell counts and HIV viral loads against all modalities of CIN treatment indicate higher recurrence among immunosuppressed patients even after hysterectomy [36]. The use of Highly Active Antiretroviral Therapy (HAART) in women infected with HIV is therefore associated with decreased CIN recurrence following treatment.

Regardless of the benefit of follow-up protocols in potentially increasing the rate of early detection of CIN recurrence and development of invasive cancer, it is limited, as is any

follow-up protocol by patient compliance in attending the scheduled appointment. The literature reports a lost to follow-up rate of 20–30% after LEEP [29]. Even a prospective study evaluating histological follow-up after LEEP had 13% of patients lost to follow-up [30]. Patients with lower-grade cervical lesions may be more likely to be non-compliant with recommended follow up than patients with higher-grade lesions [31]. An Australian study showed that scheduling colposcopy in the follow-up protocol is associated with a high degree of nonattendance [32]. Only 31% of women who required colposcopic follow up in addition to cytology showed up for the appointments, as opposed to 80% of patients who just needed smears. Only 60% of women were still being followed 17 months after the index Pap smear. Telephone counselling intervention to improve patient compliance with follow-up colposcopy revealed that fear of cancer was the main reason for patient nonattendance [33]. After the examination, however, there appeared to be some degree of relief and lessening of anxiety.

A useful approach to the reduction of anxiety and fear of scheduled follow-up visits is the use of educational brochures. Seventy-five percent of patients who received educational pamphlets at the initial booking for colposcopy completed treatment and follow up after 18–24 months, compared to 46% of patients who did not receive the brochure [34]. Anxiety was significantly reduced when explanatory video was used before treatment. Jones et al. [35] measured anxiety retrospectively in women who had colposcopic follow up and in women with cytological surveillance alone. They found that anxiety was decreased in patients where only cytology was used for follow-up. Thus, in women with a high level of anxiety it may be better to limit follow up to cytology and forego the benefits of Colposcopy because there is a high risk of noncompliance.

1.2 Justification

Cancer of the cervix is one of the leading causes of morbidity and mortality among women in the developing world. It is the commonest female reproductive tract cancer in Kenya. Cervical changes that transform into cancer occur progressively over a long period of time. This time interval provides an ideal opportunity that makes cervical cancer one of the cancers with an effective screening test; the PAP smear cytology. A

reduction in cases of cancer of the cervix has been documented where such programs have been properly rolled out. The success of such screening program depends a lot on appropriate intervention and efficient follow up of those with dysplasia. In Kenya and most of the developing world, cervical screening is opportunistic and the follow up provided even after the screening is worse. The reasons for poor follow up range from: patient, provider and system related factors. Patient related factors include lack of education, lack of finances, in adequate information at counselling or a poor attitude to follow up. Provider related factors include: lack of adequate training, lack of emphasis on follow up, and provider attitudes. System related factors include: lack of standardized guidelines and protocols, routine frequent transfer of healthcare providers and difficulties in tracing results or files.

The association between HIV and cancer of the cervix could impact on patient follow up decisions. HIV infection has been associated with persistence of dysplasia and a much more rapid forward progression of disease compared to their uninfected counterparts. This in turn may translate in a much more intensive follow up of the HIV infected population than those who are not infected. Likewise the frequent contact between the HIV-infected women with health workers in the respective comprehensive care program could play a role in making them better responsive and keen to issues related to their disease hence overall better in return visits.

No reported study has been conducted in this country on the persistence, recurrence or progression of dysplasia following LEEP for ≥CIN2 lesions. Identification of factors associated with recurrence of High grade lesions would help design follow up programs that would target better post LEEP screening practices that will ensure early diagnosis and appropriate management. This study therefore sets out to determine the disease recurrence rates after LEEP for lesions ≥CIN2 among women treated at KNH and the associated factors. At the end of the study, its findings will inform strengthening of guidelines in the management of women after LEEP and subsequent follow up.

1.3 Research question

What is the recurrence rate of ≥CIN2 lesions following Loop Electrosurgical Excision Procedure (LEEP) treatment at KNH?

1.4 Objectives

Broad Objective

To determine the recurrence rate of ≥CIN2 lesions and the associated factors following LEEP at KNH.

Specific objectives

1. To determine the post LEEP recurrence rate of lesions ≥CIN2 at KNH
2. To determine the factors associated with recurrence of ≥CIN2 disease post LEEP at KNH.

Secondary objectives

1. To describe early post LEEP complications at KNH.
2. To determine the rate of return visits for post LEEP follow up at KNH gynaecology clinic between January 1st, 2008 and December 31st, 2010.

