Low-Grade Squamous Intraepithelial Lesion, Cannot Exclude High-Grade Squamous Intraepithelial Lesion

A Category With an Increased Outcome of High-Grade Lesions: Use as a Quality Assurance Measure

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Upon completion of this activity you will be able to:

- define “low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion” (LSIL-H).
- predict the frequency of subsequent high-grade squamous lesion on biopsy following a cytology interpretation of LSIL-H.
- describe the benefit of incorporating the LSIL-H rate into the laboratory quality assurance program.

Abstract

“Low-grade squamous intraepithelial lesion (LSIL), cannot exclude high-grade squamous intraepithelial lesion” (LSIL-H) is an increasingly used, equivocal interpretive category in gynecologic cytology. In an effort to evaluate its potential usefulness as a measure of quality assurance, we studied patterns of use of the LSIL-H diagnosis compared with “LSIL” and “high-grade squamous intraepithelial lesion” (HSIL) with corresponding histologic outcomes for 10 cytopathologists in our practice. In our laboratory, while the overall rate of associated cervical intraepithelial neoplasia 2 or greater on histologic follow-up for LSIL-H was intermediate between that of LSIL and HSIL, the outcomes for individual cytopathologists varied widely. Monitoring this particular utilization-outcome data with periodic confidential feedback to individual cytopathologists offers an opportunity for practice improvement within a laboratory and serves as an additional measure of quality assurance. These data may be useful for establishing and/or realigning the diagnostic criteria for this equivocal cytologic interpretation endorsed by a pathology practice.

The designation “low-grade squamous intraepithelial lesion (LSIL), cannot exclude high-grade squamous intraepithelial lesion” (LSIL-H) represents an equivocal interpretive category in gynecologic cytology proposed to classify abnormal cervical cytologic findings with features of both LSIL and “atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion” (ASC-H). Although not a distinct diagnostic category endorsed by The Bethesda System (TBS), which represents the nomenclature standard for reporting cervicovaginal cytologic diagnoses, LSIL-H has been used by some laboratories as a variation of “squamous intraepithelial lesion of indeterminate grade” to designate those cases fulfilling criteria for both LSIL and ASC-H. Recent studies evaluating the significance of LSIL-H have shown that histologic follow-up for cervical intraepithelial neoplasia 2 or greater (CIN 2+) associated with LSIL-H is intermediate between that for cytologic diagnoses of LSIL and “high-grade squamous intraepithelial lesion” (HSIL), supporting the use of LSIL-H as a distinct diagnostic category.1-6

Our aim was to examine whether the frequency of LSIL-H diagnoses, their rate of histologic follow-up, and subsequent association with CIN 2+ on concurrent/follow-up biopsy could be informative for clinical management and laboratory quality improvement. We propose that studying the pattern of LSIL-H utilization with corresponding histologic outcome can provide a useful measure of quality assurance in a pathology practice.
Materials and Methods

Results of all Papanicolaou (Pap) tests (obtained using the SurePath technique [Becton Dickinson, Franklin Lakes, NJ]) performed at our institution between January 2009 and April 2010 were electronically retrieved. Cases of LSIL, HSIL, and LSIL-H diagnosed during this period were studied. We reviewed the records of the 10 cytopathologists at our institution to identify diagnoses of LSIL, LSIL-H, and HSIL for each individual as well as the rate of CIN 2+ in concurrent or follow-up histologic specimens for each category. The rate of the LSIL-H category relative to the overall LSIL rate (LSIL + LSIL-H) was also determined for each cytopathologist. LSIL-H data were analyzed using the Pearson $\chi^2$ test. The ratio of atypical squamous cell interpretations to squamous intraepithelial lesion (ASC/SIL) interpretations was also determined for each pathologist. The published upper limit benchmark for ASC/SIL is 3, but figures for individual laboratories have been trending downward. The criteria for an interpretation of LSIL-H are not strictly defined for our laboratory and no formal training sessions have been undertaken for cytotechnologists or cytopathologists. However, regular cytology consensus conferences for cytopathology staff/trainees and periodic sessions for cytotechnologists are convened for discussion and multitheaded review of problematic cases, including those with equivocal interpretations such as LSIL-H. The LSIL-H category is generally used when cells meeting the criteria for LSIL are present accompanied by atypical squamous cells with nuclear features worrisome but not diagnostic for HSIL. Image II.

