

THE CERVIX: Colposcopy of the Uterine Cervix

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The material that follows was developed by the 2002-04 ASCCP Section on the Cervix for use by physicians and healthcare providers. Special thanks to Section members:

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I. AN INTRODUCTION TO THE NORMAL CERVIX, NEOPLASIA, AND COLPOSCOPY

The uterine cervix presents a unique opportunity to clinicians in that it is physically and visually accessible for evaluation. It demonstrates a well-described spectrum of histological and colposcopic findings from health to premalignancy to invasive cancer. Since nearly all cervical neoplasia occurs in the presence of human papillomavirus infection, the cervix provides the best-defined model of virus-mediated carcinogenesis in humans to date. The clinical use of colposcopy for the evaluation of cervical cytologic abnormalities allows the identification and successful management of most premalignant cervical lesions. Its usefulness and efficacy in cancer prevention is undisputed and unparalleled. Interest in colposcopy has grown steadily along with the incidence of cervical disease during the past three to four decades. More and more primary care physicians are receiving training in colposcopy. This has, no doubt, improved efforts to identify and manage cervical neoplasia appropriately.

This informational site is intended to serve as an introduction to the uterine cervix in health and disease and to the clinical use of colposcopy. **It does not provide the scope of information or clinical training necessary to become a competent colposcopist.** We do hope to provide answers to basic questions and also help determine if colposcopy should play a role in your clinical practice. If so, we hope you will attend one or more of the ASCCP's Comprehensive Courses, which are held throughout the year at varying locations throughout the United States. This should always be followed by a closely supervised period of clinical training during which an experienced colposcopist provides mentoring in the development of these skills. If you are in training or already trained in colposcopy and wish to review current information, this website may provide a useful review. If you want a more compressive review of current colposcopy or treatment practices, you may wish to attend an ASCCP's Comprehensive or Advanced Colposcopy Courses (or similar course).

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SHAPE AND DIMENSIONS

The cervix is actually the lower, narrow portion of the uterus, connected to the uterine fundus by the uterine isthmus. Its name is derived from the Latin word for "neck." It is cylindrical or conical in shape. Its upper limit is considered to be the internal os, which is an anatomically and histologically ill-defined junction of the more muscular uterine fundus and the denser, more fibrous cervical stroma. The cervix protrudes through the upper anterior vaginal wall. Approximately half its length is visible; the remainder lies above the vagina beyond view. The portion projecting into the vagina is referred to as the **portio vaginalis**. On average, the portio vaginalis is 3 cm long and 2.5 cm wide. The size and shape of the cervix varies widely with age, hormonal state, and parity. In parous women, the cervix is bulkier and the external os, or lowermost opening of the cervix into the vagina, appears wider and more slit-like and gaping than in nulliparous women. Before childbearing, the external os is a small, circular opening at the center of the cervix. The portion of the cervix exterior to the external os is called the **ectocervix**. The passageway between the **external os** and the endometrial cavity is referred to as the **endocervical canal**. Its upper limit is the **internal os**. It varies widely in length and width, along with the cervix overall. Flattened anterior to posterior, the endocervical canal measures 7 to 8 mm at its widest in reproductive-aged women. The canal itself shows a complex configuration of mucosal folds or plicae. These make cytologic screening and colposcopy of the endocervical tissues technically more difficult and less reliable than for the smoother and more accessible squamous epithelium of the ectocervix.

The overall size and shape of the cervical portio, along with numerous other factors such as parity, location and severity of disease, will influence choice of management and treatment options. Cold knife conization of the cervix can be associated with subsequent adverse

pregnancy outcome in some cases, presumably secondary to shortening of the cervix. Although the determinants of obstetrical cervical competence remain enigmatic, the length of the cervix probably plays a role. In addition, an unusually small or large cervix, or one that is difficult to reach due to anatomic variations, may influence whether any needed treatment will take place in an inpatient versus an outpatient setting.

BLOOD SUPPLY

The blood supply of the cervix derives from the **internal iliac** arteries, which give rise to the uterine arteries. Cervical and vaginal branches of the uterine arteries supply the cervix and upper vagina. There is considerable anatomic variation and anastomoses with vaginal and middle hemorrhoidal arteries. The cervical branches of the uterine arteries generally descend on the lateral aspects of the cervix at 3 and 9 o'clock. The venous drainage of the cervix parallels the arterial supply, eventually emptying into the **hypogastric venous plexus**.

LYMPHATICS / MUCOSAL IMMUNITY

The lymphatic drainage of the cervix is complex and variable and includes the **common, internal, and external iliac nodes**, the **obturator** and **parametrial nodes**, and numerous other groups as well. The primary route of spread of cervical cancers is through the lymphatics of the pelvis. Radical hysterectomy for invasive cancer of the cervix includes removal of as much of the pelvic lymphatics as possible.

SUPPORT AND INNERVATION

The main support structures of the cervix are the **cardinal** and **uterosacral ligaments**. These attach to the lateral and posterior aspects of the cervix above the vagina and extend laterally and posteriorly to the walls of the **bony pelvis**. The uterosacral ligaments are the conduits of the main nerve supplying to the cervix, derived from the **hypogastric plexus**. Sensory, sympathetic, and parasympathetic fibers are present in the cervix. Instrumentation of the endocervical canal (dilatation and / or curettage) may result in a vasovagal reaction with reflex bradycardia in some patients. The endocervix also has a plentiful supply of sensory nerve endings, while the ectocervix is relatively lacking in these. This allows procedures such as small cervical biopsies and cryotherapy to be well tolerated in most patients without the use of anesthesia.

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THE CERVIX: Histology of the Normal Cervix

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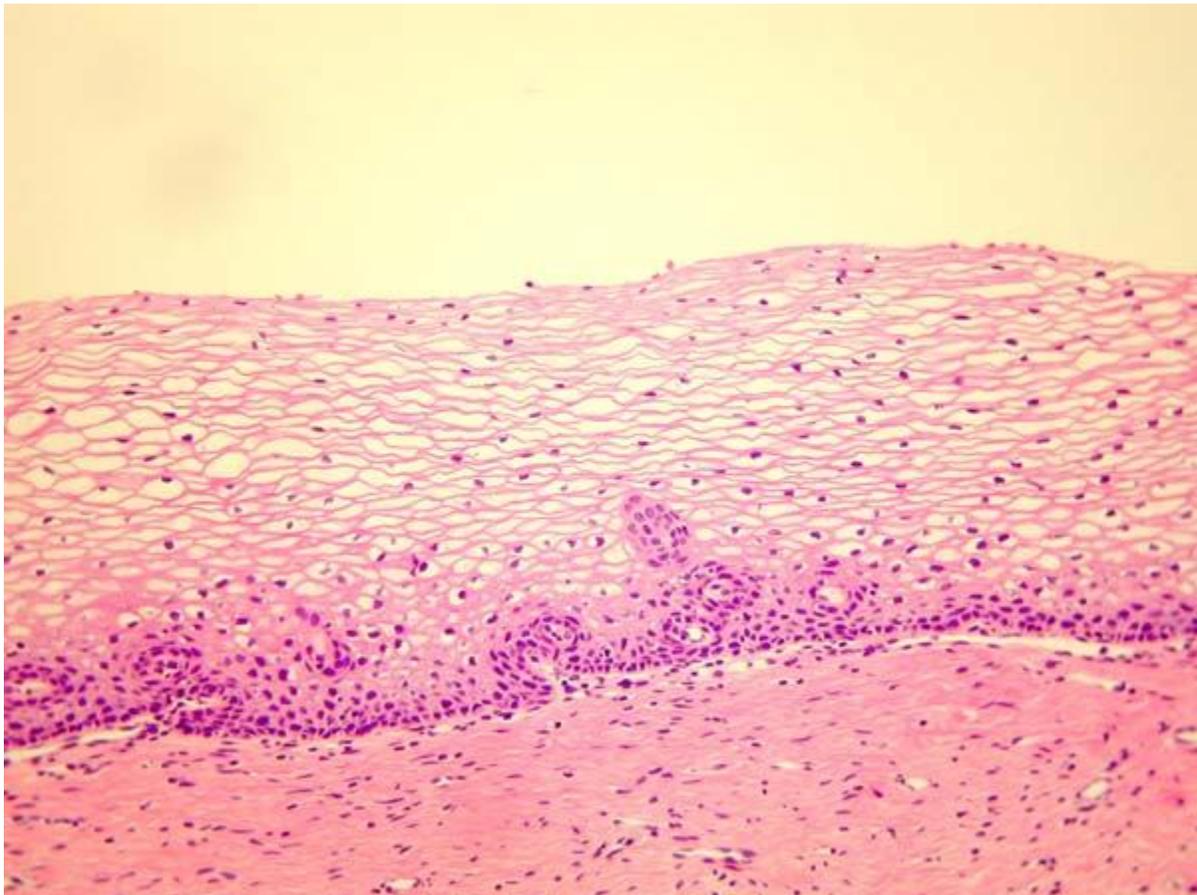
An understanding of the histology of the cervix is critical to the use of effective cytologic screening, colposcopy, and biopsy results in the management and treatment of cervical neoplasia. The **stroma** of the cervix, which accounts for most of its mass and shape, is composed of dense, fibromuscular tissue made up of collagenous connective tissue (smooth muscle and elastic tissue) and ground substance (mucopolysaccharide). Through the stroma course the vascular, lymphatic, and nervous supplies of the cervix. While of great importance to the structure and obstetrical functioning of the cervix, the stroma plays little role in cervical neoplasia. Rather, it is the **epithelium** of the cervix which gives rise to cervical neoplasia. Therefore, this section will focus on the **cervical epithelium**.

The cervix is covered by both **columnar** and **stratified non-keratinising squamous epithelia**. The **squamocolumnar junction**, where these two meet, is the most important cytologic and colposcopic landmark, as this is where over 90% of lower genital tract neoplasia arises. This junction is presumed, but not proven, to be the embryologic junction of the Müllerian and urogenital sinus epithelia.

SQUAMOUS EPITHELIUM

The squamous epithelium of the cervical portio is similar to that of the vagina, except that it is generally smooth and lacks rete pegs. Colposcopically, it appears featureless except for a fine network of vessels which is sometimes visible. The relative opacity and pale pink coloration of the squamous epithelium derives from its multi-layered histology and the location of its supporting vessels below the basement membrane. A full description of the histology and maturation of squamous epithelium can be found in any number of pathology texts and will not be detailed here.

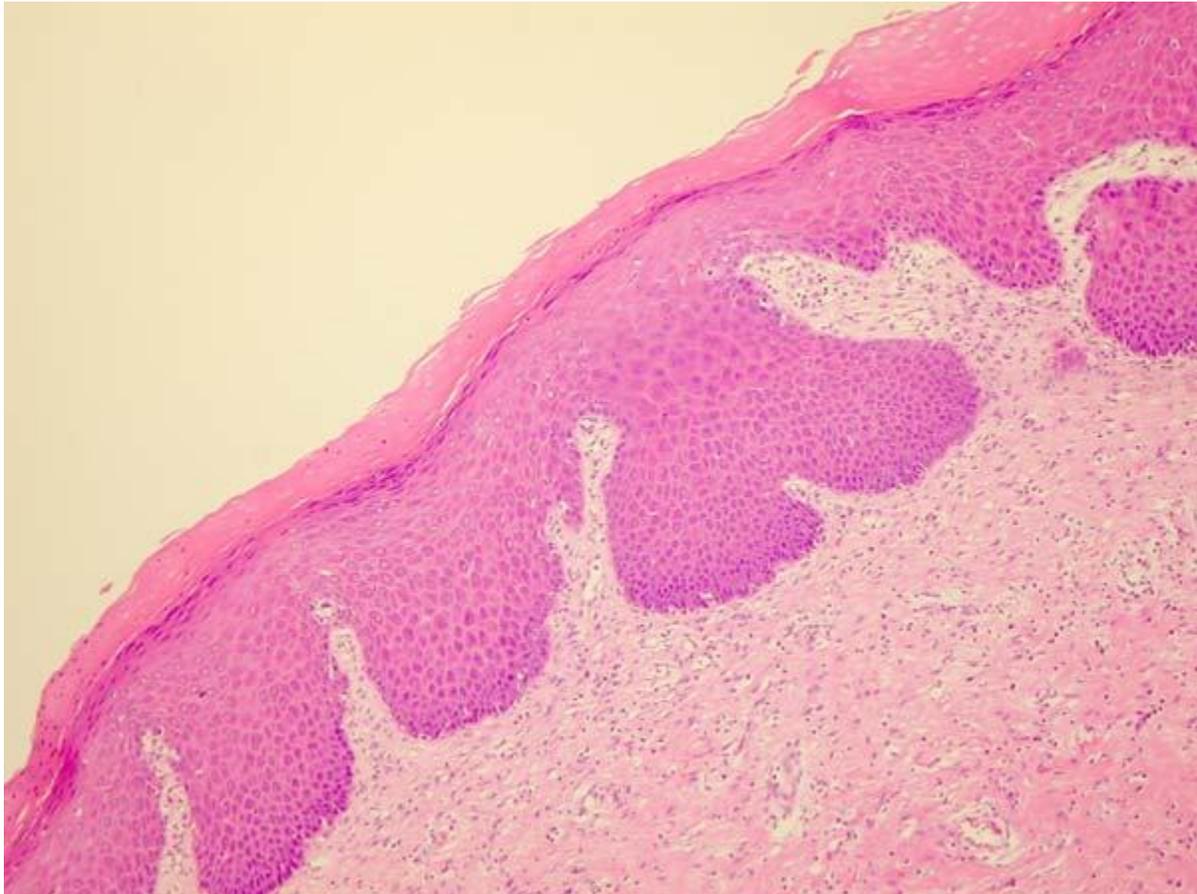
Mature squamous epithelium (H&E x 400): Different layers starting at the basement membrane (basal, parabasal, intermediate, superficial) are evident. Clear cytoplasm indicates glycogenation. As the cells mature, the nuclei get smaller and the cytoplasm amount increases.



The maturation and glycogenation of the squamous epithelia of the vagina and cervix are influenced by **ovarian hormones. Estradiol**

promotes maturation, glycogenation, and desquamation. **Progesterone** inhibits superficial maturation. This explains why the squamous epithelium appears atrophic after loss of ovarian function, with pallor and subepithelial point-hemorrhages from increased vulnerability of the underlying vessels. These atrophic changes may be seen, albeit less dramatically, with prolonged exposure to **progestins**, as with injectable progestin-only contraceptives. Glycogenation of the mature squamous epithelium of the vagina and cervix under the influence of estrogen give rise to the strong uptake of **Lugol's iodine** solution. This is the basis of **Schiller's test**, used to help distinguish normal tissue from abnormal. **Dysplastic** or **HPV-infected** squamous epithelium show arrested maturation with incomplete or absent glycogenation and will reject iodine staining. It may also show abnormal deposition of keratin in the upper layers of the epithelium.

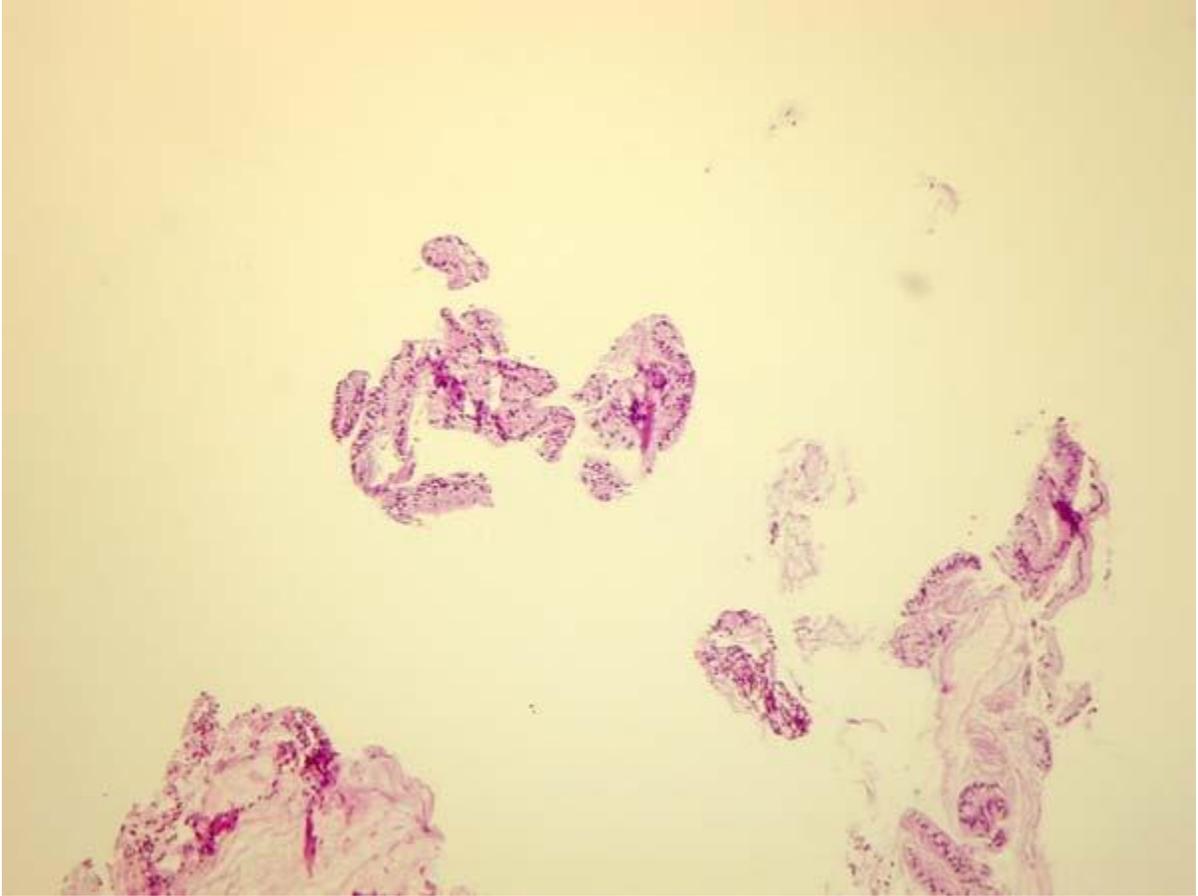
Parakeratosis (H&E x 400): Orange layer of keratin above the superficial squamous epithelial cells. The blue cell layer beneath the keratin indicates the production of keratin granules. Nuclei in the keratin is parakeratosis.



