CLINICAL GYNECOLOGIC ONCOLOGY

NINTH EDITION

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We dedicate this book in memory of our friend, colleague, and co-editor, Dr. Scott McMeekin, who recently lost his own battle with cancer at 51 years of age. Readers of this book are undoubtedly familiar with his name because he authored more than 100 publications in the field of gynecologic oncology, and his expertise in uterine cancer placed him at the forefront of defining the standard of care for the management of this disease. His dedication to helping women with gynecologic cancers was only surpassed by his dedication to his wife Cathy; their children Charlotte, Jackson, and Remy; and his loving parents, Donald and Charlene. Although we will benefit from his scientific contributions for years to come, we will all miss his presence.

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PREFACE

The first eight editions of *Clinical Gynecologic Oncology* were stimulated by a recognized need for a readable text on gynecologic cancer and related subjects addressed primarily to the community physician, resident, and other students involved with these patients. The practical aspects of the clinical presentation and management of these problems were heavily emphasized in these editions, and we have continued that style in this text. As in every other textbook, the authors interjected their own biases on many topics, especially in areas where more than one approach to management has been used. On the other hand, most major topics are treated in depth and supplemented with ample references to current literature so that the text can provide a comprehensive resource for study by the resident, fellow, or student of gynecologic oncology and serve as a source for review material.

We continued the practice of placing an outline on the first page of each chapter as a guide to the content for that section. We added "bullet" points to the chapters of this edition to emphasize important areas. Readers will notice that we have included topics not discussed in the former editions and expanded areas previously introduced. Some of these areas include new guidelines for managing dying patients; current management and reporting guidelines for cervical and vulvar cancer; current management and reporting guidelines for breast cancer; expanded discussion on the basic principles of genetic alterations in cancer; techniques for laparoscopic surgery in treatment of gynecologic cancers; and new information on breast, cervical, and colon cancer screenings and detection. The seventh edition contained, for the first time, color photographs of key gross and microscopic specimens for readers' review; we have continued that in this edition. In addition, Drs. Di Saia and Creasman have handed the reigns over to the three associate editors. We have included several new authors. Much more information is included to make the text as practical as possible for the practicing gynecologist. In addition, key points are highlighted for easy review.

Fortunately, many of the gynecologic malignancies have a high "cure" rate. This relatively impressive success rate with gynecologic cancers can be attributed in great part to the development of diagnostic techniques that can identify precancerous conditions, the ability to apply highly effective therapeutic modalities that are more restrictive elsewhere in the body, a better understanding of the disease spread patterns, and the development of more sophisticated and effective treatment in cancers that previously had very poor prognoses. As a result, today a patient with a gynecologic cancer may look toward more successful treatment and longer survival than at any other time. This optimism should be realistically transferred to the patient and her family. Patient denial must be tolerated until the patient decides that a frank conversation is desired. When the prognosis is discussed, some element of hope should always be introduced within the limits of reality and possibility.

The physician must be prepared to treat the malignancy in light of today's knowledge and to deal with the patient and her family in a compassionate and honest manner. Patients with gynecologic cancer need to feel that their physicians are confident and goal oriented. Although, unfortunately, gynecologic cancers will cause the demise of some individuals, it is hoped that the information collected in this book will help to increase the survival rate of these patients by bringing current practical knowledge to the attention of the primary care and specialized physician.

Our ideas are only intellectual instruments which we use to break into phenomena; we must change them when they have served their purpose, as we change a blunt lancet that we have used long enough.

—Claude Bernard (1813-1878)

Some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of their physician.

—Hippocrates (440-370 bc)

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We are grateful to the sincere and diligent efforts of Kate Dimock, Rebecca Gruliow, Teresa McBryan, Ashley Miner, and Beula Christopher from Elsevier in bringing this book to fruition. Through their deliberate illumination and clearing of our path, this material has traversed the far distance from mere concept to a compelling reference book.

Drs. Mannel, McMeekin, and Mutch would like to acknowledge and thank Drs. DiSaia and Creasman for their continuous and tireless mentorship throughout our careers. They have served as role models in our professional and personal lives.

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Preinvasive Disease of the Cervix

L. Stewart Massad, MD

OUTLINE

KEY POINTS

1. Human papillomavirus (HPV) persistent expression is required for progression to cancer.
2. HPV vaccination has the potential to eradicate cervical cancer.
3. Cervical cancer screening now relies heavily on HPV testing.
4. mRNA expression is as sensitive but more specific than DNA testing.
5. Screening guidelines have changed dramatically with the use of contesting and increased intervals between screenings.

Cervical cancer was once the most common cancer in women. It is among the most preventable cancers, and it has become rare among women who engage in cervical cancer prevention programs. Nevertheless, with some 100,000 preinvasive lesions diagnosed in the United States annually, it remains a substantial threat. After tremendous gains following introduction of cytology screening half a century ago, cervical cancer rates continue to fall by about 1% annually. Careful compliance with evidence-based guidelines remains critical to sustaining progress. Effective programs reflect organized public health efforts encompassing patient and clinician education, vaccination against causative types of human papillomavirus (HPV), cytology and HPV screening, colposcopy triage for abnormal screening test results, and destruction of the at-risk cervical transformation zone for women with cancer precursors.

NATURAL HISTORY

Essentially all cervical cancers arise from persistent genital HPV infections (Fig. 1.1)**.** The International Agency for Research on Cancer has designated as carcinogenic 12 HPV types: HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, and -59. As described by Halec and associates, another eight types have been designated as possibly or probably carcinogenic: HPV–26, -53, -66, -67, -68, -70, -73, and -82. Almost 200 HPV types have been identified. A new genotype is based on DNA sequencing. A new type must share less than 90% DNA homology in the L1, E6, and E7 compared with known HPV types.

HPV-16 is the most oncogenic, accounting for more than 50% of cervical cancers. HPV-18 is found in 10% of cervical cancers and plays a particularly important role in adenocarcinogenesis. Types 31, 33, and 45 each account for around 5% of cancers. The other types are less oncogenic but have been reported in large typing studies of cervical cancers. HPV-18 and related HPV-45 are linked to cancers found at a younger age.

HPV infection leads to cancer through multiple pathways, but interaction of the HPV E6 and E7 gene products with p53 and pRb are critical: By inactivating or activating degradation of their targets, E6 and E7 eliminate genetic surveillance and allow unchecked cell cycling, leading to accumulation of mutations and eventual invasive cancer. HPV-16 E6 and E7 bind their targets with greater affinity than other HPV types; this may

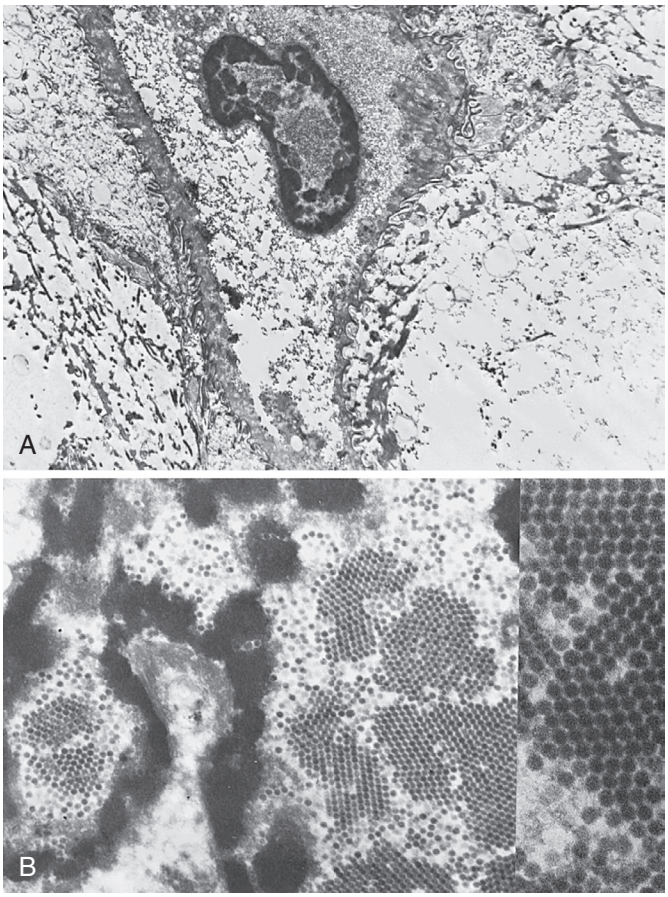

FIGURE 1.1 A, Koilocytotic cells with intranuclear virions (×6900). B, Human papillomavirus particles. Note the intranuclear crystalline array ("honeycomb") arrangement of virions (×20,500). See the *insert* (×80,000). (Courtesy of Alex Ferenczy, MD, Montreal, Canada.)

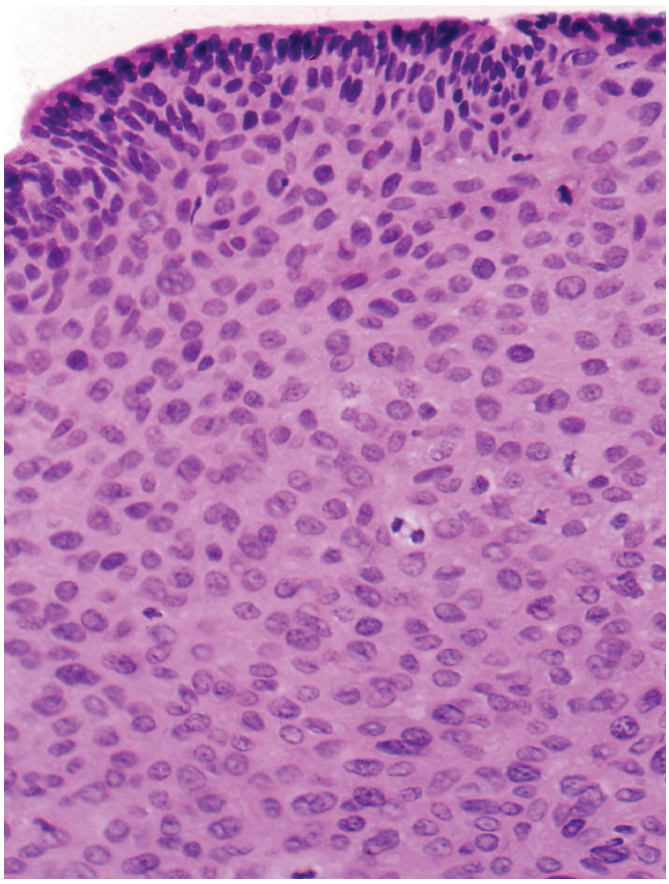

FIGURE 1.2 A cervical intraepithelial neoplasia lesion with multiple mitotic figures.

partly explain its greater oncogenicity. Persistent infections lead to cancer in steps: Initial infection into basal epithelial cells leads to establishment of a ring chromosome from which carcinogenic proteins are elaborated while virion production occurs in maturing epithelium. Disruption of the ring, often at the HPV E2 regulatory region, allows integration of E6 and E7 sequence into the host genome. The accumulation of mutations leads to nuclear changes visible cytologically as a high-grade squamous intraepithelial lesion (HSIL) and histologically as high-grade cervical intraepithelial neoplasia (CIN) (Fig. 1.2) is apparent histologically. Selection for invasiveness and metastasis through additional mutation and through gene methylation results in evolution to cancer. Multitype infections do not appear to increase cancer risk, and when multitype infections include HPV-16, most lesions are caused by HPV-16. Extant HPV infections do not appear to predispose to or protect from infection by unrelated types.

Vertical transmission of HPV from mother to infant has been documented in the Finnish HPV Family Study but does not appear to result in cervical infection, with genital HPV in only 1.5% of infants after 2 years; fathers' HPV infections did not increase infant HPV risk. Although lifetime abstinence protects against genital HPV infection, nonpenetrative sexual behaviors may transmit the virus, and male exposures modulate female risk. For example, spouses of men who engaged in sex with prostitutes were at higher risk for cervical cancer than those of men who did not, and cervical cancer risk is higher among women whose husbands had more sexual partners. Women who report recent sex only with women are also at risk, though their risk may be marginally lower than that of heterosexual women. Condom use is not fully protective against HPV infection because condoms fail to cover wide areas of genital skin, though it speeds clearance of HPV infections. Male circumcision also reduces but does not eliminate HPV and cancer risks. For these reasons, all women with prior sexual experience, including those who have not been sexually active for years, remain at risk for cervical cancer and merit screening until they have multiple negative test results.

Despite the high frequency of HPV infection, most women infected with carcinogenic HPV, including those with HPV-16, do not develop cervical cancer. Instead, most infections are cleared immunologically. HPV is an intraepithelial virus, and clearance appears to require recognition of infection by cell-mediated immune cells. Roughly half of new infections are cleared within 6 months, with half of the remainder cleared by the end of the first year after infection. Clearance is associated with greater density of CD8+ cells and lower density of

T-regulatory cells in underlying stroma. Cervical treatment speeds clearance and reduces risk for posttreatment acquisition of new HPV infections. The type distribution of HPV infection after hysterectomy shows that HPV-16 and HPV-18 have a greater predilection for cervical rather than vaginal epithelium, with HPV types of lesser oncogenicity dominating in the posthysterectomy vagina.

HPV persistence is required for progression of infection to cancer, and women who clear their infections are at low risk. New infections in older women typically do not progress to preinvasive disease or cancer, and women who clear carcinogenic HPV infections have low risk for reappearance with subsequent high-grade CIN. These findings have important implications for termination of screening. Nevertheless, aging appears to result in immune senescence, with many HPV infections in older women attributable to reactivation of previously acquired by latent infections. Oral contraceptive use reduces clearance.

Although determinants of HPV persistence and progression of HPV infection to invasive cancer are poorly understood, several risk factors are known. HPV infection of a cervix undergoing active metaplasia increases risk, as reflected by the epidemiologic observations that early onset of first intercourse is associated with cancer. Smoking is linked to both CIN and cervical cancer. Benzopyrenes have been identified in cervical mucus, and the interaction of tobacco carcinogens with carcinogenic HPV increases risk substantially. Smoking also reduces immune-mediated HPV clearance. Cervical adenocarcinoma and adenocarcinoma in situ (AIS) have been linked to oral contraceptive use. Deficiencies in nutrients such as folate have been linked to cervical oncogenesis but are uncommon among US women. Variants of common HPV types that segregate by ethnicity and polymorphisms in genes related to HPV immune recognition or HPV protein products also modulate HPV persistence and carcinogenic progression. Perhaps most important, lack of screening is a high risk factor for progression of HPV infection to precancer and cancer: Whereas appropriately screened women with multiple risk factors are at relatively low risk, women with few risk factors who are not screened are at higher risk.

Immune factors play a clear role in the clearance or persistence of HPV-related cervical lesions, but the nature of immune defects is poorly understood. Fukuda and associates showed that lesions that persist have fewer Langerhans cells and helper T cells than lesions that are cleared, and tobacco smoking also lowers Langerhans and helper T-cell numbers. In contrast, Molling and associates showed that, although natural killer cells are decreased, regulatory T-cell numbers are increased in women with persistent HPV-16. Immunosuppression related to coinfection with the human immunodeficiency virus (HIV-1) illustrates the importance of immunity in the typical control of HPV. Women with HIV have much higher rates of HPV infection, including multitype infections. HPV clearance rates are lower, although most women do clear their HPV infections if observed long enough, especially if immune reserve as measured by CD4 lymphocyte count remains above 200/cmm. Although most HPV infections in HIV-seropositive women are cleared to such low levels of viral expression that they become nondetectable even with sensitive assays, reactivation appears to occur. This is apparent in cohort studies as the reappearance of previously cleared infections in women who deny sexual activity, often because of illness. Risks in other immunosuppressed states appear to be similar.

HPV infection predicts risk for subsequent high-grade CIN, even among cytologically normal women. In most cases, persistent HPV infections result first in cytologically detectable abnormalities and then in colposcopically visible lesions that grow laterally before developing into invasive cancers. The 10-year risk of high-grade CIN after a single detected HPV infection exceeds 10%.

As developed by Richart through observational studies of the cervix using cytology and colpomicroscopy, a diagnosis of CIN was based on progressively severe nuclear aneuploidy, abnormal mitotic figures, and loss of epithelial maturation. Initially considered a progressive lesion, CIN was thought to begin as a small lesion with atypia near the basement membrane of the cervical transformation zone, gradually increasing in size and becoming less differentiated with an increasing proportion of the epithelium taken up by atypical cells until a full-thickness carcinoma in situ developed and then became invasive. Given this concept of progression from low-grade to high-grade disease to cancer, lesions of all grades were treated. When progression does occur, however, it appears to require years. The median age of sexual debut in the United States is around 17 years of age, and HPV acquisition commonly follows, but the peak age of cervical cancer diagnosis lags by some 3 decades. This long transition time allows for even moderately sensitive screening tests to identify persistent lesions for treatment before invasive cancer develops (Table 1.1).

Gradually, the regressive nature of most low- and midgrade lesions became apparent. Low-grade lesions, including warts and CIN1, are histologic expressions of HPV infection. Greenberg and associates found that of 163 women with CIN1 after low-grade cytology followed for a median of 36 months, 49% regressed, 43% persisted, and only 8% progressed to CIN3. In the Atypical Squamous Cells of Undetermined Significance/Low Grade Squamous Intraepithelial Lesion Triage Study (ALTS), a large randomized trial of management options for women with borderline cytology results conducted under the auspices of the US National Cancer Institute (NCI), 2-year risk for CIN3 were 10% among women with CIN1. **As reported by Castle and coworkers, after controlling for HPV genotype, with HPV-16–associated CIN1 progressing to CIN3 in 19% of cases, biopsy-proven CIN1 was not a risk factor for progression. These risk estimates may be substantially higher for women with prior high-grade cytology.**

TABLE 1.1 Transition Time of Cervical Intraepithelial Neoplasia

Stages	Mean Years
Normal to mild to moderate dysplasia	1.62
Normal to moderate to severe dysplasia	2.2
Normal to carcinoma in situ	4.51

Higher grades of dysplasia appear to represent clonal lesions arising from single-type HPV infections. Although women may harbor multiple HPV types in the genital tract, most multitype infections are associated with multifocal lesions. Moscicki and her team showed that 63% of adolescents and young women with CIN2 resolved lesions without treatment within 2 years; subsequent clearance was minimal, rising only to 68% after an additional year. McAllum and colleagues showed a similar 62% regression after only 8 months of observation for women with CIN2 younger than 25 years of age. No patients in either study progressed to cancer during observation. In both studies, identified CIN2 likely represented recent HPV infections. Regression rates are lower in older women, at least in part because lesions detected later may have been persistent for years, and lesions that have evolved mechanisms to evade host immune-mediated clearance are likely to continue to persist. Castle and coworkers compared CIN2 rates in the immediate colposcopy and cytology surveillance arms of the ALTS. They found that over 2 years, some 40% of CIN2 regressed. Trimble and colleagues showed that HPV-16–associated lesions are less likely to resolve. Their finding of associations with human leukocyte antigen (HLA) alleles and regression support a role for HLA-restricted HPV-specific immune responses in determining clearance.

Untreated, CIN3 poses considerable risk of progression to invasive cancer. This was best shown in a study of New Zealand women with CIN3 who were diagnosed between 1955 and 1976 and were observed. Among 143 women reported by McCredie and coworkers, managed only by punch or wedge biopsy, 31 progressed to cancer of the cervix or vagina after 30 years. Risk rose to 59% in 92 women with persistent disease after 2 years of observation. These findings show both that treatment of CIN3 is mandatory regardless of age or other factors but also that not all CIN3 lesions will inevitably progress to cancer.

Treated CIN3 continues to pose a risk of progression to cancer. Women in the New Zealand study whose treatment appeared adequate by current standards faced only 0.7% cancer risk after 30 years. Studies from Scandinavian countries with integrated health systems can link databases on procedures and subsequent cancers and provide accurate long-term results with minimal loss to follow-up. Strander and associates showed that risk for cervical cancer rose significantly in previously treated women after age 50 years, with standardized incidence ratios compared with untreated women ranging from 3 to 5. Vaginal cancer risks were elevated across all ages, although the absolute risk of vaginal cancer was low. Kalliala and colleagues in Finland confirmed this long-term increased risk and also found an increased risk for nongenital smoking-related cancers. Jakobsson and coworkers found that in addition to cervical cancer, women treated for CIN faced higher mortality rates from circulatory system, alcohol-related, and traumatic death, consistent with the demographic and behavioral factors linked to CIN.

EPIDEMIOLOGY

More than 80% of sexually active individuals acquire genital HPV infections. Some 20 million Americans and 630 million persons worldwide are infected with HPV. In the United States, about 6.2 million people will acquire a new infection annually. Prevalence rates are highest among women in their late teens and early 20s, declining with age. Risk factors for HPV acquisition include smoking, oral contraceptive use, and new male partners.

Among high-risk HPV types, HPV-53 is most common, detected in 5.8% of US women ages 14 to 59 years screened in the National Health and Nutrition Examination Survey (NHANES) in 2003 to 2006. This was followed by HPV-16 (4.7%), HPV-51 (4.1%), HPV-52 (3.6%), and HPV-66 (3.4%). HP-V18 was present in only 1.8% of screened women. In NHANES, demographic risk factors for prevalent HPV infection included younger age, peaking at ages 20 to 24 years; non-Hispanic black ethnicity; unmarried; never educated beyond high school; and living below the poverty line. Behavioral risk factors included reporting ever having sex, first intercourse before age 16 years, greater numbers of lifetime partners, and number of partners in the past year. HPV type distributions vary across continents.

HPV infection determines subsequent risk for precancer. Among women enrolled in a Portland health maintenance organization who had HPV-16, the 10-year risk for CIN3, AIS, or cancer was more than 15% after HPV-16 infection, almost 15% after HPV-18, less than 3% after other oncogenic HPV infections, and less than 1% after a negative HPV test result.

In the United States more than 400,000 cases of CIN are identified annually, at a cost of approximately $570 million. Of these, Flagg and colleagues estimate about 100,000 are true precancers. The annual incidence of high-grade CIN is some 6 to 10 times higher than cervical cancer incidence. Preinvasive lesions begin to appear some 2 years after infection. Cancer risk is quite low soon after infection: Despite a high prevalence of HPV detection among sexually active teens, cervical cancer incidence is only about 1 in 1,000,000 before 20 years of age. Among women who develop high-grade CIN, only 30% to 50% will develop cancer over years of observation.

Although demographic and behavioral risk factors cannot be used to target evaluation or therapy, clear risks for CIN and cervical cancer have been identified. The international Collaboration of Epidemiological Studies of Cervical Cancer reviewed evidence for various risk factors for cervical cancer and carcinoma in situ, although their studies were not linked to HPV data. They found that oral contraceptive use raised the risk for cervical disease by 1.9-fold for every 5 years of use. First intercourse before 15 years of age was associated with twice the risk of cervical cancer found in women with first intercourse after 23 years of age, and having more than five lifetime sexual partners carried more than double the cervical cancer risk of lifetime monogamy. Lesser but still significant increases in risk were associated with number of pregnancies and earlier age at first term pregnancy. Both squamous cancers and adenocarcinomas share epidemiologic risk factors, except that smoking is linked only to the former.

The role of family history in determining cervical cancer risk. Dissociating genetic components of familial risk from cultural ones is difficult, as sexual attitudes and behaviors, reproductive patterns, and smoking are often linked to family.

