

## Modern management of abnormal cervical smear

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### Abbreviations

BSCCP	British Society of Colposcopy and Cervical Pathology
CIN	Cervical intraepithelial neoplasia
CGIN	Cervical glandular intraepithelial neoplasia
DNA	Deoxyribonucleic acid
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LBC	Liquid-based cytology
LLETZ	Large loop excision of transformation zone
LSIL	Low-grade squamous intraepithelial lesion
NHSCSP	National Health Service Cervical Screening Programme

Papanicolaou's publication in 1940s, which showed that exfoliated cervical cells could be reliably harvested and spread, fixed and stained on a glass slide, laid the foundations of cervical screening.

In the last two decades, there has been immense progress in the understanding of cervical carcinogenesis and the currently accepted view is that HPV is an essential factor in the causation of the disease. If HPV is persistent, integration into the cellular genome may occur, which results in the inactivation of tumour suppresser genes, suppression of apoptosis, genetic instability and development of precancerous change. Additional genotoxic agents, such as smoking, contribute further to the progression of cervical cancer.

The death rate from cervical cancer was essentially unchanged until the national programme was instituted in 1988. The White Paper The Health of the Nation set a national target to reduce the mortality from cervical cancer by at least 20% by the year 2000 (from 15 per 100,000 populations in 1986 to no more than 12 per 100,000, directly standardize against the European population). The NHS Cervical Screening Programme (NHSCSP) exceeded the target by the year 1997, when the rate fell to 8.9 per 100,000. It continues to fall.

### Cervical screening programme<sup>1</sup>

The programme originally involved every woman between the ages of 20 and 64 years (20-60 years in Scotland) being called and recalled every 3-5 years for a cervical smear test. The evidence has indicated that a more effective screening

programme can be offered to women by changing the frequency of screening according to a woman's age. In 2004, the NHSCSP has issued guideline number 20 which covers all of the major aspects of screening, diagnosis, treatment and follow up.

Age group (years)	Frequency of screening
25	First invitation
25 – 49	Three yearly
50 – 64	Five yearly
65+	Only screen those who have not been screened since age 50 or those who have had recent abnormal tests

### Age at starting screening

The incidence of cervical cancer under the age of 25 years is low, and the prevalence of transient HPV infection is high. Much of this prevalent disease would resolve spontaneously. Hence, screening women under the age of 25 years may do more harm than good (unnecessary attendance to colposcopy clinic, increased anxiety and possible over treatment).

### Screening interval

A 2003 publication indicated that, to be effective in younger women, screening needs to be more frequent. Therefore, the new screening intervals are to be 3 yearly until the age of 50 years when 5 yearly screening until the age of 64 years, because the most incidences of CIN will have been prevented by prior screening<sup>2</sup>.

### Age at finishing screening

The prevalence of CIN3 and invasive cancer in women over the age of 50 is low. Although it is possible that it may be safe to withdraw well screened women with a negative smear history from screening programme at age 50 years, there is no robust evidence to withdraw this level of healthcare.

### Population coverage

A major success in the cervical screening programme has been to increase population coverage. There remain certain women who do not participate, including some ethnic minorities and some women who choose not to. A significant proportion of women who develop cancer have not been regularly screened. Additional effort is required to convince some women that screening can be life saving.

### LBC

Liquid base cytology provides almost total elimination of inadequate smear. The UK pilot studies concluded that inadequate cytology would be cut by 87 %, from 9.1% with Pap slides to an average of 1.6 % with LBC.

It has been established from systematic reviews that routine primary cervical screening carries a 50 – 70 % sensitivity to detect CIN3. LBC increases overall sensitivity, gives rise to less equivocation in low grade smear and leads to less referral for colposcopy. There is no difference between the specificity of LBC and Pap smear<sup>3</sup>.

### Smear reports

	Acceptable range <sup>4</sup>
Negative smear	
Number of abnormal smear	8.1 – 8.3%
Inadequate smears	5.8 – 12.9%
Borderline nuclear abnormality & Mild dyskaryosis	4.1 – 9.5%
Moderate & Severe dyskaryosis	1 – 2 %

### Referral guideline for colposcopy

Women with the following smear results should have the colposcopy assessment.

- 3 consecutive inadequate smears
- 3 borderline changes in squamous cells
- 3 abnormal smears at any grade in a 10 year period
- 1 borderline change in endocervical cells
- 1 or 2 mild dyskaryosis (1 mild change – acceptable to repeat a smear)
- 1 moderate dyskaryosis
- 1 severe dyskaryosis
- 1 abnormal glandular smear

### Time interval: referral – colposcopy

Abnormal smear	within 8 weeks
Moderate or severe dyskaryosis	within 4 weeks
Glandular abnormality or possible invasion	within 2 weeks

### Treatment

Recent evidence suggests that possibly all major-grade (CIN 2, CIN 3, HSIL) lesions should be treated, whereas minor-grade (CIN 1, LSIL) lesions should be managed more conservatively.

