GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF OBSTETRICS AND GYNAECOLOGY

FACTORS ASSOCIATED WITH ABNORMAL CERVICAL CYTOLOGY AMONG 6 POSTPARTUM WOMEN IN THE ACCRA METROPOLIS

DISSERTATION

SUBMITTED TO THE FACULTY OF OBSTETRICS AND GYNAECOLOGY IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE CONFERMENT OF A FELLOW OF THE GHANA COLLEGE OF SURGEONS (FGCS)

BY

DR. MICHAEL YAW AMOH

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

KORLE BU TEACHING HOSPITAL, ACCRA, GHANA

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DECLARATION

I, Michael Yaw Amoh, declare that apart from specific references which have duly been acknowledged, this work is the result of my own original research, and that this dissertation either whole or in part has not been presented elsewhere for another degree.

…… 22/05/2023

Michael Yaw Amoh Date

(Candidate)

22/05/23

Dr. Kareem Mumuni Date

(FWACS, FGCS)

(Supervisor)

22/05/23

Dr. Kwaku Asah-Opoku Date

(FWACS, FGCS)

Head of Department (Reproductive Health and Family Planning Unit)

Korle-Bu Teaching Hospital

(Supervisor)

DEDICATION

I dedicate this work to my entire family.

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I am grateful to the Lord Almighty for the gift of life and strength over the years in my quest to achieve academic excellence. I cannot express enough appreciation to my family for the support over the years. To my wife, Josephine and the children (Jessica, Lemuel and Michelle), I offer my sincere appreciation for the support I enjoyed throughout those stressful moments. I equally extend my sincere appreciation to my extended family for their support.

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LIST OF ABBREVIATIONS

aOR	Adjusted Odds Ratio
AC	Adenocarcinoma
ACIP	Advisory Committee on Immunization Practices
AGC- NOS	Atypical Glandular Cells Not Otherwise Specified
AGC	Atypical Glandular Cells
AIS	Adenocarcinoma in Situ
ASC	Adenosquamous Carcinoma
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	Atypical Squamous Cell- Cannot Exclude High Grade Squamous Intraepithelial lesion
ASR	Age-Standardized Rate
ASCUS	Atypical Squamous Cell of Undetermined Significance
BPV	Bovine Papillomaviruses
BTL	Bilateral tubal ligation
CIN	Cervical Intraepithelial Neoplasia
CIS	Carcinoma in Situ
cOR	Crude Odds Ratio
C-section	Caesarian Section
DNA	Deoxyribonucleic Acid
DMPA SC	Depot Medroxyprogesterone Acetate in its subcutaneous form
EV	Epidermodysplasia Verruciformis
FP	Family Planning
GLOBOCAN	Global Cancer Observatory
HIV	Human Immunodeficiency Virus
HSIL	High Grade Squamous Intraepithelial Lesion
HPV	Human Papilloma Virus
HrHPV	High-Risk Human Papilloma Virus
ICC	Invasive Cervical Cell Squamous Carcinoma

IUD	Intrauterine device
KATH	Komfo Anokye Teaching Hospital
KBTH	Korle-Bu Teaching Hospital
LBC	Liquid- Based Cytology
LSIL	Low-Grade Squamous Intraepithelial Lesion
LMICs	Low and Middle-Income Countries
LncRNAs	Long Non-Coding RNAs
L1	Late 1
L 2	Late 2
LrHPV	Low-Risk Human Papilloma Virus
MOH	Ministry of Health
NHIS	National Health Insurance Scheme
NILM	Negative for Intraepithelial Lesion/Malignancy
Pap	Papanicolaou
PNC	Postnatal Clinic
PIM	Post-Infection Microenvironment
RHC	Reproductive Health Centre
RHU	Reproductive Health Unit
RNA	Ribonucleic acid
SCC	Squamous Cell Carcinoma
SCJ	Squamo-Columnar Junction
SD	Standard Deviation
SIL	Squamous Intraepithelial Lesion
SPI	Subclinical Papillomavirus Infection
SPSS	Statistical Package for the Social Sciences
SLE	Systemic Lupus Erythematosus
SVD	Spontaneous Vaginal Delivery
TLR	Toll-Like Receptor

TZ	Transformation Zone
USA	United States of America
VIA	Visual Inspection with Acetic Acid
VILI	Visual Inspection with Lugol’s Iodine
WHO	World Health Organization

ABSTRACT

Background

Cervical cancer is a growing global health issue that significantly increases morbidity and mortality among women, particularly those in sub-Saharan Africa. The extended pre-invasive stage of the disease characterized by cervical cytological abnormalities can be detected early and prevented from developing into invasive tumors with the aid of robust screening procedures such as Pap (Papanicolaou) smear. Ghana does not have a national programme on screening for cervical cancer. The postpartum period presents a golden opportunity for a Pap smear to be done as most women will go through this stage at least once in their lifetime and also, a large cohort of women can be evaluated at that time.

Aim

To determine the prevalence and the types of abnormal cervical cytology as well as the associated factors among 6 weeks postpartum women in selected hospitals in the Accra Metropolis.

Methodology

In this cross-sectional study, 370 women who were 6 weeks postpartum and attended postnatal clinics at Korle Bu Teaching Hospital and the Greater Accra Regional Hospital were assessed for the prevalence and the types of abnormal cervical cytology as well as the associated factors. Participants were recruited via consecutive sampling after ethical approval and informed consent had been obtained. Pretested researcher administered questionnaire was used to collect the socio-demographic, obstetric and gynaecologic characteristics of the participants. Conventional Pap smears were taken and analyzed for all the study participants. Those with abnormal results underwent colposcopy. Data collected were summarized and analyzed using Statistical Package for the Social Sciences version (SPSS) 20. Descriptive statistics such as frequencies, mean and standard deviation were used. Bivariate analysis and multivariate analysis with logistic regression were used to model associations between the dependent and independent variables. A p-value of <0.05 was considered statistically significant at a confidence interval of 95%.

Results

In all data on 370 participants were included in the analysis. The prevalence of abnormal cervical cytology among the participants was 39/370 (10.5%) at a confidence interval of 95% (7.6%-14.1%). ASCUS (Atypical Squamous Cell of Undetermined Significance) was the most common abnormal cervical cytology representing 31/370 (8.4%). A multiple logistic regression analysis showed that a history of Sexually Transmitted Infection (aOR = 34.88; 95% CI = 13.75 – 88.48; $p < 0.001$) and a history of irregular condom use (aOR = 4.95; 95% CI = 2.03 – 12.05; $p < 0.001$) were significantly associated with abnormal cervical cytology. Colposcopy was performed on all participants with abnormal cervical cytology, excluding ASCUS, and the results were adequate and normal.

Conclusion

The prevalence of abnormal cervical cytology in the post-partum period is 10.5%. The factors associated with abnormal cervical cytology are a history of Sexually Transmitted Infection and a history of irregular condom use. Colposcopy was adequate and normal for all the participants who had abnormal cervical cytology. Efforts must be made to include routine cervical precancer screening in the care given to women during their six-week postpartum visit.

CHAPTER ONE

INTRODUCTION

1.1 Background

Cervical cancer is a growing global health issue that affects women all over the world and contributes significantly to morbidity and mortality.[1] It is the main reason for cancer-related mortality among women in underdeveloped nations and the fifth most prevalent malignancy among women worldwide.[2] Despite the high frequency of the disease, it has an excellent rate of prevention due to the prolonged pre-invasive period, especially when efficient screening techniques are implemented to find and treat the preinvasive cervical lesions.[3] Pre-invasive lesions of the cervix are mainly due to infection with sexually transmitted human papillomavirus (HPV), albeit the progression to invasive cancer of the cervix is slow-paced and sporadic.[4] Cervical cancer affects a woman's physical health, emotional state, financial situation, as well as those of her family and the larger community.[5]

Cervical cancer is currently one of the cancers found in humans which is highly preventable and can be cured when diagnosed at an early stage.[6] Notably, the availability of efficient screening programmes and facilities for the treatment of the pre-malignant and invasive lesions of the cervix, in addition to immunization against HPV infection affects the prevalence of the disease.[1] In the last half-century, these interventions have significantly reduced the occurrence of cervical cancer, particularly in advanced countries where they are commonly done.[1] Cervical Intraepithelial Neoplasia (CIN) is a designation for preinvasive lesions on the cervix detected by histology and it ranges from mild atypia to marked atypia. It is classified into CIN 1, CIN 2, and CIN 3 based on the proportion of thickness of the epithelium showing dysplasia. Pre-invasive lesions of the cervix may lead to invasive cervical cancer with time if left untreated.[7,8]

The primary screening test for preinvasive lesions of the cervix worldwide remains the Papanicolaou (Pap) smear test and it has been shown to detect 70-80% of High Grade Squamous Intraepithelial Lesions (HSIL).[9] Some other advantages of Pap smear apart from early detection of premalignant lesions include its simplicity, high specificity and acceptable sensitivity. To decrease the incidence of cervical cancer, some developed countries have added Pap smear screening for premalignant cervical lesions to the 6-week postpartum checkup.[4] However, for most developing countries such as Ghana, Pap smear screening programmes are non-existent or rare due to the lack of investment from the central government,

unavailability of screening centres, lack of awareness, poverty, and poor health-seeking attitudes of the women.[10] Some women avoid getting screened for cervical cancer because they believe they cannot develop it.[11,12] Visual inspection with acetic acid (VIA) has been proposed as a viable substitute for the Pap smear test because it is relatively inexpensive, results are almost instant and does not require any special equipment and/or training. However, Pap smear has a higher specificity for detecting abnormal precancerous lesions of the cervix than VIA, so it is preferred.[13,14]

An ideal time to screen using a Pap smear is during pregnancy and after delivery due to the relatively high number of times women see their healthcare providers compared to outside this period.[1] However, interpreting smear findings during pregnancy is difficult due to hormonal changes to the cervix.[13-15] Most of the physiological changes associated with pregnancy in women will have been reverted by the sixth week postpartum.[1] There is also little to no vaginal bleeding with a high percentage of satisfactory smears at this time.[15-17] The perceived risk of the procedure causing miscarriage in pregnant women is not present among postpartum women. The sixth-week postnatal period offers the opportunity for a sizable cohort of postpartum women to be screened with a Pap smear as most women will visit the postnatal clinic at some time in their reproductive life.[18] The prevalence of abnormal cervical cytology among 6 weeks postpartum women was found to be as high as 32% in a study.[19] This current study seeks to assess the prevalence and the types of abnormal cervical cytology as well as the associated risk factors among 6 weeks postpartum women in selected hospitals in the Accra Metropolis.

1.2 Problem Statement

Cervical cancer plagues the socioeconomic state of communities all over the world and accounts for 12% of cancers among women worldwide.[5,20] Cervical cancer is common in developing countries compared to developed countries as 85% of the cases occur there.[20] The relative lack of functional and effective screening programmes has been identified as the main contributor to the high frequency of cervical cancer in developing nations.[21] Screening programmes have been shown to lower cervical cancer incidence and its related mortality by over 50% in wealthy countries.[22]

Over 70% of cervical cancer cases in Ghana are diagnosed at advanced stages when the prognosis is bad.[23] It is therefore not surprising that cervical cancer is one of the leading causes of cancer-related deaths among Ghanaian women.[24] According to estimates, more than 3,000 Ghanaian women develop

cervical cancer yearly and more than 2,000 Ghanaian women die because of the disease every year.[24] In Ghana, women have an average cumulative risk of dying from cervical cancer that is about three times higher than the global average (0.9% vs. 3.3%, respectively).[24]

Screening programmes that investigate cervical abnormalities are relatively uncommon in developing countries, with only an insubstantial number of health facilities in the country equipped to perform the Pap smear test, especially as part of organised screening programmes, remains the oldest and the most widespread cervical cancer screening technique in the world.[14] In Ghana, a current report[26] indicates that only a meagre 2.4% of women have ever had a Pap smear test which is not different from the 2.1% reported[27] in an earlier study. This poor uptake is related to a lack of awareness of cervical cancer, cost of the test as well as religious and cultural beliefs.[25] The country does not also have any recognized national cervical cancer screening programme.[27]

The importance of using every chance to screen women for cervical cancer was stressed by Hull et al[28] in a study done in 2020. Even though most women will present for postnatal care after delivery, this window of opportunity for screening for preinvasive lesions of the cervix is not being utilized in Ghana. Routine postpartum Pap smear screening is not done at KBTH (Korle Bu Teaching Hospital) or GARH (Greater Accra Regional Hospital). Thus, there is little or no data available on it. The current study will evaluate the prevalence and types of abnormal cervical cytology in 6 weeks postpartum Ghanaian women in selected hospitals in the Accra Metropolis that is KBTH and GARH. The study considers that, since most cases of cervical cancer are diagnosed in the advanced stages, postpartum screening for cervical cytology abnormalities presents an excellent chance for early detection and management of preinvasive lesions of the cervix.

1.3 Rationale of the Study

Literature details convincing evidence that cervical cytology screening methods can effectively reduce mortality related to cancer of the cervix depending on the fraction of the population that is screened. [22,23] Due to the absence of an effective comprehensive national screening programme in Ghana, most cases of cervical cancer and preinvasive cervix lesions are discovered by chance and are typically in the advanced stages.[23] A study conducted in Elmina, Ghana showed that only 2.3% of the 392 female

participants knew about the Pap smear screening test.[25] Additionally, Ghanaian women rarely undergo routine Pap smear with reports indicating that less than 3% of them have ever done.[26,27]

Data on the nationwide prevalence of cervical smear abnormalities remain limited. However, a preliminary unpublished study done among 6 weeks postpartum women to assess the acceptability of Pap smear test in Ghana showed 87.3% of the 347 study participants were open to undergoing the test and 52.7% of them had the finances to pay for the test.[16] Similarly, studies done in Nigeria Thailand and Zambia showed over 90% acceptability of the need for the Pap smear to be done, particularly when the barrier of cost was taken away.[21,29,30] Another study done in Enugu, Nigeria compared the acceptability of Pap smear among 6 weeks post-partum women and non-pregnant women.[31] All the 76 and 82 participants in the postpartum and nonpregnant women groups respectively accepted to do the Pap smear after they had been educated. Thus, there was no difference in the acceptance of the Pap smear test between the women in the two groups. Therefore, even though there is a perceived increased discomfort associated with the procedure during the postpartum period, those in that study did not require additional motivation to get the Pap smear test done. Postpartum cervical cytology screening at postnatal clinics offers the opportunity for Ghanaian women to be screened for preinvasive cervical cytologic abnormalities. The postnatal clinic sees almost all women at some point in their reproductive lives.[1,32]

The results of the study will provide information about the frequency and types of abnormal cervical cytology among women at 6 weeks postpartum as well as the factors associated with abnormal cervical cytology. Findings from this study will be useful in policy formulation and implementation on cervical cancer screening in KBTH, GARH and the whole country. Findings will also add to the scientific information on cervical cancer screening in Ghana. Finally, the data provided can be the basis for further research into cervical cancer screening in KBTH and GARH.

1.4 Aim of the Study

To determine the prevalence and the types of abnormal cervical cytology as well as the associated factors among 6 weeks postpartum women in selected hospitals in the Accra Metropolis.

1.4.1 Research Questions

1. What is the prevalence of abnormal cervical cytology in 6 weeks postpartum women?
2. What are the types of abnormal cervical cytology in 6 weeks postpartum women?
3. What are the factors associated with abnormal cervical cytology in 6 weeks postpartum women?
4. What are the abnormal colposcopic findings in postpartum women with abnormal cervical cytology?

1.4.2 Specific Objectives

1. To determine the prevalence of abnormal cervical cytology in 6 weeks postpartum women.
2. To describe the types of abnormal cervical cytology in 6 weeks postpartum women.
3. To determine the factors associated with abnormal cervical cytology in 6 weeks postpartum women.
4. To describe the abnormal colposcopic findings of postpartum women with abnormal cervical cytology.

1.5 Hypothesis

1.5.1 Null Hypothesis

1) None of the 6 weeks postpartum women have abnormal cervical cytology.

2) There are no types of abnormal cervical cytology in 6 weeks postpartum women.

3) There are no factors associated with abnormal cervical cytology in 6 weeks postpartum women.

4) There are no abnormal colposcopic findings in postpartum women with abnormal cervical cytology.

1.5.2 Alternate Hypothesis

1) A proportion of the 6 weeks postpartum women have abnormal cervical cytology.

2) There are types of abnormal cervical cytology in 6 weeks postpartum women.

3) There are factors associated with abnormal cervical cytology in 6 weeks postpartum women.

4) There are abnormal colposcopic findings in postpartum women with abnormal cervical cytology**.**

CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

The discussion of literature is done chronologically in sub-sections to enhance understanding of the various concepts and associations between variables of interest.

2.1Overview of cervical cancer and prevention

2.1.1The anatomy of the cervix

The cervix is from the Latin word for neck and it is a tube-like structure that forms a linkage between the uterine cavity and the vagina. It is 3-4 cm in length and 2.5-3cm in width. It is also fibromuscular and cylindrically shaped (Figure 2.1). The nulliparous woman's cervix is smaller compared to that of the multiparous woman. However, the age and hormonal status of a woman can affect the shape, length and size of the cervix.[33] The bladder is anterior to the cervix, whereas the rectum is posterior to it. The upper part of the cervix called the supra-vaginal part is in touch with the uterus at the level of the internal cervical os. In contrast, the lower part of the cervix called the intravaginal part opens into the vagina. The anatomy of the cervix is illustrated in Figure 2.1.

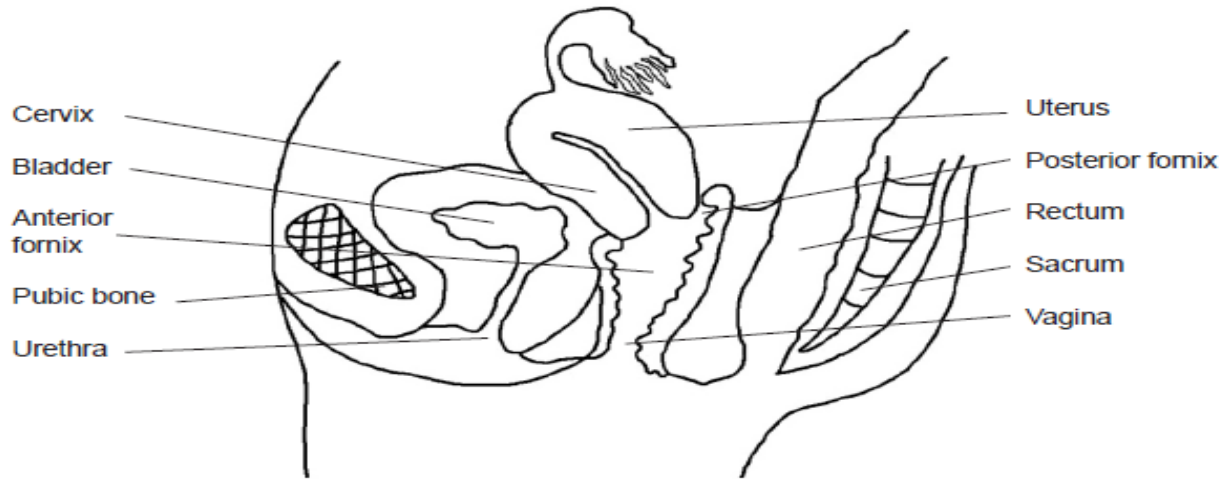


Figure 2. 1 Gross anatomy of the cervix (adopted from[34])

While the ectocervix is the portion of the cervix that is visible on the outside and lined by a squamous epithelium, the endocervix is the lining of the inner part of the cervix that is attached to the uterus and is lined by columnar epithelium.[34] The squamocolumnar junction (SCJ), which connects these two epithelia, is dynamic (Figure 2.2). The original SCJ forms in the endocervical region, and as time passes, the new SCJ gradually everts to the ectocervix (Fig 2.2 and 2.3). The transformation zone (TZ) is the epithelial lining that separates the new SCJ from the original SCJ. The TZ is crucial because more than 90% of cervical precancerous lesions begin there.[35]

Blood is supplied to the cervix by the internal iliac artery's cervical and vaginal branches. The cervical branch of the uterine arteries supplies the cervix by descending to the lateral aspect of the cervix at the 3 o'clock and 9 o'clock positions. The cervix's venous drainage enters the hypogastric venous plexus and travels parallel to the arterial supply. The common iliac, internal iliac, external iliac, parametrial, and obturator are the lymphatic vessels for the cervix. The ectocervix has fewer sensory nerves than the endocervix, and the hypogastric plexus supplies the cervix.[35]

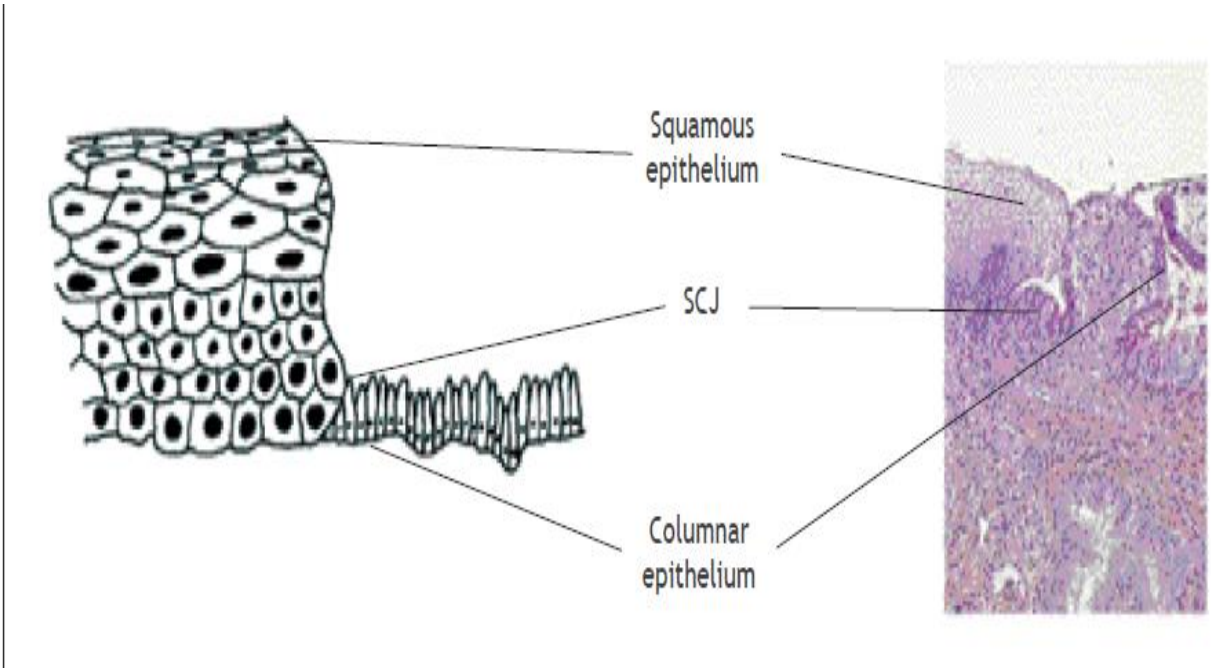


Figure 2. 2 The squamo-columnar junction (SCJ) (Adopted from[34])

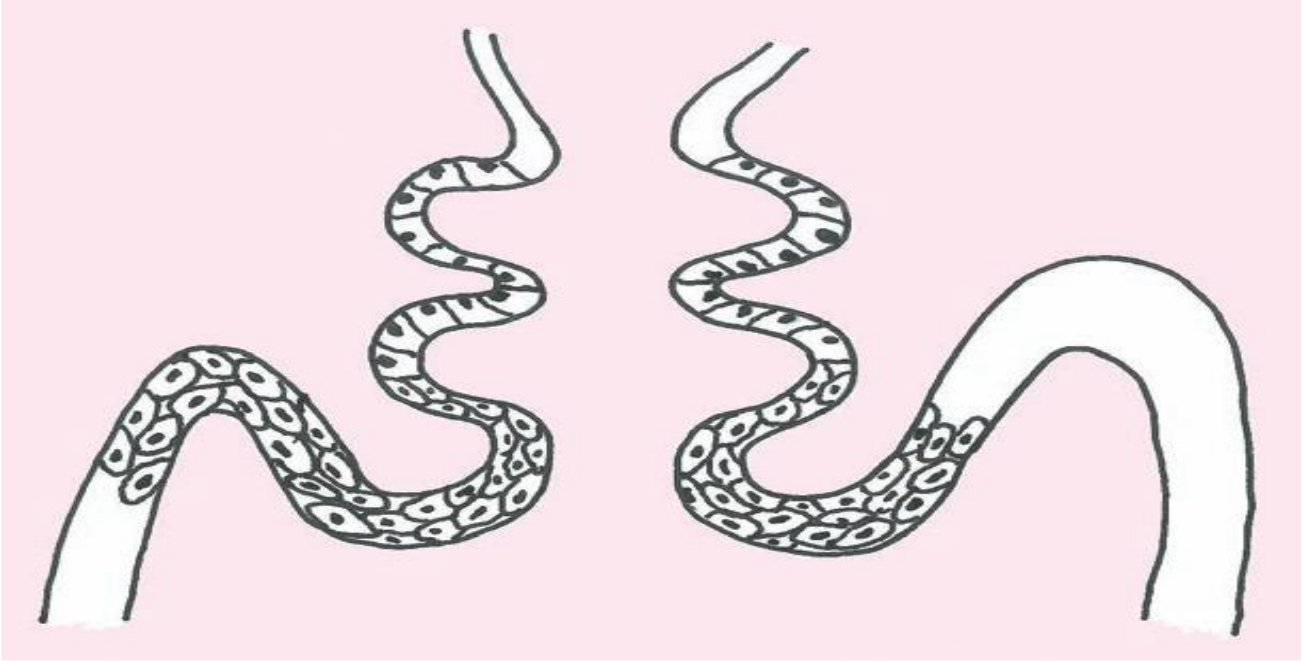


Figure 2. 3 Eversion of the columnar epithelium out unto the ectocervix (Adopted from [34])

2.1.2 Cancer of the cervix

The lowest portion of the uterus that attaches to the vagina, the cervix, is the source of the malignancy known as cervical cancer. It may present as vaginal bleeding, discharge, or pain during sexual activity.

The distribution of cervical cancer signifies a huge inequality in healthcare delivery between the developed and the undeveloped nations of the world. In tandem with other cancer types such as liver cancer, cervical cancer mainly develops in childbearing women from low- and middle-income or developing countries, with over 80% of new cases of cervical cancer occurring in these settings.[36] Hull et al [28] stated in their report that while cervical cancer is less common in places like Australia and Western Asia, it is more prevalent in Africa and Melanesia.

Cervical cancer is the second most common cause of cancer in countries that have a low ranking on the Human Development Index. It is also more prevalent in Low and Middle-Income Countries (LMICs) compared to developed economies.[37] Sub-Saharan Africa has one of the highest cervical cancer mortality rates from cervical cancer as 9 out of 10 women in that region will die.[37] The yearly age-standardized incidence rate of cancer of the cervix in Ghana, according to WHO is 29.3 per 100,000, which is among the highest in the world being four times that of the USA (United States of America).[25] It is predicted

that 5000 new cases of cervical cancer would be diagnosed and 3361 lives would be claimed in Ghana each year as a result of cervical.[37]

In terms of mortality, different regions of the world have different mortality rates. In Western Europe and New Zealand the mortality rate of cervical cancer was estimated to be around less than 2 cases per 100,000 population.[38] In contrast, in Sub-Saharan Africa, nearly 27.6 cases per 100,000 population resulted in mortality. For each region, the incidence and mortality age-standardized rate (ASR) rates are given as depicted in Table 2.1 in a 2018 study.[38]

Table 2. 1 Region-specific incidence and mortality ASR for cervical cancer in 2018

Region	Incidence Rate	Mortality Rate
Southern Africa	43.1	20.0
Eastern Africa	40.1	30.0
Western Africa	29.6	23.0
Melanesia	27.7	19.0
Middle Africa	26.8	21.1
South-Eastern Asia	17.2	10.0
Eastern Europe	16.0	6.1
Caribbean	15.5	8.5
South America	15.2	7.1
Micronesia/ Polynesia	14.2	6.3
Central America	13.0	7.0
South Central Asia	13.0	8.2
Eastern Asia	10.9	4.1
Northern Europe	9.5	2.1
Southern Europe	7.8	2.2
Northern Africa	7.2	5.1
Western Europe	6.8	2.1
North America	6.4	1.9
Australia/ New Zealand	6.0	1.7
West Asia	4.1	2.5

Source: GLOBOCAN (Global Cancer Observatory) 2018[38]

Despite the high prevalence of cervical cancer in many areas, literature suggests that these figures are widely underestimated because of the poor quality of data used to obtain these estimates. The prevalence rate of cervical cancer is usually based on population-based local cancer registries which in some places is not available, thus affecting the estimation of the prevalence rate. For instance, in a study that evaluated the incidence of HPV in Swaziland, it was found that the reported incidence rate was significantly underreported from 69.4 per 100,000 to 53.1 per 100,000 women.[39,40]

2.1.3 Histological Subtypes and Classification of Cervical Cancer

Two main histological subtypes of cervical carcinoma have been classified: squamous cell carcinoma (SCC) and adenocarcinoma (AC) with the SCC being more common.[41] While adenocarcinoma develops from glandular cells of the endocervix; squamous cell carcinoma stems from squamous cells which line the exterior parts of the cervix called the ectocervix.[42] Both types of cells (glandular and squamous cells) are located within a region termed the transformational zone and serve as the site from which most tumours arise.[35] Among the two histologically differentiated subtypes of cervical cancer, squamous cell carcinoma is the most frequently encountered, with an incidence rate of nearly 70%.[42-43] The adenosquamous carcinoma (ASC) subtype of cervical cancer has also been described in literature even though it is not common.[43]

The WHO also categorizes cervical lesions as SCC, AC or other tumours.[44] Examples of tumours that are classified as "other tumours" include ASC carcinoma, neuroendocrine tumour, and undifferentiated carcinoma.[45] Several reports indicate that the different histological subtypes of cervical cancers exhibit differences in biological behavior, immune escape, tumour growth, metastasis, prognosis as well as sensitivity to chemotherapy and radiotherapy.[45,46]

2.1.4 Risk factors and etiology of Cervical Cancer

Risk factors for cervical cancer may be either modifiable such as smoking and diet, or unmodifiable such as age or race.[47] Early age of sexual debut, having multiple sexual partners, increased number of children, smoking, consumption of alcohol as well as being HIV (Human Immunodeficiency Virus) positive are risk factors for developing cervical cancer.[48-55] Cervical cancer has also been linked to poor hygiene, illiteracy, STI (Sexually Transmitted Infection) history, repeated wearing of old clothing, and a lack of awareness of cervical cancer screening.[56] A systemic review done in 2020 where 19 studies were looked at revealed an increased risk of cervical cancer among users of oral contraceptive pills. This risk was

associated with the adenocarcinoma types and with longer usage of oral contraceptive pills.[57] Studies have linked cervical cancer to a nation's socioeconomic standing or location. For instance, in a 2018 Ugandan study, the authors found a significant correlation between geographic location and the incidence of cervical cancer.[58] According to the study's authors, with 3915 new cases and 2275 fatalities per year, East Africa has one of the highest incidences of cervical cancer.