Zelmanowicz and associates assessed the role of family history in cohorts of women prospectively studied in Costa Rica and the United States. A family history of cervical cancer in a first-degree relative tripled the risk for CIN3 or squamous cervical cancer. The effect persisted after controlling for HPV exposure. No effect of family history on adenocarcinoma risk was seen. Although several genome-wide association studies (GWASs) have identified a range of genetic variants in candidate pathways that might contribute to cervical oncogenesis, Chen and colleagues in a large Chinese GWAS found that only HLA and major histocompatibility class I polypeptide-related sequence A genes were identified as candidate risk genes across several populations.

Lower socioeconomic status (SES) and minority ethnicity are also linked to CIN and cervical cancer risk in the United States, although distinguishing cultural contributions to cervical cancer risk, such as a sense of fatalism, distrust of the medical care system providing screening services, and lack of health education about the benefits of screening, are difficult to distinguish from biologic risks related to ethnicity and SES, such as genetic predisposition, toxin exposure, and micronutrient deficiencies.

HUMAN PAPILLOMAVIRUS VACCINATION

Because HPV is the cause of essentially all cervical cancer, HPV vaccination has the potential to eliminate cervical cancer. However, the US experience with HPV vaccination has shown that several barriers will limit achievement of this goal.

Intramuscular delivery of synthetic HPV L1 capsid antigens results in humor immunity; current vaccines are created in protein synthesis using cell culture systems; because no actual live or killed virions are used, HPV vaccines cannot cause HPV-related cancer. Despite early concerns that humoral immunity would be insufficient to prevent infection, vaccine efficacy appears to approach 100%. However, currently available vaccines are prophylactic: They must be delivered before HPV exposure and do not appear to reduce risk in untreated women with established target-type HPV infections. This is reflected in the epidemiology of vaccine effectiveness, which declines with age, number of prior sexual partners, and prior abnormal cytology. These findings mean that, although vaccination is effective for type-specific HPV naïve women through 45 years of age, population effectiveness is too low to justify widespread use of vaccines beyond the upper age limit in vaccine trials, which extended to 26 years of age. Within trials, effectiveness declined with age, and the American Cancer Society has reiterated its guidance that HPV vaccination extend only through 18 years of age.

Three HPV vaccines are available. US clinicians have favored the quadrivalent HPV vaccine, which protects against HPV-16 and -18, which together account for almost 70% of all cervical cancers, as well as HPV-6 and -11, which are the most common causes of genital warts. The benefit of cervical cancer prevention, which might take decades to become manifest, is augmented by its ability to prevent genital warts, a concern for many young women. The bivalent HPV vaccine protects against only HPV-16 and -18 and is less commonly used in the United States. It may have superior antigenicity and may have some cross-protection against HPV types related to HPV-16 and -18. Most recently, a nonavalent vaccine has been introduced, which is effective against the same types as the quadrivalent vaccine and also includes coverage against HPV types 31, 33, 45, 52, and 58; enhanced coverage should prevent 90% of all cervical cancers.

Because HPV vaccines are prophylactic, population-based vaccination should begin before first sexual intercourse. Because some 5% of US 13-year-old girls are sexually active, the target age for HPV vaccination is the ages of 11 to 12 years. However, vaccination can be initiated at 9 years of age in populations in which sexual debut may occur earlier. Three injections over 6 months are recommended for all vaccines, although schedules vary. Some data suggest that two injections or even one may be sufficient, at least for adolescents, but shortened vaccination schedules have not been approved by the US Food and Drug Administration (FDA). Because teen sexual activity is unpredictable, delaying vaccination until girls are more mature risks missing the vaccination window for many. Nevertheless, many sexually active young women show no evidence of infection by target HPV types, and "catch-up" vaccination should be considered. Testing of cervicovaginal secretions and serum antibody testing are both insensitive for detecting prior HPV vaccination and are not recommended before a decision about HPV vaccination.

Several countries have instituted organized vaccination programs, either mandatory or using a school-based opt-in mechanism with high uptake. Countries that used quadrivalent vaccine have documented a dramatic decrease in genital warts among teens but not older women, and abnormal cytology rates have also fallen in the youngest women.

In the United States, vaccination rates are suboptimal, with barely one-third of girls in target populations having received all three injections. Regrettably, despite the potential for vaccination to eliminate the disparately high risk of cervical cancer among women of minority ethnicity and lower SES, uptake has been lowest in these groups, potentially widening cancer disparities in future years. Nevertheless, decreases in HPV-16 and -18 in the pool of sexually active young women have been documented, suggesting that less than ideal vaccination rates may nevertheless eventually yield population effectiveness.

Vaccine risks appear tolerable. Common side effects include fever, rash, injection site pain, nausea, headache, and dizziness. Anaphylactic and vagal reactions may be fatal, so vaccination should only be administered in sites with ability to manage anaphylaxis and fainting. Despite initial concerns, HPV vaccination status does not enter into young women's decisions to initiate sex. Vaccination is contraindicated for pregnant women, although no congenital anomalies or adverse pregnancy outcomes have been linked to HPV vaccination; the vaccine series may begin after delivery. Interruption of vaccination does not appear to require reinitiation of the three-shot series.

The duration of vaccine effectiveness is unclear, but antibody levels remain elevated for several years after vaccination. Booster doses are not recommended at this time. However,

revaccination with nonavalent vaccine may provide additional benefit and should be considered for women younger than 26 years of age who previously completed bivalent or quadrivalent vaccines, especially those who have not initiated sexual activity and so are at low risk for having acquired HPV.

A history of HPV vaccination does not alter screening recommendations for US women. This is because many women of screening age were not vaccinated before initiating intercourse, so vaccine effectiveness is unclear. There is no central US vaccine registry, and identifying vaccinated women by self-report may be inaccurate. No HPV vaccine covers all carcinogenic HPV types, so women vaccinated before first intercourse remain at risk for infection and cancer due to nonvaccine types. However, for women known to have been vaccinated against HPV-16 and -18 before first intercourse, and so at much lower risk for disease, deferring screening initiation until age 25 years and screening with HPV testing alone at 5-year intervals is rational.

SCREENING

The goal of any cancer prevention program is the reduction of morbidity and mortality through intervention before symptom onset. The current mechanism to achieve this goal is the identification and destruction of high-grade CIN lesions that are presumed precancers. Many novices and some experienced clinicians mistake the mechanism for the goal. However, identification of apparent precancers in women with comorbidities that will be fatal in the medium term, before progression to symptomatic cancer, is not helpful. High-grade CIN in young women may resolve spontaneously and in some cases may be observed to avoid the sequelae of treatment. On the other hand, some women without identified high-grade CIN face cancer risks similar to those of women with high-grade CIN and merit destructive cervical therapy.

Classically, screening has relied on Papanicolaou cytology testing followed by colposcopic assessment of women with Pap abnormalities, directed biopsy of the worst colposcopic lesion, and treatment of biopsy proven high-grade lesions. Papanicolaou testing is relatively insensitive: A single Pap test may be negative in almost half of women with high-grade CIN. However, progression from HPV infection to cancer usually requires several years, allowing for multiple rounds of screening, with greater sensitivity than single tests.

Cytology is the interpretation of all the mutations, methylations, and other genetic modifications that alter the nuclear and cytoplasmic appearance of cells. As such, it is infinitely graded. To be clinically useful, these changes must be aggregated into categories that reflect a common natural history. Papanicolaou developed a five-class grading system, from normal to invasive cancer, with atypia, dysplasia, and carcinoma in situ between. Modified systems were developed, and alternatives were proposed. To unify terminology, the NCI convened a consensus meeting that developed the 1988 terminology known as the Bethesda System for cervicovaginal cytologic diagnosis. With the most recent update in 2001, this classification system identifies cytology as satisfactory or unsatisfactory, includes nonneoplastic changes, and divides epithelial cell abnormalities into squamous and glandular changes of varying degrees of severity (Table 1.2). Distinguishing squamous from glandular abnormalities is critical because glandular abnormalities carry much higher risk for high-grade CIN, including squamous dysplasias, as well as endometrial cancer and cervical adenocarcinoma and AIS. Squamous changes related to HPV are termed "squamous intraepithelial lesions (SILs)" because some lesser changes do not reflect dysplasia or neoplasia, only cytomorphologic changes of HPV infection. Indeterminate lesions are termed "atypical squamous cells (ASC)," and these are subdivided into ASC "of undetermined significance (ASC-US)," which carries a low risk of associated high-grade CIN, or "cannot exclude high-grade SIL (ASC-H)," which is a more ominous finding that requires immediate colposcopy (see later discussion). An online atlas allows pathologists to standardize findings and interpretations against national norms (http://nih.techriver.net). The 2001 update provided the basis for subsequent consensus conferences that provided risk-based management guidelines.

TABLE 1.2 Bethesda 2001 Classification

1. Negative for intraepithelial lesion or malignancy
   - a. Organisms may be identified
   - b. Other nonneoplastic findings may be noted
     - (1) Inflammation
     - (2) Radiation changes
     - (3) Atrophy
   - c. Glandular cells status after hysterectomy
   - d. Atrophy
2. Epithelial cell abnormalities
   - a. Squamous cells
     - (1) Atypical squamous cells (ASC)
     - (2) Of undetermined significance (ASC-US)
     - (3) Cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
     - (4) Low-grade squamous intraepithelial lesions (LSIL)
     - (5) Human papillomavirus (HPV), cervical intraepithelial neoplasia (CIN) 1
     - (6) HSIL (CIN2, CIN3)
     - (7) Squamous cell carcinoma
   - b. Glandular cell
     - (1) Atypical glandular cells (AGC)—specify origin
     - (2) Atypical glandular cells favor neoplastic—specify origin
     - (3) Endocervical adenocarcinoma in situ (AIS)
     - (4) Adenocarcinoma

Traditional Pap smears were collected by smearing samples across a glass slide and applying fixative followed by staining with a Papanicolaou stain. Today most cytology tests in the United States are conducted using liquid-based assays. In these tests, cells are collected and suspended in preservative solution and then transferred to a slide. Liquid-based cytology results in an even dispersion of cells, and techniques are available that allow for elimination of red and white blood cells, but the "tumor diathesis" of pus and necrosis that allowed identification of cancer is lost, as are the "microbiopsies" that allowed

interpretation of epithelial fragments. Liquid-based cytology was marketed as more sensitive than conventional Pap smears. However, a meta-analysis by Arbyn and colleagues showed that, although liquid-based cytology yields more abnormalities, including high-grade SILs, it is not superior to conventional smears in cancer prevention. It remains preferred in the United States because it allows for molecular triage of equivocal results using HPV and other assays. Interpretation is still done visually, although some centers use automated imaging and pattern recognition software to eliminate the least abnormal slides. Cytotechnologists perform initial assessment, with slides containing abnormal findings and a proportion of normal slides read by cytopathologists.

The effectiveness of screening has not been demonstrated in randomized trials, but population studies have shown unequivocal benefits. Papanicolaou and Traut propounded the concept of screening in 1941. An NCI study by Erickson and associates assessed cytology screening by vaginal aspiration for 108,000 women in Shelby County, Tennessee. They showed a high yield of unsuspected high-grade CIN and early cancer at the first screen, with a substantial reduction in invasive lesions in the second screen. Gustafsson and associates reviewed data from 17 cancer registries and showed marked effects, especially in Scandinavian countries. Eddy assessed the impact of screening on cervical cancer incidence and death. Without screening, a 20-year-old average-risk woman faces a 2.5% risk of cancer and a 1.2% risk of cancer death. Triennial screening between ages 20 and 75 years reduces risk to less than 0.4% and 0.1%. Annual screening improves effectiveness but by less than 5% of these low rates, with substantial increase in cost.

Initially, screening was opportunistic: Women had screening when they presented for care, usually at annual visits. Opportunistic screening remains the norm in the United States, although screening intervals have lengthened; some electronic medical records prompt clinicians when screening is due; and some health care organizations have developed standards, rewards, and reminders. Several countries with centralized medical care systems have developed organized screening, with coordinated identification, invitation, and management of women due for screening. Serraino and colleagues showed that the move from opportunistic to organized screening in Italy resulted in a decline in cervical cancer incidence and a downstaging of incident cervical cancers after an increase in precursor detection. Quinn and coworkers found that institution a national call/recall system with incentive payments to general practitioners in Britain instituted in 1988 increased screening coverage to 85% of the target population, increased detection of high-grade CIN, and reduced mortality in women younger than age 55 years.

Cytology-based screening has several weaknesses. Most fundamentally, the process of screening, triage, and treatment is cumbersome, and noncompliance at any point renders it ineffective. Cytology results are reported in ways that can be confusing, and efficient, effective management may require integration of current results with prior abnormalities. Multiple studies have shown that most women who develop cervical cancer in developed countries, especially those presenting at advanced stages, are inadequately screened. Sung and associates studied incident cancers in a US prepaid health plan. They reported that 53% were nonadherent to screening, 28% had false-negative Pap tests, 4% had inadequate follow-up after an abnormal Pap test result, and the rest either developed cancer despite appropriate investigations or were unclassified. Kinney and associates in the same US health maintenance organization found that 60% of cervical cancer patients were inadequately screened. Deeper exploration of the records of long-standing plan members with inadequate screening showed that 70% had missed opportunities for screening in primary care clinics.

In addition, cytology-based screening performs poorly in younger women. Sasieni and colleagues from Britain showed that cervical screening in women ages 20 to 24 years had little impact on actual cancer risk until those women reached 30 years of age, but screening older women results in an immediate benefit. Because younger women have low rates of cervical cancer incidence and death but high rates of HPV infection, abnormal cytology, and CIN destined to regress, the benefits of early initiation of screening may be difficult to balance against potential harms. Cytology preferentially detects squamous cell carcinomas, and the impact of cytology screening on adenocarcinoma incidence has been muted.

The harms of excessive screening are more difficult to quantify. These include stigmatization, unfounded fear of cancer, and interventions without cancer prevention benefit. Sharp and associates showed that depression, distress, and anxiety occurred in 15% to 30% of women in the months after reporting of marginal cytology abnormalities. The costs, pain, and inconvenience of testing, triage, and treatment of abnormalities destined to regress with no impact on cancer morbidity or mortality must outweigh nonexistent benefits, though prospectively identifying these lesions in individuals is problematic.

Essentially all cervical cancer is caused by HPV. Castle and colleagues have shown that women who test HPV negative remain at low risk for precancer and cancer for more than a decade. Incorporation of HPV testing into screening has allowed for longer screening intervals. The development of HPV assays has allowed the development of protocols for HPV testing as a primary screening test in combination screening with cytology (co-testing) and as a triage test for women with borderline cytology results. Only high-risk HPV types have a role in screening; because low-risk types essentially play no role in screening and identification of HPV infection in the absence of visible genital warts causes stigmatization without impacting care, testing for low-risk types is contraindicated. HPV genotyping assays for types 16 and 18 identifies women at higher risk. The disadvantage of HPV testing is poor specificity, with up to 30% of young women testing positive in some studies. Because all commercially available HPV tests have a detection threshold designed to balance sensitivity and specificity, a negative test result does not absolutely exclude HPV infection, and prior cytologic or histologic abnormalities may mandate close follow-up or even treatment despite absence of detectable HPV. The performance characteristics of HPV assays that have not been FDA approved are unknown, and these tests should not be used in the absence of peer-reviewed literature describing

their sensitivity and specificity against histologically defined precancer in large screening populations. HPV tests also should not be collected in media whose effects of test performance have not been evaluated by the FDA.

Although only one HPV assay was approved in the United States for primary screening at the time of writing, four assays were approved for risk stratification for women with ASC-US cytology and for screening in conjunction with Pap testing. Comparative trials are few. Cuzick et al. studied six HPV assays, some of which are available only in Europe. They found that an mRNA test had similar sensitivity but greater specificity than DNA tests.

Beyond these weaknesses, screening has potential harms. Identification of HPV infection, abnormal cytology, and cervical cancer precursors is not without consequences, including anxiety, relationship disruption after diagnosis of a sexually transmitted infection, the inconvenience and cost of accelerated follow-up visits, and the pain of repeated examinations. Treatment of precursor lesions also carries risks, including bleeding, infection, and injury to adjacent organs. Some studies have suggested that destructive cervical treatments increase the risk for preterm delivery and pregnancy loss. US studies have failed to replicate these results in women after cervical loop electrosurgical excision procedure (LEEP). Women with cervical dysplasias are at higher risk for pregnancy loss that those who do not, perhaps because of common risk factors, including smoking, nutritional deficiencies, and lower SES, and these confounding factors may account for differences. However, there may be a threshold effect for treatment, and women with deep or repeated excisional procedures may be at higher risk for pregnancy loss. Shorter screening intervals with increasingly sensitive tests will reduce cancer risk, but benefits decline toward an irreducible asymptote, but harms and costs climb.

After the utility of screening is accepted, societies, women at risk, and clinicians must decide when to initiate screening, which screening tests to use, how often to screen, and when toward the end of life the identification of asymptomatic disease ceases to be beneficial. With all choices, sensitivity and specificity must be balanced. Earlier screening starts with more sensitive tests at shorter intervals until later in life will decrease cancer incidence and mortality, but costs and harms from diagnosing lesions that would never have progressed to cancer will increase. In developed societies, guidelines for screening have been developed by experts assessing evidence for benefit and harm and deciding how these can best be balanced. **In the United States, the most cited guidelines were released in 2012 guidelines by the US Preventive Services Task Force (USPSTF) and a consensus conference sponsored the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP)** (Table 1.3)**.** The two guidelines were developed from a common evidence assessment and reached similar conclusions. In both sets, screening is recommended to begin at 21 years of age, continuing at 3-year intervals until 65 years of age, when screening should stop if the patient is adequately screened and has no history or prior high-grade CIN. Screening also should stop at the time of total hysterectomy for indications other than high-grade CIN or cervical cancer. The ACS/ASCCP/ASCP guidelines contain a preference for screening using combination cytology and HPV testing beginning at 30 years of age; the USPSTF considered co-testing between 30 and 65 years of age to be acceptable but did not find evidence sufficiently compelling to prefer it. Table 1.3 compares the two guidelines.

TABLE 1.3 Comparison of Current US Cervical Cancer Screening Guidelines

	USPSTF	ACS/ASCCP/ASCP
When to start?	Age 21 years	Age 21 years
How often?	Pap tests every 3 years Co-tests every 5 years at ages 30–64	Pap tests every 3 years at ages 21–29 years Co-tests every 5 years at ages 30–64 years preferred Pap tests every 3 years remain an option
When to stop?	Age 65 years if adequate prior screens	Age 65 years if the patient has had three negative Pap tests or two negative co-tests After hysterectomy for benign disease

ACS, American Cancer Society; *ASCCP,* American Society for Colposcopy and Cervical Pathology; *ASCP,* American Society for Clinical Pathology; *USPSTF,* US Preventive Services Task Force.

The rationale for initiating screening at 21 years of age is founded on the low risk of cervical cancer in teens: with only one to two cases per 1,000,000 women, few cancers will be missed by a later screening start. HPV infections are common in sexually active young women, and the specificity of screening in that population is suboptimal. Although CIN2 and CIN3 are more common, most HPV infections, abnormal cytology test results, CIN1 and CIN2 in young women will regress with time. Harms from screening appear to outweigh benefits. As girls who were vaccinated before their first intercourse reach the age of screening initiation, population risk for cancer and precancer will decline. Future US screening guidelines may recommend initiation at 25 years of age. Although some societies and clinicians retain 18 years of age for screening initiation, many societies with organized programs defer screening until age 25 years, and some delay screening until 30 years of age.

Consensus conferences and professional societies in the United States have established 3-year cytology screening as providing optimal balance between benefits and harms. Because HPV testing is more sensitive than cytology, adding an HPV test to cytology should provide greater reassurance against missed disease and so lead to longer screening intervals. Dillner and colleagues have shown that a 5-year Pap/HPV co-testing interval provides superior negative predictive value against precancer than 3-year cytology testing, with a risk that is similar to 1-year cytology testing intervals (Fig. 1.3). Intervals should be based on documented cytology results; Boyce and others have shown that women's ability to recall prior screening is flawed. Centers

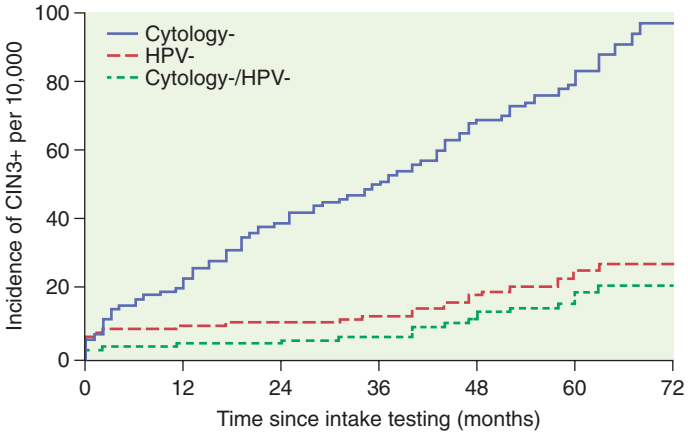

FIGURE 1.3 Incidence of cervical intraepithelial neoplasia (CIN) 3 or worse across time after negative screening test results. Five-year risk after a negative human papillomavirus (HPV) test of cytology/HPV co-test approximates risk 1 year after negative cytology. (From Dillner J, Rebolj M, Birembaut P, et al.; Joint European Cohort Study. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ* 2008;337:a1754.)

for Disease Control and Prevention (CDC) researchers have shown that despite guidelines, US clinicians continue to screen women at short intervals.

The risk for cervical cancer in adequately screened women after 65 years of age becomes negligible. Prior HPV infection that has been cleared without development of high-grade CIN does not appear to increase risk substantially. New HPV infections may be acquired after 65 years of age despite prior negative screening, but in the absence of active metaplasia, these are unlikely to progress to cancer for years and so are unlikely to result in morbidity or mortality, but evaluation and treatment of atrophic postmenopausal women is technically difficult and painful. Vaginal cancer risks are low after hysterectomy for benign disease; too low to justify screening. Women with high-grade CIN remain at risk for cervical and vaginal cancer despite treatment, including hysterectomy, and evaluation until comorbidity suggests a short residual lifespan remains indicated.

Women at low risk for disease during their remaining lifespans should not be screened. This is most apparent for women with illnesses that will be fatal in the medium term: The discomfort and risks of screening and treatment of identified precursors are not justified when the woman is unlikely to survive long enough to develop symptomatic cervical cancer. Similarly, cervical and vaginal cancer risk in the absence of a cervix is functionally zero. After hysterectomy for CIN, screening appears justified based on risk for coexistent vaginal intraepithelial neoplasia and vaginal cancer, and post-treatment surveillance for recurrent cervical cancer treated with hysterectomy is recommended. Women who reach 65 years of age after multiple negative cytology results, including three in the previous decade and two in the previous 5 years, are at low risk for cervical cancer, as are women with two negative HPV–cytology co-test results, including one in the previous 5 years. These women can stop undergoing screening. Women without adequate prior screening should continue undergoing screening until they meet these criteria. Although older women can acquire new HPV infections, they are not undergoing active metaplasia, and transition time to cancer appears to be decades long, as in younger women, so few are likely to survive to develop cancer. For this reason, acquisition of new sexual partners by women who have otherwise met criteria for stopping should not be a consideration for continuing screening.

