Cervical Intraepithelial Neoplasia: Current Management Options

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Cervical intraepithelial neoplasia is an increasingly common finding among sexually active young women. Many of these women have not completed their families, so preservation of fertility is an important factor to consider when planning appropriate treatment. In the past, management of precancerous cervical lesions was aggressive, primarily consisting of conization of the cervix. This procedure yielded excellent cure rates but was associated with a high incidence of complications. The widely accepted use of colposcopy in the evaluation of abnormal cervical cytology and the use of ablative and conservative excisional treatment modalities have resulted in a decreased number of conization procedures. More recently, management of cervical intraepithelial neoplasia has taken a more conservative approach. This article describes the risks and benefits of the multiple modalities available for the management of cervical intraepithelial neoplasia.

Key words. Cervical intraepithelial neoplasia; colposcopy; patient care management; family physician.
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There are approximately 15,000 new cases of invasive cervical cancer diagnosed each year in the United States.[1] This number represents over a 75% reduction in the incidence of invasive cervical cancer over the past 30 years, in spite of an increase in the number of precancerous lesions diagnosed.[2] The reduction in the number of cases of cervical cancer can be attributed to the use of the Papanicolaou (Pap) smear to diagnose premalignant cervical disease.

The number of cases of human papillomavirus (HPV) infection diagnosed annually is increasing.[3] Cervical cancer, considered to be a sexually transmitted disease,[4] is strongly associated with HPV and smoking.[5] During the normal process of squamous metaplasia, the introduction of oncogenic influences, such as smoking or HPV, may predispose a woman to the development of precancerous cervical changes such as squamous intraepithelial lesions (SIL) or other HPV-related genital lesions. These abnormalities may exhibit progression, regression, or persistence over the patient's lifetime.

Increasing numbers of young women have minor abnormalities, such as grade 1 cervical intraepithelial neoplasia (CIN 1) or HPV. The Bethesda System[6] groups both HPV and CIN 1 into the category of low-grade squamous intraepithelial lesions (LGSIL). Some experts still recommend treating low-grade lesions, but during the past 2 years, there has been a dramatic change from aggressive ablative therapy to one of more conservative observation of these minor lesions.[7] Careful follow-up may yield high regression rates of LGSIL, as demonstrated by some reports of spontaneous regression in up to 50% of cases.[7-10] It should be emphasized, however, that conservative management involves colposcopic as well as cytologic surveillance. To rely on cytologic examination alone is not recommended since cytologic specimens may exhibit a false-negative rate as high as 27%.[11,12] In up to 30% of patients with LGSIL on cytology, biopsy will confirm CIN 3 (severe dysplasia, carcinoma in situ) or worse.[7,13] The rates of regression for high-grade squamous intraepithelial lesions (HGSIL) are much lower than for LGSIL.[14] HGSIL includes CIN 2 and 3 (moderate and severe dysplasia and carcinoma in situ). HGSIL has a true malignant potential, and most experts recommend treating such lesions.

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Because many women with CIN have not yet completed their families, the preservation of childbearing potential is of great importance. Once the clinician has decided that active treatment is indicated, the patient should be informed about the risks and benefits of therapy, particularly with regard to cervical competency. Family physicians provide a substantial portion of routine gynecologic care, and therefore will routinely be responsible for managing the abnormal Pap smear. This is particularly true if they care for a high-risk population, such as in an urban or college setting. A significant proportion of family practice residency programs have implemented a colposcopy curriculum at their sites and offer training in colposcopy to their resident physicians.[15,16] Family practice colposcopists should be able to diagnose and treat approximately 90% of the patients they evaluate or to initiate quality referral services for selected patients.

Traditionally, family physicians who performed colposcopy were limited to cryotherapy as the primary treatment modality for CIN, formerly known as dysplasia. Recent technological advances have produced other treatment modalities, such as laser ablation and the loop electrosurgical excision procedure (LEEP) for the management of CIN. With multiple modalities available, clinicians should be knowledgeable about the practicality of all available treatment options. This article explores treatment options currently available for the management of CIN and discusses the strengths and weaknesses of each modality.

Diagnosis

It is vital for the colposcopist to make an accurate diagnosis before initiating any form of treatment. Even with expertly conducted cytologic, colposcopic, and histologic evaluations, microinvasive cancer (MIC) is missed in 0.1% of patients being evaluated for CIN.[17] This can be the result of either the clinician failing to perform a biopsy on the most abnormal area or the biopsy size not being large enough to allow assessment of invasion in the deeper glandular structures.[17] Other contributing factors include false-negative Pap smears and histologic specimens that are inaccurately interpreted.