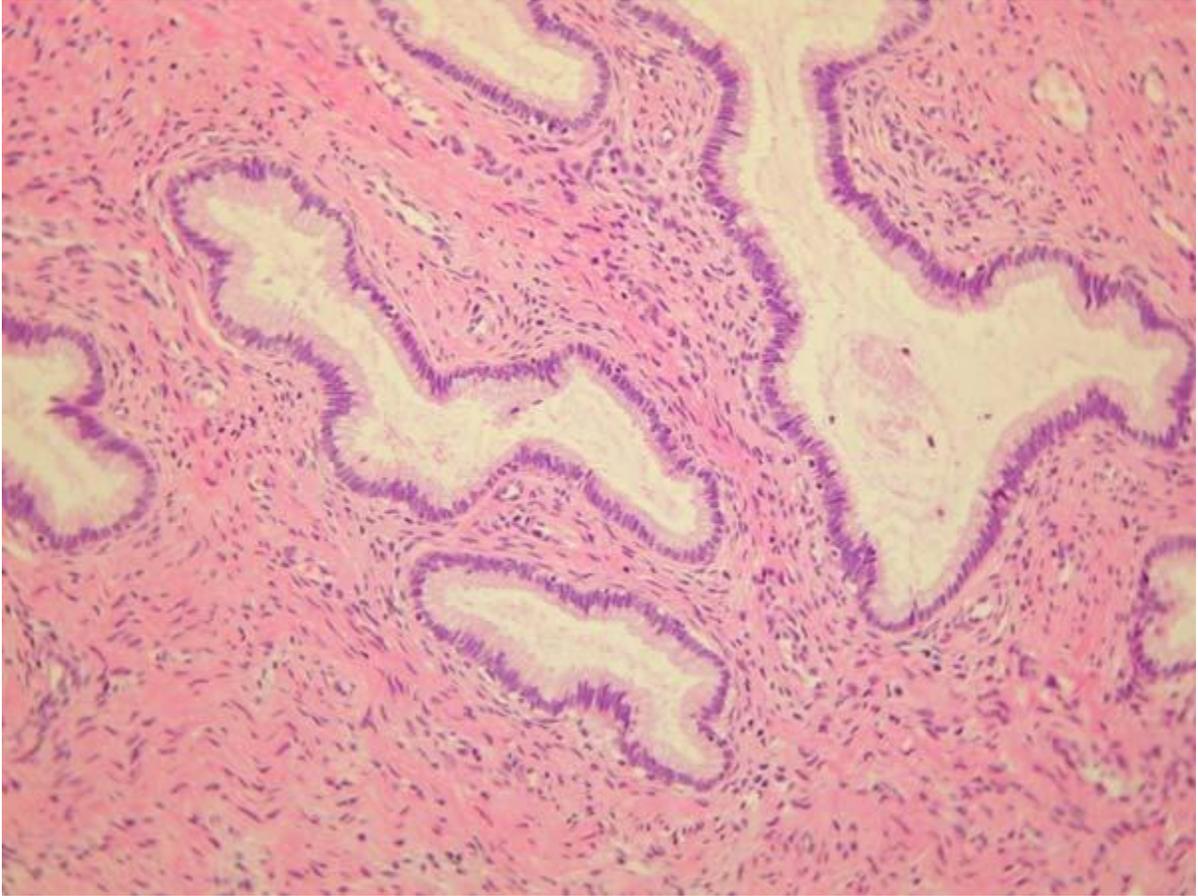
GLANDULAR EPITHELIUM

The “**glandular**” or **columnar epithelium** of the cervix is located cephalad to the squamo-columnar junction. It covers a variable amount of the **ectocervix** and lines the **endocervical canal**. It is comprised of a single layer of **mucin-secreting cells**. The epithelium is thrown into longitudinal folds and invaginations that make up the so-called **endocervical glands** (they are not true glands). These infolding crypts and channels make the cytologic and colposcopic detection of neoplasia less reliable and more problematic. The complex architecture of the endocervical glands gives the columnar epithelium a papillary appearance through the colposcope and a grainy appearance upon gross visual inspection. The single cell layer allows the coloration of the underlying vasculature to be seen more easily. Therefore, the columnar epithelium appears redder in comparison with the more opaque squamous epithelium.

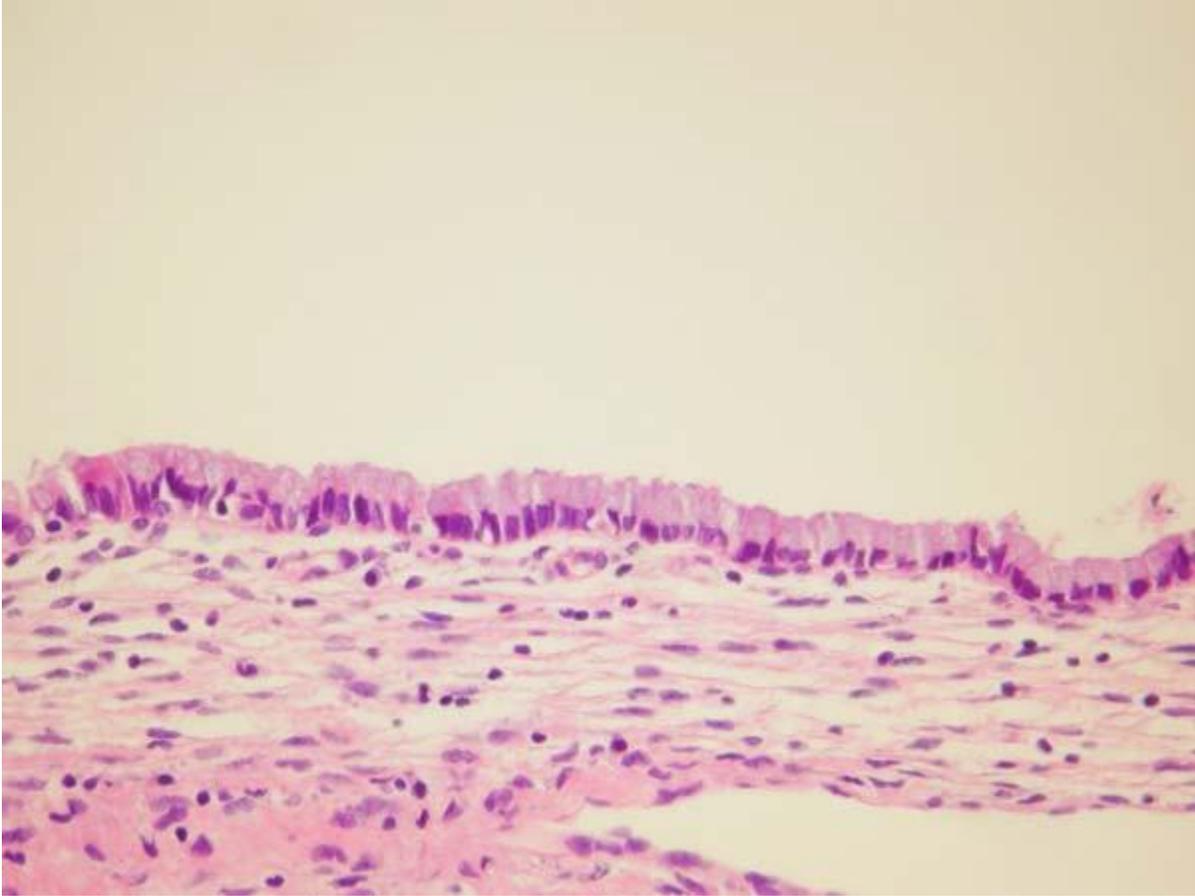
ECC: (H&E x 40): Mucus and small unoriented fragments of endocervical glands



[Endocervical glands \(H&E x 400\)](#): Actually crypts (there are no acini and ducts) lined by a single layer of columnar epithelium. Extend to a depth of 5-7 mm.



[NI endocervix \(H&E x 400\)](#): Single layer of columnar cells with basal nuclei.



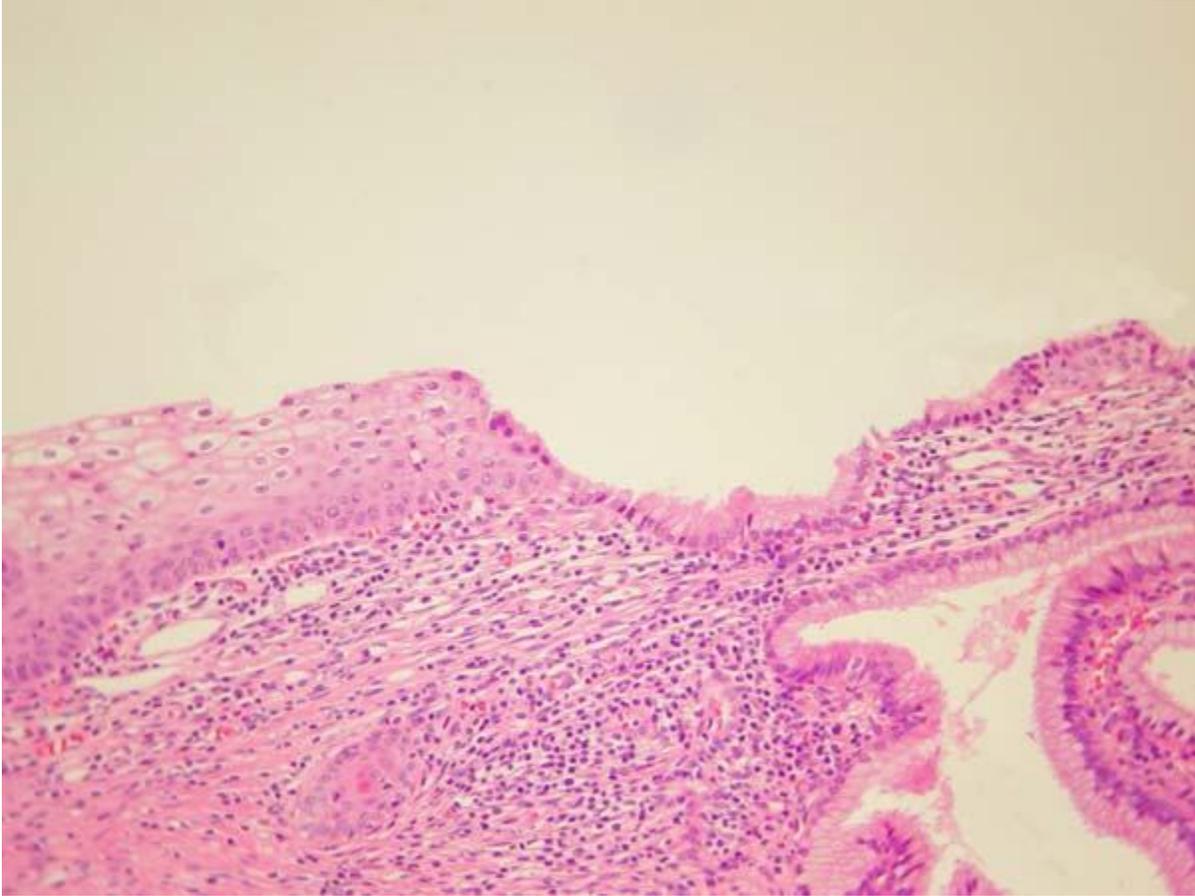
MUCOSAL IMMUNITY

Both the secretory (IgA mediated) and cellular immune systems are active within the cervical epithelia and stroma. In particular, macrophages, including some *Langerhans cells*, -lymphocytes are present. Local immunity is suspected to play an important role in the wide variety of outcomes seen among individuals following HPV infection and in the susceptibility to the development of neoplasia.

Squamocolumnar Junction

The squamocolumnar junction (**SCJ**) is defined as the junction between the squamous epithelium and the glandular epithelium. It is often marked by a line of metaplasia and its location is variable. Age and hormonal status are the most important factors influencing its location. During the perimenarche, the SCJ is located at or very close to the **external os**. The SCJ is generally located on the **ectocervix** at variable distances from the os in reproductive-aged women, as the cervix, and particularly the **endocervical canal** elongates under the influence of estrogen. The high estrogen levels of pregnancy and oral contraceptive use promote further eversion of the SCJ. Eversion is usually more pronounced on the anterior and posterior lips of the ectocervix and less so at the 3 and 9 o'clock positions. Eversion of the columnar epithelium onto the ectocervix may not be symmetrical. The resulting asymmetric appearance may cause confusion and prompt a referral for a possible cervical lesion. An eversion of the SCJ onto the ectocervix is sometimes referred to as an "ectropion" or "erosion." The latter term is a misnomer and should not be used. Occasionally, the SCJ is located in part or entirely on the vaginal fornices. The process of squamous epithelialization of the vaginal tube begins at the dorsal urogenital sinus and vaginal plate, spreading upwards along the vaginal tube. This process proceeds most rapidly along the lateral walls. If the epithelialization proceeds normally, the SCJ is located at near the external os of the cervix. If the epithelialization is arrested before completion, the SCJ will be located on the vaginal walls, usually involving the anterior and posterior vaginal fornices, as epithelialization in these locations occurs later than laterally. This type of variant in SCJ location are most striking in in-utero DES-exposed women. In some cases the entire cervical portio will be covered with columnar epithelium. From the perimenopause on, or with prolonged exposure to strong progestational agents which cause atrophy, the SCJ recedes up the endocervical canal. This makes cytologic sampling less reliable and colposcopic examination of the SCJ impossible in many cases.

Squamocolumnar junction (H&E x 400): Junction of single layer columnar cells and stratified squamous cells.

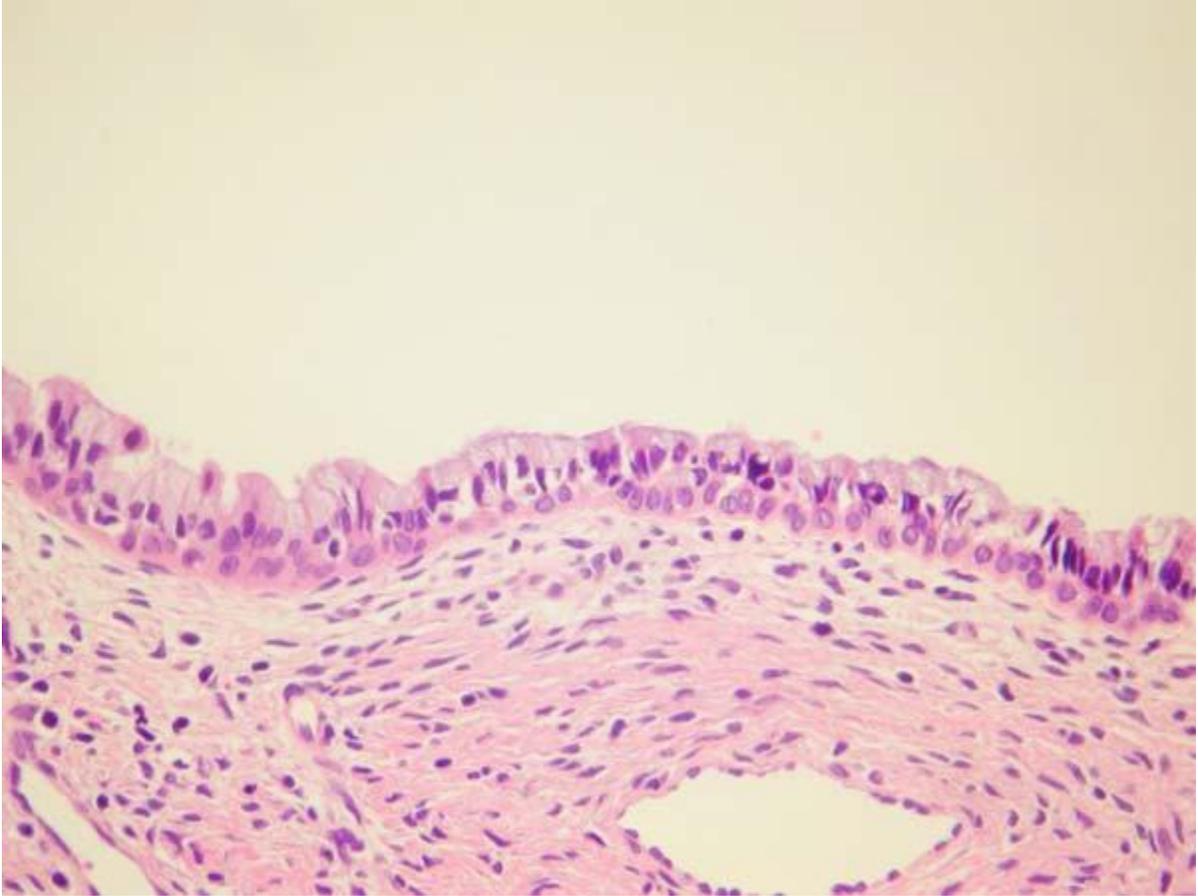


Identifying the location of the SCJ is important for the optimal collection of cytologic samples. Therefore, the acquisition of cells should be modified from patient to patient to insure that the area at risk for neoplasia is targeted. The location of the SCJ also determines in large part the efficacy of colposcopy in ruling out the presence of neoplasia. If the SCJ cannot be visualized in its entirety, the colposcopy is deemed "unsatisfactory." Finally, the location of the SCJ influences the choice of treatment modality if neoplasia is present.