STI's, epigenetic factors, and genetic polymorphisms are a few possible etiologic causes of cervical cancer. HPV infection is the main culprit behind these factors. Below is an enumeration of the etiologic factors associated with cervical cancer.

Sexually Transmitted Infections

Human papillomavirus

Cervical cancer is mainly caused by infection with the sexually-transmitted HPV although several other factors, including geographical area, screening levels, traditional beliefs and practices, socioeconomic status, accessibility to healthcare, general awareness, co-infection with HIV and use of contraceptives also play important contributory roles.[48] HPV infection can occur through vaginal, oral or anal sex. It is responsible for almost all cases of cervical cancer (approximately 90-100%), particularly among women who are younger than 35 years.[36] In addition, HPV DNA (Deoxyribonucleic Acid) is isolated in nearly all cases of cervical cancer. Of particular note are HPV subtypes 16, 18, 31, 33, 35, 45, 52 and 58, constituting approximately 91% of all HPV DNA-positive cervical cancer cases. Continual infection with HPV is a significant cause of both SCC and AC.[59]

Papillomaviruses are single double-stranded circular DNA viruses that infect many species. They are small, non-enveloped, epitheliotropic viruses with an increased tendency to infect mucosal and cutaneous epithelia in several higher vertebrates in a species-specific manner and cause the proliferation of cells. Papillomaviruses are icosahedral in shape, and possess a diameter of 52–55 nm. The viral particles are made up of a single double-stranded DNA molecule consisting of 8000 base-pairs (bp) that is attached to cellular histones and enclosed in a protein capsid comprising 72 pentameric capsomers. The viral capsid is made up of two structural proteins namely: L1 (Late 1) and L2 (Late 2), which are virally encoded. L1 has a size of 55kDa and constitutes approximately 80% of total viral proteins. Also, L2 is 70kDa in size.[60] In both mammalian and non-mammalian expression systems, virus-like particles (VLPs)

may be produced by the expression of L1 alone, or in combination with L2. For an intact virion, the estimated density is around 1.34 g/mL in cesium chloride and a sedimentation coefficient (S_{20}, W) of 300.[60]

Papillomaviruses are highly epitheliotropic and demonstrate an increased affinity to establish productive infections in stratified epithelia of the skin, anogenital tract and the oral cavity. While many types of papillomaviruses are implicated in cervical cancer, others are rarely seen, giving rise to the nomenclature of 'high-risk' and 'low-risk'. In humans, approximately 16 types of human papillomaviruses have been described as high-risk human papilloma virus (HrHPV) responsible for causing carcinogenesis in humans. Among the 16 classified HrHPV in humans, 12 types cause definitive carcinogenesis.[61] Also, the possibility of malignant transformation of cervical cells is particularly enhanced with HPV 12 subtype 16. Bovine papillomaviruses (BPVs) subtypes 1 and 2 have been described to infect mesenchymal tissues and demonstrate transmission between cross-species.[62] Other types of papillomaviruses are responsible for causing anogenital and oropharyngeal tumours. For instance, some HPV are identified in skin cancers of patients with epidermodysplasia verruciformis (EV). However, the above-mentioned types of human papillomaviruses may also be found in non-melanoma skin cancers as well as in normal skin.[63]

Papillomaviruses of all types have an identical genetic structure that is unique and distinguishes them from polyomaviruses. The presence of a double-stranded circular DNA genome encodes nearly 8 open-reading frames (ORFs). In a similar vein, papillomaviruses also possess a non-enveloped icosahedral capsid that is unique only to them. The virus obstructs the usual functional ability of cells, thus, allowing significant alterations in the epithelial cells found in the area around the transformational zone of the cervix.[34] Approximately 80% of women during their sexually active ages become exposed to HPV. In most instances, the highest incidence of HPV infection occurs within 5–10 years of the first sexual engagement, with the highest predominance rates perceived to be women aged 20–24 years.[64]

In addition, based on their association with precancerous, benign or cancerous lesions, HPV may be categorized as either HrHPV or low-risk human papilloma virus (LrHPV). [65-66] HrHPV subtypes 16 and 18 are the most frequently isolated HPV and cause a significant majority of all cervical cancer cases.[67] In fact, existing studies have identified that HrHPV subtypes 16 and 18 have demonstrated a significant relationship with malignancies relating to the cervix, penis, anus and vulva.[68,69]

HPV infection can be transmitted by coming in contact with labial, scrotal, or anal regions of an infected person. As a result, the use of condoms during sexual intercourse may not necessarily shield people from contracting the infection. In a meta-analysis report, Crosbie and colleagues[70] reported that the highest incidence of HPV is experienced during the mid-twenties, suggesting that alterations in sexual behavior during that stage may be a causative factor. A similar study also reported that an outbreak of HPV is typically observed after the onset of coitarche and may be followed by a plateau during adult ages, with a second peak observed after 45 years.[36] Over time, CIN usually develops upon infection with at least one of the HrHPV.[71]

In terms of HPV-related cervical cancer, HPVs produce alterations in histology arising from the cervical epithelium, such as the loss of terminal differentiation. This inhibition process relating to differentiation results in a cellular state which is inconvenient for the life cycle of the virus. Additionally, the circular DNA genome of the virus, which is typically seen as a nuclear plasmid, may become integrated into the genome of the host, therefore disrupting its replication.[70] The main pathogenesis of HPV in cervical cancer formation involves the activity of oncoproteins E6 and E7. These oncoproteins inhibit important tumour suppressor genes namely P53 and retinoblastoma leading to cancer via abnormal growth of the cells. Also, the oncoproteins are involved in changing the DNA of the host, as well as viral DNA methylation.[71]

Human Immunodeficiency Virus

Another common sexually transmitted infection that has been commonly associated with cervical cancer is the HIV infection. For instance, in a study whose aim was to investigate cervical cancer risk among women living with HIV and to estimate the global cervical cancer burden associated with HIV, Stelzle et al[72] conducted a systematic review of 24 studies that met their inclusion criteria and comprised 236,127 women living with HIV. The findings of the study revealed that women living with HIV were significantly predisposed to cervical cancer by six-fold. The same study also reported that globally, 5.8% of the 33000 new cases of cervical cancer recorded in 2018 were diagnosed among women living with HIV. Eastern and Southern Africa were the regions where most of the cases were recorded.

In a similar review that summarized current knowledge of important elements, characteristics and effects of post-infection microenvironment (PIM) as well as highlighting the prospect of targeting PIM as a potential strategy to improve therapeutic outcomes for cervical cancer, it was found that there exists a

significantly higher rate of persistent HPV infection with multiple oncogenic viruses, more atypical Pap smears, as well as a higher incidence of CIN and invasive cervix carcinoma in individuals who have HIV. [73]

Additionally, another study compared the incidence of HrHPV infections and abnormalities in Pap smear between HIV-infected and HIV-uninfected adolescent females in South Africa.[74] The authors of this report performed a comparative cross-sectional study. They juxtaposed the HPV DNA and Pap smear results between 35 HIV-infected and 50 HIV-uninfected adolescents in order to determine the prevalence of HrHPV genotypes and cervical cytological abnormalities using Pearson chi-square analysis and independent sample t-test analysis. It was revealed from the study that participants who had HIV had a higher chance of being infected with any HPV (88.6% versus 48.0%) as well as concurrent infection with the different types of HPV (68.6% versus 22.0%). The same study also found that HIV- infected subjects were more likely to have abnormal Pap smears (28.8% versus 12.0%). It was also revealed that smoking and HrHPV infection were significantly linked.

Epigenetic Factors

Some of the common epigenetic factors that are known to play contributory roles in the development and/ or progression of cervical cancer include tobacco smoking, frequent use of oral hormonal contraceptives, high parity and sexual promiscuity.[68,75] Out of these factors, the most frequent and important contributory factors are high parity and smoking of tobacco due to the roles they play in mediating the progression of HrHPV infection and pre-cancer of the cervix into invasive cancer.[76,77] Chatzistamatiou et al[77] found that smoking and HrHPV DNA positivity was significantly related in a study done in Greece women among aged between 25 to 55 years. However, they did not find any significant association between the intensity of smoking and HrHPV infection. Furthermore, for those with negative Pap smear results; the smokers and ex-smokers had higher odds for HrHPV infection than the non-smokers.

Additionally, contrary to the observation made Chatzistamatiou et al[77] in their study about the intensity of smoking and HrHPV infection, continuous cigarette smoking is associated with an enhanced risk of developing squamous cell carcinoma but not with adenocarcinoma.[78,79] Even passive smoking is associated with an increased risk of cervical cancer.[80]

Another important factor that predisposes individuals to cervical cancer is co-infections. For example, co-infection of Chlamydia trachomatis and HSV-2 have been identified as important causative factors for the development and/ or progression of cervical cancer.[68]

Environmental factors also play crucial roles. According to Goodson et al,[81] more than 80 different environmental chemicals have been identified and play significant roles in dysregulating host pathways and increasing the rate of cancer formation. The role of environmental factors is to activate signaling pathways while initiating the process of carcinogenesis relating to HPV-related cancers. Some of the pathways include hyperproliferative signaling, continuous angiogenesis, insensitivity to growth-factor signals, evasion of apoptosis as well as disruption of normal metabolic functions. Other known factors associated with cervical cancer include the use of solid fuel, particularly for women who are exposed to excessive smoke from coal, crop residue or wood, used mainly for heating and cooking purposes.[81] In addition, chemical constituents of tobacco such as benzyl pyrenes and tobacco-based nitrosamines, and tar-based vaginal sanitizers may potentially influence the development or progression of cervical cancer as a result of their penetrative ability into cells and tissues, by stimulating vital pathways in carcinogenesis.

Several genetic and immunological factors of the host and causative virus have been identified to play key roles.[82] Figure 2. 4 illustrates the factors that predispose an individual to cervical cancer.

Genetic Polymorphisms

Genetic polymorphisms refer to a DNA sequence that can occur in two or more different ways in different people or populations. These alterations may result in the deletion, insertion or substitution of a nucleotide. Genetic polymorphisms may or may not produce any significant effects. While insignificant forms are silent, certain forms of genetic polymorphism may yield highly relevant effects and can lead to the development of several kinds of disorders, such as SCC.[83]

The regulation of long non-coding Ribonucleic acids (LncRNAs) with their associated genetic polymorphisms, such as polymorphisms in toll-like receptor (TLR) genes, plays crucial roles in causing cancer of the cervix.[84] The long non-coding RNA, LncRNA LINC00673, has been described to be associated with the development and prognosis of several tumours such as lung cancer and cervical cancer.[85] In addition, a Chinese study sought to evaluate the relationship between cervical cancer and the genetic variant of LncRNA LINC00673, and found a positive association between this gene variant and

the chances of developing cervical cancer.[84] Figure 2.4 shown below depicts how LINC00673 can lead to the development of SCC.

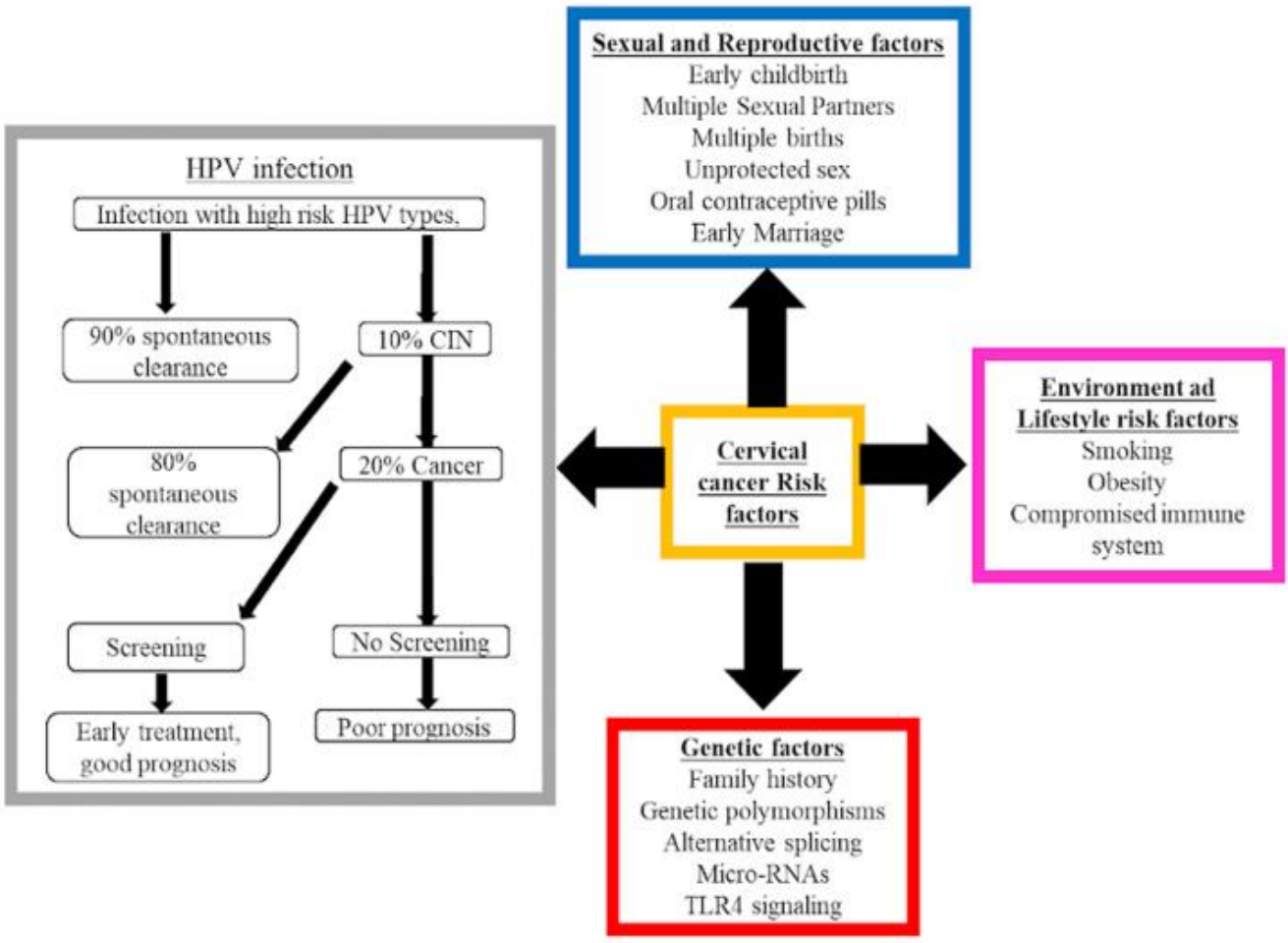


Figure 2. 5 Risk Factors of Cervical Cancer

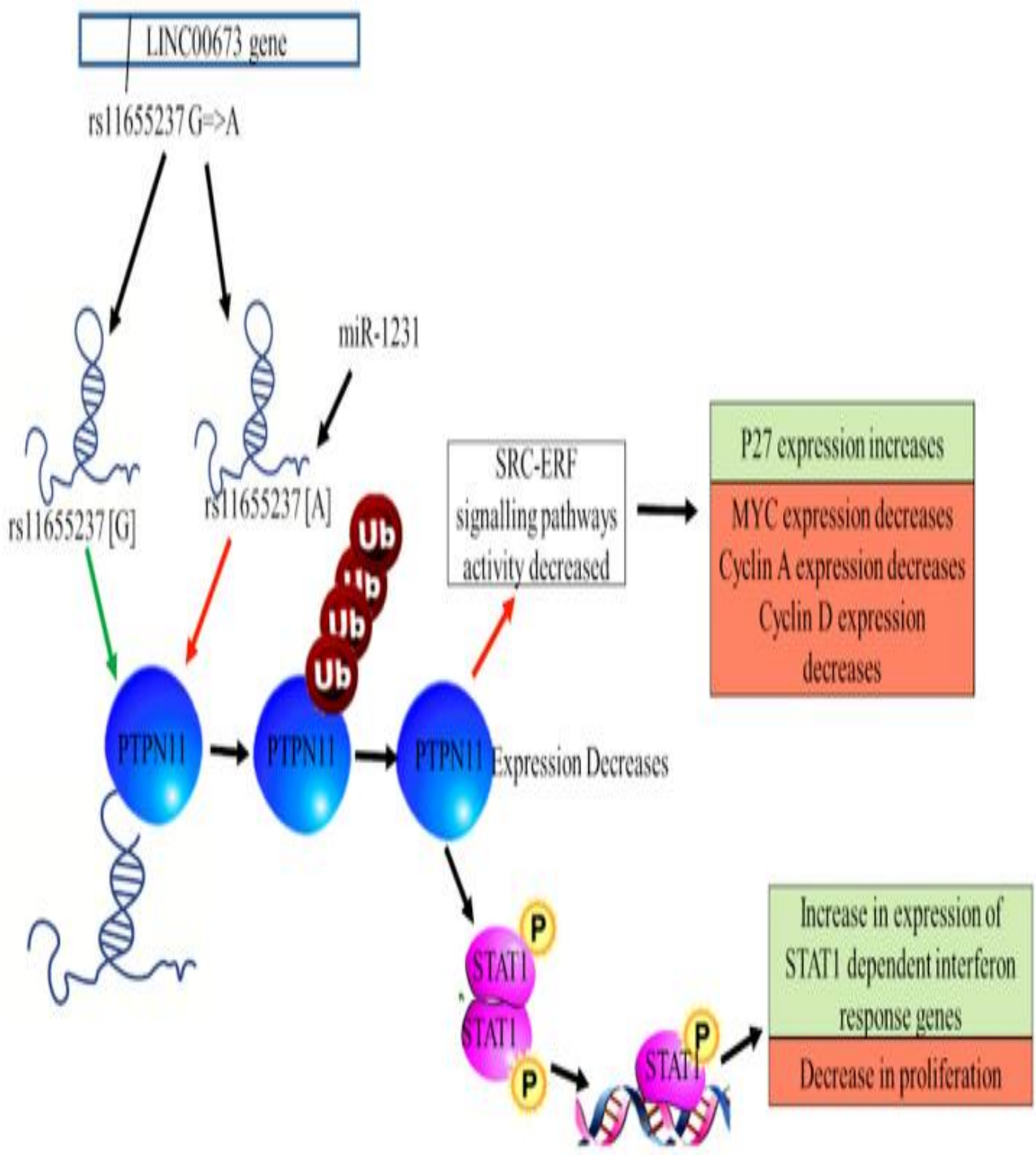


Figure 2. 5 How mutations due to Single Nucleotide Polymorphisms in LINC00673 can the development of SCC (Adopted from[84])

Another study also evaluated the relationship between the genetic polymorphisms of LncRNA HOX transcript antisense intergenic RNA (HOTAIR) and the recurrence as well as the prognosis of cancer.[86] The results of that study showed that GG-genotype carriers in the HOTAIR rs920778 gene form demonstrate enhanced chances of cervical cancer, worse prognosis and high rate of mortality as compared to individuals who possessed the AA/AG genotype. It is important to note that the AA genotype is implicated as a causative factor for causing other cancers such as gastric and esophageal squamous cancers among the Chinese population, but not cervical cancer.[87]

Similarly, Yang et al[88] evaluated the relationship between TLR gene polymorphisms and the risk of cervical cancer and found that populations that possess the C allele of the TLR 9 1486 T/C gene polymorphism and the A allele of the TLR 9 G2848A gene polymorphism were predisposed to cervical cancer. In that same study, it was found that when compared to nearby non-cancerous tissues, cervical cancer tissues had low levels of miR-214 expression.

In addition, a study conducted among Tunisian women revealed that TLR 9 promotes CIN in women from the Tunisian setting and could serve as a helpful biomarker for cervical squamous cell malignancy.[89]

2.1.5 Pathogenesis of preinvasive lesions of the Cervix and Cervical Cancer

Under normal circumstances, the outer surface of the cervix is coated with a stratified squamous non-keratinized epithelium, which is continuous with the squamous epithelial lining of the vagina. There is the mucous-secreting columnar epithelium that lines the endocervical canal and its associated crypts. The original SCJ is the meeting point between the ectocervix and the endocervix. In certain states such as pregnancy, puberty, or among individuals who frequently use steroid contraceptives, alterations in the size and shape of the cervix lead to the formation of a new SCJ.[90] The TZ refers to the region of the cervix found between the old and new SCJ.[35] It is from the TZ that almost every cervical carcinoma develops.[35] Three stages characterize the carcinogenesis in squamous lesions namely: acute infection with HrHPV, viral persistence and development of precancerous lesion, and finally, the invasion of the basement membrane of the epithelium.[91]

Persistent infection of the squamous epithelium with HPV results in two classes of intraepithelial lesions: productive and self-limited HPV infection (which may be sub-grouped as koilocytosis, condyloma and CIN1). Histologically, CIN is marked by irregular cell formation and development, and there is also the

presence of nuclear atypia. In CIN1, the characteristic abnormalities are seen in the lower third of the epithelium, where copious HPV cytopathic effects are often seen. In the CIN 2 variant, these modifications are seen in the lower two-thirds of the epithelium. The abnormalities of CIN 3 make up the entire depth of the epithelium, with dense and irregular nuclei.[91,92]

Extant literature reveals that on average, the incidence of HPV peaks during the initial ages of reproductive women. Nevertheless, precancerous lesions particularly HSIL peak between 25 – 35 years.[91] Also, the highest incidence of invasive cervical cancer is seen one or several decades later, which is around 45-60 years.[91]

Typically, SCC originally develops in the transformation zone, located at the SCJ. On the other hand, AC originates from the mucus-producing cells of the endocervix.[92] Despite being caused by HrHPV and also emanating from glandular cells adjacent to the TZ or in the endocervical canal, the pathogenesis of adenocarcinoma is comparatively less understood than invasive cervical cell squamous carcinoma (ICC).

At present, the tendency of visualizing and sampling preinvasive lesions of the cervix, and further treatment using freezing and coagulation with little or no anesthesia is a huge step in the right direction to understanding the natural progression of cervical cancer, and also in developing simple outpatient techniques of screening and treating.[93] The primary precancerous lesion is referred to as CIN and may be sub-classified as either CIN 1, CIN 2 or CIN 3. While CIN 1 and 2 signify mild and moderate dysplasia respectively, CIN3 is characterized by severe dysplasia.[94] In the Bethesda system of classification, lesions with CIN1 are classified as low-grade squamous intraepithelial lesions, while high-grade squamous intraepithelial lesions refer to lesions with either CIN 2 or CIN 3. **[94]** CIS (Carcinoma in Situ) is also known as stage 0 cervical cancer. Patients with CIS are usually asymptomatic.

Adenocarcinoma in situ (AIS) is a preinvasive lesion but it is not as common as squamous preinvasive lesions. There have not been any terminologies of glandular lesions with lower degrees of nuclear atypia due to the limited number of biopsies available. Additionally, there are few specific guidelines for managing and monitoring AIS.[95]

Historical evidence on cervical intraepithelial neoplasm suggests that cervical cancer does not originate suddenly but is preceded by a precancerous stage which is marked by several modifications of the cervix. The presence of HPV results in several modifications to cytological smears. Nonetheless, new infections

of HPV have an increased tendency to be cleared spontaneously irrespective of the age of the female. 90% of HPV infections disappear or go dormant within 12 to 24 months of exposure to the virus. [96] However, infections caused by HrHPV types may persist which then increase the risk of developing cervical cancer.[97] Additionally, evidence suggests that approximately 5% and 12% of CIN 2 and CIN 3 respectively progress to invasive cancer if they are left untreated.[98]

In a study done in the USA using 1,262,713 women who were aged 25 to 77 years; the women who tested negative for HPV had 5-year risks for CIN 3+ of 0.10 percent for NILM (Negative for Intraepithelial Lesion Or Malignancy), 0.44 percent for ASCUS (Atypical Squamous Cell of Undetermined Significance), 1.8% for LSIL (Low-Grade Squamous Intraepithelial Lesion), 3.0 percent for ASC-H (Atypical Squamous Cell- Cannot Exclude High Grade Squamous Intraepithelial lesion), 1.2% for AGC (Atypical Glandular Cells), and 29% for HSIL+ cytology (which was extremely uncommon).[99]

The carcinogenicity of HPV is linked to the activity of two oncoproteins: E6 and E7. While E6 is responsible for the inhibition of p53 to block apoptosis, the role of E5 involves inhibiting pRB (Retinoblastoma Suppression Protein) in annul cell-cycle arrest. In the infectious phase, these two oncoproteins are expressed at very low levels. However, as the infection progresses, there is deregulation of the expression of E6 and E7 which leads to their overexpression and unregulated cellular proliferation.[100]

2.1.6 Prevention of Cervical Cancer

Cervical cancer is an important health concern affecting women all over the world. The adverse health and socio-economic consequences of cervical cancer are enormous, with several reports suggesting that African women of reproductive age are the most affected by the condition.[14] Due to the frequency and severity of the condition, enhanced consideration must be given to various prevention techniques to curb the negative consequences of the condition.

The strategy for preventing cervical cancer includes; primary prevention via education and vaccination as well as secondary prevention via screening techniques such as Pap smear and VIA. Tertiary prevention strategies include hysterectomy, palliative care, chemotherapy and radiotherapy. Some of the common techniques that are currently being used as preventive measures are discussed below.

Health Education

Evidence suggests that health education programmes that seek to promote sexual risk reduction behavior influence the probability or risks associated with cervical cancer.[101] For instance, in a Ghanaian case-control study that sought to investigate the effect of a health education intervention on the incidence of cervical cancer, and the perception of women on cervical cancer screening, it was revealed that interventions of health education are necessary to improve upon the knowledge and perception of women regarding cervical cancer.[101] The same study also revealed that health education enhances the self-efficacy of women concerning cervical cancer and its screening. In a similar cross-sectional study conducted in Ghana, the results suggested that exposure to thorough education of women on cervical cancer and its associated complications is crucial to minimizing the risks related to the disease and also to improve the health of women.[102] In addition to increasing knowledge on cervical cancer, health education has also been shown to increase the uptake of screening for precancerous lesions of the cervix which will eventually result in decreasing the number of cases of precancerous as well as cancerous lesions of the cervix.[101,102]

Vaccines

Vaccinating uninfected women has proven an efficient way to curb cervical cancer. Currently, more than 200 HPV viruses have been described although the vast majority of them are not virulent. Notably, subtypes 16 and 18 are HrHPV that have the potential of causing genital tract cancer.[103] As a result, some vaccines have been developed against these HPV subtypes as a means of preventing cancer. In 1983, Zur Hausen, Gissmann and colleagues discovered HPV 16 in precursor lesions of genital cancer and showed the existence of HPV DNA in cervical cancer cells.[104] Their findings gave way to other scientists to conduct further related studies, eventually leading to the discovery of two preventive vaccines, Cervarix (bivalent HPV vaccine) and Gardasil (quadrivalent HPV vaccine).

Several clinical trials have demonstrated the effectiveness of these vaccines against HPV infections as a result of their immunologic properties. In addition, existing Randomized Controlled Trials have reported that licensed HPV vaccines in existence have proven to be highly effective against new infections of HPV subtypes 16 and 18, as well as the prevention of CIN2 and CIN3 lesions. [105] In addition, the ability of existing vaccines to cross-protect against HPV 31, HPV 33 and HPV 45 infections has also been

described.[106] Many countries have licensed both vaccines and approved their usage against HrHPV subtypes 16 and 18. Both vaccines also have good safety records and may be safely co-administered with other vaccines, like those for Diphtheria, Tetanus Pertussis (DTP) and Hepatitis B.

