CERVICAL HISTOLOGIC FINDINGS AND SIX MONTH TREATMENT OUTCOMES OF PATIENTS WITH ABNORMAL PAP SMEAR CERVICAL CYTOLOGY ATTENDING KENYATTA NATIONAL HOSPITAL, 2008-2014

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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
CAP	College of American Pathologists
CIN	Cervical Intra- epithelial Neoplasia
DNA	Deoxyribonucleic acid
ERC	Ethics Review Committee
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
ICC	Invasive Cervical Cancer
IREC	Institutional Research and Ethics Committee
KNH	Kenyatta National Hospital
LEEP	Loop Electrosurgical Excision Procedure
LSIL	Low grade Squamous Intraepithelial Lesion
MOH	Ministry of Health
RR	Relative Risk
SPSS	Statistical Package for Social Sciences
SVA	Single Visit Approach
WHO	World Health Organization

ABSTRACT

Introduction: Cervical cancer is the third commonest malignancy among women worldwide, with over 500,000 new cases diagnosed annually, an; 275,000 deaths, 88% of these occurring in the developing countries. HPV infection is implicated in causation of cervical cancer and secondary prevention is hinged on treatment of premalignant lesions caused by this virus. Kenyatta National Hospital (KNH) follows the Pap smear, colposcopy and Loop Electrosurgical Excision Procedure (LEEP) protocol in management of Cervical Intraepithelial lesions (CIN).

Study objective: To determine the colposcopy biopsy ± LEEP cervical histologic findings and six month treatment outcomes of patients with abnormal Pap smear cervical cytology attending Kenyatta National Hospital, 2008-2012

Methodology: Retrospective descriptive study was done in KNH, where medical records of patients attended to in the hospital between 2008 and 2012 were reviewed. The sample size was 197. Data was analyzed using the *Statistical Package for Social Scientists (SPSS) version 17.* Ethical approval was sought from KNH/UoN Ethical Review Committee (ERC).

Results: The study population was a predominantly married, urban population with only 34% of them unemployed. Majority (76%) of the participants who underwent colposcopy biopsy ± LEEP had HSIL on Pap smear cytology. Nearly all the participants had an abnormal cervical histology with 78% (154/197) of them having ≥ CIN 2. Of these 54 (27%), 46(23%), 40 (20%) and 13 (7%) had CIN 2, CIN3, CIS and invasive cancer respectively. Only 53% of records had the HIV status recorded. Patients who had a positive HIV status and high parity and age more than 35 years showed an insignificant trend of having a higher likelihood of cervical histology outcomes of ≥ CIN 2. There was a high (63%) loss to-follow-up, for follow up Pap smear at six months after CIN treatment; of the available cytology results 85% of them were normal.

Conclusion: Women undergoing colposcopy ± LEEP in KNH have a high rate of ≥CIN2 on cervical histology. Follow up Pap smear cytology after six months of CIN treatment with LEEP is normal for 85% of the participants who presented for follow-up. Treatment of CIN is justified and should be strengthened in order to reduce the incidence of invasive cervical cancer in Kenya. Poor documentation was identified as a glaring weakness.

INTRODUCTION AND LITERATURE REVIEW

Cervical cancer is the third most common malignancy in women worldwide and the seventh overall, with varying frequency between developed and developing countries. More than 85% of cases are reported in the developing countries, accounting for over 13% of all cancers in these countries. More than 500,000 new cases are diagnosed worldwide each year, with over 200,000 deaths resulting from the condition. The mortality to incidence ratio is 52%. Of these deaths, 80% occur in developing countries. Also noted, is that, 46,000 of these women are aged 15-49 years, with 109,000 being above 50 years of age [1]. Regional rates vary widely, ranging from an annual incidence of 4.5 cases per 100,000 in Western Asia to 34.5 per 100,000 women in Eastern Africa [2]. In Kenya, incidence is estimated at 80 per 100,000 women, with Uganda being at 40.8 per 100 000 [3]. In Nairobi, cervical cancer accounts for approximately 46% of deaths in the gynaecological wards, occurring in women 35-45 years[2].

Over a 100 human papillomavirus (HPV) sub-types have been identified, of which 40 infect the genital tract and are sexually transmitted. Of these, approximately 15 have been established as High Risk oncogenic (HR) sub-types. These are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Most women are infected shortly after coitarche, with the highest prevalence in women less than 25 years. Thereafter, prevalence decreases rapidly, until a second peak of infection in older women close to the age when the incidence of cervical cancer is at its maximum (35-45 years).

HPV16, followed by HPV18, are the sub-types most frequently detected (in 60.9% of cases) when squamous cell carcinoma is diagnosed while HPV 18 is most strongly associated with adenocarcinoma. The frequency with which HPV16 is found in integrated forms increases with the severity of cervical neoplasia [4]. In Kenya, about 38.8% of women in the general population are estimated to harbour cervical HPV infection at a given time [5].

In early adolescence and first pregnancy, squamous metaplasia occurs as a natural response to hormonal changes at the cervical squamo-columnar junction. Infection with HPV induces changes in the newly transformed cells, with viral particles being integrated into the DNA of the cells. If the virus persists in the epithelial cells, it may cause precancerous and, later, cancerous changes, by interfering with the normal control of cell growth [6]. This happens by up-regulation of viral oncogenes E6 and E7 which have the ability to complex with tumor suppressor genes p53 and Rb respectively; disabling the suppressor function, resulting in host cell immortalisation and malignant transformation. Approximately 90% of squamous cell carcinomas develop from epithelia within one centimetre of the squamo-columnar junction.

Sixty percent or more, of cases of mild dysplasia resolve spontaneously and only about 10% will progress to moderate or severe dysplasia within two to four years. Less than half of cases of severe dysplasia progress to invasive carcinoma with much lower rates seen in younger women. The natural history of progression from mild dysplasia to carcinoma takes ten to twenty years. This makes cervical cancer a relatively easily preventable disease and provides the rationale for screening [4].

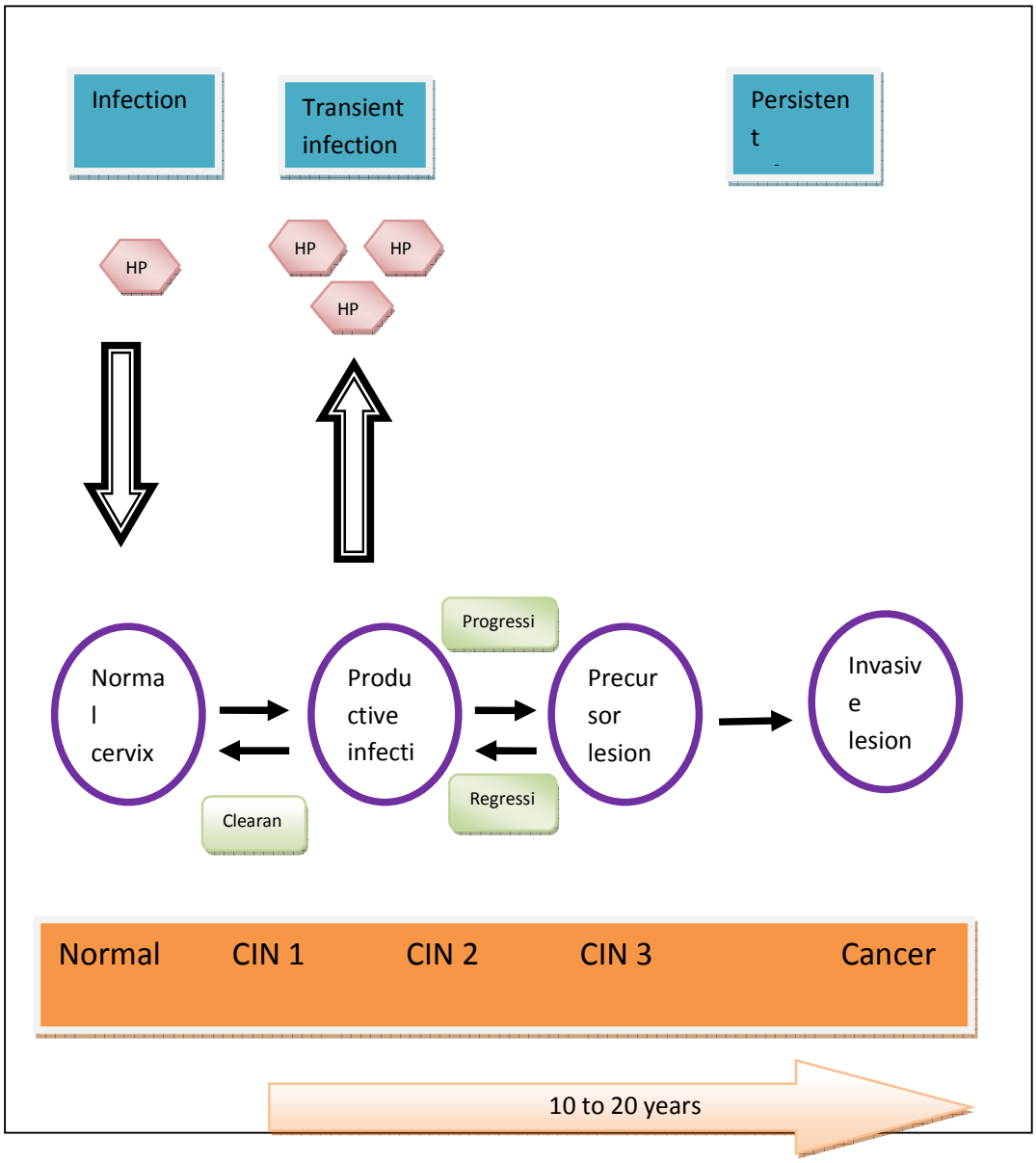


Figure1 : Natural History of Cervical Cancer[7]

Several risk factors have been identified that predispose to development of pre-invasive and invasive neoplastic lesions of the cervix [4]. HPV infection, especially the high risk sub-types. In Kenya, HPV 16 and 18 are the commonest, as demonstrated in over 60% of cervical cancer patients. History of abnormal Pap test results or dysplasia: overall, about five percent of mild dysplasias will progress to

invasive cancer over a period of ten to 20 years without intervention. Early screening and treatment of premalignant lesions curtails this progression. Unfortunately in Kenya, only about five percent of women eligible for screening are accessing screening. Smoking of cigarettes and other tobacco products is associated with a two- to four-fold increase in relative risk for developing cervical cancer as cigarette smoking[8, 9] and HPV infection have synergistic effects on development of CIN. Cigarette carcinogens have been shown to concentrate in cervical mucus, though mechanisms by with they contribute to carcinogenesis is unclear. According to the World Health Organization report on the global tobacco epidemic, approximately 1.6% of Kenyan women smoke cigarettes[10].

