Evaluation of Cervical Smear in Diagnosis the Cervical Intraepithelial Neoplastic Lesion in Saqr Hospital Ras Al khaimah Medical District
Ministry of Health, United Arab Emirate

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A dissertation Submitted to University of Gezira in Fulfillment of The partial Requirements for the Award of the Degree of Master of Science in Histopathology

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March.2017
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Date of Examination 9 / 3 /2017
قوله تعالى: "صنع الله الذي أتقن كل شيء إنه خبير بما تعملون".

رقم الآية: 88 سورة النمل

وقوله تعالى: "من أجل ذلك كتبنا على بني إسرائيل أنه من قتل نفسه بغير نفس أو فساد في الأرض فكأنما قتل الناس جميعا ومن أحياءها فكأنما أحيا الناس جميعا. ولقد جاءتهم رسولنا بالبيانات ثم إن كثيرا منهم بعد ذلك في الأرض لم يفرغون".

رقم الآية: 32 سورة المائدة

وقال رسول الله ﷺ: "إن الله يحب إذا عمل أحدكم عملًا أن يلقنه".
Dedication

To

My Parents.

To

My Wife

To

My Daughter

To

My brothers

To

My sisters.

And

To

Saqr Hospital
Acknowledgements

First, all thanks to ALLAH for giving me the power and – willing to complete this study.
I would like to thanks my supervisor of this project Dr. Albadawi Abdelbagi Talha, Dr. Sana aElfatih and Dr. Fatema Mohammed Ahmed for the Valuable guidance and advice. They inspired me greatly to work in this project. Also my thanks to Histopathology and Cytology Department at Saqr Hospital for their great help. I am deeply indebted and grateful to all who contributed to this work.
Evaluation of Cervical Smear in Diagnosis the Cervical Intraepithelial Neoplastic Lesion in Saqr Hospital Ras Al khaimah Medical District Ministry of Health, United Arab Emirate

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Abstract

The Cervical lesions are often correlated with epithelial cell abnormalities on cervical smears. The histologic lesions which are found in uterine cervix cannot be always established only with cytology. Thus, it is very important that any cytological abnormality be subsequently correlated with biopsy for confirmation of a cervical lesion. This study aimed to Evaluation of Cervical Smear in Diagnosis the Cervical Intraepithelial Neoplastic Lesion in Saqr Hospital Ras Al khaimah Medical District Ministry of Health, United Arab Emirate. The results of cervical smears and tissue diagnoses over a three year period were reviewed, being examined the correlations between the cervical smears and the surgical specimens. All cervical smears with their subsequent biopsies between 2013-2015 were retrospectively evaluated. The patient’s ages were between 18 and 70 years old. The cervical cytology records were verified and the cytodiagnosis were compared with the correspondent histopathological diagnosis. We compared the results of Pap tests, biopsies from the 743 cervical smears, diagnostic in the mentioned period of time The accuracy rate of cervical smears and histologic diagnoses was 93.0% (691/743) and showed a high correspondence (P-value, 0.000). The false-negative and false-positive rates were 0.5% (6/484) and 17.8% (46/259), respectively. The sampling and interpretation errors were identified in four and two cases of six false-negative cases and 29 and 17 cases of 46 false-positive cases, respectively. In screening high grade squamous cell neoplasms, there were no false-negative cases and only one false-positive case which resulted from sampling error. The false-negative rate of cervical smears and the false-positive rate in high-grade squamous cell neoplasms were very low. The study conclude the cervical smear is accurate in diagnosis of Cervical Intraepithelial Neoplastic Lesion. The cervical smear is a rapid and useful in diagnosis of Cervical Intraepithelial Neoplastic Lesion.
تقييم مسحات عنق الرحم لخلايا المريضية المتسلقة في تشخيص سرطان عنق الرحم الأولي

وسرطان عنق الرحم بمستشفى صقر أمة رأس الخيمة. دولة الإمارات العربية المتحدة

واليد عبد المنعم بشير علي

ملخص الدراسة

غالبا الرحم ومن جهة أخرى من الصعب الاعتماد دائمًا على الخلايا الظهارية المتسلقة لوحدها لتأسيس التشخيص النهائي لأورام عنق الرحم وبالتالي، فإن المهم جدا أن أي خلل خلوي أن يرتبط في وقت لاحق مع خزعة للحصول على تأكيد خلوه من أورام عنق الرحم. لذلك كان الغرض من دراستنا فحص مدى التطابق بين تشخيص المختبر، خلايا الأمراض، والأدلة في تشخيص أورام عنق الرحم. تم استعراض نتائج مسحات عنق الرحم وتشخيص الأنسجة المرضية على مدى فترة ثلاث سنوات، وتم فحص الارتباط بين مسحات رقبية المهبل والعينات الجراحية. تم تقييم كل مسحة عنق الرحم مع خزعة لاحقة بين 2013-2015 بأثر رجعي. تراوح عدد المرضى بين 18 و 70 عامًا. تم التحقق من السجلات خلايا عنق الرحم وقوف التشخيص خلوي مع عينات تشخيص الأنسجة. فازنا بنتائج اختراقات عنق الرحم مع عينات من مسحات رقبية المهبل من 743 مريض في الفترة المذكورة من الزمن كن معدل دقة المسحات وتشخيصات نسيجية عنق، وأظهرت الدراسة 93% (743/691) ذات قيمة عالية (0.000) و17.8% (6/46) و17.8% (6/46) عينات متشابهة كاذبة وإيجابية في تحديد الأخطاء أخذ العينات. والتمييز في حالة أربعة وستين من الحالات السمستية الكاذبة والخالفة 29 و17 من حالات 46 خالفة إيجابية كاذبة، على التوالي. في فحص الأورام ذات الدرجة المرضية العالية، لم تكن هناك حالات السلبية الكاذبة وحالة واحدة فقط كانت إيجابية الإيجابية التي نتجت عن خطأ أخذ العينة. وكان معدل سلبي كاذب من مسحات العنقية المهبلة ومعدل إيجابية كاذبة في الدرجة العالية الأورام الخلايا الحرشفية المرضية منخفضة جدا ما يرتبط أورام عنق الرحم بالتصور عينات متشابهة الظهارية المتسلقة المرضية في مسحات عنق.
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List of Abbreviations

- ASCUS: Atypical squamous or glandular cells of undetermined significance
- ACIN: Cervical intraepithelial neoplasia
- AGC: Atypical glandular cells
- CLIA ’88: The Clinical Laboratory Improvement Amendments of 1988
- DES: Diethylstilbestrol
- HE: Hematoxylin and Eosin
- HPV: Human Papilloma Virus
- HSIL: High grade squamous intraepithelial lesion
- IUD: Intrauterine device
- KPI: Key Performance indicator
- LSIL: Low grade intraepithelial squamous lesion
- LEEP: Loop electrosurgical excision procedure
- LLETZ: Large loop excision of the transformation zone
- OCs: Oral contraceptives
- OS: Ostium of uterus
- OPD: Outpatient Department
- Pap: Papanicolaou method
- SCJ: Squamous-columnar junction.
- UAE: United Arab Emirate
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Chapter One

1. Introduction

1.1 Introduction and Background:

The Cervical cancer is one of the most common cancers among women in the world and in the Middle East. Its prevention and screening strategies assume great importance especially in view of the ability to identify the illness at an early stage and disrupt its progression toward neoplasia. Cervical cancer screening program of in UAE as well as this study is oriented in this direction. The Histopathology and cytopathology form the scientific and clinical basis for current prevention and treatment of cervical cancer. Histopathology determines treatment of cancer and precancer through classifying into a diagnosis the patterns of microscopic organization of cells in tissue sections from biopsy or surgical specimens. Although morphological concepts of cervical cancer and precancer evolution are giving way to viral and molecular knowledge, histopathology also remains important as the most widely used clinical endpoints by which the performance of new techniques for cervical cancer prevention are currently evaluated. The primordial function of cervical cytology is in bringing to notice epithelial abnormalities which would otherwise escape detection because of their clinical silence (Kealy, 1986). The cervical-vaginal cytological test is now widely used both as a screening test in asymptomatic populations and in the follow-up of patients with cervical carcinomas treated by surgery or irradiation. One aspect however in the assessment of performance in cytology is the comparison of the cyto-diagnosis with the ultimate tissue appearances. Although it is not always possible to determine the exact histologic change in the cervix on the basis of the cytology smear, when a cervical abnormality is present, this is detected by cytological examination in the majority of cases. It is important to realize that it is only a screening test and, thus, it will be associated with false negative results. The present study was performed with the objective of evaluating the diagnostic acuity of cyto- and histopathological exams, analyzing the cyto-histological correlation of samples obtained from patients submitted to surgical treatment for cervical intraepithelial neoplasia. This corroborates the data in the literature, indicating that there are no reliable morphological criteria for cytological diagnosis of microinvasion. For this reason, when diagnosing CIN III it may at most be possible to add an observation questioning microinvasion, a procedure adopted in our service and in cases of diagnostic cone biopsy, investigating possible micro invasion. Although the literature shows that cyto-histological disagreement varies from 11% to
Various factors have a bearing on this discord as collection, processing, reading and interpretation of morphological alterations from the cytological exam; location and extent of the lesions, processing, number of cuts and the interpretation of the histological sample. Studies have indicated that the greatest causes of errors in cyto-histological correlation come from sampling or interpretation problems, or from both. The resulting decisions have implications for surgical procedures, which are not risk-free and may alter the woman’s reproductive and sex life. (14).