Failure to diagnose MIC can have major implications if ablative therapy is performed and can lead to a delay in diagnosing the cancer and a worsened prognosis. Colposcopic assessment will detect 90% of occult cervical cancer but only 84% of MIC.[18] Correlation of cytologic, colposcopic, and histologic findings is essential, and any unexplained discrepancies must be addressed before treatment is initiated. This is especially true if an ablative therapy is contemplated. Once the diagnosis is certain, an appropriate mode of therapy for managing the premalignant cervical disease can be chosen.

Therapeutic Options

Observation

Observation may be the most logical choice for biopsy-proven minor-grade cervical lesions, since they exhibit such a high rate of spontaneous regression. Exceptions to this rule might include patients with a questionable compliance history, smokers, immunocompromised patients, and those exhibiting large cervical lesions. It would be reasonable to consider treating these patients rather than risk losing them to follow-up care.[19,20] This course of action is based on a theoretical assumption that low-grade lesions will progress, although less than 25% actually progress to HGSIL.

There are no definite guidelines on how long to continue to follow patients with LGSIL. Recent guidelines issued by the National Cancer Institute recommend observation for 2 years through cytologic testing alone, as an alternative to immediate colposcopy.[21] Consideration should be given to treating LGSIL that persists for over 1 year.[22]

Physicians must maintain their colposcopic skills in order to use the colposcope in following up on low-grade lesions when definitive treatment has not been performed. The physician who does colposcopic examinations occasionally may miss subtle signs of disease progression. This is especially true when the patient with CIN is pregnant. The majority of lesions demonstrated in pregnancy can be followed if initial colposcopy and biopsy findings indicate only CIN. Because limited biopsy of the cervix is a safe procedure during pregnancy, clinicians should not hesitate to do a biopsy if necessary.[23] Colposcopy should be performed every 8 to 12 weeks until delivery to rule out disease progression to microinvasive or invasive disease.

Definitive management and therapy can be undertaken 2 to 3 months after delivery.[24] Because host immunity is diminished during pregnancy, CIN will occasionally progress rapidly to a high-grade lesion or even invasive cancer.[25] Therefore, it is essential that colposcopic observation and surveillance during pregnancy be performed by an experienced colposcopist.

If the initial colposcopic examination is inadequate during early pregnancy, a repeat colposcopic examination in 3 to 4 weeks will usually demonstrate the squamocolumnar junction and permit accurate assessment of the lesion. If microinvasive or invasive disease is suspected, a conization or wedge biopsy should be performed. Some

Table 1. Criteria for Ablative Therapy (Rather Than Excision) of Cervical Intraepithelial Neoplasia (CIN)

- The limits of the lesion and the squamocolumnar junction are completely visualized.
- The lesion does not extend more than 5 mm into the cervical os.
- There is no deep glandular involvement.
- There is no evidence of endocervical glandular abnormalities.
- The endocervical curettage is negative.
- There is no cytologic, histologic, or colposcopic evidence of microinvasive or invasive disease.
- The patient is compliant and agrees to return for follow-up visits.
- There is good correlation between cytology, colposcopy, and histology.

authors recommend a cone cerclage technique, reportedly associated with fewer adverse sequelae.[26]

Ablative Methods

The goal of ablative therapy is to destroy the lesion and the entire transformation zone, which may harbor CIN in glandular crypts. The mean depth of involved crypts is 1.24 mm. Destruction to a depth of 3.8 mm should eradicate the involved crypts in over 99% of cases. Therefore, at least a 5-mm depth of destruction is recommended for appropriate treatment of CIN.[27,28] Criteria for ablative therapy are listed in Table 1.

Cryotherapy

Cryotherapy is a proven effective treatment for all grades of CIN.[29–31] Freezing the tissue followed by thawing leads to the formation of intracellular ice crystals, expansion of intracellular material, and rupture of the cells with subsequent denaturation of cell proteins.[32] Cure rates diminish as the size of the lesion increases, especially if more than 2 quadrants of the cervix are involved. The grade of the lesion (CIN 1 to 3) is not in itself a factor, but higher grades of CIN are usually demonstrated by larger lesions.[29,30] Lesions located at the 3- and 9-o'clock positions on the cervix have a higher degree of inadequate tissue necrosis from the cryotherapy. This is believed to be secondary to the increased blood supply to these areas from the cervical branches of the uterine arteries.[33]

