Unsatisfactory Liquid-Based Cytology Specimens and Their Impact on Cervical Cancer Screening

Douglas P. Malinowski, Ph.D., BD Fellow
Scientific Affairs and Chief Scientific Officer – Women's Health and Cancer, BD Diagnostics, Durham, NC
Dorothy L. Rosenthal, MD, FIAC
Professor of Pathology, Oncology and Gynecology/Obstetrics, John Hopkins School of Medicine, Baltimore, MD

EXTENDED INTERVALS INCREASE THE IMPORTANCE OF ACTIONABLE RESULTS

The use of cervical cytology in conjunction with HPV testing has been shown to be an effective screening method to detect patients at risk for cervical cancer and pre-cancerous lesions. The combined use of HPV plus cytology results in a very high negative predictive value for the likelihood of harboring high-grade cervical dysplasia or cancer in patients who are negative for the presence of high-risk HPV and have normal cytology (Pap) tests. The low likelihood of cervical dysplasia in these double negative patients constitutes the basis for the 3-year extended intervals in HPV and Pap negative patients as recommended by the US screening guidelines [1, 2]. The combination of these practices and guidelines make it critical to ensure that the healthcare provider has the highest likelihood of receiving accurate and actionable results every time a sample is collected for cervical screening.

INADEQUATE SAMPLES ARE A MISSED OPPORTUNITY FOR DISEASE DETECTION

An under-appreciated and often unrecognized patient safety issue is unsatisfactory cervical cytology samples and the related issue of quantity not sufficient (“QNS”): insufficient amounts of a patient sample to support both cervical cytology and HPV testing from a single specimen. This potentially disruptive problem has been amplified with the use of liquid-based cervical cytology in conjunction with HPV testing, which represents a common approach to co-testing for cervical disease. This approach of co-testing can lead to insufficient specimen to perform multiple tests, resulting in QNS for one or more ancillary test. In the case of both unsatisfactory Pap samples and QNS results, the physician does not receive the complete diagnostic information that was requested. The patient is often recalled for repeat testing, which is inconvenient and costly to the patient; increases patient anxiety; and is disruptive to the clinician’s practice. Beyond the inconvenience, there is the risk that the patient might forego the repeat office visit to collect a second cytology specimen. This has been shown to occur at a rate of approximately 30% for patients recalled after an unsatisfactory Pap test [3].

MANY CAUSES OF UNSATS ARE SYMPTOMS OF UNDERLYING DISEASE

Unsatisfactory samples can be defined as samples which make the cytologic interpretation unreliable due to a number of potential factors, which include too few squamous cells, blood, inflammation, and the presence of other interfering materials, such as vaginal discharge or lubricants.

The presenting characteristics of inflammation, vaginal discharge, or the presence of blood often overlap with the symptoms of cervical cancer or high grade dysplasia, lending clinical significance to unsatisfactory Pap samples. Based on reports in the literature, unsatisfactory cytology samples have an inherently higher risk of CIN2+ disease (1.6 – 4 fold higher than NILM results), which can become problematic in patient populations with poor follow-up compliance [4]. Additional studies have confirmed the presence of underlying high grade disease in unsatisfactory specimens [5,6]. Equally troubling is the fact that Pap samples associated with cervical cancer are often associated with a higher unsatisfactory rate, as well as scant cellularity; thereby representing both a technical challenge as well as a risk to potentially miss disease [3, 7-10]. If a patient foregoes the repeat office visit to collect a second specimen, the patient may be put at increased risk due to the potential for underlying presence of cervical disease within the unsat specimen category, further amplified by the extension of intervals.

LIQUID-BASED CYTOLOGY REDUCES THE UNSAT RATE… BUT NOT ALL LBCS ARE THE SAME

In order to minimize the issue of unsatisfactory results in cervical disease screening, the implementation of liquid-based cytology was an improvement over the previous Pap smear technology. As evidenced in clinical trials and clinical practice, the use of liquid-based cytology (LBC) reduced the rate of unsatisfactory samples. For example, in the UK the NHS has reported that by implementing liquid-based cytology, the unsat rate has been reduced from 9-10% to approximately 1-2% in UK laboratories [11]. However, not all LBC’s are the same.

