

Management of Premalignant Lesions of the Cervix

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Abstract

The screening, detection and treatment of precancer lesions of the cervix have resulted in a dramatic decline in the incidence of cervical cancer in many parts of the world. The effect is most pronounced in countries with organised screening. The proper management of premalignant lesions of the cervix is an important and integral part of any screening programme. The importance of proper colposcopic technique and the adherence to well-established colposcopic guidelines cannot be overemphasised to ensure appropriate treatment. The colposcope is indispensable in treatment planning as it guides the optimal amount of cervical tissue to be ablated or excised and the type of cone biopsy to be taken. Various methods of treatment involving ablative procedures and excisional procedures have been found to be highly efficacious and safe. The choice of treatment modality is very much dependent on individual preferences. However, in those with extensive high-grade lesions, an excisional method has the added advantage of detecting unsuspected microinvasive disease which can be missed if ablative methods are used. Although treatment for squamous intraepithelial neoplasia is well established, the treatment for adenocarcinoma-in-situ is more controversial. Newer methods of treatment are currently being developed to further improve on the good results achievable with present treatment modalities.

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Introduction

Cervical cancer is one of the most common female cancers worldwide. It is ranked second only to breast cancer and in many underdeveloped countries, it is the most common female cancer. Although there are no randomised control trials to prove that Pap-anicolaou (PAP) smear screening and the treatment of precancer lesions have decreased the incidence of cervical cancer, observational studies in many countries have shown that the incidence of cervical cancer has declined steadily after the introduction of cervical PAP smear screening. The most dramatic decline is in countries where there is a concerted national screening programme. Organised cervical cancer screening was implemented in Sweden in the mid 60s and this has resulted in a marked decline of 60% in the incidence of squamous cell carcinoma of the cervix.¹ On the other hand, interestingly, the incidence of adenocarcinoma has increased. Even in countries with no national screening programme, but where opportunistic screening is widespread, the incidence of cervical cancer has also declined steadily albeit not at the same magnitude

as in places where there is concerted screening with a call and recall system.

The incidence of cervical cancer in Singapore has been declining steadily, but very slowly, over the past 2 decades.² It is now 4th among all female cancers. In western industrialised countries, the incidence has declined more significantly to 7th-10th position. The incidence in Singapore is intermediate between underdeveloped and developed western countries. In Singapore, there is at present no national PAP smear screening programme but there is an active opportunistic screening of women in the reproductive age group. Sexually-active, fertile women presenting for pregnancy care usually have PAP smear screening either in the antenatal or postnatal period. Those who are subfertile presenting for infertility treatment also have PAP smear screening. Those who are not ready to start family but are sexually active and do not use contraception may come for abortion which also presents an opportunity for screening. Those who come for contraception or other unrelated gynaecological problems usually have PAP smear taken as well. The group of women who do not avail themselves to

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PAP smear screening are mainly women in the post menopausal age group who are usually poorly educated and in the low socioeconomic group. These high-risk unscreened group of patients typically come with advanced cervical cancer. A national cervical cancer screening programme is now in the planning stage for Singapore to address this problem. Hopefully, we will be able to significantly reduce the incidence of cervical cancer once the programme is in place.

Although PAP smear screening has proven to be an invaluable public health tool for cancer prevention, it has limitations especially in terms of false negativity and the large number of borderline abnormal smears, commonly referred to as ASCUS (atypical squamous cells of unknown significance) which taxes the colposcopic services. Notwithstanding the limitations, it remains the best screening method we have thus far.

Premalignant Lesions of the Cervix and Risk Factors

The natural history of cervical cancer is well understood. There is a well-defined and long premalignant stage commonly described as cervical intraepithelial neoplasia (CIN) which can take as long as 5 to 10 years before progressing to malignancy. CIN is graded in increasing severity from CIN 1, CIN 2, to CIN 3 before malignancy occurs. From epidemiological studies, it has become very clear that sexual intercourse is the most important risk factor for the development of CIN. Multiple sexual partners, early age at sexual intercourse and sex with high-risk male partners (those who have many partners or whose other female partners have cervical cancer) are related to increased risk for cervical cancer and its precursor.