Results

Over a 15-month period, the utilization pattern of the diagnostic categories of LSIL, LSIL-H, and HSIL in gynecologic cytology along with available histologic outcomes was studied for the 10 cytopathologists at our institution. There was a significant difference in the proportion of LSIL-H interpretations rendered by the 10 cytopathologists during the study period ($P = .002$) Table I. The mean rate of CIN 2+ histologic findings associated with LSIL-H for all cytopathologists was 29.4% (range, 0%-50%), while the corresponding mean rates for LSIL and HSIL for all cytopathologists were 9.3% (range, 3.5%-15.4%) and 76.8% (range, 66.7%-100%), respectively. The rates of CIN 2+ on concurrent or follow-up biopsy procedure(s) after LSIL-H

**Table I** Use of LSIL-H Diagnosis Relative to LSIL and HSIL With Associated Histologic Outcomes Among Individual Cytopathologists

<table>
<thead>
<tr>
<th>CP</th>
<th>LSIL-H</th>
<th>Available Histology</th>
<th>% CIN 2+ on FU of LSIL-H</th>
<th>LSIL</th>
<th>Available Histology</th>
<th>% CIN 2+ on FU of LSIL</th>
<th>HSIL</th>
<th>Available Histology</th>
<th>% CIN 2+ on FU of HSIL</th>
<th>% LSIL-H/ (LSIL + LSIL-H)</th>
<th>ASC/SIL Ratio</th>
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<td>90.9</td>
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<td>194</td>
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<td>1,061</td>
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<td>179</td>
<td>168</td>
<td>74.4</td>
<td>12.33</td>
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ASC, atypical squamous cells; CIN, cervical intraepithelial neoplasia; CP, cytopathologist; FU, follow-up; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; LSIL-H, low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion; SIL, squamous intraepithelial lesion.
interpretation on cervical cytologic examination varied more widely compared with those for LSIL or HSIL. The mean rate of histologic follow-up (concurrent or subsequent cervical biopsy procedure within 1 year) for LSIL-H interpretations was also intermediate at 82.6%, while the rates of histologic follow-up for LSIL and HSIL were 65.4% and 93.9%, respectively (Table 1).

Cytologic interpretations of LSIL-H, LSIL, and HSIL rendered by individual cytopathologists during the study period, along with corresponding histologic outcomes (percentage of CIN 2+ findings) are summarized in Table 1. The mean percentage of LSIL-H diagnoses relative to all LSIL diagnoses (LSIL-H + LSIL) for the group is 12.3% with a range of 6.6% to 18.2% for individual cytopathologists (Table 1). Figure 1 shows a graphic comparison of associated percentages of CIN 2+ histology for cytologic interpretations of LSIL-H relative to LSIL and HSIL for individual cytopathologists. The ratio of LSIL-H to all SIL for each cytopathologist trended in the same direction as the ASC-SIL ratio.

**Discussion**

LSIL-H is an equivocal interpretive category in gynecologic cytology and has been shown to represent a diagnostic category with an intermediate risk for histologic association with CIN 2+ compared with LSIL and HSIL.1–6 It is being increasingly used in many laboratories even though it is not an official diagnostic category recognized by TBS.8 TBS was most recently revised in 2001 with further refinement of the category of “atypical squamous cells of undetermined significance” (ASC-US) and the addition of “atypical squamous cells, cannot exclude HSIL” (ASC-H) as a distinct diagnostic category.8–10 The inclusion of these equivocal categories reflects the fact that it is difficult to distinguish certain benign processes (eg, reactive changes, immature squamous metaplasia) from LSIL and HSIL; it also reflects the fact that the Pap test is generally recognized to be imperfect and has an associated percentage of false-positive and false-negative test results in a given patient population.

Given the accepted probabilities for error inherent in the Pap test, quality control strategies are routinely used to improve the overall sensitivity and specificity of this screening test. For more than a decade, the ASC/SIL ratio has been used as a quality assurance measure in gynecologic cytology.7,11–16 This measured ratio represents the degree of uncertainty or lack of specificity of cytologic interpretations rendered by a given cytopathologist or laboratory; as a marker of uncertainty, the ASC/SIL ratio traditionally has been used as a quality control method for evaluating intra- and inter-laboratory performance. In our laboratory, we previously studied individual cytopathologists’ rates for human papillomavirus positivity with respect to ASC-US with routine feedback as a proposed method for improving quality.16 In this context, LSIL-H represents another equivocal category that can be similarly applied as a measure of quality assurance in laboratories where this diagnosis is used.

In our laboratory, our data show that the overall rate of LSIL-H with concurrent or follow-up histologic finding of CIN 2+ is 29.4%, which is intermediate between that of LSIL (9.3%) and HSIL (76.8%) and is consistent with other reports in the literature (24%–49%) Table 1.1–4,6 Interestingly, the mean rate of histologic follow-up (concurrent or follow-up cervical biopsy findings) for LSIL-H interpretations was 82.6%, whereas the rates of histologic follow-up for LSIL and HSIL were 65.4% and 93.9%, respectively (Figure 1). These data suggest that cases of LSIL-H at our institution are clinically managed more aggressively with more cervical biopsy procedures (compared with LSIL alone) and are treated more similarly to HSIL (compared with LSIL alone) in terms of its concurrent or follow-up biopsy procedure rate. Although LSIL-H does not represent a distinct biological category with CIN 2+ compared with LSIL and HSIL.1–6 It is being increasingly used in many laboratories even though it is not an official diagnostic category recognized by TBS.8 TBS was most recently revised in 2001 with further refinement of the category of “atypical squamous cells of undetermined significance” (ASC-US) and the addition of “atypical squamous cells, cannot exclude HSIL” (ASC-H) as a distinct diagnostic category.8–10 The inclusion of these equivocal categories reflects the fact that it is difficult to distinguish certain benign processes (eg, reactive changes, immature squamous metaplasia) from LSIL and HSIL; it also reflects the fact that the Pap test is generally recognized to be imperfect and has an associated percentage of false-positive and false-negative test results in a given patient population.