In 2014, the Food and Drug Administration approved HPV testing as a primary screening test for cervical cancer. Approval was granted only for the cobas HPV test (Roche). At a consensus meeting sponsored by the Society of Gynecologic Oncologists and ASCCP, Huh and fellow consensus meeting delegates developed guidelines to inform clinicians and women at risk on strategies to incorporate primary screening into practice. When used according to an algorithm (Fig. 1.4) that appears to optimize disease detection while minimizing colposcopy, HPV testing is more sensitive that Pap testing when initiated at 25 years of age. Screening intervals for primary HPV testing are controversial. Huh and coauthors recommended that screening be no more often than every 3 years, language that reflected disagreement about 3-year versus 5-year testing intervals. The pivotal trial for the cobas HPV test did not extend beyond 3 years, so performance data are unknown. However, other HPV tests with similar sensitivity and specificity have been tested, and a 5-year interval seems to provide sensitivity superior to 3-year cytology screening while allowing more time for transient lesions to regress.

Few predictors of high-grade CIN have been identified that would allow clinicians to focus more intensive screening efforts on high-risk groups. Boardman and colleagues found that smokers faced a higher risk of CIN2 or worse than nonsmokers, but the odds ratio of 1.6 did not provide sufficient discrimination to allow observation of nonsmokers. Fundamentally, cytology and HPV testing are powerful tools for identifying risk, and the low positive predictive value of borderline cytology grades can be refined by triage using HPV testing or genotyping. Women with abnormal cytology or high-risk HPV infections merit further assessment regardless of demographic or behavioral risks.

CORE PRINCIPLES FOR MANAGING ABNORMAL SCREENING TEST RESULTS

In 2007, Castle and colleagues at the US NCI proposed that management of abnormal cervical cancer screening tests should be based on the associated risk for significant disease. Cancer mortality would be the ideal risk outcome for comparison across tests, but it is too uncommon in screened populations and its frequency is determined by downstream interventions after most tests. Katki and associates proposed instead that risk after various test results and combinations should be benchmarked to CIN3 or worse (CIN3+, including CIN3, AIS, and cancer). Because some lesions are present but inapparent initially because women fail to present for assessment or lesions are clinically too small for detection, the optimal benchmark endorsed by a 2012 consensus conference is 5-year risk for

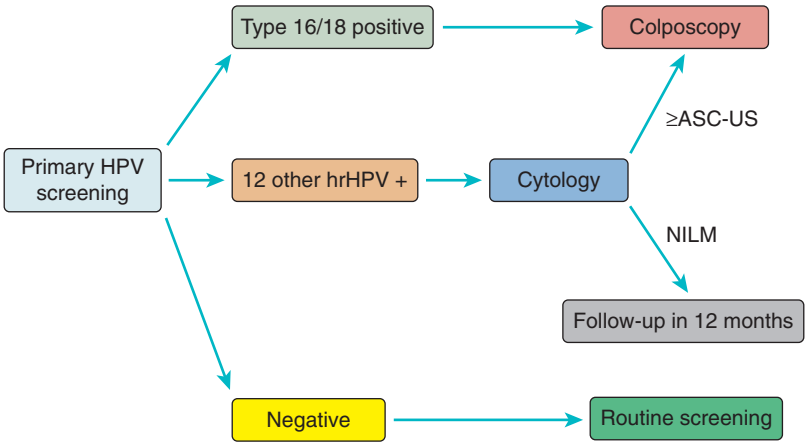

FIGURE 1.4 Strategies for incorporating primary human papillomavirus screening into practice. *ASC-US,* Atypical squamous cells undetermined significance; *hrHPV,* high risk human papillomavirus; *NILM,* negative for intraepithelial lesion or malignancy.

CIN3+. Using this benchmark, clinicians can use similar management strategies for women with similar levels of risk, without regard to how risk was determined. Conventionally, risk was defined by cytology and colposcopy findings. More recently, HPV testing allowed recalibration of risk, especially for women with borderline findings such as ASC-US. HPV genotyping for types 16 and 18 further defines risk categories. On the horizon are other molecular tests whose results will modify risk stratification and management, such as spectroscopic analysis and molecular testing for $p16^{ink4a}$, the Ki-67 proliferation marker, and others.

Determining optimal management for each test or combination can be confusing. In an ideal world, comparative trials would define which triage tests were optimal. Unfortunately, few comparative trials have been undertaken. National health budgets across the developed world are increasingly constrained. Industry lacks incentive to fund trials that might find their products inferior. With the proliferation of screening tests, management options become increasingly complex because algorithms must incorporate all options clinicians might select. In fact, current management guidelines have been criticized as too complex for even experts to master. Fortunately, computerized decision tools have eliminated the need for clinicians to memorize cervical cancer prevention strategies. Electronic medical record platforms can be programmed to generate reminders when women come due for screening. Online algorithm sets are available. Smartphone apps allow entry of patient information and lead clinicians to relevant algorithms. Clinicians still must understand the limits of algorithm-based management, especially the impact of prior abnormalities on subsequent emergence of disease.

To address these concerns, Katki and colleagues analyzed data from more than 1 million women screened by the Kaiser Permanente of Northern California health care system to define 5-year CIN3+ risk after various tests and test combinations. At the base of management options is the 5-year follow-up for women who test negative in Pap/HPV co-testing; these women have a 5-year CIN3+ risk of less than 0.01%. Women screened with cytology alone are followed at 3-year intervals when their test results are negative, with a 5-year CIN3+ risk of less than 0.1%. One-year retesting is standard for women with a positive test result for HPV but negative cytology, with a risk less than 5%. The consensus threshold for colposcopy in the United States is a low-grade SIL result, with 5-year CIN3+ risk of just above 5%; lesser results are triaged by serial testing or triage tests. The threshold for treatment is CIN2, although not all women with CIN2 require treatment, and few studies have assessed use of other test results except high-grade SIL cytology as a treatment indication.

Traditionally, colposcopy was used as the triage modality to identify women with high-grade CIN for treatment. Colposcopy is the magnified stereoscopic visualization of the cervix under intense illumination. Magnification ranges from 3× to 30×. A green filter over the light source accentuates vascular patterns and lesion margins. Although colposcopy without staining has been advocated to maximize visualization of cancer, most colposcopic assessments are augmented by the application of vital stains such as 3% to 5% acetic acid and Lugol's iodine solution.

In colposcopy, the cervical transformation zone is assessed. The transformation zone is that area of the cervix and vagina initially covered by columnar epithelium that has undergone metaplasia to squamous epithelium. A range of terms are used to describe colposcopic findings (Table 1.4 **and** Figs. 1.5 **to** 1.8)**. The procedure for colposcopy is inspection of the cervix without stains and then cleansing of the cervix with an application of 3% to 5% acetic acid for at least 90 seconds. This removes mucus and debris and accentuates vascular and epithelial patterns. Most cervical lesions stain white with acetic acid (acetowhitening).**

Because earlier lesions have been targeted via the inclusion of low-grade SIL, HPV+ ASC-US, persistent HPV infection, and HPV-16/-18 infection as thresholds for colposcopy, colposcopy is being done for women with smaller and less apparent lesions. The accuracy of colposcopy has been questioned, and now multiple colposcopic biopsies are recommended. HPV vaccination

TABLE 1.4 Abnormal Colposcopic Findings

Atypical transformation zone
Keratosis
Acetowhite epithelium
Punctation
Mosaicism
Atypical vessels
Suspect frank invasive carcinoma
Unsatisfactory colposcopic findings

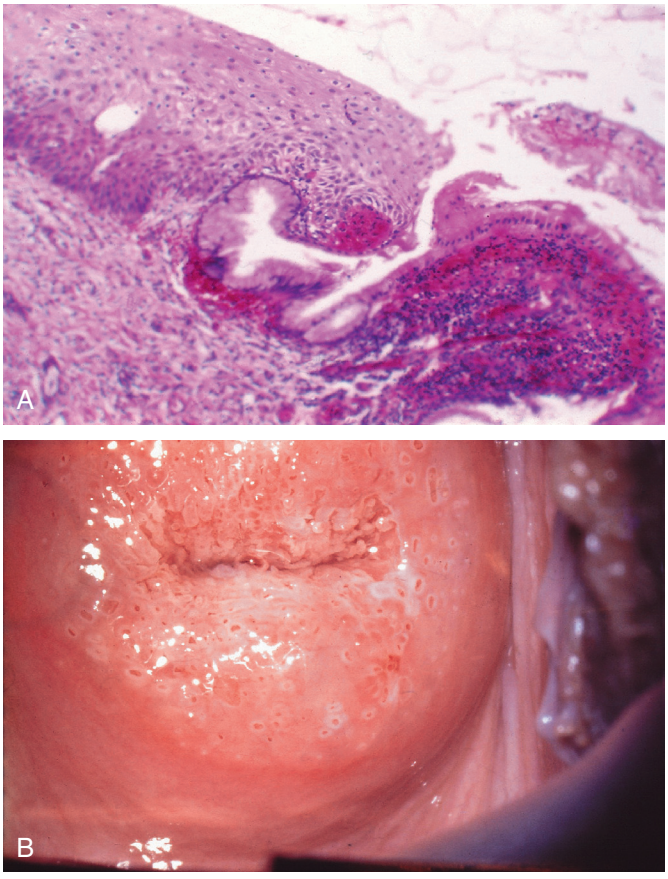

FIGURE 1.5 A, Squamocolumnar junction (transformation zone). B, Large transformation zone.

promises to reduce cervical cancer risk in coming decades but more immediately will reduce the prevalence of high-grade lesions. This in turn will reduce the specificity of screening tests and lower the sensitivity of colposcopy. Opportunities for further changes to screening and management strategies will follow, especially longer screening intervals, more HPV-based assessment, more intermediate triage tests before colposcopy, and a move toward immediate treatment without colposcopy for women at highest risk.

Immunocompromised women are screened under management guidelines defined by the CDC. Women with HIV are screened according to the guidelines for the prevention and treatment of opportunistic infections in HIV-infected adolescents and adults from the CDC. Under these guidelines, women should be screened with cytology alone twice within a year of

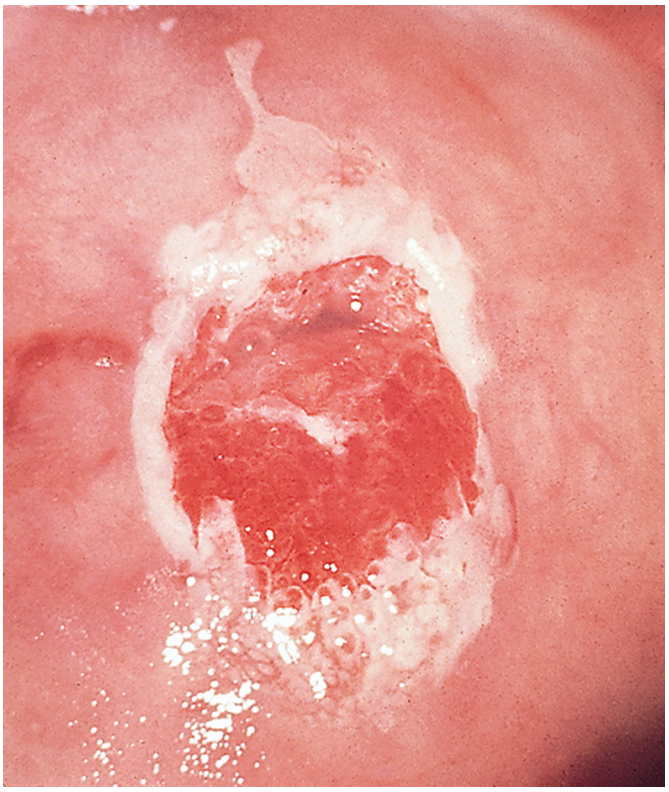

FIGURE 1.6 White epithelium at the cervical os (a colposcopic view).

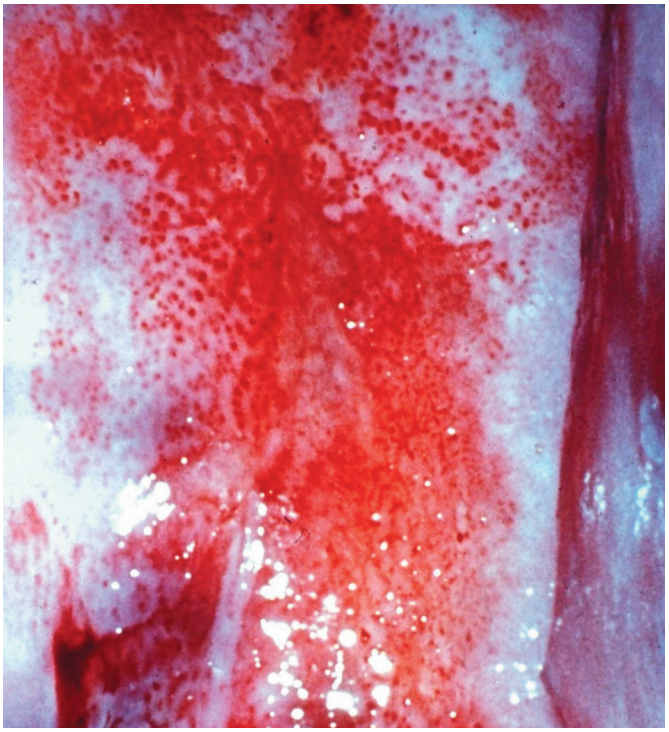

FIGURE 1.7 A punctation pattern is seen clearly above a mosaic structure (a colposcopic view).

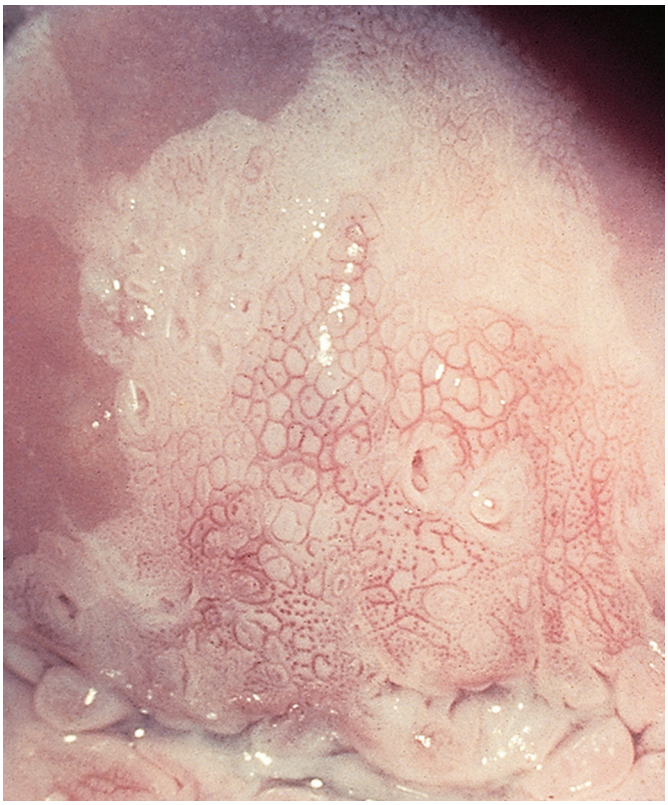

FIGURE 1.8 A large anterior lip lesion with white epithelium punctation and mosaic patterns.

sexual activity, if previously HIV infected, or within 1 year of HIV diagnosis, regardless of age, followed by lifetime annual cytology. These guidelines were in review at the time of publication and may change.

Diethylstilbestrol- (DES-) exposed women continue Pap testing annually for life; evidence on HPV–cytology co-testing for DES-exposed women is insufficient to recommend for or against it.

MANAGING ABNORMAL CERVICAL CANCER SCREENING TEST RESULTS

Since 2001, the ASCCP has led three consensus development conferences to define standard guidelines for management of US women with abnormal cervical cancer screening test results and CIN or AIS. Conferences were cosponsored by numerous professional societies, with collaboration from the American Cancer Society, federal agencies, and other stakeholder groups. The most recent conference, in 2012, used risk estimates developed by Katki and colleagues to define management.

Clinicians should keep in mind that guidelines are for women with abnormal screening tests; for women with symptoms such as abnormal bleeding or pain or abnormal examination findings such as contact bleeding, cervical friability, or cervical enlargement, biopsy may be indicated regardless of cytology or HPV results. In addition, guidelines do not cover all potential permutations of screening test, colposcopy, and biopsy results, especially accumulated abnormalities across years. Prior abnormal results raise risk for CIN3+ associated with subsequent abnormalities: Management does not "reset" after each test. For example, risk is higher after two cytology reports read as ASC-US than after only one, and ASC-US cytology after prior treatment for CIN3 is more ominous than a first ASC-US report; in both of these cases, colposcopy is indicated.

Managing Abnormal Results in Young Women

Cervical cancer risk is low among women 21 to 24 years of age, but high-risk HPV infections can be found in more than 20%. Most CIN1 and many CIN2 lesions in this age group will regress without intervention. CIN3 is unlikely to progress to cancer in the short run if missed. Treatment of intermediate-risk lesions may impact future pregnancies. For these reasons, women in this age group are managed less aggressively than older women. For women in this age group, most abnormal cytology results reflect HPV infection; HPV testing should not be ordered, and if obtained, results should not modify management.

In addition, because of concern about impact on subsequent pregnancies, women with biopsies read as CIN2, CIN2,3, or HSIL can be observed, provided colposcopy is satisfactory. There is no specific age range for observational management of these lesions, and a decision to treat or follow these lesions depends on a discussion between the woman and her clinician, balancing the potential risk to future pregnancies against the risk of progression to cancer during observation; both risks appear to be low.

Unsatisfactory Cytology

When cytology is unsatisfactory for evaluation, it must be repeated. The only exception is when the test was not indicated, as in an adolescent younger than 21 years of age, after hysterectomy for a benign condition, or in women older than 65 years of age with adequate prior screening. Some studies have suggested that rates of abnormality might be increased immediately after sampling, but a large US trial failed to validate this, suggesting that immediate resampling is acceptable. For women with atrophy, a short course of vaginal estrogen may improve sample cellularity. Women with obscuring inflammation should be assessed for specific infections and treated for any that might be identified; empiric vaginal antibiotic therapy does not appear beneficial. Samples that are unsatisfactory because of obscuring blood raise concern for cancer. When repeated samples are unsatisfactory, colposcopy should be considered.

Pap-Negative, Human Papillomavirus–Positive Women (Fig. 1.9)

Identification of a carcinogenic HPV type carries substantial risk for CIN3+, but the 5-year risk does not reach the 5% threshold for colposcopy. A positive HPV result is most often encountered in HPV–cytology co-testing for women ages 30 to 65 years.

Women with a positive HPV test but negative concurrent cytology may be managed in one of two ways. They can be reassessed with repeat HPV–cytology co-testing in 1 year, allowing

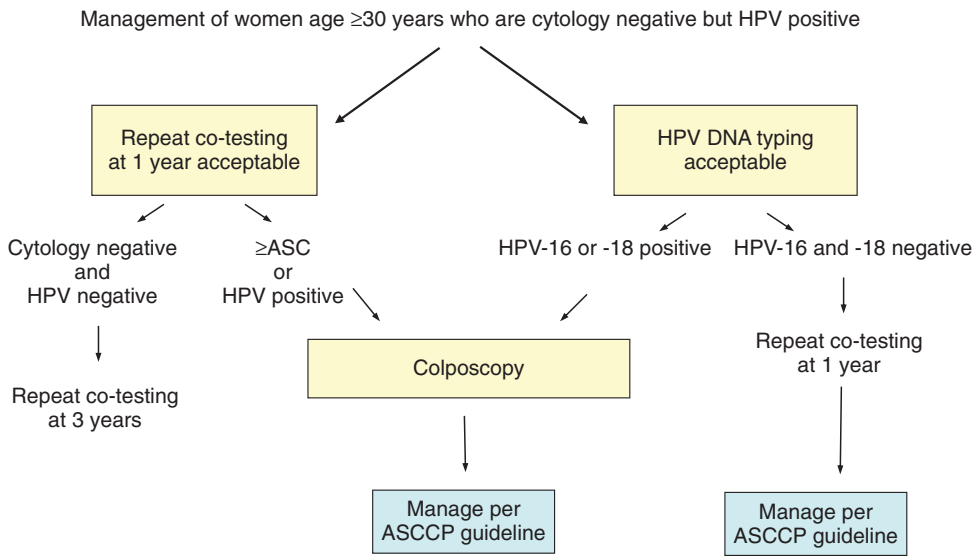

FIGURE 1.9 Management of women age 30 years or older who are cytology negative but human papillomavirus positive (HPV). *ASC,* Atypical squamous cells; *ASCCP,* American Society for Colposcopy and Cervical Pathology. (From Massad SL, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17(5 suppl 1):S1-S27, © 2013 American Society for Colposcopy and Cervical Pathology.)

time for HPV regression; if either test result is abnormal, then colposcopy is indicated. Disadvantages to this approach include losing the advantage of HPV testing for early detection of cytology-negative cancers and the inability to assess whether persistent HPV positivity results from persistence of the same HPV type or clearance of the original type followed by reinfection with a second type, with low risk for CIN3+ unless the new infection becomes persistent. Alternatively, women can be triaged immediately using a genotyping test for HPV-16 or -18; women positive for either type should have colposcopy, but those with negative results should have co-testing repeated in 1 year, with colposcopy only if either test result is abnormal.

Atypical Squamous Cells of Undetermined Significance (Fig. 1.10)

Risk of CIN3+ among women with ASC-US cytology is insufficient to justify immediate colposcopy, at about 3%. ASC-US results are common. Triage using HPV testing on the liquid-based cytology sample appears to be cost effective and minimizes delay and loss to follow-up. If HPV testing is positive for high-risk types, then colposcopy is indicated. A negative HPV result in the context of ASC-US indicates a low risk of CIN3+, though the risk is higher than among women with negative co-testing; 3-year co-testing is recommended.

HPV genotyping distinguishes between higher risk women with HPV-16/-18 and lower risk women negative for HPV-16/-18, but for all HPV-positive women, 5-year CIN3+ risk approximates or exceeds the threshold for colposcopy. Because management is not changed by results, HPV genotyping is not recommended for triage of ASC-US cytology.

Where HPV testing is not available and follow-up is reliable, ASC-US cytology results can be triaged using a repeat Pap test in 1 year with colposcopy if persistently abnormal and return to routine 3-year Pap testing if negative.

For women 21 to 24 years of age, ASC-US cytology results should be followed with annual rather than triennial Pap testing. Colposcopy is not indicated unless ASC-US or low-grade squamous intraepithelial lesion (LSIL) cytology results persist for 2 years or unless cytology returns ASC-H, HSIL, or AGC.

Low-Grade Squamous Intraepithelial Lesion (Fig. 1.11)

Low-grade squamous intraepithelial lesion is the paradigmatic threshold for colposcopy in the United States. With few exceptions (pregnancy, age 21–24 years, HPV-negative result), women with LSIL cytology should be managed with colposcopy. When HPV co-testing is available women with HPV-LSIL should have repeat co-testing in 1 year, with colposcopy if HPV positive or with persistent abnormal cytology. LSIL triage may be considered in postmenopausal women, given their lower background risk for HPV.