Numerous studies have firmly proven that human papillomavirus (HPV) infection is associated with CIN and cervical cancer. Almost all (99%) of women with cervical cancer are found to have HPV infection. There are more than 70 subtypes of HPV infection but some are more oncogenic than others. HPV types 16 and 18 have been found to be the most significant types responsible for most CIN and cervical cancer. However, it must be pointed out that not all women with HPV will suffer CIN as most will regress as a result of host immunity. Studies have shown that those with persistent HPV virus infection, especially type 16, have a 15-fold increased risk of CIN or cervical cancer. It is well established that HPV genes E6 and E7 are integrated into the host genome which then encodes tumorigenic proteins resulting in oncogenesis.

Clinical Presentation and Diagnosis of CIN

CIN lesions are usually asymptomatic and cannot be diagnosed by naked eye examination as the cervix often looks normal. Currently, the only reliable and practical way of diagnosing these patients is by cervical cytology,

colposcopy and colposcopic-guided punch biopsy. One of the major problems with PAP smear screening is that of inconsistent reporting and this varies from laboratory to laboratory. There have been attempts at standardising PAP smear reporting such as the Bethesda system. Such initiatives, however, have met with limited success and currently, there is no universally agreed reporting system. In most reporting systems, there is generally no issue with high-grade squamous intraepithelial lesions (HSILs) like CIN 2 and CIN 3. The main problem lies in the borderline group such as ASCUS (atypical squamous cells of unknown significance) or AGUS (atypical glandular cells of unknown significance). In Singapore, there is currently an attempt to standardise our reporting system which requires the co-operation of all laboratories concerned.

Colposcopy and the Diagnosis of CIN

In the precolposcopic era, an abnormal PAP smear was most often investigated and treated by cone biopsy and sometimes by even more major procedures like hysterectomy and even radical hysterectomy. A cervix with CIN lesion looks normal even in those with high-grade lesions. Without colposcopy, it is not possible to assess the condition satisfactorily as the lesion cannot be identified for biopsy. Subsequently, Schiller's iodine was used to identify CIN lesions as these lesions are deficient in glycogen and hence, stain negatively with iodine. However, iodine staining does not provide details to assess the severity of the lesion. With the introduction of the colposcope, we are now able to diagnose CIN more accurately and precisely. Colposcopic examination helps to determine the site, size and severity of the lesion and also guides biopsy of the most abnormal areas. Not only should colposcopy be considered an integral part of diagnosis, it is also vitally important in determining the correct choice and extent of treatment. All physicians involved in the treatment of CIN must therefore be proficient in colposcopic examination.

In the performance of colposcopic examination, it is important to expose the cervix with minimal trauma to the vagina and cervix as bleeding limits visual examination of the cervix and vagina. In menopausal women with vaginal atrophy, pretreatment with 4 weeks of topical oestrogen or oral oestrogen may be helpful. Choice of an appropriate size speculum is vitally important. At the end of the assessment, it is important to decide if the colposcopic examination is satisfactory or unsatisfactory as this will affect our level of confidence in the diagnosis of CIN. It is well known that CIN lesions mostly occur in the transformation zone (TZ) of the cervix. This is an area of dynamic change where the columnar epithelium transforms into squamous epithelium in a normal process of metaplasia.

The immature squamous metaplasia is more prone to oncogenesis as a result of active cellular division in the TZ. The TZ is delineated in the inner limit by the squamo-columnar junction. When the whole squamo-columnar junction can be seen, the area at risk for CIN can therefore be assessed with the colposcope in its entirety. If the squamo-columnar junction is in the endocervical canal either partially or entirely, as in many menopausal women, then the area at risk is not entirely visible to the colposcope. Under this circumstance, colposcopy is deemed to be unsatisfactory as CIN lesions in the endocervical TZ may be missed or worse, an early invasive disease may be missed unwittingly. If the upper limit of an ectocervical lesion is in the endocervical canal and therefore not seen entirely, again colposcopy is unsatisfactory as assessment is incomplete. If the cervical smear grading is of more than 1 grade difference from the colposcopic-guided biopsy result, a more severe lesion may be present in the endocervical canal making the colposcopic examination unsatisfactory. In these circumstances, a cone biopsy with removal of the endocervical canal is indicated both for adequate diagnosis and therapy. A colposcopic-directed punch biopsy showing microinvasive disease is also considered a situation where assessment is inadequate as the biopsy may not have been taken from the most invasive site and information regarding the horizontal extent of spread is not available from a punch biopsy. Both depth of invasion and extent of horizontal spread are important in assessing the stage of microinvasive disease with therapeutic implications. Further, presence or absence of lymphovascular invasion cannot be accurately assessed from a punch biopsy which again has treatment implications. For these reasons, a single large cone biopsy is indicated when punch biopsy shows microinvasive lesions.