The Advisory Committee on Immunization Practices (ACIP) in the USA recommends routine vaccination of females aged 11–12 years with 3 doses of quadrivalent HPV vaccine, starting as early as the age of 9 years**.** Vaccinating women through age 26 years as a catch-up strategy was also recommended. Although the ACIP did not advise catch-up vaccination for all adults between the ages of 27 and 45, it did acknowledge that some individuals who are not sufficiently protected may be at risk for developing a new HPV infection and may benefit from vaccination in this age group. As a result, the ACIP advised shared clinical decision-making regarding potential HPV vaccination for these individuals.[107]

Cervarix is effective against HPV 16 and 18 whereas quadrivalent Gardasil is effective against HPV 6,11,16 and 18.[108] The latest vaccine Gardasil 9 was introduced in 2014 and is effective against the HPV strains covered by the quadrivalent Gardasil as well as these additional subtypes 31, 33, 45, 52, and 58 which are responsible for 20% of cervical cancers.[109]

According to the WHO, in order to prevent primary cervical cancer, girls between the ages of 9 – 13 years (or the age stipulated by national guidelines) must be vaccinated before the commencement of sexual activity.[110]

Cervical Cancer Screening

Screening refers to testing that may be performed to aid the detection of ailments among individuals who are not showing any symptoms of overt disease. The significance of screening tests can be seen in the tendency to result in early detection and treatment of diseases. Screening tests can reveal precancerous lesions of the cervix as in the case of Pap smear and cancerous lesions of the breast as seen in the use of mammography.

The sensitivity and specificity of a screening test determine how accurate a screening test is. The sensitivity of a screening test refers to the ability of the test to correctly identify the people who have the disease being screened for whereas specificity refers to the ability of the test to correctly identify those

who do not have the disease being screened for. A screening test is more reliable where there is a high sensitivity and high specificity. Negative predictive value denotes the probability that those who test negative to a test are truly negative. In contrast, the positive predictive value of a test denotes the probability that those who test positive to a test are truly positive. Not all diseases can be screened for. The principles guiding screening test has been articulated by Dobrow et al[111] as well as the Petros et al [112] as follows:

The Wilson-Junger criteria for approaching the validity of a screening programme:

- The condition should be an important health problem
- There should be a recognizable latent or early symptomatic stage
- The natural history of the condition, including development from latent to declared disease, should be adequately understood
- There should be an accepted treatment for patients with recognized disease
- There should be a suitable test or examination that has a high level of accuracy
- The test should be acceptable to the population
- There should be an agreed policy on whom to treat as patients
- Facilities for diagnosis and treatment should be available
- The cost of screening should be economically balanced in relation to possible expenditure on medical care as a whole, and screening should be a continuing process and not a 'once and for all' project.

Frequent cervical cancer screening among childbearing women reduces the chances of cervical cancer.[113] However, cervical cancer screening among low-resource populations remains a challenge. Evidence points to various responsible factors for the low coverage of cervical screening in these environments including: lack of funding, lack of awareness, difficulty in accessing cervical screening services and absence of effective public policies.[114]

Several reports indicate that majority of cervical cancer and subsequent mortality cases from the disease occur within low and middle-income economies.[114,115] The scenario is completely opposite in advanced economies where the prevalence and/ or incidence of the condition has significantly reduced, an observation that has been consistently attributed to the availability of screening programmes that

enhances the chances of early detection of precancerous lesions and helping halt their progress to invasive cancers. In addition, the existence of robust and appropriate treatment regimens contributes to the lower incidence of the condition in more advanced countries.[8] Simply put, the epidemiological distribution of cervical cancer around the globe is due in part to the presence and/ or ease of accessibility to screening methods and options, which enable non-invasive forms of the infection to be detected early on and eliminated whenever necessary. Extant literature reveals that patients with abnormal cervical cytology who have early diagnosis demonstrate a higher chance of survival when compared to individuals suffering from advanced stages of the disease.[116] This proposition is also supported by other authors who argue that early detection of precancerous lesions is crucial to abrogating the progression of cervical abnormalities, as well as enhancing the chances of survival of patients.[117]

The screening methods for preinvasive lesions of the cervix include Visual Inspection of Cervix with Acetic Acid (VIA) and Visual Inspection with Lugol's Iodine (VILI), Pap smear test, HPV DNA Testing and colposcopy. These have been enumerated on below.

Visual Inspection of Cervix with Acetic Acid and Visual Inspection with Lugol's Iodine

VIA/VILI is one of the old means of screening for premalignant lesions of the cervix. It is seen as a cheap and simple means of screening that is not as complex as interpreting a Pap smear. Nurses and doctors can easily be trained to perform and interpret their results. The result is ready almost immediately and is a very useful tool in low-resource setting. It has been shown to reduce the lifetime risk of cervical cancer by 25-36%.[117] VIA has a sensitivity of from 55% to 96% and a specificity of 49% to 98 whereas VILI has sensitivity and specificity of 44% to 98% and from 75% to 91%, respectively.[118-122]

In VIA, 5% acetic acid is applied to the cervix and observed by the naked eye for acetowhite regions. The reflection of the rich vessels beneath the stroma changes the colour of normal epithelium to pink, while the color of columnar epithelium changes to red**.** The diseased areas and areas with high cellular proteins undergo coagulation due to the acetic acid resulting in the obliterating of the color of the stroma and thus making it appear white. The acetowhitening is restricted to specific areas in CIN whereas in invasive cancer the whole cervix is involved. Other conditions that can cause acetowhitening include leukoplakia and condyloma.

In VILI, Lugol's iodine is applied to the cervix and observed by the naked eye. Normal Squamous metaplastic epithelium contains a lot of glycogens. Columnar epithelium contains glycogen, whereas

CIN and invasive cancer cells contain little or no glycogen. Iodine has an affinity for glycogen and thus by applying iodine solution, it leads to glycogen-containing epithelium taking up iodine. As a result, normal squamous epithelium will pick up a black or mahogany brown color when iodine is applied while cells that have CIN and invasive cancer will remain saffron-colored or thick mustard-yellow since they will not be stained by iodine.

Pap smear Test

Pap smear, originally described by Georgios Papanikolaou, refers to a commonly used and powerful cytological screening test that is used to screen for the presence of cytological abnormalities in cervical sample preparations. This technique of cervical cancer screening is capable of identifying precancerous abnormalities before they become advanced and cause cancer. Pap tests are liquid-based tests that are assessed using the Bethesda Reporting System (BRS) by qualified pathologists to evaluate abnormalities associated with cervical cytology.[123] The 2001 Bethesda Reporting System categorizes squamous and glandular cell abnormalities separately.[124] Pap test has an overall sensitivity ratio of 70 – 80% in detecting high-grade squamous intraepithelial lesions.[125] On the other hand, a Pap screening done in combination with an HPV DNA test enhances the sensitivity for early detection of precancerous lesions.

The American Cancer Society recommends that five days after menstruation is the ideal time to take a sample for a Pap smear. As part of the pre-test preparation, patients who are about to undergo a Pap smear test must be instructed not to insert any vaginal douche or any type of lubricant or spermicide for at least 24 hours before having their cytological specimen obtained. There must also be no evidence of bleeding or vaginal infection. In the event of a vaginal infection being present, the infection should be thoroughly treated and the patient must be rescheduled for Pap smear test after their next menstrual cycle.[123] Samples for a Pap smear can be obtained via the conventional method or the liquid-based method.

To obtain the sample for a conventional Pap smear test, Ayre's spatula and endocervical brush should be applied around the vagina by performing a 360-degree rotation with minimal pressure. The obtained sample is then fixed onto a clean grease-free slide using 95% alcohol. The fixed smear is then stained using the Papanicolaou technique by applying the following stains. Hematoxylin (nuclear stain) and Orange - G and Eosin azure (counterstains).

Liquid-based cytology (LBC) refers to a technique used for cytological screening which involves the transfer of cellular components unto a microscope slide. Typically, sampling of the cells is accomplished either with the aid of Cervex-Brush or by using a plastic spatula and an endocervical brush. Liquid-based cytology differs from the conventional Pap test in that, instead of making a smear of the cells on the slide, the sample is immersed into a container that has a special liquid and is transferred to a specially equipped laboratory for observation. Some advantages of this technique over the conventional Pap test are that this method enhances the likelihood of only using representative smears and of less obscuring factors (such as blood, mucus, and inflammatory cells). Also, less time is required for the interpretation of samples when this technique is adopted. In addition, the sample obtained for this technique could be used for further analysis, such as the HrHPV and Chlamydia. Other merits of the liquid-based technique include the observation of a thin layer of epithelial cells and the suitability of this technique for automated screening devices. Despite the relatively high cost of operation, LBC is gradually replacing the conventional Pap technique, particularly in advanced countries.[118]

HPV DNA Test

Cervical screening for the detection of HrHPV DNA has improved sensitivity for the identification of CIN2+ when compared to cytological techniques, although the specificity is low.[126] It is also seen as one of the most objective tools for screening for preinvasive lesions of the cervix. A sample for HPV DNA testing is using obtained when performing LBC. Studies have shown that HPV-DNA testing in conjunction with cervical cytology boosts CIN3 detection by 7–31% for the initial test and lowers CIN3 and cancer detection rates for follow-up tests (absolute reduction in cancer rate at second test of 0.03–0.05%).[127,128]

Colposcopy

Colposcopy is a type of visual examination of the cervix, vagina and vulva via a low-powered microscope. An abnormal cervical cytology is an indication for a colposcopy. Colposcopy came into existence when the German scientist Hans Hinselmen described the technique in 1925 and has been utilized in the past to check for aberrant cervical cytology before the advent of Pap smear screening.[129] By magnifying these tissues, Hinselman sought to identify precursor lesions early enough to allow

successful therapy before invasive disease established or spread. He believed that endophytic or exophytic cervix lesions were likely progenitors of cervical carcinoma.[129] When abnormal Pap results are found, the role of colposcopy has recently changed to being utilized to determine the biopsy location for follow-up histological investigation. Direct biopsies from colposcopy play important roles in determining therapy modalities.

Under normal circumstances, colposcopy is indicated to evaluate the presence and/ or intensity of dysplasia. The diagnostic significance of colposcopy is seen when it is used for the assessment of women with Pap test abnormalities, VIA, women who have tested positive for HrHPV DNA, or women whose cervix appears suspicious irrespective of the results of the Pap test. Colposcopy may also be performed for several other reasons. For instance, an important objective of colposcopy is to determine the transformational zone, which is the major site on the cervix where the development of abnormal cells occurs. Colposcopy with biopsy can confirm the existence of CIN, invasive cancer or glandular disease, monitor treatment, and also, monitor the progression or regression of CIN. Overall, colposcopy aids the evaluation, management, monitoring and follow-up of cases of cervical abnormalities. Certain conditions or states are contraindications for colposcopic examinations. For instance, an active or untreated vagina/cervical infection is a contraindication for colposcopic measurement. In addition, during pregnancy, some aspects of the colposcopic procedure such as the endocervical curettage component, may be excluded due to the potential risk of adverse effects to the pregnancy.

Evidence from existing literature indicates that colposcopic diagnoses have sensitivity, specificity and accuracy rates to diagnose CIN 2+ of 54-78%, 68-79% and 67-77% respectively.[130,131] Nonetheless, other factors such as the efficiency of the skill of the physician also significantly affect the accuracy of colposcopic measurements. Due to this, there is a significant difference in the specificity and sensitivity of the test amongst various providers.[132,133]

A wide array of clinicians can practice colposcopy. For instance, a colposcopy may be practiced by advanced practice clinicians, gynaecologists, family medicine physicians, gynaecological oncologists, as well as some internists.[134] The follicular phase of the menstrual cycle, when cervical mucus is clear, is the ideal time to schedule a colposcopy as the cervix is seen more clearly at this time. However, scheduling a colposcopy based on the days of the menstrual cycle is not convenient (and also not required) in ordinary practice. A vaginal speculum, an endocervical speculum, 5% acetic acid, Lugol's solution,

biopsy forceps, an endocervical brush, and a Monsel's solution to stop bleeding are additional things needed for a colposcopy.

Precancerous lesions often have an acetowhite appearance after the application of a 3–5% of acetic acid solution on the cervix. However, squamous epithelium that is immature, healing epithelium may also appear acetowhite. Additionally, the entirety of the transformation zone must be defined. The size, position and visibility of the TZ are useful in categorizing the TZ into: TZ1, TZ2 and TZ3. The transformation zone is completely visible on the ectocervix in TZ1. However, the TZ extends into the cervical canal in TZs 2 and 3. However, TZ 3 differs from TZ 2 in that, the SCJ is also not fully visible.[96] Table 2.2 shown below gives further details of the types of transformation zones.

Table 2. 2 Classification of the Transformation Zone on the Cervix

Type of TZ	Endocervical Size	Site	Visibility	Adequacy Colposcopy
1	Small or large	Completely ectocervical	Full	Satisfactory
2	Small or large	Partially endocervical	Full	Satisfactory
3	Small or large	Partially/ Completely endocervical	Not full	Unsatisfactory

TZ: Transformation Zone

The International Federation of Cervical Pathology and Colposcopy (IFCPC) provides the nomenclature for colposcopic findings of the cervix as shown below in Table 2.3.

Colposcopy of the cervix may be grouped based on the classification below:

- Routine colposcopy: It is typically performed as a component of all gynaecological examinations.
- Screening colposcopy: It is performed concomitantly while screening for cervical cancer, bearing in mind the increased chances of false negative rate that is associated with Pap smear screen for cervical abnormalities.
- Selective colposcopy: Colposcopic examination is only performed when it is indicated. For instance, colposcopy may be performed in cases where there is increased persistence of inflammatory

cells even after treatment. Colposcopy is also recommended in the evaluation of women who have an abnormal Pap test but no obvious lesions on the cervix or vagina. In addition, selective colposcopy is indicated in women with postcoital bleeding, post-menopausal bleeding and metrorrhagia.

Despite the undeniable contribution of colposcopy to the management and treatment of cervical cancer worldwide, some question marks still linger regarding its accuracy. The issues of accuracy emanate from inconsistencies related to visible alterations in the epithelium of the cervix and the severity of premalignant lesions.[129] For instance, for high-grade CIN 2 or worse, the diagnostic sensitivity is estimated to be in the region of 59.5 – 80.0%.[130] Colposcopy accuracy is associated with a strong sensitivity to high-grade lesions.[129] Figures 2.7 and 2.8 show low-grade and high-grade lesions at colposcopy, respectively.

Description of Colposcopic Findings

The TZ is the most significant anatomical entity in colposcopy. Most cases of malignant and premalignant changes in the cervix arise from the TZ. The size, site and how visible the TZ is, are taken into account when categorizing it. [129]

As much as possible, the entire TZ must be examined without being obscured with inflammation, bleeding, atrophy, or other hindrances. This enables a colposcopist to effectively diagnose disease or otherwise.

Table 2. 3 Colposcopic Terminology from the 2011 IFCPC

	Pattern
General Assessment	Adequate or inadequate for the reason (i.e., cervix obscured by inflammation, bleeding, scar)
	Squamocolumnar junction visibility: completely visible, partially visible, not visible
	Transformational zones 1, 2 and 3
Normal Colposcopic Finding	Original squamous epithelium: mature, atrophic
	Columnar epithelium; ectopy/ectropion

	Metaplastic squamous epithelium; Nabothian cysts
	Deciduosis in pregnancy
Abnormal Colposcopic Findings	
General Principles	Location of the lesion: inside or outside the transformation zone; location of the lesion by clock position
	Size of the lesion: number of cervical quadrants the lesion covers
	Size of the lesion as percentage of cervix
Grade 1	Fine mosaic; fine punctation; thin acetowhite epithelium; irregular, geographic border
Grade 2	Sharp border; inner border sign; dense acetowhite epithelium; coarse mosaic; coarse punctuation; rapid appearance of acetowhitening; cuffed crypt (gland) openings
Non-specific	Leukoplakia (keratosis, hyperkeratosis), erosion Lugol's staining (Schiller's test): stained or non-stained
Suspicious of Invasion	Atypical vessels
	Additional signs, fragile vessels, necrosis, ulceration, tumour
Miscellaneous Findings	Congenital transformation zone, condyloma, polyp (ectocervical or endocervical), inflammation, stenosis, congenital anomaly, posttreatment consequence, endometriosis

Adopted from[129]

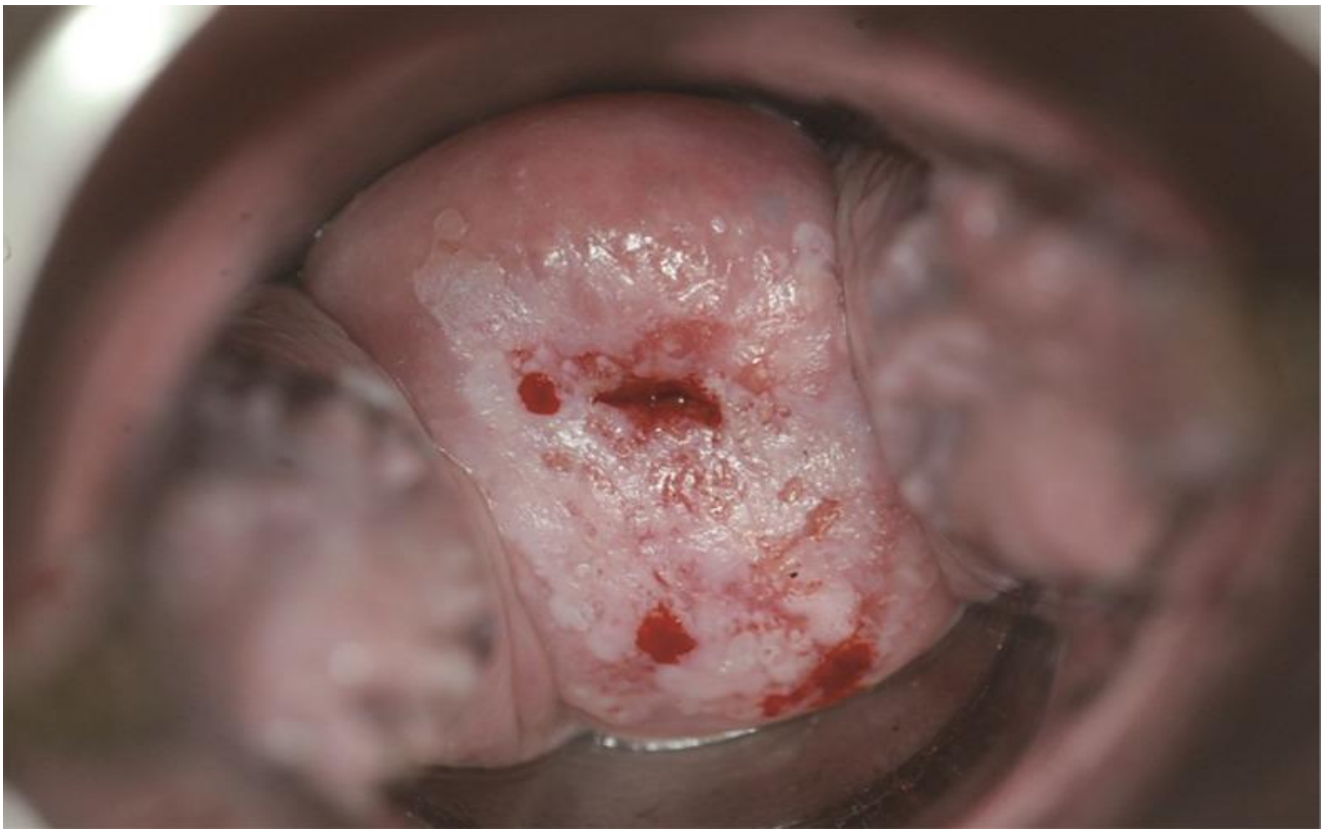


Figure 2. 6: Dense acetowhite lesion on the epithelium without any abnormal vessels (high-grade lesions) Adopted from[129]

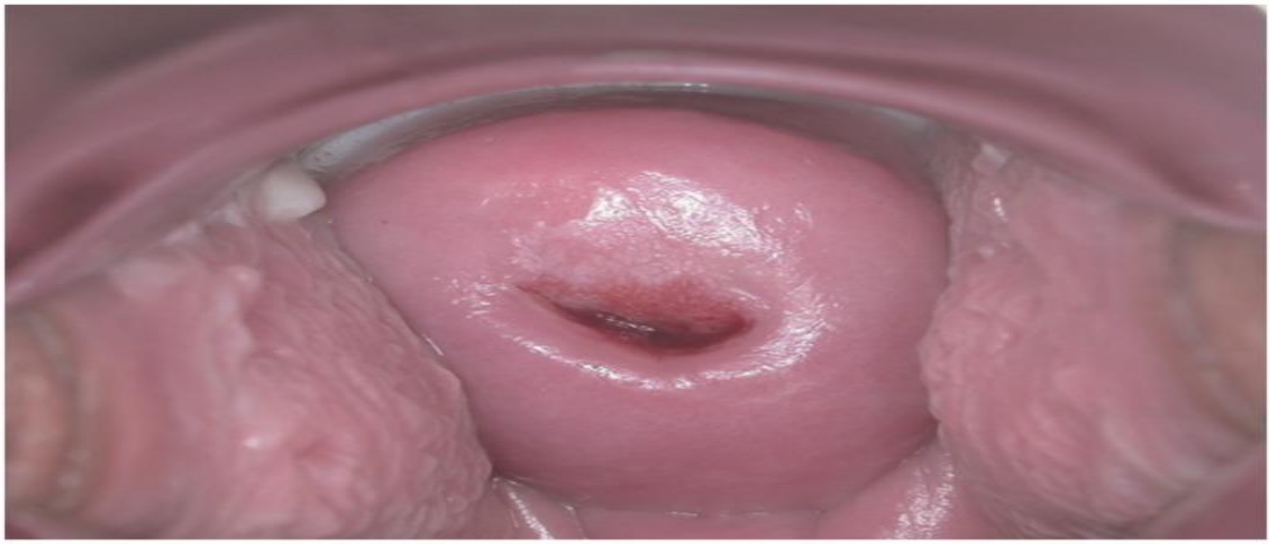


Figure 2.7: Tiny mosaic vessels in a thin acetowhite lesion (Low-grade lesion) Adopted from[129]

The ectocervical portion of the TZ is only occasionally difficult to access, while the upper portion of the TZ may be partially or entirely endocervical. Additionally, even though the ectocervical portion of the TZ that is visible may not exhibit any abnormalities, cervical neoplasia in the endocervical portion that is hidden from view cannot be ruled out.[135]

Normal Colposcopic Findings

A. Transformational Zone

The TZ is the area where the original columnar epithelium has been replaced by metaplastic epithelium and is located between the new SCJ and the initial or original SCJ. The TZ has the following components: branching vessels, Nabothian follicles and gland openings

B. Squamous epithelium

The squamous epithelium is also featureless and has no columnar remnants. The vascular patterns of squamous epithelium are characterized by hairpin capillaries and network capillaries. The initial squamous epithelium seems to be fairly dark pink when compared to the metaplastic squamous epithelium of the transformational zone.[129]

C. Columnar epithelium

The columnar epithelium is characterized by an irregular surface with an atypical grapelike or villus appearance. Each villus is made up of fine capillaries that may be visualized by saline. The presence of underlying stromal vessels renders it a reddish appearance under high magnification.[129] Columnar epithelium may also appear to be erosion at first glance and is surrounded by the new SCJ. For most young women, the new SCJ is located near the cervical os. Refer to Figure 2.9.

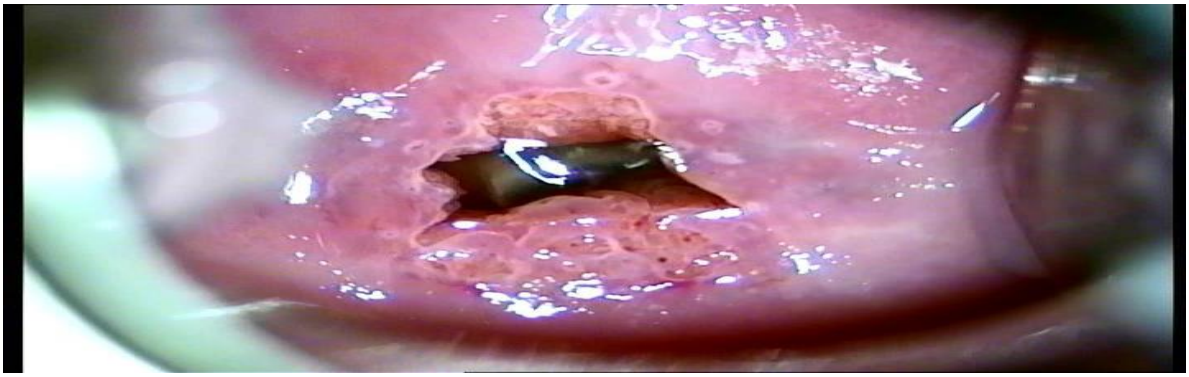


Figure 2. 8 Normal cervix under colposcopy (Adopted from[137])

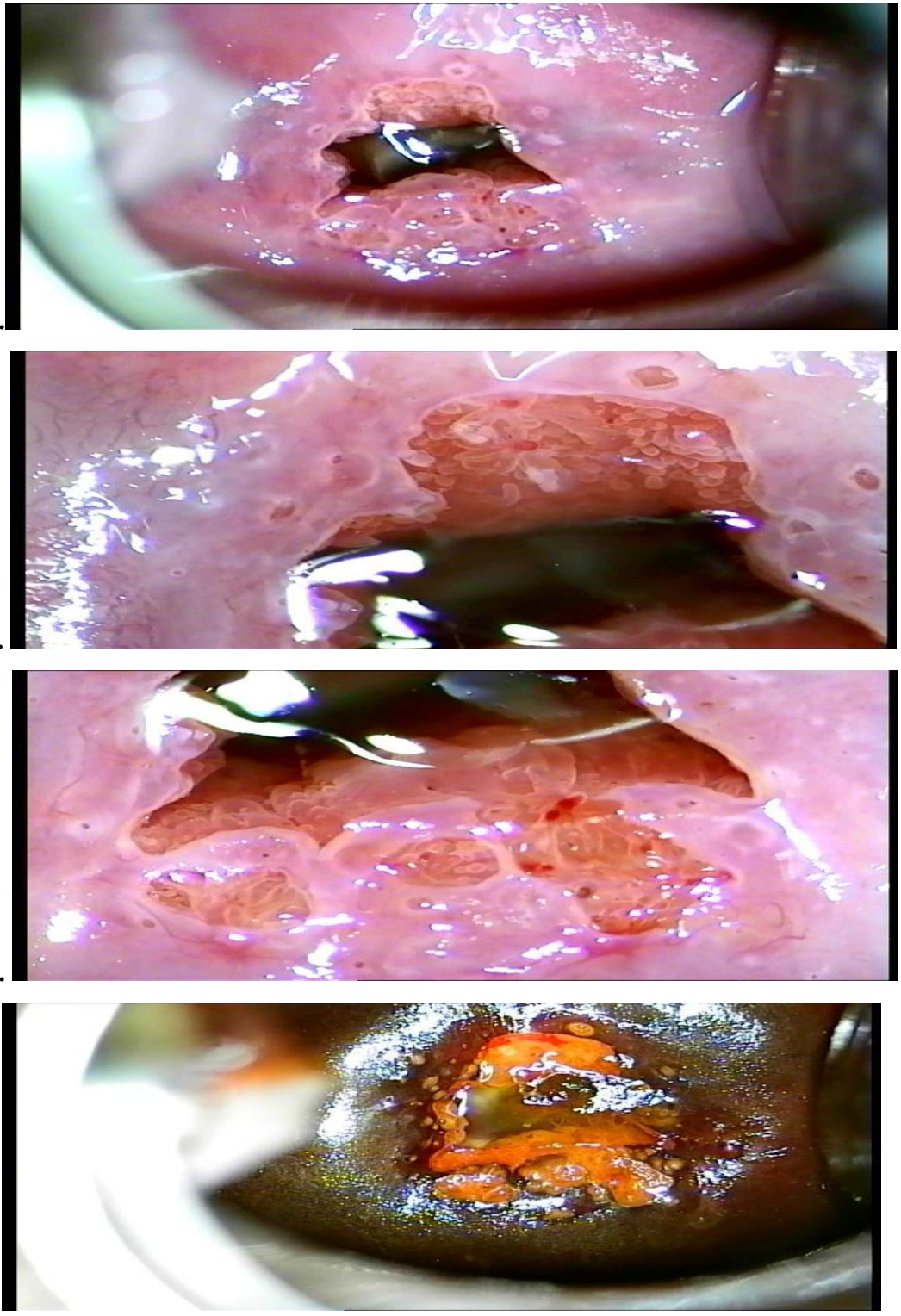


Figure 2. 9 Colposcopic images of the normal cervix (Adopted from[137])

Figure 2.10 A, B, C and D depict several images of a normal cervix. Image D shows the application of Lugol's iodine. The outer limit of the transformation zone does not coincide with iodine positivity since most of the TZ is typically engulfed by relatively mature squamous epithelium, as seen in the case presented above.

Abnormal Colposcopic Findings

Most cases of CIN are restricted to the transformational zone. However, subclinical papillomavirus infection may extend beyond the transformation zone and involve the original SCJ and / or the vagina (caudally) and columnar epithelium (cranially). Colposcopic abnormalities are divided into three categories: grade 1 (minor), grade 2 (major), and non-specific abnormalities. The parameters used for the classification are acetowhite nature of the epithelium, the pattern of vascularity, as well as the modifications observed after the use of Lugol's iodine. Grade 1 abnormalities are benign or low-grade lesions, while grade 2 are high-grade lesions. Non-specific abnormalities may be observed in both neoplastic and benign lesions.[138] Some of the commonly encountered abnormal colposcopic findings are below.