TRANSFORMATION ZONE

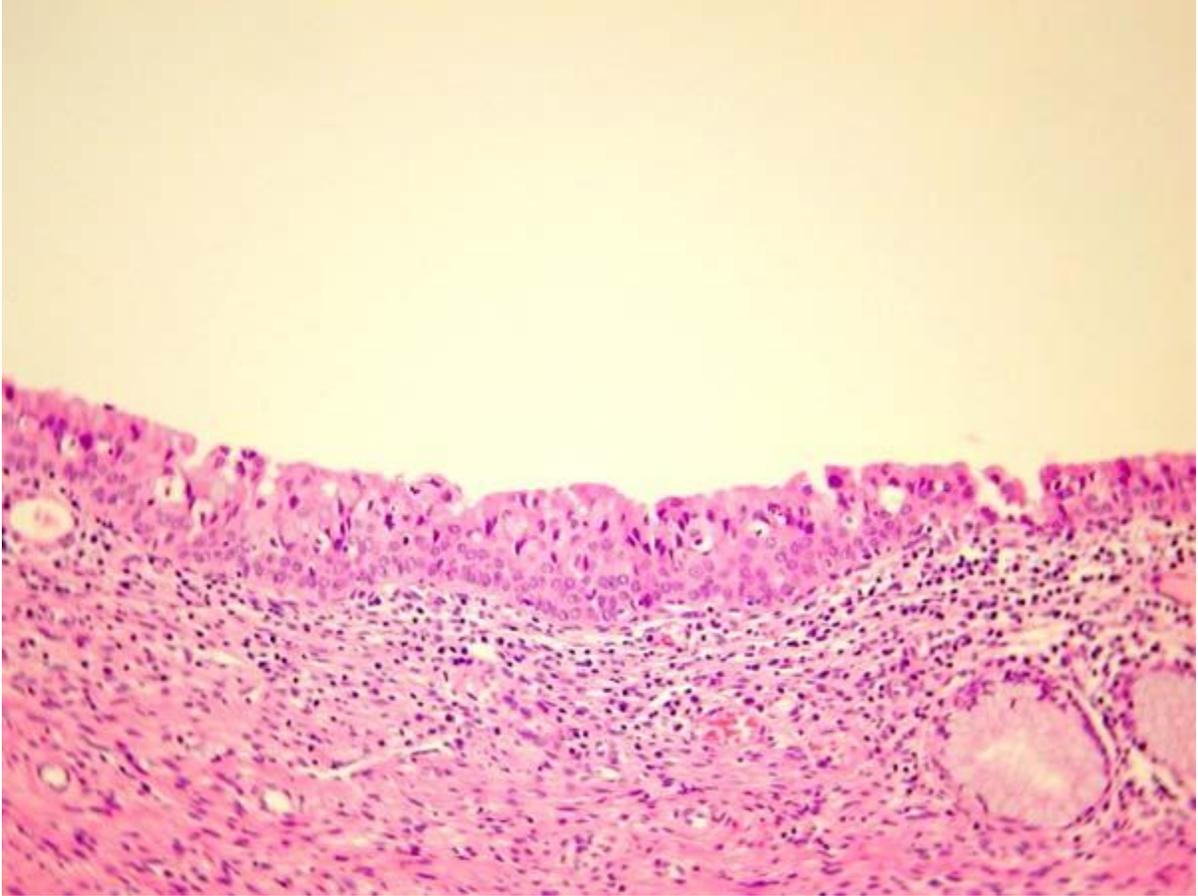
An understanding of the cervical transformation zone (TZ) is essential to the identification and management of cervical intraepithelial neoplasia. It lies between the "original" and "new" squamocolumnar junctions. The SCJ discussed above is the visible border between the squamous and columnar epithelia of the cervix and represents the new squamocolumnar junction. It is adjacent to the new SCJ that the dynamic process of squamous metaplasia occurs throughout the reproductive years. This is a normal process during which columnar epithelium is replaced by squamous. The trigger for this process is thought to be the eversion of the columnar epithelium under the influence of estrogen and its subsequent exposure to the acidic vaginal pH. In response to the "insult" of vaginal acidity, the process of metaplasia replaces the more fragile columnar epithelium with the more sturdy squamous type. This process is thought to occur by two mechanisms. One is by reserve cell hyperplasia. Reserve cells proliferate around the exposed endocervical glands and eventually obliterate and replace them. The columnar epithelium is replaced, not changed into another type of epithelium.

Reserve cells (H&E x 400): single layer of round undifferentiated cells beneath the columnar cells.



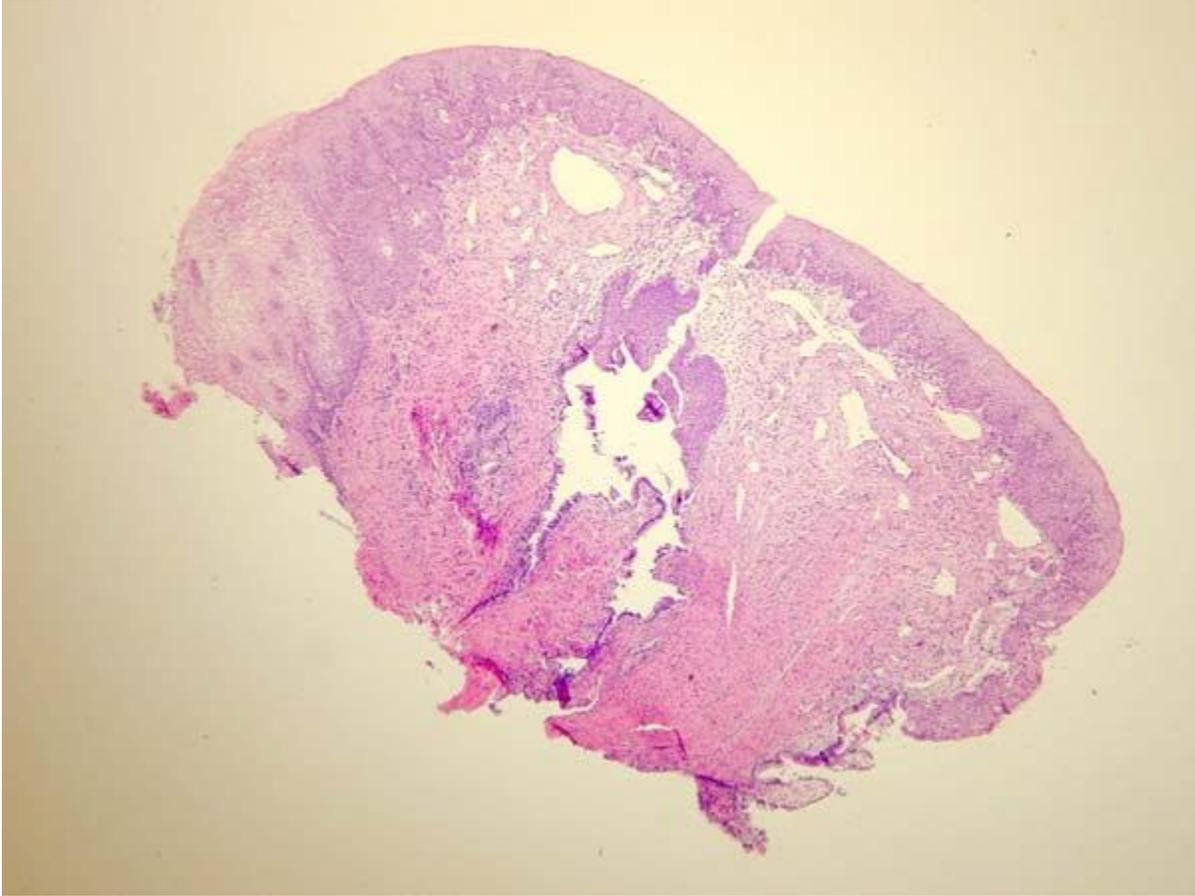
Colposcopically, this process is seen as a flattening out and merging of the villous structures of the glandular tissue, with replacement by a smoother, milky coating. It is also thought that some metaplasia occurs by the ingrowth of squamous epithelium centripetally from the squamous epithelium of the ectocervix. This ingrowth undermines and replaces the overlying columnar epithelium. The net result is a zone of squamous metaplasia of variable width distal (caudal) to the columnar epithelium and proximal (cephalad) to the "original squamous epithelium" laid down during embryogenesis.

Immature squamous metaplasia (H&E x 400): Proliferation of reserve cells results in a 3-5 cell layer of nonglycogenated metaplastic cells. The remnant columnar cells are at the surface.



The border between the metaplastic epithelium arising during the reproductive years and the original squamous epithelium is called the "original SCJ." The TZ is the area of metaplastic epithelium between the original and new SCJs. During the process of metaplasia, still-functioning endocervical glands may become covered and blocked, giving rise to Nabothian cysts.

Cervix Biopsy (H&E x 25): Squamous epithelium overlying glands indicates the presence of the transformation zone.



The metaplastic epithelium adjacent to the new SCJ is the newest and the least mature squamous epithelium on the cervix. As new metaplastic epithelium arises, the older metaplastic epithelium is moved outward toward the original SCJ, with the newest and least mature metaplasia adjacent to the new SCJ. With time, the metaplastic epithelium matures to the point where its thickness and glycogenation is indistinguishable from the original squamous epithelium. This makes the colposcopic identification of the original SCJ, and therefore the outer limits of the TZ, impossible in many cases. The location of Nabothian cysts, always formed within the TZ, is useful in identifying its limits.

The identification of the TZ is of utmost importance to the colposcopist. It is within the metaplastic epithelium, i.e. the TZ, that essentially all cervical neoplasia arises. Metaplasia is particularly active during the peripubertal years and during the first pregnancy. Perhaps this accounts for the fact that early first sexual intercourse and early age at first pregnancy are risk factors for cervical cancer. It is hypothesized that the reserve cells in adolescent and young women are especially vulnerable to the oncogenic potential of human papillomavirus infection. The size and location of the TZ will influence selection of treatment modality if neoplasia is present.

COLPOSCOPIC AND NEOPLASTIC SIGNIFICANCE OF THE TRANSFORMATION ZONE

Nearly all cervical neoplasia occurs in the TZ. This is even true of the adenocarcinomas, which are often associated with adjacent high-grade squamous disease, although they may rarely occur higher up in the endocervical canal. This is because it is the reserve cells undergoing metaplasia that are vulnerable to various carcinogens such as HPV. Since metaplasia is at peak activity during adolescence and first pregnancy, it is understandable that early age on sexual activity and first pregnancy are known risk factors for cervical cancer. It is therefore of great importance that the colposcopist be able to identify and evaluate the TZ. Given a particular lesion, the more severe disease tends to be cephalad in the TZ, where the epithelium is least mature. In order that a colposcopic exam may be deemed "satisfactory" or "adequate," the TZ must be seen in its entirety, all the way up to the columnar epithelium, 360°, which means that all areas involved in squamous metaplasia have been visualized. If this is not possible, because the new SCJ or abnormalities are up inside the canal beyond view, then one cannot be sure that a high-grade lesion or cancer has been ruled out.

The importance of the TZ to cervical neoplasia explains why it is desirable to see both columnar (endocervical) and squamous metaplastic cells on Pap smears. Their presence indicates that the area at risk has indeed been sampled.

HISTOLOGY AND COLPOSCOPY OF THE TRANSFORMATION ZONE

As reserve cell hyperplasia progresses to several layers of thickness, the columnar epithelium is pushed off and replaced. This proliferation of reserve cells is seen as the flattening and fusing of columnar villi. The areas of metaplasia are paler than the one-cell-thick columnar epithelium as the underlying blood vessels are now viewed through several cell layers. Metaplasia is usually seen as numerous small, glassy islands overlying the columnar epithelium and also as pale, translucent ingrowths of metaplasia from the original squamous epithelium. These islands and tongues of metaplasia can be irregularly shaped and distributed around the TZ, and coalesce into sheets of metaplasia, often with a thin acetowhite line at the advancing border. Immature metaplasia can turn acetowhite, causing striking "frosting" of

these areas. As the epithelium matures and pushes "outward" relative to the external os of the cervix, it shows a gradient of maturity. The maturest epithelium is densest with at most a trivial, fine vascular pattern. It does not turn acetowhite. It also has the highest level of glycogenation and therefore iodine uptake. Less mature metaplasia may be a pale acetowhite and may show fine vascular patterns that are can both be confused with low-grade lesions. When the crypts of the mucin-secreting columnar epithelium become covered up by metaplastic epithelium, they become blocked, and Nabothian cysts are formed. Therefore, these cysts are by definition located within the TZ. The vessel overlying Nabothian cysts can be large and alarming to the novice colposcopist. However, close inspection will reveal their benign, arborizing character.

The most mature metaplastic epithelium probably has little neoplastic potential, like that of the original squamous epithelium.

Some women have a large area of acetowhite, iodine-variable epithelium which extends onto the anterior and / or posterior vaginal fornices. There may also be a very fine mosaic pattern. This is called a congenital TZ and is caused by squamous epithelium of arrested maturation and variable glycogenation, probably laid down during fetal development. This epithelium is of low neoplastic potential and can be very confusing to the colposcopist.

PREGNANCY-RELATED CHANGES

The cervix in pregnancy shows stromal edema, increased vascularity, enlargement of glandular structures, and acute inflammatory response. Stromaldecidualization may occur in the second and third trimesters; these changes may appear suspicious to the inexperienced observer.

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THE CERVIX: Premalignant Lesions of the Cervix: Definition

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The incidence and mortality of invasive cervical cancer in the United States and other developed countries has decreased over 70% over the past 50 years due cervical cancer screening programs. The Pap test, despite its limitations, is the most effective screening test of modern medicine. In this country, the numbers of cases of cervical cancer diagnosed each year has been stable for over a decade at approximately 13,000; the numbers of deaths each year number just under 4,000. These numbers remain stable despite the rapid rise in the incidence of pre-invasive disease since the 1960s, coincident with the increase in number of sexual partners and earlier age of onset of sexual relations in the general population. It is important to note that over half of the women diagnosed with and dying from cervical cancer have never undergone cytologic screening, or have been inadequately screened. Older women, socio-economically disadvantaged women, and recent immigrants to the United States from underdeveloped countries are at highest risk for lack of adequate screening.

Over the past two decades, we have come to understand that human papillomviruses (HPVs) are present in nearly all cervical neoplasia, explaining the epidemiology of the disease. Of the more than 100 types of HPVs approximately 40 may involve the anogenital tract. Approximately 15 HPV types are considered oncogenic, causing virtually all cases of cervical cancer. HPV 16 alone accounts for over 50% of cancers and HPV 18 is responsible for an additional 10%. Identified risk factors for cervical cancer such as early age at first intercourse and multiple sexual partners are proxies for risk of HPV infection. However, HPV infection is very common and cervical cancer is not. Co-factors such as smoking, high parity, and host immune responses also play a role.

Serologic measurements of antibodies against HPV capsid antigens, indicative of past infection, provide evidence that a majority of sexually active individuals have been infected with HPV at some point. Prevalence studies show that between 5% and 20% of the general population has HPV DNA detectable in cervical samples; prevalence is higher in younger women (< age 30), compared to those over age 30. In most cases, infection with HPV is transient and may or may not be associated with cervical abnormalities of LSIL or CIN 1. Typically, viral DNA is no longer detected in cervical samples after 1 to 2 years. It is persistent infection with an oncogenic HPV that dramatically increases the risk for developing CIN 3 or cancer.

Potentially cancerous precursor lesions found on the uterine cervix are referred to as cervical intraepithelial neoplasia, or CIN. Traditionally, high-grade CIN is thought to arise as a small focus within a larger area of low-grade CIN that expands and eventually replaces much of the low-grade lesion. This "monoclonal" theory is supported by the fact that there is a 5-year difference between the peak prevalence of CIN 1 and CIN2/3, and detection of a LGSIL Pap greatly increases the risk that a high-grade CIN will be found on subsequent smears. It has been difficult to document the rate of progression because most studies use cervical biopsy to establish an accurate diagnosis, which influences the rate of disease progression.

With the discovery that most CIN 1 lesions regress or persist, the question has been raised as to whether high-grade CIN might be a process that develops concurrently with low-grade CIN. This theory is supported by the fact that CIN 3 can develop without a detectable preceding low-grade CIN lesion, and high-grade CIN is almost always found closer to the squamo-columnar junction (SCJ) than concomitant low-grade lesions. It has also been found that women who turned HPV 16/18 positive had a 39% rate of high-grade CIN at 2 years compared to HPV negative women. Schiffman, et al. reported that both CIN 1 and CIN 2/3 lesions developed within the same time frame in a large group of women who turned HPV positive and were followed for 4 years. This issue continues to be studied

THE CERVIX: Premalignant Lesions of the Cervix: Epidemiology and Role of HPV

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NATURAL HISTORY AND MALIGNANT POTENTIAL OF CERVICAL NEOPLASIA

Cervical cancer was once a leading cause of cancer death in the United States. Now, invasive cervical cancers are relatively uncommon. This change is probably mostly due to effective identification and eradication of cancer precursor lesions(CIN). Laboratory surveys from the College of American Pathologists (CAP) indicate that more than 1 million women each year are diagnosed with low-grade intraepithelial lesions, and 500,000 will be found to have CIN-2 or CIN-3 level lesions.