Over the last decade the trend has been directed toward more conservative methods of managing CIN. This has coincided with the introduction of the large loop diathermy excision technique. A large multicenter study covering over 13000 treatments has recorded the continuing small risk of patients treated with conservative modalities to develop invasive cancer many years after initial treatment. The risk was still present up to 14 years following treatment.

### Method of treatment

#### Local destructive techniques

It is imperative that any such method destroys the CIN contained within the cervical glands or, more correctly the crypts. Therefore, to be totally effective, these methods must destroy the tissue to the depth of at least 6-7 cm. These methods are the treatment of choice for selected cases in which the entire abnormality is visible on the ectocervix, and in which there is no suggestion of invasion. The principal disadvantage of this method is that a histologic examination of the entire lesion is not possible and early invasive cancer may remain undetected. There are four local destructive techniques:

1. Cryotherapy, or freezing the area by the application of probes; anaesthesia is not usually required.
2. Cold coagulation, usually without, or with some local anaesthesia.
3. Electrodiathermy, under either local or general anaesthesia.
4. Carbon dioxide (CO<sub>2</sub>) laser evaporation, usually with local analgesia.

#### Excisional techniques

1. Cold knife biopsy
2. Laser cone biopsy
3. Large loop diathermy
4. Hysterectomy: abdominal or vaginal

### The optimal method of CIN treatment

There is no obviously superior conservative surgical technique for the treatment of CIN. Excisional treatments permit

histological assessment of biopsy and can determine risk factors for residual disease.

The studies have led many authors to advocate the use of excision rather than local destruction techniques as the loops have discovered early invasive lesion in excised specimens. But it can be argued that many of the early micro-invasive lesions now found by the use of excision techniques would have been quite effectively destroyed by the use of local destructive techniques. Now at the moment, it must be left to the individual clinician to choose which technique gives the best results.

### **Complication**

#### Immediate

The morbidity for excisional method is 2-4 % with immediate discomfort and bleeding.

#### Long term

**Cervical stenosis and constriction:** This problem tends to occur most frequently in postmenopausal and post partum women, and result in the development of pyometra. In the younger woman, the stenosis may lead to pelvic endometriosis following on haematometra. The patient often presents with symptoms of painful and prolonged menstruation. The simple management is to perform a dilatation of cervix under general anaesthesia. Even use of a narrow endocervical brush may relieve the symptom.

**Excessive eversion of the columnar epithelium :** It is not uncommon for the cervix to appear with a large area of exposed columnar epithelium, especially after cone biopsy. Such a situation may result in complaints of postcoital and intermenstrual bleeding or discharge. Nevertheless, it is possible for this exposed transformation zone to become infected yet again with mutagenic agent that resulted in the development of CIN.

It may be necessary to stimulate metaplasia of this area by applying cryosurgery, cautery, or even laser vaporization to columnar epithelium. However, for most patients active treatment is not necessary.

**Subsequent pregnancy:** There is always concern about subsequent fertility and pregnancy outcome following treatment for CIN. The morbidity associated with the excision of a small fully visible TZ will be different from that associated with a large zone which extends 2 cm up the endocervical canal.

The evidence found no effect on subsequent fertility and pregnancy outcome following loop diathermy treatment. However, it is found to have a higher incidence of low birth-weight babies when compared with controls. More recently, other authors have shown that using the CO2 laser, a cone

biopsy greater than 10 mm in depth acts as an independent risk factor for the occurrence of preterm labour<sup>5</sup>.

### **Success rate**

Modern conservative therapies for the treatment of CIN are extremely successful, with the clearance rate in the order of 95 % or better, except cryosurgery which has a lower clearance rate than other conservative method (85%).

### **Recurrence**

The rate of dyskaryosis in 12 months following both LLETZ and laser ablation was 4.4 %. A cumulative rate of recurrence at 4 years was 10.1 per 100 women.

### **Follow up**

#### Follow up after conservative treatment

Women aged 50 years or more with positive excision margin are particularly at risk of persistent and recurrent disease. Cytology alone is recommended for follow up and should start at six month following treatment.

Women treated for high grade disease (CIN2, CIN3, CGIN) require 6 and 12 month follow up cytology and annual cytology for subsequent nine years before returning to screening at routine interval.

Women treated for low grade disease require 6, 12 and 24 month follow up cytology. If all results are negative, then women may return to screening at routine interval.

Women treated for CGIN are at higher risk of developing recurrent disease than those with high grade CIN. Ideally, six-monthly samples would be taken for five years followed by annual samples for a further five years.

#### Follow-up after hysterectomy

Women who have had a hysterectomy with CIN present are potentially at risk of developing vaginal intraepithelial neoplasia (incidence 1%) and invasive vaginal disease.