The Cervical cytopathology studies exfoliated cells taken from the surface of the cervix and are the aim of cervical screening in successful cervical cancer prevention program. These techniques have contributed hugely to reducing the burden of cervical cancer. These figures are historical comparisons and may underestimate the impact as they do not take account of observed increased rates in young women for whom screening provides little protection and the impact of increasing exposure to oncogenic HPV and other risk factors as a consequence of major behavioral changes. On this basis, in the U.A.E, the national program implementation of cytological screening started and has been estimated to prevent and reduce incidence of mortality, with a very marked decline in rates in women aged 18–70 year. This review focuses on the concepts and terminology used in classifying morphological changes of cervical precancer and HPV infection cytological and histological view, how this links to natural history through information from cervical screening.(3).

In the management of cases, a cytological diagnosis of atypical squamous or glandular cells of undetermined significance (ASCUS), SIL, or carcinoma by any of the two methods (HE, ThinPrep); Women with a biopsy-confirmed high grade squamous intraepithelial lesion (HSIL) were treated with large loop excision of the transformation zone(Schiffman M, 2007). Women with a single cytological diagnosis of HSIL confirmed on cytological review were also treated if a lesion was identified colposcopically and there were no contraindications to treatment. Women with a discrepancy between cytology and colposcopy were treated if recommended after an independent review. The remaining women were referred through the Social Security System for follow-up. Biopsy specimens were diagnosed initially in U.A.E for clinical purposes,(5).

ThinPrep diagnoses were compared with the HE biopsy diagnoses rendered in U.A.E, final case diagnoses, and the detection of carcinogenic types of HPV DNA using the Hybrid Capture tube test. Because the threshold for colposcopy referral in this study was a cytological diagnosis of ASCUS, cytological screening results were stratified into negative (normal or reactive) and positive (ASCUS, LSIL, HSIL, and carcinoma) for analytic purposes. The discrepant results between ThinPrep and surgical biopsy were adjudicated by comparison with the final case
diagnoses and the detection of carcinogenic types of HPV DNA. Statistical analyses were performed using standard contingency table methods.

An important function of cervical cytology is to stratify patients according to cancer risk. Given that nearly all carcinoma is related to HPV, the rate of detection of oncogenic types of HPV should be higher among women with SIL than among women with ASCUS smears and lowest among women with negative cytology.(5)

Histopathology has defined historically the concepts of development and progression of cervical precancer to cancer(Balan86-92). The idea of carcinoma-in-situ as a cancer precursor dates back to the early cellular pathology of Rudolf Virchow during the nineteenth century. The concept of cervical precancer has been refined over more than a century to include less severe, dysplastic, changes, and then unified into cervical intraepithelial neoplastic of three grades by Richart. Histopathology continues to drive key decisions on treatment of precancer and invasive cancer; and for this reason has been used to define clinical endpoints for research into cervical screening, HPV vaccines and biomarkers. Cytopathology forms the basis of cervical screening. Negativethe proposal can be traced to the Romanian scientist’spurel Babes and Constantin Daniel in 1927. In 1941 George Papanicolaou and Herbert Traut created widespread attention with their paper on applying the cervical smear technique to women in the Gynaecology department of New York Hospital in the USA. Therefore, this study provides a unique opportunity results.(1)

1.2 Rationale
The Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88) mandated the performance of cytologic-histologic correlation as an effort to improve anatomic pathology quality. In the cytologic-histologic correlation process, if a cytology specimen and a surgical pathology specimen are obtained from the same anatomic site (within a given time frame), the diagnoses are compared in order to detect possible discrepant cases. The cervico-vaginal smear is non-easier invasion method to screen and diagnosis the intraepithelial neoplastic lesion.

1.3 Objectives:
1.3.1 Generalobjective:
- To Evaluate the Cervico-vaginal Smear in diagnosis of cervical intraepithelial neoplastic lesion.

1.3.2 Specificobjectives:
- To compare cervico-vaginal smear and cervical biopsy
- To detect the specificity and sensitivity of cervico-vaginal smear.
Chapter Two

2. Literature Review

2.1 Literature Review:

**Cervical cancer** Cervical Cancer is a disease in which cells in the body grow out of control. Cancer is always named for the part of the body where it starts, even if it spreads to other body parts later. When cancer starts in the cervix, it is called cervical cancer. The cervix is the lower, narrow end of the uterus. The cervix connects the vagina (the birth canal) to the upper part of the uterus. The uterus (or womb) is where a baby grows when woman is pregnant. Cervical cancer is the easiest gynecologic cancer to prevent with regular screening tests and followup. It also is highly curable when found and treated early. Cervical cancer is most commonly caused by HPV or the human papillomavirus, which is highly contagious. This virus is an STI (sexually transmitted infection) and comes in many types but only some cause cervical cancer (Kurman JR, 2002). An HPV infection might go away on its own or could cause abnormal cell growth that may lead to cervical cancercervical cancer starts in the cells lining the cervix the lower part of the uterus (womb). This is sometimes called the uterine cervix. The fetus grows in the body of the uterus (the upper part). The cervix connects the body of the uterus to the vagina (birth canal). The part of the cervix closest to the body of the uterus is called the endocervix. The part next to the vagina is the exocervix (or ectocervix). The 2 main types of cells covering the cervix are squamous cells (on the exocervix) and glandular cells (on the endocervix). These 2 cell types meet at a place called the transformation zone. The exact location of the transformation zone changes as you age and if you give birth. Most cervical cancers begin in the cells in the transformation zone. These cells do not suddenly change into cancer. Instead, the normal cells of the cervix first gradually develop pre-cancerous changes that turn into cancer. Doctors use several terms to describe these pre-cancerous changes, including cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL), and dysplasia. These changes can be detected by the Pap test and treated to prevent cancer from developing (see "Can cervical cancer be prevented?"). Cervical cancers and cervical pre-cancers are classified by how they look under a microscope. The main types of cervical cancers are squamous cell carcinoma and adenocarcinoma. Most (up to 9 out of 10) cervical cancers are squamous cell carcinomas. These cancers form from cells in the exocervix and the cancer cells have features of squamous cells under the microscope. Squamous cell carcinomas most often begin in the transformation zone (where the exocervix joins the endocervix). Most of the other cervical
cancers is adenocarcinomas. Adenocarcinomas are cancers that develop from gland cells. Cervical adenocarcinoma develops from the mucus-producing gland cells of the endocervix. Cervical adenocarcinomas seem to have become more common in the past 20 to 30 years. Less commonly; cervical cancers have features of both squamous cell carcinomas and adenocarcinomas. These are called adenosquamous carcinomas or mixed carcinomas. Although cervical cancers start from cells with pre-cancerous changes (pre-cancers), only some of the women with pre-cancers of the cervix will develop cancer. It usually takes several years for cervical pre-cancer to change to cervical cancer (DiagnCytopathol 2002), but it can happen in less than a year. For most women, pre-cancerous cells will go away without any treatment. Still, in some women pre-cancers turn into true (invasive) cancers. Treating all cervical pre-cancers can prevent almost all true cervical cancers. Pre-cancerous changes and specific types of treatment for pre-cancers are discussed in our document Cervical Cancer Prevention and Early Detection. Although almost all cervical cancers are either squamous cell carcinomas or adenocarcinomas, other types of cancer also can develop in the cervix. These other types, such as melanoma, sarcoma, and lymphoma, occur more commonly in other parts of the body. This document only discusses the more common cervical cancer types, and not the rare types. (9)