CHAPTER 2: METHODS

2.1 Study Design

This was a retrospective cohort study. The records available at KNH's clinic 18 and 66 were used to identify file numbers for all women who had LEEP from January 2008 to December 2010. The respective files were then retrieved from the records department and reviewed by the investigator. All files of cases that met the inclusion criteria were set apart for extraction of socio-demographic, clinical, cytological and histological data using a data capture sheet developed [Appendix 2]. The corresponding histology results after LEEP, patient follow up plan, the actual return visit and the post LEEP follow up surveillance result were recorded as the primary endpoints. The specific dates for all clinic visits from the time of presenting with an abnormal Pap smear cytology result up to post LEEP follow up were recorded.

2.2 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 only two public institutions providing tertiary delivery services in the city.

The KNH gynaecology department's clinic 18 and 66 provide services for cervical cancer screening using Papanicolau (Pap) cytology smears. Follow up of abnormal cytology with colposcopic examination and biopsy with LEEP treatment is also provided on outpatient basis.

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. Upon receipt of colposcopic biopsy results, clients with CIN2 and CIN3 lesions are counselled on the need for LEEP and booked accordingly as

highlighted in the algorithm in figure 1 below.

Prior to the actual LEEP procedure, clients are taken through the steps involved. This include having to empty the bladder upfront, lying on an examination coach in lithotomy position, insertion of a non-conducting speculum, use of a colposcopic light source to visualise the cervix, painting of the cervix with 3% acetic acid and/or iodine solution, application of local anaesthesia, 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. Precautions such as post procedure avoidance of coitus and what to do in case of bleeding including a telephone hotline are 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 target cervical tissue. Haemostasis is achieved by electro-fulguration of the excised base or by application of a haemostatic 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 histology.

With the exemption of invasive carcinoma on the LEEP specimen, all the other cases are routinely advised to a 3 months follow up cytology partly based on the choice of the clinician and/or histology outcome. The entire process is largely patient driven. 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 cervical lesions. Patients with histological diagnosis of invasive cancer of the cervix on colposcopic biopsy or on LEEP specimens are referred for either Wertheim's hysterectomy or radiotherapy based on the staging of the disease.

2.3 Study Population

The study subjects were women who underwent LEEP at KNH gynaecology clinic 18 and 66 between January 1st, 2008 and December 31st, 2010. All their case records were retrieved and reviewed by the investigator.