Atypical Squamous Cells, Cannot Exclude HSIL

Women with a cytology report of "atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion" have a 5-year risk of CIN3+ similar to that of women with HSIL cytology, although their immediate risk of CIN3+ is lower. All women with ASC-H should undergo colposcopy, regardless of HPV result. In contrast to young women with ASC-US, women

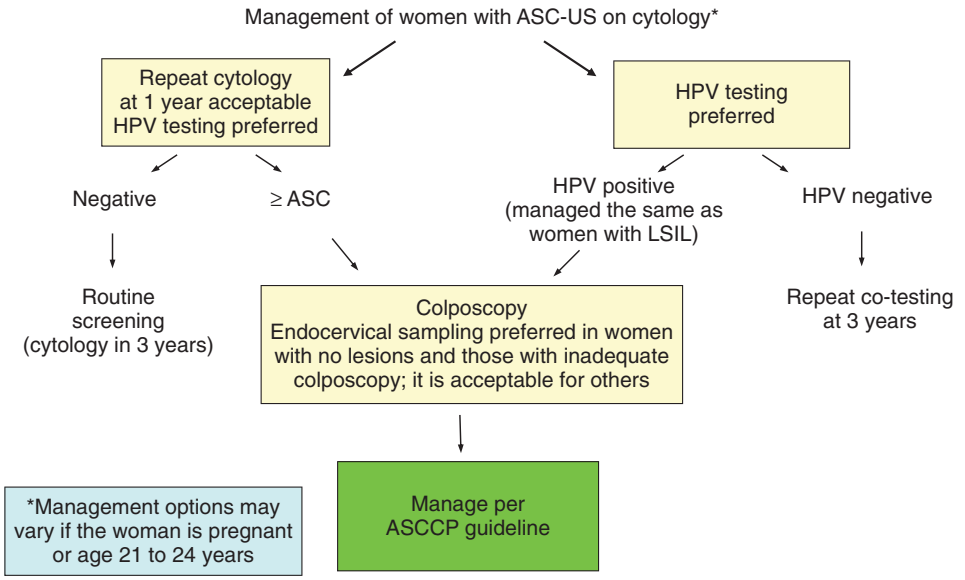

FIGURE 1.10 Management of women with atypical squamous cells of undetermined significance (ASC-US) on cytology. *ASCCP,* American Society for Colposcopy and Cervical Pathology; *HPV,* human papillomavirus; *LSIL,* low-grade squamous intraepithelial lesion. (From Massad SL, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17(5 suppl 1):S1-S27, © 2013 American Society for Colposcopy and Cervical Pathology.)

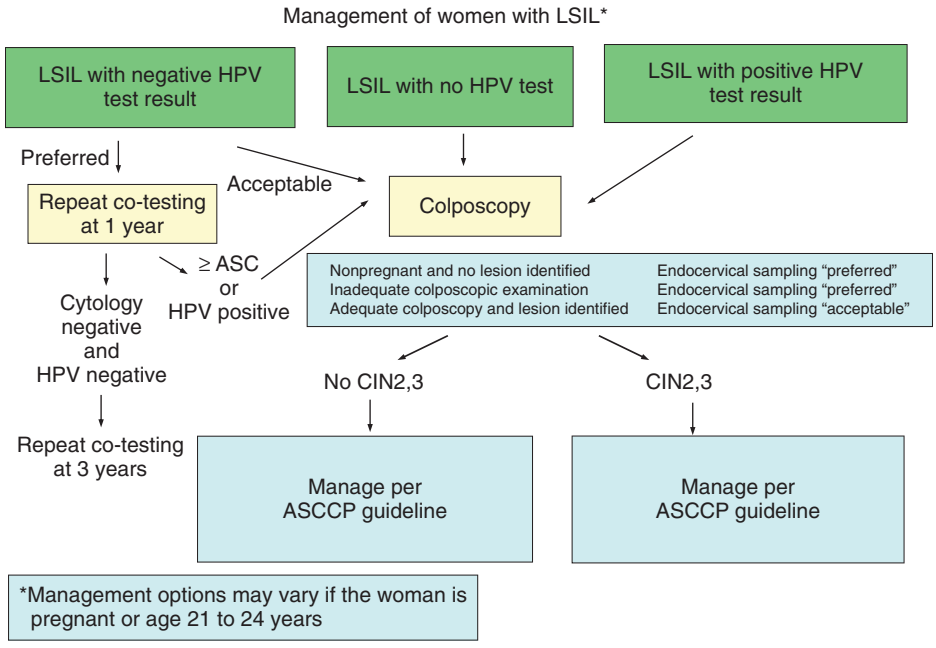

FIGURE 1.11 Management of women with low-grade squamous intraepithelial lesions (LSILs). *CIN,* Cervical intraepithelial neoplasia; *HPV,* human papillomavirus. (From Massad SL, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17(5 suppl 1):S1-S27, © 2013 American Society for Colposcopy and Cervical Pathology.)

21 to 24 years of age need colposcopy after ASC-H cytology, as do pregnant women.

High-Grade Squamous Intraepithelial Lesion

CIN2+ is found in some 60% of women with HSIL cytology, and some 2% will have cancer at colposcopy. This substantial risk justifies aggressive management. In many settings, especially for women in clinics with high rates of loss to follow-up and for women who have completed childbearing, immediate loop excision is an efficient approach to management. Immediate excision is unacceptable for women up to 24 years of age because of their low near-term risk for cancer and the likelihood that CIN2 and CIN2,3, but not CIN3, will regress. HPV results modulate risk, but even women with HPV-HSIL face a 30% 5-year risk for CIN3+. For this reason, colposcopy is required regardless of HPV result, and triage of HSIL cytology using HPV testing is unacceptable. Observation with repeat cytology is similarly unacceptable.

Atypical Glandular Cells

Despite its name, AGC cytology is more often associated with squamous than glandular lesions. The risk of CIN3, AIS, or cancer (CIN3+) after a Pap test read as AGC is almost 10%, and risk for cancer is 3%. Squamous and glandular lesions can coexist, and identification of CIN does not rule out adenocarcinoma. Many associated cancers are of endometrial origin and would be HPV negative; endometrial lesions are more common in older women and in women with such risk factors as obesity, unexplained bleeding, and anovulation. Thorough evaluation is needed regardless of HPV test results.

Women with AGC cytology need colposcopy with endocervical sampling and biopsies of any acetowhite cervical lesion. Endometrial sampling is needed if the patient is older than 35 years of age or if endometrial cancer risk factors are present. For women with AGC subcategorized as "atypical endometrial cells," evaluation can be truncated: Initial endometrial biopsy and endocervical curettage are needed, with colposcopy only if no endometrial pathology is found. In contrast to ASC-US, triage of AGC results with HPV testing or serial cytology testing is inappropriate. Management of AGC in women 21 to 24 years of age is identical to that of older women. Pregnant women with AGC cytology results need colposcopy, but endocervical curettage and endometrial sampling are contraindicated.

Endometrial Cells in Older Women

Among postmenopausal women, a finding of benign endometrial cells on cytology is associated with a 5% risk of clinically important pathology, including cancer. However, endometrial cells appear to have no association with disease in premenopausal women, and no further evaluation is needed for them. For postmenopausal women with endometrial cells on cytology, endometrial assessment is indicated using either endometrial sampling or imaging of endometrial thickness.

POSTCOLPOSCOPY MANAGEMENT

Managing Women With No Lesion or CIN1 at Colposcopy (Fig. 1.12)

A colposcopic biopsy result of no lesion or CIN1 does not exclude the presence of a higher grade lesion in an unsampled area of the cervix. Risk for subsequent CIN3+ depends on patient age and the prior abnormality. Risk is lower for women with what ASCCP terms "lesser abnormalities" than for women with ASC-H, HSIL, or AGC. Lesser abnormalities include negative cytology with either HPV-16 or repeated HPV positivity, ASC-US, or LSIL.

For women with lesser abnormalities and no lesion or only CIN1 on colposcopy, observation with serial co-testing is indicated. If a first co-test result is negative, repeat testing is indicated 3 years later. If all test results are negative, then routine screening is appropriate. If any test result is abnormal, repeat colposcopy is required. This can become burdensome. Treatment of CIN1 is acceptable once disease has persisted for 2 years, although continuing observation is also acceptable if fertility is a concern. Treatment of persistent HPV-positive tests or persistent ASC-US/LSIL cytology in the absence of a cervical lesion is not indicated because many of these women will have vaginal lesions. This includes topical therapies such as trichloroacetic acid. Hysterectomy is never indicated for CIN1 or abnormal cytology.

For women 21 to 24 years of age with no lesion or CIN1 after ASC-US or LSIL, observation with repeat cytology annually is indicated. Repeat colposcopy is only needed if cytology progresses to ASC-H, HSIL, or AGC, or if cytology remains borderline abnormal for 2 years. After a negative result, routine screening at 3 years is indicated. HPV testing and co-testing are not indicated in this age groups. For pregnant women with no lesion or CIN1 after lesser abnormalities during pregnancy, colposcopy should be deferred until postpartum.

When colposcopy reveals no lesion or CIN1 after ASC-H or HSIL cytology, risk for CIN3+ is much higher, and more aggressive management is indicated. ASCCP guidelines lump together ASC-H and HSIL, but diagnostic excision is more often indicated after HSIL; observation with annual co-testing is more appropriate after ASC-H, although either management strategies can be used after either result, according to clinical risk profiling. Observation is limited to women with satisfactory colposcopy and negative endocervical sampling; CIN1 in endocervical curettings is managed like CIN1 on cervical biopsy. If observation is elected, repeat colposcopy and biopsies are indicated after a positive HPV test or any grade of abnormal cytology. Women with persistent HSIL despite negative colposcopy should have a diagnostic excision procedure.

For women 21 to 24 years of age with no lesion or CIN1 after ASC-H or HSIL, diagnostic excision is indicated if colposcopy is unsatisfactory. When colposcopy is satisfactory in visualizing the entire squamocolumnar junction, either treatment or observation is indicated. Observation entails colposcopy and cytology every 6 months until two test result are negative, when routine screening can resume. If HSIL cytology persists,

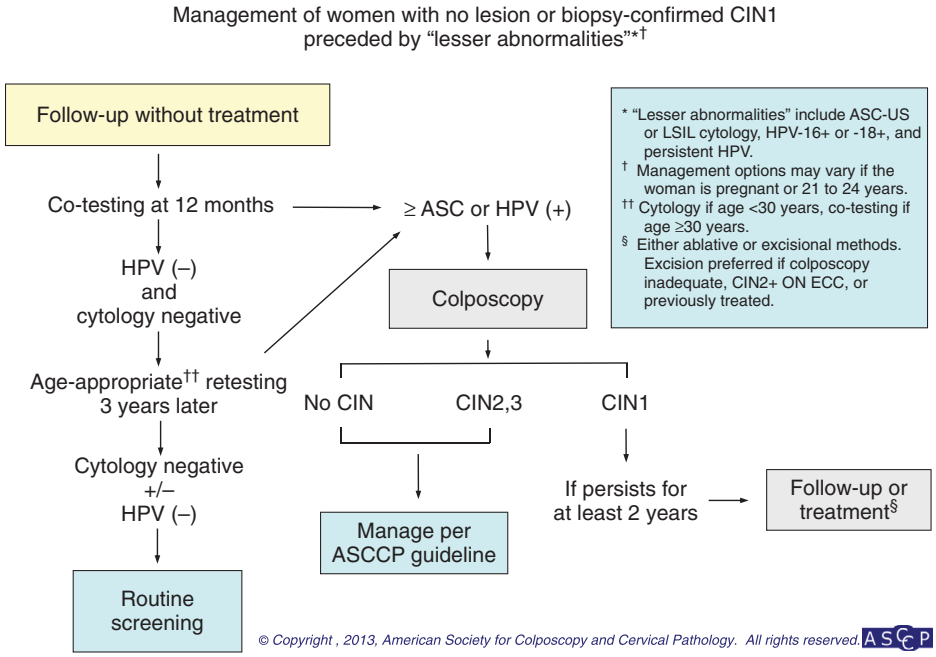

FIGURE 1.12 Management of women with no lesion or biopsy-confirmed grade 1 cervical intraepithelial neoplasia (CIN1) preceded by "lesser abnormalities." *ASCCP,* American Society for Colposcopy and Cervical Pathology; *ASC-US,* atypical squamous cells undetermined significance; *CIN,* cervical intraepithelial neoplasia; *ECC,* endocervical curettage; *HPV,* human papillomavirus; *LSIL,* low-grade squamous intraepithelial lesion. (From Massad SL, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17(5 suppl 1):S1-S27, © 2013 American Society for Colposcopy and Cervical Pathology.)

treatment is indicated. For pregnant women with no lesion or only CIN1 after ASC-H or HSIL, colposcopy should be repeated post partum: The short-term cancer risk is low, and no other intervention is needed during pregnancy

When no lesion or CIN1 is found after AGC cytology, annual co-testing is indicated, with colposcopy for any abnormality; after two negative co-test results, risk declines, and 3-year co-testing intervals are appropriate. Colposcopy is needed if any result is abnormal. Hysterectomy is unacceptable as primary therapy for any grade of CIN, although after prior excision, hysterectomy may be indicated if lesions recur or persist and repeat diagnostic excision is not feasible.

Managing Women With CIN2 or CIN3 (Fig. 1.13)

A colposcopic biopsy of CIN2 is the threshold for treatment. CIN2 is an intermediate lesion: Many represent transient but exuberant HPV infection, and half or more resolve without therapy. Some progress to CIN3 and cancer. Because compliance with follow-up cannot be assured, treatment is recommended. Testing biopsy specimens for the presence of block staining for $p16^{ink4a}$ can identify CIN2 lesions at risk for progression and can be used as a test for triage. All lesions read as CIN3 should be treated regardless of the patient's age or desire for future childbearing, because there is no margin for progression, and some will harbor undiagnosed cancer; ongoing pregnancy is the main exception to this standard. Biopsies read as high grade or CIN2,3 can be managed expectantly or with immediate treatment, depending on patient risk and preferences.

Observation is an acceptable option for women who after counseling consider risk to future pregnancies from treatment to outweigh cancer risk from observation. There is no specific age threshold: A 21-year-old woman who has had a tubal ligation should be treated, but a 43-year-old woman undergoing infertility treatment after a diagnosis of incompetent cervix might prefer to be observed. Observation is only acceptable when the entire lesion and squamocolumnar junction is observed colposcopically. Observation consists of colposcopy and cytology at 6-month intervals until the lesion resolves, as evidenced by regression of colposcopic abnormalities and normalization of cytology. After that occurs, women should be followed with a co-test 1 year later and then 3 additional years later before returning to routine screening; if either the Pap test or HPV test result is abnormal in follow-up, then colposcopy and biopsies should be repeated.

Women with a diagnosis of AIS on colposcopic biopsy should be managed with diagnostic excision to exclude associated invasive cancer. The excision should be done to produce a single specimen; traditionally, this has involved knife conization, but needle, straight wire, or loop conization is acceptable if thermal artifact is minimized. If the margins of the excision specimen are involved or uninterpretable, then reexcision or hysterectomy is required. Women with negative margins at diagnostic excision face a 10% risk of persistent AIS and a lesser

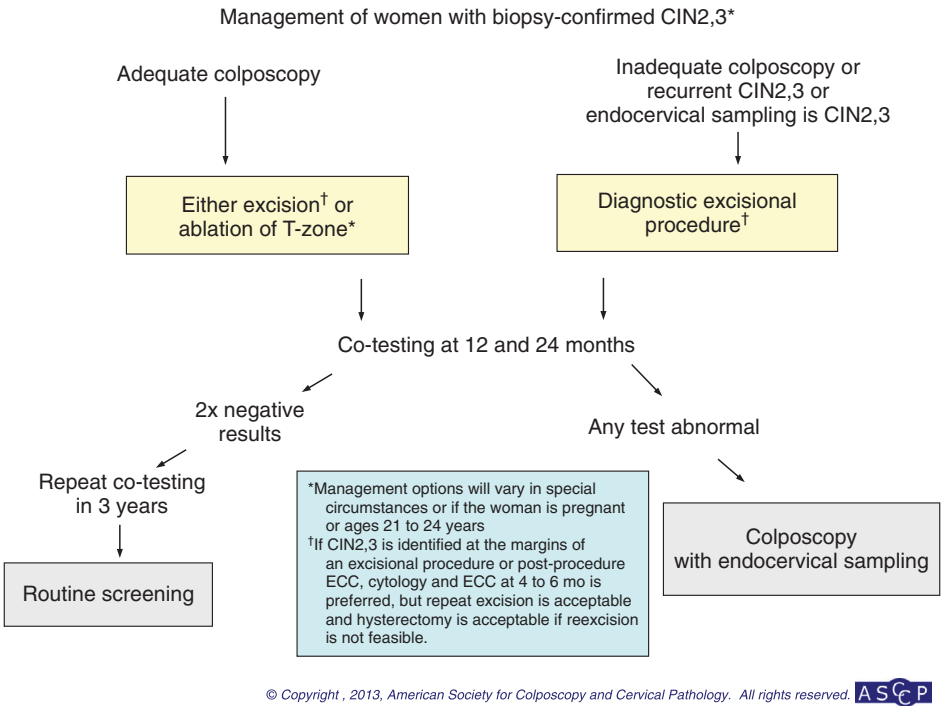

FIGURE 1.13 Management of women with biopsy-confirmed grade 2 and 3 cervical intraepithelial neoplasia (CIN2,3). (From Massad SL, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17(5 suppl 1):S1-S27, © 2013 American Society for Colposcopy and Cervical Pathology.)

risk of invasive cancer, as shown by Costa and colleagues. This risk justifies hysterectomy when childbearing is complete. However, the risk is considered acceptable for women who wish to preserve fertility, although careful monitoring is recommended using colposcopy and co-testing 6 months after the diagnostic excision procedure, with co-testing in follow-up at 1- to 3-year intervals.

TREATMENT OF CERVICAL DISEASE

Although Trimble and colleagues have shown that a therapeutic vaccine can achieve almost 50% efficacy in the elimination of CIN2/3, 90% cure rates for CIN2+ still require destructive therapies. In the United States, ablational therapies include cryotherapy and laser ablation. Excision can be accomplished with an electrosurgical wire loop or needle or with a scalpel.

Cervical ablation results in the elimination of lesional tissue without rendering a specimen for pathologic analysis. For this reason, many gynecologists consider outpatient loop excision a preferred approach. However, randomized trials showed similar failure rates for excision and ablation. This suggests that as long as invasive cancer is microinvasive, with little risk for metastasis, the method of destruction is irrelevant. Nevertheless, using ablational therapies for cervical disease requires careful attention to well-defined exclusion criteria. Ablation cannot be undertaken unless the entire squamocolumnar junction, including all lesional tissue, is visible colposcopically. Ablation of such an unsatisfactory transformation zone risks missing invasive cancer within the endocervix that then progresses undetected. A corollary to this is that ablation should not be attempted when disease extends into the endocervix above the depth that can be ablated. Thus, although manipulation may allow visualization of the squamocolumnar junction deep in the endocervical canal, ablation would remain inappropriate. Other criteria that must be met before proceeding with ablation include concordance of high-grade cytology with colposcopy and histology findings; an endocervical curettage specimen showing no dysplasia or only CIN1; and suspicion of invasive cancer by cytology, colposcopy, or biopsy.

Cryotherapy is performed using nitrous oxide, a delivery gun, and various sizes of metal probes designed to cover the transformation zone of the cervix. Figge and Creasman described use of a freeze–thaw–freeze technique with good success rates, but regardless of the use of double- or single-freeze approaches, identifying the development of at least a 5-mm "ice ball" or zone of freezing lateral to the cryotherapy probe is essential to achieving deep thermal destruction. One standard approach is outlined in Table 1.5. Advantages of cryotherapy include relatively low cost and low risk for injury. Disadvantages include a copious discharge from cervical tissues suffering from sublethal thermal injury and lack of a surgical specimen.

Cervical laser ablation involves the use of carbon dioxide laser energy to destroy abnormal cervical tissue. When optimally used, the laser energy is delivered at a power density of 750 to 1250 W/cm^2. This results in flash boiling of impacted cells, and

TABLE 1.5 Cryosurgery Technique

1. N_2O or CO_2
2. K-Y Jelly on probe
3. Double-freeze
   a. 4- to 5-mm ice ball
   b. Thaw
   c. 4- to 5-mm ice ball

energy is dissipated from the operating field through the smoke plume without causing deeper tissue injury. Lower power density may create the illusion of greater control of tissue destruction, but it requires longer beam application, with greater hidden, delayed coagulation injury to underlying stroma. As with all therapies, laser should be used to ablate the entire at-risk transformation zone. CIN can involve the metaplastic epithelium of cervical glands, which extend some 5 mm into the cervical stroma; for this reason, ablation should be carried to a depth of about 7 mm and should encompass all lesional tissue. If the lesion extends onto the vagina, ablation is carried only to 1 to 2 mm in depth. As described by Stanhope and associates, laser therapy can result in persistent CIN risk of less than 90%. Advantages include precision in application, allowing extension of therapy to lesions that involve the vagina, and rapid recovery from injury. Disadvantages include the need for an expensive laser generator that requires frequent maintenance. Unskilled use of laser energy can result in immediate and delayed injury.

Most US gynecologists treat cervical precancers by excision with electrosurgical loops, termed LEEP or large loop excision of the transformation zone (LLETZ). The entire transformation zone is excised using loops with diameters of 1.5 to 2.5 cm. Excision should extend to the deepest glands, or 7 to 8 mm. For women with disease extending into the endocervical canal and those with inadequate colposcopy, either using deeper loops or a second endocervical pass, colloquially termed a "top-hat" excision for the appearance of the stacked specimen that results; this endocervical excision must encompass the lateral extent of endocervical glands, so 6 to 8 mm from the endocervical surface. For most women, LEEP can be done in an office setting under local anesthesia. Epinephrine is injected with the local anesthetic to minimize blood loss. The injection should be subepithelial rather than stromal, and a paracervical block does not provide the same hemostatic benefit of intracervical injection. Although an operating suite it not required, office LEEP should be done in a setting that includes equipment for suturing and response to anaphylactic reactions. Colposcopic visualization allows optimal tailoring of the excision. Hemostasis is achieved with a combination of fulguration using ball electrodes and application of Monsel's paste. Delayed bleeding should occur in fewer than 5% of cases but is a known complication of the procedure. Obese women and those with anatomic variations or anxiety that prevents optimal cervical visualization in the office may require general anesthesia. Advantages to LEEP include the availability of a surgical specimen with minimal thermal artifact at margins and the ability to adapt excision to the extent of lesions and metaplasia. Disadvantages include risk of surgical injury and hemorrhage and the need for careful operator technique.

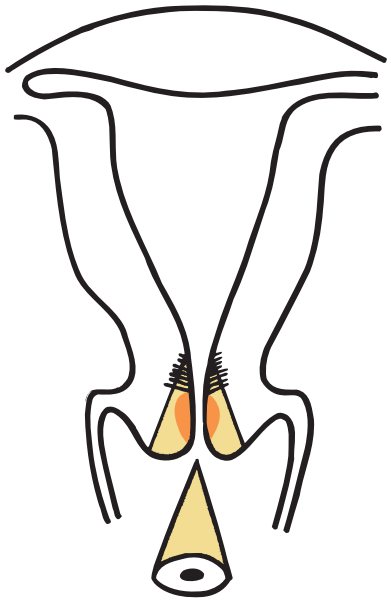

FIGURE 1.14 Cone biopsy for endocervical disease. Limits of the lesion were not seen colposcopically.