Persistent human papillomavirus (HPV) infection is requisite to the development of cervical neoplasia. Oncogenic HPV types have a molecular advantage in establishing a persistent infection that disrupts the apoptotic machinery of the cervical epithelial cell. This leads to disorganized, unchecked proliferation of cells and loss of normal maturation as they progress upwards through the epithelial cell layers. HPV persistence is demonstrated before the appearance and even after the regression of cervical cytological abnormalities (Castle, Schiffman). Multiple studies (Ho, Kulaga, Peyton, Giuliano) have shown that the mean duration of an HPV infection is between 4 and 10 months and is longer when the infecting HPV type is oncogenic versus non-oncogenic. Parity (Molano) and cytological abnormalities (Dalstein) correlate with a greater persistence of HPV and therefore an increased risk of cervical dysplasia.

The natural history and potential outcomes of cervical intraepithelial neoplasia (CIN) can be estimated from previous studies (Table 1) (Ostor).

Degree of Dysplasia	Regression (%)	Persistence (%)	Progression to CIN 3 (%)	Progression to Invasive Cancer (%)
CIN I	60	30	10	1
CIN II	40	40	15	5
CIN III	33	55	N/A	> 12

Factors that may determine the biologic behavior of cervical dysplasia remain elusive. Age greater than 35 years old, smoking, co-infection with HIV or Chlamydia have all been proposed as promoters of the malignant progression of cervical dysplasia to cancer, but none have been definitely proven. Future research should provide insight into molecular surrogates of dysplasia (e.g. HPV diagnostics, gene methylation patterns, proliferation markers) that could help predict outcomes and the safety of expectant management or need for closer follow-up and treatment.

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THE CERVIX: Premalignant Lesions of the Cervix: Spectrum of Disease

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It is well established that invasive carcinoma of cervix is preceded by a precursor lesion that morphologically resembles the adjacent invasive squamous carcinoma. This lesion is termed “**carcinoma in situ**” (**CIS**). However, CIS in itself is preceded by a spectrum of lesions with varying degrees of abnormality. The term “**dysplasia**” was introduced to refer to this spectrum of progressive cervical abnormality from normal epithelium to CIS. The word “dysplasia” means “abnormality of development.” Histologically, dysplasia is sub-classified into **mild, moderate, or severe** based on the extent to which the cervical epithelium is involved with abnormal cells: 1/3rd, 2/3rd or full thickness respectively. This classification reflects the biological potential of the precursor lesions to progress to invasive carcinoma. The majority of mild dysplasia lesions are of little if any malignant potential, but a few, perhaps 10%, will progress to a higher grade. At this time, it is not possible to distinguish which will progress clinically other than to watch over time. Moderate and severe dysplasias are considered true pre-malignant lesions with a progression rate to invasive cancer of 30% to 50% over time.

In 1960, the term “**cervical intraepithelial neoplasia**” (**CIN**) was introduced and implied the concept that precursor lesion to squamous cell carcinoma represented a single, continuous disease process. CIN nomenclature for histology is more specific to the cervix than the general term “dysplasia,” and makes clear the pre-invasive nature of lesions. The CIN nomenclature divides cervical cancer precursors into **CIN1, CIN2, and CIN3**, corresponding to **mild, moderate and severe dysplasia/carcinoma in situ**. It is the most widely used histologic terminology for cervical cancer precursors.

With the identification of **human papilloma virus (HPV)** as the etiologic agent for cervical cancer and its precursors in the 1980s, other more confusing terms became prevalent such as flat condyloma, atypical condyloma, condylomatous atypia, etc. appeared on cytology and histopathology reports. Our current understanding of the pathogenesis of cervical precursors is that that CIN is not a single disease process but rather represents two distinct entities: 1) a viral stage of productive infection which is usually self-limited and 2) neoplastic transformation in a minority of HPV-related lesions. This insight into the pathogenesis of CIN has revolutionized our understanding and approach to cervical disease. It also has led to the development of a completely new nomenclature for cervical cytologic interpretation that better reflects this biologic process: the Bethesda System (1988, revised 1991, 2001). The Bethesda terminology for cytologic reporting subclassifies squamous cervical precursor lesions into **low-grade squamous intraepithelial lesion (LSIL)**, for lesions previously classified as koilocytic atypia (HPV) and/ or CIN1, or **high-grade squamous intraepithelial lesion (HSIL)** encompassing CIN2 or 3 changes. Although originally introduced for cytologic reporting, the “**SIL**” terminology can be used for histologic classification as well, thus minimizing the confusion resulting from different terminologies for cytology and histology.

THE CERVIX: Invasive Cancer of the Cervix

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Cervical cancer is a relatively uncommon finding in comparison to the number of cases of CIN diagnosed annually in the US. In 2000, the incidence of invasive cervical cancer was estimated at 12,800 cases, and there were 4,600 cervical cancer related deaths. In other parts of the world that lack screening programs, cervical cancer is still the most common cancer among women. The major focus of colposcopic assessment of abnormal cervical cytology is to detect cancer. In order to accomplish this goal, one must maintain a high index of suspicion and stick with standard triage protocols such as assuring adequacy of the examination and a good correlation between cytology, colposcopy and biopsy findings.

Since cervical cancer is a relatively rare finding in a routine colposcopic practice, the colposcopist should be aware of the hallmark features of invasive cancer and look for these features with each patient they evaluate.

CHARACTERISTIC FEATURES OF CERVICAL CANCER

- Atypical vessels-non branching (commas, corkscrew, sausage shaped, hairpin)
- Abnormal vaginal bleeding or discharge
- Ulcerations
- Raised, irregular surface
- Yellow color to epithelium
- Firmness to palpation

As a cancer of the cervix develops, neovascularization occurs as the result of tumor angiogenic factor released by the cancer cells. These vessels do not follow the normal regular arborizing vessel pattern, but instead the new vessels have irregular course and caliber. They can run parallel to the surface of the cervical epithelium and form non-branching patterns such as corkscrews, squiggles and comma shaped vessels. Routine use of a green filter can assist the colposcopist in assessing vessel patterns at the time of colposcopy.

DIAGNOSIS

Cytologically, squamous cell cancer can be either keratinizing or non-keratinizing. Cells can occur in syncytial-like clusters or singly, and demonstrate very irregular chromatin clumping, nucleoli, and may have a background tumor diathesis of blood and cellular debris.

Cancer (cytology) (Liquid based-Papanicolaou stain x 400): Irregular cell forms; nuclei are enlarged with prominent nucleoli. The cell cluster at right shows diathesis ("cotton candy necrosis").

Colposcopically, cervical cancer can be a challenge to diagnose, especially microinvasive cancer since atypical vessels or other signs of more advanced disease may not be present. This reinforces the fact that one must maintain a high degree of suspicion and effectively address any discrepancies between colposcopy, cytology and histology before therapy is initiated, particularly ablative therapy. Cervical cancer can be squamous, glandular or mixed type. Invasion is diagnosed when there is a breach in the basement membrane. If the invasion extends 3 mm or less, it is referred to as microinvasive disease. If invasion is greater than 3mm, it is frankly invasive cancer.

Squamous cell carcinoma (H&E x 400): Irregular nests of malignant squamous cells in a fibrotic stroma (desmoplasia).

If biopsy or endocervical curettage reveals invasive cancer, a cone biopsy is not needed.

EPIDEMIOLOGY

There are approximately 12,800 new cases/year and around 4600 deaths/year in the United States. There are 50,000 new cases carcinoma in situ/year. There are 2 major histological types of cervical cancer. 93% are squamous cell cancers and contain HPV DNA; 90% are subtypes 16/18, which are most virulent. 7% of cases are adenocarcinomas -- but these are on the rise. Adenocarcinomas are associated with HPV type 18.

When considering preinvasive disease, the classic theory holds that SIL leads to squamous carcinoma. When SIL progress to invasive squamous cervical cancer, ISCC usually develops from an area of SIL located adjacent to the SCJ. Oncogenic HPV serves as initiators. Other factors relating to immune status such as cigarette smoking, nutrition, or chlamydia infections may be promoters. Adenocarcinoma develops from glandular atypia and may be preceded by an Atypical Glandular Cells of Uncertain Significance (AGUS) Pap smear. The only preinvasive stage we usually find is adenocarcinoma in situ (AIS)

Adenocarcinoma (H&E x 400): Irregularly shaped glands within a fibrotic inflamed stroma (desmoplasia). Cells are highly atypical; the nuclei contain prominent nucleoli. Higher power

The median age to develop cervical cancer is 45 to 50 years. Older women are often more susceptible due to lack of screening. Younger women have more problems with rapidly progressing disease. 50% of women diagnosed with invasive cancer have never had a Pap smear. 10% have not had a Pap smear in last 5 years.

STAGING OF CERVICAL CANCER

Stage 0 carcinoma-in-situ

Stage I the tumor is confined to the cervix

- IA** microinvasive disease, with the lesion not grossly visible: no deeper than 5 mm and no wider than 7 mm
 - IA1** invasion <3 mm and no wider than 7 mm
 - IA2** invasion >3 mm but <5 mm and no wider than 7 mm

- IB** larger tumor than in IA or grossly visible, confined to cervix
 - IB1** clinical lesion no greater than 4 cm
 - IB2** clinical lesion greater than 4 cm
- Stage II** extends beyond the cervix, but does not involve the pelvic side wall or lowest third of the vagina
 - IIA** involvement of the upper 2/3 of vagina, without lateral extension into the parametrium
 - IIB** lateral extension into parametrial tissue
- Stage III** involves the lowest third of the vagina or pelvic side wall, or causes hydronephrosis
 - IIIA** involvement of the lowest third of the vagina
 - IIIB** involvement of pelvic side wall or hydronephrosis
- Stage IV** extensive local infiltration or has spread to a distant site
 - IVA** involvement of bladder or rectal mucosa
 - IVB** distant metastases

TREATMENT AND SURVIVAL

Treatment of frankly invasive cancer usually consists of a radical hysterectomy with lymph node dissection, or radiation therapy with advanced disease. If the biopsy reveals microinvasive disease, a cone biopsy is required, since a biopsy alone is insufficient to rule out frankly invasive cancer, which may be adjacent to the biopsy site. If a cold cone or loop excision reveals microinvasive cervical cancer with clear margins, treatment can include a simple hysterectomy or, if the patient desires to maintain her fertility, observation with careful follow-up.

Stage IA-- 5-year survival 95%

- simple hysterectomy or careful observation after cone biopsy (With clear margins).

Stage IB or IIA-- 5-year survival 70% to 85%

- radical hysterectomy with pelvic-node dissection, or
- external beam and intracavitary radiotherapy (equally effective)

Stage IIB, III, IVA--5-year survival 65%, 40%, 20% respectively

- pelvic radiotherapy
- Treatment with cisplatin-based chemotherapy should strongly be considered for patients receiving radiotherapy 14

Stage IVB-- 5year survival 10%

- chemotherapy with or without pelvic radiotherapy

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THE CERVIX: Colposcopy: Brief history of colposcopy

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Colposcopy was introduced by Hans Hinselmann in 1925 in Germany. He theorized that it might be possible to detect cervical cancer at an early stage by properly illuminating and magnifying the cervix. Although the technique was widely accepted in Europe, it did not gain popularity in the U.S. or the United Kingdom primarily because of a cumbersome terminology that was difficult to translate into English.

In 1928 Shiller introduced the concept of placing iodine on the cervix to identify non-glycogen-containing areas, for biopsy. This became popular in the U.S. and further delayed the acceptance of the colposcope.

In 1941 Papanicolaou and Traut published their report on the use of vaginal pool cytology for detecting cervical cancer. In 1949 Ayre developed the wooden cervical spatula, and it became possible to obtain abrasive cervical smears rather than exfoliative cytologic samples, which improved the detection of cervical neoplasia. The Pap smear, thus, became the accepted method of screening for cervical neoplasia. Cytology is an effective screening method, and colposcopy is the appropriate clinical diagnostic technique for evaluation of an abnormal pap smear.

THE CERVIX: Colposcopy: The Colposcope and Instrumentation

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INTRODUCTION

The purpose of colposcopy is the examination of the uterine cervix and lower genital tract epithelium under magnification, identification of potentially dysplastic or cancerous areas, and performance of directed biopsies of abnormal areas to provide a histological diagnosis. Dr. Hans Hinselmann performed the first colposcopic examination by mounting lenses on a pile of books and placing an ordinary lamp above his head. The first true colposcope he developed was a fixed binocular instrument that was mounted on a tripod and equipped with a light source, with a mirror to direct the light. Since that time, a wide variety of advances have been made that improve the functioning and capabilities of the colposcope.

THE MODERN COLPOSCOPE

A colposcope is typically defined as a stereoscopic binocular field microscope with a long focal length and powerful light source. **{Two standard colposcope base configurations. Left is an articulated swing arm on a rolling base. Right is a column on a tilting base. A third configuration, the boom-style scope is not shown.}**



Modern colposcopes permit magnification between x2 and x40, although most routine colposcopic work can be accomplished at a x10 to x15 magnification. Some scopes have a single fixed magnification level. Others have a series of par-focal lenses or a smooth zoom capability that allows for easy adjustment of the magnification via knob or rotor. [\(Typical multi-magnification colposcope head showing \(left to right\) the light source, magnification adjustment knob, beam splitter with CCD camera attached, and adjustable eyepieces.\)](#)



Lower magnification yields a wider view and a greater depth of field for observation. Higher magnification can reveal small features such as abnormal blood vessel patterns and other finer details. As the magnification level increases, the field of view and illumination levels usually decrease. 2

[Interchangeable eyepieces](#) with various levels of magnification are available for most colposcopes. Changing the magnification of the eyepieces alters the magnification levels achieved by the scope. Some eyepieces can be individually adjusted to compensate for variance in individual user's vision. A diopter scale on the side of the eyepiece can identify these. Eyepieces can be adjusted in a manner similar to microscopes to adjust to each colposcopist's interpupillary distance. Eyepiece hoods or collars can be extended, or can be folded back or removed if the colposcopist wears glasses during the examination.



Changing the power of the objective lenses also alters the magnification and working distance (space between the head of the scope and

the focal point) of the scope. The usual working distance (focal length) of a colposcope is 30cm. The shorter the focal length, the closer the head of the scope must be to the introitus for clear focus, making it harder to use instruments while viewing through the scope. This also makes it more difficult to work in the vagina with the scope in place. Longer focal lengths may be uncomfortable for colposcopists with shorter arms.

Grossly moving the head of the scope forward or backward coarsely focuses most standard scopes. This can be accomplished by physically lifting and moving the scope, rocking or tilting the scope on a stationary base, rolling it on casters, or pivoting the supporting arm. Most scopes also have a fine focus handle that is attached to a machine screw under the mounting bracket for the colposcope head. Applying pressure to this handle can be used to subtly control the alignment of the scope, and twisting it produces very gradual forward or backward movements of the head for exquisite fine focus control.

A flexible articulating swivel arm or overhead boom type colposcope can be mounted on a stable base (with or without wheels), the wall, or an examination table. A column- or stick-mounted scope can easily be moved from place to place. A good scope should be easily adjustable in both vertical and horizontal directions. A weighted or wide colposcope base prevents inadvertent tipping of the scope and damage to the head or to the optics. Most colposcopes are mounted on wheels, but platform/universal joint bases also are available. The choice of mounting system depends on examination room space requirements, need for mobility, and the colposcopist's preference.

A colposcope usually has a powerful light source, with a rheostat to adjust the level of illumination. Light bulbs should be easily accessible since they may have to be changed during a procedure. Bulbs can be halogen, xenon, tungsten, or incandescent. 2 Halogen bulbs produce a strong white light and are often preferred by colposcopists. Some colposcopes have bulbs mounted in the head of the scope, while others are mounted elsewhere and the light is delivered via a fiberoptic cable to the head of the colposcope. Scopes with fiberoptic cables can utilize hotter brighter bulbs, but the cables can be damaged if twisted or bent, producing less overall illumination. The colposcope should be equipped with a green or blue filter (red-free filter). These filters remove red light, thereby enhancing vascular detail by making the blood vessels appear dark.

Commonly available colposcope manufacturers and their contact information and web addresses are shown in Table 1. There are numerous options available for many of the scopes, and the prices are often subject to discounts. Most scopes carry a standard 1-year warranty except for Wallach, which gives a standard 3-year warranty. Besides the traditional optical colposcope, an integrated video colposcope (without eyepieces [Videopath™]) {link: videopath.jpg} is now available. The video colposcope differs from the optical scope in that the colposcopist views the procedure on a video monitor.

MULTIMEDIA ACCESSORIES

When the colposcope was first developed, the colposcopist would visualize the cervix and then make a drawing of normal and abnormal findings in the patient's chart. The system for making and labeling drawings has become more standardized since that time, 3 but making a drawing of colposcopic findings in the medical record remains the standard of care for documenting the colposcopic examination. Indeed, some medical-legal experts have expressed an opinion that routine colpophotographs can increase legal risk because an "expert" can always be hired who can find something wrong in almost any photograph.

However, with the advent of better optics and charged-coupled device (CCD) cameras, more options are now available to the colposcopist for documentation and education. Photographic and digital video-printers can produce permanent records of the exact pathology found. Videocolposcopic systems allow for simultaneous interaction and education of both patients and trainees. Recently, computers have been added to the system to allow fully computerized medical records, complete with digital photographs and the capacity for doing telemedicine.