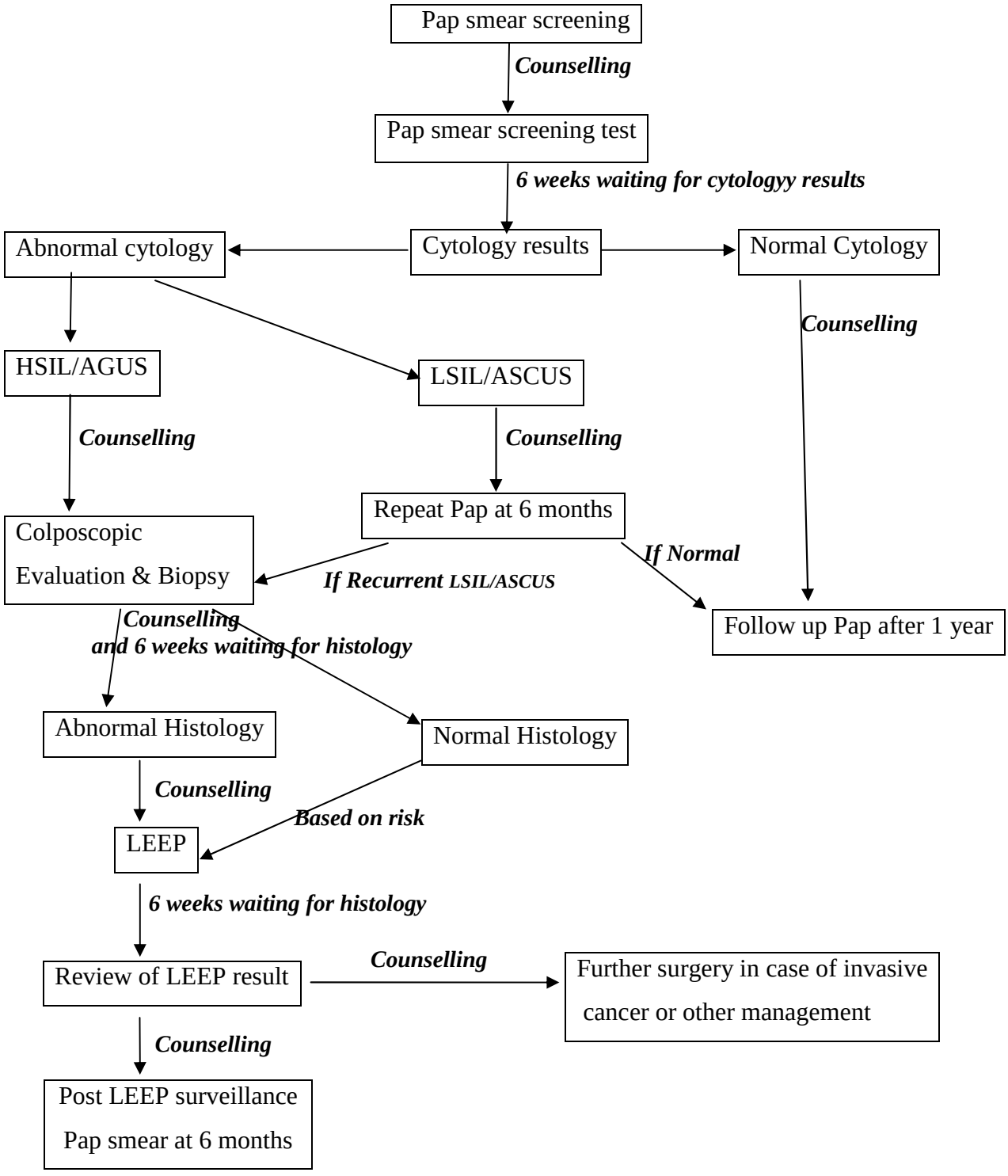
Inclusion criteria

Women who had undergone LEEP at KNH clinic 18 and 66.

Exclusion criteria

Women who had undergone LEEP at KNH but with missing records

Figure 1: Management algorithm of patients presenting for Pap smear.



2.4 Sample size and Sampling Procedure

Sample Size

The sample size was determined by the time frame. All women who had LEEP between 1st January 2008 and December 31st 2010 were to be included. According to the records, 132 women had LEEP over that duration. Only 124 case files were accessible for retrieval.

Sampling Procedure

We retrieved 132 records for women who had LEEP over the period ranging from 1st January 2008 to 31st December 2010; out of this, 8 case files could not be found therefore making them ineligible. All the 124 case files eligible and accessible for retrieval were therefore recruited.

2.5 Data management and collection methods

The data comprising of socio-demographic characteristics, clinical information, histological diagnosis and follow up visits was extracted from each file by the principal investigator and filled in a coded structured data capture sheet (Appendix 2). The completed forms were kept in locked cabinets accessible to the researcher only. All databases were password protected in order to guarantee confidentiality of the patient's details. Cross checking of the questionnaires was done for missing entries before double entry into an MS Access data base followed by cleaning and validation.

2.6 Data Analysis and Presentation of Results

The abstracted data entered into an access database was analyzed using Statistical Package for Social Sciences (SPSS Version 17.0).

Descriptive analysis

Data analysis was done beginning with the summaries of demographic characteristics, parity, marital status, HIV infection status, CD 4 levels and HAART usage. This has been presented descriptively in form of means, medians and proportions respectively.

Primary analysis

Proportions have been used to present the recurrence rates and for comparisons presented in tabular form.

Secondary analysis

Univariate and multivariate analysis has been done to determine any association between socio-demographic characteristics, HIV infection, CD4 counts, HAART status and severity of the index cervical lesion with persistence or recurrence of ≥CIN2.

2.7 Ethical Considerations

The research protocol was approved by the department of Obstetrics and Gynaecology, University of Nairobi and subsequently by the Kenyatta National Hospital Ethics and Research Committee. Informed consent was not sort because of the retrospective nature of the study. Confidentiality was observed by the researchers: all participant records did not 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 the electronic records within the database were password protected. Only data entry personnel, clinicians overseeing the database, and researchers involved on this project had access. Where a phone contact was available in the file whose histology required immediate attention yet the client had not showed up for follow up, an in-kind phone call was made with a request that her histology requires further counselling. Results from this study will be useful in advising and strengthening of guidelines used in the management of patients with cervical premalignant lesions and particularly those who need LEEP and the subsequent follow up. It will also provide pilot data for larger studies.

2.8 Study Limitations

The retrospective nature of the study predisposed it to missing data. To cater for this, the study recruited all eligible women in the time frame under investigation. Missing histology and cytology reports were minimized by checking with the backup records at the department of pathology. A notably high dropout proportion increasing at each stage of follow up post LEEP reduced the accuracy in determining recurrence rates in this group of women.