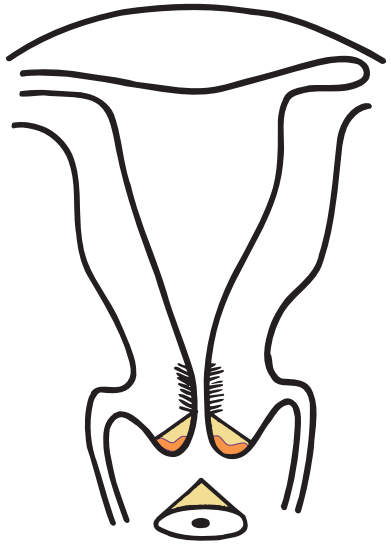

FIGURE 1.15 Cone biopsy for cervical intraepithelial neoplasia of the exocervix. Limits of the lesion were identified colposcopically

Some lesions require intact diagnostic specimens to exclude invasive cancer and assess margins. These include in situ adenocarcinomas and microinvasive cancers. Traditionally, these lesions have been treated with knife conization (Figs. 1.14 and 1.15), which results in an optimal diagnostic specimen while treating in situ and microinvasive lesions for women who wish to retain fertility. As LEEP has become pervasive in training programs, knife conization skills may be disappearing. Needle or straight wire electrosurgical conization has been developed as an alternative, allowing similar adaptation of excision while minimizing blood loss and tissue injury.

MANAGING ABNORMAL RESULTS DURING PREGNANCY

The goal of cervical cancer prevention measures during pregnancy is to identify cervical cancer so malignant lesions can be monitored closely for progression or treated. The risk is remote for cancer developing during pregnancy in women who have CIN, including CIN3. ASC-US and LSIL cytology results do not require colposcopy until postpartum, even if associated with HPV infection, although colposcopy is acceptable. Wetta and colleagues found no cancers and few high-grade lesions among 625 pregnant women with these borderline cytology results. For women with ASC-H, HSIL, or AGC cytology results, colposcopy is indicated. Because of the vascularity of the pregnant cervix, often only one biopsy can be obtained; mini-Tischler forceps should be used and immediate direct pressure applied to the biopsy site. Clinicians without experience with colposcopy during pregnancy should consider referral to a center with expertise because pregnancy will cause colposcopic abnormalities. Biopsy should be done for lesions that appear high grade because limiting biopsy to malignant-appearing lesions results in missed cancers. Women with CIN2+ may be followed with postpartum colposcopy and repeat biopsy or with serial colposcopy during pregnancy, with repeat biopsy only if the colposcopic impression worsens. Conization is indicated only when cancer is suspected by examination, cytology is read as showing malignant cells, or colposcopy or biopsy shows possible invasion. When performed, complete excision of the transformation zone is not needed because the goal is to determine if a deeply invasive cancer is present, not to definitively treat the cervix. Limited excision using an electrosurgical loop with blended current in a controlled operating room setting that allows for cervical suturing may be considered.

FUTURE DIRECTIONS

In developed countries with effective HPV vaccination programs, HPV-16 and HPV-18 are being eliminated from the circulating pool of HPV types. This will have profound implications for cervical cancer prevention. In fact, the introduction of nonavalent vaccination promises to reduce cervical cancer incidence to a rate too low to justify screening. The transition to such a welcome development over the coming decades will create opportunities and controversies as the scientific community adapts to the disappearance of what was once the most common cancer killer of women. Whether this promising future is attained in the United States, with its opportunistic approach to vaccination, remains to be measured.

As HPV-16 prevalence falls among at-risk women as vaccinated girls age, the prevalence of CIN3+ will decline. This will result in a lower incidence of abnormal Pap test results and more abnormalities that occur will reflect transient HPV infections or benign cytologic changes: As disease prevalence falls, the positive predictive value of an abnormality should decline. This should drive a shift away from cytology as a primary screening test. Primary HPV testing should replace cytology. Although cytology may be retained as a triage test for women with HPV types other than 16 or 18, as described by Huh and colleagues, other tests may prove superior, either because of greater predictive accuracy or because they can be automated.

Risk-based guidelines will need to become flexible as risk becomes dynamic. Vaccinated women are likely to face much lower risk than unvaccinated women, and epidemiologic studies suggest that vaccination will result in age-specific declines in HPV-16/-18 and CIN3+ prevalence as sexual segregation by age results in herd immunity for younger women. As vaccinated age cohorts mature, the optimal age for initiation of screening will rise. As more CIN2+ identified by colposcopy reflects infection by HPV types other than HPV-16/-18, with lower oncogenic potential, observation for immune-mediated regression may become preferred over treatment. Integrating this change into practice will be difficult because by the time age-based changes in risk are observed, published, reviewed, and integrated into new guidelines, women will have grown older yet retained immunity. This welcome challenge will structure coming debates on cervical cancer for decades to come.

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BIBLIOGRAPHY

Arbyn M, Bergeron C, Klinkhamer P, et al: Liquid compared with conventional cervical cytology: A systematic review and meta-analysis, *Obstet Gynecol* 111:167–177, 2008.

Boardman LA, Adams AE, Peipert JF: Clinical predictors of cervical intraepithelial neoplasia 2 or greater in women with mildly abnormal Pap smears, *J Reprod Med* 47:891–896, 2002.

Boyce JG, Fruchter RG, Romanzi L, et al: The fallacy of the screening interval for cervical smears, *Obstet Gynecol* 76:627–632, 1990.

Camargo MJ, Russomano FB, Tristão MA, et al: Large loop versus straight-wire excision of the transformation zone for treatment of cervical intraepithelial neoplasia: a randomised controlled trial of electrosurgical techniques, *BJOG* 122:552–557, 2015.

Castellsague X, Bosch FX, Munoz N, et al, for the International Agency for Research on Cancer Multicenter Cervical Cancer Study Group: Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners, *N Engl J Med* 346:1105–1112, 2002.

Castle PE, Schiffman M, Bratti MC, et al: A population-based study of vaginal human papillomavirus infection in hysterectomized women, *J Infect Dis* 190:458–467, 2004.

Castle PE, Sideri M, Jeronimo J, et al: Risk assessment to guide the prevention of cervical cancer, *Am J Obstet Gynecol* 197(4):356.e1–356.e6, 2007.

Castle PE, Schiffman M, Wheeler CM, et al: Evidence for frequent regression of cervical intraepithelial neoplasia—Grade 2, *Obstet Gynecol* 113:18–25, 2009.

Castle PE, Kreimer AR, Wacholder S, et al: Influence of loop electrosurgical excision procedure on subsequent acquisition of new human papillomavirus infections, *J Infect Dis* 199:1612–1620, 2009.

Castle PE, Gage JC, Wheeler CM, et al: The clinical meaning of a cervical intraepithelial neoplasia grade 1 biopsy, *Obstet Gynecol* 118:1222–1229, 2011.

Chen D, Cui T, Ek WE, et al: Analysis of the genetic architecture of susceptibility to cervical cancer indicates that common SNPs explain a large proportion of the heritability, *Carcinogenesis* 36(9):992–998, 2015.

Clarke MA, Wentzensen N, Mirabello L, et al: Human papillomavirus DNA methylation as a potential biomarker for cervical cancer, *Cancer Epidemiol Biomarkers Prev* 21:2125–2137, 2012.

Costa S, Venturoli S, Negri G, et al: Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: an analysis of 166 cases, *Gynecol Oncol* 124:490–495, 2012.

Cuzick J, Cadman L, Mesher D, et al: Comparing the performance of six human papillomavirus tests in a screening population, *Br J Cancer* 108:908–913, 2013.

Dillner J, Rebolj M, Birembaut P, et al: Joint European Cohort Study. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study, *BMJ* 337:a1754, 2008.

Eddy DM: Screening for cervical cancer, *Ann Intern Med* 113: 214–216, 1990.

Elfgren K, Kalantari M, Moberger B, et al: A population-based five-year follow-up study of cervical human papillomavirus infection, *Am J Obstet Gynecol* 183:561–567, 2000.

Erickson CC, Everett BE, Graves LM, et al: Population screening for uterine cancer by vaginal cytology: Preliminary summary of results of first examination of 108,000 women and second testing of 33,000 women, *JAMA* 162:167–173, 1956.

Figge DC, Creasman WT: Cryotherapy in the treatment of cervical intraepithelial neoplasia, *Obstet Gynecol* 62:353–358, 1983.

Flagg EW, Datta SD, Saraiya M, et al: Population-based surveillance for cervical cancer precursors in three central cancer registries, United States 2009, *Cancer Causes Control* 25:571–581, 2014.

Fukuda K, Hachisuga T, Nakamura S, et al: Local immune response in persistent cervical dysplasia, *Obstet Gynecol* 82:941–945, 1993.

Gage JR, Meyers C, Wettstein FO: The E& proteins of the nononcogenic human papillomavirus type 6b (HPV-6b) and of the oncogenic HPV-16 differ in retinoblastoma protein binding and other properties, *J Virol* 64:723–730, 1990.

Giuliano AR, Nyitray AG, Kreimer AR, et al: EUROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection, *Int J Cancer* 136:2752–2760, 2015.

Gonzalez P, Hildesheim A, Rodriguez AC, et al: Behavioral/lifestyle and immunologic factors associated with HPV infection among women older than 45 years, *Cancer Epidemiol Biomarkers Prev* 19:3044–3054, 2010.

Greenberg MD, Reid R, Schiffman M, et al: A prospective study of biopsy-confirmed cervical intraepithelial neoplasia grade 1: Colposcopic, cytological, and virological risk factors for progression, *J Low Genit Tract Dis* 3:104–110, 1999.

Gustafsson L, Ponten J, Zack M, et al: International incidence rates of invasive cervical cancer after introduction of cytological screening, *Cancer Cause Control* 8:755–763, 1997.

Halec G, Alemany L, Lloveras B, et al, Retrospective International Survey and HPV Time Trends Study Group; Retrospective International Survey and HPV Time Trends Study Group: Pathogenic role of the eight probably/possibly carcinogenic HPV types 26, 53, 66, 67, 68, 70, 73 and 82 in cervical cancer, *J Pathol* 234:441–451, 2014.

Hariri S, Unger ER, Sternberg M, et al: Prevalence of genital human papillomavirus among females in the United States, the National Health and Nutrition Examination Survey, 2003-2006, *J Infect Dis* 204:566–573, 2011.

Henk JH, Insinga RP, Singhal PK, et al: Incidence and costs of cervical intraepithelial neoplasia in a US commercially insured population, *J Lower Genit Tract Dis* 14:29–36, 2010.

Hildesheim A, Schiffman M, Bromley C, et al: Human papillomavirus type 16 variants and risk of cervical cancer, *J Natl Cancer Inst* 93:315–318, 2001.

Ho GYF, Burk RD, Klein S, et al: Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia, *J Natl Cancer Inst* 87:1365–1371, 1995.

Hogewoning CJA, Bleeker MCG, van den Brule AJC, et al: Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: A randomized clinical trial, *Int J Cancer* 107:811–816, 2003.

Huh WK, Ault KA, Chelmow D, et al: Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance, *J Low Genit Tract Dis* 19:91–96, 2015.

International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, et al: Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies, *Lancet* 370: 1609–1621, 2007.

International Collaboration of Epidemiological Studies of Cervical Cancer: Cervical carcinoma and sexual behavior: collaborative reanalysis of individual data on 15,461 women with cervical

carcinoma and 29,164 women without cervical carcinoma from 21 epidemiological studies, *Cancer Epidemiol Biomarkers Prev* 18:1060–1069, 2009.

International Collaboration of Epidemiological Studies of Cervical Cancer: Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies, *Int J Cancer* 119:1108–1124, 2006.

International Collaboration of Epidemiological Studies of Cervical Cancer: Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies, *Int J Cancer* 120:885–891, 2007.

Jakobsson M, Gissler M, Paavonen J, et al: Long-term mortality in women treated for cervical intraepithelial neoplasia, *BJOG* 116:838–844, 2009.

Kalliala I, Anttila A, Pukkala E, et al: Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study, *BMJ* 331:1183–1185, 2005.

Katki HA, Schiffman M, Castle PE, et al: Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines, *J Low Genit Tract Dis* 17:S28–S35, 2013.

Kinney W, Sung HY, Kearney KA, et al: Missed opportunities for cervical cancer screening of HMO members developing invasive cervical cancer (ICC), *Gynecol Oncol* 71:428–430, 1998.

Kjaer S, Hogdall E, Frederiksen K, et al: The absolute risk of cervical abnormalities in high-risk human papillomavirus-positive, cytologically normal women over a 10-year period, *Cancer Res* 66:10630–10636, 2006.

Khan MJ, Castle PE, Lorincz AT, et al: The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice, *J Natl Cancer Inst* 97:1072–1079, 2005.

Le T, Guijon F: Human papillomavirus infections and cervical intraepithelial neoplasia in renal transplant patients, *J Lower Genit Tract Dis* 3:155–158, 1999.

Luhn P, Walker J, Schiffman M, et al: The role of co-factors in the progression from human papillomavirus infection to cervical cancer, *Gynecol Oncol* 128:265–270, 2013.

Marks M, Gravitt PE, Gupta SB, et al: Combined oral contraceptive use increases HPV persistence but not new HPV detection in a cohort of women from Thailand, *J Infect Dis* 204:1505–1513, 2011.

Massad LS, Einstein MH, Huh WK, et al, for the 2012 ASCCP Consensus Guidelines Conference: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors, *J Low Genit Tract Dis* 17:S1–S27, 2013.

McAllum B, Sykes PHH, Sadler L, et al: Is the treatment of CIN2 always necessary in women under 25 years old?, *Am J Obstet Gynecol* 205:478.e1–478.e7, 2011.

McCredie MRE, Sharples KJ, Paul C, et al: Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: A retrospective cohort study, *Lancet Oncol* 9:425–434, 2008.

Molling JW, de Gruijl TD, Glim J, et al: CD4(+)CD25hi regulatory T-cell frequency correlates with persistence of human papillomavirus type 16 and T helper cell responses in patients with cervical intraepithelial neoplasia, *Int J Cancer* 121: 1749–1755, 2007.

Moscicki AB, Ma Y, Wibbelsman C, et al: Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women, *Obstet Gynecol* 116:1373–1380, 2010.

Papanicolaou GN, Traut HF: The diagnostic value of vaginal smears in carcinoma of the uterus, *Am J Obstet Gynecol* 42:193–206, 1941.

Quinn M, Babb P, Jones J, et al: Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics, *BMJ* 318:904–908, 1999.

Richart RM: Natural history of cervical intraepithelial neoplasia, *Clin Obstet Gynecol* 10:748–784, 1967.

Rintala MAM, Grenman SE, Puranen MH, et al: Transmission of high-risk human papillomavirus HHPV) between parents and infant: a prospective study of HPV in families in Finland, *J Clin Microbiol* 43:376–381, 2005.

Rodriguez AC, Schiffman M, Herrero R, et al: Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3:critical role of duration of infection, *J Natl Cancer Inst* 102:1–10, 2010.

Rodriguez AC, Schiffman M, Herrero R, et al: Low risk of type-specific carcinogenic HPV re-appearance with subsequent cervical intraepithelial neoplasia grade 2/3, *Int J Cancer* 131: 1874–1881, 2012.

Rositch AF, Burke AE, Viscidi RP, et al: Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women, *Cancer Res* 72:6183–6190, 2012.

Sanjose S, Quint WGV, Alemany L, et al: Human papillomavirus genotype attribution in invasive cervical cancer: A retrospective cross-sectional worldwide study, *Lancet Oncol* 11:1048–1056, 2010.

Sasieni P, Castanon A, Cuzick J: Effectiveness of cervical screening with age: Population based case-control study of prospectively recorded data, *BMJ* 339:b2968, 2009.

Schiffman S, Gary Clifford G, Buonaguro FM: Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline, *Infect Agent Cancer* 4:8, 2009.

Sellors JW, Karwalajtys TL, Kaczorowski J, et al, for the Survey of HPV in Ontario Women (SHOW) Group: Incidence, clearance, and predictors of human papillomavirus infection in women, *Can Med Assoc J* 168:421–425, 2003.

Serraino D, Gini A, Taborelli M, et al, for the IMPATTO-CERVICE Working Group: Changes in cervical cancer incidence following the introduction of organized screening in Italy, *Prev Med* 75:56–63, 2015.

Sharp L, Cotton S, Little J, et al, on behalf of the TOMBOLA group: Psychosocial impact of alternative management policies for low-grade cervical abnormalities: Results from the TOMBOLA randomised controlled trial, *PLoS ONE* 8:e80092, 2013.

Southern SA, Herrington CS: Disruption of cell cycle control by human papillomaviruses with special reference to cervical carcinoma, *Int J Gynecol Cancer* 10:263–274, 2000.

Stanhope CR, Phibbs GD, Stuart GC, et al: Carbon dioxide laser surgery, *Obstet Gynecol* 61:624–627, 1983.

Strander B, Andersson-Ellstrom A, Milsom I, et al: Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study, *BMJ* 335:1077, 2007.

Sung HY, Kearney KA, Miller Marie M, et al: Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan, *Cancer* 88:2283–2289, 2000.

Thomas DB, Ray RM, Kuypers J, et al: Human papillomaviruses and cervical cancer in Bangkok. III. The role of husbands and commercial sex workers, *Am J Epidemiol* 153:740–748, 2001.

Thomas KK, Hughes JP, Kuypers JM, et al: Concurrent and sequential acquisition of different genital human papillomavirus types, *J Infect Dis* 182:1097–1102, 2000.

Trimble CL, Piantadosi S, Gravitt P, et al: Spontaneous regression of high-grade cervical dysplasia: Effects of human papillomavirus type and HLA phenotype, *Clin Cancer Res* 11:4717–4723, 2005.

Van der Marel J, Quint WGV, Schiffman M, et al: Molecular mapping of high-grade cervical intraepithelial neoplasia shows etiological dominance of HPV-16, *Int J Cancer* 131:E946–E953, 2012.

Vinokurova S, Wentzensen N, Einenkel J, et al: Clonal history of papillomavirus-induced dysplasia in the female lower genital tract, *J Natl Cancer Inst* 97:1816–1821, 2005.

Wentzensen N, Nason M, Schiffman M, et al, for the New Mexico HPV Pap Registry Steering Committee: No evidence for synergy between human papillomavirus genotypes for the risk of high-grade squamous intraepithelial lesions in a large population-based study, *J Infect Dis* 209:855–864, 2014.

Wetta LA, Matthews KS, Kemper ML, et al: The management of cervical intraepithelial neoplasia during pregnancy: is colposcopy necessary?, *J Low Genit Tract Dis* 13:182–185, 2009.

Winer RL, Lee SK, Hughes JP, et al: Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students, *Am J Epidemiol* 157:218–226, 2003.

Zelmanowicz AM, Schiffman M, Herrero R, et al: Family history as a co-factor for adenocarcinoma and squamous cell carcinoma of the uterine cervix: Results from two studies conducted in Costa Rica and the United States, *Int J Cancer* 116:599–605, 2005.

2

Preinvasive Disease of the Vagina and Vulva and Related Disorders

Cara A. Mathews, MD, Joan L. Walker, MD

OUTLINE

KEY POINTS

1. Lichen sclerosis is associated with vulvar cancer.
2. Treatment of vaginal intraepithelial neoplasia III is laser vaporization.
3. Wide local excision is the treatment of choice for vulvar intraepithelial neoplasia III.
4. Imiquimod treatment is a potentially noninvasive treatment of vulvar dysplasia.

EMBRYOLOGY

At approximately 12 to 14 weeks of gestation, the simple columnar epithelium that lines the vaginal portion of the uterovaginal canal begins to undergo transformation into stratified Müllerian epithelium. This transformation proceeds cranially until it reaches the columnar epithelium of the future endocervical canal. The vagina, which is lined initially by simple columnar epithelium of Müllerian origin, acquires stratified Müllerian epithelium. The vaginal plate advances in a caudocranial direction, obliterating the existing vaginal lumen. By caudal cavitation of the vaginal plate, a new lumen is formed, and the stratified Müllerian epithelium is replaced by a stratified squamous epithelium, probably from a urogenital sinus origin. Local proliferation of the vaginal plate in the region of the cervicovaginal junction produces the circumferential enlargement of the vagina known as the vaginal fornices, which surround the vaginal part of the cervix.

The administration of diethylstilbestrol (DES) through the 18th week of gestation can apparently result in the disruption of the transformation of columnar epithelium of Müllerian origin to the stratified squamous successor (Fig. 2.1). This retention of Müllerian epithelium gives rise to adenosis. Adenosis may exist in many forms: glandular cells in place of the normal squamous lining of the vagina, glandular cells hidden beneath an intact squamous lining, or mixed squamous metaplasia when new squamous cells attempt to replace glandular cells.

Vaginal adenosis has been observed in patients without a history of DES exposure but rarely to a clinically significant degree. Adenosis is more common in patients whose mothers began DES treatment early in pregnancy and is not observed if DES administration began after 18 weeks of gestation. At least 20% of women exposed to DES show an anatomic deformity of the upper vagina and cervix; transverse vaginal and cervical ridges, cervical collars, vaginal hoods, and cockscomb cervices have all been described. The transverse ridges and anatomic deformities found in one-fifth of women exposed to DES make it difficult to ascertain the boundaries of the vagina and cervix. The cervical eversion causes the cervix grossly to have a red appearance. This coloration is caused by the numerous normal-appearing blood vessels in the submucosa. With a colposcope and application of 3% acetic acid solution, numerous papillae ("grapes") of columnar epithelium are observed, similar to those seen in the native columnar epithelium of the endocervix. The hood (Fig. 2.2) is a fold of mucous membrane surrounding the portio of the cervix; it often disappears if the portio is pulled down with a tenaculum or is displaced by the speculum. The cockscomb is an atypical peaked appearance of the anterior lip of the cervix, and vaginal ridges are protruding circumferential bands in the upper vagina that may hide the cervix. A pseudopolyp formation (see Fig. 2.2) has been described that occurs

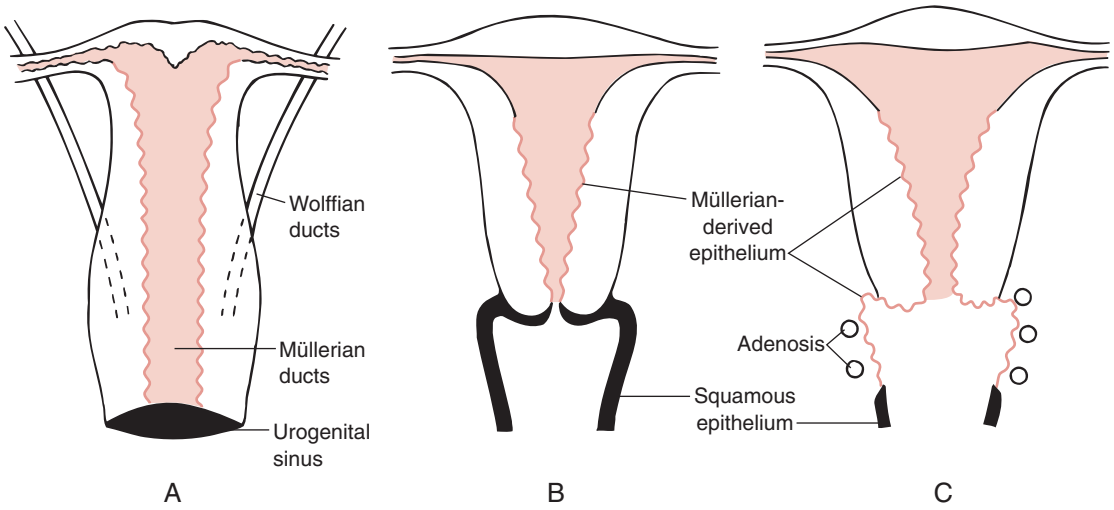

FIGURE 2.1 A–C, Schematic representations of the embryologic development of the vagina in unexposed (A) and diethylstilbestrol-exposed (B and C) women. (From Stillman RJ. In utero exposure to diethylstilbestrol: adverse effects on the reproductive tract and reproductive performance in male and female offspring. *Am J Obstet Gynecol* 1982;142(7):905.)

