Sensitivity of Colposcopy: Beyond the Mitchell Meta-Analysis

A systematic review and background information on the sensitivity of colposcopy to identify precancerous lesions of the cervix

Colposcopy is the visual inspection of the cervix with a special low-magnification microscope, in search for abnormalities, aiming to identify and sample the most atypical site for biopsy; "invented" by Dr Hinselmann in the 1920's, remains essentially unchanged to date. It is a subjective technique that depends on the skills of the practitioner.

The performance of colposcopy to identify cervical pathology and especially high-grade disease is reported in numerous publications, with contradicting results, and is often the subject of debate.

In general, different studies are presented in different ways and use different end-points and definitions on the metrics they present. Some information to look for is; *where all patients biopsied? What is the threshold for defining disease, CIN-1 or CIN-2? Why were the patients referred for colposcopy? What was the prevalence of high-grade in the studied population? What is defined as colposcopy result?*

"The Mitchell paper"

In 1998, *Mitchell et al (1)* presented the results of a meta-analysis of results found in 9 earlier studies. They used data available in the selected articles to calculate various metrics, including sensitivity and specificity, at different pathology thresholds (normal *vs* atypia, low *vs* high grade).

The reported sensitivity to identify high-grade dysplasia from low grade or normal tissue varies significantly, from *30%* to *99%*; the corresponding specificity ranges from *92%* to *39%*. The weighted means are sensitivity *85%* and specificity *69%*.

These figures are still quoted in "defence" of the sensitivity of colposcopy. However, there are several factors that one needs to consider before interpreting, and finally dismissing them.

The different studies used in the analysis were published between 1973 and 1995 (*2-10*), and included a total of 6281 patients, originating from a variety of locations (Canada, USA, Italy, India, UK).

The geographical spread and spread over >20 years means that a wide variety of information has been merged, including different screening modalities, demographics and epidemiology. The results are therefore deemed potentially unsuitable for comparison with today's clinical setting. A striking finding is the fact that the prevalence of high grade disease, and even invasive carcinoma, is remarkably high in the articles included (e.g. about 25% cases in the Stafl study (*10*) had carcinoma *in situ* (CIS) or worse and 55% had ≥CIN-2; in one study by Benedet et al (*2*), 69% had CIN-2 or worse, etc).

To evaluate any new test, its results are compared to the *"ground truth"*;

For cervical pathology, histology is the ground truth (gold standard), against which all other tests are evaluated and compared;

The comparison can be made in many different ways, depending on the point of view;

For any examination, the result of the test will be **TP** (true positive), **FP** (false positive), **TN** (true negative) or **FN** (false negative);

The *sensitivity* of a test is its accuracy in identifying the patients who are positive for disease;

The *specificity* of the test is its accuracy to identify the patients who do not have the disease;

The main factor that distorts the results is the way that the original studies were conducted and presented, and the way the data has been used, introducing a strong bias to the results.

For example, the study by Stafl et al (*10*) included a total of 1410 patients, but only the 659 with some colposcopic findings were actually biopsied and included in the meta-analysis. This means that the women not suspected by colposcopists were never evaluated further to establish their true health status. The reported sensitivity is 99%!

Similarly, the study by Seshadri et al (*9*), only includes the portion of the patients that were suspected and biopsied (152 of the 291 recruited in the study), and therefore the resulting 87% sensitivity is heavily skewed, as the potentially missed cases are not included in the calculations.

This inflation of colposcopic sensitivity has been picked up and is discussed in more recent articles, such as the *"European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1"* by Jordan et al (*11*) and "*The colposcopic impression - Is it influenced by the colposcopist's knowledge of the findings on the referral Papanicolaou smear?"* by Pretorius et al (*12*).

In recent years, numerous studies (including those on DySIS) have assessed and reviewed the performance of colposcopy in a more objective way.

Sensitivity=[TP]/[TP+FN];

Specificity=[TN]/[TN+FP];

Typically *Sensitivity* and *Specificity* are balanced; an increase in sensitivity is accompanied by a decrease in specificity and vice-versa;

If the ground truth is not established by histology for *every patient*, then the calculated sensitivity is *biased*;

Verification bias results from the assumption that an apparently healthy cervix is really healthy, without a histological confirmation this inflates sensitivity;

To reduce verification bias one needs to verify the lack of disease by collecting a sample for biopsy;

Sensitivity of Colposcopy

Being a subjective and highly varying technique, it is impossible to provide a global figure for the sensitivity of colposcopy. Some practices will do better, some will do worse. The differences in screening programs will also affect the measured numbers, making accurate comparisons difficult. However, well-planned studies do provide a good impression of its limits. Unless otherwise noted, the studies below report colposcopic sensitivity to identify high-grade dysplasia (≥CIN-2) among women referred for colposcopy after a positive screening result.

- *Massad and Collins* (2003), measured a sensitivity of 56% on 2112 women (which is the upper limit, as this study is based too) (*13*);
- *Wu et al* (2005) also reported a sensitivity of 56% (specificity 79%) on 273 women (*14*);
- In a study performed to evaluate an "optical detection system" (LUMA by MediSpectra), *Huh et al* recruited 604 patients at 6 clinics in the USA and reported a sensitivity of 67% and specificity of 56%- it is worth noting that these results may still be inflated because of lack of biopsy on some patients (*15*);
- *Pretorius et al* (2004) found that colposcopicaly directed biopsies achieved a sensitivity of 57% (*16*);
- During the large ALTS study, which took place into the USA to evaluate different management options for patients with ASCUS and LSIL cytology results, colposcopy was found to have a 54-56% sensitivity to detect CIN-3 lesions (*17, 18*);

In a similar fashion, during the two studies on DySIS, a biopsy sample was collected and evaluated also from patients that had a normal colposcopic indication, and thus the ground truth was established for all patients.

- *Soutter et al* (2009) reported a sensitivity of 49% for conventional colposcopy, which missed 37 of the 72 cases with high-grade dysplasia (*19*)
- *Louwers et al* (2011) reported a sensitivity of 55% for the conventional colposcopy part of the study (*20*).

Additional and Random biopsies

To overcome the problem of low sensitivity it is often advocated (especially in the USA) to collect more biopsies.

- *Gage et al* (2006) from the ALTS group (21), examined the influence of the amount of biopsying on the sensitivity of colposcopy, and confirmed that more sampling leads to higher sensitivity;
- *Pretorius et al* (2004) collected a "random" biopsy sample from women with no apparent colposcopic findings; colposcopicaly directed biopsy achieved a sensitivity of 57% and the "random" biopsy 37% (*16*).

"Random" or *"control"* biopsy is a biopsy collected from an apparently *normal* site for confirmation of its state;

It has been shown that additional biopsies and even random biopsies increase the sensitivity of colposcopy significantly;

Literature

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