Management of CIN

Once the diagnosis of CIN has been made, treatment of the lesion will alter the natural history of the condition thereby preventing progression to cervical cancer. With better understanding of the disease and the introduction of colposcope, the treatment approach has evolved significantly over the past 2 decades to a less radical and more individualised approach.

Premalignant lesions of the cervix do not disseminate as the epithelial basement membrane has not been breached. Hence, there is no chance of the lesion invading the lymphatic or blood vessels in the stroma to result in regional or distant spread. For this reason, treatment by either local ablation or excision has been highly efficacious in eradicating the lesions. It is generally agreed that high-grade CIN lesions, i.e. CIN 2 and CIN 3, should be treated as soon as the diagnosis is made as the risk for progression to invasive disease is significant. There is at present no way

that we can predict how fast this process is going to take. Progression within 6 months has been reported. The management of CIN 1 lesions is more controversial as many of them may regress with time and some may remain the same or progress. In a longitudinal study, 100 women with biopsy proven CIN 1 were followed up and 75% of the cohort were noted to have spontaneous resolution of the lesions as shown by consecutive negative cytology and colposcopy.³ Only 4.5% had progressed to higher lesions. The management of these patients should be individualised. In young women, it is perhaps better to observe as treatment may affect the cervix by scarring and the risk for malignant change is extremely small. In older women who have completed their family, treatment may be advocated so that the cervix may return to normal speedily thereby allaying anxiety. Consequently, these patients would also require less follow-up. Some women may become emotionally and psychologically distressed knowing that they have a precancerous condition. Early treatment may be indicated in such patients. If a "watch policy" is undertaken for CIN 1, it is important to ensure that the patient is compliant. Otherwise, treatment may be indicated at an earlier stage. If the CIN 1 lesion persists for more than 12 months, treatment is usually indicated.

The treatment of CIN depends on whether the colposcopic assessment is satisfactory. Treatment can be by ablation or excisional methods. Particularly for ablation methods, the diagnosis of CIN must be confident and colposcopic assessment satisfactory. As these methods do not provide a pathological specimen, inadvertent undertreatment of a more severe unsuspected invasive lesion is a possibility resulting in less than optimal outcome. Before embarking on ablative therapy for CIN lesions, it is vitally important to perform colposcopic-guided biopsy with histopathological confirmation of the diagnosis before treatment is carried out to prevent inappropriate treatment. Patients with extensive high-grade lesions should preferably be treated by excisional methods rather than ablation as there is a higher chance of treating unsuspected microinvasive disease in such cases. In histological studies, it has been found that CIN 3 lesions with extensive involvement of the surface epithelium and deep endocervical gland involvement are associated with higher incidence of microinvasion.⁴ The mean size of CIN 3 lesions showing microinvasion is 7 times greater than that for severe dyskaryosis without invasion and 100-fold greater than with mild dyskaryosis.⁵ In a study, microinvasive carcinoma of the cervix was not suspected cytologically or colposcopically in 34% of cases.⁶ Ablative therapy should therefore be reserved only for low-grade CIN or small high-grade lesions with satisfactory colposcopy as these patients have a small chance of unsuspected microinvasive disease.

It is interesting to note that in those patients with CIN associated with high-risk HPV treated with electrosurgical removal of the abnormal TZ, 94% became negative for HPV after surgery.⁷ Similar results were reported after laser conisation for CIN.⁸ A persistently positive high-risk HPV test after treatment for CIN has been found to be more predictive for recurrent CIN 2 to 3 than an abnormal PAP smear with a sensitivity of 90%. Negative predictive value of a negative high-risk HPV was 99%.⁹ In another study, 45% of patients with persistent HPV infection after conisation developed CIN recurrence whereas none developed CIN recurrence in HPV negative patients.¹⁰ HPV testing has therefore been advocated as a useful follow up test for treated CIN lesions.