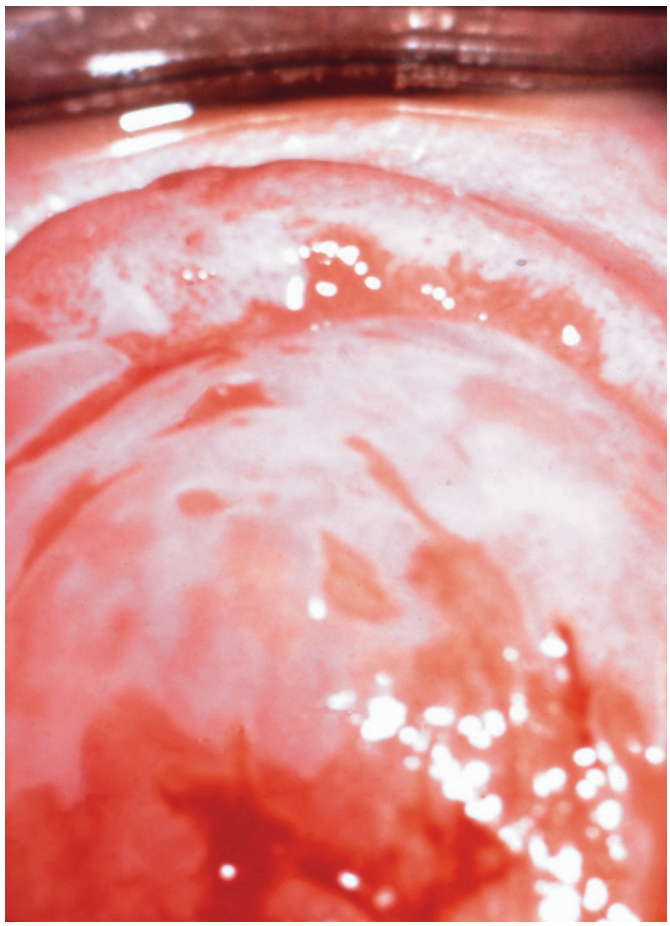

FIGURE 2.2 Hood surrounding the small diethylstilbestrol-exposed cervix, which is completely covered by columnar epithelium (pseudopolyp).

when the portio of the cervix is small and protrudes through a wide cervical hood.

The occurrence of vaginal adenosis among young women without in utero DES exposure implies that an event in embryonic development is responsible. The development of the Müllerian system depends on and follows formation of the Wolffian, or mesonephric, system. The emergence of the Müllerian system as the dominant structure appears unaffected by intrauterine exposure to DES when studied in animal systems. However, it is apparent that steroidal and nonsteroidal estrogens, when administered during the proper stage of vaginal embryogenesis in mice, can permanently prevent the transformation of Müllerian epithelium into the adult type of vaginal epithelium, thus creating a situation like adenosis. The colposcopic and histologic features of vaginal adenosis strongly support the concept of persistent, untransformed Müllerian columnar epithelia in the vagina as the explanation of adenosis.

EXAMINATION AND TREATMENT OF FEMALES EXPOSED TO DIETHYLSTILBESTROL

Essentially no DES has been prescribed to pregnant women since 1971, when the US Food and Drug Administration issued an alert regarding the risk of vaginal clear cell adenocarcinoma for females exposed in utero. The youngest women with in utero exposure were born in 1972, and many previously important clinical topics have become less relevant in everyday practice. The associated congenital anomalies and teenage cancers, for example, are no longer being diagnosed. However, an understanding of the disease process remains essential in order to care for this cohort of women as they age. Additionally, the evolution and understanding of DES is of great historical importance with many implications and lessons for today's practice.

Approximately 60% of women with in utero DES exposure have vaginal adenosis, cervical-like epithelium in the vagina, which appears red and granular. This is a benign condition that does not require treatment unless symptomatic, and it will generally resolve on its own over time. The premenopausal risk of clear cell adenocarcinoma is approximately 40 times higher among women with in utero DES exposure compared with those without the exposure. In unexposed women, clear cell adenocarcinoma occurs almost exclusively in menopause; in women with in utero exposure, most cases are diagnosed during the late teens and 20s. The oldest reported patient with DES-associated clear cell adenocarcinoma was diagnosed at 51 years. Overall, the incidence of clear cell adenocarcinoma is low in women with in utero exposure (≈1.5 cases/1000 women), but the risk is significantly higher than among unexposed women. The etiology of clear cell adenocarcinoma is unclear, and evolution of adenosis to cancer has never been directly proven, only suspected. Because of an increased risk of clear cell adenocarcinoma of the cervix and vagina and an increased risk of cervical intraepithelial neoplasia (CIN), annual examinations with Pap cytology testing are recommended for the entire lifetime of women with in utero DES exposure. No increased association has been observed between DES and squamous cell cervical cancer.

All DES-exposed females should have an annual gynecologic examination with cytology screening (Table 2.1). Cytology should include separate sampling of the cervix and upper vagina. If suspicious lesions are present, colposcopy and directed biopsies should be performed regardless of the cytology results. If delineations of the vagina, cervix, and endocervix are difficult, Lugol's solution may be helpful in detecting abnormal areas. Colposcopic examination of these patients is hindered by the abnormal patterns seen with squamous metaplasia (Fig. 2.3), which can be confused with neoplastic lesions. Histologic confirmation is essential before any treatment is undertaken. Marked mosaic (Fig. 2.4) and punctation patterns that normally herald intraepithelial neoplasia are commonly seen in the vagina of DES-exposed women as a result of widespread metaplasia. The purpose of regular examination is to permit

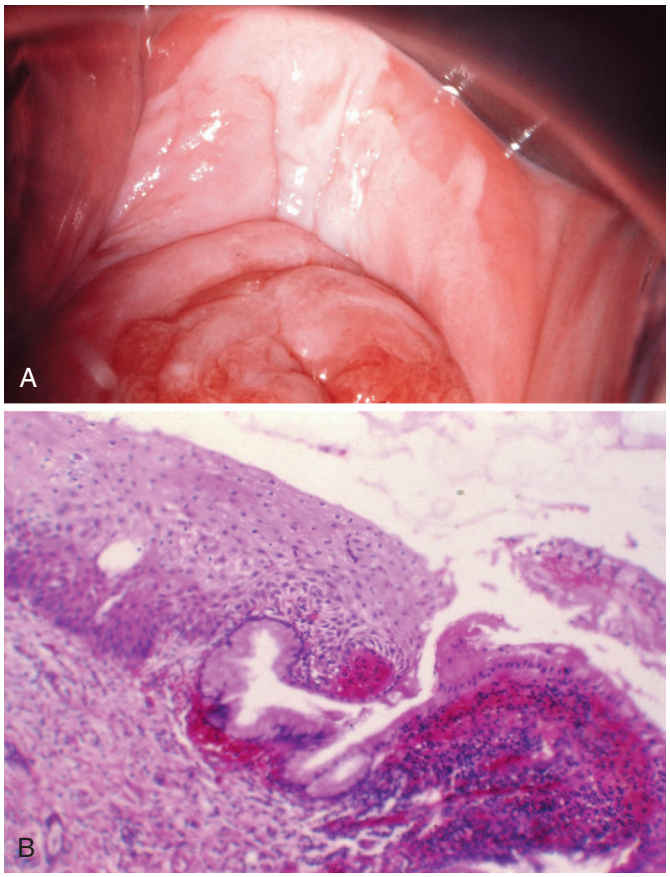

FIGURE 2.3 **A,** Area of white epithelium of squamous metaplasia. **B,** Histologic section of the area in *A* showing metaplasia to the left partially covering the adenosis (columnar epithelium) to the right.

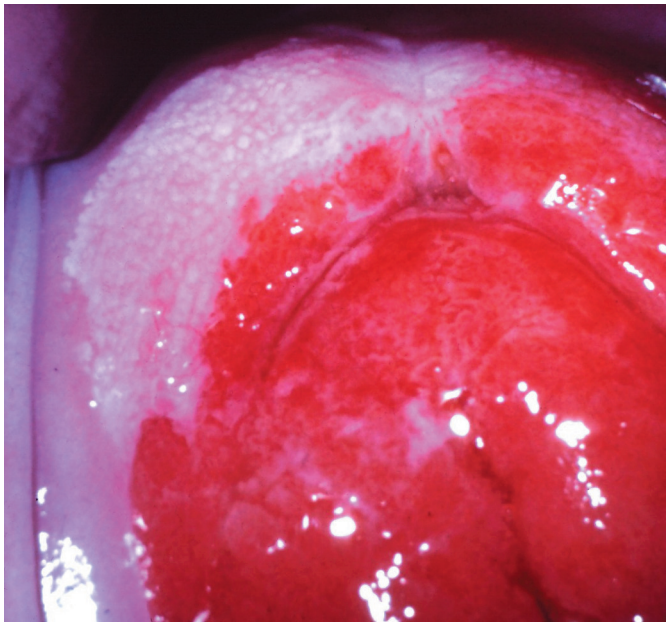

FIGURE 2.4 Heavy mosaic pattern (histologically proven metaplasia) in a hood surrounding the cervix of an offspring exposed to diethylstilbestrol.

TABLE 2.1 Examination of the Female Offspring Exposed to Diethylstilbestrol

1. Inspect the introitus and hymen to assess the patency of the vagina.
2. Palpate the vaginal membrane with the index finger (especially noting non–Lugol-staining areas), noting areas of induration or exophytic lesions, which should be considered for biopsy.
3. Perform a speculum examination with the largest speculum that can be comfortably inserted (virginal-type speculums are often necessary). Adenosis usually appears red and granular (strawberry surface).
4. Obtain cytologic specimens from the cervical os and the walls of the upper third of the vagina.
5. Perform a colposcopic examination or Lugol staining on the initial visit.
6. Do a biopsy of indurated or exophytic areas and colposcopically abnormal areas with a dysplastic Papanicolaou smear.
7. Perform a bimanual rectovaginal examination.

detection of adenocarcinoma and squamous neoplasia during the earliest stages of development. Although many therapies have been attempted, no recommended treatment plan for vaginal adenosis exists. In most cases, the area of adenosis is physiologically transformed into squamous epithelium during varying periods of observation, and no therapy is necessary.

NONNEOPLASTIC EPITHELIAL DISORDERS OF THE VULVA

Nonneoplastic epithelial disorders of the vulvar skin and mucosa are frequently seen in clinical practice. Diagnosis is difficult without a biopsy to provide a histologic result, and multiple changes in terminology over the past 25 years add confusion to clinical management. The most recent classification guidelines were published in 2007 by the International Society for the Study of Vulvovaginal Disease (ISSVD) (Table 2.2). The lichenoid pattern subset includes two chronic diseases, lichen sclerosus and lichen planus, which are relevant to this review because of the association of those two diseases with vulvar cancer. Lichen simplex chronicus is not included in the lichenoid subset; it is classified in the acanthotic pattern subset. This is appropriate from an oncology viewpoint because lichen simplex chronicus is not associated with invasive cancer. With similar presenting symptoms and a hyperkeratotic appearance, however, lichen simplex chronicus can be difficult to discriminate from lichen sclerosus and lichen planus on examination (Table 2.3).

TABLE 2.2 2006 World Congress International Society for the Study of Vulvovaginal Disease (Classification of Vulvar Dermatoses)

Pathologic Subset	Clinical Correlate
Spongiotic pattern	Atopic dermatitis
	Allergic contact dermatitis
	Irritant contact dermatitis
Acanthotic pattern	Psoriasis
	Lichen simplex chronicus
	Primary (idiopathic)
	Secondary (superimposed on other vulvar disease)
Lichenoid pattern	Lichen sclerosus
	Lichen planus
Dermal homogenization/sclerosis pattern	Lichen sclerosus
Vesiculobullous pattern	Pemphigoid, cicatricial type
	Linear IgA disease
Acantholytic pattern	Hailey-Hailey disease
	Darier disease
	Papular genitocrural acantholysis
Granulomatous pattern	Crohn's disease
	Melkersson-Rosenthal syndrome
Vasculopathic pattern	Aphthous ulcers
	Behçet disease
	Plasma cell vulvitis

Lichen Simplex Chronicus

Lichen simplex chronicus presents in girls and women of all ages, but it is more common in the reproductive and postmenopausal years. Lichen simplex chronicus is a chronic eczematous condition, and most women with this condition also have a history of atopic dermatitis. Pruritus is the most common symptom, and over time, scratching leads to epithelial thickening and hyperkeratosis. The status of the skin usually relates to the amount of scratching. Exacerbating agents may include heat, moisture, sanitary or incontinence pads, and topical agents. Lichen simplex chronicus may be seen in conjunction with other processes such as *Candida* infections or lichen sclerosus; these primary diseases must be treated in order to treat the pruritus leading to scratching and hyperkeratosis.

The locations most often involved on the vulva include the labia majora, interlabial folds, outer aspects of the labia minor, and clitoris. Changes can also extend to the lateral surfaces of the labia majora or beyond. Areas of lichen simplex chronicus are often localized, elevated, and well-delineated, but they may be extensive and poorly defined. The appearance of lesions may vary greatly even in the same patient. The vulva often appears dusky red when the degree of hyperkeratosis is slight and may appear thickened and leathery when hyperkeratosis persists. At other times, well-defined white patches may be seen, or a combination of red and white areas may be observed in different locations. Thickening, fissures, and excoriations require careful evaluation because carcinoma may be exhibited by these same features. For this reason, biopsy is essential in ascertaining the correct diagnosis.

Biopsy reveals a variable increase in the thickness of the horny layer (hyperkeratosis) and irregular thickening of the

TABLE 2.3 Other Dermatoses

Disorder	Lesion	Genital	Other Locations
Seborrheic dermatitis	Erythema with mild scale oval plaques	Mild scaling; also "inverse type"	Central face, neck, scalp, chest, back
Psoriasis	Annular scaly plaques that bleed easily	Red plaques with gray-white scale	Scalp, elbows, knees, sacrum
Tinea	Annular plaques with central clearing	Common	Skinfolds or single "ringworm" lesion
Lichen simplex chronicus	Lichenified plaques, some dermatitic	Scrotum or labia majora	Nape of the neck, ankle, forearm, antecubital and popliteal fossae
Lichen planus	Flat-topped lilac papules and plaques	White network, erosive vaginitis	Volar wrists, shins, buccal mucosa

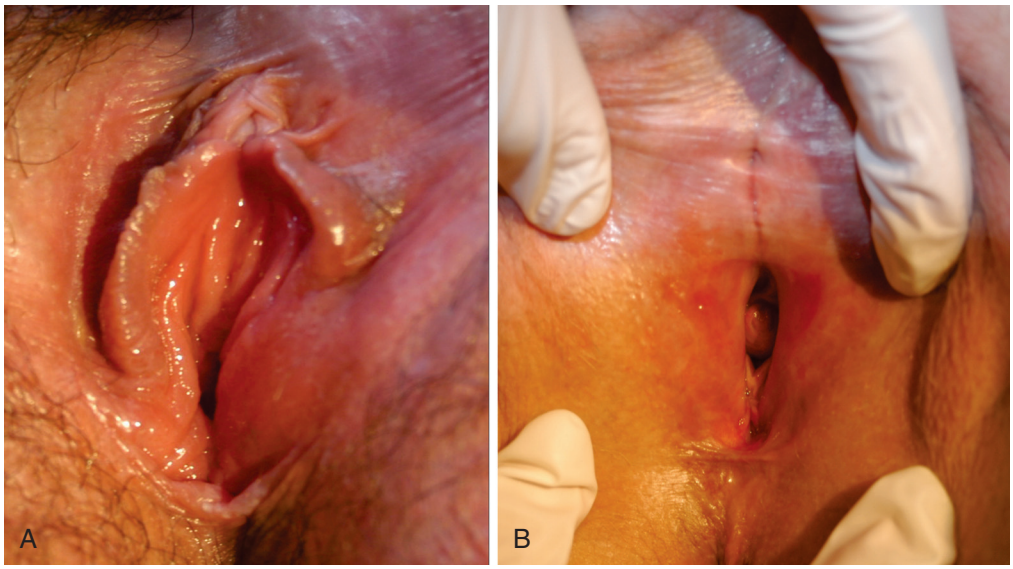

FIGURE 2.5 Progression from early (**A**) to late (**B**) lichen sclerosus, with characteristic loss of labial architecture. (Courtesy Dr. Lori Boardman, MD, ScM, University of Central Florida College of Medicine.)

malpighian layer (acanthosis). This latter process produces a thickened epithelium and lengthening and distortion of the rete pegs. Parakeratosis may also be present. The granular layer of the epithelium is usually prominent. An inflammatory reaction is often present within the dermis with varying numbers of lymphocytes and plasma cells.

Lichen Sclerosus

Lichen sclerosus represents a specific disease found in genital and nongenital sites. The vulva is the most common lesion site in women. The age distribution of the disease is bimodal with peaks during the premenarchal and postmenopausal years, but the highest incidence is among postmenopausal women. Although the overall incidence and prevalence are unknown, Leibovitz and colleagues reported the prevalence among elderly women in a nursing home setting as 1 in 30. The mean age in this population was 82 years, 88% were wheelchair users, and 86% were incontinent (Figs. 2.5 and 2.6).

Over time, pruritus occurs with essentially all lesions, leading to scratching, which can develop into ecchymosis and ulceration. Symptoms evolve to include burning, tearing, and dyspareunia. Studies have suggested that the epithelium in lichen sclerosus is metabolically active and nonatrophic. A chronic inflammatory, lymphocyte-mediated dermatosis is present. The etiology of the disease is poorly understood, but autoimmune mechanisms appear to be involved.

The microscopic features of lichen sclerosus include hyperkeratosis, epithelial thickening with flattening of the rete pegs, cytoplasmic vacuolization of the basal layer of cells, and follicular plugging. Beneath the epidermis is a zone of homogenized, pink-staining, collagenous-appearing tissue that is relatively acellular. Edema is occasionally seen in this area. Elastic fibers are absent. Immediately below this zone lies a band of inflammatory cells that is consistent with lymphocytes and some plasma cells. Lichen sclerosus is often associated with foci of both hyperplastic epithelium and thin epithelium. Lichen simplex chronicus has been found in 27% to 35% of women with lichen sclerosus after microscopic study of vulvar specimens, likely secondary to pruritus and scratching.

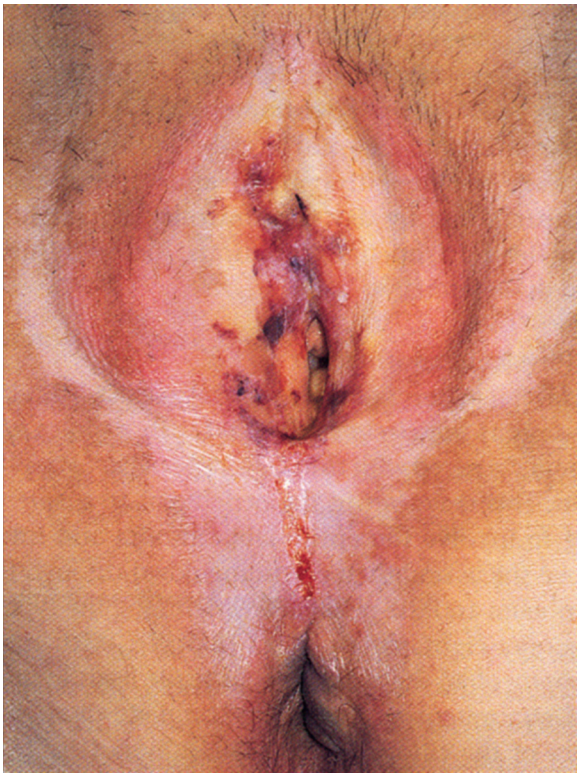

FIGURE 2.6 Lichen sclerosus with stenosis of the introitus, fissuring in the posterior fourchette, and perianal involvement producing the "keyhole appearance." (Courtesy of Dr. Lori Boardman, MD, ScM, University of Central Florida College of Medicine.)

In a well-developed classic lesion, the skin of the vulva is crinkled ("cigarette paper") and thinned, or appears parchment-like. The process often extends around the anal region in a figure-of-8 or keyhole configuration, and 30% of women have perianal lesions. At other times, the changes are localized, especially in the periclitoral area or the perineum. Clitoral involvement is usually associated with edema of the foreskin, which may obscure the glans clitoris. Phimosis of the clitoris is often seen late in the course of the disease. As the disease progresses, there is loss of architecture of the normal external genitalia. The labia minora may completely disappear as a result of atrophy. Synechiae often develop between the edges of the skin in these locations, causing pain and limited physical activity. Fissures also develop in the natural folds of the skin and especially in the posterior fourchette. The introitus may become so strictured or stenosed that intercourse is impossible. The vaginal mucosa is generally spared in this disease, which is helpful in discriminating between lichen sclerosus and lichen planus. In a study by Dalziel, 44 women with lichen sclerosus were evaluated for sexual dysfunction. Apareunia was experienced by 19 of the women at some point. Dyspareunia and decreased frequency of intercourse were noted by 80%, and orgasm was altered and relationships were affected in half. Local steroids improved sexual function in two-thirds of these patients.

Lichen sclerosus is a risk factor for invasive vulvar cancer, likely as a result of chronic inflammation and sclerosis. In untreated populations, approximately 5% of patients with lichen sclerosus also have intraepithelial neoplasia. Wallace followed 290 women with lichen sclerosus for an average of 12.5 years and found that 4% (n = 12) developed vulvar cancer. Carlson et al. reported that 4.5% of patients with lichen sclerosus developed vulvar cancer over a mean of 10 years. In treated populations, however, the risk may be lower. Cooper and associates treated 233 women in a vulvar teaching clinic over a 10-year period; 89% of the cohort received superpotent steroid treatment. Invasive vulvar cancer developed in 3% (n = 7), and vaginal intraepithelial neoplasia (VAIN) developed in 2% (n = 4). Jones and colleagues reported one case of cancer from a vulvar clinic treating 213 girls and women older than age 8 years. Renaud-Vilmer et al. reported results from an urban dermatology clinic caring for 83 girls and women with no prior treatment of vulvar lichen sclerosus. Invasive cancer was present at the time of presentation in 7% (n = 6) and developed in 2% (n = 2); in those who developed cancer, one did not return for follow-up, and one did not use the prescribed treatment. In a cohort followed prospectively with repeat vulvar examinations at the University of Florence by Carli and associates, two cases of invasive cancer and one case of vulvar intraepithelial neoplasia (VIN) developed among 211 women with treated lichen sclerosus. All three cases occurred after more than 3 years of follow-up in the cohort.

The absolute incidence of vulvar cancer is low in women with lichen sclerosus, but 50% to 70% of squamous cell vulvar cancers occur in a background of lichen sclerosus. Currently, there is no diagnostic tool to differentiate between lichen sclerosus that will remain benign versus lichen sclerosus that will evolve into squamous cell carcinoma (SCC). Two biomarkers, p53 and monoclonal antibody MIB1, have shown promise in retrospective tissues studies, but further testing is necessary. The standard of care for cancer screening in this population remains serial examination with directed biopsies for new, evolving, or suspicious lesions, teaching self-examination with a mirror, and having self-reporting to a physician when lesions change visibly and to palpation.

