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Treatment of Cervical Precancers: Back to Basics

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Abstract

Both ablative (cervical cryotherapy, laser ablation) and excisional methods (loop electrosurgical excision procedure [LEEP], cold knife conization) can be effective at treating cervical precancer. Excisional procedures are associated with adverse obstetric outcomes including preterm delivery and perinatal mortality, with the depth of excision potentially contributing to the adverse outcomes. Ablative therapies are now used much less commonly than LEEP, but have less of an impact on adverse obstetric outcomes, and hence are effective alternatives for treating cervical precancer in reproductive-aged women. Morphometric data indicate that the vast majority of precancerous lesions are less than 5 mm deep, suggesting that treatments that reach 6–7 mm below the epithelium are adequate in women with satisfactory colposcopy. Cone biopsies, “top-hat” LEEPs, or the use of loop electrodes greater than 10 mm are therefore unnecessary for the majority of reproductive-aged women and increase risk of adverse obstetric outcomes. New consensus guidelines allow observation instead of treatment in appropriately selected young women. Until the association of excisional methods with adverse obstetric outcomes is clarified with more data, ablative methods should be revitalized and utilized by providers in appropriately selected patients. Treatment should be individualized based on patients’ age, fertility desires, and colpopathologic findings.

BACKGROUND

Over the past 4 decades, incidence and mortality from invasive cervical cancer have decreased remarkably with the adoption of widespread screening programs based on cytology and more recently, testing for cancer-associated human papillomavirus types. Abnormal screening results lead to referral for colposcopy, a diagnostic procedure that can visually detect dysplastic changes and guide biopsies to obtain a histological diagnosis. Lesions are graded as cervical intraepithelial neoplasia (CIN) 1, 2 or 3 based on the degree of cellular and epithelial abnormality. CIN1 lesions represent a benign manifestation of human papillomavirus infection. The majority of CIN1 is spontaneously cleared by the immune system, hence surveillance rather than treatment of women with CIN1 is recommended. CIN3 lesions represent a full-thickness neoplastic lesion with a high

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likelihood of progressing to cancer if left untreated. CIN2 lesions are intermediate in their biology between CIN1 and CIN3, with up to 40% regressing if left untreated. The cornerstone of cervical cancer prevention is the detection of CIN2 and CIN3 lesions through screening, and their eradication through treatment.

The traditional treatments for CIN used to be conization and hysterectomy. With the introduction of colposcopy in the 1970s, more conservative treatments such as electrocautery, cryotherapy, and laser ablation were adopted and were widely used until the 1990s when loop electrosurgical excision procedure (LEEP), an office-based excisional procedure, became widespread. Ablative methods are now used much less commonly than LEEP.(1, 2) The LEEP was readily adopted, and ablative therapies abandoned, due to concerns that ablative therapies were undertreating occult invasive cancer.(3, 4) Due in part to the impact from these studies, cryotherapy has suffered from the misperception that it is not as effective as other treatment modalities, despite meta-analytic data showing that cryotherapy and laser ablation have comparable efficacy to excisional techniques.(5) In this article, we will make the case that it is time to revitalize cryotherapy and laser ablation in gynecologic practice, in order to mitigate potential harms associated with excisional treatment of cervical precancers.

RISKS OF TREATMENTS

All available therapies for CIN are associated with risks of bleeding, infection, scarring and recurrence of disease. As noted above, they all show equivalent efficacy in meta-analysis.(5) However, excisional techniques such as LEEP and cone biopsy are associated with a greater risk of preterm delivery than ablative techniques, although the effects of LEEP are modest in some studies. In one meta-analysis, the relative risk (RR) for preterm delivery (before 37 weeks gestation) after LEEP was 1.70 (95% confidence interval [CI] 1.2–2.4; 156/1402 [11.1%] vs. 120/1739 [6.9%]) and after cone biopsy was 2.59 (95% CI 1.8–3.7; 100/704 [14.2%] vs. 1494/27674 [5.4%]).(6) Ablative techniques were not associated with an increased risk of preterm delivery before 37 weeks in this meta-analysis. Retrospective studies often compare the intervention group undergoing treatment of the cervix to population-based or hospital-based (“external”) comparison groups, and often cannot control for potential confounding risk factors. A more rigorous approach is to compare risks in women in whom treatment preceded delivery to women in whom treatment followed delivery (“internal” comparison group). In a more recent meta-analysis, the authors separated studies into two categories based on whether the comparison group was external or internal.(4)(7) Excisional procedures (type not specified) were associated with an increased risk of preterm delivery before 37 weeks in studies using either internal (RR=1.96, 95% CI 1.5–2.6; 119/846 [14.1%] vs. 60/846 [7.1%]) or external (RR=2.19, 95% CI 1.9–2.5; 1549/17344 [8.9%] vs. 54068/1227449 [4.4%]) comparison groups.(7) For ablative techniques, an increased risk of preterm delivery was found in studies that used external comparison groups (RR 1.47, 95% CI 1.2–1.7; 432/6355 [6.8%] vs. 50815/1167288 [4.4%]), but not in studies using more rigorous internal comparison groups (RR 1.24, 95% CI 0.7–2.1; 30/495 [6.1%] vs. 23/445 [5.2%]). In summary, excisional therapies are associated with a risk of preterm delivery before 37 weeks, whereas ablative therapies are alternative options that are not associated with prematurity.