Ablative Therapy for CIN

The main aim of ablative treatment for CIN is the destruction of the whole TZ of the cervix. It has been found that treatment of only the abnormal areas sparing the normal looking part of the TZ is associated with a high risk of persistent or recurrent disease. The CIN lesions may affect cervical glands which may be as deep as 5.2 mm below the cervical surface. It is therefore important to destroy the abnormal TZ up to a depth of about 6 to 8 mm from the surface in order to have a high chance of cure.

Destruction of the whole TZ by various ablative methods have been used with consistent and high success rates of about 90% regardless of whichever method is chosen.¹¹⁻¹⁴ Commonly used methods include:

- 1) laser vaporisation with CO₂ laser,
- 2) cold coagulation where the lesion is treated with teflon-coated probe to 100°C,
- 3) cryosurgery, and
- 4) diathermy.

In patients who have low-grade lesions or those with high-grade small lesions where colposcopic examination is satisfactory, ablative treatment is both safe, convenient and efficacious. All ablative methods can be performed as outpatient procedure, usually taking less than 10 minutes. Laser vaporisation can be done under local anaesthetic, whilst cryosurgery and cold coagulation are well tolerated even without any anaesthesia. Patients may, however, complain of mild lower abdominal cramps during the procedure. Morbidity for all the procedures is low. The main complication is excessive vaginal discharge which usually lasts for 2 to 3 weeks. Some may present with vaginal bleeding when the necrotic area sloughs off exposing the vessels. This can usually be controlled easily as out-patients.

The main drawback for ablative procedures is that of inadvertent destruction of an early invasive disease missed on colposcopy and colposcopy-directed punch biopsy.

This can occur in about 4.7% of cases.¹⁵ There have been reports of cervical cancer occurring in women who had cervical ablative procedures for CIN.¹⁶ In many of these women, the treatment may have been carried out without following established colposcopic guidelines such as the use of ablative procedures in women with unsatisfactory colposcopy where an early cancer may have been missed and hence undertreated with ablation. Because of the small chance of missing occult cancer at colposcopy, excisional methods have proven to be more popular as the current treatment of choice particularly in those with large high-grade lesions.

After treatment with laser ablation, 70% of recurrences occur in the first 2 years.¹³ Thereafter, the recurrence rate tapers off and after 10 years, recurrence is uncommon. Yearly follow-up should therefore be carried out for at least 10 years.

Excisional Treatment for CIN

Cartier¹⁷ from France pioneered the low voltage small loop diathermy for biopsy of the cervix and he obtained good histological specimens. It was Prendiville et al¹⁸ from the UK, who modified and developed the large loop diathermy to excise the abnormal TZ (LLETZ). Since then, this method has been used very commonly worldwide in the treatment of CIN. The main advantage of LLETZ is that a tissue specimen is obtained which can be assessed by the pathologist thereby minimising the chance of inadvertent destruction of an early cancer as may be possible with ablation methods. Another major advantage is that a “see and treat” policy can be safely carried out without prior punch biopsy. This will reduce the number of visits necessary thereby improving efficiency of the colposcopic services, a particularly important consideration in countries where colposcopic services are limited. LLETZ can also be done in the outpatient setting under local anaesthetic and this is very well tolerated.

It is important in LLETZ to ensure that colposcopy is satisfactory as the therapeutic aim of LLETZ is to remove about 8 mm depth of the cervical TZ, the same criteria as for ablative methods. If colposcopy is unsatisfactory, a cone biopsy is indicated where the depth of tissue removed should be 2 cm or more as the cervical canal needs to be removed for adequate assessment.

In the performance of LLETZ, it is vitally important to ensure that the cervix is exposed adequately and the bivalve speculum comes with a suction port to extract the plumes produced by the electrosurgical excision. A detailed colposcopy is essential to delineate the extent of excision which must include the whole lesion and TZ. Sometimes, the area of involvement may be so large that the LLETZ procedure may need to be supplemented with laser

vaporisation. Another technique is to use a smaller wire loop to excise outlying areas of CIN outside the main area removed by the main wire loop. Another important point is that the cervix must face the colposcope squarely so that the wire loop can be introduced perpendicular to the surface of the cervix to ensure that one removes a cylindrical piece of cervix.