For women on routine recall for at least 10 years prior to hysterectomy and no CIN in the sample at hysterectomy, no vault cytology is required.

For women with less than 10 years' routine recall and no CIN at hysterectomy, a sample should be taken from the vault six months after surgery and there should be no further cytology follow-up if it is negative.

For women with completely excised CIN at hysterectomy, a sample should be taken from the vault at 6 and 18 months after surgery and there should be no further cytology follow-up if both are negative.

For women with incomplete or uncertain excision of CIN, follow-up should be conducted as if the cervix is still in situ.

### Summary of follow up

Histology/ Pre-treatment smear history	Follow up
<u>After conservative treatment</u>	
Low grade CIN	6, 12 and 24 months and then routine screening
High grade lesion (CIN2, CIN3, CGIN)	6, 12 and annual cytology for 9 years and then routine screening
<u>After hysterectomy</u>	
Routine recall in last 10 years, No CIN	No vault smear
Less than 10 years, Routine recall, No CIN	Vault smear 6 months after hysterectomy
<u>After hysterectomy for CIN</u>	
Complete excision of CIN	Vault smear 6 and 8 months after hysterectomy
Incomplete or uncertain excision of CIN	Follow up as if the cervix is still in situ

### The potential role of HPV testing

The type II hybrid capture is a new method for the detection of HPV DNA in cervical mucosa. The following list of clinical uses of hybrid capture is suggested:

- As a screening method, together with cytology:
- For patients with abnormal cytology, to select patients who will be referred to a colposcopic clinic.
- To evaluate the low-grade lesions forecast.

The use of hybrid capture as a screening method is based on the principle that the cytology has a sensitivity of approximately 56%, and the sensitivity of virus typification is 77%; but using both at the same time, the diagnostic sensitivity amount to 93%. Whether hybrid capture should be used as a screening method is still being debate<sup>6</sup>. A recent RCT<sup>7</sup> reported that adjunctive HPV testing did not add significantly to the effectiveness or cost effectiveness of LBC to the detection of CIN 3.

### Vaccination against cervical cancer<sup>8</sup>

Without further preventive measures, death from cervical cancer are predicted to jump four-fold to over a million a year by 2050 as a result of the explosion in HPV infection rates across the world. Vaccination as a primary prevention has obvious advantages in countries where screening programmes are not established but may also offer advantages in countries like the UK, where secondary prevention by screening and treating premalignant lesions is not only expensive but

sometimes imprecise, resulting in unnecessary anxiety and intervention for some women, while at the same time failing to detect lesions in others.

### Rationale

Women previously infected with a particular HPV type are unlikely to become reinfected by the same type, because of immunity largely provided by antibodies targeted against the major papillomavirus capsid protein L1. When made in the laboratory, L1 protein self-assembles into virus-like particles (VLPs) that are morphologically identical to HPV and highly immunogenic but not in themselves infectious because of lack of viral genome.

Gardasil (Merk) is a quadrivalent vaccine offering protection against HPV types 6, 11, 16 and 18. The longevity of this immune response varied, with only 76% of vaccines showing detectable antibody response to 36 months after immunisation. There is preliminary evidence of cross protection against infection with related HPV 31 and 45. Gardasil and Cervarix has an excellent safety record with only transient injection site reaction and no evidence of adverse effects on chronic disorders.

In the UK, the HPV vaccination programme targets the girls from 12 to 13 year old and additional programme for the girls from 13 to 18 years old, starting in September 2008 and finishing in 2011. HPV-specific antibodies generated by vaccination may wane with time, although current data indicate that immune responses persist through 5 years. The need for booster immunisations to maintain protection against infection will become apparent after prolonged periods of follow up.

### The abnormal smear in pregnancy

Ten to fifteen in 1000 pregnant women have their smear abnormal. Recommendations for referral colposcopy are the same in pregnancy as in non-pregnant women. Much more reassurance is required, with emphasis on the fact that the colposcopy will not harm the fetus or cause miscarriage. The treatment for preinvasive lesions may be postponed until after delivery. The essential role of biopsy is to rule out an invasive disease.

### The cervical smear in menopausal women

Oestrogen deficiency causes atrophy of tissue and a retraction of squamocolumnar junction. The epithelium becomes thinner and more easily traumatized. There is a greater incidence of unsatisfactory smear reports and unsatisfactory colposcopy. It is generally preferable to repeat smear after oral, transdermal or vaginal estradiol for a period of 7 to 10 days.

### Conclusion

The cervical smear is a simple and effective screening which has a number of deficiencies. False-negative smears are principally

due to imperfect sampling, errors of cytological interpretation, and in rare cases to rapid progression of lesions in sites which are difficult to access. New technologies can improve the sensitivity of screening. The emphasis is on developing systems that will screen for preinvasive stage of cervical cancer and thereby allow assessment and appropriate management.

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**COMPETING INTERESTS**

None Declared

**AUTHOR DETAILS**

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