Should a smear result of H-SIL always be followed by a biopsy?

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Cervical cytology is a well-established screening tool for cervical neoplasia. The introduction of the Papanicolaou test in the 1950's has led to sustained reductions in both the incidence and mortality from cervical cancer in developed countries. Cervical cancer incidence rates in the United States have dropped from 14.8 / 100 000 in 1975 to 6.7 in 2005.[1]

The 2001 Bethesda classification identifies four categories of cytological abnormalities, namely:
- Atypical Squamous Cells (ASC)
- Low grade Squamous Intra-epithelial Lesion (L-SIL)
- High grade Squamous Intra-epithelial Lesion (H-SIL) and
- Atypical Glandular Cells (AGC).[2] The ASC category is further subdivided into ASC of Undetermined Significance (ASC-US) and ASC favour H-SIL (ASC-H). The latter represents 5 - 10 % of all ASC's, and a CIN 2 or 3 is identified in 24 - 94 % of women.

The incidence of H-SIL varies with age, with rates as high as 45 % reported in the 20 – 25 year age group.[3] Women with H-SIL are at a risk of progressing to cervical cancer. Although CIN 2 lesions are more heterogeneous and more likely to regress than CIN 3, histological distinction between CIN 2 and 3 is poorly reproducible. The goal of treating these women is to prevent possible progression to cancer, while avoiding over-treatment of lesions that will regress.

Natural history of H-SIL

A cytology result showing H-SIL includes changes consistent with a diagnosis of CIN 2 and 3. Since most patients with CIN 2 and 3 are referred for further management, data on outcome of untreated lesions are lacking. A woman with H-SIL on smear has a 60 – 75 % chance of having CIN 2 or worse found on colposcopically directed biopsy. Of those treated with a diagnostic excisional procedure, 94% will have CIN 2 or worse.[3,4] Approximately 2 % of women with H-SIL have an invasive cancer.

Using data from the Atypical Squamous cell of undetermined significance-Low grade Squamous epithelial Triage Study (ALTS trial), Castle et al found that up to 40 % of patients with CIN 2 will regress within 24 months if untreated.[5] This was however less likely in patients whose lesion was associated with HPV- 16. Menlikow et al reported similar regression rates of 35 % in a meta-analysis on the natural history of SIL.[6] Of women with CIN 2, 35% will develop persistent disease and 5 % will progress to invasive cancer.

The natural history of CIN 3 was reported recently in a retrospective study by McCredie et al.[7] A group of 143 women who received close follow-up but no treatment were compared to 593 women who received adequate or probably adequate treatment. 92 of the 143 women (64 %) who had close follow-up had cytological evidence of persistent disease at 6 and 24 months after the initial diagnosis of CIN 3. Even more important was the finding that in this subgroup, the cumulative incidence of invasive cancer of the cervix and vaginal vault at 10 and 30 years was 31.3 % and 50.3 % respectively.

In comparison, the cancer risk was only 0.7 % in the 593 women that had treatment deemed to be adequate or probably adequate. A possible explanation could be due to the common association of CIN 3 with HPV 16 and 18.

Management of H-SIL

The prevalence of HPV DNA positivity in women with H-SIL is high, and triage using HPV testing is inappropriate. All women with H-SIL on Pap test should therefore be referred for further management. The issues to be addressed at colposcopy are whether a lesion is seen, and whether both the upper and lower extents of the lesion are visualised.[8]

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Colposcopy is deemed adequate when the entire margins of the lesion are identified. Colposcopic examination of the cervix is prone to intra-observer variability and commonly produces inconclusive findings. In a series involving 2100 women, Massad et al found that accurate colposcopic and histologic agreement was achieved in only 37 % of cases.[9] In cases of colposcopic impression of H-SIL or cancer, histology confirmed colposcopic findings in 85 % of cases.

Treatment options fall into two categories – ablative and excisional procedures. The cure rates for both techniques are over 90 %.[10] Since ablative techniques produce no tissue for histology, only women who have no suspected glandular or invasive squamous disease should be considered, typically not with a H-SIL lesion. Cryotherapy has been widely used, with sufficient positive evidence about its safety. Anaesthesia is not required. The equipment is inexpensive and requires few consumable supplies. Compliance with follow up is very important.