Early age at first coitus increases the risk of HPV infection due to the newly forming transformation zone. According to the Kenya AIDS Indicator Survey report of 2007; eleven percent of women and twenty one percent of men had their first sexual encounter before the age of fifteen [11]. This means that the age of development of invasive disease is lowered in this group to about 30 to 40 years, in keeping with the expected natural progression of the disease.

The higher the number of sexual partners a woman has, the higher the risk of acquiring HPV infection. This also includes the number of partners her sexual partner has. Having more than six lifetime sexual partners imposes a significant increase in the relative risk of cervical cancer [12]. In Kenya, in the age group of fifteen to forty five years, men have an average of 6.3 sexual partners, compared to 2.1 for women, according to the Kenya Demographic Health Survey[13]. This means

therefore that the woman's risk is still high as she is likely to have a partner with multiple sexual partners anyway.

Co-infection of HPV with other sexually transmitted agents such as herpes simplex virus 2 (HSV-2), *Chlamydia trachomatis* and *Neisseria gonorrhoeae* increases the risk for development of premalignant lesions by breaching the epithelium, allowing easy access by the virus into the cells. According to Schneider V. et al, iatrogenic immunosuppression in renal transplant patients conferred a higher risk of developing cervical cancer and condyloma acuminata [14].

Long-term combined oral contraceptive (COC) pill use may be a cofactor. The COC pill is a combination of low dose synthetic estrogens (30 to 35 micrograms) and progestins (0.5 to 0.75mg). There is a significant positive correlation between a low serum estradiol: progesterone ratio and shorter overall cervical cancer survival in premenopausal women (Hellberg, 2005). In vitro studies suggest that hormones might have a permissive effect for the growth of cervical cancer, by promoting cell proliferation and thus allowing cells to be vulnerable to mutations. In addition, estrogen acts as an anti-apoptotic agent permitting proliferation of cells infected with oncogenic HPV. In women who are positive for cervical HPV DNA and who use COCs, risks of cervical carcinoma increase by up to fourfold compared with women who are HPV-positive and have never used COCs [6]. Additionally, current COC pill users and women who are within nine years of use have a significantly higher risk of developing both squamous cell and adenocarcinoma of the cervix [12, 15] In Kenya, approximately 23.9% of women in reproductive age group are on COC pills [13]. Nevertheless, the WHO recommendation is that there is no need to limit the use of

hormonal contraceptives, despite the small increased risk of cervical cancer noted with use of combined oral contraceptives, as the benefits far outweigh the risk.

Low socioeconomic status and race has been demonstrated as a risk factor for cervical cancer. The incidence rate of cervical cancer among African Americans in the United States is higher than that among white women, with approximately 11 new cases per 100,000 blacks and 8 cases per 100,000 whites per year. The incidence is even higher in the Native American populations and Hispanics, with 14 new cases per 100,000 women each year [5].

The risk of cervical cancer increases with higher parity. Women with seven prior full-term pregnancies have an approximately fourfold risk, and those with one or two have a twofold risk compared with nulliparous women [6, 15]. In Kenya, the total fertility rate is at 4.6, with a range of 6.7 for the uneducated woman to about 3.7 for those with at least a secondary school education. The incidence of cervical intraepithelial neoplasia is four to five times higher among HIV-infected compared to HIV-negative women. The risk of cervical cancer among HIV-infected women is five- to eightfold the risk for HIV-negative women [7-11]. The CDC AIDS case definition includes cervical cancer in an HIV-infected person as criterion for AIDS, even in the absence of an opportunistic infection [13], while moderate and severe cervical intraepithelial neoplasia are conditions defining a stage of early symptomatic HIV infection (category B). CIN is common in HIV infected women because;

- Both HIV and human papilloma virus (HPV) are sexually transmitted, and
- HIV infected women are more likely to have persistent HPV infection, and

- Persistent infection with one or more oncogenic HPV subtypes is a major factor in the pathogenesis of premalignant and malignant cervical disease
- Progression to SIL and cancer is faster and occurs at younger ages among those HIV infected compared to those not infected

HIV has been shown to increase the risk of progression of cervical cancer especially in the twenty to thirty four year age group. While immune deficiency increases the risk of cervical cancer disease progression, the occurrence of cervical cancer is not dependent on immune compromise, unlike other AIDS-defining neoplasms such as Kaposi's sarcoma and non-Hodgkin's lymphoma. HIV appears to alter the natural history of HPV infection, causing a much more rapid progression to high grade and invasive lesions that are refractory to treatment, or which regress more slowly. This may be due to an HIV-related change in the molecular pathway leading to cervical cancer, possible due to an interaction between viral proteins, with HIV proteins enhancing the effectiveness of HPV proteins, and contributing to cell cycle disruption.

Among the HIV-infected patients, the disease is characterised by [16];

- Advanced stages at presentation
- Metastasis in unusual locations
- Poor response to treatment
- Higher recurrence rate
- Shorter interval to death

In Kenya, HIV prevalence among women 15-64 years is 8.4%, as per the KAIS report 2007. With such a huge disease burden, the risk of cervical cancer and its effects cannot be overly emphasized [11]. Primary prevention of cervical cancer is based on preventing HPV infection, and vaccination against HPV. This includes delaying of coitarche among the youth, limiting number of sexual partners, male circumcision, and consistent and correct use of condoms [17].

Two types of vaccines against HPV infection are currently available on the market: one acts against HPV genotypes 6, 11, 16 and 18 (quadrivalent vaccine, brand name Gardasil by Merck) and the other against genotypes 16 and 18 (bivalent vaccine, brand name Cervarix by GlaxoSmithkline) [17]. These are available in Kenya though the cost is still prohibitive to the general population. Awareness about the vaccine is still wanting. Some corporates have taken up the responsibility to ensure their female workforce is vaccinated. The Ministry of Health is currently carrying out a pilot project of vaccinating class four primary school pupils with the bivalent vaccine in Kenya, with the support of GAVI [18]. The programme will be coordinated by the division of vaccines and immunization under the school health programme, hence requires collaboration with Ministry of Education (23).

Condom use has been shown to offer partial protection against HPV transmission (as the virus can be transmitted through body surfaces not covered by the condom, e.g. perineum, vulva and perianal region), but it provides important benefits, including faster HPV clearance, increased regression of cervical lesions, protection from other STIs which are possible co-factors, and prevention of HIV(23).

In Kenya, health education efforts have been stepped up over the last few years with major campaigns like October cervical and breast cancer month. The efforts are marked, but coverage is still poor, especially with key target populations like the pre-coitarche age group to create awareness of preventable risks [19].

Secondary prevention of cervical cancer is by screening for precancerous lesions and early diagnosis followed by adequate treatment. The main techniques used are cytological screening of cervical cells, visual inspection of the cervix and DNA typing for HPV sub-types [19]. Cervical cytology by Papanicolaou test (Pap smear) is the basis for cervical cancer screening in the United States. The 2009 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Cervical Cytology Screening recommends that screening be initiated at age twenty one, regardless of age of onset of sexual intercourse [20]. Screening is recommended every two years until the age of thirty. Thereafter, screening frequency may be decreased to every three years following three consecutive negative Pap smear results for intraepithelial dysplasia and malignancy. Screening may be discontinued in low-risk women at age sixty five to seventy.

The National Cancer Institute recommends utilization of *The Bethesda System* for the reporting of cervical / endocervical / vaginal cytology (Pap smears) specimens to allow for consistent communication of findings between laboratories, clinicians and patient (see appendix 2) [4]. Mass screening with pap smears has led to a decline in the incidence of cervical carcinoma. In the United States, the incidence of has declined by 2.1% since 2004 in women below 50 years of age and by 3.1% for those over fifty years. Cervical cancer rates continue to rise in many developing countries,

Kenya inclusive, due to lack of proper screening. In Kenya, women undergo opportunistic screening [21], where screening is done independent of an organized or population-based programme, on women who are visiting health services for other reasons. Screening may be recommended by a provider during a consultation, or requested by a woman. Opportunistic screening tends to reach younger women at lower risk, who are attending antenatal, child health and family planning services. Organized screening is more cost-effective, making better use of available resources and ensuring that the greatest number of women will benefit. However, both organized and opportunistic screening can fail because of poor quality-control, low coverage of the population at risk, over-screening of low-risk populations, and high loss to follow-up [22].

Two visual methods for pre-malignant cervical lesions are available:

- Visual inspection with acetic acid (VIA)
- Visual inspection with Lugol's iodine (VILI)

Abnormalities are identified by inspection of the cervix without magnification, after application of dilute acetic acid (vinegar) (in VIA) or Lugol's iodine (in VILI). When vinegar is applied to abnormal cervical tissue, it temporarily turns white (acetowhite) allowing the provider to make an immediate assessment of a positive (abnormal) or negative test.

HPV DNA testing was first approved by FDA in 2000. It is used to identify women with high risk HPV subtypes. It is done in conjunction with Pap smear testing, or with VIA, never alone. It is recommended for women above twenty nine years of age who

are HIV negative, not immunocompromised, and have no history of in-utero diethylstilbestrol exposure.