Lichen Planus

Lichen planus is a distinct dermatologic disease that may affect the oral mucosa, esophageal mucosa, skin, scalp, nails, and eyes in addition to the vulva. Approximately 1% of the population likely develops lichen planus; 25% to 50% of women with lichen planus are believed to have vulvar symptoms. Both vulvovaginal-gingival syndrome and penile-gingival syndrome have been described. The disease appears to be a cell-mediated immune disorder causing chronic inflammation. Similar to lichen sclerosus, symptoms are most common in postmenopausal women in their 50s and 60s; usually include pruritus; and can evolve as the disease progresses to include burning, pain, and dyspareunia. Labial agglutination and loss of architecture of the labia and clitoris may occur. The vaginal mucosa is frequently involved, as opposed to lichen sclerosus, which rarely involves the vagina (Fig. 2.7).

The relationship between lichen planus and vulvar cancer is not as well-established as the association between lichen sclerosus and cancer. Small studies have suggested an increased risk of vulvar cancer, and subjects with oral lichen planus may also

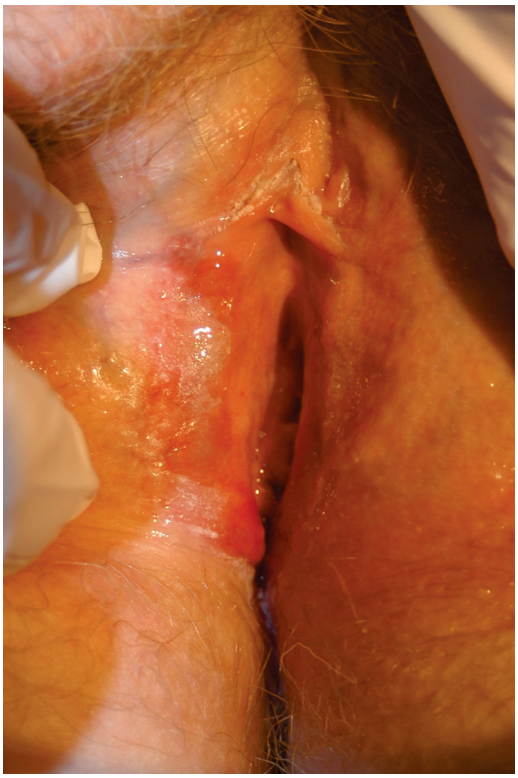

FIGURE 2.7 Erosive lichen planus. (Courtesy of Dr. Lori Boardman, MD, ScM, University of Central Florida College of Medicine.)

have an increased risk of oral cancer. In the early 1990s, case reports by Franck and Young, Lewis and Harrington, and Dwyer and colleagues reported incidences of vulvar SCC in subjects with lichen planus and within erosive lichen planus lesions. In a review of 113 patients with erosive vulvar lichen planus followed by Kennedy and colleagues over an 8-year period, one woman developed vulvar cancer. Of interest, two women in this cohort with oral lichen planus were subsequently diagnosed with oral or esophageal cancer, and two additional women were diagnosed with cervical adenocarcinoma in situ and rectal adenocarcinoma. Similar findings were reported by Cooper and associates. Of 114 women with erosive vulvar lichen planus, seven developed VIN, one developed oral SCC, two developed anogenital SCCs of the labium minora and perianal area.

Diagnosis and Treatment

Biopsies are critical to appropriate management; before any treatment is given on a long-term basis, biopsies should be performed from representative areas to ensure the correct diagnosis. (The exception for biopsy is the pediatric population, which will not be discussed here.) Biopsies should be focused at sites of fissuring, ulceration, induration, and thick plaques. Patient education regarding hygienic measures for keeping the vulva clean and dry is important; any soaps, perfumes, deodorizers, or other contact irritants should be avoided. A thorough history should be taken to evaluate possible causes of vulvar pruritus. After lesions with malignant potential have been ruled out, local measures for control of symptoms, primarily pruritus, can be instituted (Table 2.4). Additionally, infectious vaginitis should be ruled out with a saline wet preparation, potassium hydroxide (KOH) wet preparation, and yeast culture to evaluate for atypical yeast that may be missed on plain microscopy.

Lichen Simplex Chronicus

Therapy for lichen simplex chronicus is treatment of the underlying cause of irritation and pruritus. All offending environmental agents should be avoided, including wipes, lubricants, sanitary and incontinence pads, detergents, perfumes, and soaps. A thorough history is often necessary to identify possible sources of irritation. Any underlying vaginitis also requires treatment. For isolated lichen simplex chronicus, a topical steroid ointment such as triamcinolone 0.1% or hydrocortisone 2.5% can be applied daily (after bathing to help seal in moisture) until symptoms are improved, generally in 3 to 4 weeks. If symptoms are particularly severe or a course of low-dose steroids is insufficient, a trial of higher dose steroid ointment is acceptable. Pruritus is often most severe at night, and short-term use of a pharmacologic sleep aid may be necessary. Lichen simplex chronicus should resolve with removal of the offending agent and treatment; if symptoms persist or recur, repeat biopsies and the diagnosis should be reconsidered.

TABLE 2.4 Vulvar Nonneoplastic Epithelial Disorders

Disorder	Treatment
Lichen sclerosus	Topical high-potency steroid ointment
Lichen planus	Topical high-potency steroid ointment
Lichen simplex chronicus	Topical corticosteroid after evaluation and removal of offending environmental agents and treatment of concurrent vaginitis, lichen sclerosus, or lichen planus

Lichen Sclerosus

Lichen sclerosus is a chronic condition with no curative treatment; the goal is symptom control. The standard treatment for lichen sclerosus is a topical corticosteroid. Typical regimens begin with a superpotent steroid ointment (ie, clobetasol propionate ointment 0.05%) used nightly until resolution of symptoms (usually 8–12 weeks). Because of the chronicity of lichen sclerosus, maintenance therapy is necessary after initial treatment; application one to three times per week is usually sufficient. Many women stop treatment when their symptoms improve and then present again months later with recurrent symptoms. Therapy can be reinitiated at treatment levels for 6 to 12 weeks, and emphasis given to maintenance therapy. Theoretically, long-term use of topical steroids may result in striae and thinning of the dermis, but this is infrequently observed in patients with lichen sclerosus. Topical testosterone is no longer the treatment of choice for lichen sclerosus.

A prospective randomized study by Bracco and associates evaluated 79 patients with lichen sclerosus using four different treatment regimens: a 3-month course of testosterone (2%), progesterone (2%), clobetasol propionate (0.05%), and a cream base preparation. Patients experienced greater relief of symptoms with clobetasol (75%) than with testosterone (20%) or other preparations (10%). Clobetasol therapy was the only treatment in which the gross and histologic evaluation of patients improved after treatment. Recurrences after stopping the steroid occurred, but symptoms were relieved when therapy was resumed. Clobetasol was also more effective than testosterone in the randomized trial performed by Bornstein and colleagues, with a significant improvement in long-term relief experience by clobetasol users. Lorenz and colleagues reported 77% had complete remission of symptoms with clobetasol therapy but again noted that maintenance therapy was needed after baseline treatment. In the cohort followed by Cooper and associates discussed previously, 65% were symptom free, 31% had a partial response, and 5% has a poor response after steroid use. Improvement was also seen on physical examination; 23% had total resolution, 69% had partial resolution (improvement in purpura, hyperkeratosis, fissures, and erosions but no change in color and texture), 6% had minor resolution, and 2% had no improvement. Renaud-Vilmer and colleagues noted a different response rate by age group in women treated with 0.05% clobetasol propionate ointment. Complete remission, defined as complete resolution of symptoms, normalization of physical examination, and histologic regression of lichen sclerosus, was observed in 72% of women younger than age 50 years, 23% of women between 50 and 70 years, and 0% in women older than 70 years. Relapse was 84% at 4 years but was not associated with subject age.

Occasionally, vulvar pruritus is so persistent that it cannot be relieved by topical measures. Topical treatment may also fail

if significant hyperkeratosis is present. In such cases, intradermal and lesional injection of steroids has been reported to be effective. If lesions persist and symptoms do not improve after a course of superpotent topical steroids, biopsies should be repeated to confirm the initial diagnosis. It is again critical to rule out cancer and VIN to ensure appropriate treatment. Other regimens have been reported for lichen sclerosus recalcitrant to corticosteroids. Specifically, tacrolimus and photodynamic therapy may have some efficacy, but further trials are necessary.

Lichen Planus

Lichen planus is similarly treated with complete evaluation, patient education, and topical steroids. Additionally, the physical examination should exclude the presence of lichen planus on the skin, scalp, nail beds, and oral mucosa. If systemic disease is present, consultation with a dermatologist is useful. Treatment of vulvar lesions should begin with an ultrapotent steroid ointment (ie, clobetasol propionate ointment 0.05%) applied nightly for 6 to 8 weeks. If symptoms improve, the frequency of application can be reduced to two to three times weekly for 4 to 8 additional weeks. Cooper and associates reported that in a cohort of 114 women followed and treated for lichen planus, 71% of those treated with ultrapotent topical corticosteroids experienced relief of symptoms with treatment. On examination, 50% experienced healing of erosions, but no patients had resolution of scarring. When lichen planus symptoms are in a prolonged remission, the lowest effective dose is used for maintenance therapy, which may involve less frequent administration and a lower potency steroid. Similar to lichen sclerosus, symptoms will return if maintenance therapy is not used.

Lichen planus does appear more resistant to therapy than lichen sclerosus. In a small series of women with vulvar lichen planus that was nonresponsive to other treatments, Byrd and colleagues at the Mayo Clinic reported that 15 of 16 subjects experienced symptomatic relief after a course of topical tacrolimus. The mean response time was 4 weeks, and six subjects experienced mild irritation, burning, or tingling that resolved with persistent use. Tacrolimus therapy was less successful in the subjects followed by Cooper and associates, who were nonresponsive to topical steroid treatment. Of seven patients treated, two had complete symptomatic relief, three had some relief, and two had no improvement in symptoms.

INTRAEPITHELIAL NEOPLASIA OF THE VAGINA

Clinical Profile

The incidence of VAIN is not well described. The first report was by Graham and Meigs in 1952. They reported three patients with carcinoma of the vagina, two intraepithelial and one invasive, that were discovered 6, 7, and 10 years, respectively, after total hysterectomy for CIS (carcinoma in situ) of the cervix. Carcinoma in situ is a historical diagnosis, equivalent to the modern diagnosis of HSIL or CIN2/3. The most recent analysis of the incidence of VAIN in the United States, published in 1977, reported 0.2 to 0.3 cases per 100,000 women. Data published by Joura and colleagues from a large vaccine trial give a more recent estimate: The incidence of high-grade VAIN in the placebo group—women from 24 countries between 16 and 26 years of age who were followed for a mean of 36 months—was 21 cases in 9087 subjects. There may be multiple reasons for the higher incidence observed in the vaccine trial such as a true rise in incidence since 1977 similar to the increase seen for VIN, a higher rate of diagnosis because the women were being followed with serial examinations, or a different population from a more heterogeneous international setting. VAIN has many of the same risk factors associated with CIN, including smoking, earlier age at first intercourse, increased number of sexual partners, and HPV infection.

CIN of the vagina is much less common than that of the cervix or vulva. For the year 2015, the American Cancer Society estimated that 4080 cases of invasive cancer of the vagina would be diagnosed in the United States. Although the incidence of vaginal cancer has increased over the past several years, it remains rare. Because of the low prevalence of the disease, routine screening for VAIN and vaginal cancer is not recommended. After hysterectomy for benign disease, the incidence of VAIN is extraordinarily low, and guidelines from the American College of Obstetricians and Gynecology (ACOG) and the American Society for Colposcopy and Cervical Pathology (ASCCP) do not support Pap testing in this population. These guidelines were written in part based on evidence from Pearce and colleagues, Noller and Stokes-Lampard and colleagues showing that a huge number of women would undergo unnecessary cytology screening and colposcopy in order to diagnose a rare outcome. The exceptions to this guideline include women who have a history of in utero DES exposure, are immunosuppressed, or have a history of cervical or vulvar dysplasia. Many women have accepted historical guidelines recommending annual Pap testing and may require counseling and patient education to accept these new guidelines. Rare, unfortunate cases of VAIN or invasive cancer will occasionally be diagnosed in women who have undergone hysterectomy for benign disease, but these exceptional cases cannot drive screening guidelines. Additionally, because VAIN and vaginal cancer are strongly associated with HPV infection, the HPV vaccination should drive a decrease in the number of these cases in the future.

Patients with VAIN tend to have either an antecedent or coexistent neoplasia in the lower genital tract. This is the usual situation in at least half to two-thirds of all patients with VAIN. In patients who have been treated for disease in the cervix or vulva, VAIN can appear many years later, necessitating long-term follow-up. First van der Linde, then Gusberg and Marshall, and later Parker indicated that 2%, 1.9%, and 0.9% of patients, respectively, had vaginal recurrences after hysterectomy for a similar lesion in the cervix. More recently, Schockaert and associates were able to follow 94 women who had hysterectomies and concurrently carried a diagnosis of CIN II, CIN III, or FIGO stage Ia1 cervical cancer. In a median interval of 35 months, 7.4% ($n = 7$) developed VAIN II+ (vaginal intraepithelial neoplasia II or greater), including two vaginal cancers. Ferguson and Maclure reported positive cytologic findings in 151 (20.3%) of 633 previously treated patients. This large group included invasive and in situ cancers of the cervix, which were

treated by irradiation or hysterectomy. The long-term recurrence rate for CIS of the vagina is uncertain, but it is sufficient to merit continued careful follow-up.

Vaginal intraepithelial neoplasia and invasive cancer are both associated with HPV. HPV positivity rates reported in the literature range from 82% to 94% for VAIN and 60% to 75% for vaginal cancer, and HPV-16 and -18 account for the majority of HPV positivity. In early reports, vaccination appears to be effective at preventing HPV-16– and HPV-18–associated vaginal lesions in women who receive the vaccination before HPV exposure. HPV mapping has shown identical DNA integration loci between primary lesions of cervical dysplasia and later dysplastic lesions of the vagina and vulva, indicating that later disease may result from monoclonal lesions from the primary cervical dysplasia. Vaginal dysplasia appears to mimic cervical dysplasia with a high prevalence of HPV infection, as opposed to vulvar dysplasia, which displays inconsistent associations.

Isolated lesions can usually be recognized colposcopically (Fig. 2.8). The most frequent finding is acetowhite epithelium; mosaicism and punctuation can also be present, and some authors have described a "pink blush" appearance or a slightly granular texture. The diagnosis is confirmed by biopsy. The extent of the lesion can be evaluated with the colposcope or with Lugol's solution. Almost all lesions are asymptomatic, although a patient will occasionally have discharge or postcoital staining. An abnormal Pap smear result usually initiates the diagnostic survey. In almost all series, the upper third of the vagina is most frequently involved (as is the case with the invasive variety), and the posterior wall of the vagina appears more susceptible.

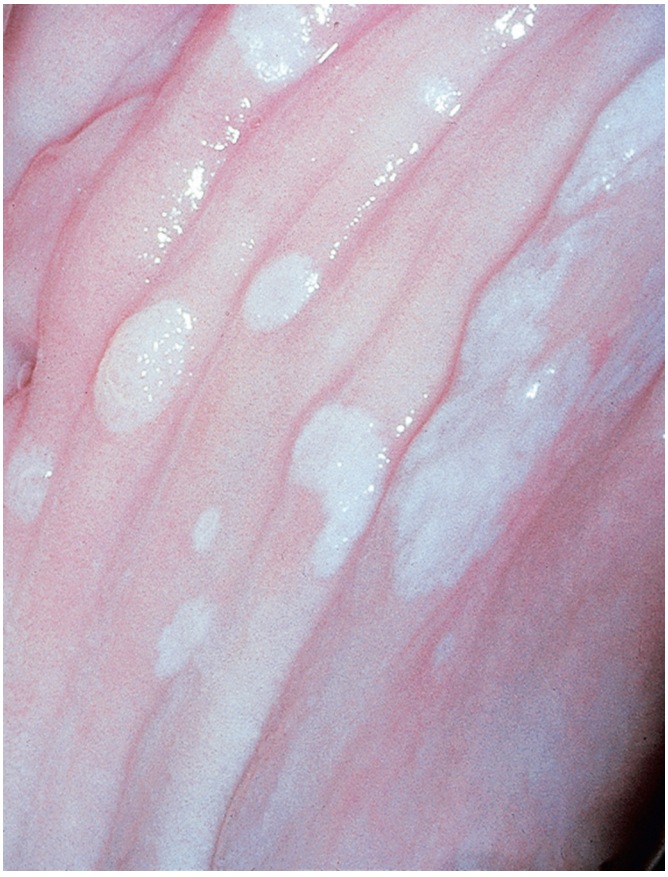

FIGURE 2.8 Carcinoma in situ of the vagina (colposcopic view).

Diagnosis

Patients with an abnormal Pap test result who do not have a cervix or patients with an abnormal Pap test result and no cervical abnormality visualized should undergo a careful examination of the vaginal epithelium. Colposcopic examination of the vagina can be difficult to perform. The largest possible speculum should be used and repositioned frequently to allow inspection of all surfaces. Colposcopic findings are similar to those described for the cervix. Each of the four walls should be examined from the apex to the introitus as separate and sequential steps. Small biopsy specimens are taken with a Tischler or Kevorkian–Younge alligator-jaw forceps. Sometimes a sterilized skin-hook for traction at the biopsy site may be helpful. Most patients can tolerate these biopsies without local anesthesia, but the anticipated pain from the biopsies versus pain from a local anesthetic injection should be considered. Lugol's solution is often helpful in delineating lesions of the vagina. Normal vaginal epithelium is stained brown, but dysplastic lesions with abnormal glycogen levels remain pale. In postmenopausal patients, local use of estrogen creams for several weeks helps to highlight the abnormal areas for identification by colposcopy.

The majority of VAIN is multifocal; even if a lesion is identified, one must search the entire vagina for coexisting, multiple lesions. Lesions are more common in the upper third of the vagina, but disease-free skip areas may be encountered with additional VAIN in the lower vagina. In hard-to-locate lesions, selective cytologic methods, such as obtaining Pap smears from different locations in the vagina, can often pinpoint the area of abnormality so that attention can be paid specifically to the area of highest suspicion.

Management

Local excision of the involved area has been the mainstay of therapy. In many cases, a single isolated lesion can be removed easily in the office with biopsy forceps. If larger areas are involved, an upper colpectomy may be necessary if the lesion is to be removed by surgery. A dilute pitressin solution or lidocaine with epinephrine can be injected submucosally at the beginning of the procedure and will greatly facilitate the vaginectomy.

As in CIN, outpatient modalities of therapy have been investigated for VAIN. Many patients have been treated historically with 5-fluorouracil (5-FU), but toxicity generally makes this a less desirable option, particularly in women who are sexually active. However, studies by Petrilli and associates and Caglar and colleagues indicate that this modality can be effective. One of the problems with 5-FU is the selection of the best mode of application, dosage, and length of treatment. Several techniques have been suggested with equivalent results. One-quarter applicator of 5% 5-FU cream is inserted high in the vagina each night after the patient is in bed. The patient can be instructed to coat the vulva and introitus with white petroleum because the cream leaks out during sleep. A small tampon or cotton ball at the introitus is also helpful to prevent leakage. Because of irritation

to the vagina and perineum, the cream should be removed by douching with warm water the next morning. This is done every night for 5 to 8 days followed by a 10- to 14-day rest period, and then the application cycle is repeated. This usually allows an adequate treatment time without having the patient experience the tremendous local reaction that can occur with prolonged use. Treatment can be repeated if it is not successful after the first cycle. Weekly insertions of 5-FU cream, approximately 1.5 g (one-third of an applicator), deep into the vagina once per week at bedtime for 10 consecutive weeks has also been shown to be efficacious. Placement of cotton balls at the introitus and application of a petroleum barrier on the perineum and vaginal introitus help prevent 5-FU contamination of the perineum with resultant skin irritation. Douching the next morning, which is advocated by some, is unnecessary with the weekly instillation. Patient compliance is likely higher and toxicity less with the second approach.

Dungar and Wilkinson noted an interesting finding in the vagina after 5-FU therapy, and it has been confirmed by others. After treatment, a red area suggestive of a lack of squamous epithelium may be present. They found that this represented columnar epithelium consistent with a metaplastic process in which squamous epithelium is replaced with columnar epithelium. They called this finding "acquired vaginal adenosis." These changes are usually found in the upper third of the vagina but may extend into the middle third. The columnar epithelium was of a low cuboidal or mucus-secreting endocervical type. In some cases, squamous epithelium was noted overlying the glandular elements. Marked superficial chronic inflammation was also present. This has also been noted in the vagina after laser therapy.

Cryosurgery has largely fallen out of favor in the treatment of VAIN, and laser therapy is preferred as an ablative technique. To give guidance about the depth of vaginal destruction required by the laser, Benedet and associates evaluated 56 patients who ranged from 22 to 84 years of age. Measurement of the epithelium was performed on involved and uninvolved tissue. The involved epithelium had a mean thickness of 0.46 mm (range, 0.1–1.4 mm). Uninvolved tissue was thinner and had a mean thickness of 0.28 mm. No statistical difference was seen in the thickness of the involved epithelium in the premenopausal and postmenopausal patients; however, the uninvolved epithelium was thinner in the postmenopausal patients compared with the premenopausal patients (0.25 vs. 0.37 mm). Based on this study, the authors believed that destruction of 1 to 1.5 mm would only destroy the epithelium without damaging underlying structures.

Over a 6-year period, Townsend and associates treated 36 patients from two large referral hospitals with a CO_2 laser. In 92% of the patients, the lesions were completely removed by the laser without significant side effects. Almost one-fourth of the patients, however, required more than one treatment session. Krebs treated 22 patients with topical 5-FU and 37 patients with laser therapy. The success rate was similar for the two treatments. Pain and bleeding have been the main complications but appear to be minimal. Healing is excellent, and impaired sexual function has not been a problem. The optimal technique of laser therapy for vaginal lesions has yet to be determined; whereas some investigators suggest removing only the identified lesions, others advocate treating the entire vagina to avoid missing other lesions. A thorough diagnostic investigation of the vagina to rule out invasive cancer can be difficult, but it is obviously mandatory. Evidence from vaginectomy series shows that invasive cancer may be present concurrently with VAIN. In the 105 patients with VAIN II or VAIN III treated with vaginectomy by Indermaur and colleagues, 12% ($n = 13$) had invasive cancer on final pathology, and 22% ($n = 23$) had negative findings. Multifocal lesions, particularly posthysterectomy, with deep vaginal angles may be difficult to treat with the laser. Small skin hooks and dental mirrors can be used as adjuncts to successful laser therapy.

More recently, experience with 5% imiquimod cream in the management of VAIN has been reported. In a study by Buck and Guth, 56 women with VAIN (mostly low grade) were treated with 0.25 g of the cream placed in the vagina once weekly for 3 weeks. Of 42 women available for follow-up, 36 (86%) were clear of VAIN on colposcopic evaluation 1 week or later after the last treatment. Five patients' disease required two treatment cycles, and one needed three treatment cycles before clearing of their lesions. Vulvar or vestibular excoriation was reported in only two individuals. No vaginal ulcerations were noted.

Ultrasonic surgical aspiration has been successfully used by Robinson, von Gruenigen and colleagues, and Matsuo and colleagues, but the technique is not widely practiced. Some have advocated surface irradiation using an intravaginal applicator, but adverse effects may be severe and include vaginal stenosis, urinary symptoms, and vaginal ulceration. Additionally, vaginal stenosis can make follow-up extremely difficult. Total vaginectomy, with vaginal reconstruction using a split-thickness skin graft, should be reserved for the patient who has failed more conservative therapy because there appears to be no recurrence benefit from the more invasive procedure.