2.2 Histological Structure of cervix

The cervix is about 2 cm (1 in) long. It is made up mostly of connective tissue and muscle. It is divided into 2 main parts: The endocervix is the inner part of the cervix lining the canal leading into the uterus. The ectocervix, or exocervix, is the outer part of the cervix. It is rounded, lip-like and sticks out into the vagina. The endocervical canal are the passageways from the uterus to the vagina. The 2 main types of cells in the cervix are: Columnar cells line the endocervical canal (Am J ClinPathol 1995). They are glandular cells that make mucus. They are called columnar cells because they are tall and shaped like columns. Squamous cells line the ectocervix and vagina. They are flat and thin like the scales on a fish. The squamous cell join the columnar cells in an area of the cervix called the squamo-columnar junction. This is also called the transformation zone because the tall columnar cells are constantly being changed into flat squamous cells, especially during puberty and child-bearing years. Precancerous changes of the cervix and most cervical cancers start in the transformation zone. (11)
2.3 Physiology of cervix:

The cervix (Latin for neck) is the lower-most portion of the uterus. Cylindrical in shape, the cervix consists of the following two major structures: the ectocervix and the endocervix. The ectocervix is the portion of the cervix which is touchable and visible through the vaginal canal. This is also the area is swabbed during a Pap smear. The endocervix is the internal, canal-like portion of the cervix which opens into the uterus. The size, shape and color of the cervix depend on a woman’s age, hormonal state and whether or not she has given birth.1 For women who are nulliparous, or have not given birth, the cervix appears to have a small circular opening (external OS) at its center. In women, the cervix is bulkier and the external os has a more slit like appearance. The cervix contains two types of cells, columnar and squamous epithelial cells, columnar epithelial cells form a single layer of mucous-secreting cells located in the endocervix and a variable portion of the ectocervix. And squamous epithelial cells are located on the ectocervix. Both types of cells are collected during a Pap smear to detect the presence of abnormal cell growth. During pre-adolescence, the endocervix is located on the vaginal portion of the cervix, but retreats as a woman ages. The transformation zone is the region on the ectocervix where over time the more the cervix of a woman who has not given birth (nulliparous) the cervix of a woman who has given birth. Fragile columnar epithelial cells are replaced with more durable squamous epithelial cells. This area is particularly vulnerable to pre-cancerous changes (dysplasia) due to the high turnover rate and low maturation level of the cells. (3).

2.4 Signs and symptomsof cervical cancer:

Women with early cervical cancers and pre-cancers usually have no symptoms. Symptoms often do not begin until a pre-cancer becomes a true invasive cancer and grows into nearby tissue. When this happens, the most common symptoms, Abnormal vaginal bleeding, such as bleeding after sex (vaginal intercourse), bleeding after menopause, bleeding and spotting between periods, and having longer or heavier (menstrual) periods than usual. Bleeding after douching, or after a pelvic exam is a common symptom of cervical cancer but not pre-cancer. An unusual discharge from the vagina, When the cancer begins to grow inside the cervix, the cells of the uterine wall begin to rid, which produces a watery discharge, the discharge may contain some blood and may occur between your periods or after menopause. Pain during sex (vaginal intercourse). According to gynecologist Rosa Maria Leme, "The appearance of small warts (externally or internally) serve as a red flag diseases such as HPV, which can greatly increases the chances of cervical cancer in women.". These signs and symptoms can also be
caused by conditions other than cervical cancer. Cervical cancer grows on the walls of the cervix which can dry out and even crack, causing discomfort and bleeding. There may also be rectal or bladder bleeding. Any bleeding outside your menstrual period should be investigated. For example, an infection can cause pain or bleeding. Still, if you have any of these problems, you should see your health care professional right away.(5).

2.5 Epidemiology and risk factor of Cervical Cancer

Cervical cancer is one of the most common neoplastic diseases affecting women, with a combined worldwide incidence of almost half a million new cases annually, second only to breast cancer. Basic and epidemiologic research conducted during the past 15-20 years have provided overwhelming evidence for an etiologic role for infection with certain types of sexually-transmitted human papillomavirus (HPV) as the primary cause of cervical cancer. The available evidence indicates that the HPV-cervical cancer association satisfies all relevant causal criteria for public health action. Other cervical cancer risk factors, such as smoking, parity, use of oral contraceptives, diet, other infections, and host susceptibility traits must be understood in the context of mediation of acquisition of HPV infection or in influencing events of the natural history of cervical neoplasia that occur following the establishment of a persistent HPV infection. Virtually all cervical carcinoma specimens contain HPV DNA, which suggests that HPV infection is a necessary cause of cervical neoplasia. This is the first instance in which a necessary cause has been demonstrated in cancer epidemiology a realization that has obvious implications for primary and secondary prevention of this neoplastic disease. Other risk factor The best-known risk factors for cervical cancer are mocking or breathing in second-hand, multiple sexual partners, having unprotected sex, Having low immunity. Smoking is a risk factor for many cancers. But having a risk factor, or even several, does not mean that you will get the disease. Several risk factors increase your chance of getting cervical cancer. Women without any of these risk factors rarely develop cervical cancer. Although these factors increase the odds of getting cervical cancer, many women with these risk factors do not develop this disease.In thinking about the following risk factors, it helps to focus on those you can change or avoid (like smoking or human papilloma virus infection), rather than those that you cannot (such as your age and family history). It’s still important, though, to know about risk factors that cannot be changed, because it's even more important for women who have these factors to get regular Pap tests to detect cervical cancer early. Cervical cancer risk factors include: Human papilloma virus infection is the most important risk factor for cervical cancer is infection by the human papilloma virus (HPV). HPV is a group of more than 150 related viruses, some of which cause a type of growth called papillomas, which are more commonly known as warts. HPV can infect cells on the surface of the skin, and those lining the genitals,
anus, mouth and throat, but not the blood or internal organs such as the heart or lungs. HPV can be spread from one person to another during skin-to-skin contact. One way HPV is spread is through sex, including vaginal, anal, and even oral sex. Different types of HPV cause warts on different parts of the body. Some types cause common warts on the hands and feet. Other types tend to cause warts on the lips or tongue. Certain types of HPV may cause warts to appear on or around the genital organs and in the anal area. These warts may barely be visible or they may be several inches across. These are known as genital warts or condyloma acuminatum. HPV 6 and HPV 11 are the 2 types of HPV that cause most cases of genital warts. These are called low-risk types of HPV because they are seldom linked to cervical cancer. Other types of HPV are called high-risk types because they are strongly linked to cancers, including cancers of the cervix, vulva, and vagina in women, penile cancer in men, and anal and oral cancer in men and women. The high-risk types include HPV 16, HPV 18, HPV 31, HPV 33, and HPV 45, as well as some others. There might be no visible signs of infection with a high-risk HPV until precancerous changes or cancer develops. Doctors believe that a woman must be infected by HPV before she develops cervical cancer. Although this can mean infection with any of the high-risk types, about two-thirds of all cervical cancers are caused by HPV 16 and 18. Infection with HPV is common, and in most people the body is able to clear the infection on its own. Sometimes, however, the infection does not go away and becomes chronic. Chronic infection, especially when it is with high-risk HPV types, can eventually cause certain cancers, such as cervical cancer. Although HPV can be spread during sex – including vaginal intercourse, anal intercourse, and oral sex – sex doesn't have to occur for the infection to spread. All that is needed to pass HPV from one person to another is skin-to-skin contact with an area of the body infected with HPV. Infection with HPV seems to be able to be spread from one part of the body to another – for example, infection may start in the cervix and then spread to the vagina. Completely avoiding putting the areas of your body that can become infected with in contact with those of another person may be the only way to truly prevent these areas from becoming infected with HPV. The Pap test looks for changes in cervical cells caused by HPV infection. Other tests look for the infections themselves by finding genes (DNA) from HPV in the cells. For some women, the HPV test is used along with the Pap test as a part of screening. The HPV test may also be used to help decide what to do when a woman has a mildly abnormal Pap test result. If the test finds a high-risk type of HPV, it could mean she will need a full evaluation with a colposcopy procedure. Although there is currently no cure for HPV infection, there are ways to treat the warts and abnormal cell growth that HPV causes. For more information on preventing HPV infection, see the “Can cervical cancer be prevented?” section in this document or ask for our documents called HPV Vaccines and HPV and HPV Testing.
Although scientists believe that it’s necessary to have had HPV for cervical cancer to develop, most women with this virus do not develop cancer. Doctors believe that other factors must come into play for cancer to develop. Some of these known factors are listed below. Smoking Women who smoke are about twice as likely as non-smokers to get cervical cancer. Smoking exposes the body to many cancer-causing chemicals that affect organs other than the lungs. These harmful substances are absorbed through the lungs and carried in the bloodstream throughout the body. Tobacco by-products have been found in the cervical mucus of women who smoke. Researchers believe that these substances damage the DNA of cervix cells, and may contribute to the development of cervical cancer. Smoking also makes the immune system less effective in fighting HPV infections. Immunosuppression Human immunodeficiency virus (HIV), the virus that causes AIDS, damages the immune system and puts women at higher risk for HPV infection. This might, in part, explain the increased risk of cervical cancer in women with AIDS. Also, that the immune system may be important in destroying cancer cells and slowing their growth and spread. In women with an impaired immune system from HIV, a cervical pre-cancer might develop into an invasive cancer faster than it normally would. Another group of women at risk of cervical cancer are those taking drugs to suppress their immune response, such as those being treated for an autoimmune disease (in which the immune system sees the body’s own tissues as foreign and attacks them, as it would a germ) or those who have had an organ transplant. Chlamydia infection Chlamydia is a relatively common kind of bacteria that can infect the reproductive system. It’s spread by sexual contact. Chlamydia infection can cause pelvic inflammation, leading to infertility. Some studies have seen a higher risk of cervical cancer in women whose blood test results show signs of past or Current chlamydia infection (compared with women with normal test results). Women who are infected with chlamydia often have no symptoms. In fact, they may not know that they are infected at all unless they are tested for chlamydia during a pelvic exam. A diet low in fruits and vegetables Women whose diets don’t include enough fruits and vegetables may be at increased risk for cervical cancer. Being overweight Overweight women are more likely to develop adenocarcinoma of the cervix. Long-term use of oral contraceptives (birth control pills) there is evidence that taking oral contraceptives (OCs) for a long time increases the risk of cancer of the cervix. Research suggests that the risk of cervical cancer goes up the longer a woman takes OCs, but the risk goes back down again after the OCs are stopped. In one study, the risk of cervical cancer was doubled in women who took birth control pills longer than 5 years, but the risk returned to normal 10 years after they were stopped. The American Cancer Society believes that a woman and her doctor should discuss whether the benefits of using OCs outweigh this very slight potential risk. A woman with multiple sexual partners should use
condoms to lower her risk of sexually transmitted infections no matter what other form of contraception she uses. Intrauterine device use A study found that women who had ever used an intrauterine device (IUD) had a lower risk of cervical cancer. The effect on risk was seen even in women who had an IUD for less than a year, and the protective effect remained after the IUDs were removed. Using an IUD might also lower the risk of endometrial (uterine) cancer. However, IUDs do have some risks. A woman interested in using an IUD should first discuss the potential risks and benefits with her doctor. Also, a woman with multiple sexual partners should use condoms to lower her risk of sexually transmitted illnesses no matter what other form of contraception she uses. Having multiple full-term pregnancies Women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer. No one really knows why this is true. One theory is that these women had to have had unprotected intercourse to get pregnant, so they may have had more exposure to HPV. Also, studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that pregnant women might have weaker immune systems, allowing for HPV infection and cancer growth in younger than 17 at your first full-term pregnancy Women who were younger than 17 years when they had their first full-term pregnancy are almost 2 times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older. Poverty is also a risk factor for cervical cancer. Many women with low incomes do not have ready access to adequate health care services, including Pap tests. This means they might not get screened or treated for cervical cancers and pre-cancers. Diethylstilbestrol (DES) DES is a hormonal drug that was given to some women to prevent miscarriage between 1940 and 1971. Women whose mothers took DES when pregnant with them are often called DES daughters. These women develop clear cell adenocarcinoma of the vagina or cervix more often than would normally be expected.(12)