The American Society for Colposcopy and Cervical Pathology (ASCCP) developed guidelines for the management of women with cervical cytologic abnormalities (see appendix 7 and 8). In Kenya, the Ministry of Health guidelines for cervical cancer screening address both the use of pap smear, VIA/VILI and HPV testing (see appendix 6). The use of VIA/VILI is strongly advocated for as it is cost-effective and allows for the single visit approach (SVA), which improves patient compliance to treatment and reduces chances of loss of follow-up. The guidelines advocate for opportunistic screening for all women as currently the country faces inadequate resources for an organized screening programme. They also recommend screening should ideally be done for women above thirty years if they are HIV negative, as most of the women below thirty will have regression of premalignant lesions hence it is not cost-effective to treat them all. For the women who are HIV positive, they are recommended for screening immediately they are diagnosed with HIV and are to be screened six-monthly for the first year and annually after that if they are found to be normal (23).

Kenyatta National Hospital adopts its guidelines from the ASCCP and the Ministry of health guidelines, but there are limitations to this e.g. HPV sub-typing is not available. Of note too is the absence of categorization of patients as per the age when it comes to pap smear screening. Currently there is no organized Pap smear screening protocol in KNH, though one is currently in the process of being developed. Patients attending various service points in the obstetric and

gynaecological department are referred for pap smears in the specialized reproductive health services clinic as per need. This includes women attending the family planning clinic, the emergency department and the gynecology clinic.

Patients on follow-up at the KNH comprehensive care center for HIV undergo screening by VIA/VILI as part of their care. Those found positive are referred for colposcopy with biopsy. Their care protocol is also not complete yet and for some patients, there is a lot of time wasted between initial diagnosis of a lesion and eventual treatment. The follow up of patients with premalignant cervical lesions in KNH is represented in an algorithm. (See appendix 6). Of note is that HPV subtyping is not available.

Patients with premalignant lesions will be subjected to various treatment options, including cryotherapy, loop electrosurgical excision procedure, or cold knife conization. Cryotherapy as a treatment option is not available in KNH. This service is offered in other facilities outside of KNH and patients who are ineligible for cryotherapy in these facilities are then referred to KNH. Treatment of premalignant cervical lesions by loop electro-surgical excision procedure was officially started in Kenyatta National Hospital in 2007 in the gynecology department. To date, about 500 patients have undergone colposcopy with biopsy and LEEP.

A lot has been done to improve the function of this essential service, with specialist training to enhance the skills of the service providers. A lot of effort has been put into record-keeping to enhance completeness of data, hence the development of the colposcopy and LEEP/cryotherapy form which is filled for every patient. The

gynaecological oncology team, responsible for patient care at the unit is also responsible for patients who require further management, where lesions are beyond premalignant stage, maintaining smooth patient transition to inpatient care and beyond.

Despite the advances made in the facility in treatment of premalignant cervical lesions, protocols dictating practice in the unit are still being developed for the institution. Current practice is guided by the American Society for Colposcopy and Cervical Pathology guidelines and the Ministry of Health cervical cancer screening guidelines, which may not be fully implementable in the KNH set-up. Tertiary prevention of cervical cancer involves the diagnosis and treatment of confirmed cases of cancer. For patients with overt cancer, diagnosis and staging is done by examination under anesthesia, with biopsy sampling for histological examination. Treatment is through surgery, radiotherapy and chemotherapy. Palliative care is provided to patients when the disease has already reached an incurable stage, in cooperation with the Nairobi Hospice team [17]. In invasive cervical cancer, treatment options available include hysterectomy (simple, Wertheims), radiotherapy (external beam radiation and brachytherapy) and chemotherapy. These treatments may be used alone or in combination.

Currently, KNH is the only public facility in Kenya offering the full range of services for the management of cervical cancer. Other Key facilities offering surgery and chemotherapy include Moi Teaching and Referral Hospital, Jaramogi Oginga Odinga Referral Hospital and Coast Provincial General Hospital.

STUDY JUSTIFICATION

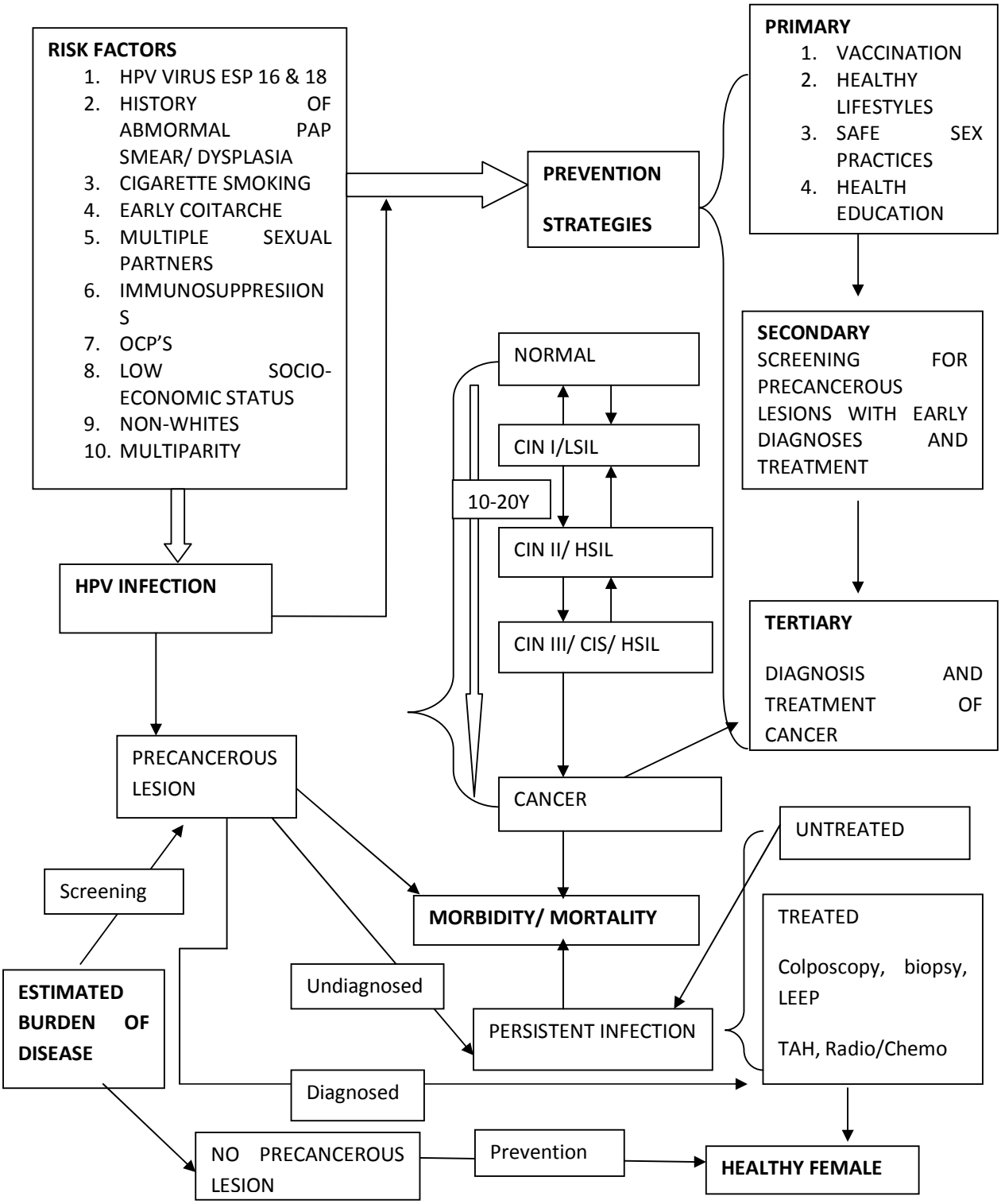
The Ministry of Health has put a lot of effort in recent years through the Divisions of Reproductive health and Public health to address primary and secondary prevention of cervical cancer. The health systems in place that facilitate cervical cancer prevention are not robust due to scarcity of resources. The numbers of recipient referral facilities in place are inadequate for appropriate patient coverage, are inaccessible and unaffordable by the majority of the poor population. Health information services are still weak, hence likelihood of loss to follow-up and poor data capture. Screening in Kenya is opportunistic hence uptake is poor and this contributes to the disease burden. Cervical cancer diagnosis is expensive to both the health system and the patient. Similarly, treatment options are very expensive with costly delays that adversely affect treatment outcomes hence markedly decreasing cure rates.

The Ministry of Health recommends screening of women to start at 30 years for HIV negative women and at point of diagnosis for the HIV positive to avoid over-diagnosis and over-treating which is deemed not cost-effective. It is worrying to note that according to the KAIS 2012 preliminary report, only 47% of HIV positive adults in Kenya, aged between 15-64 years, were aware of their status. Anecdotal evidence in our setting shows that women as young as 25 years get diagnosed with advanced cancer of the cervix. This underscores the importance stringent cervical screening in HIV positive women. It was therefore necessary to examine patient characteristics and outcomes in KNH colposcopy and LEEP clinic. Findings will inform clinical practice and enhance prioritization of available resources for successful secondary prevention strategies.

CONCEPTUAL FRAMEWORK

Cervical cancer is the second commonest cancer in women. Various risk factors have been identified, HPV being the most prominent. Prevention strategies ensure that women do not acquire HPV, and if they do, the precancerous lesions if any are identified early and treated accordingly. If cancer is confirmed, treatment is instituted to improve quality of life. Figure 3, demonstrates the conceptual framework.

Figure 3: Conceptual framework



RESEARCH QUESTION

What are the colposcopy biopsy ± LEEP cervical histologic findings and six month treatment outcomes of patients with abnormal Pap smear cervical cytology attending Kenyatta National Hospital, 2008-2012?