Of even greater concern is the finding that excisional procedures are associated with pregnancy outcomes more severe than preterm delivery before 37 weeks. In one meta-analysis, cone biopsy was associated with significantly increased risks of preterm delivery before 28–30 weeks (RR 5.33, 95% CI 1.6–17.4; 29/479 [4.2%] vs. 3959/472246 [0.8%]) and perinatal mortality (RR 2.87, 95% CI 1.4–5.8; 33/761 [4.3%] vs. 2305/442385 [0.5%]). (8) Although this meta-analysis did not find an association of LEEP or ablative techniques with severe adverse pregnancy outcomes, a more recent meta-analysis found that LEEP was associated with increased risk of preterm delivery before 32–34 weeks (RR= 1.98, 95% CI 1.3–3.0; 159/11337 [1.4%] vs. 7830/860883 [0.9%]) and before 28 weeks (RR= 2.33, 95% CI 1.8–2.9; 97/9611 [1.0%] vs. 1559/618382 [0.3%]).(9)

Biological explanations for the association of excisional therapies with preterm delivery before 37 weeks are not fully understood, but possibilities include the presence of similar risk factors for both conditions (eg, smoking), changes in the volume of the cervix resulting in cervical incompetence, or treatment effects on the structure and function of the endocervical canal. (2, 10) The latter hypothesis is supported by the finding from several studies that the risk of preterm delivery increases with the depth of the sample excised, but not with its circumference or volume.(10) The more recent meta-analysis did not find an association between LEEP depth and risk of preterm delivery.(9) Nevertheless, the possibility of this association with depth of excision raises an important question: how deep is deep enough to adequately treat CIN without imparting unnecessary risk of preterm delivery in reproductive aged women?

MORPHOMETRIC STUDIES

Fortunately, careful morphometric studies have been performed to provide guidance to clinicians on this issue. Although CIN lesions are by definition confined to the epithelium, they can extend into glands in the cervical stroma, requiring treatment to extend below the epithelial surface. One study examined 343 conization specimens from women treated for cervical neoplasia.(11) The women ranged in age from 18 years to 64 years old. The authors calculated the depth of destruction necessary to eradicate the majority of CIN lesions by examining the depth of involved crypts (glands) in the cervical stroma. They found that the mean depth of glands containing CIN was 1.24 mm from the surface, and the deepest gland containing CIN was 5.22 mm from the surface. They concluded that 99.7% of CIN lesions (3 standard deviations from the mean) are located 3.80 mm from the surface. The depth of gland involvement differed by age, with older women being more likely to have deeper gland involvement (age 41–50 years, mean 1.61 mm) than younger women (age 15–20 years, mean 0.64 mm).

Another morphometric study looked at the extent and severity of CIN lesions in 319 conization specimens.(12) They found that the extent of the lesion increased with lesion grade. The mean depth of CIN1, CIN2, and CIN3 was 0.42 mm, 0.93 mm, and 1.35 mm, respectively, and the mean linear extent of CIN1, CIN2, and CIN3 was 4.10 mm, 5.84 mm, and 7.60 mm, respectively. They concluded that a treatment depth of 4.8 mm would eradicate 99.7% of CIN3 lesions. In this study, the location of lesions also varied with age,

with older women more likely to have disease located in the endocervical canal (28.6% of women older than 50 years of age) compared with younger women (10%).