Blood loss at the time of LLETZ is minimal as electrosurgical excision seals off small capillaries. However, delayed bleeding is the most common complication. This can generally be controlled on an outpatient basis with silver nitrate cautery, Monsel solution or cold coagulation. The amount of vaginal discharge is usually less than after ablative methods as there is less tissue necrosis and sloughing. There is generally no effect on subsequent pregnancy in terms of preterm labour, cervical incompetence or cervical stenosis as the amount of cervical tissue excised is small in the LLETZ procedure. The cure rates from LLETZ are well above 90% in many series.^{11,19} One of the pitfalls of the “see and treat policy” for LLETZ is that of negative loop specimens. This constitutes overtreatment especially in young women desiring fertility. This can range from 14%,¹⁹ 18%²⁰ to 32%.¹¹ A study looking at negative LLETZ specimens found that there were significant associations between negative LLETZ specimens and negative or low-grade dysplasia and negative colposcopic findings.²⁰ To minimise negative LLETZ specimens, the “see and treat policy” should be confined to patients who have unequivocal CIN on cytology and colposcopy. Cases where the cervical smear is low grade or reported as ASCUS, a colposcopic-directed punch biopsy should be carried out before treatment. If no lesion is found on colposcopy, LLETZ should not be performed and these patients should be followed up by repeat cytology and colposcopy.

Follow-up after LLETZ will depend on whether there are any risk factors for recurrence or persistent disease. Those with positive resection margins and aged >50 years are found to have a higher chance of recurrence or persistent disease of 43%.²¹ These patients should have repeat treatment or very close surveillance. Those with clear resection margins and age <50 years have a very low risk of recurrence at 8% and hence can be followed up less intensively. In another study, women with incomplete excision of CIN following LLETZ had significantly higher risk of recurrent CIN compared to those with clear margins with a relative risk of 8.23.²²

In an extensive review of 23 trials looking at various surgical treatment modalities for CIN, there is no obviously superior surgical technique for treating CIN among the 7 methods reviewed.¹⁴

Cone Biopsy

Cervical cone biopsy is indicated when:

- 1) colposcopy is unsatisfactory,
- 2) the cervical punch biopsy shows microinvasion,
- 3) there is discordance between cervical biopsy and cervical smear of more than 1 grade,
- 4) the PAP smear shows atypical glandular cells favouring high-grade lesion,
- 5) persistent AGUS, or
- 6) smear showing adenocarcinoma-in-situ cells.

The main aim of a cone biopsy is to remove the cervical canal to look for and assess a possible endocervical lesion. In the case of microinvasion, the aim is to produce a large single cone biopsy to remove the entire lesion so that the maximal depth of invasion, horizontal spread of the disease and status of lymphovascular invasion can be assessed accurately. A clear resection margin should always be aimed for as the chance of cure is affected by the resection margin status.

With the help of the colposcope, the size of cone biopsy can be tailored to the clinical situation. If the entire TZ is seen and only a small part of the CIN lesion has gone into the cervical canal, a shallow cone biopsy may suffice. If the SCJ is not seen at all in the presence of a high-grade smear, then a deep cone biopsy to include the entire cervical canal may be necessary. When performing a cone biopsy, it is important to ensure that the surface epithelium must be left intact so that the pathologist can assess the specimen adequately. It is also advisable to remove a single cone to include the entire lesion. A single large cone biopsy is particularly vital in cases of cervical smear showing abnormal glandular lesion and microinvasion. The traditional method is by cold knife cone biopsy. However, this is usually associated with significant bleeding. CO₂ laser cone biopsy is also commonly used. In inexperienced hands, there may be thermal damage and charring of the tissue resulting in difficulties with pathological interpretation. Electrosurgical loop can also be used to perform cone biopsy. However, in inexperienced hands, the cone biopsy may be removed in many pieces which can be frustrating for the pathologist in interpreting the findings. In this case, an appropriate sized loop has to be used to achieve adequate specimen. Careful tissue handling and special care during excision generally produces good quality specimens.