BROAD OBJECTIVE

To determine the colposcopy biopsy ± LEEP cervical histologic findings and six month treatment outcomes of patients with abnormal Pap smear cervical cytology attending Kenyatta National Hospital, 2008-2012

SPECIFIC OBJECTIVES

Among women with abnormal Pap smear cervical cytology being managed in Kenyatta National Hospital, 2008-2012 to:

1. Describe the socio-demographic and clinical characteristics of patients undergoing colposcopy biopsy ± LEEP
2. Determine the correlation of Pap smear cytology and cervical histology findings
3. Correlation of cervical histology with HIV status, parity, age group and history of oral contraceptive use
4. Determine the six month follow up Pap smear cytology following treatment of cervical intraepithelial neoplasia

METHODOLOGY

Study design

This was retrospective descriptive cohort study using routinely collected patient data. Women with abnormal Pap smear cervical cytology attending Kenyatta National Hospital (KNH), 2008-2012, were described for their socio-demographic and clinical characteristics. Pap smear cytology was correlated with cervical histology and clinical characteristics. Cervical histology findings were for either colposcopy biopsy or LEEP specimen, this is because not all patients had LEEP histology, in cases where both were available the worst diagnosis was recorded. Six month follow up Pap smear cytology was also determined.

Study site and setting

The study was conducted in KNH, Clinic 66, which is a specialist oncology clinic for the Reproductive Health Department, and at the Health Information Department. The clinic serves patients requiring routine pap smears, and patients referred with abnormal pap smears or positive VIA/VILI tests from other facilities in the country. Once a patient is diagnosed to have an abnormal pap smear, the care given to that patient is determined by treatment guidelines described above. This is where patients undergo colposcopy, biopsy and LEEP procedures. Treatment protocols for women with a cytological diagnosis of ≥ high grade squamous intraepithelial lesions (HSIL) or recurrent low grade intraepithelial lesion (LSIL) are triaged for colposcopy and biopsy. Those with a confirmation of CIN 2/3 are treated with LEEP and reviewed with histology results four weeks later.

Study population

Medical records of patients managed in KNH clinic 66 with abnormal pap smears. Those who were referred for colposcopy, in the period 2008 to 2012 were included and analyzed for the study.

Selection criteria

Clinical records were included or excluded from analysis based on the following criteria:

Inclusion Criteria

- Completeness of colposcopy records with a filed histology report

Exclusion criteria

- Those whom the procedure (colposcopy /LEEP) was abandoned

Sample size

A sample size of 197 participants was sufficient to determine the colposcopy biopsy ± LEEP cervical histology findings and six month treatment outcomes of patients with abnormal Pap smear cervical cytology attending Kenyatta National Hospital. Since the proportion of the colposcopic and histologic outcomes of patients undergoing colposcopy and LEEP procedures has not been documented, an estimated proportion of 50% was chosen so as to provide the highest possible sample size.

From the KNH, clinic 66 colposcopy clinic records, it is estimated that 400 patients (study) were referred for colposcopy examinations over the study period (2008-2012).

Since the sample size was over 5% of the study population (i.e. total number of patients referred to Clinic 66 for colposcopy) *the formula for finite population correction* was applied as shown below [23];

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

Where:

n^1 = Sample size

N= Study population. This is the total number of patients referred to Clinic 66 for colposcopy / LEEP over the entire study period=400

Z = Z statistic for a level of confidence which was put at 95% which gives a value of 1.96

P = expected proportion of the colposcopic and histologic outcomes and of patients undergoing colposcopy and LEEP procedures. Since there was no published data on PICT uptake, a proportion of 50% was selected to estimate the highest sample size.

d = Precision with a 95% confidence interval which gives a margin of error of ±0.05.

$$n^1 = \frac{400 \times 1.96^2 \times 0.5\ (1-0.5)}{(0.05)^2\ (400-1) + 1.96^2\ 0.5\ (1-0.5)}$$

$$n^1 = \frac{400 \times 3.8416 \times 0.25}{0.0025 \times 399 + 3.8416 \times 0.25}$$

$$n^1 = \frac{384.16}{0.9975 + 0.9604}$$

$n^1 = 196.2$

$n^1 =$ 197 patient records

Sampling Procedure

Data was extracted from all the patient files that met the eligibility criteria outlined below in the period between 2008 and 2012. All file numbers of patients having undergone colposcopy/biopsy and LEEP in the study period were extracted from the procedure register in the colposcopy clinic. These numbers were used to extract the actual files in the Kenyatta National Hospital health information department. All the files that were extracted were reviewed to ascertain their completeness of information. Files selected for sampling were sorted according to each year studied (2008, 2009, 2010, 2011 and 2012). This was done as follows:

1. Percentage of total sample size (n=197) of the total population studied (N=502) of the medical records, was calculated (39%)
2. This percentage was applied to each year of study, to determine the number of files (n) out of the total number of files of patients who underwent colposcopy/biopsy and LEEP as per that year (N)
3. Having established the final number of files per year to be studied, the files were sorted according to the year and from each pile, simple random sampling was done to select the files to be studied. The file numbers of each pile were written down on papers and then these papers rolled up to conceal the numbers and put in basket. The papers were then drawn randomly until the number of required files was reached. The file numbers borne in the drawn papers were selected from the pile for the study.

A data abstraction form (see appendix) was used to collect data from all the files with complete histology information in the study period. Patient registration numbers were collected for purposes of retrieving their files from health

information department and tracking the files during data abstraction but were eliminated at the data entry and analysis stage.

Research assistants, who are qualified clinical officers, were trained on the data collection methods outlined above and assisted the principle supervisor in data collection.

Data Management

Data collected through the data abstraction form was entered into the central database created using *Statistical Package for Social Scientists (SPSS)*. The data was then be analysed using the *Statistical Package for Social Scientists (SPSS) version 17*.These databases were resident in a personal computer under password protection and backed up on an external hard drive and CD. The hard drive and CD were under the safe custody of the principal investigator at all times. Each data record entered into the database was assigned a unique identification number so as to protect the privacy of the patients.

The data abstraction forms were filed and stored in a safe cabinet where verification of results could be done whenever necessary to ensure quality of data was maintained. At the conclusion of the study, all raw data was destroyed permanently by incineration.

Quality Assurance

Data was extracted from files that have complete histological diagnosis information for this study.

Data Analysis Plan

Descriptive analysis

Demographic and relevant gynecological history

The patients'; age, marital status, parity, previous pap smear, HIV status and history of contraceptive use were summarized and presented in forms of means, medians, ranges and standard deviation.

Summary of colposcopy/LEEP outcomes

The summary of histologic diagnosis following colposcopy/LEEP outcomes in the period 2008-2012 was illustrated using tables. The dependent variables were the histologic outcomes (Normal, CIN1, CIN2, CIN3, CIS, Invasive cancer) while the independent variables are the patient characteristics (age, baseline pap smear report, HIV status and COC use)

Inferential statistics

Outcome of Colposcopy / LEEP

The differences in the means of continuous exposure variables by the outcome of colposcopy/LEEP was determined using the one way ANOVA test.

Ethical Considerations

Confidentiality: In order to safeguard the confidentiality of patient information, the investigators ensured that no identifiers were included in the dataset during the data collection e.g. names, patient numbers etc. No persons were allowed access to patient records apart from the principle investigator and the research assistants. All the records were locked in a safe cabinet and were only accessed by authorized persons.

Risks: There was no anticipated physical, social or economic harm to the patients whose files were used, as a result of this research.

Social justice: Findings from this study will be shared with the health community and disseminated widely through peer reviewed journals.

Ethical approval: This was sought from Ethical and Research Committee (ERC) at Kenyatta National Hospital.

Administrative clearance to conduct this study was sought from the Kenyatta National Hospital, Health Information department; and University of Nairobi, College of Health Sciences, Department of Obstetrics and Gynaecology.

Possible Bias

Being a retrospective study, some data was missing from patient files and tracing of this information was impossible.

RESULTS

A total of 197 eligible medical records of women who attended the colposcopy clinic in KNH between 2008 and 2012 were analyzed. The mean age (SD) was 38.5 (9.6) years, with a range of 20 to 80 years. Results will be presented according to specific objectives.

Objective 1 results: socio-demographic and clinical characteristics of patients with abnormal cervical cytology undergoing colposcopy with biopsy ± LEEP

Table 1: Socio-demographic characteristics of patients with abnormal Pap smear cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH (2008-2012)

Patient characteristics	**N=197 n(%)**
Marital status:	
Married	144 (73)
Single	43 (22)
Separated	2 (1)
Widowed	8(4)
Education level:	
None	5(3)
Primary	67(34)
Secondary	97(49)
College	22(11)
University	6(3)
Residence:	
Rural	29(15)
Urban	146(75)
Informal settlement	21 (10)
Occupation:	
Student	2 (1)
Employed	58 (29)
Self employed	70(36)
Unemployed	67(34)

Majority (73%) of the participants were married, about half (45%) had up to secondary level education, most (75%) resided in the urban area and only 34% were unemployed (table1).

Table 2: Clinical characteristics of women with abnormal Pap smear cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH (2008-2012)

Clinical characteristic	**N=197** **n (%)**
Previous pap smear:	
Normal	5(3)
AGUS	4 (2)
ASCUS	7 (4)
LSIL	31(16)
HSIL	150 (76)
***Colposcopy clinical diagnosis**:*	
CIN 1	22 (11)
CIN 2	10(5)
CIN 3	18 (9)
CIS	5 (3)
Invasive cancer	3 (2)
Not documented	139 (71)
****Cervical Histology:***	
Normal	8(4)
CIN 1	35 (18)
CIN 2	54 (27)
CIN 3	47 (24)
CIS	40 (20)
Invasive cancer	13 (7)
*****HIV status:***	
Positive	72 (37)
Negative	20 (10)
Unknown	105 (53)
******Combined Contraceptives:***	
Yes	16 (8)
No	79(40)
Not documented	102 (52)

*Histology findings were for either colposcopy or LEEP specimen. This is because not all patients had a LEEP histology, in cases where both were available the worst diagnosis was recorded

**HIV status last 3 months

*** Past history of combined contraceptive use

Table 2, shows clinical characteristics of patients with abnormal Pap smear cytology who underwent, colposcopy biopsy ± LEEP. Of the participants, 150(76%) had HSIL

on Pap smear cytology and 139 (71%) had colposcopy clinical diagnosis not documented. A majority of patients had ≥ CIN2 diagnosis on cervical histology: 54(27%) were CIN 2, 47(24%) were CIN 3, 40(20%) were CIS and 13(7%) were CIS. About half (53%) had an unknown HIV status, 72 (37%) were HIV positive and 20 (10%) were HIV negative. Half (52%) had their contraceptive status not documented, of those documented 16 (8%) had history of oral combined contraceptive use while 79 (40%) had no history of oral contraceptive use.