2.6 The Prevention of cervical cancer:
Since the most common form of cervical cancer starts with pre-cancerous changes, there are 2 ways to stop this disease from developing. One way is to find and treat pre-cancers before they become true cancers, and the other is to prevent the pre-cancers in the first place. A well-proven way to prevent cervix cancer is to have testing (screening) to find pre-cancers before they can turn into invasive cancer. The Pap test (sometimes called the Pap smear) and the HPV (human papilloma virus) test is used for this. If a pre-cancer is found, it can be treated, stopping cervical cancer before it really starts. Since no HPV vaccine provides complete protection against all of the HPV types that can cause cancer of the cervix, it cannot prevent all cases of cervical cancer. This is why it is very important that women continue to have cervical cancer
screening even after they’ve been vaccinated. Most invasive cervical cancers are found in women who have not had regular screening.

Avoid contact with the human papilloma virus (HPV). Since HPV is the main cause of cervical cancer and pre-cancer, avoiding exposure to HPV could help you prevent this disease. HPV is passed from one person to another during skin-to-skin contact with an infected area of the body. Although HPV can be spread during sex including vaginal, anal, and oral sex, sex doesn't have to occur for the infection to spread. All that is needed is skin-to-skin contact with an area of the body infected with HPV. This means that the virus can be spread through genital-to-genital contact (without intercourse). It is even possible for a genital infection to spread through hand-to-genital contact. Also, HPV infection seems to be able to be spread from one part of the body to another. This means that an infection may start in the cervix and then spread to the vagina and vulva. It can be very hard not to be exposed to HPV. It may be possible to prevent genital HPV infection by not allowing others to have contact with your anal or genital area, but even then there might be other ways to become infected that aren’t yet clear. For example, a recent study found HPV on the surface of sex toys, so sharing sex toys might spread HPV. HPV infections occur mainly in younger women and are less common in women older than 30. The reason for this is not clear. Certain types of sexual behavior increase a woman's risk of getting HPV infection, such as having sex at an early age and having many sex partners. Women who have had many sex partners are more likely to get infected with HPV, but a woman who has had only one sex partner can still get infected. This is more likely if she has a partner who has had many sex partners or if her partner is an uncircumcised male. Waiting to have sex until you are older can help you avoid HPV. It also helps to limit your number of sex partners and to avoid having sex with someone who has had many other sex partners. Although the virus most often spreads between a man and a woman, HPV infection and cervical cancer also are seen in women who have only had sex with other women. Remember that someone can have HPV for years and still have no symptoms; it does not always cause warts or other problems. Someone can have the virus and pass it on without knowing it.(11).

Still, since all that’s needed to pass HPV from one person to another is skin-to-skin contact with an area of the body infected with HPV, even never having sex doesn’t guarantee that you won’t ever get infected. It might be possible to prevent anal and genital HPV infection by never allowing another person to have contact with those areas of your body. HPV infection in men: For men, the main factors influencing the risk of genital HPV infection are circumcision and the number of sex partners. Men who are circumcised (have had the foreskin of the penis removed) have a lower chance of becoming and staying infected with HPV. Men who have not been circumcised are more likely to be infected with HPV and pass it on to their partners. The
reasons for this are unclear. It may be that after circumcision the skin on the glans (of the penis) goes through changes that make it more resistant to HPV infection. Another theory is that the surface of the foreskin (which is removed by circumcision) is more easily infected by HPV. Still, circumcision does not completely protect against HPV infection — men who are circumcised can still get HPV and pass it on to their partners. He risk of being infected with HPV is also strongly linked to having many sexual partners (over a man's lifetime). Use condoms, Condoms (“rubbers”) provide some protection against HPV but they don’t completely prevent infection. Men who use condoms are less likely to be infected with HPV and to pass it on to their female partners. One study found that when condoms are used correctly every time sex occurs they can lower the HPV infection rate by about 70%. One reason that condoms cannot protect completely is because they don’t cover every possible HPV-infected area of the body, such as skin of the genital or anal area. Still, condoms provide some protection against HPV, and they also protect against HIV and some other sexually transmitted infections. Condoms (when used by the male partner) also seem to help the HPV infection and cervical pre-cancers go away faster. Female condoms fit inside the vagina and can help protect against pregnancy. They also can protect against sexually transmitted infections, including HPV and HIV, although for this they aren’t as effective as male condoms.

Don’t smoke, Not smoking is another important way to reduce the risk of cervical pre-cancer and cancer. Get vaccinated, Vaccines are available that can protect against certain HPV infections. All of these vaccines protect against infection with HPV subtypes 16 and 18. Some can also protect against infections with other HPV subtypes, including some types that cause anal and genital warts. The vaccines only work to prevent HPV infection they will not treat an infection that is already there. That is why, to be most effective, the HPV vaccines should be given before a person becomes exposed to HPV (such as through sexual activity). These vaccines help prevent pre-cancers and cancers of the cervix. Some HPV vaccines are also approved to help prevent other types of cancers and anal and genital warts.

