Uterine Cervix Conization Based on Pap Smear Results: The "See And Treat" Approach

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ABSTRACT: **Background:** The "see and treat" approach, proceeding without a biopsy directly to uterine cervix conization in women diagnosed with high grade squamous intraepithelial lesion (HGSIL) on Pap smear, shortens the treatment duration, lessens patient anxiety, and reduces health care costs.

Objectives: To evaluate the level of diagnostic accuracy and the over-treatment rate in the "see and treat" versus conventional management of women diagnosed with HGSIL.

Methods: We retrospectively reviewed all women with HGSIL who had undergone the "see and treat" approach during 2001–2011 at Soroka University Medical Center. Similar cohorts, who were managed conventionally with a cervical biopsy prior to the conization, served as a comparison group.

Results: The study population consisted of 403 women: 72 (18%) had undergone the "see and treat" approach and 331 (82%) conventional management. The false positive rate was 11% for the "see and treat" group, compared to 6% for the conventional management group ($P = 0.162$). Similarly, no statistically significant difference was observed when comparing the positive predictive value (PPV) of high grade dysplasia diagnosed on Pap smear (PPV 88.9%) versus cervical biopsy (PPV 93.8%) ($P = 0.204$). Moreover, both the false positive rate and PPV remained similar in subgroups of patients, according to age, menopausal status, number of births, and colposcopy findings.

Conclusions: The accuracy level of HGSIL diagnosis on Pap smear is similar to that of high grade dysplasia on a cervical biopsy. We therefore recommend referring patients with HGSIL directly to conization. Skipping the biopsy step was not associated with significant over-treatment or other adverse effects.

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KEY WORDS: high grade squamous intraepithelial lesion (HGSIL), cervical intraepithelial neoplasia (CIN), Pap smear, "see and treat," conization

Cervical cancer remains a significant health threat around the world. Cervical intraepithelial neoplasia is a relatively common problem, especially in women of reproductive age. More than 1 million women worldwide are diagnosed each year with low grade cervical intraepithelial lesions, referred to as CIN1, and approximately 500,000 are diagnosed with high grade lesions, namely CIN2,3 [1]. Papanicolaou (Pap) smears detect pre-invasive and early invasive disease and have led to a significant reduction in its incidence and associated mortality in many countries [2]. The Bethesda classification of Pap test combines CIN2 and CIN3 into the category of high grade squamous intraepithelial lesion [3].

According to the current consensus guidelines, any woman with a cytology specimen suggesting the presence of HGSIL should undergo colposcopy and directed biopsy [4]. Management is often based on the combined results of cytology and histopathology [5,6]. However, colposcopy with biopsy shows varying degrees of correlation with Pap smear in detecting HGSIL, in the range of 50–80% [7,8]. When the diagnosis of high grade dysplasia of the uterine cervix is established, or even when colposcopically directed biopsy does not confirm the Pap diagnosis of HGSIL, the next step in the standard treatment protocol is loop electrosurgical excision procedure or conization. In addition to being an effective treatment option, the LEEP provides a tissue specimen that allows definitive histologic diagnosis, reducing the possibility of failure to diagnose an early invasive carcinoma [9]. Thus, the conventional management of HGSIL involves at least two steps, resulting in a delay in diagnosis and relatively high treatment cost [10].

An alternative management named "see and treat" is a one-step treatment of cervical precancerous lesions by LEEP without intervening colposcopically directed biopsy; the LEEP is used simultaneously to diagnose and treat premalignant cervical disease in one visit [4,7,11-14]. This strategy eliminates a second visit usually required for treatment, and provides several advantages including low costs, decreased patient anxiety, and increased compliance. In particular, the strategy is beneficial when the patient is unlikely to return for follow-up care. However, the "see and treat" strategy does have potential disadvantages, most important of which is the possibility of

CIN = cervical intraepithelial neoplasia
HGSIL = high grade squamous intraepithelial lesion
LEEP = loop electrosurgical excision procedure

over-treatment. Patients with lower grade lesions (such as low grade squamous intraepithelial lesion, or infection with reactive repair) may receive excessive treatment and be unnecessarily exposed to bleeding and infection – the most common complications of this procedure [15]. Moreover, over-treatment is a waste of economic resources.

The purpose of this study was to determine whether colposcopically directed biopsy is a necessary step in the management of patients with HGSIL, and to assess the incidence and predictors of over-treatment with the "see and treat" approach.

PATIENTS AND METHODS

Between January 2001 and July 2011, cervical conization using the loop electrosurgical excision procedure was performed in 475 patients in the Unit of Gynecologic Oncology at Soroka University Medical Center. Of these, 72 were excluded for the following reasons: 47 had no evidence of high grade dysplasia on Pap smear or on biopsy prior to their conization; they underwent conization because of at least one of the following factors: persistent CIN1, persistent vaginal bleeding, Pap smear with atypical glandular or squamous cells of uncertain significance, and suspicious colposcopic findings. An additional 23 patients underwent conization as a diagnostic rather than a definitive procedure prior to simple/radical hysterectomy because of at least microinvasive carcinoma, and 2 underwent only re-conization in our hospital and no information about their first conization was available. The remaining 403 are the subject of this report.