CHAPTER 3: RESULTS

We retrieved 132 records of women who underwent Loop Electrosurgical Excision Procedure (LEEP) at Kenyatta National Hospital between 1st January2008 and 31st December 2010; of which 124 case files were available for review.

Table 1: Baseline characteristics of women who had LEEP at KNH from 1st Jan 2008 to 31st Dec 2010

Variable		N (%)
Age – Mean(SD)	36yrs(8)	123(99.2%)
Telephone contact present		103(83.1%)
Marital status		
Single		35(28.2%)
Married		71(57.3%)
Separated/Divorced		8(6.5%)
Widowed		6(4.8%)
Not stated		4(3.2%)
Highest Level of education		
None/Nursery		6(4.8%)
Primary		39(31.5%)
Secondary		42(33.9%
College		25(20.2%)
Not given		12(9.7%)
Referring Hospital		
KNH		44(35%)
Other facilities in Nairobi		67(54%)
Facilities outside Nairobi		11(8.9%)
Not indicated		2(1.6%)
Parity - Mean(SD)	2.6(1.75)	
HIV Infection status		
Positive Result in the file		34(27.4%)
Positive self report		15(12.1%)
Negative Result in the File		18(14.5%)
Negative self report		4(3.2%)
Unknown HIV status		53(42.7%)
HIV Positive		
On HAART		31(63.3%)
Not on HAART		12(24.5%)
Unknown HAART status		6(12.2%)
CD 4 count recorded(range)	(8 – 1200)	35(71.4%)
CD4 mean(SD)	373(298)	

Continuation of table 1: Baseline characteristics		
Index Pap smear Cytology		
LSIL+ ASCUS		23(18.6%)
HSIL		91(73.3%)
AGUS		4(3.2%)
Invasive Cancer		1(0.8%)
Missing Results		5(4.1%)
Colposcopic Histopathology		
CIN1		10(8.1%)
CIN2		42(33.9%)
CIN3		67(54.0%)
Invasive Cancer		2(1.6%)
Missing results		3(2.4%)

The mean age of the participants was 36 years (SD- 8) years, the youngest was 20years and the oldest 61years; 1 (0.8%) participant had no age documented. 71 (57.3%) were married, 67 (54.1%) had a minimum of secondary education and 11 (8.9%) were referred from facilities outside Nairobi(Table 1).

Telephone contacts were retrieved in (103) 83.1% case records. The majority had a parity of 2 with a mean of 2.6(SD-1.75). The HIV infection rate was 39.5% while 42.7% lacked HIV status documentation. Among the HIV infected, 63.3% were on HAART and 71.4% had a documented CD4 count with a mean of 373(SD - 298). (Table 1)

In 91(73.3%) of the cases reviewed, the index Pap smear cytology result was reported as a High grade squamous intraepithelial lesion (table 1).

Table 2: Post LEEP follow up

Variable	HIV infected	HIV Negative	Unknown HIV status	Total	P value
LEEP Histology result					
Normal	2(4.7%)	2(9.5%)	2(4.1%)	6(5.3%)	0.590
CIN1	3(7.0%)	2(9.5%)	9(18.4%)	14(12.4%)	0.209
CIN2	8(18.6%)	9(42.9%)	15(30.6%)	32(28.3%)	0.078
CIN3	21(48.8%)	6(28.5%)	14(28.6%)	41(36.3%)	RR 4.533(.017)
Invasive Cancer	5(11.6%)	1(4.8%)	2(4.1%)	8(7.1%)	-
Inflammatory	4(9.3%)	1(4.8%)	7(14.2%)	12(10.6%)	
Total	**44(100%)**	**21(100%)**	**49(100%)**	**113(100%)**	
		N (%)			
Post LEEP complication					
Bleeding		5(5.6%)			
Foul discharge		1(1.1%)			
Persistent Discharge		8(8.9%)			
Pain		7(7.8%)			
None		68(75.5%)			
No entry		1(1.1%)			
Post LEEP return Visit					
Return for LEEP Histology result		90 (72.6%)			
Follow up screening					
1st cytology		52(41.9%)			
Normal		43 (34.7%)			
LSIL		1 (0.8%)			
HSIL		6 (4.8%)			
ASCUS		2 (1.6%)			
2nd cytology		21(16.9%)			
Normal		20(16.1%)			
LSIL		0			
HSIL		1(0.8%)			
ASCUS		0			
3rd cytology					
Normal		7 (5.6%)			
Colposcopic biopsy		14(11.2%)			
Normal		4(3.2%)			
Cervicitis		2(1.6%)			
CIN 2		3(2.4%)			
CIN 3		1(0.8%)			
ICC		4(3.2%)			
******Called up during the study 3 cases of CIN3 (2.4%)***					

Out of 124 women who had LEEP, 113 (91.3%) histology results had been posted in the files. A confirmatory check at the Pathology department showed that histology specimens for the 11(8.7%) results that were missing in the files were never received for processing by there laboratory.