There is debate over whether a single freeze or double freeze produces a better cure rate.[34] In general, a freeze–thaw–freeze regimen is recommended.[33,34] The length of time the tissue should be frozen is variable, but the initial freeze time is usually 3 to 5 minutes, and the time for the second freeze is somewhat less. The formation of an iceball around the cryoprobe is of greater importance than the length of time of the actual freeze.[35] Since cryotherapy will usually not penetrate deeper than 5 mm into the tissues or beyond 5 mm from the edge of the cryoprobe, overlapping treatments may be necessary to treat large transformation zones. Freezing more than 5 minutes does not appreciably increase the size of the iceball.[33] Therefore, it is important to choose a probe that will cover the entire lesion and transformation zone. The creation of an iceball that extends at least 5 mm beyond the edge of the cryoprobe is recommended to ensure an adequate freeze. This is a more accurate assessment of successful tissue penetration than relying on time alone. A cryosurgical iceball gauge that assesses the size of the freeze zone in an objective manner may lead to a more consistent freeze and uniform degree of cell damage.[36]

The choice of a cryoprobe depends on the size of the lesion and the transformation zone. The use of a flat cryoprobe without a nipple will diminish the possibility of cervical stenosis to approximately 1%. This type of probe is less likely to cause the squamocolumnar junction to recess into the endocervical canal, resulting in an unsatisfactory colposcopy on follow-up examination.[37–39] Large probes should be avoided on cervices with a portio diameter of less than 3.0 to 3.5 cm.[33] If endocervical disease is present, an excisional method of treatment is preferred, since cryotherapy failure rates are high in this instance.[30,40] Patients will experience a profuse, watery discharge for 2 to 3 weeks after the cryotherapy.

The protocol for follow-up after cryotherapy may consist of cytologic and colposcopic assessment at 4, 8, 12, 18, and 24 months. Some experts recommend colposcopy only at the 4- and 12-month visits and then cytologic assessment alone for the 8-, 18-, and 24-month visits. A biopsy of any suspect areas should be performed. The cytologic smear at 4 months may show reparative changes, but no intervention is indicated unless there is clear-cut residual CIN. The majority of treatment failures will be detected within the first 2 years following treatment.[39,41] Patients who have treatment failures and adequate repeat colposcopic examinations may be treated again with cryotherapy if the standard criteria for ablative therapy are met (Table 1). Cure rates after retreatment may approach 98%.[34]

If the colposcopic examination is unsatisfactory, a conization should be performed. There are reports of MIC or invasive cancer being discovered within a short time after cryotherapy. This may represent new disease, but more than likely, MIC was present but was not initially recognized on colposcopy or biopsy. Some authors, therefore, recommend excisional treatment of any CIN that recurs after cryotherapy.[42] If posttreatment examinations are normal, the patient should have annual Pap smears for the rest of her life.

Laser Ablation

Light amplification by stimulated emission of radiation (laser) uses monochromatic, coherent, and collimated light to cut or ablate tissue. Several types of lasers are currently in clinical use, the most common being the CO_2 laser. Laser ablation has been extensively used in treating CIN, although its use during the past 2 to 3 years has decreased, in part because of the introduction of other treatment modalities such as LEEP. Laser, an ideal modality for treating large lesions, is especially appropriate for teenagers in whom 20% of CIN lesions extend onto the periphery of the cervix or even into the vagina.[43,44] Colposcopically directed laser ablation can be performed in the office using local anesthesia. Complications are minimal; postoperative bleeding is the most frequently reported. Patients treated with laser ablation must meet the routine guidelines for ablative therapy (Table 1). Success rates for ablating all grades of CIN with the laser are approximately 90% to 95%, depending on the experience of the operator.[43,45–47] The cost of laser equipment ($40,000) and maintenance is high. A family physician who wishes to perform laser ablations should receive appropriate training or defer this treatment to other specialists.

Electrocautery, Electrocoagulation Diathermy, and Cold Coagulation

Destruction of precancerous cervical lesions and the transformation zone can be accomplished by the use of a red-hot metal cautery tip (electrocautery),[48] by the use of high-frequency current to coagulate tissue (electrocoagulation diathermy),[49] or by "cold coagulation," using a 100° to 110°C teflon-coated thermosound (Semm's coagulator).[50] These modalities have reported cure rates of over 90% and are associated with relatively few complications. They are popular in European countries but are not used to any great extent in the United States.