Multimedia accessories can be added to colposcopes through three major mechanisms. The simplest method of attaching a light-sensitive device to a colposcope is to replace an eyepiece ocular with a camera or a device that redirects the light path to a camera or other viewing apparatus. Unfortunately, this sometimes removes this light channel from use for stereoscopic viewing. Another method of adding multimedia accessories is to have an independent optic system supplying a separate optic port that can have a teaching tube, camera, or CCD video or photographic camera attached. Since the multimedia light channel and the viewing channels must have a completely separate set of lenses and objectives, this adds cost, and the accessory port often has only one magnification level regardless of the number of magnification levels of the viewing ports. The most popular method of adding accessory multimedia ports is via the use of a beam splitter. The beam splitter actually splits a light beam in half and sends the image to two separate ports, one to a viewing port and one to an accessory port. The advantage of this arrangement is that both ports present essentially the same image at the same time. This is especially useful in teaching with teaching tubes or video, since the teacher and learner see the same image at the same time. It also provides the patient with the added benefit of the teaching colposcopist's experienced assessment and input during the procedure.

COLPOPHTOGRAPHY

Colpophotographic systems are useful for documentation of treatment results or pathology that may have to be followed serially over time. They produce more detailed records of pathology than hand-drawings and can be useful with documenting and consulting on unusual findings. They also produce permanent images that can be useful in educating patients and colposcopy trainees. Colpophotographs can be retrospectively checked against pathology results to hone the colposcopist's ability to grade lesions.

When using colpophotography, a permanent camera port is desirable so that fewer image opportunities are missed while finding or attaching the camera to the colposcope. 4 Most colposcopes permit the use of a 35mm or Polaroid camera. Some systems make use of high intensity strobe flashes, which allow for higher shutter speeds that decrease the common problem of blurring on the image due to

movement of the colposcope or the patient. Some manufacturers also have cameras available with data systems that record vital patient information onto the colpophotographs. Remote hand or foot shutter release switches are useful in decreasing blurring due to inadvertent motion during shutter activation. Digital colpophotography is being introduced. Accuscope's Twincam is an eyepiece replaceable digital camera that can be used as a normal digital camera or may put into the eyepiece port of a microscope or colposcope. DFV has an attachment that fits most beam-splitters and allows attachment of certain commercially available digital cameras.

Cervicography overcomes some of the problems of standard colpophotography. This photography technique is part of a proprietary service marketed as an adjunct to the Pap by the National Testing Laboratories. The cerviscope consists of a 35mm camera body, a 50mm extension ring, a 100mm macrolens, and a strobe flash. The procedure involves obtaining and evaluating a panoramic photograph of the cervix and upper vagina using the cerviscope. After the Pap smear has been obtained, 5% acetic acid is applied twice to the cervix, and then 2 images are taken using the cerviscope.

VIDEOLPOSCOPY

Videocolposcopy systems can be used for the same purposes as colpophotography, with the added advantage of real-time discussion of pathology with patients or trainees. Covisualization can allow the patient to become aware of normally inaccessible anatomy. By allowing visualization and the opportunity to ask questions, patients may feel some control over the procedure, thereby decreasing anxiety. 4 It also provides higher levels of patient satisfaction. 7 In addition, the patient has the added benefit of a teaching colposcopist's experienced assessment and input during the procedure.

This type of system is especially useful in teaching colposcopy, since the teacher and learner see the same image at the same time, allowing the teacher to actively assess and critique the learner's cognitive and tactile skills during the procedure. Teaching heads provide similar teaching capabilities but are less efficient because they require close physical proximity to the scope (which may be uncomfortable to the observer, colposcopist, or patient), produce a less realistic depth of field, and preclude any benefit the patient might derive from seeing the procedure. Due to the inherent limitations of currently available CCD cameras, the image on a video monitor is almost always less sharp than the image viewed through the eyepieces. 4 This is less pronounced with the Videopath™ integrated videocolposcope. With either type of instrument, using a slightly higher magnification usually resolves resolution problems.

With the recent advent of smaller charged coupled device (CCD) cameras (digital cameras) that are connected via cable to video digitizing boards, the camera can now be mounted on the scope without interfering with the colposcopic examination. The electrical signal put out by the CCD video camera can be recorded by standard VHS or Super-VHS recording devices, or captured by a computer. Images can also be printed via a standard or high-resolution video printer. Videotaped colposcopic examinations can be useful as a means for secondary expert screening. 8 The camera's output may also be digitized and transmitted to remote locations so that distant or rural colposcopists can directly consult or be supervised by expert colposcopists at major medical centers via telemedicine or Internet resources.

COMPUTERIZED COLPOSCOPY

With the advent of modern CCD cameras attached to digitizing boards, it became possible to create high-resolution digital images of the cervix that could be displayed real-time, or (along with pertinent patient and examination data) stored, printed, or manipulated by a computer. The image captured can be reviewed and recaptured if suboptimal, unlike with colpophotography where the photograph is developed at a later date. Areas of interest can be enlarged, enhanced, or measured. 9 Images also can be stored and retrieved for comparison at future visits or for consultation with expert colposcopists. As medicine moves toward more computerization of medical records, computerized colposcopy allows for easier integration into the electronic medical records. Computerized digital image processing may also facilitate a more quantitative method for following dysplastic lesions over time. 10 Studies are being done on computer-assisted colposcopy, which may help improve training and the accuracy of colposcopic impression. 11

Many computerized colposcopy systems were originally stand-alone systems made for colposcopy, but integrated systems have now been developed. The features of computerized colposcopy systems are shown in Table 1. The Digital Imaging and Medical System (DIMS) from DenVu Incorporated is a high-resolution image, information, treatment, and scheduling database system that produces customized reports. Welch-Allyn's Videopath Image Management System performs similar functions and is being designed to have integration with all Videopath systems in the future. The ImageQUEST Image Communication Software from Leisegang Medical, Inc. serves databasing and telecommunication functions. The is Cooper Surgical's Cerveillance scope which has an integrated digital camera and Pentium based computer system with patient management software.

INSTRUMENTS

Visualization of the cervix is one of the most critical technical components of the colposcopy procedure. Numerous **vaginal specula** are available for this purpose. A medium Grave's speculum is appropriate for most women. Pederson specula have narrow blades for use in virgins (rare in colposcopy) and women with a narrow vaginal diameter. A large metal Grave's speculum may be required for obese women, pregnant women, and women with vaginal wall laxity. Women with an extremely long vagina may require the use of a long Grave's or Pederson speculum. The light source from the colposcope may be used for vaginal speculum insertion. Internally illuminated plastic speculums may also be used but tend to have thinner blades than standard Grave's speculums.

If the patient has extremely lax vaginal walls, lateral **vaginal side-wall retractors** can be helpful. The use of these instruments require a degree of skill, for if proper perpendicular alignment with the vaginal speculum is not maintained, severe vaginal pinching occurs. Alternatively, a condom, a penrose drain, a latex ultrasound vaginal probe sheath with the end removed, or the cut middle finger or thumb of a latex glove with the end removed can be placed over the speculum blades to gently hold the side-walls back and allow better

visualization of the cervix and vaginal fornix.

The purpose of colposcopic biopsy forceps is to take a small but adequate tissue sample of lower genital tract tissue. Many types of biopsy forceps have been developed. The four most common types of forceps used in the United States are the Tischler, Baby Tischler, Eppendorfer, and Kevorkian biopsy forceps. [Tischler cervical biopsy forceps](#): A. Standard surgical instrument grips, B. "Pistol grip" }



{Close-up of cervical biopsy forceps jaws and the silhouette of their biopsy: A. Baby Tischler, B. Tischler, C. Kevorkian. Note the Eppendorfer has the same silhouette and jaw as the Tischler except it has no teeth.}

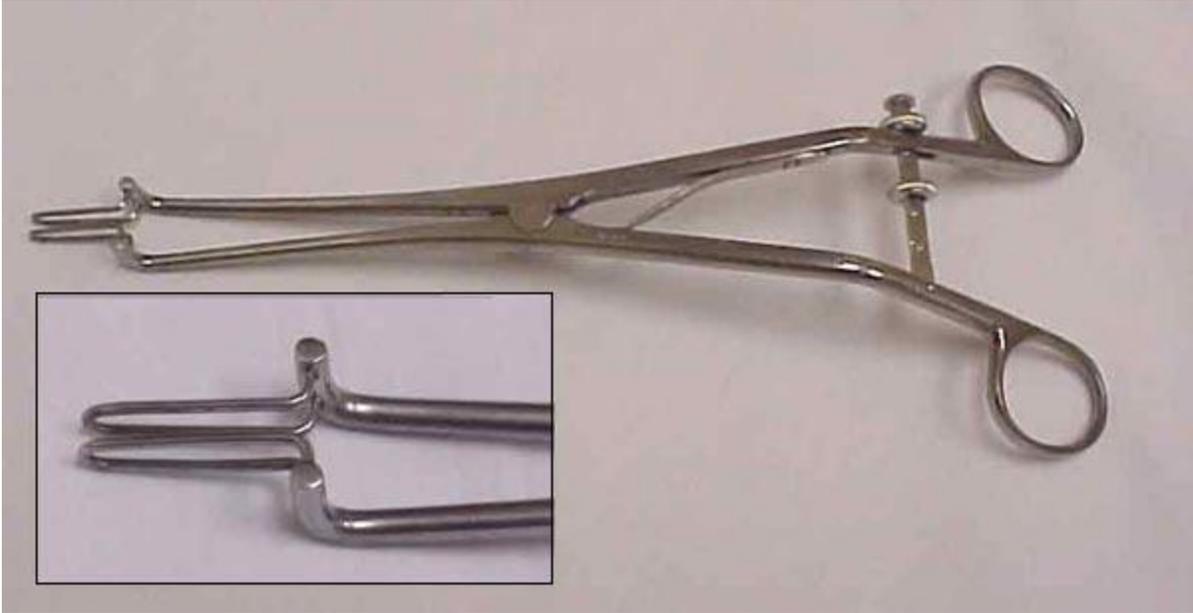


The Tischler forceps is probably the most commonly used in the United States. It combines a rounded jaw and stabilizing tooth with scissors-like blades for minimal crushing artifact and pain. The Baby Tischler combines a stabilizing tooth with scissors-like blades, but has a smaller size, producing a smaller biopsy site with less bleeding and pain. This is especially useful in the biopsy of hypervascular pregnant patients. However, these forceps can produce more crushing artifact and can be more prone to producing inadequate biopsies. The Eppendorfer forceps is basically a Tischler without teeth. It produces minimal crushing artifact and pain, and possibly better endocervical and vaginal biopsies, but makes it more difficult to take excessively deep biopsies. The Kevorkian forceps is less commonly used today. It has a square jaw, with a distal row of teeth on the lower jaw designed to fix the cervix for biopsy. However, it frequently prevents a deep biopsy by stripping only the superficial epithelium.

Regardless of the type of forceps used, keeping the instrument sharp is the most important factor in producing good biopsies and reducing the pain perceived by the patient. Autoclave sterilization can prematurely dull biopsy forceps. 2 Less-damaging sterilization methods include soaking in glutaraldehyde, sterilization with gas, or heating in a bead sterilization system.

The **endocervical curette** is used to obtain a histologic sample (endocervical curettage or ECC) by scraping the endocervical canal. The distal end of the basket is sharp to act as a blade for the curettage. The Kevorkian curette is most commonly used. It can have an open basket, or the bottom of the basket can be closed or partially closed. A newer method of obtaining an endocervical specimen is to rapidly spin a cytobrush in the endocervical canal. 12 The cytobrush can be placed into a sheath such a short soda straw, the sheath is placed against the cervical os, the cytobrush is advanced into the canal and spun 5 to 10 times, the brush is retracted into the sheath, and the whole apparatus is removed. This can produce a specimen that is more sensitive but slightly less specific than the traditional ECC. 13

To obtain a satisfactory colposcopy, visualization the entire squamo-columnar junction (SCJ) is necessary. When the SCJ or part of a lesion recedes into the endocervical canal, the colposcopist may need to apply pressure near the os with a cotton-tipped applicator in order to open the canal. If this is not adequate for visualization, an **endocervical speculum** may be necessary. {[Kogan endocervical speculum](#). Blades typically come in 2mm, 4mm (shown here) or 6mm sizes. The blades may be inserted into the cervical os and gently opened to allow better visualization.}



The blades of the endocervical speculum are inserted into the canal to gently retract tissue for proper visualization. This procedure is usually not painful unless the os is stretched. Several of these instruments should be made available, since a size should be selected for each patient that is large enough to allow visualization but not so large that it stretches the os. Endocervical speculums come in several sizes, from 2mm for stenotic os to 6mm for large parous os. Some colposcopists remove the thumbscrews or ratchet lock on the endocervical speculums to allow more dynamic and precise control of the instrument.

CHEMICAL AGENTS

Several solutions are used during the colposcopic exam. Normal saline is used as a moistening and cleansing solution during colposcopy. It does not alter the cervical epithelium. It is usually obtained in standard stock bottles from hospital suppliers or from drug stores.

Acetic acid (3%-5%) is used as a contrast solution to enhance the detection of cervical neoplasia during the colposcopic examination. It can be obtained from a supermarket as white vinegar or from a medical supply source. It may be slightly diluted to a 3% solution in an attempt to decrease the stinging sensation to the patient, but this also decreases its time of action on the cervix. Most colposcopists use it straight from the bottle.

Aqueous Lugol's solution is an iodine-based contrast solution that is mainly used when examining the vagina, but it may also be used in cervical colposcopy. **Lugol's solution** is less irritating and just as effective when diluted to half-strength by adding an equivalent amount of tap water or saline. Patients always should be asked about a potential iodine allergy before application of Lugol's solution.

Monsel's solution (Ferric subsulphate) is the most common hemostatic agent used after lower genital track biopsy or excision. It performs best when it has a thick, toothpaste consistency. It can be bought this way or produced by allowing the stock solution to sit exposed to the air in a small open container. This allows evaporation and thickening of the agent, a process that can be enhanced by placing the open container in a warm place, such as on top of a refrigerator. The resulting paste texture can be maintained by keeping the paste in a closed container and by adding small amounts of Monsel's solution whenever the paste becomes excessively thick. Application of silver nitrate sticks and gelfoam are less commonly used methods of hemostasis.

CLINIC NEEDS

A height-adjustable stool is strongly recommended to allow proper back posture for the colposcopist. A height and tilt adjustable table also may help the colposcopist maintain a better posture and also assist in difficult examinations. Table stirrups are usually used for the examination. However, obstetric style knee crutches (padded under-the-knee leg supports) may provide more comfort and less leg strain for the patient. Other useful clinic supplies are shown in Table 2 and a typical mayo tray set-up is shown below.

{Typical Mayo tray set-up for colposcopy. From left to right: cotton balls, Monsel's solution, saline, vinegar, Lugol's iodine, cotton-tipped applicators, rectal swabs (Texas Q-tips), Ring forceps, vaginal speculum, biopsy forceps, ECC curette, endocervical speculum. Additional possible items not shown include benzocaine solution, side-wall retractors, and cervix brush.}



Skin hooks can be used to stabilize tissue or to change the orientation of vaginal epithelium for examination or biopsy. They can cause obscuring bleeding, so should be used sparingly, especially on the cervix. Ring forceps can be used for applying soaked cotton balls to the mucosal surfaces, for removing mucus, and to gently manipulate the cervix. Long-handled scissors, needle driver, and pickups are rarely necessary to stop bleeding from a biopsy site. Although not proven to reduce the pain of biopsy, many colposcopists prefer to use a topical benzocaine solution just prior to biopsy. 14

Sterilization processes are a basic requirement. Bactericidal solutions such as glutaraldehyde can be used for instrument sterilization. Other possible methods of sterilization include gas sterilization and steam autoclaving.

Table 1. Features and Characteristics of Colposcopes

Colposcope Manufacturer	City, State	Phone	Web Address
Accuscope; Vineland Medical Products,	Vineland, NJ	856-692-5140	
Circon/Cryomedics	Racine, WI	888-524-7266 414- 639-7205	www.circoncorp.com/index.html
Cooper Surgical	Shelton, CT	800-645-3760 203-929-6321	www.coopersurgical.com
DFV	19360 NE 22nd Rd North Miami Beach, FL 33179	800-933-0009 305-792-0449 fax	www.dfv.com.br
Gyne-tech Instruments	Burbank, CA	800-496-3832 818-842-0933	
Leisegang Medical, Inc	Boca Raton FL	800-448-4450 561-994-0202	www.leisegang.com
Olympus America, Inc	Melville, NY	800-548-555 631-844-5000	www.olympusamerica.com
Techman International	Charlton, MA	508-248-3211	www.techmaninc.com
Wallach Surgical Devices, Inc	Orange, CT	203-799-2000 800-243-2463	www.wallachsurgical.com
Welch Allyn	Skaneateles Falls NY	800-535-6663 315-685-4100	www.welchallyn.com
Carl Zeiss, Inc	Thornwood, NY	800-442-4020	www.zeiss.com/spd

Computerized Colposcopy Systems	City, State	Phone	Web Address
DenVu LLC	3450 S. Broadmont Dr Suite 108 Tucson, AZ 85713	888-346-7123 520-670-1228 520-670-1241 fax	Email: dims@denvu.com
Welch Allyn	Skaneateles Falls, NY	800-535-6663 315-685-4100	www.welchallyn.com
Leisegang Medical, Inc	6401 Congress Ave Boca Raton, Florida 33487	561-994-0202 800-448-4450	
Cooper Surgical	Shelton, CT	800-645-3760 203-929-6321	

We have tried to be comprehensive but we apologize if we left anyone out by accident. Please contact Dr. Mayeaux (emayea@lsuhsc.edu) with additions or changes.