Objective 2 results: correlation of Pap smear cytology and cervical histology findings

Table 3: Cross tabulation of Pap smear cytology results and cervical histological findings of patients with abnormal cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH (2008-2012)

Pap smear Cytology	***Colposcopy guided histology or LEEP histology N=197**						
	Normal n	**CIN 1 n**	**CIN 2 n**	**CIN 3 n**	**CIS n**	**Invasive n**	**Total number**
Normal n(%)	1(20)	0(0)	4(80)	0(0)	0(0)	0(0)	5
AGUS n(%)	1 (25)	0(0)	0(0)	1 (25)	2 (50)	0(0)	4
ASCUS n(%)	1(14)	4 (57)	1 (14)	1(14)	0	0	7
LSIL n(%)	1(3)	12 (39)	11(36)	2(6)	3(10)	2(6)	31
HSIL n(%)	4 (3)	19 (13)	38(25)	42 (28)	35(23)	11 (7)	150
Total n(%)	8(4)	35 (18)	54(27)	46(23)	40(20)	13(7)	197 (100)

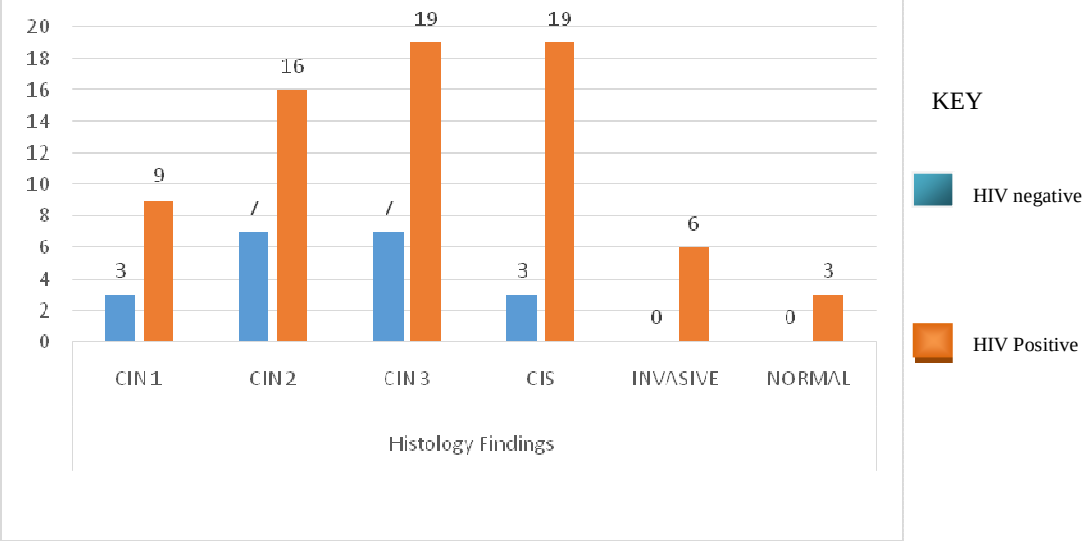
*Histology findings were for either colposcopy or LEEP specimen. This is because not all patients had a LEEP histology, in cases where both were available the worst diagnosis was recorded

Table 3, shows cross tabulation of Pap smear cytology and cervical histology results. Of the total 197 patients who had Pap smear cytology: 54 (27%), 46(23%), 40 (20%) and 13 (7%) had CIN 2, CIN3, CIS and invasive cancer respectively.

Four of the 5 patients who had normal cytology had CIN 2 on cytology. Of the 4 patients who had AGUS on cytology, 1 and 2 of them had CIN 3 and CIS respectively on histology. Of the 7 who had ASCUS on cytology, only 1 had CIN 2 and another 1 had CIN 3. A total of 31 patients had LSIL on cytology, of these more than half had an histology diagnosis of $\geq$ CIN 2: CIN 2 was recorded in 11, CIN 3 recorded in 2, CIS recorded in 3 and invasive cancer recorded in 2. A total of 150 patients had HSIL on cytology, of these: CIN 2 was recorded in 38(25%), CIN 3 recorded in 42(28%), CIS recorded in 35 (23%) and invasive cancer recorded in 11(7%).

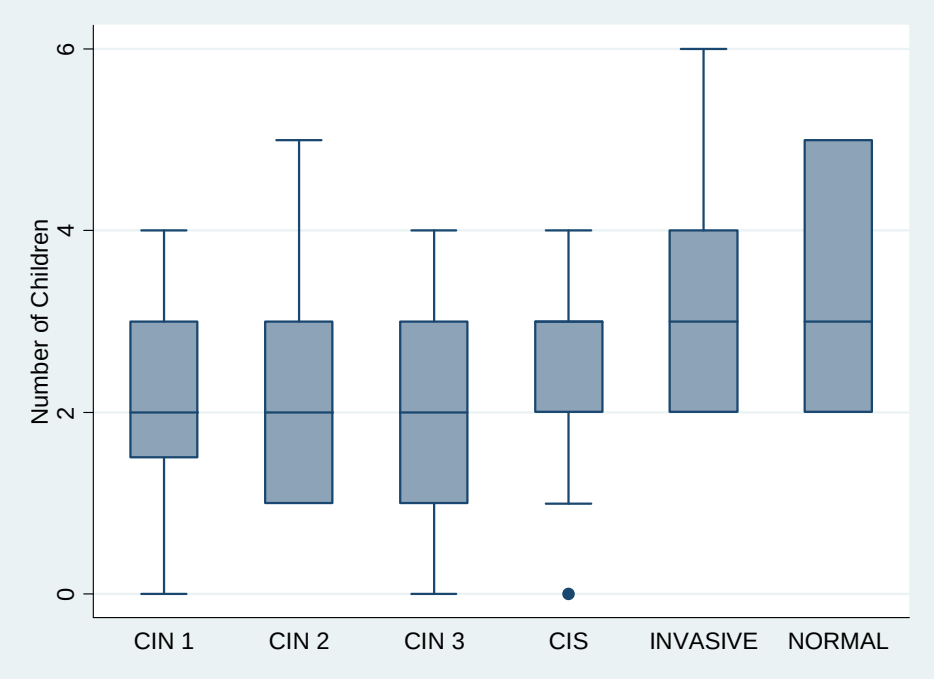
Objective 3 results: correlation of cervical histology with HIV status, parity, age group and history of oral contraceptive use

Figure 1: Correlation of cervical histology findings with HIV status (n=92), of women with abnormal Pap smear cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH (2008-2012)



Only 92 records had the HIV status recorded. Figure 1, shows correlation of cervical histology results with HIV status. Across all histological findings, those with a positive HIV status have higher proportions compared with those who are HIV negative. This difference was found to be statistically insignificant, though it demonstrates a trend (p= 0.3).

Figure 2: Correlation of cervical histology findings with parity of women with abnormal cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH in 2008-2012



Although the women who had normal histological findings had a slightly higher parity, there was no significant difference in parity and the histological findings (p=0.86) as illustrated in figure 2.

Figure 3: Correlation of cervical histology findings with age-groups, of patients with abnormal cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH in 2008-2012

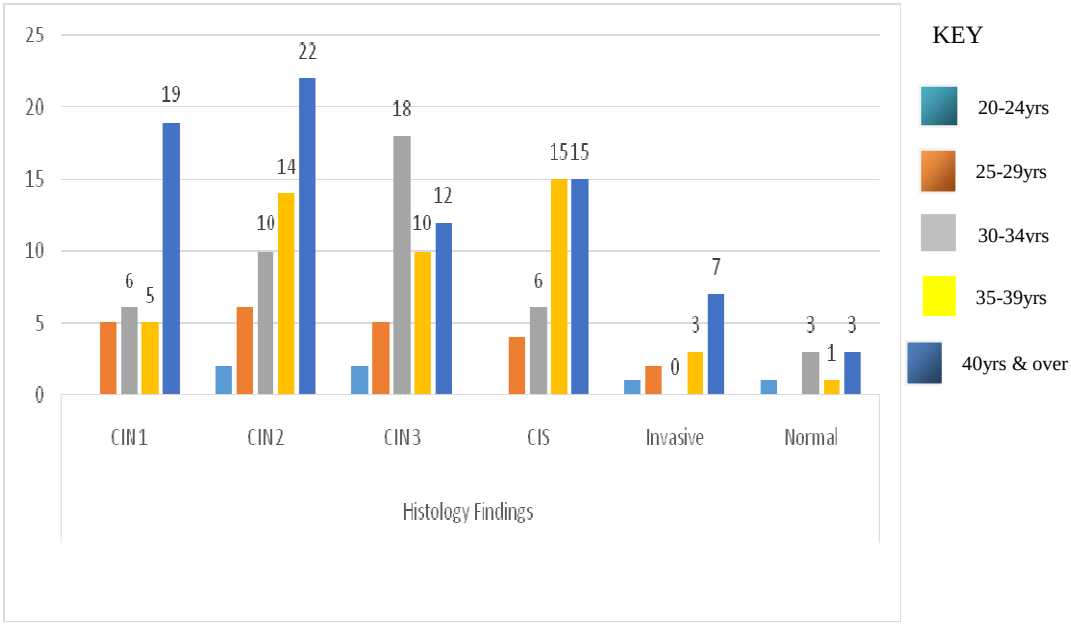
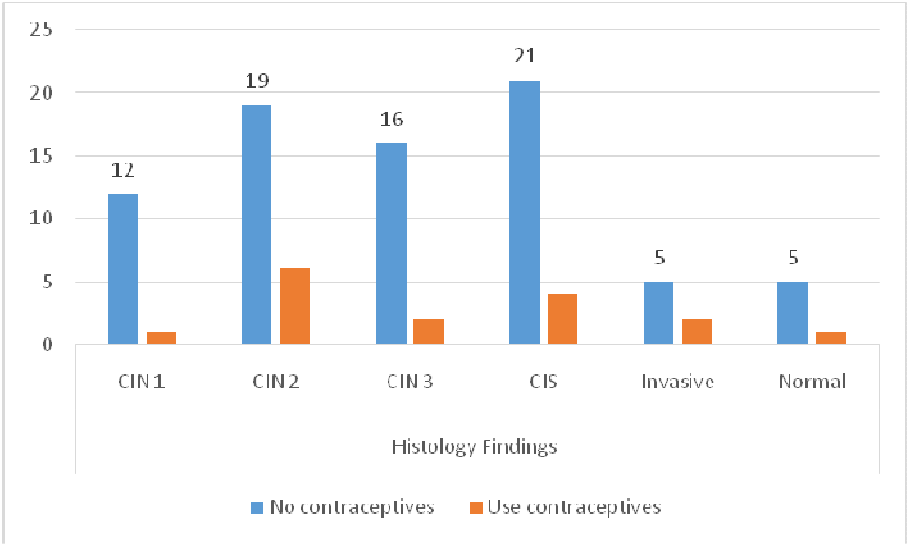