The vaccines require a series of 3 injections over a 6-month period. Side effects are usually mild. The most common one is short-term redness, swelling, and soreness at the injection site. Rarely, a young woman will faint shortly after the vaccine injection. The Federal Advisory Committee on Immunization Practices recommends that females aged 11 to 12 routinely vaccinated for HPV with the full series of 3 shots. Females as young as age 9 may also receive the HPV vaccine at the discretion of their doctors. also recommended women ages 13 to 26 who have not yet been vaccinated get “catch-up” vaccinations. The American Cancer Society also recommends that the HPV vaccine be routinely given to girl’s ages 11 to 12 and as early as age 9 at the discretion of doctors. The Society also agrees that “catch-up” vaccinations should
be given to females up to age 18. The independent panel making the Society recommendations found that there was not yet enough proof that catch-up vaccinations for all women aged 19 to 26 years would be beneficial. As a result, the American Cancer Society recommends that women aged 19 to 26 talks with their health care provider about their risk of previous HPV exposure and potential benefit from vaccination before deciding to get the vaccine. At this time, the American Cancer Society’s guidelines do not address the use of the vaccine in older women or males. It’s important to realize that no vaccine provides complete protection against all cancer-causing types of HPV, so routine cervical cancer screening is still necessary. For more information on the vaccine and HPV, please see our document, HPV Vaccines.

2.7 Diagnostic test:

The HPV DNA test, as mentioned earlier, the most important risk factor for developing cervical cancer is infection with HPV. Doctors can now test for the types of HPV (high-risk or carcinogenic types) that are most likely to cause cervical cancer by looking for pieces of their DNA in cervical cells. The test is done similarly to the Pap test in terms of how the sample is collected, and it sometimes can even be done on the same sample. The HPV DNA test is most often used in 2 situations, The HPV gene test can be used in combination with the Pap test to screen for cervical cancer. The American Cancer Society recommends this combination for women 30 and older. In the American Cancer Society guidelines, the HPV test does not replace the Pap test for most women. The American Cancer Society does not recommend using the HPV DNA test to screen for cervical cancer in women fewer than 30. That is because women in their 20s who are sexually active are much more likely (than older women) to have an HPV infection that will go away on its own. For these younger women, results of this test are not as significant and may be more confusing. For more information, see the American Cancer Society document HPV and HPV Testing.

The HPV DNA test can also be used in women who have slightly abnormal Pap test results (ASC-US) to find out if they might need more testing or treatment. See the section “Work-up of abnormal Pap test results. “An HPV DNA test has been approved by the FDA to be used without a Pap test to screen for cervical cancer. At this time, the American Cancer Society is considering the evidence supporting the use of this test for screening and may issue updates to our screening guidelines in 2015. Follow-up of HPV testing, If your Pap test result is normal, but you test positive for HPV, the main options are, Repeat co-testing (with a Pap test and an HPV test) in one year Testing to see if you test positive for HPV types 16 or 18 (this can often be done on the sample in the lab). If you are, colposcopy would be recommended (colposcopy is discussed in the section, “Work-up of abnormal Pap test results”). If you test negative, you should get repeat co-testing in one year. He Pap (Papanicolaou) test The Pap test is the main
screening test for cervical cancer and pre-cancerous changes. A woman should know how it is done and how often they should have a Pap test. How the Pap test is done

The health care professional first places a speculum inside the vagina. The speculum is a metal or plastic instrument that keeps the vagina open so that the cervix can be seen clearly. Next, using a small spatula, a sample of cells and mucus is lightly scraped from the exocervix. A small brush or a cotton-tipped swab is then inserted into the opening of the cervix to take a sample from the endocervix (see illustration in “What is cervical cancer?” section). If your cervix has been removed (because you had a trachelectomy or hysterectomy) as a part of the treatment for a cervical cancer or pre-cancer, the cells will be sampled from the upper part of the vagina (known as the vaginal cuff). The cell samples are then prepared so that they can be examined under a microscope in the laboratory. This is done either by smearing the sample directly onto a glass microscope slide and spraying it with a preservative. The slide is then sent to the laboratory. This is called conventional cytology. Putting the sample of cells from the cervix into a special preservative liquid (instead of putting them on a slide directly). The bottle containing the cells and the liquid is sent to the lab. The cells in the liquid are spread onto slides in the lab. This is called liquid-based cytology, or a liquid-based Pap test. Liquid-based testing does not find more cancers or pre-cancers than conventional cytology but it does have some advantages. These include a lower chance that the Pap test will need to be repeated, and the ability to use the same sample for HPV testing. A drawback of the liquid-based test is that it is more likely to find cell changes that are not pre-cancerous but that will need to be checked out further – leading to unnecessary tests. This method is also more expensive than conventional cytology. Although the Pap test has been more successful than any other screening test in preventing a cancer, it’s not perfect. One of the limitations of the Pap test is that the results need to be examined by humans, so an accurate analysis of the hundreds of thousands of cells in each sample is not always possible. Engineers, scientists, and doctors are working together to improve this test. Because some abnormalities may be missed (even when samples are looked at in the best laboratories), it’s not a good idea to have this test less often than American Cancer Society guidelines recommend. Unfortunately, many of the women most at risk for cervical cancer are not being tested often enough or at all. Making your Pap tests more accurate you can do several things to make your Pap test as accurate as possible: Try not to schedule an appointment for a time during your menstrual period. The best time is at least 5 days after your menstrual period stops. Don’t use tampons, birth-control foams or jellies, other vaginal creams, moisturizers, or lubricants, or vaginal medicines for 2 to 3 days before the test. Don't douche for
2 to 3 days before the test. Don’t have sexual intercourse for 2 days before the test pelvic exam is not the same as a Pap test many people confuse pelvic exams with Pap tests. The pelvic exam is part of a woman’s routine health care. During a pelvic exam, the doctor looks at and feels the reproductive organs, including the uterus and the ovaries and may do tests for sexually transmitted disease. Pap tests are often done during pelvic exams, but you can have a pelvic exam without having a Pap test. A pelvic exam without a Pap test will not help find abnormal cells of the cervix or cervical cancer at an early stage. The Pap test is often done during a pelvic exam, after the speculum is placed. To do a Pap test, the doctor removes cells from the cervix by gently scraping or brushing it with a special instrument. Pelvic exams may help find other types of cancers and reproductive problems, but a Pap test is needed to find early cervical cancer or pre-cancers. Ask your doctor if you had a Pap test with your pelvic exam. How Pap test results are reported the most widely used system for describing Pap test results is the Bethesda System (TBS). There are 3 main categories, some of which have sub-categories:

- Negative for intraepithelial lesion or malignancy.
- Epithelial cell abnormalities.
- Other malignant neoplasms.
- Negative for intraepithelial lesion or malignancy.

This first category means that no signs of cancer, pre-cancerous changes, or other significant abnormalities were found. Some specimens in this category appear entirely normal. Others may have findings that are unrelated to cervical cancer, such as signs of infection with yeast, herpes, or Trichomonas vaginalis (a microscopic parasite), for example. Specimens from some women may also show “reactive cellular changes”, which is the way cervical cells respond to infection or other irritation.

The epithelial cell abnormalities this means that the cells lining the cervix or vagina show changes that might be cancer or a pre-cancerous condition. This category is divided into several groups for squamous cells and glandular cells.

The Squamous cell abnormalities, Atypical squamous cells (ASCs): This category includes atypical squamous cells of uncertain significance (ASC-US) and atypical squamous cells where high-grade squamous intraepithelial lesion (SIL) can’t be excluded (ASC-H).

ASC-US is a term used when there are cells that look abnormal, but it is not possible to tell (by looking at the cells under a microscope) if this is caused by infection, irritation, or if it is a pre-cancer. Most of the time, cells labeled ASC-US are not pre-cancer, but more testing is needed to be sure. If the results of a Pap test are labeled ASC-H, it means that a SIL is suspected. Pap test results of either type of ASC mean that more testing is needed. This is discussed in the section, “Work-up of abnormal Pap test results. “Squamous intraepithelial lesions (SILs):
These abnormalities are subdivided into low-grade SIL (LSIL) and high-grade SIL (HSIL). In LSIL, the cells are mildly abnormal, while in HSIL, the cells are severely abnormal. HSILs are less likely than LSILs to go away without treatment. They are also more likely to eventually develop into cancer if they are not treated. Treatment can cure most SILs and prevent true cancer from developing. The Squamous cell carcinoma: This result means that the woman is likely to have an invasive cancer. Further testing will be done to be sure of the diagnosis before treatment can be planned.

Glandular cell abnormalities, Adenocarcinoma: Cancers of the glandular cells are called adenocarcinomas. In some cases, the pathologist examining the cells can tell whether the adenocarcinoma started in the endocervix, in the uterus (endometrium), or elsewhere in the body. Atypical glandular cells: When the glandular cells do not look normal, but have features that do not permit a clear decision as to whether they are cancerous, the term used is atypical glandular cells (AGCs). The patient should have more testing if her cervical cytology result shows atypical glandular cells.

Other malignant neoplasms: This category is for forms of cancer that only rarely affect the cervix, such as malignant melanoma, sarcomas, and lymphoma. Her descriptions of Pap test results have also been used in the past.