These morphometric studies can be translated into important didactic points for trainees and practitioners:

- In our judgment, in women with satisfactory colposcopy, a treatment depth of 6–7 mm below the epithelium will achieve successful treatment in the vast majority of cases but minimize potential adverse obstetric outcomes, given that CIN3 lesions are located within 4.8 mm of the surface of the cervix(12) and the deepest gland containing CIN3 was 5.2 mm.(11)
- Many commercially available loop electrodes are designed to remove depths of 10–15 mm, and therefore should be shortened with the mechanical guard or used judiciously to prevent excessive depth of excision in reproductive-aged women with satisfactory colposcopy.
- “Top-hat” LEEP, in which a second excision of the endocervical canal is made after the first pass of the wire loop, is unnecessarily deep and should not be performed as a routine procedure in reproductive-aged women. It should be reserved for situations in which colposcopy indicates that the transformation zone or the high grade lesion extend into the endocervical canal.
- Cone biopsies are associated with the highest risks of adverse obstetric outcomes. If excisional therapy is warranted in young women, LEEP is almost always a better choice than cone biopsy. However, if the anatomy of the cervix is distorted, the scalpel rather than the wire loop may be better able to adapt to the shape of the cervix, in which case cold knife conization would be a better option. Also, if a glandular abnormality or cancer is suspected, cone biopsy can provide a more interpretable surgical margin.
- Cryotherapy typically generates an iceball that is 5–7 mm deep, which is sufficient for treatment given the morphometric data enumerated above. Despite the fact that results from meta-analyses showed an equal efficacy of cryotherapy with other treatment methods,(5) results from a large retrospective study indicated that failure rates of cryotherapy were consistently higher than those of other methods, and in women over the age of 40 years, the failure rate of cryotherapy rose to 34%.(13) This result could be due to the findings noted above that older women have deeper glands and have disease extending further into the canal. Thus, the choice of ablative therapy will vary with the patient’s age and clinical characteristics; cryotherapy should ideally be avoided in women over the age of 40 years.

Given the concern about adverse pregnancy outcomes related to treatment for cervical precancers, recent consensus guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP) advise against treatment of CIN1 and offer conservative options for following young women with CIN2 and CIN2-3,(14) based on strong epidemiologic evidence that regression rates are high for CIN in young women, and that cancer rates are low. The term *young women* “indicates those who after counseling by their clinicians consider risk to future pregnancies from treating cervical abnormalities to

outweigh risk for cancer during observation of those abnormalities. No specific age threshold is intended.”(14) The guidelines recommend that young women with high-grade CIN can be offered either treatment or observation, provided colposcopy is satisfactory (adequate). When CIN2 is specified, observation is preferred. When CIN3 is specified, or when colposcopy is unsatisfactory (inadequate), treatment is preferred. If observation is selected, the patient should undergo colposcopy and cytology every 6 months, with re-biopsy if the colposcopy worsens or if the lesion persists for one year. Treatment is recommended if the high-grade lesion persists for 24 months, or if a repeat biopsy shows CIN3.

CLINICAL CASE SCENARIOS

The following clinical scenarios describe two women with similar findings requiring treatment to prevent the development of cervical cancer. However, due to distinct features of their individual circumstances, the preferred therapies are different for each woman.

Patient A

A 27 year-old G1P1 woman has an abnormal cervical cancer screening result. Diagnostic evaluation with colposcopy is satisfactory (adequate) and reveals a discrete lesion from 12:00–4:00, the biopsy of which shows precancer. She is on oral contraceptives and has one child. She and her husband want to have another child in the next year.

Patient B

A 48 year-old G3P3 woman has an abnormal cervical cancer screening result. Diagnostic evaluation with colposcopy is satisfactory (adequate) and reveals a discrete lesion from 12:00–4:00, the biopsy of which shows precancer. She had a tubal ligation after her last delivery.

The principles of individualized management and consideration of future fertility goals should be applied to the treatment planning for each of the two women:

Patient A is a 27 year-old G1P1 woman with plans for future pregnancy. She has satisfactory colposcopy, so she meets the criteria for observation if the biopsy shows CIN2. If the biopsy shows CIN3, therapy is recommended. She is a candidate for ablative therapy given her satisfactory (adequate) colposcopy, so in light of her reproductive goals, she should be offered cryotherapy or laser ablation. However, if this patient had an unsatisfactory (inadequate) colposcopy or a positive endocervical curettage, she should be offered an excisional procedure (and avoid cold knife conization if possible).