Figure 3, shows correlation of histological findings with age group. Women aged 40 years and above had a higher number of pathological findings compared to the other age groups. This was followed by the age groups 35 to 39 years and 30 to 34 years (p=0.158).

Figure 4: Correlation of cervical histology findings with history of oral combined contraceptive use (n=95) of patients with abnormal cervical cytology, who underwent colposcopy with biopsy ± LEEP in KNH in 2008-2012



Out of the 95 records on women who use contraceptives documented, only 16 had history of combined oral contraceptive use. Figure 4, shows correlation with cervical histology findings. Across all histological findings those with no history of oral combined contraceptive pill use had higher percentages (p=0.428). This correlation could not be further subjected to a logistic regression because, of the few numbers of those with history of oral contraceptive use, hence remains inconclusive.

Objective 4: The six-month follow up Pap smear cytology following treatment of cervical intraepithelial neoplasia

Table 4: six month follow up Pap smear cytology following treatment of cervical intraepithelial neoplasia, of patients with abnormal cervical cytology, who underwent colposcopy with biopsy and LEEP in KNH in 2008-2012

Six month post-treatment outcome Pap smear cytology	***N=197 n(%)***
Normal	62(31)
AGUS	4 (2)
ASCUS	3 (2)
LSIL	3(2)
HSIL	1(<1)
Lost to-follow-up	124 (63)

Table 4, show the six month follow up Pap smear cytology post cervical intra-epithelial lesion treatment. There is a high lost to-follow-up rate of 63% (124/197), of these women who were lost to-to-follow up most 73% (90/124) were noted to be residing in urban areas. Of the available six month Pap smear cytology follow up of the total: 62(31%) were normal, 4 were AGUS, 3 were ASCUS and 3 were LSIL. Of the available 73 follow up results 85% (62/73) had a normal Pap smear cytology. The patient who had HSIL was also HIV positive

DISCUSSION

This was a predominantly married, urban population with only 34% of them unemployed. Majority of the participants who underwent colposcopy biopsy ± LEEP had HSIL on Pap smear cytology. Nearly all the participants had an abnormal cervical histology with 78% (154/197) of them having ≥ CIN 2. Of these 54 (27%), 46(23%), 40 (20%) and 13 (7%) had CIN 2, CIN3, CIS and invasive cancer respectively. Of note, is that 20% had carcinoma in situ while 7% had invasive cervical cancer. Despite HIV infection being a known risk factor of progression of CIN to invasive cancer, in 53% of records the HIV status was not recorded. Patients who had a positive HIV status and high parity and age more than 35 years showed an insignificant trend of having a higher likelihood of cervical histology outcomes of ≥ CIN 2. Correlation between combined hormonal contraceptive pill and cervical histology was inconclusive due to a high percentage of undocumented data on this variable. There was a high (63%) loss to-follow-up for follow up Pap smear at six months after CIN treatment; of the available cytology results 85% of them were normal.

The study population was predominantly married, urban population and employed. This finding is plausible because KNH is situated in the capital city Nairobi. The socio demographic characteristics were consistent to those from similar settings [24, 25]

Majority of the participants who underwent colposcopy biopsy ± LEEP had HSIL on Pap smear cytology. This is not a surprising finding; the entry criteria for colposcopy is HSIL on Pap smear. This criterion is in keeping with the KNH and American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines [24, 26].

This qualifies that KNH, as an institution, does adhere to local and international guidelines. Abnormal cervical histology of ≥ CIN 2 was recorded in 78% of cases; this is the cut off point for treatment of CIN with LEEP [27]. This finding supports a well-known finding that cervical cancer screening and treatment of CIN reduces the incidence of invasive cancer of the cervix [28] [27, 29]. Treatment of CIN by LEEP as is done in KNH, curtails progression to invasive cancer by removing the transformation zone [24, 29, 30]. Of note though, is the 20% and 7% cervical histology that was carcinoma in situ and invasive cervical cancer respectively. This finding is alarming as it points to a weakness in the cervical cancer screening program and also poor health seeking behavior of the populace. Cervical cancer screening in Kenya remains opportunistic, and women rarely go for screening or appear late for screening.

HIV infection status was the most poorly documented. This is despite it being a known risk factor of progression of CIN to invasive cervical cancer [8, 25, 31-33]. Similar lack of complete documentation was identified with contraceptive use. This finding is a red flag for the glaring poor documentation of clinical findings. This becomes a huge concern especially, when findings that affect management such as HIV status are missing.

In keeping with findings from other studies, this study found that, patients who had a positive HIV status, high parity and age more than 35 years showed an insignificant trend of higher likelihood of having a cervical histology outcome of ≥ CIN 2 [8, 25, 31] Based on this, there is a need to have stringent screening and management of CIN among these patient groups and more analytical research on these is warranted.

There was a high (63%) loss to-follow-up based on follow up Pap smear at six months after CIN treatment. This finding is disturbing, especially since most of the patients in this study had cervical histology of ≥CIN 2. Despite the high lost to-follow-up, it is reassuring that of the available follow up Pap smear cytology at six months results show that 85% of them were normal. Follow up Pap smear cytology at six months in a study by Ferris et al found a 40% normal rate, which was lower than what was found in this study [29]. Even as interventions to strengthen documentation should be considered, it is still justified to treat CIN in this setting.

The results of this study should be interpreted with the following limitation in context. Missing data for some variables due the retrospective nature of the study, made further analysis on some variables impossible. Despite this limitation, this study is valuable since its pragmatic, meaning that the findings mirror the reality in the routine setting. In addition, the findings will be used to strengthen existing guidelines on screening and treatment of CIN.

CONCLUSIONS

Women undergoing colposcopy ± LEEP in KNH have a high rate of ≥CIN2 on cervical histology. Follow up Pap smear cytology after six months of CIN treatment with LEEP is normal for 85% of the participants. Treatment of CIN is justified and should be strengthened in order to reduce the incidence of invasive cervical cancer in Kenya. Poor documentation was identified as a glaring weakness.

RECOMMENDATIONS

1. Scale up treatment of CIN with LEEP to other tertiary health facilities with ability to offer colposcopy, to enable more Kenyan women access the service outside of KNH
2. Improve documentation of cervical cancer screening and CIN treatment data for quality improvement. Complete data is important for clinical audits.
3. Strengthening HIV screening during cervical cancer screening and CIN treatment
4. There is need for interventions to reduce the loss to-follow-up rate

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APPENDIX 2: RESEARCH TIMELINES

	Aug 2013	Sept 2013	Oct 2013	Nov 2013	Dec 2013	Jan 2014	Feb 2014	Mar 2014	Apr 2014	May 2014	Jun 2014	Jul 2014	Aug 2014	Sep 2014	Oct 2014	Nov 2014
Refining of research question and objectives																
Proposal writing																
Ethical committee submission and review																
Data collection																
Data analysis																
Writing dissertation																
Departmental presentation																

APPENDIX 3: PROJECT BUDGET

ITEM	QUANTITY	UNIT PRICE	TOTAL
TRANSPORT	5 X 10	200	10000
STATIONERY/PRINTING			
Questionnaires	200	5	1000
Pens	12	15	180
Box files (office point)	6	250	1500
Note books(50 leaves)	6	100	600
Petty cash vouchers	1	230	230
Final manuscripts	7	1000	7000
Poster presentations	1	5000	5000
RESEARCH ASSISTANTS	5	20,000	100,000
COMMUNICATION			
Airtime	5 x 6	1000	30000
Internet data bundles	5 x 6	1000	30000
DATA ANALYSIS			30000
TOTAL			**Ksh.215510**

APPENDIX 4: DATA ABSTRACTION FORM

Colposcopic and Histological Outcomes of Patients with Abnormal Cervical Cytology in Kenyatta National Hospital from 2008 to 2012 **Data Abstraction Form** **File number: ……..** **Date:** dd/mm/yyyy	
Year patient underwent procedure	
Age (yrs) Age of coitarche (yrs) Parity Number of previous sexual partners	
Marital status	1. Single 2. Married 3. Separated 4. Widowed
Education level	1. None 2. Primary 3. Secondary 4. College 5. University
Residence	1. Urban 2. Rural 3. Slum
Occupation	1. Student 2. Housewife 3. Employed 4. Self employed 5. Unemployed

Previous abnormal pap smear	1. ASCUS ☐ 2. AGUS ☐ 3. LSIL ☐ 4. HSIL ☐
Previous VIA/VILI	1. Normal ☐ 2. Positive ☐ 3. Suspicious for cancer ☐
Colposcopic diagnosis	1. CIN1 ☐ 2. CIN2 ☐ 3. CIN3 ☐ 4. CIS ☐ 5. Invasive ☐
HIV status in the last 3 months	1. Positive ☐ 2. Negative ☐ 3. Unknown ☐
Histology	1. Normal ☐ 2. CIN1 ☐ 3. CIN2 ☐ 4. CIN3 ☐ 5. CIS ☐ 6. Invasive ☐
Combined Contraceptive use	1. Yes ☐ 2. No ☐
Post-LEEP pap smear findings	1. Normal ☐ 2. ASCUS ☐ 3. AGUS ☐ 4. HSIL ☐ 5. LSIL ☐

APPENDIX 5: BETHESDA CLASSIFICATION

Table 50–1. The Bethesda System 2001.