Table 2. Stock Items Used in Colposcopy

Cotton-tipped applicator
Rectal swabs
Cotton balls to apply solutions or tamponade a bleeding site
Telfa pads for histologic specimens
Formalin
Absorbable suture on a cutting needle to control bleeding
Monse's solution or silver nitrate sticks
4 by 4 inch gauze pads
Cytobrush
Sanitary napkins (for post procedure)

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CERVIX: Colposcopy: Indications

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- III. [Histology of the Normal Cervix](#)
- IV. [Premalignant Lesions of the Cervix](#)
- V. [Invasive Cancer of the Cervix](#)
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Colposcopy is indicated whenever a magnified examination of cervical topography and epithelial character are needed. Common indications include:

- Grossly visible or palpable abnormality of the cervix
- Abnormal cervical cytology
- Positive screening test for cervical neoplasia such as spectroscopy, cervicography, speculoscopy
- Cervical cytology unsatisfactory due to unexplained inflammation
- History of in-utero diethylstilbestrol (DES) exposure
- Unexplained cervico-vaginal discharge
- Unexplained abnormal lower genital tract bleeding
- History of lower genital tract neoplasia (cervical, vaginal, vulvar)
- Post-treatment surveillance

THE CERVIX: Colposcopy: Basic Components of the Colposcopic Exam

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Disclaimer: The following is an introduction to the basic colposcopic examination. The actual performance of colposcopy should be done only after comprehensive didactic and clinical instruction under the supervision of an experienced and well-trained colposcopist. [See ASCCP Mentorship Requirements.](#)

1. Prepare your patient. Obtain informed consent and answer her questions. Assure her you will attempt to minimize pain (often a consuming worry). Make sure to know the pregnancy status of your patient. Ibuprofen 800 mg may be offered prior to procedure or the night before and morning of the procedure, although its efficacy is questionable.
2. A bimanual exam should have been done with the annual exam. If a bimanual examination is needed, perform it here.
3. Quickly examine the vulva for obvious condylomata or other lesions. If cervical biopsy is well-tolerated and things are going well, examine the vagina/vulva after the biopsies as the speculum is withdrawn. The excess vinegar from the cervical exam will often stain the vulva. The vulva can also be examined at the time your patient returns for follow-up and/or definitive treatment.

4. Insert the speculum. Consider the use of vaginal side wall retractors, a Penrose, or glove thumb with obese or multiparous women with vaginal redundancy (pregnancy too, if you develop colposcopy skills with pregnant patients). Warm the speculum with water or water soluble lubricants.



5. Examine the cervix. Is the cervix inflamed or infected-looking (see image to the right)? An active cervicitis confounds colposcopic detail. Do cultures if necessary. Repeat Pap only if this is critical information. Even a correctly performed Pap smear may irritate the cervix and often causes bleeding. Gently blot (not wipe) away any excess mucous using normal saline. Look for leukoplakia and abnormal vessels.



6. Apply 5% acetic acid with a cotton ball held in a ring forceps or a rectal swab. This gently applies lots of vinegar quickly and without trauma. Repeat application every five minutes, as the vinegar effect is only temporary. Warn patients, "this may burn a little." Calling the solution "acetic acid" may help increase the patient's perception of burning. Calling it "vinegar" usually will not.

7. Perform colposcopy. Start with low power (typically 5x). Scan the entire cervix with white light. Use a vinegar-soaked Q-tip to help manipulate the cervix and transformation zone into view if necessary. It is almost never necessary to use a tenaculum to move the cervix. A Kogan endocervical speculum (above) can greatly aid the examination of the distal endocervical canal if necessary. Use higher magnification to carefully document abnormal vascular patterns. The green filter can help find vascular areas.



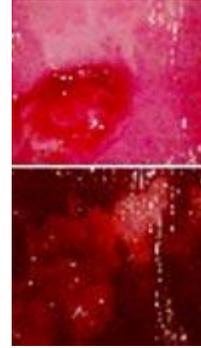
8. Is colposcopy satisfactory? The entire transformation zone, including the entire squamocolumnar junction (shown above), must be visualized. The borders of all lesions also must be entirely seen (not disappearing into the canal for instance) for visualization to be adequate. The uncooperative patient or severely flexed uterus with inadequate visualization are potential causes of inadequate colposcopy. Inadequate colposcopy with cytologic evidence of dysplasia frequently requires cervical cone biopsy for work-up.



9. Mentally map abnormal areas. Remember that colposcopic observation's main goal is to highlight areas for biopsy. It is not, per se, a diagnostic tool. However, acetowhite areas that have sharp geographic borders and a dimension of thickness or roughness are likely to be histologically more severe. Furthermore, all other things being equal, the presence of vessel atypia in any lesion implies more severe dysplasia. Use the following parameters to grade severity of lesions:

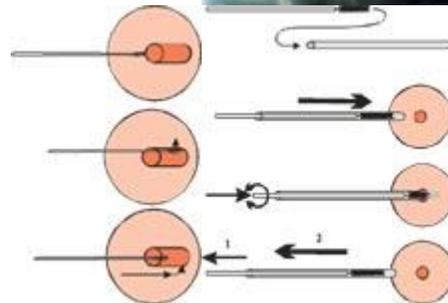
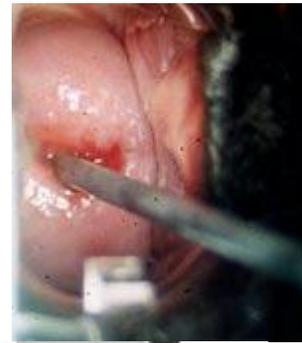
- Mild acetowhite epithelium < Intensely acetowhite
- No blood vessel pattern < Punctation < Mosaic
- Diffuse vague borders < Sharply demarcated borders
- Follows normal contours of the cervix < "humped up"
- Normal iodine reaction (dark) < Iodine-negative epithelium (yellow)
- Leukoplakia - usually a very good (condylomata) or a very bad sign
- Atypical vessels - usually cancer

10. Lugol's solution (Schiller's test) may be used by the beginning colposcopist or at any time when further clarification of potential biopsy sites is necessary. It need not be used in all cases. The sharp outlining afforded by Lugol's iodine (Schiller's test) can be dramatic and very helpful. Iodine staining does not interfere with histology. Lugol's solution is often very helpful on the vagina and proximal vulva (non-keratinized skin). It can be used to thoroughly and simultaneously examine the entire vagina for glycogen-deficient areas, which correlate with HPV and/or dysplasia in non-glandular mucosa. It is often reserved for difficult cases when a non-cervical source of cervical Pap smear atypism is suspected (as in "normal cervical colposcopy" with dysplasia on Pap smear or normal ECC histology).

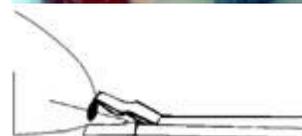


11. If desired, apply topical benzocaine (Hurricane) solution to the entire face of the cervix using a cotton ball, although its efficacy is questionable.

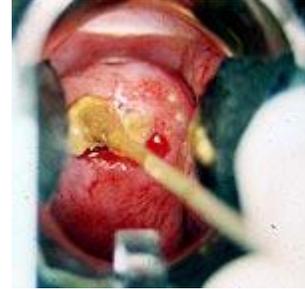
12. Perform an endocervical curettage if indicated. Use a Kevorkian curette (preferably without a basket) and scrape the canal, 360 degrees, twice. The sample appears as a coagulum of mucus, blood, and small tissue fragments. Use ring forceps or a cytobrush to gently retrieve the sample. Submit on paper and label "ECC." Do not do an ECC on pregnant patients. Alternatively, a cervix Pap smear brush (the "pipe-cleaner type brush") may be placed into the os and spun around 5 times. The resulting tissue and blood coagulum may be submitted as a histological specimen in formalin. A short drinking straw may be placed over the brush to act as a sheath to protect the brush from contamination by the ectocervix while the device is being introduced or withdrawn. Place the brush inside the straw and place the straw against the os. Then advance the brush, obtain the sample, and withdraw the brush back into the straw for removal. This results in sensitivity about the same as the Kevorkian curette with a higher specificity.



13. Perform cervical biopsy. Begin by mentally mapping a biopsy strategy. Biopsy posterior areas first to avoid blood dripping over future biopsy sites. The cervix can be manipulated with a Q-tip or hook if necessary to provide an adequate angle for biopsy. A depth of 3 mm is typically all that is necessary. Always include the area with vessel atypism in at least one biopsy site. It is not necessary to include normal- appearing tissue with biopsy samples (i.e., biopsy the margins of lesions). Beginning colposcopists can enhance their skills initially by separating samples from different biopsy sites in different bottles and subsequently correlating them with colposcopic impression. If bleeding is profuse from a particular site and more biopsies are needed, apply a Q-tip to the area and proceed with the next biopsy. Do not apply Monsel's solution until all biopsies are completed. Monsel's will ruin good histology.



14. Apply pressure and Monsel's solution to bleeding sites. The Monsel's should be as thick as toothpaste to be most effective. Swab out the excess Monsel's and blood debris, which appears as a nasty black substance that eventually will pass, possibly causing alarm (and potential late night phone calls).



15. Gently remove the speculum and view the vaginal wall collapse around the receding blades of the speculum. Are any abnormal areas apparent?
16. Have the patient rest supine for at least several minutes and then sit up slowly and rest again. Fainting and light-headedness are not uncommon.
17. Carefully draw and label a picture of lesions and biopsy sites. Correlate the pictures with the submitted samples, if placed in different containers.
18. Provide careful post-procedure instructions. Advise no douching, intercourse, or tampons until spotting subsides (or until return visit). Patients are instructed to return for foul vaginal odor or discharge, pelvic pain, or fever. Tylenol, ibuprofen, or Aleve may be used for cramps (if any). Otherwise, follow-up is usually in 1 to 3 weeks to discuss histology results.

THE CERVIX: Colposcopy: Colposcopic Appearance of Benign Lesions

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The International Federation for Cervical Pathology and Colposcopy classification system categorizes the findings of keratosis, erosion, inflammation, atrophy, decidualosis, and polyps under the miscellaneous category. An appreciation of these benign colposcopic findings is essential.

Keratosis or leukoplakia: Lesions that appear white on visual inspection of the cervix prior to the application of acetic acid are termed keratosis or leukoplakia. Microscopy of these lesions reveals a thick hyperkeratotic or parakeratotic surface. Located within or outside of the transformation zone, keratotic lesions are raised and bright white. Leukoplakia is a nonspecific finding and may arise secondary to trauma such as with diaphragm or pessary use, human papilloma virus infection or even invasive keratinizing squamous carcinoma. Biopsy is necessary to establish the exact diagnosis.



Erosions and Ulcers: Simply defined, an erosion arises from denuded epithelium which exposes the underlying stroma. Ulcers are deeper and involve the underlying cervical stroma. They may be secondary to trauma, such as insertion of a speculum or from tampon use. The edges of traumatic erosions are sharp and consist of normal epithelium. High grade neoplastic lesions are easily denuded and may appear as a erosions with a peeling, rolled back margins of markedly atypical epithelium. Ulcerations may also result from infectious agents such as herpes virus. The base of the infectious ulcer is necrotic and contains inflammatory debris. Concern always exists that the ulceration is secondary to an underlying invasive neoplasm. Biopsy may be necessary, especially with persistent ulcers or erosions.



Cervicitis: Cervicitis may make Pap interpretation more difficult and less accurate, and make colposcopic assessment more difficult. Cervicitis secondary to trichomoniasis results in coalescent erythematous patches giving a reverse punctation also called a "strawberry cervix". The mucopurulent cervicitis of chlamydia and gonorrhea is associated with prominent vascularity and hypertrophy of the cervical ectropion. Many authorities recommend diagnostic tests and any indicated treatment before biopsy when any cervicitis (STD) or severe vaginitis is strongly suspected.



Atrophy: Prolonged hypoestrogenization results in a thin, friable epithelium. Iodine staining is negative or demonstrates only partial (stippled) uptake due to a lack of glycogenation of the squamous epithelium. Vascularity is prominent with fine, branching capillaries. The tissue is thin, easily traumatized and petechiae or small submucosal hemorrhages may be present.



Nabothian cysts: Single or multiple, the translucent cysts appear yellow and can be as large as several centimeters. Formation occurs secondary to blockage of mucin secreting endocervical crypts by overlying metaplastic squamous epithelium. Nabothian cysts are always located within the transformation zone. Prominent large vessels are often noted overlying the attenuated epithelial surface of the cyst. On close inspection, the vessels arborize normally and are not atypical (disorganized) in appearance. Nabothian cysts are normal. They do not require any treatment.



Ectopy: Ectopy results from eversion of the squamocolumnar junction onto the portio cervix or in rare cases, the vagina. On gross appearance, the everted columnar epithelium appears velvety red and on close inspection the typical villi of the endocervical mucosa are readily apparent. Iodine uptake is negative because columnar epithelium is not glycogenated. Varying stages of squamous metaplasia may be present throughout the surrounding current squamocolumnar junction or as fine acetowhite islands within the endocervical mucosa. Cervical ectopy is most pronounced in adolescence and the first pregnancy when squamous metaplasia is most active. It is also common with the use of oral contraceptives. It is an entirely normal finding, and does not warrant any kind of diagnostic or therapeutic response.



Deciduosis: During pregnancy, the stroma of the cervix may undergo focal decidual change which appears as a raised plaque or a pseudopolyp. This polypoid surface irregularity with prominent vascularity may mimic a high grade lesion or cancer.

Endometriosis: Implantation of endometrial glands and stroma may be secondary to cervical trauma. Endometriosis usually presents as small blue or red surface nodules, a few millimeters in diameter, located on the portio or in the cervical canal.

Endocervical polyps: Focal hyperplastic growth of endocervical epithelium and stroma results in polyp formation. Polyps arise within the endocervical canal and protrude out the cervical os. Erythema is due to the increased vascularity and inflammation. Squamous metaplasia may occur on the surface of the polyp. Friability and ulceration of the polyp may account for postcoital spotting. Polyps can be neoplastic, and may be the presenting sign of cervical neoplasia or endometrial cancer. They should be biopsied or removed for histologic evaluation.

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THE CERVIX: Colposcopy: High Grade Cervical Intraepithelial Neoplasia: Cytology, Histology, & Colposcopy

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HSIL TERMINOLOGY

A high-grade squamous intraepithelial lesion (HSIL) is a cytologic or histologic abnormality that encompasses nuclear and other cellular changes indicative of pre-invasive squamous neoplasia of a moderate to severe nature. This terminology came into use in 1988 with the creation of the Bethesda System, which standardized the nomenclature used for cervical cytology classification. "HSIL" is also used for histologic interpretations. In terms of previously accepted nomenclatures, HSIL encompasses the disease spectrum from moderate dysplasia / cervical intraepithelial neoplasia grade 2 (CIN 2) to severe dysplasia / cervical intraepithelial neoplasia grade 3 (CIN 3) and carcinoma-in-situ (CIS).

Cervical squamous intraepithelial lesions constitute a spectrum of disease. The divisions between CIN 2, CIN3, and CIS are arbitrary and subjective. The distinction between these grades of disease on cytology or histology specimens is characterized by low inter- and intra-observer reproducibility. The use of the HSIL terminology clearly communicates an abnormality at the more severe end of the disease spectrum and is a more reliable, reproducible way to classify lesions with malignant potential.

CLINICAL SIGNIFICANCE OF HSIL

HSIL lesions are asymptomatic and invisible to unaided visual examination. In 1990, 70,000 cases of HSIL were treated in the United States. The incidence of HSIL appears to be increasing. The modal age at diagnosis has decreased from 35 in the 1960s to 25 in the 1990s. These are worrisome trends. HSIL lesions have significant malignant potential. It is estimated that 30 to 50% of HSIL lesions will progress to invasive disease if left untreated. Moderate dysplasia (CIN 2) lesions exhibit progression and spontaneous regression rates intermediate to those of mild and severe dysplasia. Spontaneous regression may occur in up to 40% of CIN 2 lesions. Nonetheless, HSIL lesions diagnosed by histopathology are treated because of their malignant potential. The 2001 ASCCP Consensus Guidelines do allow for the close follow-up of small CIN 2 lesions in adolescents. This carries with it serious risk if the patient is noncompliant to follow-up.

VIROLOGY OF HSIL

HSIL is strongly associated with oncogenic (high-risk) types of human papilloma viruses (HPV). Infection with high-risk HPV is essential to the development of cervical cancer. Such infection is very common in the general population and is asymptomatic and not apparent without special means of detection (subclinical infection). Low-risk, warty infections are productive of new viral particles and therefore demonstrate cytopathic HPV effects (koilocytosis) typical of LSIL. However, in HSIL, HPV infection is not productive and is instead transforming, with oncogenic HPV becoming integrated into host DNA. The cytopathic effects seen in LSIL lesions are less pronounced or absent in HSIL cytology and histology. Integration of the HPV DNA into the host (human) DNA leads to the over-expression of the viral E6 and E7 genes. This interferes with the function of host tumor suppressor gene products. This can lead to the development of cervical neoplasia. HSIL lesions are usually monoclonal. Their infectivity, as compared with low-risk, productive HPV infections, is uncertain.

HSIL AND CYTOLOGIC SCREENING

- The cytologic diagnosis of HSIL is more frequent with liquid-based cytology. This suggests, but does not prove, that liquid-based cytology may be more sensitive for HSIL than conventional smears. Nonetheless, conventional smears remain an acceptable and effective technique for cervical cancer screening.
- HPV DNA testing is of no use for Pap smears read as HSIL since over 90% are HR-HPV DNA positive.
- Due to the significant false-negative rate of a single Pap smear, cytology should not be relied upon or delay the evaluation of a patient whose history and / or physical exam are suspicious for cervical cancer.

