



## Clinical Topic of the Month



### Unsat Paps: More Than Aggravation

*Raheela Ashfaq, MD*

One of the most aggravating aspects of routine Pap screening is an unsatisfactory result from the laboratory. "Unsat" Paps induce irritation all around—for the physician, for the clinic staff, and for the patient. Although this category constitutes less than 1% of all Pap results, the ensuing hassle of rescheduling the patient for a repeat Pap is inconvenient for everyone involved and oftentimes creates friction in the physician-lab interaction. From a laboratory's viewpoint, this is a multifaceted

problem that requires a multifaceted solution.

### Guidelines

According to Bethesda 2001 guidelines, adequate squamous cellularity for conventional smears is defined as the presence of "an estimated minimum of approximately 8,000 to 12,000 well-preserved and well-visualized squamous epithelial cells."<sup>1</sup> The Bethesda 2001 guidelines define adequacy of the squamous component for liquid-based Pap tests "as a minimum of 5,000 cells." The estimation is determined by comparison with computer-generated reference images, not by actual counting of the cells.

Whether or not the estimated range of squamous cells is the most clinically relevant cutoff to achieve sample adequacy in conventional preparations has been studied. Compared with the old 10% rule, more Pap smears have been ruled as unsatisfactory using the Bethesda 2001 criteria.<sup>2</sup> The effect on liquid-based preparations is less obvious because these methods tend to produce higher-quality slides than conventional smears.

### Sampling Errors

Despite improvements in guidelines, errors persist. Poor sample collection is the most common source of unsat Paps. Other causes include scant cellularity due to obscuring inflammation or blood and interpretive errors.<sup>3</sup>

Optimal sampling technique typically involves proper choice of collection devices. One clinical study of sampling devices found that the combination of sampling the endocervix with a brush and the ectocervix with a spatula significantly improved quality indicators, including the presence of endocervical cells.<sup>4</sup> Another study found that using a cytobrush decreased the unsatisfactory rate from 14.4% to 3% ( $p < 0.001$ ) while increasing the detection of atypia from 10% to 16.7% ( $p < 0.001$ ) and HSIL from 1.7% to 3.7% ( $p < 0.001$ ).<sup>5</sup> Other ways that poor clinical sampling techniques decrease specimen quality include missing the transformation zone and sampling during active infection or bleeding.

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### Steps to Prevent

#### Unsatisfactory Paps

- Don't sample with improper collection device or techniques
- Don't sample during menses or obvious infection
- Do transfer the cervical sample according to specified instructions
- Do sample postmenopausal women with symptomatic bleeding
- Do follow women with unsat Paps according to guidelines

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Scant cellularity is another source of unsatisfactory Pap samples, which may be entirely attributable to poor technique. If the Pap test meets the minimal quantitative criterion of cellularity of 5,000 cells in a liquid-based preparation, the Pap result may go out as "satisfactory but limited by scant cellularity." Atrophic vaginal mucosa in peri- or postmenopausal women presents a unique challenge, especially in cases of severe atrophy. For example, a Pap from a 70-year-old woman may show only a few basal/parabasal cells that may not meet the minimal criterion. Depending on age and previous history, this Pap may be deemed as satisfactory.

Another common source of errors is a form of interpretation error introduced by interobserver variability during screening process. Within organized Italian cervical cancer screening programs, the sample inadequacy rate due to interobserver variability range from 1% to 20%.<sup>6</sup> Another study compared interobserver variability on specimen adequacy and found that the Bethesda 2001 criteria, including the use of reference images, increased interobserver agreement ( $\kappa = 0.60$ ,  $p < 0.001$ ) compared with the 10% method ( $\kappa = 0.49$ ,  $p < 0.001$ ). The improvement was statistically significant ( $p = 0.007$ ).<sup>7</sup> Individual labs generally have their own internal procedures for minimizing interobserver variability.

It is imperative that the patient meets all the requirements for obtaining a high-quality Pap sample, including abstaining from sampling during active menstruation and obvious cervical infection. In both situations, there is a dilutional effect on sample cellularity with either blood or inflammation, resulting in an unsatisfactory Pap. If obvious infection is present, a "treat and repeat" strategy is useful.

Sampling during symptomatic vaginal bleeding especially in postmenopausal women presents another unique challenge due to high incidence of endometrial adenocarcinoma in this age group. Even in premenopausal women, vaginal bleeding is an important and tell-tale symptom of cervical and uterine tumors. In this situation, some labs will use additional techniques, such as glacial acetic acid, to rid the sample of blood in order to visualize the underlying epithelial component. This practice occasionally helps to cinch the diagnosis of adenocarcinoma.

In general, more clinicians are taking liberties with sampling during bleeding. In the era of conventional Pap smears, clinicians were cautious not to sample during active bleeding because the slide would be covered with blood. With increasing use of liquid-based cytology (LBC), a misperception exists that LBC techniques will get rid of the excessive blood, which is true only to some extent and depends entirely on how much blood is present in comparison with the epithelial cells. The real issue is that blood is the predominant factor in these kinds of samples and that because of too much blood and too few epithelial cells, the result can be unsatisfactory.

The standard of care for a clinical laboratory that receives a bloody Pap sample is to perform a manual screen and apply the current Bethesda criteria. Manual screening of a bloody slide is resource-intensive for the lab. If manual screening determines there are less than 5,000 epithelial cells and excessive red blood cells, then the result returned is unsatisfactory. Alternatively, at this point the lab may choose to proceed with a reprocessing technique using glacial acetic acid. Reprocessing significantly decreases the unsatisfactory rate and increases the detection of cervicovaginal abnormalities.<sup>8</sup> However, not all laboratories perform reprocessing due to time and cost involved.