Specimen Type

Indicate conventional smear (Pap smear) vs. liquid-based vs. other

Specimen Adequacy

Satisfactory for evaluation (*describe presence or absence of endocervical transformation zone component and any other quality indicators, eg, partially obscuring blood, inflammation, etc*)

Unsatisfactory for evaluation. . . (*specify reason*)

Specimen rejected/not processed (*specify reason*)

Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

General Categorization (optional)

Negative for intraepithelial lesion or malignancy

Epithelial cell abnormality: See Interpretation/Result (*specify squamous or glandular as appropriate*)

Other: See Interpretation/Result (*eg, endometrial cells in a woman 40 years of age*)

Automated Review

If case examined by automated device, specify device and result

Ancillary Testing

Provide a brief description of the test methods and report the result so that it is easily understood by the clinician

Interpretation/Result

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY (*when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether or not there are organisms or other non-neoplastic findings*)

ORGANISMS:

Trichomonas vaginalis

Fungal organisms morphologically consistent with *Candida* spp.

Shift in flora suggestive of bacterial vaginosis

Bacteria morphologically consistent with *Actinomyces* spp.

Cellular changes consistent with herpes simplex virus

OTHER NON-NEOPLASTIC FINDINGS (*Optional to report; list not inclusive*):

Reactive cellular changes associated with inflammation (includes typical repair)

Radiation

Intrauterine contraceptive device (IUD)

Glandular cells status posthysterectomy

Atrophy

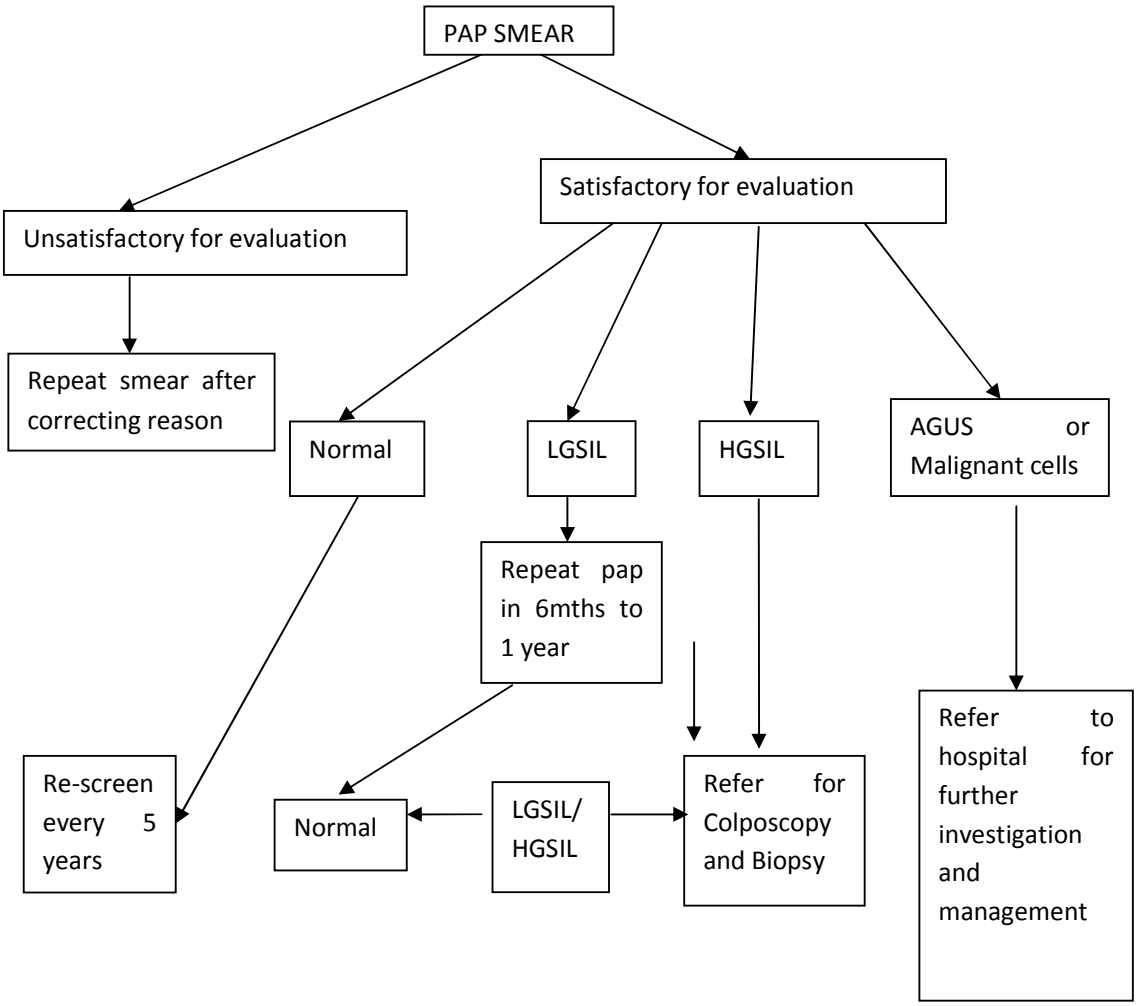
OTHER

Endometrial cells (in a woman 40 years of age) (*Specify if negative for squamous intraepithelial lesion*)

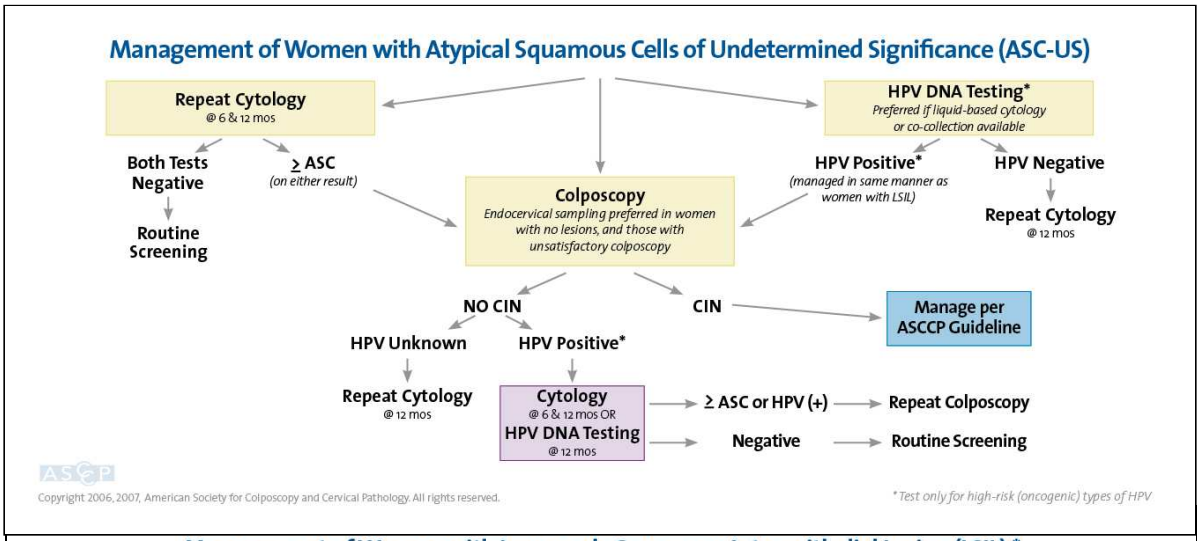
EPITHELIAL CELL ABNORMALITIES
SQUAMOUS CELL
Atypical squamous cells of undetermined significance (ASC-US) cannot exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/CIN
High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, CIN 2 and CIN 3/CIS
Squamous cell carcinoma
GLANDULAR CELL
Atypical (AGC)
endocervical cells
endometrial cells
glandular cells not otherwise specified (NOS)
Atypical, favor neoplastic
endocervical cells
glandular cells NOS
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma
endocervical
endometrial
extrauterine
not otherwise specified (NOS)
OTHER MALIGNANT NEOPLASMS: *(specify)*
Educational Notes and Suggestions (*optional*)
Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included)

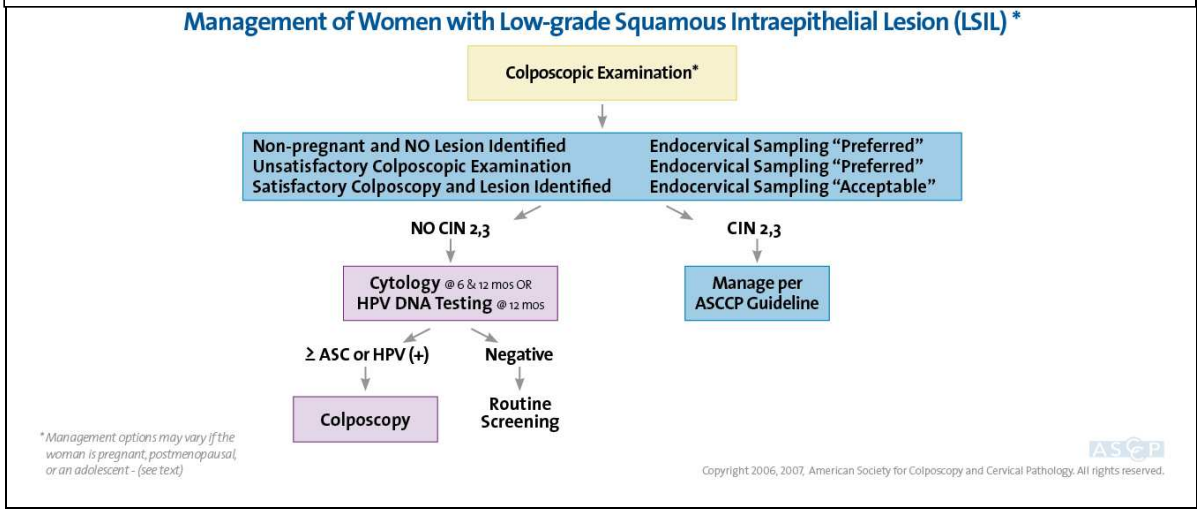
Adopted from Current Diagnosis and Treatments in Obstetrics and Gynaecology (2007)