Histology results from colposcopic biopsies had 67(54%) with CIN3, 42(33.9%) with CIN2 and 10 (8.2%) with CIN1 lesions (table 1) whereas LEEP histopathology results had 41 (36.3%) were CIN3, 32(28.3%) were CIN2, and 14 were CIN1 lesions (Table 2). Pap smear cytology results indicating High grade lesions were in 86.8% of cases confirmed to be ≥CIN2 on histopathology.

No admission was made after LEEP as there were no major complications. Minor complications including pain, bleeding and a discharge were reported by 21(23.4%) of the women during their first post LEEP review (table 2).

90(72.6%) of the women who underwent LEEP returned for the first appointment and review of histopathology results. (52) 41.9% had at least a first post treatment Pap cytology smear done and (21)16.9% had a second Pap smear (table 2). Through the use of telephone contacts in the file, 3(2.4%) women with abnormal margins on LEEP were successfully recalled.

Table 3: Cascade of outcomes during follow up

Stage of follow up	**N**
Initial Primary LEEP	124 (100%)
Returned for LEEP Histology Results	90 (72.6%)
At least 1 Post LEEP Pap Smear done	52 (41.9%)
Abnormal Post LEEP Cytology warranting Colposcopic biopsy (HSIL +ASCUS + persistent LSIL)	17 (32.7%)*****
Post LEEP recurrence of ≥CIN2 documented	11(21.2%)*****

****-expressed as a proportion of those who were followed up***.

The recurrence rate of ≥CIN2 among women who had Post LEEP screening was 21.2%.

Table 4: Time interval between diagnosis and treatment of abnormal cervical Premalignant lesions

	Interval between Pap cytology & Colposcopic biopsy	Interval between Colposcopic biopsy & LEEP	Interval between 1st visit with abnormal Pap & LEEP	Interval between LEEP & First Follow up
Duration In Months	**N (%)**	**N (%)**	**N (%)**	**N (%)**
< 1	32 (27.1%)	15 (12.5%)	2 (1.7%)	33 (36.7%)
1-3	42 (35.6%)	56(46.7%)	24 (20.3%)	42 (33.9%)
4-6	28 (23.7%)	24 (20%)	40 (33.9%)	6 (4.8%)
7-9	6 (5.1%)	12(10%)	22 (18.7%)	2 (1.6%)
>9	10(8.5%)	13 (10.8%)	30(25.4%)	7 (5.6%)
+/-x in weeks	14 / 18	17 / 19	32 / 28	11 / 17

Among women presenting to colposcopy clinic with abnormal Pap smear cytology, 32(27.1%) got a colposcopic biopsy done in one month, (42)35.6% in 3 months while 71(59%) got LEEP done within 3 months. The mean duration between presenting to clinic with an abnormal Pap smear cytology and LEEP was 32 weeks (SD 28), the shortest being 3 weeks and the longest being 155 weeks; 10(8.4%) women took more than 18 months to get LEEP done(table 4).

Table 5: The number of clinic visits Made from the time of presenting with an abnormal Pap smear cytology to LEEP

Number of clinic visits	N (%)	Estimated total hospital costs incurred per patient in Ksh
≤3	17(13.8%)	3730.00
4-6	83(67.5%)	4400.00
7-9	19(15.4%)	5243.00
10-15	4(3.2%)	6813.00
+/-x => 5.2 / 2.3		

The mean number of clinic visits made between presenting with an abnormal Pap smear cytology result and LEEP was 5.2(table 5).