Intralesional Interferon

Intralesional interferon has no effect on CIN. It is associated with significant side effects and is not a part of the standard care of patients with CIN.[51]

Vitamin A

The use of topical tretinoin (vitamin A) for the treatment of cervical dysplasia has recently been investigated. In a study of 20 patients with various grades of CIN, Meyskens and Surwit[52] reported that 50% experienced complete regression of their disease. All patients, however, had colposcopically directed biopsies at the start of the study that may have altered the natural course of the CIN, resulting in an increased rate of regression. At present, the use of vitamin A has not been studied sufficiently to recommend it for the treatment of CIN.[52]

Table 2. Criteria for Treatment Selection for Patients With Cervical Intraepithelial Neoplasia

Lesion Characteristic	Ablative	Excisional
Size	<2 quadrants	>2 quadrants
Grade	LGSIL, focal HGSIL	All grades SIL
>5 mm in os	No	Yes

LGSIL denotes low-grade squamous intraepithelial lesion; HGSIL, high-grade squamous intraepithelial lesion.

Trichloroacetic Acid

Although 85% trichloroacetic acid is useful in the management of condyloma,[53] it has not been shown to be effective in the management of CIN.

Excisional Methods

When cervical lesions are large, involve more than 2 quadrants, are high-grade, or if prior ablation has been performed, an excisional method of treatment should be considered (Table 2).

Loop Electrosurgical Excision Procedure

Also known as large loop excision of the transformation zone (LLETZ), LEEP involves excision of the entire transformation zone using a monopolar loop electrode at the end of a pencil-like wand. Because the procedure uses low-voltage, high-frequency electrical current, the patient must be adequately grounded. LEEP should not be performed unless safety is assured for both the patient and the clinician.

LEEP is a refinement of a small loop biopsy technique used by René Cartier[54] in the 1950s. Prendiville[55,56] increased the size and depth of the loop to allow for removal of the transformation zone in one pass. Loops in current use are generally smaller than the ones developed by Prendiville. A standard loop of 2.0 cm × 0.8 cm is capable of excising the majority of transformation zones. Since CIN rarely extends deeper than 5 mm into cervical glandular crypts, this loop allows for adequate depth of excision without excessive removal of stromal tissue.[27] LEEP can be performed in the office using subepithelial infiltration with 2% xylocaine and epineph-

rine.[57] A paracervical block is not necessary. In most cases, the entire procedure can be accomplished in less than one minute. Preoperative administration of nonsteroidal anti-inflammatory drugs may help decrease cramping following the procedure. An exocervical LEEP can be performed if there is an adequate colposcopic examination and a negative endocervical canal evaluation.[58]

LEEP is contraindicated in pregnancy, in the presence of cervicitis, and within 8 to 10 weeks postpartum because of an increased incidence of significant perioperative and postoperative bleeding. Squamous lesions that extend 1 cm or less into the endocervical canal can be excised with a 1 cm × 1 cm loop, followed by an exocervical excision of the transformation zone. The crater produced by LEEP is fulgurated with a ball electrode to produce adequate hemostasis. Monsel's solution is then applied, even if the crater is dry.

A LEEP conization can be performed if the colposcopic examination is inadequate, the squamous lesion is deeper than 1 cm in the endocervical canal, the endocervical curettage is positive, or the cytologic abnormality cannot be identified colposcopically. For this procedure, the cervix is anesthetized with xylocaine mixed with either epinephrine or vasopressin to reduce bleeding. A fine-needle electrode is used to excise a core of cervix. The base is excised using a tonsillar snare to prevent thermal artifact at the apex of the conization specimen.[59] A "cowboy hat" excision may be performed using an 8-mm loop for the exocervical excision followed by a 10-mm endocervical excision using a square or round loop. Tissue margins may not be free of disease, but experts have demonstrated that there is a low incidence of recurrence even with positive margins.[57] Most likely, this is because residual disease is destroyed or displaced during fulguration or the reparative process.

Patient acceptability of LEEP is high and complication rates are low. In published studies, cervical stenosis is relatively rare, occurring mostly in postmenopausal women.[57] Short-term studies demonstrate no adverse effect on cervical competence. Postoperative bleeding occurrs in only 4% of cases and can be managed in the office by removing any clots in the crater followed by either the application of Monsel's solution or refulguration of the crater. There is no increased hemorrhagic morbidity in relation to age, parity, contraception method, size of lesion, or day of menstrual cycle on which LEEP was performed[60]; however, performing LEEP just after the completion of menses makes it easier to assess for postoperative bleeding, which may occur approximately 1 week after treatment.