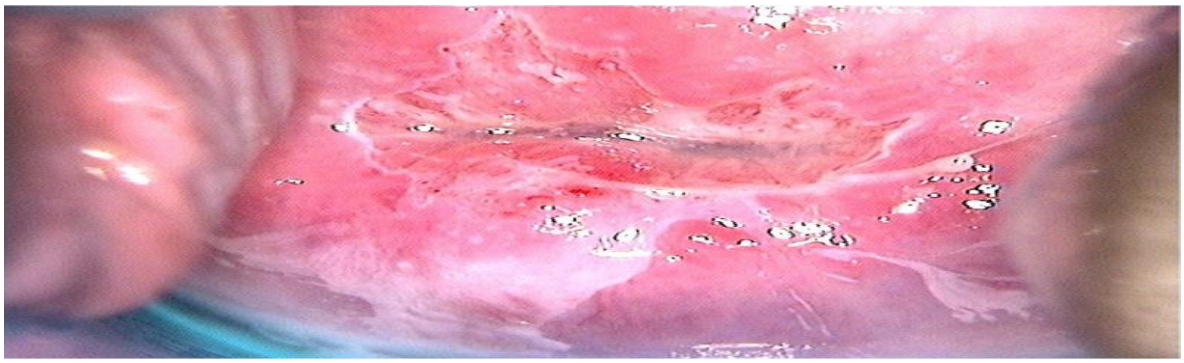
Abnormalities Within and Outside the TZ

The following observations may be encountered within the transformational zone:

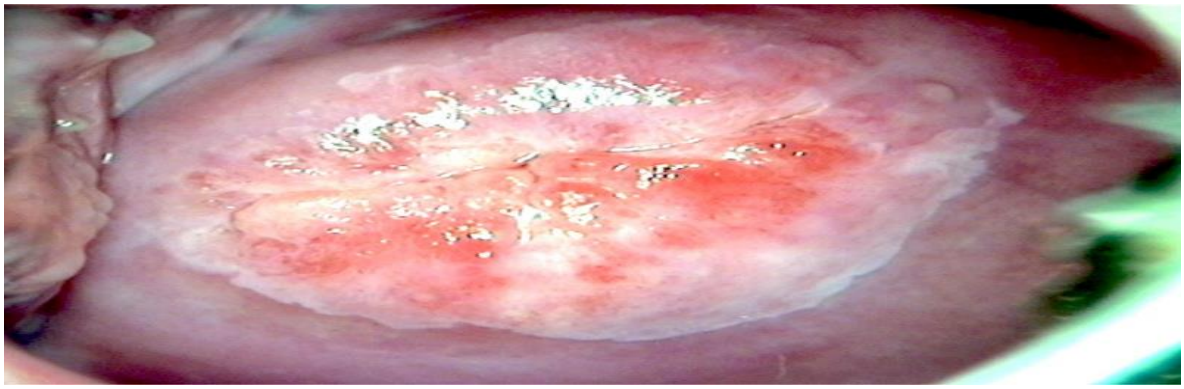
- Acetowhite epithelium

Acetowhite epithelium is the major abnormal lesion that is observed after applying 5% acetic acid. Acetic acid is responsible for the agglutination and removal of cervical mucus, coagulation of epithelial proteins and also the removal of vaginal discharge. The effect of acetic acid is observed within 10 – 30 seconds after application and fades away within 30 – 40 seconds. The white epithelium dissipates over time and is typically seen in regions of increasing nuclear density. As the severity of the lesion intensifies, the density of the acetowhite region also increases concomitantly. An indistinct, patchy or transparent thin acetowhite region is predictive of immature metaplasia or inflammation. On the other hand, the observation of a dense and opaquer lesion suggests the presence of CIN or subclinical papillomavirus infection. When milky acetowhite is observed, it indicates the presence of CIN1 lesion.[138-143] Figure 2.11 A, B and C show acetowhite epithelium.

A. Thin acetowhite epithelium, patchy and transparent



B.Milky acetowhite epithelium



C. Thin but opaque acetowhite epithelium

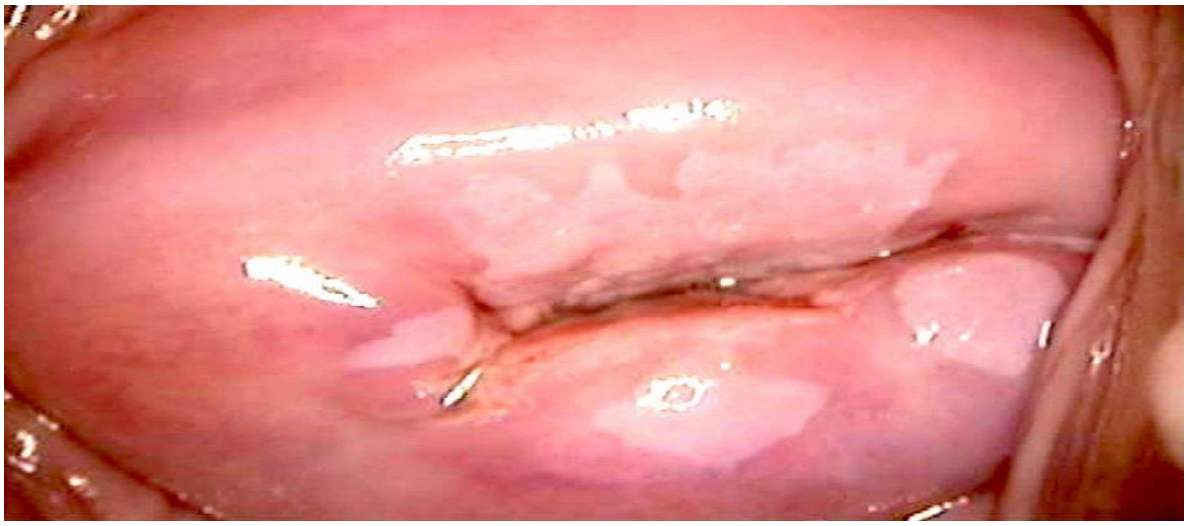


Figure 2. 10 Examples of thin acetowhite epithelium (Adopted from[138])

The dense acetowhite epithelium shown in Figure 2.12 is characterized by a dense opaque white region after acetic acid is added and is indicative of HSIL that is CIN2 or CIN 3. Dense acetowhite epithelium is a grade 2 colposcopic finding and indicates the presence of high-grade lesions. The color is usually greyish-white.

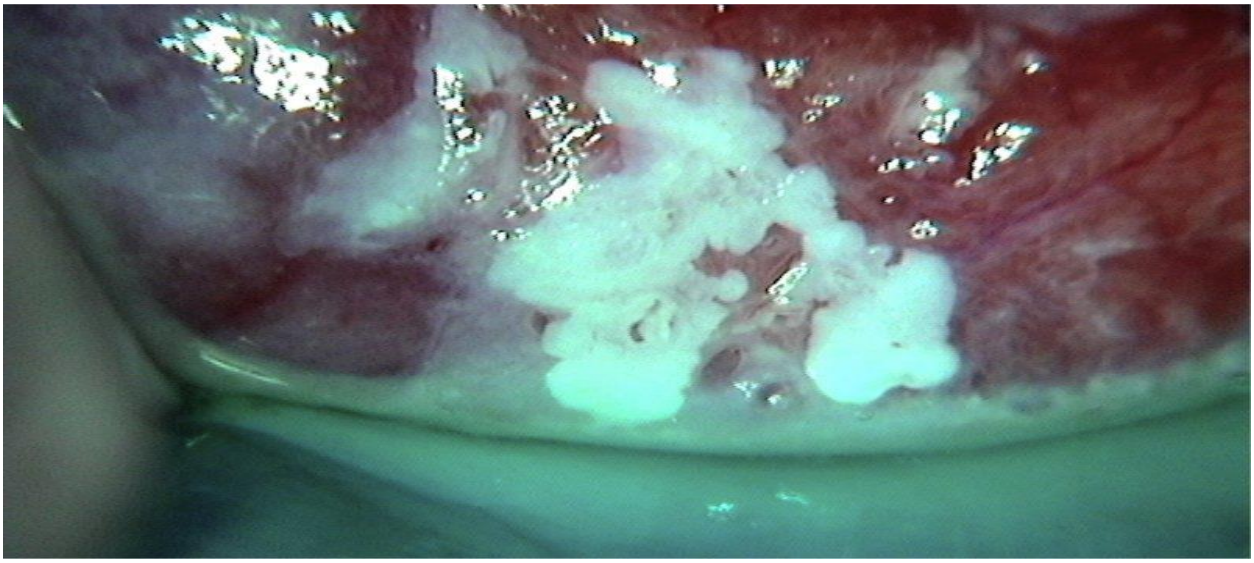
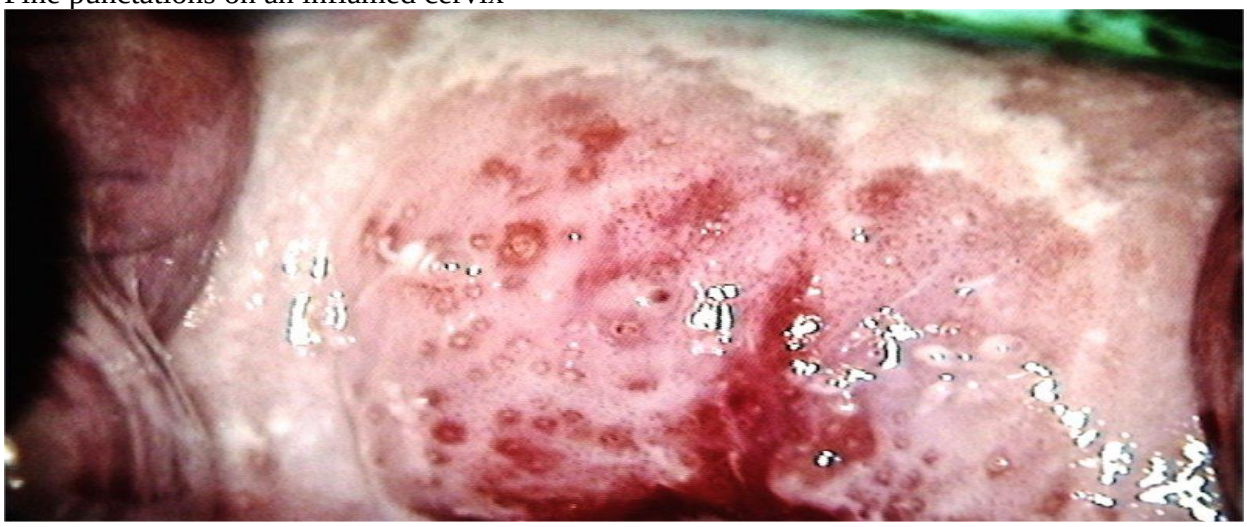


Figure 2. 11 Dense, thick acetowhite epithelium (Adopted from[138])

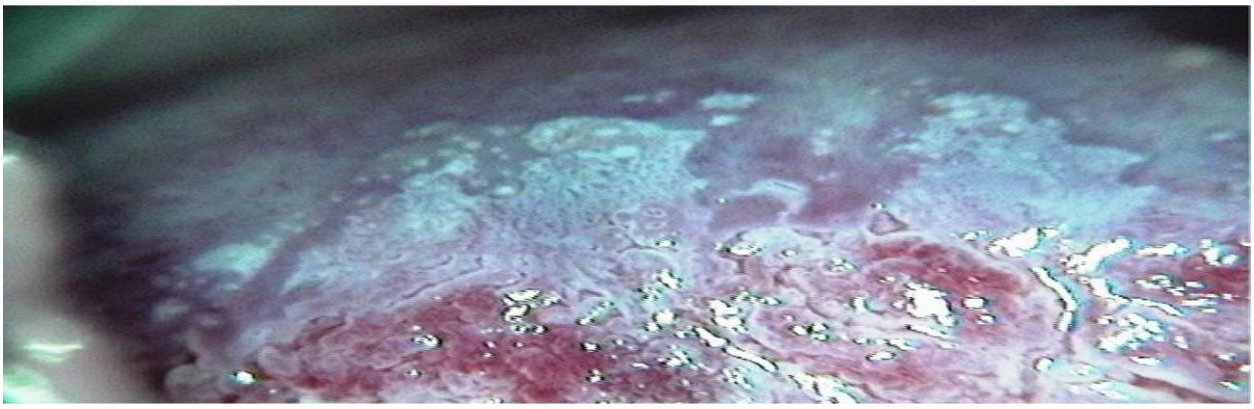
- **Punctation**

Punctations are seen as fine stippling that is formed by the terminal end of intraepithelial capillaries closely spaced with grid-like patterns. When punctations worsen, vessel caliber and spacing increase. It is also not uncommon to find minimal projections of the capillary from the stromal capillary network extending towards the surface. These projections may be tiny and appear to be uniformly placed. They are referred to as fine punctations. Typically, fine punctations may be seen in an inflamed cervix or immature metaplasia. Nonetheless, fine punctations are sometimes seen in subclinical papillomavirus infection (SPI) and CIN1. Figure 2.13 A, B and C show punctation.

A. Fine punctations on an inflamed cervix



B.Acetowhite patch with punctation



C. Coarse punctation with dense acetowhite region in the background

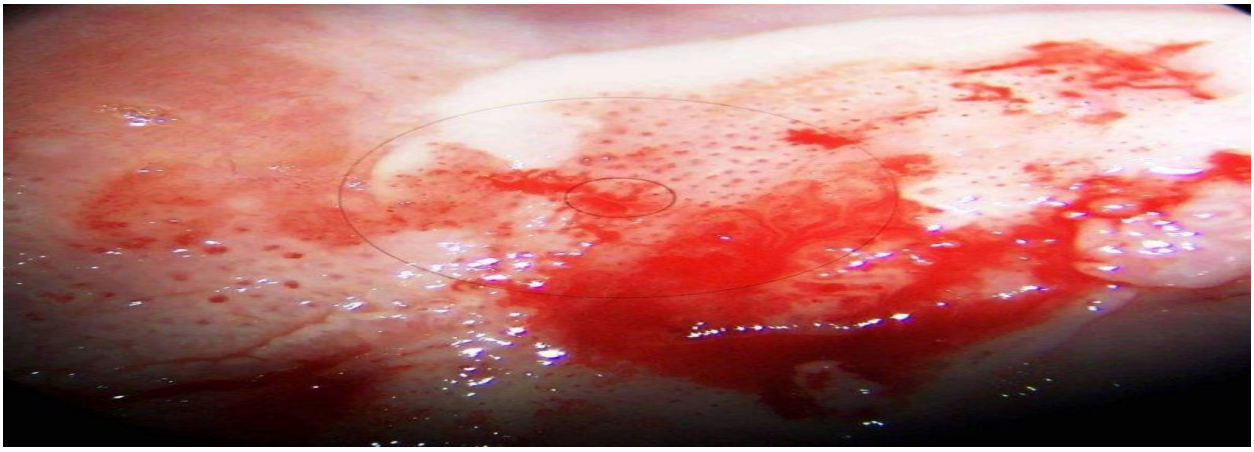


Figure 2. 12 Punctation (Image A, B and C) (Adopted from[140])

- **Mosaic**

- In mosaic patterns shown Figure 2.15, fine blood vessels develop partitions between the acetowhite epithelium, and are typically regular in size and shape. Higher grades are characterized via vessels with longer intercapillary distances and rougher patterns. In coarse mosaic patterns, vessels can be seen readily, are often irregular in caliber, and are unevenly spread out. Coarse mosaic is a typical of high-grade or invasive lesions. They become even more observable after the application of acetic acid.

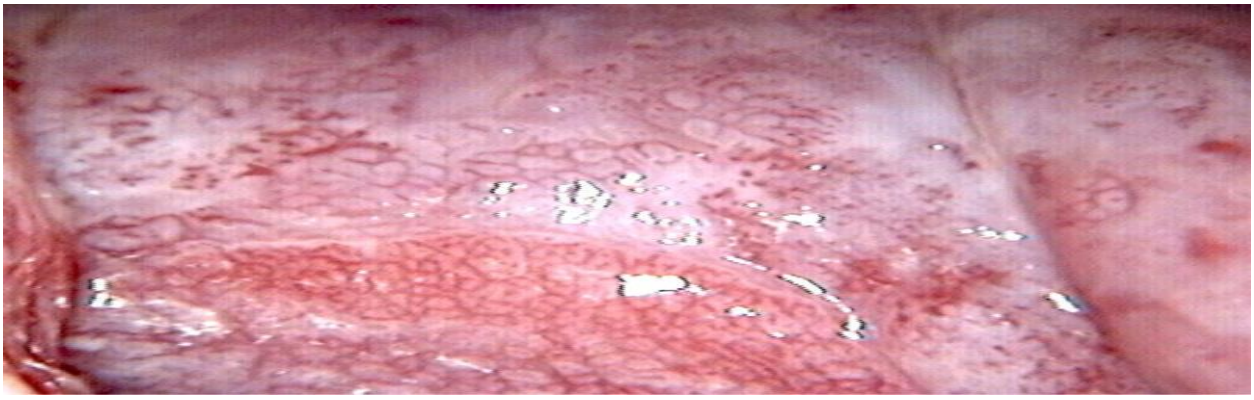


Figure 2. 13 Coarse mosaic pattern on the background of a dense acetowhite area (Adopted from[140])

- **Lugol's iodine staining**

Lesions of CIN, particularly CIN2 or CIN3, are typically iodine- negative (uniform) and are observable as bright yellow (canary yellow/ mustard yellow) iodine-negative regions on the background of normal epithelium (which stain dark brown with iodine). The detection of iodine-negative areas indicates a positive Schiller test. Figure 2.16 shows the cervix after Lugol's iodine staining.

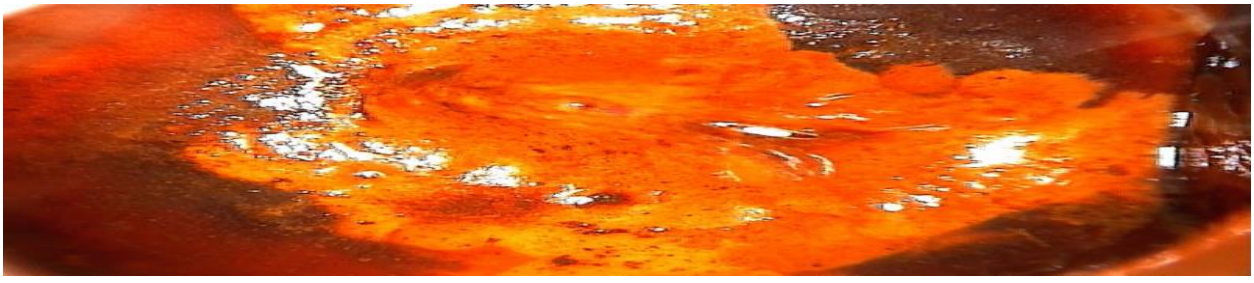
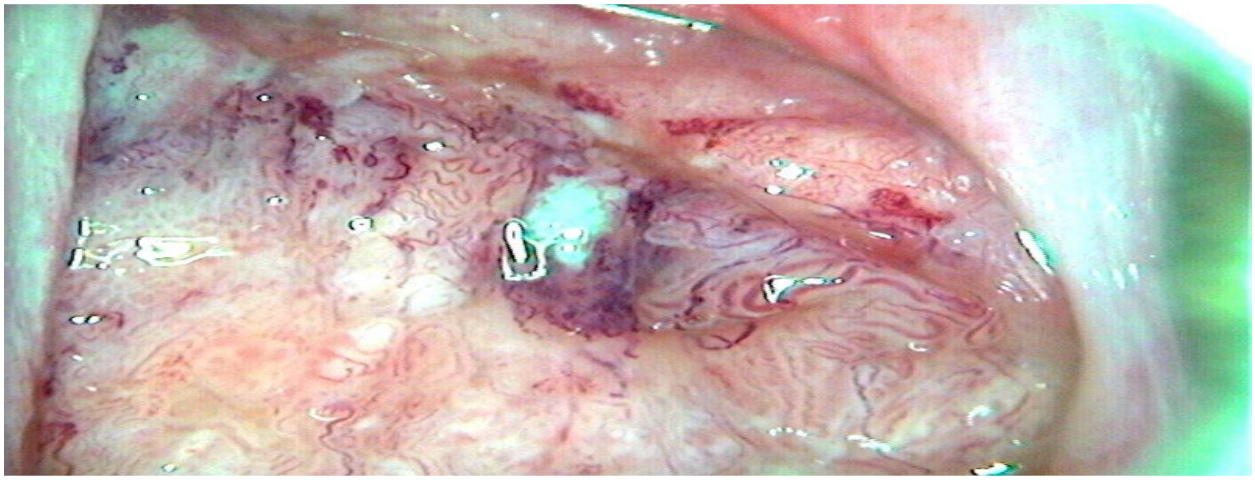


Figure 2. 14 Iodine non-stained area (Adopted from[140])

- **Atypical vessels**

Atypical vessels represent colposcopic abnormalities whereby blood vessels appear irregular with pronounced variation in caliber and with peculiar branching patterns. Atypical vessels are suggestive of invasive cancers. Figure 2.16 A and B show atypical vessels.

A Atypical vessels with bizarre shapes



B. Atypical vessels with 'wasted thread' appearance

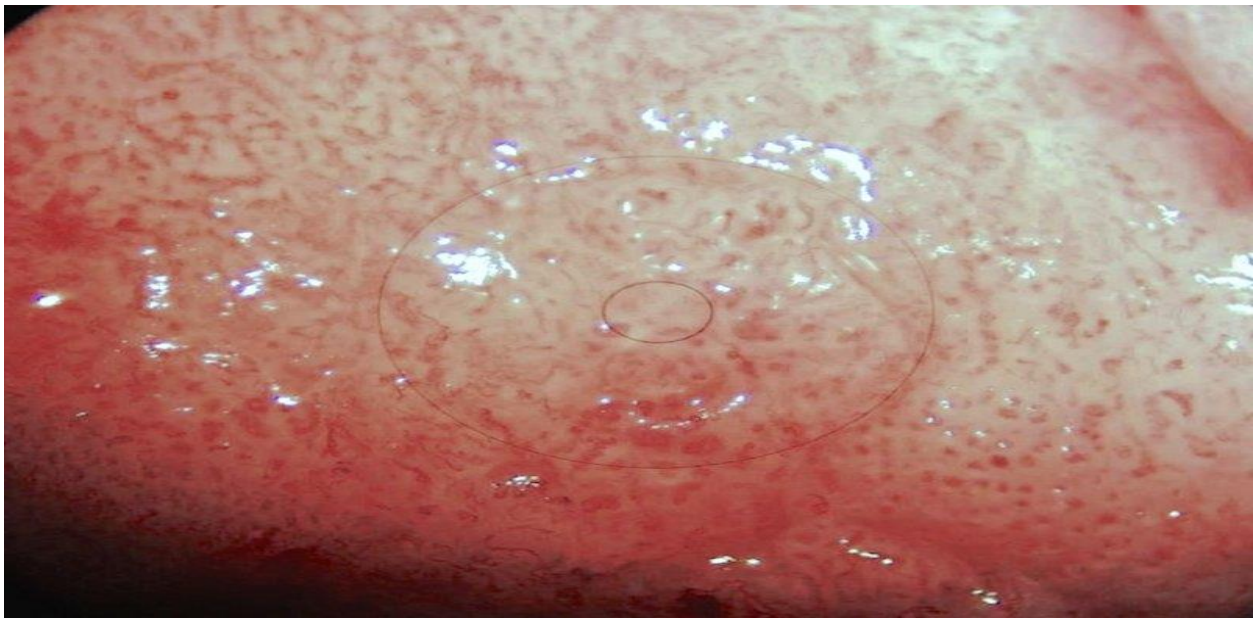


Figure 2. 15 Atypical vessels (Figure A and B) (Adopted from[140])

Suspected invasive carcinoma at colposcopy

Typically, this is not evident upon clinical examination. The lesion is usually raised with irregular surface contour, abnormal vessels, dense acetowhite change, wide irregular and coarse punctate or mosaic pattern of vessels.

Unsatisfactory Colposcopy

Unsatisfactory colposcopy is observed in the following scenarios:

- Squamocolumnar junction invisible
- Severe inflammation or atrophy
- Cervix not visible

Miscellaneous Findings

Miscellaneous findings are indicative of benign abnormalities in the cervix. Examples of miscellaneous findings include:

- Exophytic condyloma, Keratosis (Leucoplakia)
- Inflammation
- Atrophy
- Ulcer, Erosion
- Deciduosis
- Polyps

A systematic, objective way of measuring the severity of premalignant cervical lesions colposcopically is Reid's Colposcopic Index (RCI). The index takes into account; intensity (color tone) of acetowhitening, acetowhite region boundaries and surface shape, vascular characteristics, and color variations after iodine application.

New Guidelines for Cervical Screening

In July 2021, an updated edition on the guidelines for screening and treating cervical cancer was published by the WHO.[144,145] Recommendations that aid countries to improve public accessibility and uptake of cervical cancer screening services, as well as treatment options using up-to-date technologies

were enumerated by WHO. Ultimately, WHO aims to enhance cervical screening and treatment options, in order to minimize morbidity and mortality linked to cervical cancer.[144,145]

In the new guideline, the World Health Organization recommends the use of HPV DNA testing as the gold standard for the diagnosis of cervical abnormalities. Women in the general population should be screened with HPV DNA testing every 5-10 years from the age of 30. There are 2 groups of women of utmost importance: those between 30-49 years and those between 50-65 years who have never been screened before. The shift from Pap smear and VIA has been informed by the relatively higher accuracy of the HPV DNA technique in detecting all the strains of HPV. The HPV DNA technique also provides an advantage of an objective assay for the presence of the viruses which are responsible for cervical cancer unlike methods like Pap smear which are frequently associated with subjective interpretation of cytological smears based on factors such as the experience and competence of the cytopathologist. Any positive cases seen on HPV DNA testing are subjected to genotyping to identify the HPV strain and determine the likelihood of getting cancer. It does not rely on visual inspection like the other methods and is thus less prone to human error. HPV DNA testing is relatively simple, cost-effective, save more lives, and prevents the development of precancerous as well as cancerous lesions.[144,145] The sampling procedure for HPV DNA testing is similar to that of the Pap smear. To obtain the coverage required for an effective decrease in cervical cancer mortality, the use of a less intrusive and more user-friendly primary screening technique (such as self-collected swabs for HPV DNA testing) may be necessary. The global strategy of WHO to accelerate the elimination of cervical launched in 2020 is to screen 70% of eligible women at least twice in their lifetime.[145]

Two main approaches for screening and treating cervical precancer and cervical cancer prevention have been detailed by the WHO in the new guidelines. There first approach is the screen, triage and treat where a patient may be provided treatment based on a positive screening test alone, without triage. That is, treatment will be provided without any second screening test and no histopathological diagnosis. In some instances, if a patient is eligible for ablative treatment, the single-visit approach may be used. That is, it must be done on the same day as the day screening was performed. However, in case the single-visit approach is not feasible, a second visit may be required. The second approach is the screen, triage and treat where a triage test is done in the event of a positive primary test. If there is also a positive triage test then treatment can be offered. A positive triage test is an indication for a colposcopy with biopsy and

histopathological examination. In the event of a positive screening test but a negative triage test, a robust follow-up is recommended.[144]

HIV infection has been shown to enhance the risk of cervical cancer compared to the normal population.[145] The increased risk for cervical cancer is demonstrated throughout the course of life for women living with HIV, starting with an enhanced risk of acquiring HPV infection. In addition, it has been suggested that women living with HIV also have a more rapid progression of HrHPV infection to pre-cancer lesions and subsequently to cervical cancer. Also, there is a reduced likelihood of regression of pre-cancer lesions and higher rates of recurrence following treatment. In the new guideline for cervical screening, 16 new and updated recommendations have been made by the WHO for cervical screening in women living with HIV.[145] For women living with HIV, HPV DNA detection in a screen, triage and treat approach commencing from age 25 with frequent screening every 3 – 5 years.

Other Preventive Measures

The use of barrier methods of contraception such as condoms has been associated with a decrease in the risk of cervical cancer.[146] In a systemic review of 82 publications by Morris et al[147] to determine the association between male circumcision and the probability of infecting their female spouses with STIs, it was found that male circumcision decreases the risk of sexually transmitted oncogenic HPV genotypes. Another systematic review showed a possible protective factor of diet that contains fruits, vegetables, and some bioactive components such as vitamins C and E as well as carotenoids against HPV persistence.[148]

2.1.7 Recommendation for management of preinvasive lesions of the cervix and cervical cancer

Cervical cancer is a serious malignant tumour that causes severe adverse repercussions to women all over the world. Literature reveals that most cases of cervical cancer are attributed to persistent infection with HrHPV.[149] In the past few years, enhanced knowledge of the history of infection with HPV has been adopted as a tool for improving the efficiency of treatment and management methods for cervical cancer. For instance, HPV testing has been used frequently as a screening tool for cervical abnormalities.[150] Due to the high sensitivity of HPV testing, patients are less likely to develop cervical cancer or precancerous lesions within 5 years after a negative HPV test compared to negative results of a Pap test.[151] In addition, compared to the conventional Pap smear test, HPV testing has also been shown to detect more glandular

cervical lesions.[152] HPV testing may also enhance the screening of cervical precancer forms such as adenocarcinoma of the cervix, which may not be sufficiently screened by Pap smear alone. Despite the obvious advantages of HPV testing over conventional Pap smear, patients who test positive for HPV testing may still require further testing or surveillance, leading to significant advances in screening and management practices for cervical cancer.[153]

The American Society for Colposcopy and Cervical Pathology (ASCCP) recently reviewed the 2012 ASCCP management guidelines as its risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors.[150] Even though most of the management recommendations remain do not differ compared to the 2012 ASCCP guidelines, some significant changes were made. For instance, unlike the 2012 ASCCP guidelines that are based on test results-associated algorithms, the new guidelines follow a risk-based approach to ascertain the importance of surveillance, colposcopy or treatment. Also, the new guidelines recommend consideration for the screening history of patients, together with current test results, to inform clinical decision-making.[150] For most patients who have abnormal Pap smear and/ or HPV test results, colposcopy is recommended. Table 2.4 below shows the ASCCP recommendations for managing common cervical abnormalities based on the 2019 management guidelines.[150] Colposcopy is recommended for most patients with positive HPV tests and abnormal Pap tests. The 2019 management guidelines provide the option of hastened treatment for result combinations when the risk of currently having a precancer (CIN3 or above) exceeds 25%, acknowledging that colposcopy is imperfect and that patients may prefer treatment to monitoring. This guideline is aimed at reducing the prevalence of cervical cancer and to standardize screening practices.