The Colposcopy, If you have certain symptoms that suggest cancer or if your Pap test shows abnormal cells, you will need to have a test called colposcopy. In this procedure you will lie on the exam table as you do for a pelvic exam. A speculum will be placed in the vagina to help the doctor see the cervix. The doctor will use a colposcope to examine the cervix. The colposcope is an instrument that has magnifying lenses (like binoculars). Although it stays outside the woman’s body, it lets the doctor see the surface of the cervix closely and clearly. The doctor will apply a weak solution of acetic acid (similar to vinegar) to your cervix to make any abnormal areas easier to see. Colposcopy itself causes no more discomfort than any other speculum exam. It has no side effects, and can be done safely even if you’re pregnant. Like the Pap test, it’s rarely done during your menstrual period. If an abnormal area is seen on the cervix, a biopsy will be done. For a biopsy, a small piece of tissue is removed from the area that looks abnormal. The sample is sent to a pathologist to look at under a microscope. A biopsy is the only way to tell for certain if an abnormal area is a pre-cancer, a true cancer, or neither. Although the colposcopy procedure is not painful, cervical biopsy can cause discomfort, cramping, or even pain in some women.

The Cervical biopsies, Several types of biopsies are used to diagnose cervical pre-cancers and cancers. If the biopsy can completely remove all of the abnormal tissue, it may be the only treatment needed. In some situations, additional treatment of pre-cancers or cancers is
needed. The Colposcopic biopsy For this type of biopsy, a doctor or other health care professional first examines the cervix with a colposcope to find the abnormal areas. Using a biopsy forceps, the doctor will remove a small (about 1/8-inch) section of the abnormal area on the surface of the cervix. The biopsy procedure may cause mild cramping or brief pain, and you may bleed lightly afterward. A local anesthetic is sometimes used to numb the cervix before the biopsy. Endocervical curettage (endocervical scraping) Sometimes the transformation zone (the area at risk for HPV infection and pre-cancer) cannot be seen with the colposcope. In that situation, something else must be done to check that area for cancer. This means taking a scraping of the endocervix by inserting a narrow instrument (called a curette) into the endocervical canal (the passage between the outer part of the cervix and the inner part of the uterus). The curette is used to scrape the inside of the canal to remove some of the tissue, which is then sent to the laboratory for examination. After this procedure, patients may feel a cramping pain, and they may also have some light bleeding. This procedure is usually done at the same time as the colposcopic biopsy. The Cone biopsy In this procedure, also known as conization, the doctor removes a cone-shaped piece of tissue from the cervix. The base of the cone is formed by the exocervix (outer part of the cervix), and the point or apex of the cone is from the endocervical canal. The transformation zone (the border between the exocervix and endocervix) is contained within the cone. This is the area of the cervix where pre-cancers and cancers are most likely to develop. The cone biopsy can be used as a treatment to completely remove many pre-cancers and some very early cancers. Having a cone biopsy will not keep most women from getting pregnant, but if the biopsy removes large amount of tissue these women may have a higher risk of giving birth prematurely. There are 2 methods commonly used for cone biopsies, the loop electrosurgical excision procedure (LEEP) (also called large loop excision of the transformation zone or LLETZ) and the cold knife cone biopsy. Electrosurgical procedure (LEEP or LLETZ), with this method, the tissue is removed with a thin wire loop that is heated by electrical current and acts as a scalpel. For this procedure, a local anesthetic is used, and it can be done in your doctor’s office. It can take as little as 10 minutes. You may have mild cramping during and after the procedure, and mild to moderate bleeding for several weeks. Knife cone biopsy, this method uses a surgical scalpel or a laser instead of a heated wire to remove tissue. It requires general anesthesia (you are asleep during the operation) and is done in a hospital, but no overnight stay is needed. After the procedure, cramping and some bleeding may persist for a few weeks.
2.8 Reporting System:

The terms used for reporting biopsy results are slightly different from the Bethesda System for reporting Pap test results. Pre-cancerous changes on a biopsy are called cervical intraepithelial neoplasia (CIN), while on a Pap test they would be called squamous intraepithelial lesion (SIL). CIN is graded on a scale of 1 to 3 based on how much of the cervical tissue looks abnormal when viewed under the microscope. In CIN1, not much of the tissue looks abnormal, and it’s considered the least serious cervical pre-cancer. In CIN2 more of the tissue looks abnormal, and in CIN3 most of the tissue looks abnormal. CIN3 is the most serious pre-cancer. Sometimes the term dysplasia is used instead of CIN. CIN1 is the same as mild dysplasia, CIN2 is the same as moderate dysplasia, and CIN3 includes severe dysplasia as well as carcinoma in situ.

The terms for reporting cancers (squamous cell carcinoma and adenocarcinoma) are the same for Pap tests and biopsies.

2.8.1 Atypical squamous cells (ASC-US and ASC-H):

If the Pap results show atypical squamous cells of uncertain significance (ASC-US), some doctors will repeat the Pap test in 12 months. Another option is to test for human papilloma virus (HPV). What is done next depends on how old you are. If you are 21 to 24 years old, and HPV DNA is found, the doctor will recommend a repeat Pap test in a year. If you are at least 25 years old and HPV is detected, the doctor will recommend a colposcopy. If HPV is not detected, then the doctor will recommend the Pap test be repeated in 3 years. If you are at least 25 years old, an HPV test will be done at the same time as the repeat Pap test.

If the results of a Pap test are labeled atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), it means that a high grade SIL is suspected. The doctor will recommend colposcopy.

2.8.2 Squamous intraepithelial lesions (SILs):

These abnormalities are divided into low-grade SIL (LSIL) and high-grade SIL (HSIL).

For LSIL, further testing depends upon HPV testing: the HPV test result was negative (meaning the virus wasn’t detected), then repeating the Pap test and HPV test in one year is recommended. HPV was found, and then colposcopy is recommended. No HPV test was done and the woman is at least 25 years old, colposcopy is recommended. The woman is under 25, she should have a repeat Pap test in a year. Women with LSIL should have colposcopy. For HSIL, either colposcopy or a loop electrosurgical procedure is recommended for women 25 and older. For women under 25, colposcopy is recommended.
2.8.3 Atypical glandular cells and adenocarcinoma in situ (on a Pap test):
If the Pap results read atypical glandular cells or adenocarcinoma but the report says that the abnormal cells do not seem to be from the lining of the uterus (the endometrium), guidelines recommend colposcopy with the biopsy type called endocervical curettage (endocervical scraping). The doctor may also biopsy the endometrium (this can be done at the same time as the colposcopy). For information about endometrial biopsy, see our document Endometrial (Uterine) Cancer. If the atypical glandular or adenocarcinoma cells look like they are from the endometrium (based on how they look under the microscope), experts recommend a biopsy of the endometrium along with the endocervical curettage, but a colposcopy isn’t needed unless the results from the endometrial biopsy are negative and do not explain the Pap test result.

2.9 Treatment of cervical cancer:
If you have cervical cancer, your healthcare team will create a treatment plan just for you. It will be based on your health and specific information about your cancer. Treatment may include a combination of different treatments. When deciding which treatments to offer for cervical cancer, your healthcare team will consider: the stage your age your general health whether or not you want to become pregnant in the future your personal preferences You may be offered the following treatments for cervical cancer. Surgery Depending on the stage and size of the tumor, you may have one of the following types of surgery. A cone biopsy removes a cone-shaped piece of tissue from the cervix that includes the abnormal area of the cervix. The cone is formed by removing the outer part of the cervix closest to the vagina and part of the endocervical canal. It is done to diagnose and treat cervical cancer in the earliest stages. A radical trachelectomy removes the cervix, upper part of the vagina, some of the structures and tissue around the cervix (parametrium) and the lymph nodes in the pelvis. It can be done instead of a hysterectomy to try to maintain fertility. It may be an option for younger women with early stage cervical cancer who want to become pregnant after treatment. A total hysterectomy removes the cervix and uterus. A total hysterectomy may be used to treat women with stage IA1 cervical cancer. A radical hysterectomy removes the cervix, uterus, parametrium and nearby lymph nodes. A radical hysterectomy may be used to treat stage IA2 or IIA1 cervical cancer or cancer that recurs, or comes back, in the cervix or uterus after radiation therapy. A lymph node dissection removes lymph nodes in the pelvis to see if they contain cancer. It is commonly done during surgery for cervical cancer to help predict prognosis and decide if a woman needs other treatment. A pelvic exoneration removes the cervix, uterus, vagina, ovaries, fallopian tubes and lymph nodes. The rectum, bladder or both may also be removed. A pelvic exoneration is sometimes done when cervical cancer recurs, or
comes back, in the pelvis after it has been treated with radiation therapy. Ovarian transposition moves the ovaries higher up inside the abdomen away from the pelvis. Moving the ovaries helps to protect them from potential damage from radiation therapy, which can cause early menopause. Radiation therapy may be used to treat any stage of cervical cancer. Women usually receive combination of both external beam radiation therapy and brachytherapy. Chemoradiation: Chemotherapy is commonly given during the same time period as radiation therapy to make the cells more sensitive to radiation. This is called chemoradiation. Chemoradiation may be used to treat any stage of cervical cancer. Chemotherapy alone may be used to treat some stages of cervical cancer. Targeted therapy: Bevacizumab (Avastin) is a targeted therapy that may be used to treat stage IVB and recurrent cervical cancer. Bevacizumab is given with chemotherapy. Follow-up care: Follow-up after treatment is an important part of cancer care. You will need to have regular follow-up visits, especially in the first 2–3 years after treatment has finished. These visits allow your healthcare team to monitor your progress and recovery from treatment. You may have follow-up tests such as a physical exam or a Pap test during these visits. Treating women with abnormal Pap test results and pre-cancers can prevent cervical cancer from developing. If an abnormal area is seen during the colposcopy, your doctor will be able to remove it with a loop electrosurgical procedure (LEEP or LLETZ procedure, which were discussed in the previous section). Other options include a cone biopsy and destroying the abnormal cells with cryosurgery or laser surgery.