Appendix 6: National guidelines for prevention and management of cervical, breast and prostrate cancer: guidelines for management of abnormal cytology results (feb 2012)

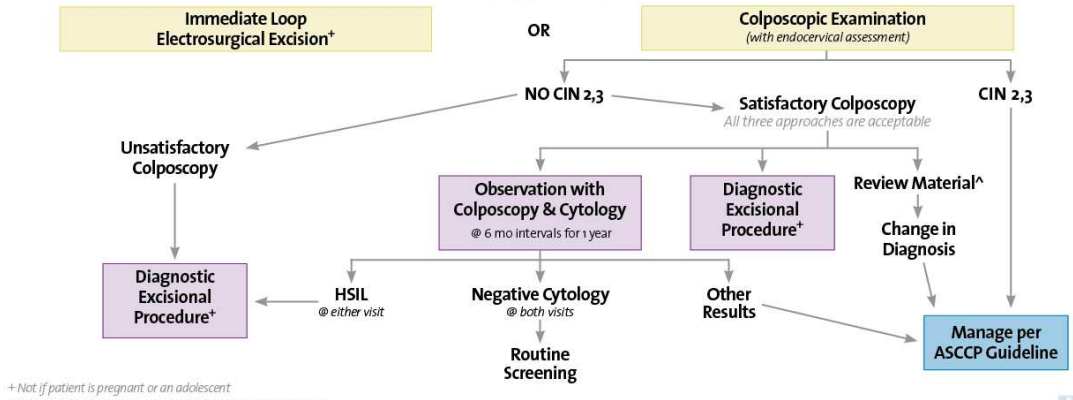


Appendix 7: ASCCP guidelines for management of abnormal Pap smear



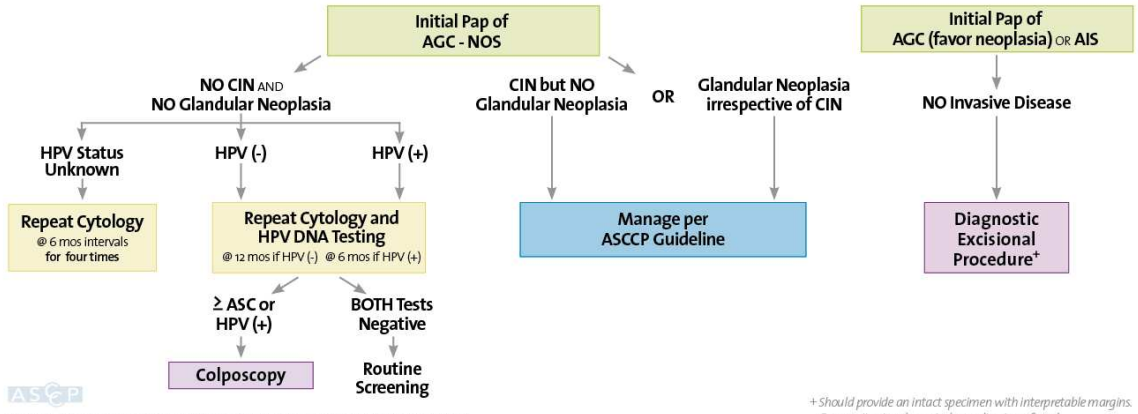


Management of Women with High-grade Squamous Intraepithelial Lesion (HSIL) *



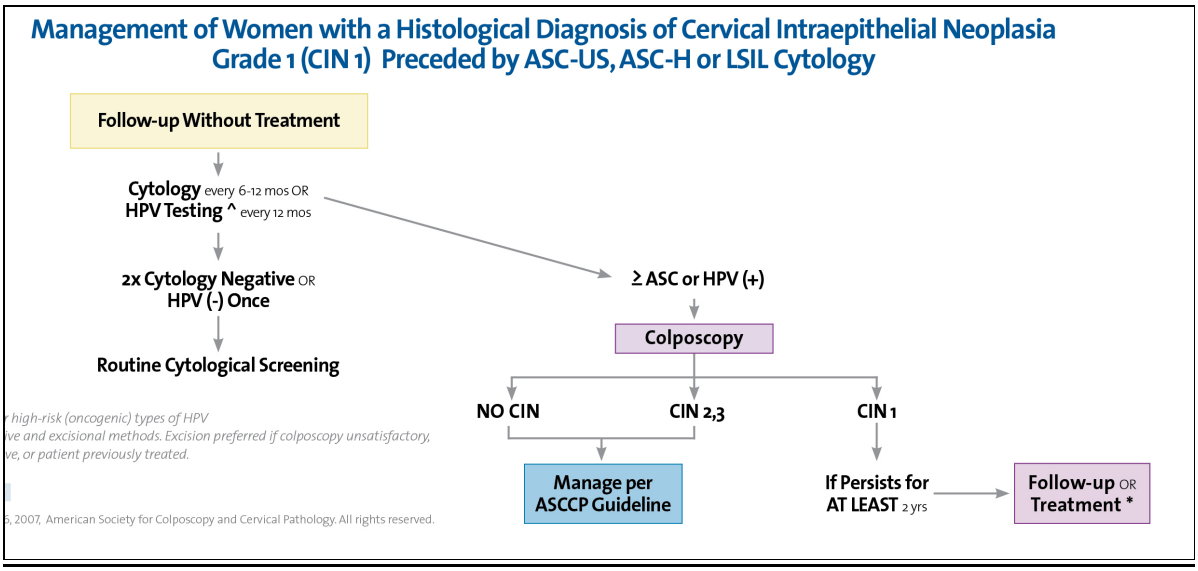
+ Not if patient is pregnant or an adolescent
^ Includes referral cytology, colposcopic findings, and all biopsies
* Management options may vary if the woman is pregnant, postmenopausal, or an adolescent

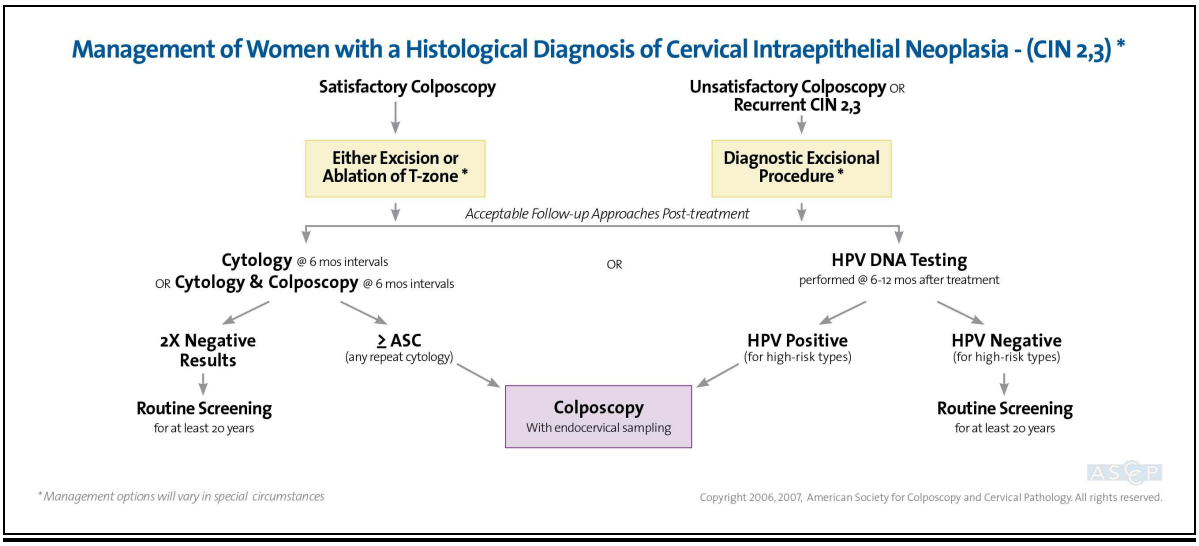
Subsequent Management of Women with Atypical Glandular Cells (AGC)



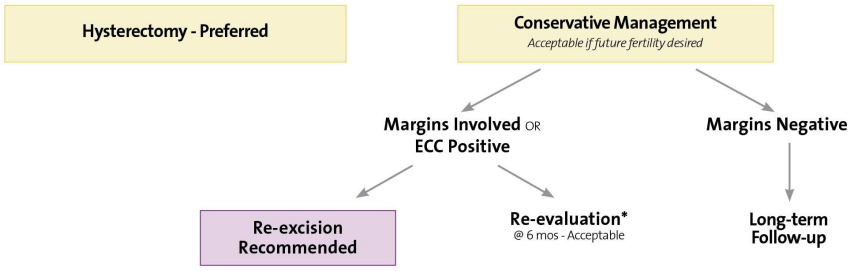
+ Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred.

Appendix 8: ASCCP guidelines for management of abnormal cervical biopsy





Management of Women with Adenocarcinoma in-situ (AIS) Diagnosed from a Diagnostic Excisional Procedure



*Using a combination of cytology, HPV testing, and colposcopy with endocervical sampling

Appendix 9: management of pre-malignant cervical lesions in KNH