According to new data, prior history is crucial when common low-grade results are being considered for management: HPV-positive ASCUS or LSIL. For instance, if a patient presents with a normal history of normal screening results, but has a recent negative screening test result for HPV testing or co-test within approximately 5 years, a new result of HPV-positive ASCUS or LSIL does not indicate a high risk of a current a high-grade precancerous lesion (which is defined as CIN 3 or higher). In such cases, the risk is considered low because the infection is considered new, and usually benign, irrespective of the age of the patient. As such, follow-up HPV testing or co-testing within a year is recommended instead of colposcopy.[154]

In previous guidelines, a colposcopy at which CIN 2 was absent was considered to lower the chances of developing cervical precancer within 1 year although patients were recommended to have annual colposcopy.[155] New risk estimations suggest that a colposcopy where CIN 2 was not found, undertaken within the past year, significantly lowers the chances of developing a high-grade precancerous lesion within the next year.[153]

Table 2. 4 2019 ASCCP Consensus Recommendations for Management of Common Abnormalities

Current HPV result	Current Pap test result	Prior results	Management by 2019 guidelines
Negative	ASCUS	Unknown or HPV-negative	Repeat HPV test with or without concurrent Pap test in 3 years
Negative	LSIL	Unknown or HPV-negative	Repeat HPV test with or without concurrent Pap test in 1 year
Negative	ASC-H	Noncontributory	Colposcopy
Noncontributory	AGC	Noncontributory	Colposcopy
Positive	NILM	Unknown or HPV-negative	Repeat HPV test with or without concurrent Pap test in 1 year
Positive	NILM	HPV-positive	Colposcopy
Positive for genotype HPV16 and/or HPV18	NILM	Noncontributory	Colposcopy
Positive for genotype HPV16 and/or HPV18	ASCUS or LSIL	Noncontributory	Colposcopy
Positive	ASCUS or LSIL	Unknown or HPV-positive	Colposcopy
Positive	ASCUS or LSIL	Negative screening results with HPV testing or HPV plus Pap testing within past 5 years	Repeat HPV test with or without concurrent Pap test in 1 year
Positive	ASCUS or LSIL	Colposcopy confirming the absence of high-grade lesion within the past year	Repeat HPV test with or without concurrent Pap test in 1 year
Positive	ASC-H	Noncontributory	Colposcopy or expedited treatment
Positive: untyped Positive: genotype other than HPV 16 Negative	HSIL	Noncontributory	Colposcopy or expedited treatment
Positive: genotype HPV16	HSIL	Noncontributory	Expedited treatment

ASCUS: Atypical Squamous Cells of Undetermined Significance
AGC-Atypical Glandular Cells
ASC-H: Atypical Squamous Cell Cannot Rule Out High Grade Squamous Intraepithelial Lesions

LSIL: Low-Grade Squamous Intraepithelial Lesions
HSIL: High-Grade Squamous Intraepithelial Lesions
NILM: No Intraepithelial Lesion or Malignancy

For such patients, colposcopy may be deferred while follow-up may be recommended as an alternative. On the other hand, since persistent infection with HPV is a crucial risk factor for the development of cervical lesions, colposcopy is still recommended if the patient remains HPV-positive at the 1-year follow-up.[150]

For patients with unknown history, or with only Pap test results, management criteria are dependent upon the most recent test results of Pap smear and HPV screening. In addition, colposcopy is recommended for all patients with two consecutive positive HPV tests and a normal Pap test result. Also, colposcopy may be done on all results of HPV-positive ASCUS or a more severe cytology interpretation. HPV-negative ASCUS subjects may be followed up in three years.[154,155]

In addition, all patients with HPV 16 and/ or 18 infections must undergo a colposcopy, regardless of the results of Pap smear test.[156] Endocervical curettage (ECC) or endocervical sampling may be recommended in patients with HPV 18 during colposcopy as a result of the relationship between HPV 18 and ACs.[157]

Furthermore, expedited treatment may be preferred for patients who have recent HPV-16 positive HSIL since their current chances of developing CIN2 or higher lesions is more than 70%.[156] Expedited treatment may also be recommended for HPV-positive HSIL irrespective of HPV genotype for patients who are yet to undergo screening within the past 5 years. Expedited treatment may also be regarded as a treatment strategy for subjects with HPV-positive with Pap results of ASC-H and also for subjects with HSIL Pap test results regardless of their HPV status.[150]

All of the TZ can be treated via ablative techniques such as thermal ablation and cryotherapy or excisional techniques such as cold knife conization and large loop excision of the transformation zone in cases of precancerous lesions of the cervix. The size and site of the lesions are also factors that influence the management options. Hysterectomy is also an option mainly for women who have completed their families.

While both excisional and ablative techniques have comparable safety profiles, the former is more effective.[170] Also, one can obtain a sample for histopathology with excisional methods as compared to

the ablative methods. However, the ablative methods are suitable for low-resource setting as it is simpler, cheaper and have a lower risk of complication. The see-and-treat approach has been adopted to reduce the number of patients lost to follow. In this point-of-care approach, abnormal lesions that are seen on screening such as acetowhite areas on VIA are immediately treated with cryotherapy or LEEP (Loop Electrosurgical Excision Procedure) before the patient goes home in a single visit. In cryotherapy, the cervical epithelium is crystallized when Nitrous oxide (N_2O) or carbon dioxide (CO_2) gas freezes it to a temperature of −20°C via a probe. The gases used are in a compressed state. In Thermal ablation, the cervical epithelium is destroyed by heating with the probe at a temp of 100°C applied for 20 to 45 seconds. Both the stroma and the underlying crypts are dried due to the heat. Large loop excision of the transformation zone is done on outpatient bases using local anaesthesia. The cervix is excised from the transformation zone in a cone-shaped manner using a loop electrode which is powered by an electrosurgical unit. Most patients can be treated by this method. Cold knife conization is mainly used for those with microinvasive carcinoma and AIS under general anaesthesia, as better tissue can be obtained for histology. A scalpel is used to make the excision. The excision depth is better adequately controlled in this method than in LLETZ (Large Loop Excision of the Transformation Zone).[156]

Treatment is typically not necessary for CIN 1 lesions unless the lesions continue for more than two years, there is suspicion of undiagnosed more advanced disease, or the abnormalities progress to a higher grade on cytology, colposcopy, or histopathology. CIN 2 and CIN 3 will need further categorization and treatment. Definitive treatment can only be withheld for a while in pregnant women.

For patients with an invasive disease on histology, follow-up treatment such as radiotherapy or surgery is arranged by the oncologist after the disease's staging. If the endocervical margin is affected after an excisional technique for precancerous lesions has been done, a repeat treatment may be necessary. However, a positive ectocervical margin does not require a repeat procedure.[157]

2.2 Prevalence of Abnormal Cervical Cytology in Postpartum Women

Gynaecologic malignant tumours have gained much attention in recent times, in part due to the rising number of old-age pregnancies. Cervical cancer accounts for 71.6% of the most prevalent gynecological malignant tumors in pregnancy, followed by ovarian malignant tumors with a 7.0% prevalence.[158] The incidence of pregnancy-related cervical cancer is on the increase as a significant proportion of women nowadays tend to postpone childbearing until older ages. Additionally, although pregnancy is not known

to either increase the incidence or affect the progression of cervical cancer, an estimated 1 – 3% of all cases of cervical cancer are diagnosed during pregnancy or postpartum.[158] Despite the relatively low incidence rate, the absolute number of postpartum or pregnant cervical cancer patients is considerably high, requiring the attention of practitioners and researchers alike. The majority of women are asymptomatic in the early stages of the condition. Nonetheless, a few symptomatic patients may present with irregular vaginal bleeding or foul-smelling vaginal discharge.[159] The advent of effective screening techniques has decreased the incidence of cervical cancer through an increase in the detection and treatment of preinvasive lesions of the cervix.[18-20]

Most women in developing countries do not find it necessary to visit a gynaecologist until during pregnancy or after delivery. Consequently, cytological screening of women during pregnancy has become an important tool in identifying the early stage of the disease and initiating treatment whenever necessary.[160] Studies indicate that cytological screening of pregnant women can attain similar accuracy to that of non-pregnant women.[161] However, cervical cytological screening during pregnancy poses some significant challenges. For instance, hormone-induced cervical alterations render the identification and evaluation of abnormal findings difficult in pregnancy, particularly due to normal pregnancy-associated metaplastic changes. In addition, alterations in maternal estrogen levels result in glandular hyperplasia of the mucosa of the cervix, migration of squamous-columnar junction as well as other irregular morphological presentation of cells, which may be mistaken for dysplasia.[162] The challenges experienced with Pap testing during pregnancy are not seen in the postpartum period making it probably a better time to take the test. It must also be noted that Pap smears showing cytological abnormalities in pregnant women are repeated in the early weeks after childbirth as some of them may regress to normal findings after delivery.

The 2014 Bethesda method is used to categorize abnormal smears such as squamous intraepithelial lesions (SIL).[163] Per the severity of the pathological alterations, squamous intraepithelial lesions are further categorized into low-grade and high-grade subtypes, respectively. The most frequently encountered cervical abnormalities in Pap smear tests are Atypical Squamous cells (ASCs), which may be further subdivided into ASCUS or ASC-H. Cells of the ASCUS do not exhibit complete abnormality, although there is some degree of uncertainty regarding the nature of cell changes. Cells of the ASC-H category also appear to be abnormal but also possess a higher tendency of being preneoplastic as

compared to lesions of the ASCUS category.[164] LSIL and HSIL have also been described as abnormal Pap smear findings. HSILs are more likely to develop into carcinoma in situ (CIS) or cervical cancer if not appropriately controlled or treated.[143] Other classifications of abnormalities of cervical smears include NILM, Atypical Glandular Cells Not Otherwise Specified (AGC-NOS), AGC suspicious for AIS or cancer (AGC-neoplastic) and AIS. [165]

Studies have shown varying prevalence for abnormal cytology in different parts of the world in both pregnant and non-pregnant women including those in the postpartum period.[1,31,166] A number of these studies have been enumerated below. The prevalence of abnormal cervical cytology among 6 weeks postpartum women and non-pregnant women was 9.3% and 10.5% respectively in a 2022 study done in Enugu, Nigeria.[31] The difference between the two different prevalences was not statistically significant. It was a cross-sectional study that involved 172 postpartum women and 172 non-pregnant women selected via systemic sampling method. Pap smear was done for all the participants after they had been educated, as a number of them were not aware of a Pap smear prior to the study. LSIL was the commonest abnormal cervical cytology in both groups. Because just one centre was used in this investigation, it is challenging to generalize the results.

A 2012 population-based study done in Nigeria also had a prevalence of 7.6% for abnormal cervical cytology among 11,104 participants.[167] To be included in this study, the participants had to be 15 years or more and had to be sexually active as well. This is in contrast to other studies where the starting age was 21 years and above.[16,168] Before 21 years, the likelihood of having an abnormal Pap smear is low due to the pathophysiology of the disease and this explains the relatively low prevalence rate of abnormal smear abnormality in this Nigerian study though the mean age of the participants was 39.8 years. The study also postulated that for low-resource countries, the age for initiation of Pap testing can be 30 years as that is the population who are most at risk of cervical cancer.

The prevalence of abnormal cervical cytology was found to be 3% in a 2016 study done in Calabar, Nigeria.[21] It was a prospective study done among 6 weeks postnatal women and the conventional method of smear collection was used. In contrast to other research, this one went ahead and performed colposcopy on those who had abnormal cervical cytology. 3 out of the 100 women had LSIL and the colposcopy done showed no abnormal lesions. The sample size of 100 was also relatively small. Over 90% of the

participants had not heard of Pap smear or cervical cancer before the study. The prevalence of 3% for abnormal cervical cytology in this Nigerian study[21] was very similar to another study[169] done in Jordan.

Another Nigerian study was also conducted in 2017 to determine the incidence, possible risk factors and the course of preinvasive cervical lesions in pregnant women.[170] In that cross-sectional study, 250 pregnant women who visited the hospital's antenatal clinic were enrolled, and their conventional Pap smears were collected using the accepted protocol. In the same study, the authors reported that out of the total number of participants who underwent a Pap smear test during their antenatal period, 15 (6%) had preinvasive cervical lesions, of which 13 (87%) were LSIL while 2 (13%) were HSIL. A total of 158 women (63.2%) had negative smears and the remaining 77(30.8%) had inflammatory conditions of the cervix. Postpartum Pap smear follow-up revealed that 9 (69.2%) of women had a persistent disease while 2 (15.4%) of the women who had LSIL became negative. Two women who initially had LSIL were lost to follow-up. For participants who initially had HSIL, disease progression was observed in one woman (50%), while regression was seen in the other. Because some of the lesions regressed after the antenatal screening, the researchers concluded that all women who undergo an antenatal smear should also get a postpartum smear.

In a 2020 Indian study, Gill and colleagues[1] conducted a prospective observational study at AIIMS, Rishikesh, between January 2018 and January 2019 by performing Pap smear testing on 237 spontaneously conceived antenatal women with ages ranging between 20 and 35 years. In the same study, participants were followed-up for postpartum reassessment after 6 weeks of delivery. This is different from other studies where either only postpartum women or antenatal women were assessed. The results of the study were as follows: eight (8) women out of the total 237 sampled had positive results for pre-malignant lesions of the cervix in the antenatal testing (5 cases of ASCUS, 1 case of AGC, 1 case of ASC-H and 1 case of HSIL). When post-natal Pap smears were performed, only one case of HSIL from the antenatal testing remained the same in the postnatal period. Positive cases recorded in the antenatal smears that had regressed to normal findings were as follows: ASCUS (n= 4), AGC (n= 1), and ASC-H (n= 1). The authors of this research also agreed with the 2017 study by Bakari et al[170] and the 2021 study by Nungrutai[171] that postpartum smears must also be repeated for women with abnormal cervical smears during the antenatal period due to the significant regression rate.

Khaengkhor and compatriots[166] conducted a study in Thailand to ascertain the prevalence of aberrant cervical cytology using LBC in pregnant women who attended the antenatal care clinic at Thammasat University Hospital in 2011. The study adopted a total of 143 pregnant women with an average age of 27.09 years whose cytological smears were taken and subsequently reviewed by experienced cytopathologists using the Bethesda System 2001 criteria for precise diagnosis. Participants who had abnormal results were referred for further examination using colposcopy. The results of the study revealed 10 abnormal Pap smear results with 4, 5 and 1 cases each of ASCUS, LSIL and HSIL respectively. The study reports a 7.0% prevalence of abnormal cervical cytology with 0.7% being HSIL.

Chakraborty et al[3] did a retrospective study in a tertiary hospital in India where the conventional Pap test of 1058 women were assessed starting from 2012 to 2015. The participants aged 20 to 90 years had complained of symptoms such as vaginal discharge. The prevalence of abnormal cervical cytology was 16.3% (13.3% of them having SIL (8.1%-LSIL, 4.9%-HSIL, 1.1%-ASCUS) and 3% having ICC. The reason for the high incidence of abnormal cervical cytology is probably because the participants presented with symptoms of disease compared to the other studies where asymptomatic participants were screened with Pap smear testing. This corroborates with another study by Sachan et al[9] in 2018 where all the cases of abnormal cytology were in women who had symptoms such as dyspareunia, postcoital bleeding and irregular bleeding. In addition, Sachan et al[9] also found a prevalence of abnormal cervical cytology to be 8.47% among 1645 women who were sexually active and above the age of 21 **y**ears. The percentage for ASCUS, LSIL and HSIL were 2.90%, 5.09% and 0.48% respectively. A 2014 study done in 2 different sites in Ghana located in Ashanti region showed significant differences in the prevalence of abnormal cervical cytology.[115] The prevalence was 12.6% in Agogo and 3.5 % in Nkawie.

A Chinese study done by Fan et al[172] in 2008 involving a rather large sample size of 11906 cases showed a prevalence of abnormal cervical cytology of 13%. The commonest abnormality was ASCUS consisting of 1134 women (9.52%,) followed by LSIL among 229 women (1.92%). The remaining abnormalities were AGUS 112(0.94%) and HSIL 74 (0.62%). Abnormal cervical cytology significantly correlated with ($P < 0.01$) infection with Trichomonas Vaginalis and HPV infection.

A study done in Gauhati Medical College, India by Sarma et al[181] had a prevalence of abnormal cervical cytology of 11.95% which is close to the 13% obtained by Fan et al [172]. This study was done among 242 participants who were between the ages of 20 and 60 years with all of them having symptoms of

gynaecological disease. White vaginal discharge was the most common clinical presentation with 171(70.66%) of the participant having it. A total 16 of the samples were unsatisfactory thus only 226 of the Pap test results were analyzed. Out of the 11.95% of abnormal cervical cytology; the pattern of the distribution was ASCUS 3(1.32%), LSIL 8(3.53%), HSIL 8(3.53%) and SCC 8(3.53%).

A study done in 2014 delved into the prevalence of abnormal cervical cytology among adolescents in South Africa with HIV and those without HIV.[92] It was premised on the fact adolescents are a high-risk group for cervical smear abnormalities due to their high-risk sexual behaviour. HPV DNA testing was done in addition to the Pap smear testing in this study via a self-collected sampling technique. A total of 35 HIV-positive adolescents and 50 HIV-negative adolescents were accessed and those with a history of HPV vaccination and cervical surgery were excluded. The prevalence of abnormal cytology was 10% and 6% respectively for the participants who were HIV positive and those who were HIV negative respectively. The higher incidence among those where HIV positive is not surprising as being HIV positive increases the risk of abnormal cervical smear.

Another comparative study on the prevalence of abnormal cervical cytology was also done in 2012 by Orlando et al[47] where 3 different groups; women living with HIV, recent migrants and a control group were studied.[65] The prevalence of abnormal cervical cytology were 16.3%, 8.4 % and 9.3% for the women living with HIV, recent migrants and the controls respectively. Women who were recent migrants surprisingly had the lowest prevalence of abnormal cervical cytology. This was attributed to the relatively small number of participants in that group as they had 417 participants compared to the 1910 in the control group and 766 in the HIV infected women group.

Another study was done in known HIV-discordant couples where 64% (283/441) of the women were HIV infected and the remaining 36% (158/441) of the women were HIV-uninfected but with HIV-infected partners in Kenya.[173] There was no statistically significant difference between the prevalence of cervical smear abnormalities in the HIV-infected women (26%) compared to HIV uninfected women (20%; p=0.35).

A 2011 study among pregnant women also showed a prevalence of 7% for abnormal cervical smear abnormalities in Thailand[166]. This study made use of liquid-based cytology unlike the conventional

methods used in most other studies. Those with abnormal cytology were referred for colposcopy. Another study made use of postmenopausal women as the study participants and as high as 37.5% out of the 320 participants had varying degrees of cervical smear abnormalities including ICC.[125]

Another dimension was added when the prevalence of abnormal cervical cytology was studied strictly among HIV-positive mothers at 6 weeks postpartum in Kenya in 2008.[174] It is well known that women with HIV tend to have more aberrant cervical cytology.[175] As high as 65(37%) of the 175 participants had abnormal cervical cytology. The types of abnormal cytology found were as follows: 9% -ASCUS, 7%- AGUS, 17%- LSIL, 6 %- HSIL and 3%-SCC. In that same study, VIA was also done for the participants alongside the Pap smear to compare the two screening tests. A total of 68 (39%) of the participants has positive results from the VIA with 25% of the smears having infections or bacterial vaginosis. The agreement between VIA and Pap smear results was moderate.[174]

A prevalence of 76% (114/150) of abnormal cervical cytology was recorded in a similar study done among HIV-positive women in Zambia in 2006.[176] This is said to be one of the highest prevalence of abnormal cervical cytology in a study done in any population of the world. The distribution of the 76% abnormal cervical cytology was as follows; 23.3% was LSIL, 32.6% was HSIL, and 20% represented lesions suspicious of SCC. Aside from the fact that the study was conducted on HIV patients, who have a higher risk of aberrant cervical cytology than the general population, the prevalence found was attributed to the sophisticated liquid-based cytology utilized in place of the traditional methods that prior studies had used.

In a related study, 442 women were evaluated over a year in 2 tertiary hospitals at Oman in 2019.[177] The study's goal was to determine the prevalence of abnormal cytology and risk factors associated with it among women aged between 21 years and 65 years. The mean age of the participants was 39.0 years. The prevalence of abnormal cytology was 3.7 % with a distribution of ASCUS (1.8%), LSIL (1.4%) and SCC (0.5%). This low prevalence was attributed to the Oman’s extreme conservative culture where sex outside marriage is prohibited thus reducing the incidence of high-risk sexual behavior. One can be imprisoned for up to 3 years for having sex outside marriage in that country.

A prevalence of 5.92% for abnormal cervical cytology was discovered among 287 India women in a study done between 2013 and 2016.[178] Additionally, abnormal cervical cytology prevalences of 9.05%,

12.60% and 11.95%, respectively were found in the investigations conducted by Patel et al[179], Al Eyd et al[180], and Sarma et al[181].

2.3 Description of the Types of Abnormal Cervical Cytology in Postpartum Women

The possible abnormal cervical cytology findings include ASCUS, ASC-H, LSIL, HSIL, AGC and ICC. Distribution of abnormal smears were; 38 (9%) cases of ASCUS, 41 (9%) cases of LSIL, 9 (2%) cases of ASC-H, 14 (3%) cases of HSIL, and 2 (<1%) cases of SCC in a study done among 441 HIV discordant couple in Kenya among.[173] Unsurprisingly, there was a higher prevalence of high-grade lesions among the HIV-infected women compared to the HIV-uninfected women whose partners were HIV-positive. (7% vs. 4%; p=0.17).

Out of the 100 participants in the 2015 study conducted by Padmini et al[182], an abnormal cervical cytology distribution of 8%, 5%, 3% and 1% for ASCUS, LSIL, HSIL and ICC were seen respectively. Thus, ASCUS was the most common cervical smear abnormality. This study looked at the cytology findings and colposcopy finding of patients who had an unhealthy cervix.

In a research done at Turkey in 2012 using 100 pregnant women and 86 non-pregnant, there was a disparity in the pattern of abnormal cervical cytology occurrence between the two groups.[135] 0.9% of pregnant population had ASCUS compared to the 3.5% ASCUS in the non-pregnant population. Additionally, LSIL was found to be the next common abnormality in the non-pregnant population but it was not present at all in the pregnant population.

In studies by Fan et al[172] and Suzuki at al.[183], ASCUS was the most prevalent cervical cytology anomaly. Suzuki et al[183] analyzed the results of 1213 Japanese women's early pregnancy and postpartum Pap smear tests on 234 of them. The hormonal effects of pregnancy led researchers to the conclusion that Pap smear results obtained during the postpartum period were more reliable than those obtained during pregnancy. Saha et al[178] reported ASCUS (5.92%) to be the most common cytological abnormality.

In other studies, ASCUS has been shown not to be the most common cervical smear abnormality.[15,31,166,174] Khaengkhor et al[166] found that among the 143 women who participated in the

study, there were 5 cases of LSIL, 4 cases of ASCUS, and 1 case of HSIL. Thus, LSIL was the most prevalent cervical cytology anomaly. This was followed by ASCUS with a prevalence of 2.8% and HSIL also with a prevalence of 0.7%. Bakari et al[170] reported 13 (5.2%) and 2 (0.8%) instances of LSIL and HSIL among pregnant women in a related investigation carried out in Nigeria. LSIL was therefore the most prevalent abnormality.

In a study done in 2014 among South African adolescents, it was found that LSIL was the most common cervical smear abnormality among those with HIV and those without HIV with prevalences of 17.1% and 4.0% respectively.[74] The least common smear abnormality in both groups was ASC-H with a percentage of less than 6% in both groups. Sachan et al[184] found a distribution of abnormal smear abnormalities to be ASCUS (2.90%), LSIL (5.09%) and HSIL (0.48%). Thus, LSIL was the most predominant and HSIL was the least common. This study was done among 1650 Indian women who reported to the outpatient gyaenecology clinic presenting with symptoms such as vaginal discharge.

Similarly, Verma et al[185] found a similar pattern where LSIL was the most common cytological abnormality whereas ASCUS was the least common. The distribution of abnormal smears was as follows; ASCUS (1%), LSIL (5.5%), and HSIL (2.5%). A similar pattern of LSIL being among the commonest abnormal cytology finding was also found in a recent study done by Patel et al[186] using 330 women. LSIL was 2.42 % whereas ASCUS was 1.82% of the study participants. These were the only abnormalities seen in this study.

A study done in 2 different sites in Ghana showed differences in the most common cervical smear abnormality underscoring the effect of location where a Pap smear is performed.[115] Among the 119 in Agogo and 255 participants in Nkawie, the most predominant smear abnormality were LSIL (7.6%) and HSIL (2%) respectively. 1 case of ICC was seen in the participants in Agogo whereas there was no case of ICC in Nkawie. The 26 abnormal cases comprised 17(5.92%) cases with ASCUS, 5(1.74%) cases of LSIL, 1(0.35%) case of HSIL, 3(1.04%) cases of SCC in a 3-year study done in rural India.[187] 300 Pap smears were done for non-pregnant women in another India study where 15 out of the 300 had abnormal smear. LSIL was the highest being 2.7% (8/300) followed by SCC 1% (3/300) in 2012.[188] The least common abnormality was AC 0.3% (1/300). The participants in that study had presented to the gyaenecology clinic with minor complaints.

2.4 Factors Associated with Abnormal Cervical Cytology in Postpartum Women

Several factors are associated with the persistence of abnormalities in cytological smears of women, particularly during pregnancy and postpartum. According to a 2016 paper by Ago and colleagues, in women who were six weeks postpartum, abnormal cytology of the cervix was linked to a positive family history of cervical disease.[21] However, sexual behaviour was not statistically significantly associated with abnormal cytology in that population.

A similar finding was seen in a 2008 study among 6 weeks postpartum women who were HIV positive, where only a confirmed history of cervical cancer in the family was found to be strongly linked to aberrant cervical cytology. Other factors such as age, marital status, educational status, parity, the number of lifetime sexual partners, mode of last delivery, and contraceptive use were not significantly associated with abnormal cervical cytology.[174]

In a different study, the risk of abnormal Pap test findings appearing after a diagnosis of SLE (Systemic Lupus Erythematosus) was examined along with the factors that are linked to the lifetime occurrence of abnormal Pap smears in women with SLE, Bernatsky et al[189] pooled data from the SLE cohorts from three centres together with available information on smoking, history of STI gynaecologic history, the use of oral contraceptive use, and cervical cytology finding. In the study, the authors used logistic regression to ascertain the chances of lifetime cervical abnormalities based on exposure to these factors. The study's findings showed that, in adjusted analyses, a history of STI and continued use of oral contraceptives were both positively associated with reports of cervical dysplasia. A similar finding of multiple sexual partners, advanced age and a history of STI were associated with an increased risk of precancerous lesions of the cervix in other studies.[190,191]

Another study investigated the factors associated with abnormal cervical cancer found in pregnant women in Beijing. [192] In this 2010 study, Ling and compatriots sampled 12,112 pregnant women reporting for prenatal examinations at the Beijing obstetrics and gynecology hospital. Exclusion criteria adopted for the study included those who had threatened miscarriage, placenta previa and prelabour membrane rupture. The results of the study showed that 10,354 women had normal thin prep cytology (TCT) results, while 1134 women (9.52%, 1134/11,906) presented with ASCUS. In addition, 112 women (0.94%), 229 women (1.92%) and 74 women (0.62%) had AGUS, LSIL and HSIL respectively. In the same study, age

of coitarche, the number of lifetime sexual partners, and the number of attempted abortions demonstrated significant relationships with AGUS and ASCUS. For the HSIL and LSIL sub-groups, the number of lifetime sexual partners, age of coitarche, smoking and several attempted abortions were notable risk factors. The study also reports that HPV infection, as well as columnar epithelium dystopia, were also important abnormal cervical cytology risk factors.