During cryosurgery, a metal probe cooled with liquid nitrogen is placed directly on the cervix. This kills the abnormal cells by freezing them. This can be done in a doctor’s office or clinic. After cryosurgery, you may have a lot of watery brown discharge for a few weeks. In laser surgery, a focused laser beam, directed through the vagina, is used to vaporize (burn off) abnormal cells or to remove a small piece of tissue for study. This can be done in a doctor’s office or clinic and is done under local anesthesia (numbing medicine). For a cone biopsy, a cone-shaped piece of tissue is removed from the cervix. This is done using a surgical or laser knife (cold knife cone biopsy) or using a thin wire heated by electricity (the loop electrosurgical, LEEP or LEETZ procedure). After the procedure, the tissue removed (the cone) is examined under the microscope. If the margins (outer edges) of the cone contain abnormal (cancer or pre-cancer) cells (called positive margins), some cancer (or pre-cancer) may have been left behind, so further treatment is needed. These treatments are almost always effective in destroying pre-cancers and preventing them from developing into true cancers. You will need follow-up exams to make sure that the abnormality does not come back. If it does, the treatments can be repeated. Rarely, surgery to remove the cervix (often with the body of the
uterus) is used to treat pre-cancers. These, called trachelectomy and hysterectomy, are more often used to invasive cancers, and are discussed in our document Cervical Cancer.
Chapter Three

3. Materials and Methods

3.1 Study Design:
This is a retrospective study conducted in Saqr hospital, U.A.E to correlation the Cytology-histological cervical intraepithelial neoplastic lesion.

3.2 Study Setting:
Saqr Hospital is Specialty hospital in RasAlkhaimah, United Arab emirate in surgery, pediatric, gynecological, post natal, orthopedic, ENT, ICU, SCBU, labor room and emergency. It is a 149-bed hospital and outpatient department. Beside pharmacy, diagnostic services in radiology and clinical laboratory including hematology, microbiology, clinical chemistry, blood bank, phlebotomy outpatient, and histopathology and cytology sections. Offering specialized medical treatment at Time conducts this paper about 600,000 Patients in the Outpatient Department (OPD) and 200,000 Patients from ministry Primary healthcare centers during the study period.

The histopathology and cytology department is equipped with processing machine Thermo models 1000, Thermo embedding machine, Lecia RM2135 microtomy, Automatic HE stainer MEDITE MEDIZIN TECHNIK TISSUE STAINER COT 20, Gross Thermo-Electron Corporation Shandon, T ELSTAR BIO-II-A SAFTY CABINET class II and Thinprep for liquid base cytology.

Inpatient ward section, the nurse staff responsible to send the biopsy from operation and labor room. The specimen are delivered to the lab by the clerk to histopathology and cytology section, whereas biopsy Specimens from Outpatients are receive by Laboratory personnel. The data analyzed by excel sheet and SPSS 16.

3.2 Study Population:
743 samples of Pap smear and cervical biopsy from women between 18 and 70 years old, the data are collected retrospective.

3.3 Ethical Consideration:
Permission for conducting this research was taken from the head of clinical laboratory and medical director of Saqrhospital.
3.4 Method of data collection:
Data were collected from registration book, cancer register from histopathology department and patient medical file, which include all needed information concerning each case investigated.

3.5 Data Validation:
To insure the reliability and accuracy of the data, the study excluded unsatisfactory Pap smear, the biopsy taken without pre-cytology smear

3.5.1 Inclusion criteria:
The current analysis including the data only from the patient investigated by two methods (cytology smear / biopsy).

3.5.2 Exclusion criteria:
The current analysis excludes the unsatisfactory and inadequate smear, and the patient they investigated only by one of the two method.

3.5.3 Data Analysis:
Once the data collection is over, the data are summed and entered into Microsoft excel sheet and data analyzed and compared between the cytology smear and biopsy from the same patient, by using 2x2 table. In a retrospective study, reports on 743 patients submitted to cone biopsy and/or hysterectomy due to diagnosis of cervical intraepithelial neoplasia (CIN) in the period between January 2013 and December 2015 were reviewed, comparing. Cytological and histological exams (guided biopsy and surgically-removed tissue). In cases of discordance, the cytological and histological preparations were reviewed to try to evaluate the causes of errors.
ThinPrep cytological slides smears were prepared and diagnosed, while the residual material on the sampling device was collected. Cytological diagnoses based on the two techniques, categorized according to the Bethesda System, were compared with the surgical specimens were routinely fixed, paraffin-embedded and stained with Hematoxylin and Eosin stained with Hematoxylin and Eosin. A “gold standard” final case diagnosis for each patient. The “gold standard” diagnosis for each patient reflects the integrated interpretation of all available data. The cone biopsy and/or hysterectomy specimens fixed in 10 % formaldehyde; the cone biopsy or cervix material is cut into pieces of about 1mm in thickness, perpendicular to the surface of the endocervical mucosa and all the material is processed for inclusion in paraffin. One histological cut of each block is stained with hematoxylin-eosin. Additional cuts are made when necessary.
All the cytological specimens were liquid base cytology, and these were selected for the present study only among those which were satisfactory for the result.
The smears were stained with classic Papanicolau technique and diagnostic using Bethesda
classification. The cellular samples that were fixed in PreservCyt. In the ThinPrep system, cervical specimens collected with brush sampling devices are placed directly into vials containing 15 mL of liquid preservative (PreservCyt). For preparation as ThinPrep slides. Briefly, ThinPrep slides were prepared by placing a PreservCyt vial and a microscopic slide on the ThinPrep processor, which mixes the sample and draws cells onto a membrane filter by suction. When the filter has collected sufficient cells to produce a slide, the suction is released and the cells are transferred to a 20-mm circular area on a glass slide under slight positive pressure. The slide is then immersed in 95% ethanol and stained by Papanicolaou method. All of the ThinPrep slides were screened. And then reviewed and diagnosed.
Chapter Four

4. Results

Table (4.1): Correlation between cervicovaginal smear and histologic diagnoses

<table>
<thead>
<tr>
<th>Histologic diagnosis</th>
<th>Correlation</th>
<th>ASCUS</th>
<th>ASC-H</th>
<th>LSIL</th>
<th>SIL</th>
<th>SqCC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>478</td>
<td>11</td>
<td>3</td>
<td>31</td>
<td>1</td>
<td>0</td>
<td>524 (70.5%)</td>
</tr>
<tr>
<td>CIN 1</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>105</td>
<td>2</td>
<td>0</td>
<td>119 (16.0%)</td>
</tr>
<tr>
<td>CIN 2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>15</td>
<td>0</td>
<td>30 (4.0%)</td>
</tr>
<tr>
<td>CIN 3</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>15</td>
<td>0</td>
<td>25 (3.4%)</td>
</tr>
<tr>
<td>CIS</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>7</td>
<td>20 (2.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>484 (65.1%)</td>
<td>22</td>
<td>14 (1.9%)</td>
<td>156 (21.0%)</td>
<td>58 (7.8%)</td>
<td>9 (1.2%)</td>
<td>743 (100.0%)</td>
</tr>
</tbody>
</table>

ASCUS, atypical squamous cell of undetermined significance; ASC-H, atypical squamous cells, but cannot exclude high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SqCC, invasive squamous cell carcinoma; CIN 1, cervical intraepithelial neoplasia 1; CIN 2, cervical intraepithelial neoplasia 2; CIN 3, cervical intraepithelial neoplasia 3; CIS, Carcinoma in situ.