Treated VAIN often recurs, regardless of the treatment method, and there is no clear standard of treatment. In a retrospective series of 121 women treated for VAIN between 1989 and 2000 by Dodge and colleagues, 33% of subjects experienced recurrence of VAIN, and 2% progressed to invasive cancer; multifocal lesions were more likely to recur. When stratified by treatment type, VAIN recurred in 0% ($n = 0$ of 13) of those treated with partial vaginectomy, 38% ($n = 16$ of 42) of those treated with laser, and 59% ($n = 13$ of 22) of those treated with 5-FU. However, Indermaur and colleagues noted a higher rate of recurrence in their cohort of patients treated with vaginectomy. Of 52 patients available for follow-up who received vaginectomy as treatment for VAIN II or VAIN III, six patients recurred at a mean of 24 months, and one was diagnosed with invasive cancer. Sillman and associates reported on 94 patients with VAIN who were treated by various methods. The remission rate was high, but 5% of the cases progressed to invasive disease despite close follow-up.

Incomplete excision of sufficient vaginal cuff with hysterectomy for CIS of the cervix with involvement of the fornices may explain an early recurrence. The finding of CIS in the vaginal

cuff area in less than 1 year after hysterectomy makes this explanation likely. Therefore, it is important to perform a preoperative evaluation of the upper vagina by Schiller tests or colposcopy at the time of hysterectomy for CIS of the cervix. This allows the surgeon to determine accurately how much of the upper vagina has to be removed. It is also apparent that both CIS and dysplasia may develop in the vagina as primary lesions without an association with a similar process on the cervix or vulva. Still other preinvasive lesions of the vagina may appear after irradiation therapy for invasive carcinoma of the cervix. Data from MD Anderson suggest that these postradiation lesions are premalignant and can progress to invasive cancer if they are not treated. Without therapy, approximately 25% of the patients in this series progressed to the invasive state over varying periods of follow-up. Local therapy must be executed with care because of the previous irradiation.

VULVAR INTRAEPITHELIAL NEOPLASIA

Clinical Profile

Many pathologists still identify intraepithelial lesions of the vulva as VIN I, VIN II, and VIN III, but terminology has recently changed. In 2004, the ISSVD clarified the VIN classification system (Table 2.5), and in 2012, a consensus group was cosponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology to further clarify terminology (Lower Anogenital Squamous Terminology [LAST]) among HPV-associated lesions of the lower genital tract, including the cervix, vagina, vulva, and anus.

The ISSVD eliminated the previous term "VIN I" because there was no evidence that it was a precancerous lesion. The term "VIN" now refers only to lesions previously classified as VIN II or VIN III. In the current system, there is no discrimination between VIN II and III, and the two previously distinct classifications are consolidated as "VIN." Many pathology laboratories still include the older VIN I, II, and III terminology in parentheses for clarity.

Two distinct subtypes of VIN exist: the usual type and the differentiated type. The two subtypes are different in epidemiology, morphology, and their association with vulvar cancer (Table 2.6). Whereas the differentiated type may also be called simplex VIN, the usual type may be called warty, basaloid, or undifferentiated VIN. In comparison with the usual type, the differentiated type tends to occur in older women, be unifocal and unicentric, be found at the edge of vulvar SCC and in the setting of lichen sclerosus or planus, and be less associated with HPV. Usual type VIN, with warty and basaloid subtypes, is found in younger women, has a strong association with cigarette smoking, is often multifocal, is less frequently found in conjunction with squamous cell cancer, and is usually associated with HPV. Although there is an association between VIN and vulvar cancer, the relationship is less clear than the known progression from CIN to invasive cervical squamous carcinoma.

The LAST Project attempted to unify terminology referring to HPV associated-intraepithelial neoplasia of the lower genital tract. The recommended terminology for all cervical, vaginal, vulvar, and anal lesions is "low-grade" or "high-grade" squamous intraepithelial lesion (SIL) based on a combination of cell morphology and p16 immunostaining. Unfortunately, vulvar intraepithelial lesions are not as strongly associated with HPV as cervical lesions, so these guidelines would only be applicable to usual type VIN as differentiated VIN is normally p16 negative and p53 positive. Additionally, VIN I was eliminated by the ISSVD in 2004, so all currently diagnosed HPV-associated VIN should by definition be HSIL vulvar intraepithelial lesions. As clinical pathology practice continues to catch up to new guidelines, it is important to understand all of the terminology used recently and to talk to the pathologist before making meaningful clinical decisions if there is any doubt about terminology being used.

According to a Surveillance, Epidemiology, and End Results (SEER) data analysis by Judson and colleagues, whereas the incidence of vulvar CIS increased 411% between 1973 and 2000, the rates of invasive vulvar cancer rose only 20%. Several hypotheses regarding the changing incidence of VIN exist: increased physician awareness and evaluation of vulvar disease, increased prevalence of smoking among women, and increased HPV prevalence. Women with a history of preinvasive cervical disease or cervical cancer are at increased risk of preinvasive

TABLE 2.5 2003 International Society for the Study of Vulvovaginal Disease (Classification of Vulvar Intraepithelial Neoplasia (VIN)*

A. VIN, usual type
   1. Warty type
   2. Basaloid type
   3. Mixed (warty or basaloid) type
B. VIN, differentiated type

*The previous classifications of VIN II and VIN III were consolidated as VIN, and the previous classification of VIN I was eliminated.

TABLE 2.6 Vulvar Intraepithelial Neoplasia Histologic Subtypes and Associations

	Usual (Warty-Basaloid, Undifferentiated)	Differentiated (Simplex)
Age	Premenopausal women (30s–40s)	Postmenopausal women (65 years)
Overall %VIN	≈95	≈5
HPV associated	Yes	No
HPV type	16	N/A
Risk factors	Smoking, immunosuppression	None identified
Distribution	Multifocal	Unifocal, unicentric
Background histology	Lichen sclerosus	
Progression to	Warty, basaloid squamous cell cancer	Keratinizing squamous cell cancer
	Invasive cancer	(Rare)

NA, Not applicable.

vulvar dysplasia. HPV is a risk factor for vulvar disease, but the progression from HPV infection to precancer to invasive cancer is poorly understood. In contrast to cervical cancer, which has a peak age in dysplasia incidence followed by a peak age in invasive cancer (after a lag period), there is no similar time course established in vulvar cancer. In fact, the peak incidence of VIN occurs during the mid-40s followed by a declining incidence, but the incidence of invasive vulvar cancer continues to increase and never stabilizes, reaching approximately 13 in 100,000 women by the age of 80 years.

Case reports definitively document the development of invasive squamous cell cancers in VIN usual type lesions in patients followed prospectively. In a review of more than 3300 patients with VIN III, van Seters identified occult invasive cancer in 3.2% of subjects at the time of excision, and an additional 3.3% developed cancer during follow-up. Chafe and associates noted that 19% of women who were thoroughly evaluated and thought to have VIN actually had invasive cancer on the vulvectomy specimen. Kagie and associates reported on 66 women with invasive vulvar SCC; 39 (62%) had synchronous VIN. In other cases, it appears that invasive lesions may arise de novo rather than from precursor VIN lesions, but this may be from a misdiagnosis of differentiated VIN previously diagnosed as lichen sclerosus. In a population of 405 women followed for VIN II and III in New Zealand between 1962 and 2003, 2% of cases recurred as invasive cancer at a median time of 2.4 years, and 1.8% of cases recurred as invasive cancer in new fields at a median time of 13.5 years. Additionally, 11.6% of biopsy-proven VIN regressed before treatment (mean age, 24.6 years). If observation is considered in young women with small lesions and usual type histology, frequent examinations with directed biopsies are necessary. Barbero and colleagues noted three of 55 patients treated with VIN whose conditions progressed to carcinoma in 14 months to 15 years. These three patients ranged in age from 58 to 74 years. In the New Zealand cohort, there were 10 cancers diagnosed in untreated patients; Jones and McLean have previously reported on five of the cases diagnosed between 1970 and 1974, and an additional five cases were diagnosed between 1983 and 1992. The median interval between VIN and invasive cancer was 3.9 years (range, 1.1–7.3 years).

HPV is strongly associated with VIN usual type, but it is less commonly associated with VIN differentiated type. There is a wide variation in the reported presence of HPV in VIN because of the changing terminology and classification of VIN and the improved sensitivity of recent HPV testing. The usual type comprises the majority of VIN, so a high prevalence of HPV positivity would be expected in studies that do not differentiate between the two histologies. In more recently published literature, HPV is present in 61% to 100% of VIN. HPV-16 appears to be the most common type, accounting for as high as 91% of infection in some series. The prevalence of HPV infection in VIN and vulvar cancer decreases with age, probably reflecting a change in the underlying histology. The efficacy of HPV vaccines in preventing vulvar dysplasia and cancer will be determined not only by the vaccine properties but also by the prevalence of HPV-related vulvar disease in the population. For example, the HPV VVAP (Vulvar, Vaginal, and Penile) study group published an analysis of HPV contribution to VIN and invasive cancers worldwide. In their sample, whereas approximately 89% of VIN was associated with HPV positivity, 25% of invasive cancer was HPV positive, and HPV-16 was the most common type, accounting for 72.5%. Among geographic regions, however, HPV was more likely in cases from North America.

In initial publications from the vaccine studies, there does appear to be efficacy against VIN. Joura and colleagues report on the vaccine efficacy in reducing specifically HPV-16– or HPV-18–related VIN with a mean duration of follow-up of 36 months. Among subjects who remained HPV negative while receiving the vaccination series, the vaccine was 100% efficacious; zero cases were diagnosed in 7811 vaccinated women, and eight cases were diagnosed in 7785 women who received placebo. Among subjects who were HPV negative at the time of the first injection but did not necessarily remain HPV negative for the duration of the vaccination series, the vaccine was 95% efficacious; one case was diagnosed in 8757 vaccinated women, and 20 cases were diagnosed in 8774 women who received placebo. An analysis was also performed on the incidence of VIN, regardless of HPV association, among all subjects, HPV naïve and HPV exposed at the time of vaccination, and the rate of VIN II/III was reduced by half in the vaccinated group, but there did not appear to be any benefit for those who were HPV exposed at the time of vaccination.

One recent study by Kenter and colleagues tested a synthetic long-peptide vaccine as treatment for VIN in women with HPV-16–positive VIN using a series of three or four vaccinations. Among 19 patients examined on 12-month follow-up, nine had a complete clinical response, and this was maintained at 24 months. This suggests a potential treatment role for vaccines in addition to prevention.

Diagnosis

The disease is asymptomatic in more than 50% of cases. In the remainder of cases, the predominant symptom is pruritus. The presence of a distinct mass, bleeding, or discharge strongly suggests invasive cancer. The most productive diagnostic technique is careful inspection of the vulva in bright light during a routine pelvic examination followed by biopsies of suspicious lesions. A handheld lens or colposcope can be very helpful, especially after application of 5% acetic acid to the skin and introitus.

Careful inspection of the vulva during routine gynecologic examinations is essential; this remains the most likely diagnostic technique. The milder forms of VIN first appear clinically as pale areas that vary in density. More severe forms are seen as papules or macules, coalescent or discrete, or single or multiple. Lesions on the cutaneous surface of the vulva usually appear as lichenified or hyperkeratotic plaques or white epithelium (Figs. 2.9 and 2.10). By contrast, lesions of mucous membranes are usually macular and pink or red. Vulvar lesions are hyperpigmented in 10% to 15% of patients (Fig. 2.11). These lesions range from mahogany to dark brown, and they stand out sharply when observed solely with the naked eye.

The entire vulva, perineum, and perianal area must be evaluated for multifocal lesions. It is not uncommon to find

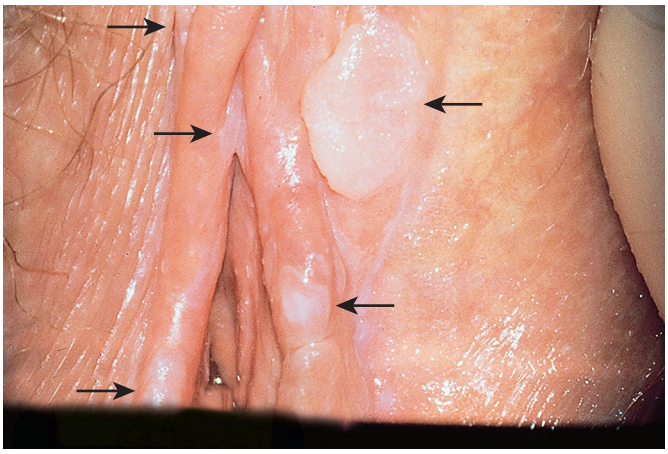

FIGURE 2.9 Multiple white lesions *(arrows)* of the vulva caused by vulvar intraepithelial neoplasia.

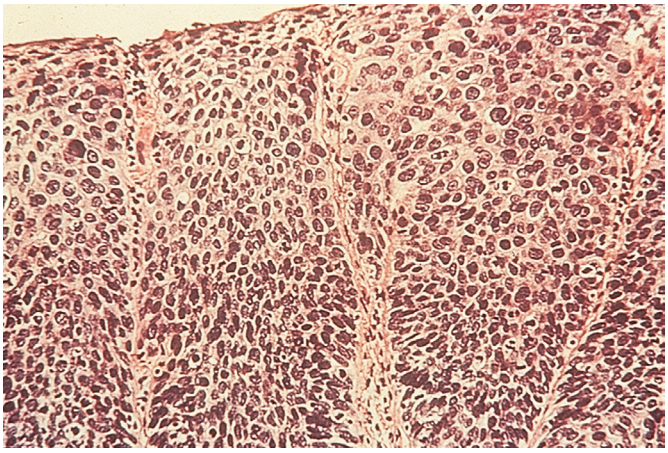

FIGURE 2.10 Histologic section of carcinoma in situ of the vulva.

intraepithelial lesions on hemorrhoid tags or more superiorly in the gluteal cleft. The use of acetic acid is helpful in identifying subtle lesions. In contrast to the mucous membrane of the cervix, the keratinized epithelium of the vulva requires application of acetic acid for 5 minutes or longer before many lesions become apparent. Placement of soaked cotton balls or sponges on the vulva for several minutes before examination is effective. After a lesion has been diagnosed, colposcopic examination of the entire vulva and perianal area should follow to rule out multifocal disease. A handheld magnifying glass can also be used, which allows greater viewing area at one time compared with the colposcope. In general, whereas multifocal lesions are more common in premenopausal patients, postmenopausal patients have a higher rate of unifocal disease.

Some investigators prefer to use toluidine blue to identify vulvar lesions. A 1% aqueous solution of the dye is applied to the external genital area. After drying for 2 to 3 minutes, the region is then washed with 1% to 2% acetic acid solution. Suspicious foci of increased nuclear activity become deeply stained (royal blue); normal skin accepts little or none of the dye. Hyperkeratotic lesions, even though neoplastic, are only lightly stained, but benign excoriations are often brilliant, an observation that accounts for the high false-positive and false-negative rates.

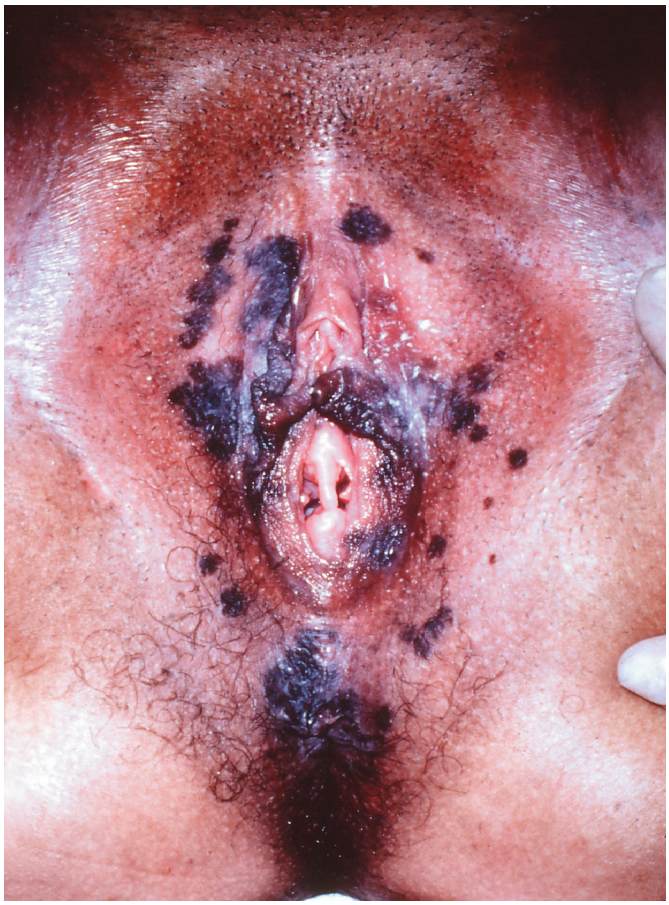

FIGURE 2.11 Pseudopigmented lesions of vulvar carcinoma in situ.

The diagnosis of VIN can be subtle. To avoid delay, the physician must exercise a high degree of suspicion. Vulvar biopsy should be performed on any suspicious lesion. It is best accomplished under local anesthesia (lidocaine or bupivacaine) with a Keyes dermatologic punch (4- to 6-mm size). This instrument allows removal of an adequate tissue sample and orientation for future sectioning. The biopsy site can be made hemostatic with silver nitrate, Monsel's, a stitch, or a piece of absorbable gelatin powder (eg, Gelfoam) cut with the Keyes punch; this is positioned in the skin defect and kept in place with a small dressing for at least 24 hours. Adequate biopsy specimens can also be obtained with a sharp alligator-jaw instrument if one has proper traction on the skin. The problem with ordinary knife "shave" biopsies is that only superficial epithelium can be reached. If this technique is used, one must be careful to get full-thickness skin to adipose tissue for adequate sampling of deeper layers.

Pigmented Lesions

Pigmented lesions of the vulva are usually intraepithelial, with the exception of melanoma. Pigmented lesions account for approximately 10% of all vulvar disease. The most common pigmented lesion is a lentigo, which is a concentration of melanocytes in the basal layer of cells. It can have the clinical

appearance of a freckle, although it is more commonly confused with a nevus. The borders are fuzzy, but it is not a raised lesion. A lentigo is benign, and the diagnosis is usually made by inspection with magnification. If there is any doubt, a biopsy should always be performed.

Intraepithelial neoplasia of the vulva may appear as a pigmented lesion. Friedrich found that CIS of the vulva was more frequent in pigmented lesions than in nevi. Characteristic raised, hyperkeratotic pigmented lesions are suggestive of CIS and should be biopsied.

Bowenoid papulosis is a variant of a pigmented lesion noted by dermatologists for some time. These are small pigmented papules that develop and spread rapidly. According to dermatologists, these papules often regress spontaneously. Histologically, at least on the vulva, these are SCCs in situ. These lesions have been reported to have an aneuploid DNA pattern. Many authorities have not found bowenoid papulosis of the vulva to spontaneously regress. Regardless of the clinical characteristics, if VIN is present histologically, the physician should treat the patient accordingly.

The management of nevi can be conservative. A nevus can often be detected only microscopically. Unfortunately, a simple nevus and an early melanoma cannot be differentiated on clinical evaluation. Excisional biopsy of these raised, smooth, pigmented areas can be done easily in the physician's office. If the nevus changes in color, size, and shape, it should be removed for diagnostic purposes. After a nevus is removed, no further therapy is needed regardless of whether it is a compound, intradermal, or junctional type.

Management

Surgical excision has been the mainstay of therapy for VIN, although laser is a frequently used technique, especially for multifocal lesions, and medical management with immune modulators has gained recent prominence. An important advantage of surgical excision is that complete histologic assessment is performed; lesions with early invasion can thus be found. Most localized lesions are managed effectively by wide local excision with end-to-end approximation of the defect. The vulvar skin and mucous membrane are usually very elastic, and cosmetic results are satisfactory after uncomplicated healing. There are inadequate data to evaluate the best surgical ablative techniques, but studies are ongoing.

Excision

Wide local excision is the most commonly performed treatment of VIN. The goal of VIN surgery is to obtain a 5-mm disease-free margin. Margin status and histology results are available on final pathology results, which is a benefit of the excisional procedure. Modesitt and associates reported that recurrences were three times higher (46% vs. 17%) when margins were positive for residual VIN II and III. In the New Zealand study discussed earlier, 50% of those with positive margins versus 15% of those with negative margins required further treatment. Hillemanns and colleagues showed an overall recurrence rate of 43% in subjects retrospectively analyzed who had been heterogeneously treated with laser, photodynamic therapy, excision, or vulvectomy. No patients recurred in the vulvectomy group ($n = 8$). In the natural history review by van Seters and colleagues, 1921 patients were surgically treated. Recurrence was noted in 19% after vulvectomy, 18% after partial vulvectomy, and 22% after local excision. Recurrences were significantly lower after free surgical margins (17%) than after positive surgical margins (47%). Progression to invasive disease occurred in 58 patients, 52% of the time after vulvectomy, and 48% of the time after local excision. In this retrospective review, the surgical approach was likely selected based on individual patient characteristics so that patients considered at higher risk for invasive cancer may have more frequently received vulvectomy. However, there is no definitive evidence or randomized controlled trial (RCT) to show that vulvectomy is associated with better outcomes and the morbidity associated with the procedure is much greater. Wide local excision is the accepted excisional procedure for VIN.

In the series by Modesitt and colleagues, 17 of 73 subjects were diagnosed with invasive cancer at the time of treatment for VIN III. Similarly, 16 of 78 patients undergoing surgical excision for VIN III had invasive cancer in the report by Husseinzadeh and Recinto. To avoid returning to the operating room for deeper reexcision and lymph node dissection, biopsies must be liberally performed preoperatively. Multiple biopsies may be required. Adequate postoperative follow-up with repeat biopsy for any suspicious lesions is also essential.

Occasionally, a skinning vulvectomy is indicated. With multicentric lesions (Fig. 2.12), the involved skin can be excised and substituted with a split-thickness skin graft taken from the buttocks or inner aspect of the thigh. This skinning vulvectomy and skin graft procedure was introduced by Rutledge and Sinclair in 1968 (Fig. 2.13). Its purpose was to replace the skin at risk in the

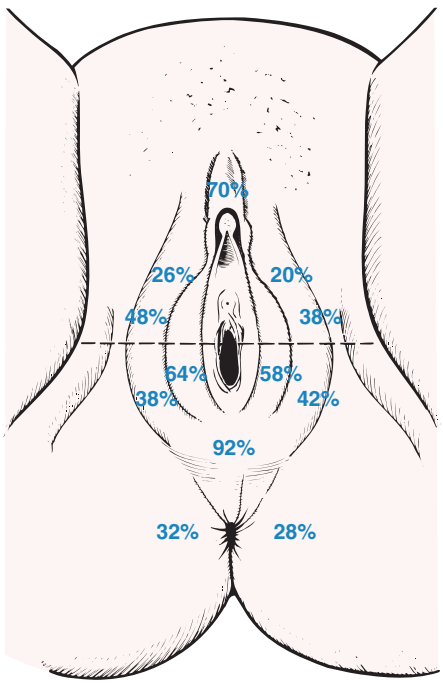

FIGURE 2.12 Plot of lesion locations in 36 patients treated for multifocal carcinoma in situ of the vulva.