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entity, patients receiving this diagnosis based on cervical cytologic study are treated differently in clinical practice, reflecting the effect of this diagnosis on patient care.

The rate of LSIL-H as a percentage of all LSIL and LSIL-H interpretations among the cytopathologists at our institution varied from 6.6% to 17.9%. These figures fall within the range of 7% to 20% in reported studies (Table 2). Furthermore, studying the pattern of use of the LSIL-H diagnosis with corresponding histologic outcome yielded interesting performance data for individual cytopathologists in comparison with the group as a whole. As expected, the variability in corresponding CIN 2+ rates on follow-up for abnormal cytologic diagnoses among cytopathologists was more significant for LSIL-H than for LSIL and HSIL, which showed generally closer agreement (Figure 1). While the overall rate of associated CIN 2+ on follow-up for LSIL-H was intermediate between that of LSIL and HSIL, the outcomes for individual cytopathologists varied considerably.

Two cytopathologists had LSIL-H rates associated with CIN 2+ of 0% and 50% which significantly deviated from the group average (29.4%). Although these extreme rates may partially reflect these cytopathologists’ lower commitment to gynecologic cytopathology service (because both cytopathologists were among the lowest quartile in terms of case load during this study period), these outlying rates may still offer practical feedback for these individuals in terms of their frequency and pattern of LSIL-H use. The significant difference in the proportion of LSIL-H interpretations rendered by the different cytopathologists during the study period is most likely because of a combination of factors. Most important of these factors may be the heterogeneous application of cytologic criteria for this equivocal interpretative category, which may be reflective of other factors, such as experience, variable cytopathology case load, and individual diagnostic confidence levels. Ascertaining the actual criteria application differences that result in variable interpretation in this category is beyond the scope of this initial survey. A future study is planned that will review the cytologic features in cases of LSIL-H that were followed up as HSIL or LSIL to better document and understand the morphologic differences.

In the context of quality improvement measures, the rate of LSIL-H usage with corresponding CIN 2+ histologic findings provides quantitative data of laboratory performance and individual cytopathologist performance. Monitoring these particular utilization-outcome data with periodic confidential feedback to individual cytopathologists offers an opportunity for practice improvement in a laboratory and serves as an additional measure of quality assurance. Using this strategy, cytopathologists at the extreme ends of the average may consider reevaluating their diagnostic criteria for application of LSIL-H to improve alignment with the laboratory group. Routine monitoring of individual application of LSIL-H compared with the laboratory benchmark also may be helpful in establishing a group consensus for the use of this equivocal interpretative category in practice.

Conclusions

Although not representing a distinct biological entity, LSIL-H is an equivocal interpretative category in gynecologic cytology that can have important clinical implications for patient management. At our institution, patients receiving this diagnosis based on cervical cytologic study appear to be followed more aggressively than patients with LSIL alone, and are treated more similarly to patients with HSIL based on associated cervical biopsy procedure rates. Furthermore, studying the pattern of use of the LSIL-H diagnosis with corresponding histologic outcome for individual cytopathologists can provide a useful measure of quality assurance in a pathology practice. In our laboratory, while the overall rate of associated CIN 2+ on histologic follow-up for LSIL-H was intermediate between that of LSIL and HSIL, the outcomes for individual cytopathologists varied considerably. Given this observation, feedback of individual and group patterns of LSIL-H usage with associated outcome data may be particularly useful for establishing and/or realigning the diagnostic criteria used by individual cytopathologists and endorsed by a pathology practice. Subsequent data on the efficacy of such feedback have yet to be studied. It will be interesting to observe whether any practice modification based on this feedback affects future pattern of LSIL-H use. Repeat analysis of our data at a later date after gathering routine feedback of individual and group performance data will be interesting and important for documenting any effect of this proposed quality improvement strategy.

The evaluation of the use of the LSIL-H category in our laboratory proved to be an informative exercise that can be recommended either as an ongoing quality monitor or as a periodic analysis to gauge the uniformity of usage and outcomes for this interpretation. Laboratory-wide consensus on the definition of LSIL-H is needed and will become available with future case review conferences. Also, individual pathologists can judge if they are overusing the category relative to the laboratory average and make adjustments if necessary. Monitoring the rates of follow-up biopsy of women with ASC-US, ASC-H, LSIL, LSIL-H, and HSIL interpretations on prior cytologic examination is helpful in understanding local clinical practice and clinicians’ perception of where LSIL-H fits into the published American Society for Colposcopy and Cervical Pathology follow-up guidelines.

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Nishino et al / LSIL-H as an Interpretive Category

References