In European countries, it is common to use LEEP to diagnose and treat abnormal Pap smears during a single visit (a "see and treat" approach). This practice reduces the number of required visits for evaluation and treatment from two to one and is an especially useful strategy for noncompliant patients. In a large study of "see and treat" visits, however, 27% of specimens either were normal or showed only koilocytosis.[61] LEEP is generally discouraged at the time of the initial visit unless there is a clear-cut, high-grade lesion. This practice will prevent overtreatment of minor-grade abnormalities or normal variants, such as immature squamous metaplasia.[62]

Cure rates with LEEP are over 90% for all grades of CIN. LEEP has an advantage over ablative techniques because it provides an excellent specimen for histologic evaluation.[63] Significantly higher grade lesions may be found in the LEEP specimen than were noted on colposcopically directed biopsy.[64,65] Since the entire transformation zone is excised in LEEP, the patient can be returned to the cytologic surveillance pool more rapidly (after negative results from colposcopic and cytologic examinations at 6 and 12 months) than with ablative therapy (generally 2 years of cytologic and colposcopic follow-up).[58] Whether ablative or excisional therapy is instituted, annual cytologic screening is necessary for the patient's lifetime.

There is concern about what effect LEEP will have on fertility and pregnancy outcome. Most of the available studies lack long-term data or involve small sets of women. Blomfield et al[66] recently performed a case-controlled retrospective study of 40 women who were treated by LEEP and had a subsequent pregnancy. There was no statistical difference in the incidence of midtrimester miscarriage after 20 weeks, labor performance, cesarean section rates, or length of gestational age after LEEP. In this study, women who gave birth after LEEP had lower birthweight infants than did controls, although this was probably related to maternal smoking.[66]

Laser Conization

Laser may be used to perform an excisional conization in instances of endocervical extension of the CIN.[67] Some authors recommend that all patients be treated with laser excision rather than ablation to decrease the possibility that unsuspected microinvasive disease is being vaporized.[68–70] The advantage of laser excision is that it provides a specimen to ensure that the lesion is not any more advanced than what was expected based on colposcopic evaluation and findings on biopsy. Shallow laser conization specimens have demonstrated that in 13% of cases, the histologic diagnosis was two to three grades more severe than what was observed on punch biopsy.[69] Depending on operator experience, the specimen produced by laser conization can be either worthless because of

thermal artifact or of excellent quality for histologic evaluation.[67,71,72]

Laser conization can be performed in the office setting with local anesthesia.[67] Pretreatment with a nonsteroidal anti-inflammatory drug (NSAID) may help reduce postoperative cramping.[73] The immediate and delayed complication rate is less frequent with laser excision than with laser ablation.[45] Cure rates for excisional laser therapy are generally over 95%.[43,70] Although excisional margins may be positive in about 12.5% of cases, the majority of these cases (approximately 90%) will not demonstrate residual disease on cytologic and colposcopic follow-up.[70,74] Therefore, expectant management is warranted in these circumstances.

Cold-Knife Conization

The use of cold-knife conization (CKC) had been the standard of care in the management of moderate and severe dysplasia and carcinoma in situ until it was predominately replaced by colposcopy over the past 20 to 30 years. The rationale for the use of this antiquated practice was that high-grade lesions were thought to have a high rate of progression to invasive cancer.[75] Conization is still indicated in certain situations, such as inadequate colposcopic assessment of CIN that has been found by cytologic evaluation, a discrepancy between cytologic, histologic, and colposcopic findings, or when a suspicion of adenocarcinoma in situ exists.[76] CKC should be performed under colposcopic guidance to ensure the removal of the transformation zone but not excessive amounts of normal tissue. A colposcopic examination should always be performed before CKC.[77] If a punch biopsy indicates invasive cancer, the patient should be treated with radical hysterectomy and pelvic lymph node dissection and spared an unnecessary conization.[78] CKC is performed under general anesthesia, and the cone bed is either left open or closed with sutures. Cervical stenosis after CKC can occur in up to 17% of cases.[79] The incidence of stenosis and dysmenorrhea after CKC is increased if cone length is greater than 2 cm.[80]

Hysterectomy

Before the advent of colposcopy, it was common to perform a hysterectomy if the Pap smear indicated carcinoma in situ and a CKC if severe dysplasia was present. These practices based radical treatments on an arbitrary pathological diagnosis. It is now known that there is poor intraobserver correlation when reading severe dysplasia and carcinoma in situ on cytologic and histologic preparations.[14]

Hysterectomy has minimal place in the modern management of CIN. If a hysterectomy is performed and the patient is found to have invasive cancer, she has been undertreated.[81] If a hysterectomy is performed for microinvasive or invasive disease, care must be taken to assess the vaginal cuff so that vaginal intraepithelial neoplasia (VAIN) is not missed and inadvertently incorporated into the suture lines. Because undetected VAIN may progress to high-grade VAIN or invasive cancer, annual Pap smears of the vaginal cuff are essential in the follow-up of these patients.

Multiple treatment modalities for the management of CIN are available to the practicing colposcopist. Treatment selection should be based on history, colposcopic, cytologic, and histologic findings, anticipated patient compliance, and the skill of the clinician.

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