Table 6: Factors associated with ≥CIN2 recurrent lesions

Variables	No Recurrence	Recurrence of ≥CIN2	P Value
	N (%)	N (%)	
Age group			0.786
20-29	13(27.7%)	2(18.2%)	
30-39	19(40.4%)	5(45.5%)	
40-49	13(27.7%)	4(36.4%)	
50-59	2(4.2%)	0	
Telephone contact			0.669
Present	39(81.3%)	10(91%)	
Absent	9(18.7%)	1(9.0%)	
Marital status			0.497
Single	15(31.2%)	2(18.2%)	
Married	26(54.1%)	6(63.6%)	
Separated/Divorced	3(6.3%)	2(18.2%)	
Widowed	2(4.2%)	1(9.1%)	
Not Stated	2(4.2%)	0	
Education level			0.326
No education +Nursery	3(6.3%)	0	
Primary	16(33.3%)	4(36.4%)	
Secondary	18(37.5%)	2(18.2%)	
College	8(16.6%)	4(36.4%)	
Not given	3(6.3%)	1(9.1%)	
Referring hospital			0.972
KNH	18(37.5%)	3(27.3%)	
Other facilities in Nairobi	25(52.1%)	5(45.4%)	
Hospitals outside Nairobi	5(10.4%)	1(9.1%)	
HIV Infection			0.012
Positive	12(25%)	8(72.7%)	
Negative	12(25%)	0	
HAART Status			0.119
Not on HAART	4(33.3%)	0	
On HAART	7(58.3%)	7(87.5%)	

Continuation of table 6; Factors associated with ≥CIN2 recurrent lesions			
CD4 Count	0	3(37.2%)	0.228
≤ 250	3(42.9%)	1(12.5%)	
251 - 350	3(42.9%)	3(37.5%)	
351-500	1(14.2%)	1(12.5%)	
> 500			
Parity			
0 - 2	31(65.9%)	6(54.5%)	0.517
3 - 5	14(29.8%)	5(45.5%)	
6 – 10	2(4.3%)	0	
Index Pap smear			0.616
LSIL & ASCUS	11(23.4%)	2(18.2%)	
HSIL	35(74.5%)	8(72.7%)	
Colposcopic biopsy Histology			
CIN1	4(8.3%)	0	0.083
CIN2	18(37.5%)	1(9.1%)	0.142
CIN3	24(50%)	9(81.8%)	0.017, RR 4.533
Invasive Cancer	0	1(9.1%)	0.001
LEEP Histology			
Normal	3(6.2%)	0	0.345
CIN1	9(18.8%)	0	
CIN2	17(35.4%)	2(18.2%)	0.083
CIN3	14(29.2%)	6(54.5%)	0.142
Invasive Cancer	0	3(27.3%)	0.017 RR 4.533
Duration from LEEP to follow up cytology in			
Months: 1 - 6	38(4.8%)	9(81.8%)	0.147
7 - 12	2(4.8%)	1(9.1%)	
13 -15	2(4.8%)	1(9.1%)	

Recurrence of HSIL following LEEP was significantly associated with HIV infection, RR 4.5(p - 0.014), and an initial histopathologic diagnosis of CIN3, RR 4.5(p - 0.017) at LEEP or colposcopic biopsy (table 6).

CHAPTER 4: DISCUSSION

4.1 Discussion

The rate of recurrence of ≥CIN2 lesions following LEEP for the period ranging from January 1st 2008 to December 31st 2010 was found to be 21.2 % (table 3) .This is higher than the rates of between 7%-14% documented at 24 months in Zimbabwe by Chokunoga et al [5] and by Kreimer et al [23] in North America. Various factors have been associated with recurrence of high grade CIN following LEEP, this include initial severe CIN grade, presence of lesions in several quadrants, smoking, margin involvement, gland involvement, immune suppression, type of HPV and the experience of the provider. The factors associated with recurrence in this study were HIV infection, RR 4.5 (p- 0.014), the presence of CIN 3 on colposcopic biopsy, RR 4.533(p- 0.017) and LEEP histology with CIN 3, RR 4.5 (p value 0.017).(Table 6) Women with these characteristics require close surveillance and emphasis to avoid loss to follow up. However, multivariate analysis did not identify independent predictors associated with recurrence.

HIV infection has been associated with higher persistence, recurrence and progression of CIN [28]. This pattern has been observed in all modalities of treatment aimed at managing CIN in HIV sero-positive women leading to the opinion that all grades of CIN in such situations warrant treatment [36]. In this study, 49(39.5%) of participants were HIV infected; the HIV status of 53(42.7%) women was unknown (table 1). This may result in the unknown positive cases missing out on the intensive interventions targeting HIV infected women. Lower CD4 counts are associated with persistence of HPV infection which is the principle factor in the pathogenesis of cervical cancer and its precursor lesions, only 35(71.4%) of the HIV infected women had a CD4 count documented at the time of LEEP, out of which 15(12.1%) came back for the follow up Pap smear cytology testing. This study did not show any association between the CD4 count level and recurrence of High grade lesions (p value 0.228; table 6). This is probably attributed to the small number of women who had a documented CD4 count that was followed up. Use of HAART improves immune reconstitution which in turn has been

associated with decreased cervical cytological anomalies. In this study, 31(63.3%) of women infected with HIV were on HAART; however, on analysis, there was no association between disease recurrence and use of HAART (p value 0.119) (table 6)