In a 2014 prospective cohort of Kenyan HIV-discordant couples, individual and sexual partner properties that promote the chances of abnormal cervical cytology among 441 women were studied by Soh et al[173] Out of these participants; it was found that 79 (18%) and 25 (6%) had low-grade and high-grade cervical abnormalities respectively. The study also showed that factors such as male HSV-2 seropositivity, as well as couple socioeconomic status were significantly correlated with abnormal cervical cytological smears. Similarly, a 2014 study done in the USA by Adler et al[74] also showed that women with HIV infection had a higher prevalence of abnormal cervical cytology of 28% as against the 12% seen in the control groups. Interestingly, the participants who were HIV positive were 35 compared to the 50 in the control group. The former group had a much higher prevalence of abnormal cytology. As such, the study showed that a history of HIV infections was significantly associated with abnormal cervical cytology. A South African study also showed a similar finding of an increased incidence of abnormal cervical cytology among HIV-positive adolescents compared to HIV-negative adolescents.[92.] However, due to the sample size of fewer than 50 participants, multivariate analysis was not done. It has been shown from other studies that women with HIV have a shorter preinvasive stage and an earlier age of diagnosis of ICC.[193,194]

In a similar study published by the Turkish Journal of Pathology in 2014, Simavli et al[135] aimed to investigate the incidence of abnormal cervical cytological findings in Turkey and also to evaluate the possible relationship between the socio-demographic elements of the study participants and cervical cytological abnormalities. To achieve this goal, the researchers retrospectively reviewed the results of 11,539 cervical smears that were assessed using the Bethesda system 2001. Exclusion criteria used included unsatisfactory smear results, a history of gynaecologic cancer, a history of hysterectomy and outcomes of patients' smear tests for whom sociodemographic data could not be gathered. For participants that met the inclusion criteria, the results showed an incidence rate of 1.8% for cervical cytological abnormalities. The outcome of the study also showed that risk factors for abnormal cervical cytology

included advanced age, low educational level (primary school or less) and not having health insurance. In addition, women with relatively higher levels of education and a history of previous Pap smear testing had a lower risk of developing abnormalities in cervical cytology. High parity (4 or more previous births), low educational status (primary school or less|) and increasing age were also risk factors for cervical cytology abnormalities in another study.[195]

Similarly, a 2012 study done in Italy showed that being married, having a positive smoking status, advanced age, having 2 or more lifetime sexual partners, having no history of Pap smear and non-current use of condoms were significantly associated with abnormal cervical cytology.[47]

Oral contraceptive pill (COCP) is one the oldest contraceptive methods that is still widely used by a lot of people. The role COCP plays in the development of cervical cancer remains debatable. A systematic review of 19 papers done from 1990 till 2019 by Asthana et al[57] found a positive association between the use of COCP and cervical cancer. This was true for cases of adenocarcinoma. The association was also related to the duration of use of the COCP particularly 5 years of more.

Tao et al[196] also found low socioeconomic status, postcoital bleeding and age (46-55 years) as being significantly associated with abnormal cervical cytology among 728,704 women in Beijing, China with the overall prevalence of abnormal cytology being as low as 0.12% in a study done in 2014. A 2011 Indian study where 320 postmenopausal women were studied showed that; parity, age, and duration of menopause were associated with abnormal cervical cytology.[125]

In a study conducted among HIV discordant couples in Kenyan, low socioeconomic status of the couple was associated with an increased risk of abnormal cervical cytology.[173] HIV-uninfected women with HIV-infected male sex partners (cd4>350 Cells/µl) had the lowest prevalence of high-grade cervical lesions. Other individual factors that were associated with abnormal cervical cytology were lower age of sexual debut and use of hormonal contraceptives. At the couple level, a higher income of more than 8,000 Kenyan shillings was also associated with abnormal cytology.

Also, a study done in the western black sea region in 2014 found that advanced age, low education level (primary school or less) and not having health insurance were found to be risk factors for preinvasive and invasive lesions.[135] This was a retrospective study of 7,740 cervical smears taken from 2011 to 2012. The prevalence for abnormal smear was a pre-invasive lesion in our study was 1.77% compared to the 0.025%

prevalence of cervical cancer. The prevalence of abnormal cytology was 70 times more than the prevalence of cervical cancer bringing to the fore the importance of screening for preinvasive lesions of the cervix. With more premalignant lesions being diagnosed and treated, the incidence of cervical cancer will reduce. Fan et al[172] also looked at the factors associated with the individual abnormal cervical smears instead of all of them aggregated together as seen in other studies. The age of first sexual intercourse, the number of sex partners and the number of abortions were associated with an increased risk of ASCUS and AGUS. In addition, for the LSIL and HSIL groups; the age of first sexual intercourse, the number of sex partners, the number of abortions and smoking were significantly associated. This study was done among 11,906 pregnant women who were between the gestational ages of 12 weeks to 36 weeks. Having multiple sexual partners has been associated with an increased risk of HPV infection.[172] It is the persistence of HPV infection which is responsible for precancerous lesions and cervical cancer. HPV infection is also a risk factor for other STIs as well. Nulliparity has also been shown to be associated with an increased risk high-grade dysplasia in a recent study by Gomez et al in 2021.[197] That study specifically looked at factors associated with postpartum high-grade lesions.

2.5 Description of Colposcopic Findings in Postpartum Women

Colposcopy is a visual examination of the cervix, vagina and vulva using a low-powered microscope. Abnormal cervical cytology is an indication for colposcopy. It is not recommended before 4 weeks postpartum.[142] The waiting period of 4 weeks after birth allows the cervix to heal.[143] The changes that occur during pregnancy cause prominent changes in the cells in the transformation zone, which may increase abnormalities in colposcopic patterns. Reporting an inaccurate result is common since the tissues are also more fragile at this time, which makes traumatic bleeding more frequent.[198]

The 2021 WHO guideline on the screening for precancer lesions of the cervix recommends colposcopy for all abnormal Pap smears beyond ASCUS, including LSIL, HSIL, ASC-H and AGC. Colposcopy is also indicated for those with ASCUS and a positive HPV DNA test.[145]

Data is scanty on colposcopy for postpartum women. However, a colposcopy done for 3 postpartum patients with abnormal Pap smears of LSIL out of the 100 patients showed no abnormal findings in a 2016 study done in Nigeria.[21] In another study conducted in Italy among the 52 postpartum women with

abnormal cytology who underwent colposcopy,19 had normal transformation zone/grade 1 abnormal colposcopic findings, whereas the remaining 33 had grade 2 abnormal colposcopic findings in 2018.[199]

In a study that was done among 100 non-postpartum population; 62 % of them had Reid's score of 0-2, 19% had Reid's score 3-5, 18% had Reid's score 6-8 and 1% had invasive carcinoma on colposcopy. 83% of these participants had NILM on Pap smear. Histopathology reports from biopsies taken during the colposcopy showed patients who had LSIL and HSIL on Pap smear had a higher degree of cervical dysplasia compared to those who had ASCUS.[186]

Another study delved into the discordance or otherwise of results from Pap smears compared to the colposcopy-directed histopathology results.[197] Overall, 3 cases each of LSIL and HSIL showed discordance with the colposcopy results. Concerning the 3 LSIL cases; 2 showed inflammatory lesions whereas 1 showed HSIL on histopathology from colposcopy-directed biopsy. With the 3 who had HSIL on Pap smear; 2 showed chronic cervicitis whiles 1 showed LSIL. There was however, concordance between the Pap smear and biopsy results in 6 of the cases of HSIL, 9 cases of SCC and 3 cases of AC. A LEEP operation was performed on 34 of the 45 women with persisting HSIL/CIN2+ diagnoses during postpartum colposcopy follow up, confirming high-grade non-invasive dysplastic lesions.

Among the 258 participants in a study by Demir et al[200] in 2020; 168 (65.1%) had normal cervical cytology, while the remaining 90 (34.9%) cases had abnormal cervical cytology. Among those with normal cytology;157(60.9%) had normal biopsy findings whereas 11(4.3%) had abnormal biopsy findings. However, among those who had abnormal cervical cytology, 49 (19.0%) had normal findings on biopsy whereas 41(15.9%) had abnormal biopsy findings. The false-negative and false-positive rates in the cyto-histological comparison, independent of class ratio, were 4.3% and 19%, respectively. Except for atypical classes of cytologic diagnoses; the sensitivity, selectivity, positive and negative predictive values were 69%, 98%, 89%, and 93%, respectively. Thus, the study confirms the fact that those who have abnormal cervical cytology have an increased risk of abnormal biopsy findings.

Suchońska et al[201] did a study in 2020 in which a colposcopy was done for 53 pregnant women and then followed up during the postpartum period. Overall, 35 (66%) of the participants had CIN including CIN1 8(22.9%), CIN2+ 26(74.3%) and ICC 1(2.9%). During the postpartum period; 50% of the initial findings during the antenatal period did not change, 2.9% had progressed and 47.1% had regressed.

CHAPTER THREE

MATERIALS AND METHODS

3.0 Study Type

This study was an analytical cross-sectional study that evaluated the prevalence of abnormal cervical cytology and associated risk factors among 6 weeks postpartum women in selected hospitals in the Greater Accra Region. Cross-sectional study was chosen as it helps address the research questions of the study such as determining the prevalence of abnormal cervical cytology and it is also cost efficient and requires less time compared to other study types such as case-control and randomized control trials. It also allows for the dependent and the independent variables to be studied at the same time referred to as a 'snapshot' of the population. The downside to the use of cross-sectional study is that it is subject to selection, recall and non-response biases.[202] The study covered 6 months (1st January 2022- 31st July 2022) during which the data was collected.

3.1Profile of Study Site

The study took place at the Family Planning (FP) and Reproductive Health Centre (RHC) of the KBTH and GARH where Pap smear testing are offered. These facilities are a part of the Accra metropolis's public reproductive health facilities with a high Pap test client turnout within a year. Accra Metrolpolis is one of the 26 districts that make up the Greater Accra Region, and it is located in its southernmost section. The Ga West Municipal District and the Gulf of Guinea, respectively, form the northern and southern boundaries of the Accra metropolis. Additionally, it shares borders with the La Dadekotopon District in the east and the Ga South Municipal District in the west.[203]

3.1.1 Korle Bu Teaching Hospital

The KBTH, founded on October 9th, 1923, is one of the three biggest hospitals in Africa and the top referral facility in the nation.[203] In the southern part of Ghana, in the Accra Metropolis' South Ablekuma District, is where it is situated. The KBTH is Ghana's largest healthcare facility, and top teaching hospital which acts as the primary referral site for all of Southern Ghana and beyond. With an average of 978 patients per day in the outpatient department (OPD), over 200 admissions per day, and a bed capacity of over 2000, KBTH is Ghana's top referral hospital.[203]

It has 17 departments/units including three centres of excellence namely; the Reconstructive Plastic Surgery and Burns Centre, the National Cardiothoracic Centre, and the National Centre for Radiotherapy and Nuclear Medicine.

The FP and RHC is one of the units under the Obstetrics and Gynaecology Department of the Korle Bu Teaching Hospital. Its activities are based on the four priorities of Reproductive Health. These are FP, Comprehensive Abortion Care, Prevention and Management of Cancers of Reproductive System and Prevention and Management of Sexually Transmitted Infections. A total of 30,894 women were seen at the FP and RHC with 2258 undergoing Pap smear in the year 2020 and 56 abnormal Pap smear. Both conventional and LBC are done at KBTH. These are done on request by the health care providers. A room in the RHC has been dedicated to the performance of colposcopy by trained medical personnel.

There were 129 cervical cancer cases seen in that year, being the 7th most common gynaecological condition. A total of 31,145 gynaecological cases were seen in 2020. Also, 7,359 deliveries were conducted in the facility in the year 2020. There is an average of 100 women seen per week for postnatal services at KBTH.[203] One consulting room was dedicated to postnatal women where they were seen every day of the week by the different Obstetric teams. Postpartum women in KBTH are not routinely screened for premalignant lesions of the cervix and therefore there is no data. The results of this study will help in developing and implementing policies on cervical cancer prevention in KBTH and the country. The findings will also serve as the foundation for additional research.

3.1.2 Greater Accra Regional Hospital

Established in the late 1920s, the GARH is located in Ghana's Greater Accra Region's Osu Klottey Sub-Metro. In Greater Accra region, it is the only secondary healthcare facility. It was upgraded to a Regional Hospital in 1997. The Greater Accra Region, with a population of about 4,283,322 people, is its whole catchment area. The suburbs of Nima, Accra New Town, Kanda, Kotobabi, La, Osu, Adabraka, Achimota, Airport Residential Area, and Central Accra are all within the near catchment area. The hospital acts as a point of reference and offers a variety of services to its clients. The Out-Patient department, Dental, Laboratory, Emergency, FP, Pediatrics, Obstetrics and Gynecology, X-ray, Surgery, Internal Medicine, are just a few of the services offered. The facility typically records 17 900 in-patients with a bed capacity of 191 and 291,887 outpatients per year.

It is also among the few facilities that can offer cytological screening, diagnosis and manage preinvasive lesions of the cervix as well as cervical cancer cases in the Greater Accra region of Ghana.[204] A total of 7,292 women were seen at the FP and Reproductive health unit (RHU) of the facility with 1,557 undergoing Pap smear in the year 2020 with 5 abnormal Pap smear findings. Both conventional and LBC are done. However, colposcopy services are not available.

A total of 7,020 deliveries were conducted in the year 2020. There is an average of 80 postpartum women seen per week. One consulting room had been dedicated to postnatal women where they were seen only on Mondays of each week.

3.2 Study Population

The study population included postpartum women attending postnatal clinics in KBTH and GARH.

3.2.1 Inclusion Criteria

1. 6 weeks postpartum attending postpartum clinics in the KBTH and GARH who consent to partake in the study.

3.2.2 Exclusion Criteria

1. Abnormal genital bleeding-This could obscure the interpretation of the smear.[205]
2. Obvious lesions on the cervix-Lesions on the cervix will need a biopsy before a Pap smear will be considered.[206]
3. Obvious cervical infection- This could lead to difficulties in the interpretation of the smear.[205]
4. Age below 21 years- It takes a long time for the HPV to cause the changes that are seen on cytology and women below 21 years may not have developed these lesions.[168]
5. History of intrapartum or peripartum total hysterectomy – The absence of the cervix in such individuals renders them unlikely to develop premalignant lesions of the cervix**.**

3.3 Variable

3.3.1 Dependent variable

Abnormal cervical cytology (All smear results excluding NILM such as ASCUS, ASC-H, LSIL, HSIL and ICC)

3.3.2 Independent Variable

Factors associated with the abnormal cervical cytology such as;

Socio-demographic factors-Age, marital status, religion, occupation, partner's occupation, smoking status

Obstetric factors- parity, age of first birth, interpregnancy interval, mode of delivery of last birth, outcome of last pregnancy

Gynaecologic factors- age of menarche, age of coitarche, number of lifetime sexual partners, postcoital bleeding, HIV status, history of STI, Family history of cervical cancer, contraception history, regular use of condom

3.4 Sample Size Calculation

With a prevalence of 32% abnormal Pap smear at 6 weeks postpartum[19], the sample size was calculated using the Cochrane formula as shown below:

n= $(z^2pq)/ x^2$

Where:

n= Estimated sample size

z- score

p= prevalence

x= Margin of error

Considering a confidence interval of 95%: z- score= 1.96

p= 0.32

q= (1-p) = (1- 0.32) = 0.68

x= 0.05

n= (1.962^2 *0.32* 0.68) / (0.05^2)

n= 335.055=336

With adjustment of 10% for inconsistencies= 336* 1.1=369.6

Sample size =369.6=370

Proportionate sampling based on the number of postpartum women done per week (100 cases per week at KBTH and 80 cases per week at the GARH) was employed to determine the number of participants by facility. 206 and 164 participants were obtained from KBTH and the GARH respectively.

3.5 Sampling and Sampling Techniques

Participants were recruited at postnatal clinics of the facilities involved in the study that is KBTH and GARH. The sitting positions of the postpartum women were arranged in terms of their time of arrival as it was first come first serve basis by the postnatal nurses. The research assistants talked to the postpartum women as a group on the research after which they were talked to individually and recruited using their sitting position if they met the criteria for selection until the required sample size was obtained. Consecutive sampling was used as it is cost-effective and requires less time. However, selection bias could occur if participants with a different set of characteristics do not present themselves during the study. Results cannot also be generalized when a consecutive sampling technique is used due to its non-probability nature. Patients who met the inclusion criteria were recruited after informed written consent had been taken. Participants were recruited and enrolled in the study on the same day.

3.6 Data Collection Techniques and Tools

Information on the study participants attending the six-week postnatal clinic at KBTH and GARH were gathered employing quantitative data collection tools. An interviewer-administered structured questionnaire adapted from Thomas et al[167] work in 2012 was used. It contained 3 sections including sections A, B and C. Section A looked at the sociodemographic characteristics of the participants including age, education level and marital status. Section B looked at the awareness of the participants of cancer of the cervix, history of Pap smear and history of HPV vaccination. Section C looked at the obstetric and gynaecologic characteristics of the participants.

The questionnaire was pretested at Mamprobi Polyclinic and modified before it was used for final data collection to ensure accuracy during data collection. The principal investigator taught three research assistants for a total of two days at Mamprobi Polyclinic to obtain participant informed consent and usage of the data collection tool. Research assistants comprised midwives in the FP and RHU, who had been regularly involved with specimen collection for Pap smears for over 5 years. A total of 2 research assistants were from KBTH whereas 1 was from GARH.

Inquiring about the 6 weeks postpartum women's willingness to engage in the study, the research assistants gave each one of them a brief introduction and went through various components of the investigation with them. The women were allowed to ask questions, and all of their inquiries received full responses. Before the questionnaire was administered, the women who accepted to participate were required to read and sign the consent form. Interpreters were engaged to assist when the participants did not understand English.

After the completion of the filling of the questionnaire, the screening test (conventional Pap smear) was done by the research assistants. The questionnaires were filled at the consulting rooms at FP and RHC of each of the study sites. The subject was given a thorough explanation of the process before the research assistant positioned her in the dorsal position with her legs flexed to reveal the vulva in a room dedicated to this procedure at the FP and RHC where privacy is secured. The procedure was done in a room with total privacy. An unlubricated bivalve speculum was also passed to aid in the inspection of the cervix for bleeding, obvious masses and obvious infections. Excessive mucous on the cervix was then cleaned with a saline-soaked swab gently. The slide was then labelled with the name of the participant and identification number in pencil.

Using an Adwin Scientific No Touch One Slide Pap Smear Kit with an expiration date of September 1, 2023, scrapings of the cervix were taken under aseptic conditions using an Ayre's spatula and endocervical brush were spread out on the labelled glass slide and promptly fixed with 95% alcohol. The slide was then allowed to dry and the cytology request form was filled. The slides were then transported to the laboratory in a protective slide holder in addition to the filled cytology request forms

With the help of a cytopathologist at Lal Pathlabs located in Mamprobi, all slides were processed, stained and analyzed. All the smears were read by Mr Daniel Potakey who is a registered Principal Biochemical Scientist affiliated with the Ministry of Health (Ghana)and the Lal Pathlabs. He is the only person who read all the Pap smears to reduce interobserver variability. Pap smears were categorized using the 2001 Bethesda system. An abnormal Pap smear included the following results; ASCUS, ASC-H, AGC, LSIL and HSIL. The Pap smear result for ICC was likewise abnormal. As soon as the Pap smear results were available, participants were contacted to come in for them. A full explanation of each individual's results was given to them.

Afterward, colposcopy was done for the participants with abnormal cytology including LSIL, HSIL, AGC and ASC-H excluding ASCUS as recommended by WHO[145] by experienced doctors who have been doing colposcopy for at least five years after informed consent had been obtained with the cost covered by the researcher. Those with suspected ICC also qualified for a colposcopy. These participants were called on the phone and booked for the procedure to be done usually 10-14 days from the onset of their menses. On the booked day, the procedure was done for the participants in a dedicated room at KBTH where there was privacy in the presence of a chaperone. All the colposcopies were done at KBTH.

The things needed for the procedure included; a bivalve speculum, examination gloves, cotton wool balls, biopsy forceps, 3 gallipots (for saline, acetic acid and **Lugols** iodine), sponge holding forceps, and solution for hemostasis such as Monsel's solution. Each participant was placed in the lithotomy position and made comfortable. An inspection of the external genital was done, after which a bivalve speculum was passed to also aid in the inspection of the cervix. Cotton soaked with saline was used to clean the cervix in case of excessive discharge to allow for inspection with the eye and also with the colposcope. The addition of a green filter aided in detecting any abnormal vessels while viewing with the colposcope in addition. Any abnormal lesions such as leukoplakia were noted. 3-5% acetic solution was then applied to the cervix with cotton balls and further examination was done after 60 seconds. Abnormal areas showed acetowhiteness. Further delineation of the abnormal area was noted after the application of the Lugol's iodine. Abnormal areas failed to take up the stain due to the lack of glycogen. For a colposcopy to be said to be satisfactory, the entire transformation was observed. Biopsies of the abnormal areas will have been done, particularly those closest to the SCJ if indicated. No random biopsies were taken.

Participants with normal colposcopy findings were encouraged to do an HPV DNA test. However, those with precancerous or invasive lesions from the biopsy reports will have been referred immediately to the gynaecologic oncologist for treatment. The cost of some treatment modalities like hysterectomy is covered by the National Health Insurance Scheme (NHIS) of Ghana. Others such as conization are not covered by the NHIS.

3.7 Data Management and Analysis

Microsoft Excel was used to clean the data before it was exported to SPSS (Statistical Package for the Social Sciences) version 20 for more thorough cleaning and analysis. Data were entered twice into SPSS version 20; the two entries were compared, and any errors were fixed before data analysis The analyzed data was presented using frequencies, percentages and charts. The association between participant characteristics (sociodemographic, obstetric and gynaecologic) and abnormal cervical cytology was examined using bivariate analysis. In addition, multivariate analysis and logistic regression were done to adjust for the possible confounders regarding the factors related to abnormal cytological smears. A p-value of less than 0.05 with a 95% confidence interval was regarded as statistically significant in all statistical analyses.

3.8 Ethical and Legal Considerations

Prior to the start of the investigation, appropriate ethical permission was sought. Scientific and Technical Committee (STC) and Ethics Committee of KBTH and Ghana Health Service (GHS) Ethics Review Committee, each with the ethical identification numbers KBTH-IRB/000160/2021 and GHS-ERC 027/09/21, respectively, reviewed the study protocol and procedures. The heads of administration for KBTH and GARH were contacted for administrative clearance to enable the use of human subjects for the study. Participants were informed on the use of their history and medical records for the study. Participants informed consent was taken before being recruited for the study. Serial numbers were assigned to the consent forms and questionnaires. These assisted in preventing data duplication and loss. Under the close supervision of the Principal Investigator, these signed consent papers were safely stored in a safe. Only scholarly uses were made of the study's information. Additionally, participant information was held with the utmost confidentiality. A secure safe was used to store all physical copies of the information collected, and any data typed into a computer was password-protected. The lead investigator and the supervisor would be the only people with access to both forms of data storage, which would be kept secure for at least five years. All covid 19 protocols were strictly adhered to.

CHAPTER FOUR

RESULTS

4.0 Introduction

A total of 463 women (252 from KBTH and 211 from GARH) were approached. However, 93(20.2%) were excluded for declining to give consent and having abnormal vaginal bleeding. Finally, a total of 370 were included in the study with 206 from KBTH and 164 from GARH.

4.1 General Characteristics of the Participants

4.1.1 Socio-demographics Characteristics

The average age of the study participants was 29.7 ± 3.3 years, whereas the average age at menarche was 12.0 ± 1.2 years. Majority of the participants 359(97%) were above the age of 25 years. Two hundred and sixty-six (71.9%) of the participants were married, 100 (27.0%) were single, and only 3 (0.8%) were divorced.

Most of the participants, 357 (95.4%), were educated. In addition, the commonest religion among the participants was Christianity 325 (87.8%), followed by Islam 41 (11.1%). Three hundred and twenty-one of the participants representing 86.8% and three hundred and fifty-two of the participants' partners representing 95.4% were employed.

The participants were primarily non-smokers 354 (95.7%), and most had ever heard of cervical cancer 327 (88.4%). Refer to Table 4.1.

Table 4. 1 Socio-Demographic Characteristics of the Study Population (n = 370)

Characteristics	Frequency	Percent	Mean (SD)
Age			29.7(SD=3.3)
Age group (in years)			
21 – 25	11	3.0	
> 25	359	97.0	
Marital Status			
Married	266	71.9	
Single	100	27.0	
Divorced	3	0.8	
Widowed	1	0.3	
Formal Educational background			
Primary or less	54	14.6	
Secondary or more	316	85.4	
Religion			
Christian	325	87.8	
Islam	41	11.1	
Traditional	2	0.5	
Other	2	0.5	
Participant Occupation			
Employed	321	86.8	
Unemployed	49	13.2	
Partner occupation			
Employed	353	95.4	
Unemployed	17	4.6	
Ever smoked cigarette			
Yes	16	4.3	
No	354	95.7	
Ever heard of cervical cancer			
Yes	327	88.4	
No	43	11.6	

SD- Standard deviation

4.1.2 Obstetric Characteristics of the Participants

The mean parity of the participants was 2 (SD = 0.9). Most of the participants, 305 (82.4%) had their first birth at the age 20 years or older and 228 (61.6%) had two or more children. For the participants who had multiple births, 179 (78.5%) had a birth interval of more than 1 year. Furthermore, most of the participants 303 (81.9%) delivered via spontaneous vaginal delivery as seen in Table 4.2. High parity was defined as 4 or more pregnancies with gestation periods of ≥ 28 weeks.

Table 4. 2 Obstetric Characteristics of the Participants

History	Frequency	Percent	Mean (SD)/ Median (IQR)
Mean parity			2(SD=0.9)
Parity			
< 4	354	95.7	
≥ 4	16	4.3	
Median age of first birth			25(IQR=15-40)
Age group at first birth			
< 20 years	65	17.6	
≥ 20 years	305	82.4	
Birth interval (n = 228)			
< 1 year	49	21.56	
≥ 1 year	179	78.5	
Mode of delivery of last birth			
SVD	303	81.9	
C-section	67	18.1	
Outcome of last pregnancy			
Live term birth	345	93.2	
Live preterm birth	14	3.8	
Still birth	11	3.0	

C-Section-Caesarian section, SVD-Spontaneous vaginal delivery

4.1.3 Gynaecologic Characteristics of the Participants

A total of 310 (83.8%) of the study participants had coitarche aged 16 years or older, while 272 (73.5%) had their menarche at age 12 years or older. For the majority of the participants 308 (83.2%), they had a regular menstrual cycle history. The average age for their sexual debut was 18.5 (SD = 3.2).

Most of the participants also had more than one-lifetime sexual partners 278(75.1%). Having multiple sexual partners was defined as having 2 or more lifetime sexual partners.

Table 4. 3 Gynaecologic Characteristics of the Participants

	Frequency	Percent	Mean(SD)/Median(IQR)
Median age at coitarche			19(IQR=11-30)
Age group at coitarche			
<16 years	60	16.2	
≥ 16 years	310	83.8	
Mean age at menarche			12(SD=1.2)
Age group at menarche			
<12 years	98	26.5	
≥ 12 years	272	73.5	
History of menstruation before last conception			
Regular	308	83.2	
Irregular	62	16.8	
Mean of lifetime sex partners			2(SD=1.1)
Lifetime sex partners			
1	92	24.9	
More than 1	278	75.1	
Current post-coital bleeding (n=83)			
Yes	21	25.3	
No	62	74.7	
Regular condom use			
Yes	205	55.4	
No	165	44.6	

IQR-Interquartile Range SD-Standard Deviation

In addition, majority of the participants 205 (55.4%) used condom during sexual intercourse regularly, while only 21(5.7%) had a history of current post-coital bleeding as seen in Table 4.3. Regular condom use was defined as using a condom at least twice in the three months preceding the participants' most recent pregnancy.[207]

4.1.4 Contraceptive Use by Method

Although 219 (59.2%) of the women had ever used FP methods. Only (63)17.0% of the participants were current users of FP whereas the remaining 307 were not currently using any FP method. Contraceptive Injectables 211(57.0%) was the most common contraceptives ever used. Currently, 11(3%) had performed bilateral tubal ligation. Refer to Table 4.4.