HSIL CYTOLOGY

- Relatively small cells
- Abnormal cells may be isolated or in groups
- Round or oval cells with nuclear pleomorphism
- Hyperchromatic, granular chromatin
- Denser, thin rim of basophilic cytoplasm

HSIL SITE AND TOPOGRAPHY

- HSIL lesions are usually within the transformation zone; the most severe disease is found at the most proximal (cephalad) extent of lesion.
- May extend into endocervical canal
- Usually single lesions
- May be located alongside or within low-grade lesions

- Size of lesions variable but tends to correlate with severity of disease and risk of occult invasion
- Size of lesion correlates with risk of treatment failure



HSIL COLPOSCOPY

Normal Saline and Green Light Filter:

Colposcopy of HSIL cytology should start with the application of normal saline to remove mucous, and allow visualization of any obvious findings indicative of invasive cancer such as erosion, surface contour abnormality, leukoplakia, or exophytic lesions. The prominent, abnormal vascular patterns of HSIL and cancer can be more visible before the application of acetic acid and should be looked for with the aid of a red-free (green) filter.

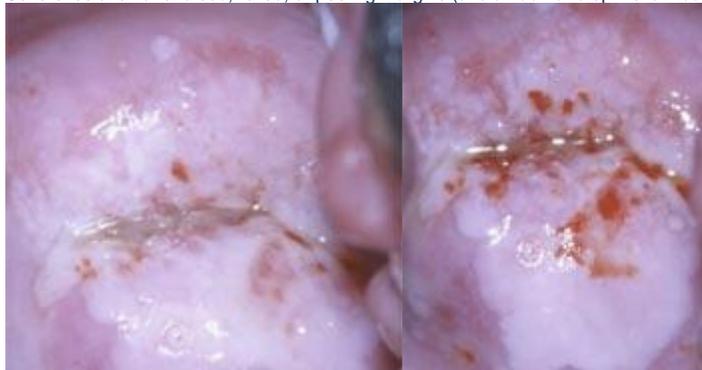
Acetic Acid and Lugol's Iodine:

The next step is the application of 3 to 5% acetic acid to the cervix. This should be done in a manner without abrading the surface epithelium, as HSIL lesions can detach from the underlying stroma relatively easily and peel away. Lesion margins, color, and vascular patterns are then assessed and graded, with biopsies taken from the areas that are judged as the most severe. The application of Lugol's iodine is optional. It may help determine the most abnormal area if there is extensive disease, or assist in locating a lesion when none is apparent after the application of acetic acid.

The following descriptions refer to the colposcopic appearance of HSIL lesions after the application of acetic acid.

Margins:

- Sharply demarcated lesion edges, often with very straight contours; lack the geographic, feathered, or indistinct margins of LSIL.
- HSIL often coincides with and may be difficult to distinguish from a larger LSIL lesion. Internal margins (borders) describe abrupt change in the nature of a lesion(s) as the examining eye moves radially from outer to inner (proximal) transformation zone. A so-called "lesion within a lesion" or "border within a border" is a feature of high-grade neoplasia, with the inner, more proximal lesion being more severe.
- Severe lesions have raised, rolled, or peeling margins (avoid trauma to epithelium during exam).



Color:

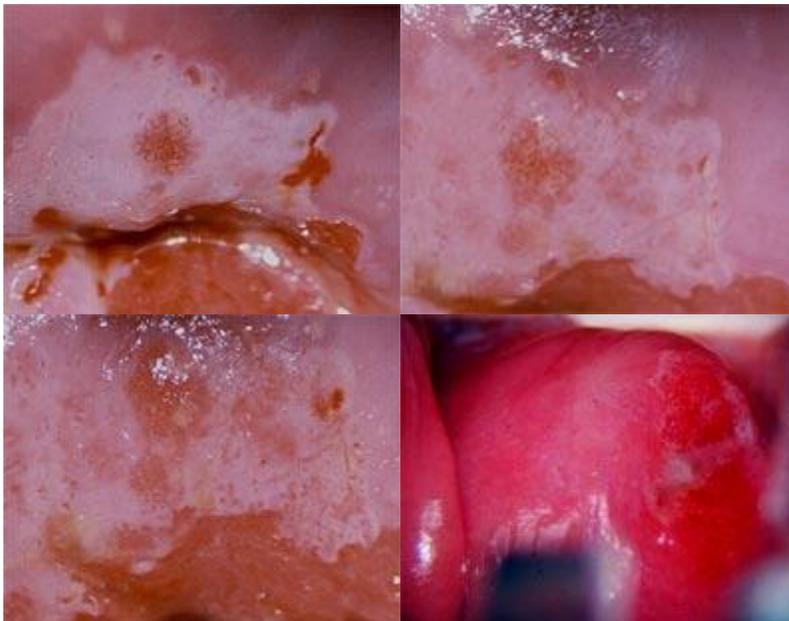
- Distinct, denser acetowhitening than LSIL lesions
- Dull surface due to increased nuclear density and less reflection of incident light
- Dull or gray-white to oyster gray color

- More prompt and persistent aceticowhite change



Vascular Pattern:

- Fine vascular patterns of normal and LSIL epithelia absent
- Absence of vessels due to increased lesion density and occlusion small of vessels consistent with HSIL
- "Coarse" vascular patterns (punctuation, mosaicism, or both) characterized by:
 - Larger and varied caliber of vessels
 - Larger and variable intercapillary distances
 - "Umbilicated" mosaic patterns, with punctuation in the middle of the "tiles" suggests CIN 3 / carcinoma-in-situ.
 - Vascular patterns can be striking and visible even at lower magnification
 - Vascular patterns change as acetic acid effects develop, then fade: keep watching!
 - Prominent and dilated vessels may blunt acetowhite change; Don't miss the HSIL or invasive cancer because the examining eye is drawn to acetowhite change and away from the less-white HSIL or cancer!



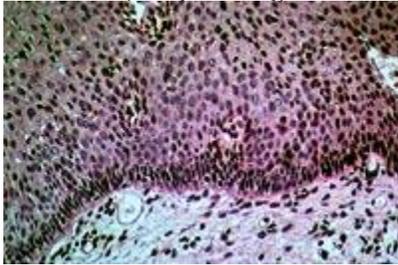
Iodine Staining:

HSIL lesions are strongly non-staining with the application of Lugol's iodine; appearing bright yellow or pink. (Normal epithelium stains dark purple-black or brown with iodine in estrogenized women because it is glycogenated).

Histology of HSIL

- Cellular maturational abnormality extends into the upper third of the epithelial thickness; basement membrane intact

- Cellular and especially nuclear hyperchromasia and pleomorphism; some mitoses may be seen



THE CERVIX: Colposcopy: Colposcopic appearance of malignant lesions

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The most important goal of the colposcopist is to rule out the presence of invasive disease. More advanced disease is often accompanied by a history of menorrhagia or other types of abnormal bleeding. Early invasive disease is commonly asymptomatic, and colposcopy allows diagnostic at a potentially curable stage.

SQUAMOUS LESIONS

Early squamous cancer of the cervix usually presents as very thick white epithelium (either acetowhite or leukoplakia) with uneven density, giving the appearance of piling of thick keratotic layers upon each other. The surface is, therefore, irregular but the borders tend to be sharply defined. In some cases, subtle ulceration can be the only feature present, and may be missed by the inexperienced examiner. Invasive cancer should be suspected in the presence of multiquadrant, high grade disease with extension into the endocervical canal. Areas of coarse punctuation and mosaicism are usually visible in the periphery of the thick, white, "mountain range"-like epithelium. Atypical vessels, which are highly variable in caliber and form, are the hallmark of invasive neovascularization. Not infrequently, hemorrhagic changes and easy contact bleeding are found. Later stages of cervical cancer defy the need for colposcopy, as large, ulcerated lesions are visible without magnification. A punch biopsy of the periphery of the lesion rather than any ulcerated portion becomes instrumental for pathological diagnosis.



1

- 1: Early Invasive Squamous Cell Carcinoma
- 2: Advanced Squamous Cancer
- 3: Microinvasive Cancer
- 4: Invasive Cervical Cancer



2



3



4



GLANDULAR LESIONS

The diagnosis of adenocarcinoma in situ or early invasive adenocarcinoma of the cervix is one of the most challenging aspects of colposcopy. The colposcopic findings are often subtle and nonspecific for entities that are clinically infrequent. The stark acetowhitiness of fused, irregular heaps of glandular villi can be seen in the transformation zone and maybe surrounded by completely normal glandular epithelia. Glandular neoplasia is often accompanied by high grade squamous dysplastic lesions. The vascular patterns are usually less striking than in squamous dysplasia or early cancer. Some describe the vascular changes associated with glandular dysplasias as "tendrill-like".

Adenocarcinoma in situ

THE CERVIX: Cervical Cancer Screening and Colposcopy During Pregnancy

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INTRODUCTION

This section is intended to reinforce the importance of cervical cancer screening and introduce the use of colposcopy during pregnancy. Cervical cancer screening has become a standard part of routine prenatal care. Colposcopy during pregnancy, in response to cervical cytological (Pap) abnormalities, is more challenging technically than in the nonpregnant patient. It is our recommendation that colposcopy of pregnant women be done by experienced colposcopists, as the challenges encountered may discourage the novice colposcopist. Additionally, a lack of experience can cause abnormalities to be overlooked or misinterpreted.

EPIDEMIOLOGY OF CERVICAL CANCER DURING PREGNANCY

It is rare to find invasive cancer of the uterine cervix in pregnancy. Nonetheless, cervical cancer is the most common cancer diagnosed during pregnancy. An increase in the incidence of invasive cervical cancer in younger women is suspected. Women are delaying child-bearing later than ever in history. These trends together may work together to make cervical cancer more common during pregnancy in the future. Currently, the incidence of cervical cancer varies from 1 to 15 cases per 10,000 pregnancies. The mean age of diagnosis is 34 years. The incidence of each stage at diagnosis is 83% Stage I, 10% Stage II, 3% Stage III, 2% Stage IV. Stage for stage, the prognosis is similar to that of nonpregnant patients. It is fortunate that over 80% of these cases are Stage I at presentation.

Obtaining a cervical smear is a standard component of routine antenatal care in the U.S., usually at the first prenatal visit. The objective of evaluating an abnormal cervical cytology during pregnancy is to exclude the presence of invasive cancer. Treatment of preinvasive disease is deferred until postpartum, after complete reassessment has taken place.

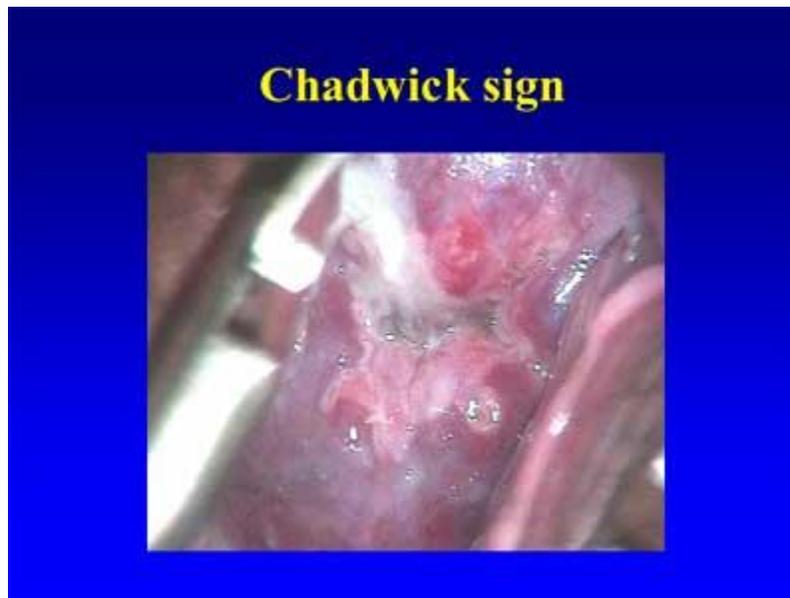
MANAGEMENT OF ABNORMAL CERVICAL CYTOLOGY DURING PREGNANCY

The NIH / ASCCP sponsored 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities state:

- It is preferred that the colposcopic evaluation of pregnant women with HSIL be conducted by clinicians who are experienced in the evaluation of colposcopic changes induced by pregnancy.
- Biopsy of lesions suspicious for high-grade disease or cancer is preferred; biopsy of other lesions is acceptable.
- Endocervical curettage is unacceptable in pregnant women.
- Since unsatisfactory colposcopy may become satisfactory as the pregnancy progresses, it is recommended that women with an unsatisfactory colposcopy undergo a repeat colposcopic examination in 6-12 weeks.
- In the absence of invasive disease, additional colposcopic and cytological examinations are recommended, with biopsy only if the appearance of the lesion worsens or cytology suggests invasive cancer.
- Unless invasive cancer is identified, treatment is unacceptable.
- A diagnostic excisional procedure is recommended only if invasion is suspected.
- Re-evaluation with cytology and colposcopy is recommended no sooner than 6 weeks postpartum.

COLPOSCOPIC APPEARANCE OF THE CERVIX DURING PREGNANCY

The hormonal changes of pregnancy produce dramatic alterations in the colposcopic appearance of the cervix. Increased vascularity produces a cyanotic, bluish hue.



Increased vascularity, stromal edema, and stromal hypertrophy, cause marked enlargement of the cervix.

Vaginal wall laxity limiting visualization



Vaginal wall laxity and increased cervical mucus also may make visualization of the cervix more challenging.

Chadwick sign and thick cervical mucous



On the other hand, progressive eversion of the squamocolumnar junction onto the ectocervix makes colposcopy satisfactory more often. Grading of lesions is more difficult than in the nonpregnant patient.

Large transformation zone with active squamous metaplasia



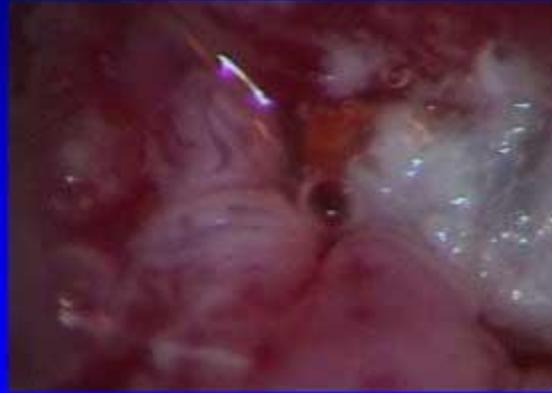
Pregnancy triggers very active squamous metaplasia which shows an exaggerated acetowhite change in response to acetic acid. Increased vascularity and stromal edema can cause a decrease in acetowhitening but an exaggeration of vascular patterns.

HSIL in pregnancy



Decidual changes can be confusing, and may even have features consistent with invasive cancer, such as yellow coloration, topography changes, and atypical appearing vessels.

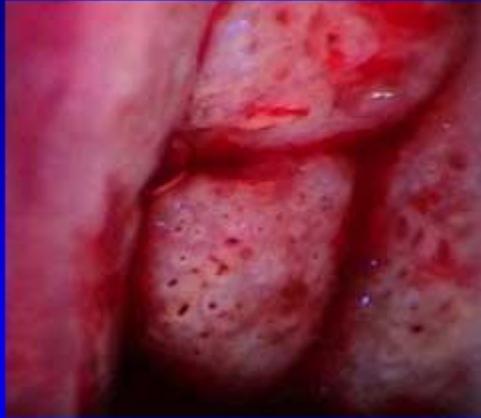
Atypical Vessels



Colpo in Sections



Carcinoma in situ



THE COLPOSCOPIC EXAMINATION DURING PREGNANCY

Colposcopy and directed biopsies are safe to perform during pregnancy. They do not increase risk of adverse pregnancy outcome. Due to less accurate lesion grading during pregnancy, and the small chance of missing an invasive cancer, directed biopsy should be considered for high-grade appearing lesions and for any lesion in the presence of a high grade cytological abnormality. Experienced colposcopists may elect to omit biopsies of low-grade appearing lesions, especially if the cervical cytology is also low-grade.

LSIL in Pregnancy



While colposcopy during very early pregnancy is not much different than in nonpregnant patients, adaptations of technique are generally needed. In the third trimester, it is wise to elevate the patient's right hip slightly with a folded sheet to prevent supine hypotension, which can cause distressing flushing, discomfort, nausea, and vomiting in some patients. The use of a larger speculum and a vaginal sidewall retractor may be needed to provide unhindered access to the cervix. If a sidewall retractor is unavailable, a condom, latex glove finger, or ultrasound probe sheath with the tip removed may be rolled onto the speculum for better visualization. Tenacious endocervical mucus, the so-called "mucous plug," is encountered in pregnancy. The routine application of 5% acetic acid is mucolytic and will aid in mucus removal. Doing so is in no way harmful. Use of sponge or ring forceps may also be used to carefully to remove viscous mucus. Due to progressive cervical enlargement, it may be necessary to perform colposcopy of cervical quadrants.

Colpo in Sections



The increased vascularity of the cervix in pregnancy can cause bleeding even with minimal trauma, including speculum insertion and performance of the Pap test. Therefore, biopsies are expected to bleed more during pregnancy. The colposcopist should be experienced in achieving hemostasis, using sponges, pressure, and Monsel's paste as needed. Serious bleeding requiring suturing or packing is rare (<1%), and can nearly always be avoided with prompt pressure, then a well-aimed swab with Monsel's, to the biopsy site. Colposcopy with biopsy has not been shown to cause preterm labor, but judgement and caution should be used when performing colposcopy on patients with histories of past preterm deliveries, or when applying Monsel's paste when the cervical os is open.

CLINICAL RESPONSE TO NEOPLASIA IN PREGNANCY

Preinvasive disease and microinvasive cancer of the cervix is not treated during pregnancy. The only indication to treat during pregnancy is histologically confirmed, frankly invasive cancer.