Excisional procedures are more commonly used in the see-and-treat management protocol for both L-SIL and H-Sil lesions. The ''see and treat'' protocol minimises default rates but increases the risk of over treatment. The loop electrosurgical procedure can be done in the out patient setting under local anaesthetic with minimal discomfort. Tissue is available for histological assessment. The benefit of performing excision of the lesion is that it will allow detection of unobserved invasive cancers. If hysterectomy is performed as first choice procedure once H-SIL is diagnosed, without the interposition of colposcopy and resection of the lesion, this opportunity is lost. If an invasive cancer should be present at that point in time the hysterectomy would have been inappropriate.

Patients that should undergo diagnostic excisional procedures include:
- Suspected micro invasion
- Unsatisfactory colposcopy
- Lesions extending into the endocervical canal
- Recurrence after an ablative or previous excisional procedure

Patients with no lesion seen on colposcopy can be followed up with repeat colposcopy, cytology and endocervical curettage at 6 and 12 months provided colposcopy is adequate. Patients with a lesion managed with the ''select and treat'' protocol should have a colposcopically directed biopsy for histologic confirmation. These patients are followed up every 6 months for colposcopy, cytology and endocervical curettage. This protocol demands repeat visits, increasing the risk of loss to follow up and work load.

Special groups

Adolescents

Adolescents, age < 20 years, are at a high risk for the acquisition of HPV and subsequent cervical abnormality. HPV infection rates in this age group can be as high as 70 %.9 Most of these infections are transient, with the virus cleared within 24 months in up to 90 % of women. L-SIL are more common in this age group, with up to 94 % of these lesions regressing spontaneously.[11,12]

Though initially thought to be uncommon in this age group, two recent studies have shown a high incidence of CIN 2 and 3.[11,12] In the study by Moore et al involving 324 patients, 35 % had biopsy proven CIN 2 or worse. With 18 months of follow up, 65 % of lesions regressed, 20 % remained stable and 5 % progressed. There was no case of invasive cancer in this cohort.

Cervical conization is not without complications. Both the cold knife cone and Large Loop Excision of the Transformation Zone (LLETZ) have been associated with cervical stenosis and poor obstetric outcomes, cone biopsy more so than LLETZ however. After cone biopsy pregnancies are at increased risk of incompetent cervix, premature rupture of membranes and pre-term labour. Many patients in this group have either not started or not completed child bearing. Observation with colposcopy and cytology at six months interval up to two years is preferable. If there is a histological diagnosis of CIN 2, observation is acceptable. Ablation or preferably excision is recommended for those with CIN 3.

Pregnant women

Treatment of H-SIL in pregnancy is not recommended during the pregnancy due to the high regression rate of CIN 2 and 3 found in pregnancy. Yost et al followed up 153 women with CIN 2 and 3 in pregnancy[13] and found that 70 % of lesions in both categories regressed. 8 % of patients with CIN 2 progressed to CIN 3. None of the lesions progressed to invasive cancer. The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends serial colposcopy and cytology at least every 12 weeks in pregnant patients.[4,11] Treatment should be deferred until six weeks after delivery unless invasive cancer is identified.

HIV infected women

The incidence of CIN as confirmed by colposcopy is four to five times higher in HIV infected women. The risk of cervical cancer is 5 – 8 fold the risk for HIV negative women. The severity of the disease seems to be related to the T-cell function. Patients with a low CD4 have:
- Higher incidence of H-SIL
- Faster progression to invasive cancer
- Higher treatment failures
- Higher recurrence rates

For these reasons, all HIV infected patients with H-SIL should be referred for definitive management.

Conclusion

Cervical cancer is the second leading cause of cancer death in the world. Although rates have decreased significantly in developed countries, the incidence is still very high in sub-Saharan Africa. Screening is largely opportunistic. CIN 2 lesions are more likely than CIN 3 to regress. Colposcopy has a low specificity in differentiating between the two groups. HPV-16 related H-SIL is less likely to regress, and therefore the risk of cancer is higher in these patients. Up to 40 % of patients are lost when managed by serial cytology. This makes the see and treat option a more practical approach. The only exception is adolescents and pregnant women, where the risk of progression to cancer is insignificant.

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