Table 4. 4 Contraceptive Use by Method

FP Method	Current use, n (%)	Ever used, n (%)
Any FP method	63 (17.0)	219(59.2)
Pills	0 (0.0)	23 (6.2)
Implant	6 (1.6)	72 (19.5)
Injectable	14 (3.8)	211(57.0)
Condom	3 (0.8)	205 (55.4)
IUD	7 (1.9)	29 (7.8)
BTL	11 (3.0)	0 (0.0)
Others	22 (5.9)	63 (17.0)

FP- Family Planning, BTL- Bilateral tubal ligation, IUD- Intrauterine device,

4.1.5 Participant and Participant Partner History Of STI

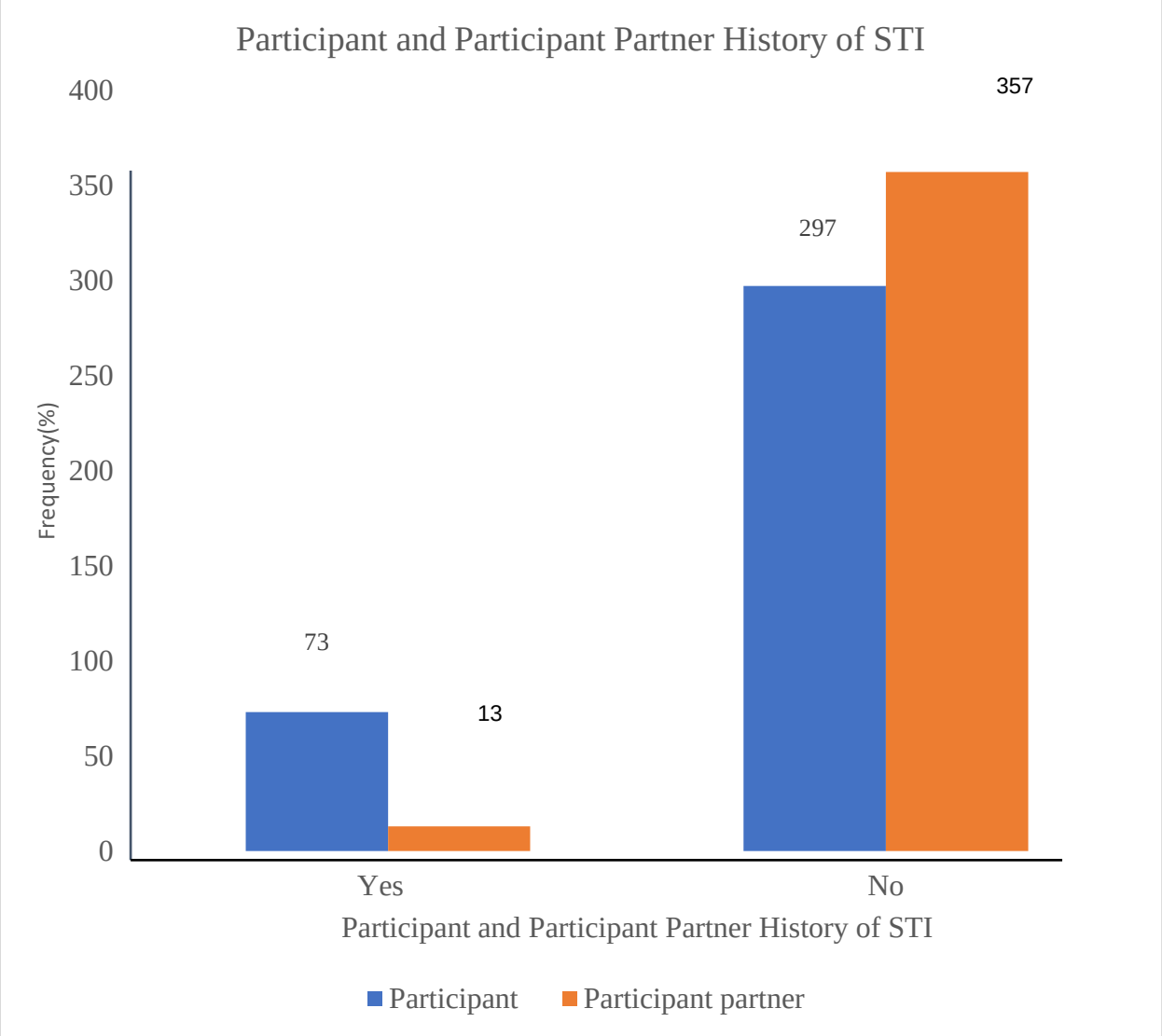


Figure 4. 1 History of STI among Participants and their Partners

Majority of the participants 297 (80.3%) and participant partners 357 (96.5%), had no history of sexually transmitted infections [Figure 4.1].

4.1.6 Participant Family History of Cervical Cancer

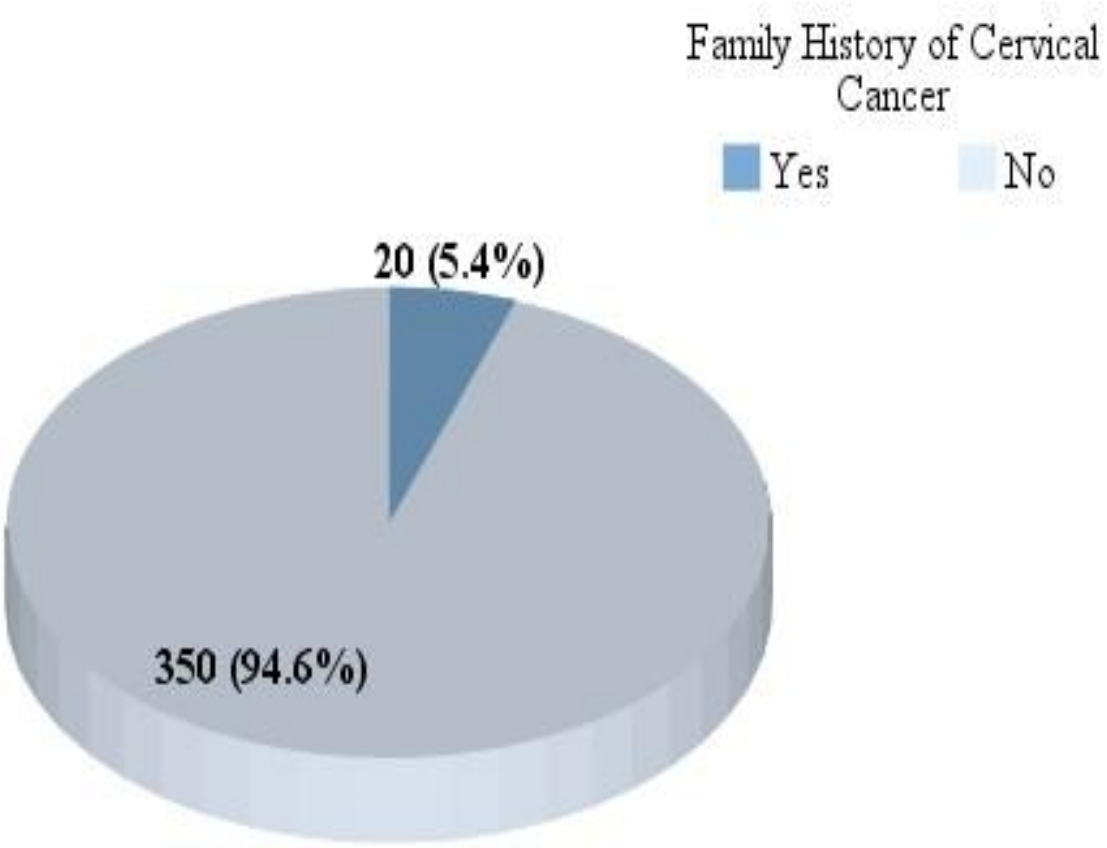


Figure 4. 2 Participant Family History of Cervical Cancer

A family history of cervical cancer was defined as any woman whose mother, sister or daughter has been diagnosed with cervical cancer. Family history of cervical was found to be low among the studied participants. Twenty (5.4%) of the study participants had a family history of cancer of the cervix [Figure 4.2].

4.1.7 Participant History of Pelvic Infection

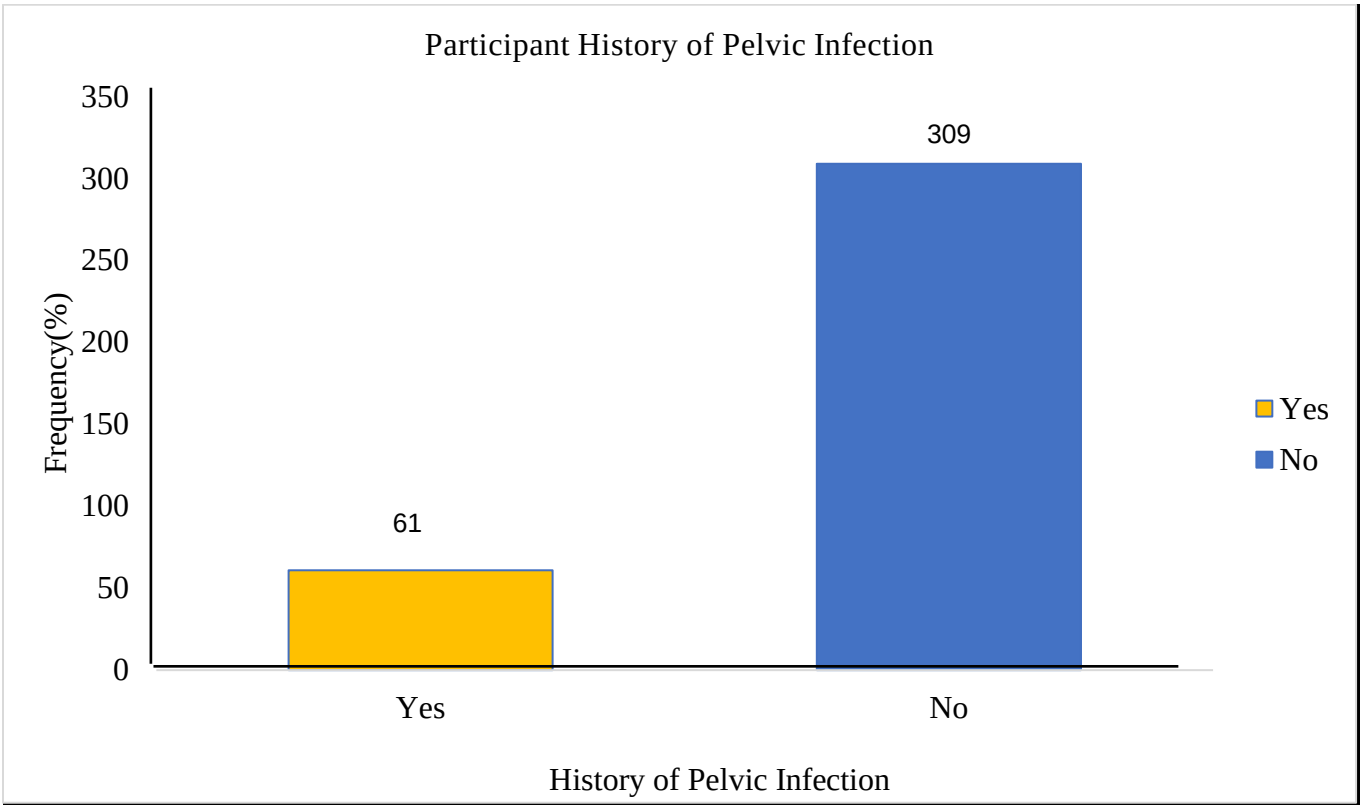


Figure 4. 3 Patient History of Pelvic Infection

The study also recorded a considerable number of participants 309 (83.5%), without a history of pelvic infection. However, 61 (16.5%) of the participants had a positive history of pelvic infection [Figure 4.3].

4.1.7 Participant History of HIV Infection

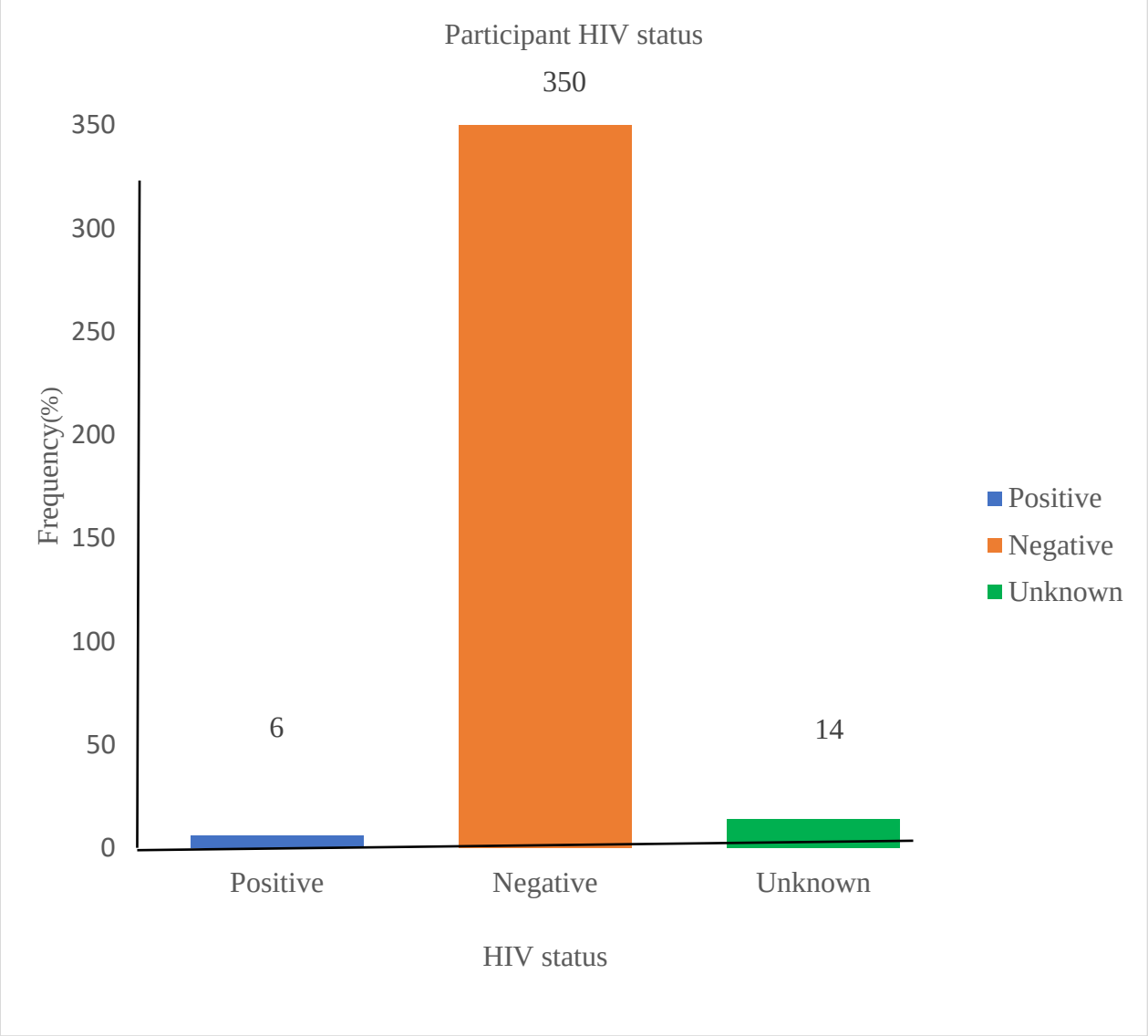


Figure 4. 4 Participant History of HIV Infection

Majority of the participants had a negative history of HIV infection 350 (94.6%), while only 6 (1.6%) had a positive history of HIV. The remaining 14 (3.8%) did not know their HIV status [Figure 4.4].

4.1.8 Participant History of HPV Vaccination

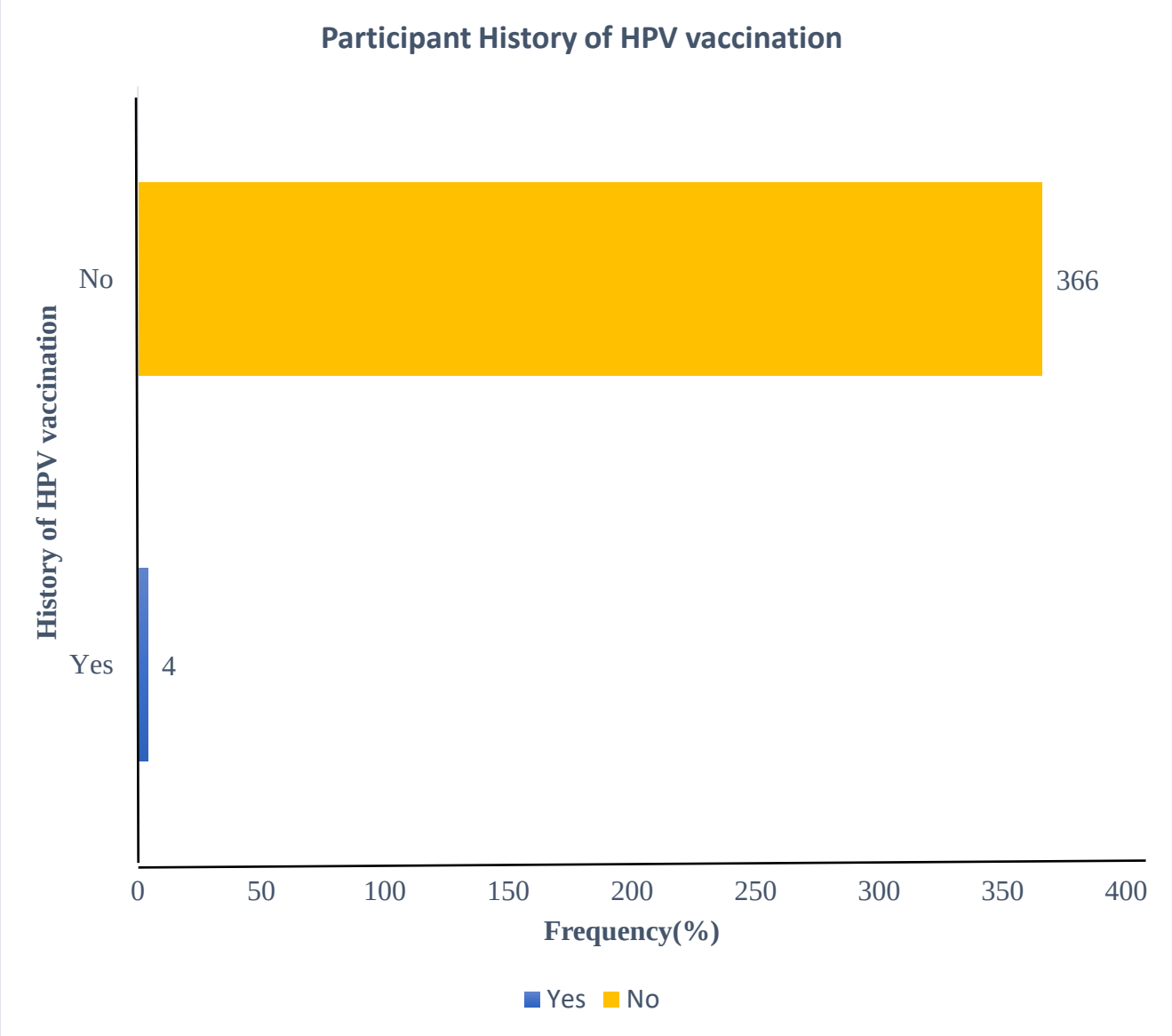


Figure 4. 5 Participant History of HPV Vaccination

Only 4 (1.1%) of the participants had ever been vaccinated against HPV, as shown in Figure 4.5.

4.2 Utilization of Pap Smear

Most of the **women 351 (94.9%)** had never had a Pap smear test, whiles 19(5.1%) had done a Pap smear test in the past. Out of the women with a positive Pap smear history, 16 (84.2%) had done it only once and the remaining 3(15.2%) had done it more than once. Majority of the participants 18 (94.7%), had last undergone a Pap smear test 3 years or more ago [Table 4.5]. The history of the participant's use of VIA to test for cervix premalignant lesions was not examined in this study.

Table 4. 5 Utilization of Pap Smear

	Frequency	Percent
History of Pap smear (n= 370)		
Yes	19	5.1
No	351	94.9
Number of times (n= 19)		
Once	16	84.2
More than once	3	15.8
Last time screened (n= 19)		
< 3 years	1	5.3
≥ 3 years	18	94.7
Result of last screen (n= 19)		
Positive	0	0.0
Negative	19	100.0
Unknown	0	0.0

4.3 Cytological Findings at Postpartum

Most of the participants 331(89.5%) had normal postpartum Pap smear results. Among the 39 (10.5 %) with abnormal cervical cytology; 31(8.4%) had ASCUS, 7(1.9%) had LSIL and 1(0.3%) had HSIL [Table 4.6]. The prevalence of abnormal cervical cytology at 95 % confidence was 10.5% (7.6%-14.1%) [Table 4.6].

Table 4. 6 Postpartum Pap smear results

Pap smear finding	Frequency	Percent
NORMAL (NILM)	331	89.5
ABNORMAL	39	10.5 at 95% confidence interval (7.6-14.1)
ASCUS	31	8.4
LSIL	7	1.9
HSIL	1	0.3

NILM: Negative for Intraepithelial Lesion/Malignancy

ASCUS: Atypical Squamous Cells of Undetermined Significance

LSIL: Low-Grade Squamous Intraepithelial Lesions

HSIL: High-Grade Squamous Intraepithelial Lesions

4.4 Association between Cytological Cervical Abnormalities and Sociodemographic Factors

Age, religion, educational background, marital status, and smoking status were not significantly associated with the development of abnormalities in cervical cytology ($p > 0.05$) [Table 4.7].

Table 4. 7 Cytological Cervical Abnormalities and Sociodemographic Factors

Socio-demographic Factor	Cervical Cytology Finding [n (%)]		df	X^2	p-value
	Normal	Abnormal			
Age group			1	0.03	+0.874
21 - 25 years	10 (3.0)	1 (2.6)			
> 25 years	321 (97.0)	38 (97.4)			
Marital status			3	1.84	+0.607
Married	239 (72.2)	27 (69.2)			
Single	89 (26.9)	11 (28.2)			
Divorced	2 (0.6)	1 (2.6)			
Widowed	1 (0.3)	0 (0.0)			
Religion			3	0.59	+0.898
Christian	291 (87.9)	34 (87.2)			
Islam	36 (10.9)	5 (12.8)			
Traditionalist	2 (0.6)	0(0.0)			
Other	2 (0.6)	0(0.0)			
Educational background			1	0.66	+0.630
Primary or less	50 (13.5)	4 (1.1)			
Secondary or more	281 (75.9)	35(9.5)			
Occupation			1	0.34	+0.561
Employed	286 (86.4)	35 (89.7)			
Unemployed	45 (13.6)	4 (10.3)			
Partner occupation			1	0.03	+0.866
Employed	316 (95.5)	37 (94.9)			
Unemployed	15 (4.5)	2 (5.1)			
Smoking status			1	1.20	+0.274
Yes	13 (3.9)	3 (7.7)			
No	318 (96.1)	36 (92.3)			
Heard of cervical cancer			1	0.60	0.438
Yes	294 (88.8)	33 (84.6)			
No	37 (11.2)	6 (15.4)			

*- statistically significant, p<0.05, *df*-degrees of freedom, X^2 -Chi-square, + -Fisher's exact

4.5 Association between Cytological Cervical Abnormalities and Obstetric Factors

Participant obstetric factors also showed no statistically significant association with abnormal cytology of the cervix (p> 0.05) [Table 4.8].

Table 4. 8 Cytological cervical abnormalities and obstetric factors

	Cervical Cytology Finding [n (%)]				
Obstetric Factor	**Normal**	**Abnormal**	**df**	**X^2**	**p-value**
Parity			1	0.33	$^{+}$0.568
< 4	316 (95.5)	38(97.4)			
≥ 4	15 (4.5)	1(2.6)			
Age group at first birth			1	0.68	0.410
< 20 years	60 (18.1)	5 (12.8)			
≥ 20 years	271 (81.9)	34 (87.2)			
Birth interval (n = 228)			1	0.02	0.882
< 1 year	44 (21.4)	5 (22.7)			
≥ 1 year	162 (78.6)	17(77.3)			
Mode of delivery of last birth			1	0.01	0.978
C-section	271 (81.9)	32 (82.1)			
SVD	60 (18.1)	7 (17.9)			
Pregnancy outcome			2	0.24	0.888
Live term birth	309(93.4)	36(92.3)			
Live preterm birth	12(3.6)	2(5.1)			
Stillbirth	10(3.0)	1(2.6)			

*- statistically significant, p<0.05, *df*-degrees of freedom, X^2 -Chi-square, + -Fisher's exact

4.6 Factors Associated with Abnormal Cervical Cytology

A bivariate analysis was conducted to ascertain the factors that were linked with the development of abnormal cytological findings in 6 weeks postpartum women is shown in Table 4.9. The odds of developing abnormal cervical cytology were about 22 times higher among women with a positive history of STI ($p< 0.001$), whiles the irregular use of condom during coital activity also predisposed the participants to about two times the chances of developing cervical abnormalities, when compared to those who used condoms (cOR= 2.44, p= 0.011).

After adjusting for all other variables, analysis showed that a history of STI (aOR = 34.88; 95% CI = 13.75 – 88.48; $p < 0.001$) and the irregular use of condom during intercourse (aOR = 4.95; 95% CI = 2.03 – 12.05; $p < 0.001$) were significantly associated with abnormal cervical cytology depicted in Table 4.9.

4.7 Description of Colposcopy Findings of Participants with Abnormal Cervical Cytology

A total of 39 abnormal Pap smear results were found; 31-ASCUS,7-LSIL and 1 HSIL. As per the WHO recommendation, [145] only the cases of LSIL and HSIL proceeded to do a colposcopy excluding those with ASCUS. A total of 7 cases (6 LSIL and 1 HSIL) underwent colposcopy examination of their cervix. One of the participants with LSIL was lost to follow-up. The colposcopic findings for all the 7 cases were normal. There were no suspicious lesions. No biopsies were taken as a result. This is in line with the new WHO guidelines on screening for premalignant lesions of the cervix where further treatment or otherwise after colposcopy is based on the colposcopy diagnosis or the histopathology diagnosis. A cone biopsy will be necessary for women with abnormal Pap test such as HSIL, a positive HPV DNA test and a normal colposcopy.

Table 4. 9 Logistics Regression of Selected Independent Variables on Cervical Cytology

Variables	Cervical Cytology Finding [n (%)]		cOR (95% CI)	p-value	aOR (95% CI)	p-value
	Normal	Abnormal				
Number of lifetime sexual partners						
1 partner	160 (48.3)	10 (25.6)	1.00		1.00	
Multiple partners	171 (51.7)	29 (74.4)	1.11 (0.51 -2.45)	0.785	0.86 (0.33 -2.26)	0.759
History of STI						
Yes	43 (13.0)	30 (76.9)	22.33 (9.92 - 50.23)	<0.001*	34.88 (13.75 –88.48)	<0.001*
No	288 (87.0)	9 (23.1)	1.00		1.00	
Regular Condom use						
Yes	191 (57.7)	14 (35.9)	1.00		1.00	
No	140 (42.3)	25 (64.1)	2.44 (1.22 – 4.86)	0.011*	4.95 (2.03 – 12.05)	<0.001*
Age group at coitarche						
< 16 years	54 (16.3)	6 (15.4)	1.00		1.00	
≥ 16 years	277 (83.7)	33 (84.6)	1.07 (0.43 – 2.68)	0.882	1.33 (0.44 – 4.08)	0.614
Smoking						
Yes	13 (3.9)	3 (7.7)	1.00		1.00	
No	318 (96.1)	36 (92.3)	0.49 (0.13 – 1.80)	0.274	1.59 (0.29 – 8.80)	0.596

cOR- crude odds ratio; aOR- adjusted odds ratio; *- statistically significant; p<0.05; CI- confidence interval.

CHAPTER FIVE

DISCUSSIONS

5.0 Summary of Key Findings

The prevalence of abnormal cervical cytology among the 6-week postpartum women in this study was 10.5%. at a confidence interval of 95% (7.6%-14.1%). ASCUS was found to be the commonest cervical cytology. History of STI and irregular use of a condom during coitus are the key factors identified as being linked to abnormal cervical smear results. Seven patients who had abnormal Pap smear results (HSIL and LSIL) underwent colposcopy, which came back normal. However, 1 of the participants with LSIL was lost to follow-up for the colposcopy.

5.1 Sociodemographic Characteristics of Participants

The mean age of the participant in this current study was 29.7 years with a standard deviation of 3.3. Thus, majority of the study participants were therefore of a young population which is consistent with the findings of the Ghana Demographic and Health Survey 2017[208], which suggested that more than half of Ghanaian women are under the age of 30 years. The young population of the participants in this current study means they could have a high fertility rate due to an increased sex drive in that age bracket. In order to address their demands for sexual and reproductive health, it is necessary to provide reproductive health services including Pap smear screening for premalignant lesions of the cervix. This mean age of the participants is close to the age of participants involved in a study done to assess the correlates of cervical screening participation among Muslim women in Ghana.[209] Gill et al[1] also assessed cervical screening during pregnancy and postpartum in 237 spontaneously conceived women and found a mean age of 26.6±3.8 years for the participants which is similar to that found in this current study.