The safety of LEEP is re-affirmed by this study, no major complication was encountered to warrant hospital admission. 68(75.5%) of participants had no complains at review; the remaining had minor complications that included minimal bleeding, a persistent discharge and pain (table 2). As compared to cone Biopsy, LEEP has the added advantage of lower operative times, elimination of general or regional anaesthesia, reduced blood loss and admissions [21].

Much as cryotherapy has been prioritised by the Division of Reproductive Health (DRH) in the treatment of cervical precancerous lesions in government facilities on the basis of see and treat approach [37], LEEP achieves comparable treatment efficacy with the added advantage of providing a specimen for histology [16]. Availability of a histological specimen result could alter the follow up plan especially having observed a higher recurrence rate in colposcopic biopsy samples that had CIN 3 lesions (table 6). Cryotherapy is equally unacceptable in situations where colposcopy is unsatisfactory and large lesions that cannot be appropriately covered by the probe.

Failure to follow up is a major setback in this study; 72.6% of clients turned up for LEEP histology results, 41.9% for the follow up Pap smear at six months and 16.9% at 12 months (table 2). This reflects a significant loss to follow up that will in the long run compromise the effectivity of LEEP in the management of precancerous lesions. A loss to follow up of 20-30% rates was observed by Hannau and Bibbo [29] in a retrospective study. A prospective study evaluating histological follow up at two years had 13% of patients lost to follow up [30]. A re-evaluation focused on reducing the number of visits made to the clinic between the time of presenting with an abnormal Pap smear and when LEEP is done is necessary to cut down on the mean observed at 5.2 visits over a prolonged time interval (table 4) to the current American College of Colposcopy and Cervical pathology ideal of 3 visits to be achieved within a month. This will equally cut

down on costs incurred on the multiple visits.

The observation that 86.8% of reported high grade lesions on Pap smear cytology ended up being ≥ CIN2 lesions on histology either at colposcopic biopsy or LEEP may guide our future practice. Such a high agreement between the two tests may support a view that women with a high grade lesion on Pap smear may undergo LEEP directly without a need for an intermediate colposcopic biopsy. This will offer the advantage of limited clinic visits, lower costs and faster turn-over. However the long time interval between the Pap smear cytology and LEEP as noted in this study could have resulted in forward progression in severity of lesions hence responsible for the high agreement between the two tests. More studies are needed in this area.

The presence of a telephone contact in 103(83.1%) of the charts reviewed(table 1) suggests a potential tool that could be utilized as a linkage to encourage, remind and reinforce adherence to the recommended multiple clinic visits needed for surveillance following LEEP. Telephone counselling to improve compliance with follow up has been observed to minimise patient nonattendance [33]. An active recall program could therefore potentially reduce the fall out rate observed in this study.

Noting that 106 (85.5%) of participants had a minimum of primary education, use of educational materials such as brochures and video demonstrations could improve the follow up rates. Anxiety associated with a follow up pelvic exam has been shown to be reduced in women who had video demonstration and literature material hence enhancing return rates [35].

Due to the retrospective nature of this study, data on known risk factors such as smoking, sexual habits, prior Pap smear results and HPV infection could not be sought for.

4.2 Conclusion

The recurrence rate of ≥CIN2 lesions among women who were followed up after LEEP was 21.2%. Recurrence was higher among HIV infected women and those with a histopathologic diagnosis of CIN3 on colposcopic or LEEP biopsy. LEEP was associated with minimum post procedure complications. However the major limitations observed were the multiple visits made by patients before the procedure is done and a high dropout rate at the level of follow up; this is despite availability of telephone contacts in the majority of case files that could be used to trace them. The retrospective nature of this study did also expose the poor documentation, lack of consistency in reporting and varied follow up plans among clinicians.

4.3 Recommendations

1. A standard post LEEP follow up program ought to be developed and adopted for use by all clinicians at Kenyatta National Hospital. This should comprise predesigned forms that capture individual risks for disease recurrence and the follow up plan.

2. An active program that focuses on recalling patients should be incorporated in order to achieve higher return rates.

3. Adequate counselling with use of pamphlets and audio visual material should be adopted in order to improve follow up return rates

4. A feasibility study should be carried out on the possibility of doing both colposcopic examination and LEEP in one sitting. This will reduce cost to the clients, decrease individual clinic visits, reduce waiting time and improve re-attendance.