The conizations were performed under colposcopic examination by oncologic gynecologists. The specimens were sent fresh to the Department of Pathology. The surgical margins were marked with India ink, and the specimen was pinned flat on a cork board and fixed in 10% formalin overnight. Sections of the entire fixed specimen were taken perpendicular to the mucosal surface at 3 mm intervals.

With institutional review board approval, the medical charts were reviewed and the following data retrieved: age, menopausal status, number of births, colposcopy examination findings, Pap smear results (when applicable), cervical biopsy results (when applicable), whether the conization was based on Pap smear or cervical biopsy results, and conization specimen diagnosis.

All biopsies and conization slides were examined by one of the authors (R.S.L.) who determined the degree of dysplastic changes. The final pathology diagnosis was defined as the most advanced lesion on the specimen. Severity of disease on the biopsy and conization specimens was classified as CIN1 (low grade dysplasia), CIN 2-3 (high grade dysplasia), microinvasive carcinoma, and invasive cancer.

The conization was considered to be based on Pap smear in cases with HGSIL and no cervical biopsy before the conization. Conversely, the conization was regarded as based on a biopsy in cases with high grade dysplasia on a cervical biopsy prior to the conization, either with or without evidence of HGSIL on Pap smear.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, version 18. Descriptive statistics were performed for all variables. Categorical variables were described by percentage distributions. Continuous variables with normal distributions were expressed by average and standard deviation, and continuous variables without normal distributions were described by median and interquartile range. Comparison between groups for possible differences was performed using the paired *t*-test, Mann-Whitney test, chi-square test, or Fisher's exact test, according to the variable type and whether it was normally distributed or not. For example, the over-treatment rate was compared between women who underwent conization based on Pap smear and those who had a preceding biopsy, using chi-square or Fisher's exact test. A logistic regression analysis was then used to evaluate the possible association between patient characteristics and over-treatment. Variables with statistically significant correlation in univariate analysis were candidates for multivariate analysis. The odds ratios and their 95% confidence intervals were calculated for possible interactions between variables. The Hosmer-Lemeshow goodness-of-fit test was used for the final logistic regression model. $P < 0.05$ was considered statistically significant.

RESULTS

This study included 403 women who underwent cervical conization, 72 due to HGSIL on Pap smear with no preceding biopsy and 331 because of high grade dysplasia diagnosed on a previous cervical biopsy. The mean age was 38 years (median 38, range 18–83 years). The age of 259 women (64.3%) was > 35 years, and 45 (11.8%) women were menopausal. The average birth number was 2.1 (median 2, range 0–11). Among the 203 women who had documented colposcopy findings, the examination was diagnostic in 149 (73.4%). Twenty-three (15.5%) had findings consistent with high grade dysplasia, 113 (75.8%) were suspected of having low grade dysplasia, and 13 (8.7%) had an unremarkable colposcopic examination.

Table 1 summarizes the clinical and pathological features of both groups. The two groups were similar in terms of age, menopausal status and number of births. However, the colposcopy examination was diagnostic in 76% of those who had conization based on a biopsy, as compared to 32% of those whose conization was based on Pap smear ($P < 0.001$). Additionally, colposcopy findings suspicious of high grade dysplasia were more common in the group that underwent conization based on Pap smear results ($P = 0.03$).

It is noteworthy that the cone specimen was negative for high grade dysplasia (false positive cases) in 11% of the

Table 1. Clinical and pathological features

	Cone based on Pap smear (n=72)	Cone based on cervical biopsy (n=331)	*P* value
Age (yr)	39.0 ± 9.0	38.2 ± 10.2	0.522
Age › 35 yr	52 (72.2%)	207 (62.5%)	0.120
No. of births (n=376)	2.2 ± 1.5	2.1 ± 1.9	0.518
Menopause (n=381)	9 (12.9%)	36 (11.6%)	0.764
Diagnostic colposcopy (n=203)	22 (32.4%)	102 (75.6%)	‹0.001
Colposcopy findings (n=150) Normal Mild dysplasia Severe dysplasia	 2 (5.3%) 26 (68.4%) 10 (26.3%)	 12 (10.7%) 88 (77.7%) 13 (11.6%)	0.030
Cone results Normal / CIN 1 CIN 2/2–3/3/microinvasive SCC/SCC	 8 (11.1%) 64 (88.9%)	 21 (6.3%) 310 (93.7%)	0.162

CIN = cervical intraepithelial neoplasia, SCC = squamous cell carcinoma

Table 2. Univariate analysis of factors that may influence the false positive rate of Pap smear and cervical biopsy

	High grade dysplasia in conization (true positive) (n=374)	No high grade dysplasia in cone (false positive) (n=29)	*P* value
Test used			
PAP	64 (17.1%)	8 (27.6%)	0.156
Biopsy	310 (82.9%)	21 (72.4%)	
Age (yr)	38.3 ± 10.0	39.1 ± 9.7	0.651
Age › 35 yr	240 (64.2%)	19 (65.5%)	0.884
No. of births (n=375)	2.1 ± 1.8	2.0 ± 1.9	0.820
Menopause (n=381)	43 (12.1%)	2 (7.4%)	0.462
Diagnostic colposcopy (n=201)	113 (61.4%)	11 (57.9%)	0.765
Colposcopy findings (n=150) Normal Mild dysplasia Severe dysplasia	 12 (8.8%) 102 (75.0%) 22 (16.2%)	 2 (14.3%) 11 (78.6%) 1 (7.1%)	0.576

cases based on Pap smear compared to 6% of those following cervical biopsy ($P = 0.162$) [Table 1]. The false positive rate remained similar also in subgroups of patients according to age, menopausal status, number of births, and colposcopy findings [Table 2].

No statistically significant difference was observed when comparing the positive predictive value of HGSIL on Pap smear (PPV 88.9%) to high grade dysplasia on cervical biopsy (PPV 93.8%) ($P = 0.204$). Moreover, the PPV remained similar after assigning the patients to various subgroups according to age, menopausal status, number of births and colposcopy findings [Table 3].

PPV = positive predictive value

Table 3. Positive predictive value of Pap smear and cervical biopsy in all patients and in various subgroups

Group	PPV cone based on PAP	PPV cone based on biopsy	*P* value
All patients	88.9% (64/72)	93.8% (310/331)	0.204
Age group (yr) ‹ 30 30–39 40–49 ≥ 50	 85.7% (12/14) 90.3% (28/31) 83.3% (15/18) 100.0% (9/9)	 96.3% (77/80) 94.2% (114/121) 92.8% (77/83) 88.9% (32/36)	 0.159 0.427 0.198 0.569
Age › 35 Yes No	 90.4% (47/52) 85.0% (17/20)	 93.4% (183/196) 94.4% (117/124)	 0.546 0.145
No. of births (n=376) 0 1 2	 80.0% (8/10) 80.0% (12/15) 93.5% (43/46)	 94.1% (64/68) 92.2% (47/51) 93.7% (164/175)	 0.168 0.188 1.000
Menopause (n=381) Yes No	 100.0% (9/9) 88.5% (54/61)	 93.9% (31/33) 93.7% (251/268)	 1.000 0.175
Diagnostic colposcopy (n=203) Yes No	 90.9% (20/22) 87.0% (40/46)	 91.1% (92/101) 96.2% (25/26)	 1.000 0.410
Colposcopy findings (n=150) Normal Mild dysplasia Severe dysplasia	 100.0%.0 (2/2) 84.6% (22/26) 90.0% (9/10)	 81.8% (9/11) 92.0% (80/87) 100.0% (13/13)	 1.000 0.273 0.435

DISCUSSION

Although the "see and treat" approach was found by many previous studies to be advantageous for women with HGSIL [5,6,9,10,12-16], the general recommendation in the literature is still to perform cervical biopsy before conization [4]. Performing conization based on Pap smear alone without confirming the diagnosis of high grade dysplasia by a biopsy became feasible only recently [17]. The greatest concern with skipping the cervical biopsy stage is over-treatment or, in other words, performing conization unnecessarily for low grade dysplasia or reactive lesions [11,15].

In this study we compared the cone specimen diagnosis in 72 women whose conization was based on HGSIL by Pap smear with that of 331 women who were diagnosed with high grade dysplasia on a cervical biopsy before the conization. The two groups were similar in terms of age, menopausal status and number of births. The false positive rate of HGSIL on Pap smear was 11.1% as compared to 6.3% for high grade dysplasia diagnosed on cervical biopsy ($P = 0.162$). In addition, the PPV of HGSIL on Pap smear (88.9%) did not differ significantly from that of cervical biopsy (93.8%), $P = 0.204$. Thus, the results of our study indicate that the accuracy of Pap smear is not inferior to that of cervical biopsy in diagnosing high grade dysplasia. Noteworthy, our Pap smear PPV of 88.9% is high compared to the approximately 80% in the literature [5,10,17].

Interestingly, diagnostic colposcopy examination was more common among women who had cervical biopsy before con-

ization ($P < 0.001$). It is possible that women who had diagnostic colposcopy examination underwent biopsy from suspicious areas, while those who had an unsatisfactory examination had no suspicious areas to be biopsied and therefore were referred to conization without a biopsy.

The weaknesses of this study are its retrospective nature and the relatively small size of the group that had conization based on Pap smear. The study's strengths are the relatively large size of the group that had cervical biopsy before the conization, and the examination of all histological slides by an experienced pathologist (R.S.L.).

In conclusion, based on previous studies [5,6,9,12-16] and on our results, since the accuracy level of HGSIL diagnosis on Pap smear is similar to that of high grade dysplasia on a cervical biopsy, we recommend referring patients with HGSIL directly to conization. While skipping the biopsy step shortens the treatment duration, lessens patient anxiety, and reduces health care costs, it was not found to be associated with significant over-treatment or other adverse effects.

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