Cone biopsy has been shown to be efficacious in eradicating CIN lesions. In a longitudinal study of 4417 patients with cold knife cone biopsy for CIN 3 where the resection margins are clear, 99% of patients were free of CIN after a mean follow-up period of 18 years.²³ Positive resection margin, however, is an important risk factor for

recurrence and persistent disease.²⁴ In those with involved margins recurrent CIN lesions usually appear shortly after surgery indicating residual disease.

In a prospective randomised clinical study comparing cold knife cone biopsy and loop electrosurgical excision procedure, there were no significant differences in terms of complications, rate of lesion clearance and disease recurrence.²⁵

Hysterectomy

In present day practice, hysterectomy is seldom indicated in the treatment of CIN as it is unnecessary to remove the entire uterus for a lesion that involves only the cervix. It has been shown that hysterectomy has similar efficacy in the treatment of CIN 3 lesions when compared to LLETZ.²⁶ However, hysterectomy may be indicated when there is recurrent CIN after repeated treatment with less radical methods. Interestingly, very often, histological specimens from hysterectomy done for positive resection margins show no sign of residual CIN lesion. Even when the resection margins are involved, not all will require treatment as the vast majority, more than 50%, will show no evidence of lesion on follow-up.²¹

Adenocarcinoma-in-situ of the Cervix

Although the treatment of squamous CIN has been very well established, the management of adenocarcinoma-in-situ of the cervix is far from clear as little is known about its natural history and invasive potential. One of the most important issues is whether conservative management is safe in young women with this condition. Generally, in patients who have completed their family, hysterectomy is advocated after a cone biopsy has confirmed adenocarcinoma-in-situ with no evidence of invasion. This is because 29% of adenocarcinoma-in-situ lesions are not located near the TZ²⁷ and 16% are found to be multifocal and these lesions may extend as high as 3 cm up the endocervical canal.²⁸ There may therefore be “skipped lesions” higher up in the endocervical canal. Further, these patients generally need a deep and large cone biopsy to achieve complete excision, making cervical stenosis a real problem. In patients with cervical stenosis, it is often difficult and sometimes impossible to obtain adequate samples from the endocervix for cytology. Colposcopy is also affected as the squamocolumnar junction is often not visible in these patients. However, there seems to be a place for conservative treatment in a select group of young women whose cone biopsy shows clear resection margins. In these patients, it has been found that about 17% require further treatment for recurrent cytological abnormalities and 15% are found to have recurrent disease at 4 years of follow-up.²⁹ Therefore, women who opt for conservative treatment have to be regularly followed up in the colposcopy

clinic with cytology and colposcopy. As recurrence often occurs in the endocervical canal in these patients, cytology should include endocervical specimen using a cytobrush or similar sampling device.

In those with involved resection margins, there is a high incidence of residual disease. A second cone biopsy is appropriate treatment and if this shows clear resection margins, fertility of young women can be conserved. Even when hysterectomy has been planned as a definitive treatment after a cone biopsy shows involved resection margins, a second cone biopsy is indicated as there is a chance of finding an early invasive disease in a repeat cone biopsy or hysterectomy.²⁹

HIV Patients

Studies have consistently shown that HPV infections in HIV sero-positive patients are detected more frequently and tend to be more persistent and more difficult to eradicate than HIV sero-negative women.³⁰ This is probably the result of immunosuppression induced by HIV infection. Not surprisingly, it has also been found that cervical cone biopsy is not an effective method of treatment for CIN in HIV positive patients.³¹ Most will recur even when the excision seems to be complete. Although multiple procedures are often necessary in many patients, cone biopsy has been found to be effective in preventing cancer progression. HIV patients with low CD4 counts have a 2-fold increase in the incidence of CIN compared to those with high CD4 count. Antiretroviral treatment may reduce risk by improving immune function.³²

Future Methods of Treatment for CIN

Cervical cancer is almost invariably associated with high-risk HPV especially types 16 and 18. Expression of E6 and E7 oncogenes has been used as a target for CTL-mediated immunotherapy. It is feasible to induce HPV specific CTL responses in patients with cervical cancer using several vaccine strategies. Restricted response has been demonstrated using intradermal live vaccinia virus HPV 16 and 18. However, further clinical trials are needed to determine the anti-tumour potential of vaccine-based immunotherapy.³³