Patient B is a 48 year-old G3P3 woman who has completed childbearing and has satisfactory (adequate) colposcopy and a well-defined ectocervical lesion. She could have either laser ablation or LEEP. Cryotherapy is not a good option for her given her age, in light of the unacceptably high failure rate of cryotherapy in women older than 40 years discussed above. As with Patient A, if she had an unsatisfactory (inadequate) colposcopy or a positive endocervical curettage, she should be offered an excisional procedure with LEEP.

CONCLUSION

As with these hypothetical patients, clinicians should routinely assess the patient's age, desire for future childbearing, and colpopathologic findings when considering specific treatment options for patients with cervical precancer. Clinicians should be willing and able to offer ablation, rather than excision, to women who may desire future childbearing and who meet standard criteria (adequate colposcopy, lesion fully visualized, no endocervical disease, and no glandular dysplasia or suspicion of cancer).(2) Office-based rather than operating room-based methods should always be considered to decrease patient inconvenience and possible morbidity. When excision is indicated in reproductive-aged women (unsatisfactory colposcopy, lesion extends into the canal, or high-grade lesion on endocervical curettage), consideration of the size and depth of excision should be individualized to spare as much cervix as possible in young women. Based on the new consensus management guidelines, providers can offer conservative options for following young women with CIN2 and CIN2-3 in appropriately selected patients.(14)

In conclusion, there is a wide range of options for managing our patients with cervical precancer, and we must look beyond the LEEP to individualize the treatment plan in order to avoid unnecessary adverse outcomes.

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References

1. Patel DA, Saraiya M, Copeland G, Cote ML, Datta SD, Sawaya GF. Treatment patterns for cervical carcinoma in situ in Michigan, 1998–2003. *J Registry Manag.* 2013 Summer;40(2):84–92. [PubMed: 24002133]
2. Paraskevaidis E, Kyrgiou M, Martin-Hirsch P. Have we dismissed ablative treatment too soon in colposcopy practice? *BJOG.* 2007 Jan; 114(1):3–4. [PubMed: 17233854]
3. Ferenczy A, Choukroun D, Arseneau J. Loop electrosurgical excision procedure for squamous intraepithelial lesions of the cervix: Advantages and potential pitfalls. *Obstet Gynecol.* 1996 Mar; 87(3):332–7. [PubMed: 8598950]
4. Ferris DG, Hainer BL, Pfenninger JL, Zuber TJ, DeWitt DE, Line RL. Electrosurgical loop excision of the cervical transformation zone: The experience of family physicians. *J Fam Pract.* 1995 Oct; 41(4):337–44. [PubMed: 7561706]
5. Kyrgiou M, Tsoumpou I, Vrekoussis T, Martin-Hirsch P, Arbyn M, Prendiville W, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: The cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach. *Cancer Treat Rev.* 2006 Nov; 32(7):516–23. [PubMed: 17008015]
6. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: Systematic review and meta-analysis. *Lancet.* 2006 Feb 11; 367(9509):489–98. [PubMed: 16473126]
7. Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: A systematic review and meta-analysis. *BJOG.* 2011 Aug; 118(9):1031–41. [PubMed: 21449928]

8. Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: Meta-analysis. *BMJ*. 2008 Sep 18;337:a1284. [PubMed: 18801868]
9. Jin G, Lanlan Z, Li C, Dan Z. Pregnancy outcome following loop electrosurgical excision procedure (LEEP) a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2013 Jul 11.
10. Kyrgiou M, Arbyn M, Martin-Hirsch P, Paraskeva E. Increased risk of preterm birth after treatment for CIN. *BMJ*. 2012 Sep 4;345:e5847. [PubMed: 22951549]
11. Anderson MC, Hartley RB. Cervical crypt involvement by intraepithelial neoplasia. *Obstet Gynecol*. 1980 May; 55(5):546–50. [PubMed: 7366912]
12. Abdul-Karim FW, Fu YS, Reagan JW, Wentz WB. Morphometric study of intraepithelial neoplasia of the uterine cervix. *Obstet Gynecol*. 1982 Aug; 60(2):210–4. [PubMed: 7155483]
13. Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: Long-term follow-up from the British Columbia cohort study. *J Natl Cancer Inst*. 2009 May 20; 101(10):721–8. [PubMed: 19436026]
14. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 2013 Apr; 121(4):829–46. [PubMed: 23635684]