In addition to these precautions, it is important to follow instructions appropriately in regard to transfer of the cervical sample into the liquid preservative. Different instructions apply regarding transfer when collecting with SurePath<sup>®</sup> versus ThinPrep<sup>®</sup>. With SurePath<sup>®</sup>, the tip of the sampling device is broken off; whereas with ThinPrep<sup>®</sup>, the device has to be vigorously swished in the PreservCyt<sup>®</sup> solution to dislodge the sample.

### Clinical Relevance

The clinical relevance of unsatisfactory Pap results has been studied. In a large clinical trial, unsatisfactory specimens were more likely to come from patients with a history of a cervicovaginal epithelial abnormality (26%,  $p = 0.02$ ), either ASCUS (6%) or SIL/carcinoma (20%).<sup>9</sup> Another large, prospective study found that an unsatisfactory Pap smear indicated a 1.6 to 4.0 times increased risk of harboring

### Ob/Gyn Tip

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When sampling the cervix, limit lubricant use on the speculum so as to not occlude the surface of the cervix or interfere with the specimen.

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Dr. Ashfaq received her F.Sc (Faculty of Science) Degree from the Government College in Rawalpindi, Pakistan in 1976 and thereafter received her Bachelor of Medicine and Bachelor of Surgery from Fatima Jinnah Medical College. She received post-graduate medical training in pathology at UT Southwestern Medical Center. Thereafter, she did a surgical pathology fellowship at UT Southwestern and a cytopathology visiting fellowship at Baylor College of Medicine and M.D. Anderson Cancer Center Houston, Texas. Currently, she is a Professor of Pathology at UT Southwestern and the Director of Cytopathology and Oncodiagnostics at UT Southwestern and Parkland Memorial Health & Hospital Systems respectively.

Dr. Ashfaq is licensed and board certified in pathology and cytopathology. She is a member of several key professional associations, including the American Society of Cytopathology, College of American Pathologists, American Society of Clinical Pathology(R), US and Canadian Academy of Pathology and American Society of Colposcopy and Cervical Pathology.

Dr. Ashfaq has received numerous honors such as the 1996-

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CIN 2/3 or invasive cervical cancer compared to women with a normal Pap smear.<sup>10</sup> Patients with unsatisfactory Pap results are more likely to have a history of abnormalities, and therefore, it is important to follow them.<sup>11</sup>

Until a few years ago, there was no consensus on the management of patients with “unsatisfactory for evaluation” Pap results. In 2002 a task force convened by the American Society for Colposcopy and Cervical Pathology (ASCCP) published guidelines for the management of such patients.<sup>12</sup> The ASCCP guidelines recommend that women with unsatisfactory Paps undergo repeated testing within 2 to 4 months. For patients whose Paps have other limiting factors, such as obscuring blood or inflammation and lack of an endocervical component, ASCCP guidelines recommend that patients undergo repeated testing in 12 months. The ASCCP guidelines do not explicitly discuss management for patients with Paps with “limited squamous cellularity.”

The repeat Pap interval for unsatisfactory results has been evaluated. One study compared repeat intervals as short as 8 days to as long as 184 days (mean of 61.3 days) and found that repeat cytological interpretations of unsatisfactory findings, ASCUS, and high-grade squamous intraepithelial lesion (HSIL) did not appear to vary among the Pap interval groups; however, low-grade cytologic regression occurred with an increasing Pap interval.<sup>13</sup> A repeat Pap test has been found to be adequate follow-up of an unsatisfactory Pap.<sup>14</sup>

It is possible to reduce the aggravation that comes from unsat Pap results by eliminating sources of error that create them. Useful strategies include sampling only those patients who meet all the requirements for obtaining a high-quality Pap and sampling with tools and techniques that are best supported by evidence. Because of the increased risk of harboring CIN 2/3 and invasive cervical cancer, it is important to follow women with unsatisfactory Paps.

1997 and the 2001-2002 Best Doctors in America award. She has also served as the principal investigator for countless clinical trials. In addition, she has published extensively in peer reviewed journals, totaling more than 65 studies and more than 90 abstracts and meeting presentations.

<sup>1</sup> Solomon D, Davey D, Kurman R, et al. *JAMA*. April 24, 2002;287(16):2114-2119.

<sup>2</sup> Adams A, et al. *Am J Clin Pathol*. 2005;123:738-743

<sup>3</sup> Ransdell JS. *Cancer Cytopathology*. 1997;81(3):139-143.

<sup>4</sup> Marchand L, Mundt M, Klein G, Agarwal SC. Optimal collection technique and devices for a quality pap smear. *WMJ*. August 2005;104(6):51-55.

<sup>5</sup> Shlay JC. *Sexually Transmitted Diseases*. 1998;25(9):468-475.

<sup>6</sup> Montanari G. *Diagnostic Cytopathology*. 2003; 8(4):224-226.

<sup>7</sup> Sheffield MV. *Am J Clin Pathol*. 2003;119:1-7.

<sup>8</sup> Islam S, West AM, Saboorian MH, Ashfaq R. *Cancer*. April 25, 2004;102(2):67-73.

<sup>9</sup> Ransdell JS. *Cancer Cytopathology*. 1997;81(3):139-143.

<sup>10</sup> Nygard JF, et al. *J Med Screen*. 2004;11:70-76.

<sup>11</sup> Ransdell JS. *Cancer Cytopathology*. 1997;81(3):139-143.

<sup>12</sup> Wright TC. *JAMA*. 2002. Apr 24;287(16):2120-9.

<sup>13</sup> Jeronimo J. *Cancer Cytopathology*. 2005;105(3):133-138.

<sup>14</sup> Nygard JF. *J Med Screen*. This sentence refers to smears, not tests.