There are two FDA approved liquid-based cytology tests for use in cervical disease screening: BD SurePath® and ThinPrep® (Hologic). Although both sample types permit the cytologic examination for cervical abnormalities, they use different transport media and sample processing approaches, and have inherently different characteristics with respect to unsat rates. The ThinPrep test specimen processing uses a membrane filtration method to prepare cells for the slide while the BD SurePath test specimen is processed through a density gradient to enrich the cells prior to cytologic examination. These two processing methods differ in both the ability to handle interfering substances such as blood or mucus, as well as the corresponding unsatisfactory rates. The ThinPrep test has a known inability to process bloody specimens [5]. In contrast, the BD SurePath test has been documented to successfully process both bloody and mucoid specimens in independent studies [12, 13].

PRACTICAL EFFECTS OF THE UNSAT RATE

As a result, the two liquid-based cytology tests have different reported rates for unsatisfactory specimens. In recent clinical trials that compared the effectiveness of both the BD SurePath and ThinPrep tests to facilitate the detection of CIN2+ disease, the BD SurePath test demonstrated enhanced cytologic detection of this disease, as well as a significant reduction in unsatisfactory specimens relative to the ThinPrep test [14]. In a separate meta-analysis that compared the BD SurePath and ThinPrep tests, BD SurePath was shown...
to have a statistically significant reduction in the unsatisfactory rates when compared with the ThinPrep test [6]. In clinical practice, we suggest that this difference in unsat rates would manifest itself in fewer recalls of patients for repeat cytology specimen collection, reduced duplication of laboratory work and fewer office revisits. In one of the author’s institution (Dr. Rosenthal), the use of the BD SurePath test as the collection and processing method has reduced the unsatisfactory rate to 0.1%. To put this into perspective, for a large group practice that collected 10,000 cytology samples the estimated number of unsatisfactory cases using the BD SurePath test would be 0.3%, i.e., 30 cases per year. In a similar practice using the ThinPrep test, the estimated unsat rate would be 1.3% or 130 cases per year. That would equate to an additional 100 unsatisfactory results each year, with a higher risk of missed disease when using the ThinPrep test as opposed to the BD SurePath test for this hypothetical Ob/GYN practice. This is a practical example of the potential impact of the differing unsatisfactory rates between the two LBCs, based on the reported performance differences between the BD SurePath Pap test and the ThinPrep Pap test.

ELIMINATING QUANTITY NOT SUFFICIENT (QNS)

Another, issue is that of quantity not sufficient (QNS) described above. The use of the ThinPrep test specimen to support both cervical cytology as well as out of vial testing for HPV can lead to insufficient material to perform both tests. This is especially true when performing the digene Hybrid Capture 2 DNA HPV test, which requires a higher sample volume than other FDA-approved HPV tests. Published literature has demonstrated QNS rates that range from 7 – 18% for the ThinPrep test [15-17]. This adverse situation can likely be avoided by co-collecting specimens: one for cervical cytology in a medium that is FDA-approved for Pap testing and the other in a medium that is FDA approved for the HPV test that will be performed. The use of two separate collections, one for cervical cytology and the second for HPV testing, eliminates the potential for QNS specimens and ensures that a reliable HPV/cytology co-test can be performed on every patient. Taking a moment to collect a second sample allows the clinician to avoid QNS results, which lead to disruption in the practice, inconvenience and anxiety for the patient, and increased risk of patient loss to follow-up.

CONCLUSION

As outlined in this brief review, it is important to note the importance of unsatisfactory specimens relative to cervical disease detection, patient convenience and clinician practice. Given that liquid-based cytology specimens are not equivalent when viewed with respect to unsatisfactory status, and that using a single sample does not always provide sufficient specimen to conduct both Pap and HPV testing, clinicians are encouraged to review the salient performance features of the two liquid-based cervical cytology specimens for routine patient management.

DISCLOSURES

Dr. Rosenthal is a paid consultant for BD Diagnostics–Women’s Health and Cancer. Her compensation is managed through a contract with Johns Hopkins University and reviewed by the Office of Conflict of Interest and Office of Research Administration. Dr. Malinowski is an employee of BD Diagnostics, the manufacturers of the BD SurePath™ Liquid-based Pap Test.

REFERENCES


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