The majority of women are often diagnosed with cervical cancer between the ages of 35 and 44, according to a recent report by the American Cancer Society on important statistics for the disease.[210] This observation emphasizes the significance of age as a crucial predisposing factor for cervical abnormalities. Even though age is a criterion that cannot be changed about an individual, it is a useful tool for guiding our screening, education, and other strategy decisions. In several studies, age has also been a predictor of

participation in screening programmes as younger people have been keen to participate in screening for precancer lesions of the cervix.[211-214] Some older women have the notion that they cannot get cervical cancer.[213]

Out of the 370 participants in this study, 266(71.9%) were married whereas 100(27.0%) were single. Only one woman (0.3%) was divorced. In similar related study by Bakari et al[170], the researchers sampled women who were mostly married. Marital status has also been found to be a predictor of having a Pap smear test done by a study done in Ghana by Calys Tagoe et al[26]. The higher proportion of married women who had a Pap smear done in this study can be attributed to the fact that in most cultures as in Ghana, it is not ethical for women to engage in coitus before marriage. Issues concerning precancerous lesions of the cervix are directly related to coital activity as such some unmarried women may see it as a taboo**.** Ghana is a sex-closed society, thus, even visiting the gynaecologist for procedures such as Pap smear may be attached with stigma particularly for the unmarried women.[215]

Also, just 16(4.3%) of the participants in this study had ever smoked a cigarette, which is higher than the 0.1% figure quoted for females in the most recent Demographic Health Survey report though it was done as far back as 2014.[216] The commonest religion among the participants in this study was Christianity 325(87.8%), followed by Islam 41(11.1%) was an additional finding. This is not surprising as 71% of the Ghanaian population are Christians followed by Islam which forms 19.9% of the population.[217]

Most of the participants 321(86.8%) and their partners 353(95.4%) were employed. It was also observed that majority of the participants 353(95.4%) were educated. Education has been linked to participation in screening programmes. Studies carried out in various places of the world have proven this.[226,227] These characteristics of respondents being mostly educated and employed agree with the expectations of the general characteristics of women living in the geographical location used for the study. A 2019 Ghana Living Standards Survey showed that an appreciable proportion of women living in the Accra Metropolis are educated and belong to the working class.[218]

Similar to the findings of this study of over 80% of the study participants had heard of cancer of the cervix, Obioha et al[31] also recorded a high level of awareness of over 90% of cervical cancer among their study participants in a Nigerian study conducted in 2022. Several studies have also shown such high

levels of awareness of cervical cancer, which is similar to the finding of this study.[10,219,220] A qualitative study done in Ghana by Williams and Boateng in 2012 showed that majority of the study participants had no knowledge of cervical cancer, which is in variance to the finding of this study.[221] In a 2015 study done in Elmina, Ghana, 68.4% of the participants had never heard of cervical cancer, which is in variance to the findings of this study, where over 80% of the participants had heard of cervical cancer.[102] Since Elmina is less urban than Accra, it has a lower percentage of educated people than Accra.[218] This could account for the low level of knowledge of cervical cancer in that study. Low socioeconomic position, which has been linked to inadequate awareness of cervical cancer, is a sign of low education.[76] In contrast, the current study was done an urban area where most of the participants were educated and a majority of them had knowledge of cervical cancer. A 2016 study done in Nigeria also showed poor knowledge of cervical cancer, even among the educated, which is in contrast to what was seen in this current study. Out of the 100 participants in that study, only 13 had ever heard of cancer of the cervix.[21]

In this study, 5.1 % of participants had taken a Pap smear before. This number is far lower than the WHO target of 70% of women being screened by the age of 30 years.[222] It must however be noted that this study's prevalence of Pap smear history is higher than that of two earlier studies conducted in Ghana, where the prevalence in both studies was less than 3%.[26,27] This could be explained by the fact that more Ghanaians are becoming aware of cervical cancer and its prevention helping to increase the uptake of screening techniques such as Pap smear. Cervical cancer awareness month has been introduced and promoted by several organizations in Ghana to increase the awareness of cervical cancer among the populace.[223-225]Awareness of cancer of the cervix has also been linked to increased uptake of preinvasive lesions of the cervix screening in several studies.[226-229] The National Strategy for Cancer Control document released in 2011 states that cervical cancer screening and testing were first made available in Ghana in 2001 by the Ministry of Health (MOH) in collaboration with the Johns Hopkins Programme for International Education in Gynecology and Obstetrics (JHPIEGO).[230] It also stated that the Ministry of Health incorporated cervical cancer screening in its National Reproductive Health Policy in 2004. The policy advised cervical cancer screening techniques such as the Pap test and visual inspection with acetic acid (VIA) could be used. The GHS Reproductive Health strategic plan (2007-2011) was made to increase access to these screening services via an increase in the cadre of staff who can provide the services and also an increase in the number of facilities that can provide the service.[231] Additionally,

gynecological cancer screening has been incorporated into already-existing health initiatives, such as reproductive health initiatives including family planning and STI management services.

In this study, the contraceptive injectable was the most common contraceptive that had ever been used by the participants with 57.0% having ever used it. In the current 2017 Ghana Maternal Health Survey, eight percent each of married women and sexually active unmarried women in Ghana utilize this form of family planning, making it the most popular among both groups.[232] The reason for its common use of contraceptive injectables has been attributed to the discreet nature of its application. The World Health Organization suggests making self-administered injectable contraception (depot medroxyprogesterone acetate in its subcutaneous form, or DMPA SC) available as an additional method of injectable contraception delivery for people of reproductive age.[233]

Only 17% (63/370) of the study participants were currently using a family planning method. This may be because the majority of them were not sexually active, as they were only 6 weeks postpartum and did not see the need for contraception.

5.2 The Prevalence of Abnormal Cervical Cytology Among Postpartum Women

The researcher in this current study evaluated the prevalence of abnormal cervical cytology among 6 weeks postpartum women. The results showed that among the 370 women studied, 10.5% was the prevalence of abnormal cytology of the cervix at a confidence interval of 95% (7.6%-14.1%).

This result is similar to several studies especially in underdeveloped countries such as Nigeria[31], Ghana[115], India[127] and also other countries like China[189,234]. For example, Obioha et al[31] who did their study in neighboring Nigeria in 2022 had a prevalence of 11.6% abnormal cervical cytology in 6 weeks postpartum women. In that study, they compared the prevalence of 11.6% in the postpartum group to the 10.5% in a matched non-pregnant group, and it was found not to be statistically different. This study by Obioha et al[31] was done in only one centre using systemic random sampling making it possible to generalize the findings. Similarly, a study done in Ghana in 2014 also showed a prevalence of 12.6% for abnormal cervical cytology in one of the two sites involved in the study. The study was done in a non-pregnant population only.[115] It was a joint effort between the Mayo Clinic in the USA and Ghana's Komfo Anokye Teaching Hospital (KATH), with samples from each patient being tested at both facilities. A Chinese study done in 2010 found a prevalence of 13% among non-pregnant making use of a very large

sample size of 11 906 which is in consonance with what was obtained in this current study.[192] Similarly, Ma et al[234] also found a prevalence of 9.4 % of cervical cytology abnormalities which is close to what was obtained in this current study in a study done in 2011. That study used a large sample size of 5152 Chinese pregnant women.

In contrast to the prevalence of abnormal cervical smear in this study, several studies have prevalences that were very different from what was obtained from this study with some being higher and others being lower. These are enumerated below. For instance, in a 2017 study, which was carried out in Nigeria, Bakari et al[170] also noted that the prevalence of abnormal cervical smear results was less than 6% in postpartum women. Among the 15(6%) that had antenatal cervical cytology abnormalities, only 9 had persistent disease during the postpartum period even though 2 participants were lost to follow-up. Much lower prevalence rates of 3% and 3.8% were recorded in 2 studies done with one done in Nigeria and the other in Jordan.[21,169] Khaengkhor and compatriots[166] also evaluated the incidence of abnormal cervical smear among 143 pregnant women using LBC method of sample collection in a study done in Thailand in the year 2011. In that study, the researchers reported an incidence rate of 7% of cervical smear abnormalities. Thomas et al[167] also did a study in 2012 involving 1204 Nigerian women who were sexually active and found a 7.6% prevalence of abnormal cervical cytology. Other studies done in different parts of the world have shown very low prevalence rates ranging from 0.6% to 6%.[183,245-246] Much higher prevalence has been recorded in immunocompromised women, particularly those with HIV in several studies.[174,176] For example, Terer[174] reported a high abnormal cervical cytology prevalence of 37% among the 175 women with HIV infection at 6 weeks postpartum who participated in his study done 2008 in Kenya. Another study done in another African country of Zambia among a similar population of HIV-positive women showed a much higher prevalence of 76% (114/150) being one of the highest recorded in literature in 2006. This higher prevalence could be attributed to the added risk factor of the women being HIV positive.[176]

The relatively high prevalence rate of abnormal cervical cytology of 10.5% of the 370 postpartum women in this current study may be a reflection of the general lack of public knowledge and awareness of cervical abnormalities, as well as its associated risks, in terms of morbidity and long-term repercussions. Effective screening of women of childbearing age allows early detection of abnormalities and swift action to be taken when the need arises. Additionally, existing statistics indicate that lack of screening is linked with

a higher prevalence of cervical abnormalities and the observance of a comparatively high prevalence rate in this study further emphasizes this fact.[140] The National Breast and Cervical Cancer Programme's accessible, free or low-cost screening programmes ensure that cases of cancer of the cervix and premalignant cervical lesions are maintained to an absolute minimum in wealthy nations like the USA.[140] However, in underdeveloped countries like Ghana, the regular citizen is either poor, underprivileged, or unable to afford the cost of cervical assessments. In some cases, when patients can afford cervical assessment methods, however, facilities that offer such services are either absent, under-resourced, or over-subscribed with long waiting queues. Midwives, physicians, and other caregivers of pregnant, postpartum and non-pregnant women must develop strategies to increase the awareness of their clients on cervical cancer, its preventive measures and the need to participate in routine screening. Population diversity and heterogeneity may be the cause of the variations in prevalence of abnormal cervical cytology around the globe.[1,18,172]

5.3 Description of the Types of Abnormal Cervical Cytology in Postpartum Women

In the current study, the researcher also evaluated the cervical cytology findings among participants at 6 weeks postpartum and found that most women (89.5%) were normal cervical cytological findings. The remaining participants (10.5%) had abnormal cervical cytology (8.4% had ASCUS, 1.9% had LSIL and 0.3% had HSIL).

Similar to the findings of this study, ASCUS was the commonest cervical cytology abnormality in studies by Fan et al[172], Simavli et al[135] and Suzuki at al[183]. In the study by Suzuki et al,[183] the Pap smear test for 1213 Japanese women was compared during their early pregnancy and the postpartum period. It was concluded that Pap smear during the postpartum period was more reliable than during pregnancy due to the hormonal factors that come with pregnancy. The most common smear abnormality during the postpartum period was ASCUS which agrees with the findings of this present study of ASCUS being the most common cervical smear abnormality. ASCUS is a common diagnostic category that is regarded as a challenging and indeterminate as it lies between a confirmed SIL and a negative diagnosis. The aberrant cytologic alterations in ASCUS are suggestive of squamous intraepithelial lesion (SIL), but they are less severe qualitatively and quantitatively than those of a diagnosis of SIL. Patients with ASCUS will require regular screening using the available methods like HPV DNA, Pap smear or VIA, as this has been proven to reduce the risk of acquiring invasive cancer of the cervix.[22,23]

Khaengkhor et al[166] discovered, in contrast to this study, that there were 5 cases of LSIL, 4 cases of ASCUS, and 1 case of HSIL among the 143 women who took part in the study. Thus, LSIL was the commonest cervical cytology abnormality, not the ASCUS reported in this study. In a related study conducted in Nigeria, Bakari et al[170] recorded 13 (5.2%) and 2 (0.8%) cases of LSIL and HSIL respectively among pregnant women. Thus, LSIL was the commonest abnormality. Differences in populations could be the reason for the differences in the distribution of the various cervical smear abnormalities in this study compared to that in other studies.[166,169] Also, the participants involved in this study had no gynaecological problems compared to other studies[3,187] and this could also account for the differences in the result. Individuals with symptoms might have a higher likelihood of having abnormal cervical cytology including ICC compared to those who are asymptomatic.

5.4 Factors Associated with Abnormal Cervical Cytology in Postpartum Women

In the current study, the researcher further evaluated the factors associated with developing abnormal cervical cytology in 6 weeks postpartum women. The results noted from the current study show that the odds of developing abnormal cervical cytology was about 33 times higher among the study participants with a positive history of having an STI. At the same time, the irregular use of condom during coitus also predisposed them to five times the chances of developing cervical abnormalities when compared to those who used condom regularly

In contrast to the results of the present investigation, Ago and his colleagues[21] found that the only predictor linked with abnormal cervical smear results in women who were six weeks postpartum was having a family history of cervical cancer. Factors such as sexual behaviour and age of coitarche were not associated with cervical smear abnormalities. Only 100 women made up the study's limited sample size. Also, Tao et al[196] in 2014 reported that low socioeconomic status, postcoital bleeding and age (46-55 years) as the only variables that may contribute to abnormal cervical cytology in 728,704 women in China, which is in contrast to the present study where irregular use of condom and history of STI were associated with cervical smear abnormalities. Being uneducated, unmarried, having more children and previous pregnancies as well as being old (mean age of 56.2 years) were the factors that were significantly associated with abnormal cervical cytology in Nigerian the study by Thomas et al[167] in the year 2012 which contrasts with the findings of his study.

Comparable to the findings of this present study, Bakari et al[170] noted that age of sexual intercourse, having multiple partners, previous history of STIs and HIV, and educational level influence the development of abnormal cytology in a Nigerian study conducted in the year 2017. It was argued that all these factors are interrelated since they are linked with the acquisition of HPV infection. In a 2006 Zimbabwean study by Parham et al[176], women who were HIV positive at 6 weeks postpartum had one of the highest prevalence of abnormal cervical smear results (76%). The researchers emphasized that HIV, which is a sexually transmitted disease, was related to the high prevalence of abnormal cervical cytology. This result is consistent with the current study that found Pap smear abnormalities to be linked with a history of STIs. In 2004, Bernatsky et al[189] also established that a history of STI and the persistent use of oral contraceptives were significantly associated with cervical smear abnormalities after adjusting for other variables even though the research was done among only women with SLE. The study had the strength of a large sample size and the findings were similar to that obtained in this study in terms of the factors associated with abnormal cervical cytology that is a history of STI. Similarly, several studies have shown a history of STI to be associated with developing cervical smear abnormalities which agrees with this study.[191,235,236]

Gavric-Lovrec et al[237] also confirmed the use of condom as protective in preventing cervical smear abnormalities in a study done conducted in 2010 in Slovenia which is comparable to that of this study. In that study, various contraceptives were studied, and it was found that the usage of condom was not associated with HPV 16/18 infection and cervical smear abnormalities. Thus, that study suggests that women who did not use condoms regularly were more likely to have abnormal cervical cytology.

The history of STIs and the irregular use of condom during sexual intercourse being associated with cervical abnormalities can be explained by several reasons. History of STI predisposes women to the possible acquisition of HPV, which is a very important factor involved in the emergence of abnormal cervical cytology and cancer of the cervix. STI's causes damage to the epithelium of the cervix, thus allowing the entry of HPV which increases the risk of cervical abnormalities. WHO also reported that sexually transmitted agents such as chlamydia and gonorrhoea are associated with the persistence of HPV infection in 2021.[145] It is the persistence of infection with HPV that leads to cervical abnormalities. This is also true for women who do not use condom during sexual intercourse and are consequently prone to developing cervical smear abnormalities.[238]

Regular condom use has been proven to provide good protection against infection with HPV infection, the main infection linked to abnormal cervical smear results and cancer of the cervix.[239] The use of condoms has also been demonstrated to promote HPV clearance, hence decreasing the probability of abnormal cervical smear results by lowering infection with HPV and enabling the immune system of the body to heal any lesions of the cervix.[239,240]

The regular use of condoms has also been linked with the regression of cervical smear abnormalities.[240] Condom is a barrier method that prevents direct contact between the cervix and the semen. It is thought that semen has an immunosuppressive impact that is advantageous for the reproductive process. However, when cervical lesions have formed, it has been hypothesized that the absence of semen with its immunosuppressive effect enhances the regression of cervical abnormalities. Furthermore, it has been mentioned that synthetic latex used in condoms may boost cellular immunity and promote the healing of cervical lesions.[239,240]

Other factors such as the age of sexual debut, smoking status, having multiple partners, and other characteristics did not increase the risk of developing an abnormal cervical smear which could be due to population differences in this study compared to other studies where these factors were significant.[241,242]

5.5 Description of Colposcopy Findings in Postpartum Women

In this study, there were 39 abnormal cervical cytology results including 31 ASCUS, 7 LSIL and 1 HSIL. The recommendation is to perform a colposcopy for all abnormal cervical cytology including LSIL, HSIL and ASC-H excluding ASCUS.[145] As a result, 7 of the participants who were eligible for a colposcopy underwent one, while the eighth participant was lost to follow-up. The colposcopy result was normal in all 7 participants. Endocervical curettage was not done as the complete transformation zone was visualized and there was no suspicion of glandular disease. These 7 participants with abnormal cervical cytology (HSIL and LSIL) and normal colposcopy were advised to undergo a follow-up screening test, particularly HPV DNA in within 1 year. The 31 participants who just had ASCUS were counselled to do an immediate triage with HPV DNA Test as recommended by WHO.[145]

The study participants in this study with abnormal cervical cytology had normal colposcopies, which is comparable with a study done in Nigeria[21] in which all 3 participants with LSIL had normal colposcopies

as well. Colposcopy can be used as a triage test following an initial primary positive screening test like HPV DNA or Pap smear.[145] Despite playing a significant role in clinical diagnosis, colposcopy is usually not utilized as a primary screening method due to its low accuracy.[243] The essence of colposcopy as a triage test is to prevent overtreatment. Thus, it is not out of place that all those with abnormal cytology in this study had normal colposcopy. All these individuals with abnormal cervical cytology with normal colposcopy in the current study will benefit from follow-up screening methods such as HPV DNA testing.

In contrast to this study, another study found 19 grade 1 abnormal colposcopic findings and 33 grade 2 abnormal colposcopic findings among the 52 postpartum women who had abnormal cytology.[199] Grade 1 changes such as fine mosaic, fine punctation and thin acetowhite epithelium suggest benign conditions or low-grade lesions, whereas grade 2 changes such as coarse mosaic, coarse punctation and dense acetowhite epithelium are indicative of high-grade lesions.

Also, a study by Gomez et al[197] showed an agreement between the findings of the Pap smear of 6 HSIL cases, 9 SCC cases and 3 AC cases with their colposcopic results which is also in contrast to the findings in this current study. If Pap smear results show high-grade lesions rather than low-grade lesions, there is a greater probability that colposcopy will find abnormalities in the cervix.[153,155] This may help to explain why the results of this study differ from those of previous studies where there was agreement between the results of the Pap smear and the colposcopic examination, as there were many more high-grade lesions in those earlier studies.[197]

5.7 Limitations

1. One challenge of the study was the refusal of 17 women to undergo the Pap smear test after filling out the questionnaire and receiving adequate counseling on the procedure. Thus, those filled questionnaires had to be discarded and new ones started for new participants.
2. The self-reported nature of answering questions like the history of STI and age of coitarche might lead to errors from recall, hesitancy or social desirability.
3. The study was also limited by the use of only conventional Pap test for cervical smear analysis due to financial constraints. Pap test can give false negative results.
4. The use of Ayre's spatula was associated with bleeding and pain due to its rigid nature. This made the participants less comfortable and uncooperative sometimes. 13 postpartum women were

excluded due to significant bleeding per vaginam provoked by the use of the Ayre's spatula. To avoid bleeding and pain, an alternative is to use a cervix brush, which has semicircular, flexible and soft bristles.

5. The cost of the Pap test being borne by the principal investigator made some participants skeptical that it may be an inferior test.
6. A non-probability sampling technique in the form of convenient sampling was used in this study due to time constraints. Convenient sampling can lead to selection bias when only participants with similar characteristics are included in the study.
7. The study used only two centres in the same Metropolis, suggesting that enough caution must be exercised when extrapolating the study findings to the general population. Multiple studies must be conducted across the country, taking into account the different ethnic groups and heterogeneity among the Ghanaian people. This will make the generalization of the findings more accurate.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

The current study evaluated the prevalence and types of abnormal cervical cytology as well as the associated factors among 6 weeks postpartum women in selected hospitals in the Accra Metropolis. Most of the participants in this current study are older than 25 years, educated (secondary and above), employed and have a spouse or partner. The study found a prevalence of 10.5% for abnormal cervical cytology among women at 6 weeks postpartum. It also concludes that ASCUS, LSIL, and HSIL are the most frequent types abnormal cervical cytological findings. Women with a history of STI and those who used condoms irregularly were more likely to develop abnormal cervical cytology. The colposcopy done for the participants with abnormal cervical cytology excluding ASCUS was normal in all of the cases**.**

6.2 Recommendations

1. The GOG (Government of Ghana) and the MOH should consider implementing routine postpartum Pap testing as part of 6 weeks postnatal care.
2. MOH should consider placing postpartum screening under the free maternal care programme which is covered by the NHIS.
3. MOH should invest in building a workforce and infrastructure in the screening of precancer lesions of the cervix.
4. In this study, aberrant cervical cytology was linked to a history of STI and irregular use of condoms. GHS and RHC should strengthen their advocacy for healthy sexual lifestyles and the regular use of condoms to reduce the risk of HPV infection.
5. Further research must also consider a larger, multi-centre study using a probability sampling technique where it is possible to apply the study's findings to the broader population.
6. Additional studies in this area should take into account other cervical screening techniques, particularly HPV DNA, which has been demonstrated to be the most objective screening technique for identifying precancerous cervical lesions though it is more expensive than other screening tests such as Pap smear.

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LOGISTICS AND TIME SCHEDULE

ACTIVITIES	TIMELINES (2021/2022)											
	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Preparation of proposal												
Proposal submission												
Application for ethical clearance												
Data collection												
Data entry and analysis												
Final report writing												
Submission of thesis												

BUDGET/RESOURCES

Item	Unit Cost (GHC)	Quantity	Total Cost (GHC)
Stationery and Communication Consumables, Pap smear kits and colposcopy	30	370	11,100
Training for Team Snacks Venue	 100 70	 3 days 3 days	 300 210
Allowance Research assistant (3)	800 for each person	6 months	2400
Ethical Approval	150		150
Data analysis and Report writing Meeting	100	2 days	200
Dissemination of findings	200		200
Miscellaneous	600		600
Grand Total			**15,160**

Budget is self-funded and the funds administrator will be the Principal Investigator.

JUSTIFICATION FOR THE BUDGET

11,100 cedis was used to procure consumables and the Pap smear kit with each unit of the 370 costing 30 cedis. This cost included the payment for the pathologist to read the Pap smears. A total of 510 cedis was also spent on training the team of research assistants taking into account their accommodation and the snacks that they will take. An allowance of 2400 cedis was allocated to the 3 research assistants with each receiving 800 cedis for the 6 months. They were involved in the data collection. 150 cedis was spent on applying for ethical approval. 200 cedis was spent on the data analysis, and a further 200 cedis was allocated to disseminate the findings. 600 cedis was used for miscellaneous activities. The grand total of the budget was 15,160 cedis.

APPENDICES: APPENDIX I

Participants Information Sheet (PIS)

Study Title: Factors associated with abnormal cervical cytology among 6 weeks postpartum women in selected hospitals in the Accra Metropolis**.**

Introduction

I am [Name of Research Assistant] and I am a research assistant Michael Yaw Amoh who is a senior resident in the Department of Obstetrics and Gynaecology at Korle Bu Teaching Hospital whose contact number is 0248184224.

We want you to take part in a Research titled: Factors associated with abnormal cervical cytology among 6 weeks postpartum women in selected hospitals in the Accra Metropolis.

Background and purpose of the study

Cervical cancer is one of the most common gynaecological cancers in developing countries such as Ghana. It is preventable via the use of screening procedures such as the Pap smear. However, inGhana, there is no national screening programme for detecting preinvasive lesions of the cervix. The postpartum period is an important period where most women in their reproductive age group can be screened. This will be explained to the participants in English or translated to their local dialect through an interpreter. You have been chosen for this research because you meet the criteria for those eligible for this research. There will be 370 participants involved in this study. 206 participants will be from Korle Bu Teaching Hospital, whereas the remaining 164 will be from Greater Accra Regional Hospital. The duration of the study will be 6 months starting from January 2022. There will be no compensation for participating in this study and it will not cost the participant anything apart from transportation to the facility. The study would involve your answering a few questions and taking of the Pap smear test which will include taking a sample from the cervix.

Benefits

Information gathered from this study will help the Ministry of Health and other stakeholders to implement strategies to improve upon preventing cervical cancer. You will be told the findings of your report with will be beneficial to you. You will be given a copy of the information gathered for keep.

Potential risks

There is minimal risk associated with taking part in this study as some of the questions may appear personal. In case of psychological distress, the services of a psychologist will be employed to deal with the situation.

Participant's rights to refuse or withdraw

Participating in this study is on voluntary bases, and you may decide to withdraw from the study at any point in time without incurring any punitive actions. Also, if you feel uncomfortable answering certain questions, it is within your rights to avoid them.

Compensation

There will be no compensation for taking part in this study

Confidentiality

All the information you provide will be anonymized, and be assured of the maintenance of your privacy in all published and written data resulting from the study. The performance of the Pap smear is invasive as a little sample will be taken once from the cervix of about 2mls.

Samples taken will be examined by the pathologist for changes in the cells. Information obtained from participants will be coded and stored to ensure security.

Conflict of Interest

There is no conflict of interest for us the investigators.

Contact information

Should you have any concerns regarding this study, you must first contact Dr Kareem Mumuni followed by Dr Michael Yaw Amoh whose address are below:

Dr Kareem Mumuni

Korle-Bu Teaching Hospital

Box 77

Accra

Tel-: +233244671595

Email: mumunikareem@yahoo.co.uk

Dr Michael Yaw Amoh

Korle-Bu Teaching Hospital

Box 77

Accra

Tel-: +233248184224

Email: michaelmoh123@gmail.com

Naana Abena Apatu

GHS- Ethics Review Committee Research and Development Division Ghana Health Service

P. O. Box MB 190

Accra

Email address: ethics.research@ghsmail.org

Telephone-: +233503539896

APPENDIX II: CONSENT FORM

Study Title:

Factors associated with abnormal cervical cytology among 6 weeks postpartum women in selected hospitals in the Accra Metropolis**.**

Participants' Statement

I acknowledge that I have read or have had the purpose and contents of the Participants' Information Sheet read and satisfactorily explained to me in a language I understand (**English, Ga or Twi).** I fully understand the contents and any potential implications as well as my right to change my mind (i.e., withdraw from the research) even after I have signed this form.

I voluntarily agree to be part of this research.

Name or Initials of Participant …….

Participants' Signature ……... or Right thumb Print ……

Date: …….

Investigator Statement and Signature

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed.

Researcher's name …….

Signature …….

Date……

Witness'/ Interpreter's Statement

The information in the participant information sheet as well as additional information conveyed to the participant was presented in a language preferred by and understandable to the subject.

Name or Initials of Witness/Interpreter …….

Witness'/Interpreters' Signature ……...or Right thumb Print ……

Date: …….

Investigator Statement and Signature

I certify that the witness/interpreter was involved in relaying the details of the participant information sheet to the participant.

Researcher's name ……..…….

Signature …….

Date …….

APPENDIX III: QUESTIONNAIRE
DATA COLLECTION TOOL

Project Title: Factors associated with abnormal cervical cytology among 6 weeks postpartum women in selected hospitals in the Accra Metropolis

GENERAL INFORMATION

Name of facility _____

Participant's code number: _____

Telephone number: _____

Date: _____

SECTION A: SOCIODEMOGRAPHICS CHARACTERISTICS

1. Age (in years since last birthday) _____

2. Marital Status A. Married [ ] B. Single [ ] C. Divorced [ ]
D. Widowed [ ]

3. Educational Level A. Tertiary [ ] B. Secondary [ ]
C. Basic/primary [ ] D. None [ ]

4. Religion A. Christian [ ] B. Islam [ ]
C. Traditional [ ] D. Other [ ]

5. Occupation A. Employed [ ] B. Unemployed [ ]

6. Partner Occupation A. Employed [ ] B. Unemployed [ ]

SECTION B: AWARENESS OF CERVICAL CANCER AND PREVENTION

7. Have you heard of cervical cancer

A Yes B No

8. (i) Have you taken a Pap smear before A Yes B No

If yes;

(ii) How many times? _____

(iii) When was the last time? _____

(iv) What was the result of the last test? A. Positive B. Negative C. Don't know

9. History of HPV vaccination A Yes B No

SECTION C: GYNAECOLOGIC AND OBSTETRIC CHARACTERISTICS

10. At what age did you have your first menses? _____

11. How has your menstrual history been? A. Regular [ ] B. Irregular [ ]

12. At what age did you have your first sexual encounter? _____

13. How many lifetime sexual partners have you had? _____

14. Are you experiencing post-coital bleeding currently? A. Yes [ ] B. No [ ]

15. (i) Have you ever smoked? A. Yes [ ] B. No [ ]

(ii) If yes, for how long? _____

16. Do you use condom regularly during sex? A. Yes [ ] B. NO [ ]

17. (i) Have you ever used contraception? A. Yes [ ] B. No [ ]

(ii) If yes, which ones have you used before (chose as many as apply)

A. Pill [ ] B. Injectable [ ] C. Implant [ ] D. Intrauterine Device[ ]

E. Natural [ ] F. Condom [ ] G. Other (specify): _____

(iii) Which contraceptive do you use currently?

A. Pill [ ] B. Injectable [ ] C. Implant [ ] D. Intrauterine Device [ ]

D. Condom [ ] E. Bilateral tubal ligation [ ] F. Natural [ ] G. None [ ]

H. Other (specify): _____

18. (i)Have you been tested for HIV before? A. Yes [ ] B. No [ ]

(ii). If YES, what was the result? A. Positive [ ] B. Negative [ ] C. Unknown [ ]

(iii). If 20 (ii) was positive, did you start antiretroviral therapy? A. Yes [] B. No []

19. (i) Does your partner have other partners? A. Yes [ ] B. No [ ]

(ii). If yes, how many? _____

20. Have you been diagnosed with an STI before? A. Yes [ ] B. No [ ]

21. Does your partner have a history of STIs? A. Yes [ ] B. No [ ]

22. Do you have a family history of cervical cancer? A. Yes [ ] B. No [ ]

23. (i). Have you ever given birth? A. Yes [ ] B. No [ ]

(ii). If yes, how many? _____

(iii). How old were you when you first gave birth? _____

(iv). What is the average birth interval between your births? _____

(v). What was the mode of delivery of your last birth?

A. Vaginal delivery [ ] B. Caesarian section [ ]

(vi). What was the outcome of your last pregnancy?

A. Live-term birth [ ] B. Live preterm birth [ ] C Stillbirth [ ]