CHAPTER 5: APPENDICES

Appendix 1: References

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Appendix 2: Data Capture sheet.

1. Serial Number ☐☐☐☐☐

2. Clinic Number ☐☐☐☐☐

3. Age in Years ☐☐

4. Documentation of telephone contact in the file

   I. Present ☐

   II. Absent ☐

5. Marital status? (*Tick one)*

   I. Single ☐

   II. Married ☐

   III. Separated/Divorced ☐

   IV. Widowed ☐

   V. Not stated ☐

6. Level of Education

   I. No Education ☐

   II. Nursery ☐

   III. Primary ☐

   IV. Secondary ☐

   V. College ☐

   VI. Not given ☐

7. Referring hospital/clinic

I. KNH ☐

II. Pap camp ☐

III. Other Facilities in Nairobi ☐

IV. Hospitals outside Nairobi ☐

8. HIV infection:

I. Positive[result in the file] ☐

II. Negative[result in the file] ☐

III. No HIV Result ☐

IV. Positive [Client report] ☐

V. Negative [client report] ☐

VI) If positive; On HAART ☐ Not on HAART ☐ Not documented ☐

Latest CD4 count ☐

9. Parity given as x + y: ☐ ☐

10. Pap smear test date (Before LEEP) (*dd/mm/yy*) ☐☐ ☐☐ ☐☐

11. Reasons for the pap smear above

I. Routine screen ☐

II. Concurrent illness ☐

12. Result for the Pap smear

I. Normal ☐ V) ASCUS ☐

II. LSIL ☐ VI) Severe dysplasia ☐

III. HSIL ☐ VII) Others ☐

IV. Invasive cancer ☐

13. Colposcopic biopsy date (*dd/mm/yy*) ☐☐ /☐☐ /☐☐

14. Colposcopic histology result

I. Normal ☐
II. CIN 1 ☐
III. CIN2 ☐
IV. CIN3 ☐
V. ICC ☐
VI. Others(state) ☐

15. Post colposcopic biopsy return date (*dd/mm/yy*) ☐☐ / ☐☐ / ☐☐

16. Date LEEP was done (*dd/mm/yy*) ☐☐ / ☐☐ / ☐☐

17. No of visits to clinic between 1st contact [with abnormal pap] and LEEP .....

18. Result for LEEP

I. Normal ☐
II. CIN1 ☐
III. CIN2 ☐
IV. CIN3 ☐
V. Invasive Cancer ☐
VI. Others(State) ☐

19. Post LEEP complication noted

I. Bleeding ☐

II. Foul discharge ☐

III. Pain ☐

IV. Persistent discharge ☐

V. Other (state) ☐ .....

20. Post LEEP follow up visit date (*dd/mm/yy*) ☐☐ ☐☐ ☐☐

21. Post LEEP procedure

A)Pap smear	Date	Result
No 1		
2		
3		
4		
5		

B)Colposcopic biopsy	Date	Result
No. 1		
2		
3		

C) LEEP	Date	Result
No 1		
2		
3		

D) Other – State.....

22. Latest post LEEP surveillance result

I. cytology ☐

II. Histology ☐

III. None ☐

Appendix 3: Time frame and budget

TIME FRAME	
Activity	**Time Frame**
Ethical Approval	October- December 2010
Data collection and entry	January- March 2011
Data Analysis	April 2011
Thesis writing	April -May 2011

BUDGET	
ITEM	COST IN SHILLINGS
Proposal development	12,000.00
Research assistant wage	45,000.00
Stationery costs	10,000.00
Telephone costs	8,000.00
Data entry/analysis	30,000.00
Thesis writing	8,000.00
10% Overhead	11,300.00
Grand Total	**124,300.00**

Appendix 4: Ethical approval

KENYATTA NATIONAL HOSPITAL
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February 3, 2011

Ref: KNH-ERC/ A/12

Dr. Muruka Kays
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Dr. Muruka

RESEARCH PROPOSAL: "CERVICAL INTRAL EPITHELIAL NEOPLASIA: FACTORS ASSOCIATED WITH POST LOOP ELECTROSURGICAL EXCISION PROCEDURE (LEEP) DISEASE RECURRENCE AT KENYATTA NATIONALHOSPITAL" (P335/10/2010)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and **approved** your above revised research proposal for the period 3rd February 2011 – 2nd February 2012.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The HOD, Records, KNH
The Dean, School of Medicine, UON
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