Table 4.2: Analysis of 46 false positive cases

<table>
<thead>
<tr>
<th>Cervicovaginal smear diagnosis</th>
<th>SCUS</th>
<th>ASC-H</th>
<th>LSIL</th>
<th>SIL</th>
<th>SqCC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling error</td>
<td>5</td>
<td>1</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>29 (63.0%)</td>
</tr>
<tr>
<td>Interpretation error</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>17 (37.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>3</td>
<td>31</td>
<td>1</td>
<td>0</td>
<td>46 (23.9%)</td>
</tr>
</tbody>
</table>

Table 4.3: Accuracy of cytologic diagnoses according to grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sensitivity</th>
<th>False Positive Rate</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL</td>
<td>92.9% (105/113)</td>
<td>19.9% (31/156)</td>
<td>67.3% (105/156)</td>
</tr>
<tr>
<td>SIL or greater than HSIL</td>
<td>76.2% (64/84)</td>
<td>1.5% (1/67)</td>
<td>95.5% (64/67)</td>
</tr>
</tbody>
</table>
**Table 4.4:** Frequency table of cytologic diagnosis according to smear method

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>ASCUS</th>
<th>ASC-H</th>
<th>LSIL</th>
<th>HSIL</th>
<th>SqCC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>159 (70.4%)</td>
<td>7 (3.1%)</td>
<td>3 (1.3%)</td>
<td>33 (14.6%)</td>
<td>19 (8.4%)</td>
<td>5 (2.2%)</td>
<td>226 (100%)</td>
</tr>
<tr>
<td>Quid</td>
<td>325 (62.9%)</td>
<td>15 (2.9%)</td>
<td>11 (2.1%)</td>
<td>123 (23.8%)</td>
<td>39 (7.5%)</td>
<td>4 (0.8%)</td>
<td>517 (100%)</td>
</tr>
</tbody>
</table>

P-value=0.05. ASCUS, atypical squamous cell of undetermined significance; ASC-H, atypical squamous cells, but cannot exclude high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SQCC, invasive squamous cell carcinoma.

**Table 4.5:** Comparative analysis of cytologic and histologic diagnoses according to smear method

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Quid-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance rate</td>
<td>93.4% (211/226)</td>
<td>93.8% (458/491)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98.1% (53/64)</td>
<td>96.5% (138/143)</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.5% (158/162)</td>
<td>92.0% (320/348)</td>
</tr>
<tr>
<td>False negative rate</td>
<td>0.6% (1/159)</td>
<td>1.5% (5/325)</td>
</tr>
<tr>
<td>False positive rate</td>
<td>7.0% (4/57)</td>
<td>16.9% (28/166)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>93.0% (53/57)</td>
<td>83.1% (138/166)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99.4% (158/159)</td>
<td>98.5% (320/325)</td>
</tr>
</tbody>
</table>

**Table 4.6:** Causes of discordance between cytologic and histologic diagnoses according to smear method

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Quid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling error</td>
<td>0.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Interpretation error</td>
<td>6.9%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Total</td>
<td>42.3%</td>
<td>32.5%</td>
</tr>
</tbody>
</table>

p-value=0.15
Chapter Five

5. Discussion and Conclusion

5.1 Discussion:
The cervicovaginal smear is considered to be a good method to evaluate the status of uterine Cervical epithelium with low cost and easy methodology. Thus, this method has been widely used as a screening test for epithelial neoplasms of the uterine cervix in population-based cancer screening programs and a biannual cervicovaginal smear is recommended for women over the age 30 years.

The major problem with cervicovaginal smears is the rate of false negative cytology, which has been reported to range between 6 and 50% in several studies. In the current study, the false negative rate was 1.2% (6 of 484 cases) and was much lower than previous studies. All of the false negative cases were CIN 1 lesions and no false negative case was detected in CIN 2 or higher lesions. Because false negative cytology in CIN 3 lesions give false reassurance to patients and clinicians and postpones the diagnosis of early cervical cancer, which can be cured by conservative treatment, my results are encouraging for cancer screening. False negative cytology can result from interobserver variation of interpretation, sampling method, smear method, and the expressiveness of pathologists and cytotechnologists. In my study, four sampling errors of false negative cases were all liquid-based smears and the remaining two interpretation errors were noted in conventional smears. These traits were also identified in the entire cases.

The rate of false positive cases was 17.7% (46/259) and seemsto be high, but most of the cases were LSIL or ASC and only one case was HSIL on cytology. Because the false positive test results of HSIL in cytology can lead a patient with unnecessary invasive treatment, such as biopsy or diagnostic conization, it is also important in quality control of cervicovaginal smears. The one false positive Case of HSIL in my study was due to sampling error on review of a slide. The interpretation errors of false positive cases were almost always found in ASC and LSIL, especially ASC. The low reproducibility and high interobserver variance of ASC and LSIL was previously reported in a few studies, and this trait was also confirmed in our study.

The College of American Pathologists (CAP) uses the ASCUS/SIL ratio as an index of quality management and recommends a range Of<2-3.22 although the ASCUS/SIL ratio in the current study was not a true index of quality Assurance because my study group was exclusively made up of cases which were histologically-confirmed, the ratio was 0.16 (36/223).
The rate of sampling error in liquid-based smears was higher than the conventional smear method, regardless of cytologic diagnoses. Conversely, interpretation error was higher in the conventional Smear method than the liquid-based method. In general, liquid-based smears have been reported to lower interpretation and screening errors by reduction of unsatisfactory specimens, compared with the conventional smear method. This trait was similarly identified in our study. Interpretation error of Conventional smears usually results from unsatisfactory smear quality, which induces morphologic distortion. Conversely, interpretation error of liquid-based smears usually results from the clear background or unfamiliar morphologic perception. The liquid-based smear method supplies more Clean background and vivid cellular details by removing the unnecessary mucus, blood, and inflammatory cells from the specimen via filter or density gradient centrifugation and by quick Fixation without drying artifact. The clean background removes tumor diathesis and makes under-diagnoses of SQCC as CIS or HSIL. The vivid cellular details frequently lead to over diagnose ASCUS or reactive cellular changes as LSIL, such as the human papillomavirus (HPV) cytopathic effect. A high rate of LSIL and the rate of misdiagnosis of Sqcc as CIS or HISL with the liquid-based smear method in our study can be explained by these characteristic of the liquid-based smear method.

Another pattern of the interpretation error was the distinction of CIN 2 and CIN 3 lesions on cytology. In our study under-diagnosed cases of LSIL were confirmed as CIN 2 lesions on histology.

The 2001 Bethesda system uses a two-tiered classification as low- and high-grade precursor lesions and sets the cytologic threshold between CIN 1 and CIN 2. Because the natural history of CIN 2 is closer to CIN 1 than CIN 3, some pathologists controvert the 2001 Bethesda system. However, considering that the reproducibility of interpretation of CIN2 lesions in cytology is low, and the cervicovaginal smear test is a screening test, rather than a diagnostic test, the 2001 Bethesda system recommends the two-tiered classification. Actually, the pathologists frequently confront the borderline cases between LSIL and HSIL and diagnose the more apparent grade to avoid over-diagnosis. The 2001 Bethesda system comments in explanatory note that this lesion can be reported as “SIL, grade cannot be determined” or “LSIL, but with rare cells suggestive of HSIL”.

The higher sampling error rate of liquid-based smear method may not only result from the unskilled sampling method or process, but also from the problem of the representativeness. Because the number of screened cells in the liquid-based smear method is generally lower than the conventional smear method, the rep-representativeness of liquid-based smears can be debated. The 2001 Bethesda system reports that the liquid-based smear method is a more random sampling method than the conventional method and recommends a minimum cellularity of
5,000 cells for a liquid-based smear which may assure representativeness. However, it has also been mentioned that additional studies relating sensitivity to cell number would be required for all preparation types. Because the enrolled period (2013-2015) was the transitional period when the conventional cervicovaginal smear method was gradually replaced by the liquid-based smear method, the high sampling error rate of liquid-based smears in our hospital may have resulted from the inexperienced sampling method or process, rather than the representativeness of the test method.

5.2 Conclusion
The false-negative rate of cervicovaginal smears was very low in my institute and confined to LSIL without HSIL. Thus, the cervicovaginal smear is still a powerful and sensitive tool for screening of cervical squamous cell neoplasms. The current study showed that false negative rate was 1.2% (6/484).

5.3 Recommendations
- To use the cyto-histological correlation as Key Performance indicator to monitor the reporting performance.
- To continue communicate with physician to improve the patient report outcome.
- To continue in training the pathologist and cyto-screener and monitor their competency.
References:
