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ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Clinical Significance of Cervical Low-Grade Squamous Intraepithelial Lesions: 8 Years' Experience

Serviksin Düşük Dereceli İntraepitelyal Lezyonlarının Klinik Önemi: Sekiz Yıllık Deneyim

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Summary

Background: The aim of the present study was to evaluate the follow-up results in patients who initially had cervical smear results showing low-grade squamous intraepithelial lesions (LSIL) in order to determine their histologic outcomes and develop a management guideline.

Methods: A total of 240 non-pregnant women with LSIL in their cervical smears were evaluated with colposcopy, and colposcopically directed biopsies and endocervical sampling were done as indicated. Patients had follow-up smears every 3 to 4 months.

Results: Of the 240 patients with LSIL, 108 patients (62.8%) were classified as having cervical intraepithelial neoplasia 1 (CIN 1), 28 (16.3%) cases had CIN 2, 12 patients (6.8%) had CIN 3, and 4 patients (2.3%) were diagnosed with invasive cervical carcinoma. At 12-month follow-up, persistence was observed in 38 (22%) cases, and progression to high-grade dysplasia was seen in 16 (9%) cases. Regression to normal smear was observed in 118 cases (68%).

Conclusion: Since cervical minor abnormalities can change to low-grade lesions, high-grade lesions, or even cervical carcinoma, colposcopy was found to be an appropriate method for a correct diagnosis. Colposcopy in combination with smear was the ideal approach during follow-up.

Keywords: *Colposcopy; low-grade squamous intraepithelial lesions; smear.*

Özet

Amaç: *Bu çalışmada, servikal smearlerinde düşük dereceli skuamöz intraepitelyal lezyon (LGSIL) saptanan hastaların izlemleri sonucundaki histolojik tanılarının değerlendirilmesi ve bir tedavi rehberi geliştirilmesi amaçlandı.*

Gereç ve Yöntem: *Servikal smear incelemesinde LGSIL saptanan 240 gebe olmayan hastanın kolposkopik incelemesi ve gerekli görülenlerde kolposkopi rehberliğinde servikal biyopsi ve endoservikal örnekleme yapıldı. Hastalar üç–dört ay aralıklarla servikal smear kontrolüne alındı.*

Bulgular: *İki yüz kırk LGSIL saptanan hastanın 108'inde (%62.8) servikal intraepitelyal neoplazi 1 (CIN 1), 28'inde (%16.3) CIN 2, 12'sinde (%6.8) CIN 3 ve dördünde invazif serviks kanseri saptandı. On iki aylık takiplerinde hastaların 38'inde (%22) persistans, 16'sında (%9) yüksek dereceli displaziye progesyon, 118'inde ise (%68) regresyon olduğu gözlendi.*

Sonuç: *Servikal minör anormallikler, düşük dereceli lezyonlara, yüksek dereceli lezyonlara ve hatta serviks kanserine dahi değişebildiği için kolposkopinin doğru tanıya ulaşmada uygun bir yöntem olduğu görüldü. Takipteki en ideal uygulama kolposkopinin smear ile beraber yapılması olarak bulundu.*

Anahtar sözcükler: *Düşük dereceli skuamöz intraepitelyal lezyon; kolposkopi; smear.*

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Introduction

Low-grade squamous intraepithelial lesions (LSIL) are an abnormal test result frequently encountered in cervical smears.[1] Despite many studies and research having been conducted for a long time, there is no consensus among clinicians regarding the evaluation of these smears.[2] Quite diverse diagnosis, treatment, and follow-up algorithms have been put forward for patients with LSIL. These differences in follow-up can lead to many unwanted results.

Primarily, it may cause unnecessary and unreasonable anxiety in patients. Physicians face various questions and complications, including an obligation to make a fast diagnosis, yet excessive intervention and overtreatment that can include colposcopic examination, cervical biopsy or biopsies, Human papillomavirus (HPV) tests and excisional surgery often only adds to the burden of both clinician and patient.[3] In addition, cases of carcinoma can be missed due to varying nature of diagnostic criteria in smear examinations, significantly high rate of false positives, significantly high rate of preneoplastic changes under cells with unknown importance to cytological examination, and follow-ups that are carried out with only cytological examination, colposcopic imaging or macroscopic imaging.[4]

The present study sought to determine the significance of minor cytological abnormalities by clinically evaluating 8 years of LSIL-diagnosed smears from the hospital.

Patients and Methods

Of all the patients from obstetrics and gynecology clinic of the hospital over 8 years, 240 non-pregnant women with LSIL cervical smear result according to Bethesda System criteria were taken under review. All patients had colposcopy, biopsy samples were taken from those with positive signs (e.g., punctuation, mosaic image, acetowhite area, lugol-free area, atypical vascularization), and endocervical curettage was performed if necessary. All patients were called for follow-up examination at 3-month intervals. Smear was performed again and biopsy sample collected during repeat colposcopy, if necessary. Histopathological results were compared to LSIL cytologies, and diagnoses were classified according to cervical intraepithelial neoplasia (CIN) stage: CIN 1, CIN 2, or CIN 3, and invasive carcinoma. The sensitivity of the method was tested by comparing colposcopic findings to histological diagnoses.

Results

The age of patients with LSIL ranged between 19 and 57 years. Only 5% of patients were in the age group of 25 and under. Biopsy samples were taken during colposcopy from 71.7% of patients (Table 1).

Histological distribution of 172 patients with LSIL cytology for whom biopsies were performed was as follows: 11.6% chronic cervicitis, 62.8% CIN 1, 16.3% CIN 2, 6.8% CIN 3 and 2.3% invasive cervical cancer. When CIN was assessed in terms of age distribution, it was seen that CIN was more commonly observed in premenopausal patients between 25 and 56. On colposcopic examination, dense acetowhite epithelium, mosaicism, punctuation, or atypical vascularization were observed in 71.7% of the patients with LSIL. Biopsies were performed for all of these patients. CIN

Table 1. Age distribution of patients with LSIL for whom colposcopic biopsy was performed

Age group (years)	Colposcopic biopsy follow-up				
	LSIL cases		Biopsy cases		Biopsy taken-LSIL
	n	%	n	%	%
<25	12	5	8	7.4	66.7
26–35	88	36.7	64	37.2	72.7
36–45	80	33.3	64	37.2	80
46–55	36	15	24	14	66.7
≥56	24	10	12	6.9	50
Total	240	100	172	100	71.7

LSIL: Low-grade squamous intraepithelial lesions.

Table 2. Histology results of patients with LSIL smear according to age group

Age group (years)	Histological diagnosis											
	Cervicitis		CIN-I		CIN-II		CIN-III		Invasive carcinoma		Age group	
	n	%	n	%	n	%	n	%	n	%	n	%
<25	0	0	4	50	4	50	0	0	0	0	8	4.7
26–35	4	6.3	48	75	8	12.5	4	6.3	0	0	64	37.2
36–45	0	0	48	81.3	12	18.8	4	6.3	0	0	64	37.2
46–55	8	33.3	8	33.3	0	0	4	16.7	4	16.7	24	14
≥56	8	66.7	0	0	4	33.3	0	0	0	0	12	9.6
Histology (%)	20	11.6	108	62.8	28	16.3	12	6.8	4	2.3	172	100

LSIL: Low-grade squamous intraepithelial lesions. CIN: Cervical intraepithelial neoplasia.

Table 3. Results of LSIL cytologies

	Cytology		Persistent		Progression		Regression	
	n	%	n	%	n	%	n	%
LSIL	172	100	38	22	16	9	118	68

LSIL: Low-grade squamous intraepithelial lesions.

was revealed histologically in 85.9% of patients with LSIL and invasive carcinoma in 2.3% of the patients (Table 2). Accordingly, the sensitivity of colposcopy in this study was determined to be 100%.

All patients were called for smear follow-up at 3-month intervals (mean: 9 months). In LSIL cytologies during follow-up, persistence was seen in 22% (n=38) of cases, and progression to CIN 2 was detected in 9% (n=16). Regression in LSIL smear pathologies took place in 68% (n=118) of patients (Table 3).

Discussion

As a result of joint research with 38 participants representing 14 countries, Scheungraber et al. reported that LSIL treatments are diverse and invasive, patients are generally young and want to conceive, and that a coordinated effort is needed to develop an applicable algorithm to prevent overtreatment.[1]

LSIL is still the most frequently encountered anomaly in smear examinations, seen in 1.5% to 1.8% of total smears. Kaygusuz et al. analyzed 37884 results of cervical smear and 153 biopsy results and determined LSIL rate to be 0.15%.[5] Yalti et al. examined 28469 smear results and detected 67 LSIL cases (0.23%).[6]

There are some concerns regarding the accuracy of smear examinations. As a result of studies conducted on cytological diagnostic values, it has been established that detection sensitivity of cytology for histologically proven LSIL ranges between 38% and 89%. The specificity of cytology in detecting LSIL or high-grade squamous intraepithelial lesions (HSIL) has been established as 37.7%, and it has been stated that adding colposcopy to cytology only increases this rate to 40%.[7]

Another important finding is that about 30% of invasive cancers are found in women during regular smear checks (at intervals of less than 3 years). It is the opinion of the authors that smear examinations are not sufficiently accurate. Research has shown false negatives at a rate of 20–45%. It has been recommended that fluid-based cytology should be preferred, since it has a higher sensitivity compared to conventional smear (83% vs 66%).[4] The latest fluid-based cytology is now in use at our clinic.

Secondary test used frequently in the diagnosis of LSIL is colposcopy. Jones et al. conducted research on the necessity of colposcopy. As a result of a 5-year retrospective study, they recorded persistent disease in 11 of 250 patients; presence of LSIL was detected by colposcopy in only 1 patient who had not had abnormal smear result. Consequently, they stated that routine colposcopy adds minimal contribution to cytology. Their study included patients with LSIL who were receiving local ablation or excisional treatment. Electrocautery was used for 46% of these patients, laser ablation for 35%, large loop excision of the transformation zone (LLETZ) for 17%, and conization for 2%. HSIL was detected in 2 cases. Additional treatment was implemented for 8 of 11 persistent cases. Spontaneous regression was observed in 3. Success rate after initial treatment was determined to be 95.6%.[3] In the present study, persistent disease was found in 38 of 240 patients, and progression was seen in 16.

It has been established that cervical biopsy with colposcopy advances the results of colposcopic examination and provides histological result. It has also been stated that the results of cervical biopsy are related to the area where the biopsy sample is taken. Consequently, it has been expressed that histological examination conducted after transformation zone surgery guarantees diagnostic clarity.[7]

Montz and colleagues evaluated 632 patients with atypical squamous cells of undetermined significance (ASCUS) or LSIL smear results. Patients were followed for at least 9 months with colposcopy or smear carried out once every 3 months. Moderate and severe dysplasia were encountered on first colposcopy in 19% of patients. While 18.2% remained the same in the LSIL group, 78.3% returned to normal and 3.4% progressed.[8] The present study had similar results. In our study, moderate to severe dysplasia was observed in 40 cases and regression was seen in 118 cases during follow-up visits.

Fallani and colleagues compared biopsy histologies of cases with ASCUS or LSIL cytological diagnosis from colposcopy. They found diagnosis of ASCUS in 358 of 584 women, and 226 received LSIL diagnosis. According to the results, colposcopic examination was recommended for all patients with cytological diagnosis of ASCUS or LSIL.[9] Schiffman et al. reported in an article that 1572 LSIL cases had been analyzed as part of ASCUS-LSIL Triage Study (ALTS) study. At the end of 2-year period, more than 63% of the women would have been referred for colposcopy using any of the cytological or virological strategies that detected 90% of CIN 3 lesions and cancers.[10]

In the present study, dense acetowhite epithelium, mosaicism, punctuation or atypical vascularization were seen in 71.7% of study participants on colposcopic examinations. Biopsies were performed and CIN was revealed histologically in 85.9% of patients and invasive carcinoma in 2.3% (Table 2). Accordingly, the sensitivity of colposcopy in this study was determined to be 100%.

Uncertainties remain regarding how follow-up should be conducted for patients with LSIL. Previous studies have shown that using merely colposcopy on follow-up has low sensitivity.[3] It has been shown that 70% of LSIL lesions regress on their own; however, 10% progress to HSIL.[11,12] Petry et al. reported 30.2% CIN 3 and 1% cervical carcinoma in LSIL patients.[13] These rates are compatible with current study research.

As a result of studies looking at how patients respond to treatment, it has been determined that the success rate after LSIL treatment ranges between 85% and 95%.[8–13] Histological distribution of 172 patients with LSIL cytology from whom biopsy samples were taken in present study was as follows: 11.6% chronic cervicitis, 62.8% CIN 1, 16.3% CIN 2, 6.8% CIN 3 and 2.3% invasive cervical cancer. Persistence was observed in 22% (n=38) of cases, and progression to HSIL was seen in 9% (n=16). Regression in smear pathologies took place in 68% (n=118) of LSIL patients.

As a result of all of these evaluations, it is certain that repetition of Papanicolaou smears is recommended for patients with LSIL.[14] However, it carries the risk of false negativity. A study has noted a 22% false negative result for CIN 2 and CIN3 in repeated smears right before biopsy. Furthermore, 2 of 6 invasive cervical cancers were missed.[15] The present study results revealed differences between initial smears and follow-up smears of patients whose initial test was not analyzed, possibly due to false negative results.

Information regarding rate low-grade lesions will regress or whether there will be progression or not is inconsistent. Since no test can predict the natural evolution of CIN beforehand, earliest possible histological diagnosis can be advantageous in terms of early

treatment. Moreover, there is a possibility of losing patients to follow-up.

It is of grave importance for patients with low grade abnormal smears to have regular follow-up visits even after colposcopic examination. Just as there can be false negative results from initial colposcopic examination, colposcopy can also be insufficient. In present study, 22% persistence, 9% progression, and 68% regression was observed in LSIL patients.

In cases of low-grade abnormal cytologies, there is a high rate of amelioration in pathology on follow-up. [16] However, it is clinically important to perform colposcopy evaluation of patients with LSIL cytology and conduct biopsy when needed as well as follow-up, due to the possibility of progression in lesions.

Conclusion

It is critical not to delay histological evaluation of cervical and endocervical area of a patient in whom LSIL has been detected. However, the ideal frequency of follow-up visits and treatment method has not become clear yet. The most important reason for this is that we trust smear examinations with normal result or colposcopic examinations that look normal.

It is the opinion of the authors that new methods in the evaluation of cervical pathologies, such as fluid-based cytology, will decrease false negativity and false positivity and eliminate the current uncertainties.

Conflict of interest

None declared.

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