Historically, cervical conization was used for diagnosis and treatment of dysplasia and cancer. Fortunately, conizations are rarely indicated during pregnancy since the introduction of colposcopy. Conization in pregnant patients is associated with a 12% hemorrhagic complication rate, a 5% perinatal mortality, and a preterm labor rate of 30%. Therefore, conization is reserved for the rare cases in which invasive cancer is strongly suspected by cytology, histology, or colposcopic impression, but less invasive evaluation is inconclusive. Expert colposcopic evaluation and consultation with the pathologist are critical before the decision is made to perform cervical conization in the pregnant patient. Conization during pregnancy is not performed for unsatisfactory colposcopy, even in the presence of a high grade lesion, unless invasive cancer is suspected. Instead, colposcopy is repeated at intervals until the examination becomes satisfactory, which occurs by the second trimester in most cases.

The diagnosis of invasive cancer in pregnancy dictates referral to and management in conjunction with a gynecological oncologist. Vaginal delivery is avoided in the presence of frankly invasive cancer; the preferred method of delivery of a viable pregnancy is by cesarean section with radical hysterectomy.

POSTPARTUM REEVALUATION

The likelihood of disease progression during pregnancy is small. Regression is more likely; the incidence of this ranges widely in the literature, from approximately 12% to 70%. It is controversial whether severity of disease diagnosed and route of delivery influence postpartum persistence. Patients should be reevaluated at least six weeks postpartum to allow healing to occur. Treatment, if indicated, should be based on the grade and location of disease identified postpartum.

Postpartum Colposcopy



Persistent HSIL 2 months postpartum

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THE CERVIX: Invasive Cancer of the Cervix

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Cervical cancer is a relatively uncommon finding in comparison to the number of cases of CIN diagnosed annually in the US. In 2000, the incidence of invasive cervical cancer was estimated at 12,800 cases, and there were 4,600 cervical cancer related deaths. In other parts of the world that lack screening programs, cervical cancer is still the most common cancer among women. The major focus of colposcopic assessment of abnormal cervical cytology is to detect cancer. In order to accomplish this goal, one must maintain a high index of suspicion and stick with standard triage protocols such as assuring adequacy of the examination and a good correlation between cytology, colposcopy and biopsy findings.

Since cervical cancer is a relatively rare finding in a routine colposcopic practice, the colposcopist should be aware of the hallmark features of invasive cancer and look for these features with each patient they evaluate.

CHARACTERISTIC FEATURES OF CERVICAL CANCER

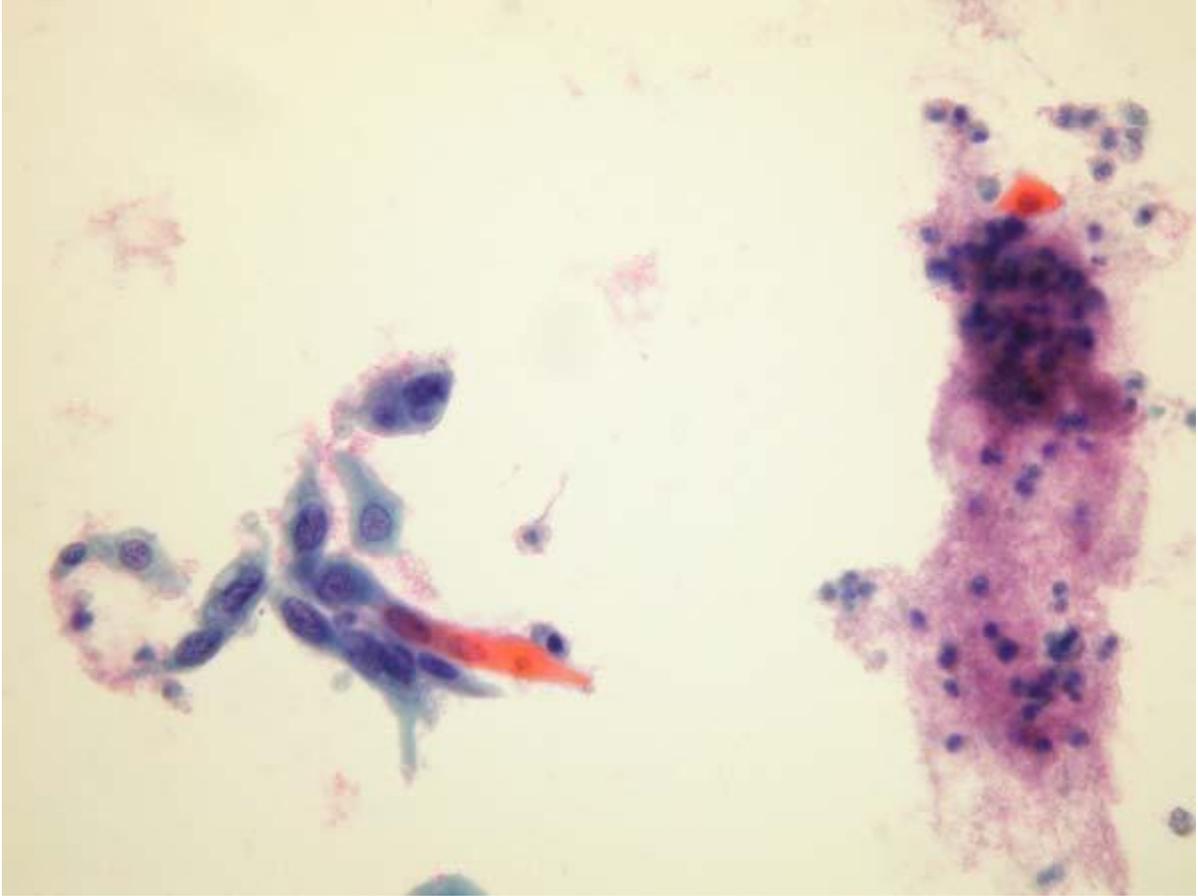
- Atypical vessels-non branching (commas, corkscrew, sausage shaped, hairpin)
- Abnormal vaginal bleeding or discharge
- Ulcerations
- Raised, irregular surface
- Yellow color to epithelium
- Firmness to palpation

As a cancer of the cervix develops, neovascularization occurs as the result of tumor angiogenic factor released by the cancer cells. These vessels do not follow the normal regular arborizing vessel pattern, but instead the new vessels have irregular course and caliber. They can run parallel to the surface of the cervical epithelium and form non-branching patterns such as corkscrews, squiggles and comma shaped vessels. Routine use of a green filter can assist the colposcopist in assessing vessel patterns at the time of colposcopy.

DIAGNOSIS

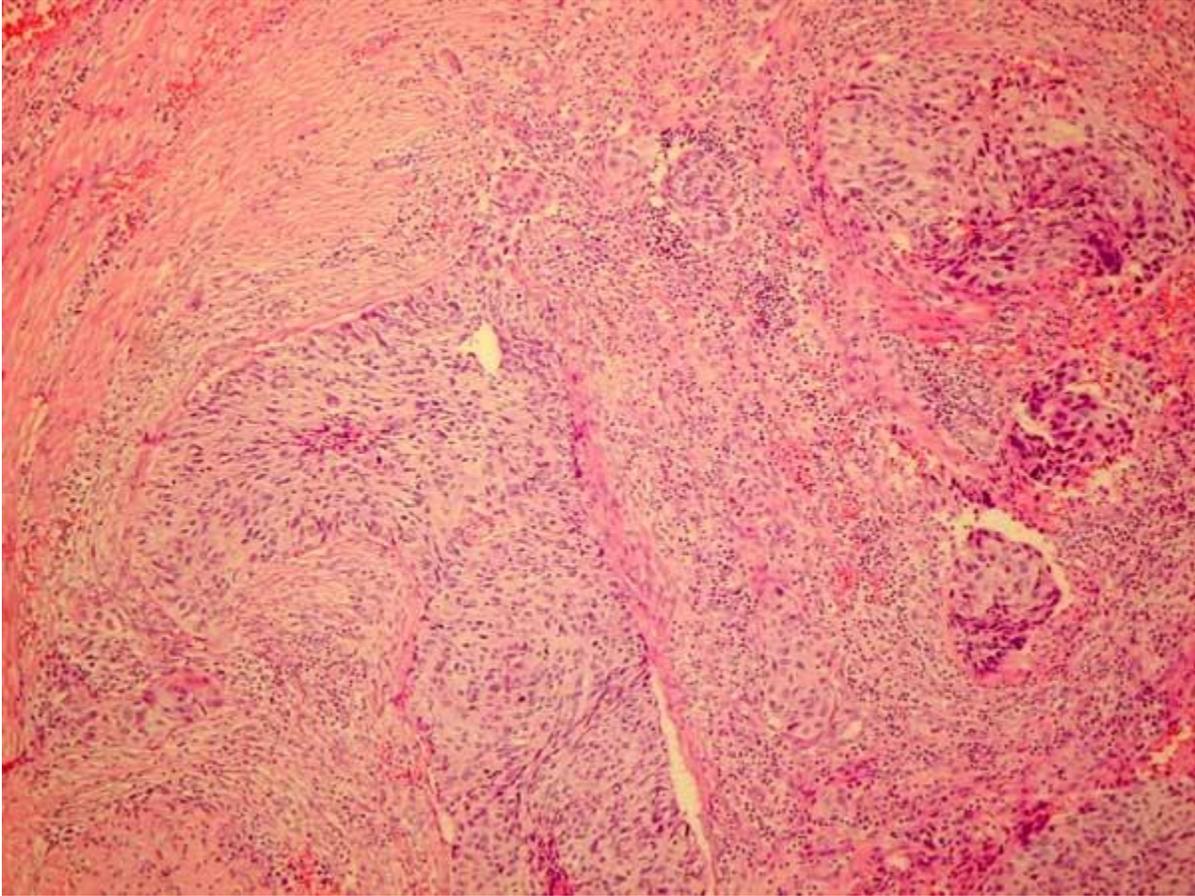
Cytologically, squamous cell cancer can be either keratinizing or non-keratinizing. Cells can occur in syncytial-like clusters or singly, and demonstrate very irregular chromatin clumping, nucleoli, and may have a background tumor diathesis of blood and cellular debris.

Cancer (cytology) (Liquid based-Papanicolaou stain x 400): Irregular cell forms; nuclei are enlarged with prominent nucleoli. The cell cluster at right shows diathesis (“cotton candy necrosis”).



Colposcopically, cervical cancer can be a challenge to diagnose, especially microinvasive cancer since atypical vessels or other signs of more advanced disease may not be present. This reinforces the fact that one must maintain a high degree of suspicion and effectively address any discrepancies between colposcopy, cytology and histology before therapy is initiated, particularly ablative therapy. Cervical cancer can be squamous, glandular or mixed type. Invasion is diagnosed when there is a breach in the basement membrane. If the invasion extends 3 mm or less, it is referred to as microinvasive disease. If invasion is greater than 3mm, it is frankly invasive cancer.

Squamous cell carcinoma (H&E x 400): Irregular nests of malignant squamous cells in a fibrotic stroma (desmoplasia).



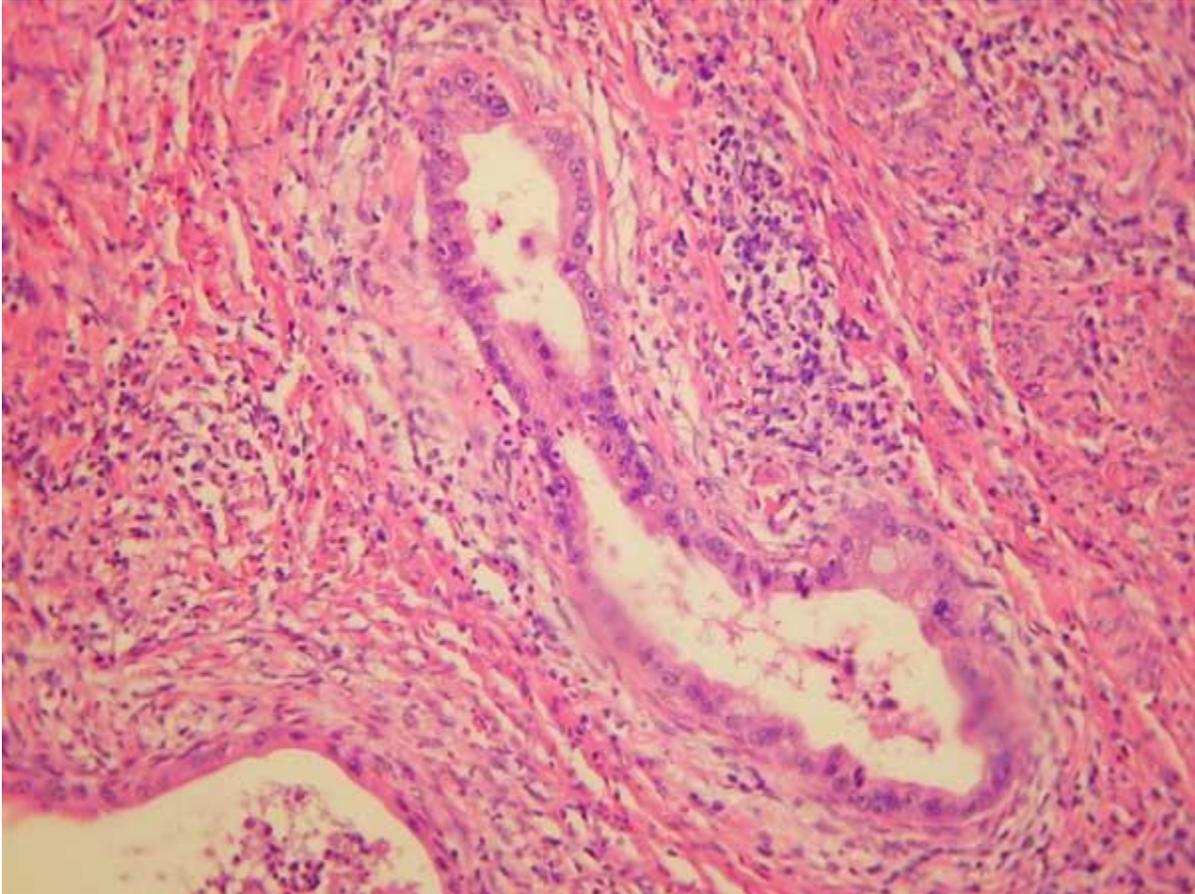
If biopsy or endocervical curettage reveals invasive cancer, a cone biopsy is not needed.

EPIDEMIOLOGY

There are approximately 12,800 new cases/year and around 4600 deaths/year in the United States. There are 50,000 new cases carcinoma in situ/year. There are 2 major histological types of cervical cancer. 93% are squamous cell cancers and contain HPV DNA; 90% are subtypes 16/18, which are most virulent. 7% of cases are adenocarcinomas -- but these are on the rise. Adenocarcinomas are associated with HPV type 18.

When considering preinvasive disease, the classic theory holds that SIL leads to squamous carcinoma. When SIL progress to invasive squamous cervical cancer, ISCC usually develops from an area of SIL located adjacent to the SCJ. Oncogenic HPV serves as initiators. Other factors relating to immune status such as cigarette smoking, nutrition, or chlamydia infections may be promoters. Adenocarcinoma develops from glandular atypia and may be preceded by an Atypical Glandular Cells of Uncertain Significance (AGUS) Pap smear. The only preinvasive stage we usually find is adenocarcinoma in situ (AIS)

Adenocarcinoma (H&E x 400): Irregularly shaped glands within a fibrotic inflamed stroma (desmoplasia). Cells are highly atypical; the nuclei contain prominent nucleoli. Higher power



The median age to develop cervical cancer is 45 to 50 years. Older women are often more susceptible due to lack of screening. Younger women have more problems with rapidly progressing disease. 50% of women diagnosed with invasive cancer have never had a Pap smear. 10% have not had a Pap smear in last 5 years.

STAGING OF CERVICAL CANCER

Stage 0 carcinoma-in-situ

Stage I the tumor is confined to the cervix

IA microinvasive disease, with the lesion not grossly visible: no deeper than 5 mm and no wider than 7 mm

IA1 invasion <3 mm and no wider than 7 mm

IA2 invasion >3 mm but <5 mm and no wider than 7 mm

IB larger tumor than in IA or grossly visible, confined to cervix

IB1 clinical lesion no greater than 4 cm

IB2 clinical lesion greater than 4 cm

Stage II extends beyond the cervix, but does not involve the pelvic side wall or lowest third of the vagina

IIA involvement of the upper 2/3 of vagina, without lateral extension into the parametrium

IIB lateral extension into parametrial tissue

Stage III involves the lowest third of the vagina or pelvic side wall, or causes hydronephrosis

IIIA involvement of the lowest third of the vagina

IIIB involvement of pelvic side wall or hydronephrosis

Stage IV extensive local infiltration or has spread to a distant site

IVA involvement of bladder or rectal mucosa

IVB distant metastases

TREATMENT AND SURVIVAL

Treatment of frankly invasive cancer usually consists of a radical hysterectomy with lymph node dissection, or radiation therapy with advanced disease. If the biopsy reveals microinvasive disease, a cone biopsy is required, since a biopsy alone is insufficient to rule out frankly invasive cancer, which may be adjacent to the biopsy site. If a cold cone or loop excision reveals microinvasive cervical cancer with clear margins, treatment can include a simple hysterectomy or, if the patient desires to maintain her fertility, observation with careful follow-up.

Stage IA-- 5-year survival 95%

- simple hysterectomy or careful observation after cone biopsy (With clear margins).

Stage IB or IIA-- 5-year survival 70% to 85%

- radical hysterectomy with pelvic-node dissection, or
- external beam and intracavitary radiotherapy (equally effective)

Stage IIB, III, IVA--5-year survival 65%, 40%, 20% respectively

- pelvic radiotherapy
- Treatment with cisplatin-based chemotherapy should strongly be considered for patients receiving radiotherapy 14

Stage IVB-- 5year survival 10%

- chemotherapy with or without pelvic radiotherapy

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