There has always been a continuing search for a better way to perform cone biopsy as most methods have limitations. Cold knife cone biopsy has been the traditional standard but this procedure is associated with significant morbidity such as bleeding. CO₂ laser was in vogue in the 80s but this method is often time consuming, equipment is expensive and it is associated with significant charring of tissue with suboptimal specimens. In the 90s, loop electrosurgical technique became very popular but the main criticism was that some gynaecologists removed multiple pieces of tissue instead of a single cone biopsy.

There is often thermal damage and surface epithelium denudation as a result of rough and improper handling resulting in difficulties in histopathological interpretation. Harmonic scalpel is a new surgical tool that cuts and coagulates by converting electrical energy to ultrasonic vibrations and has been advocated as a suitable cutting tool for cone biopsy. When compared to electrosurgical technique, harmonic scalpel cone biopsy specimen is often removed in 1 piece and the thermal artifacts are less than that produced by electrosurgical techniques.³⁴ Operating time, intraoperative and postoperative blood loss are not significantly different from loop excision. However, this new technique needs to be evaluated in larger studies to confirm its superiority. Another method that was recently described is needle excision of the TZ with a diathermy needle. The operations were performed under local anaesthesia and all cones were removed in single piece. The authors claimed high quality histological specimens, minimal blood loss, short operating time, mean depth of thermal damage of 0.29 mm and a cure rate of 94.8%.³⁵

Most treatment methods for CIN include surgery or ablative therapy. A small, placebo-controlled trial using oral indole-3-carbinol in the treatment of CIN showed statistically significant regression of CIN in about 50% of treated patients versus no response in the placebo group.³⁶ This, however, is a very small study involving 30 subjects. A bigger study is needed to confirm this finding.

Photodynamic therapy is a novel treatment modality that produces local tissue necrosis with laser light after prior administration of a photosensitising agent. It has been found that dysplastic cervical cells selectively take up topical 5-aminolevulinic acid, which is a photosensitising agent for CIN. However, in a study by Hillemanns et al,³⁷ it was found that photodynamic therapy did not significantly improve CIN lesions.

Conclusion

Cervical cancer is one of the most preventable cancer in humans. Some would even venture to say that we should not be having patients with cervical cancer at all. However, there are some limitations inherent in the current screening methods that we have today. None of the tests that we have are close to 100% sensitive and specific. Cervical cytology remains the most useful screening test we have at present. There is also the problem of the unscreened high-risk population particularly when there is no organised screening programme. Even with organised screening, uptake is never 100%. Despite all the pitfalls, cytological screening and treatment for cervical precancer have made a tremendous impact on the incidence of cervical cancer and mortality from the disease. Timely and proper management of cervical precancerous conditions goes a long way to

combat this common female cancer. Once diagnosed, cervical precancer can virtually be cured in all patients. The various modalities of treatment are highly efficacious. However, to obtain optimal result, medical personnel dealing with precancer must understand how to assess this condition properly and be aware of and follow established colposcopic and treatment guidelines. Currently, active research is underway to look for better screening methods such as Polarprobe, Fourier-Transform Infrared Spectroscopy and automated screening. New modalities of treatment are being developed to improve on the already good results that we have today.

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QUESTIONS

1. The following statements are true for the diagnosis of CIN 3 except:
 - a) Patients often present with post coital bleeding
 - b) An abnormal PAP smear is the commonest presentation
 - c) Colposcopy is an indispensable tool for diagnosis
 - d) Lugol's iodine can be used to assess these lesions
 - e) Coarse mosaic patterns, punctation and severe acetowhite epithelium are characteristic
2. The following are indications for a cervical cone biopsy in the presence of an abnormal PAP smear except:
 - a) The squamo-columnar junction cannot be seen in its entirety
 - b) PAP smear showing high-grade, abnormal glandular cells
 - c) PAP smear showing likelihood of carcinoma-in-situ
 - d) Cervical punch biopsy showing microinvasive disease
 - e) The upper limit of an acetowhite lesion cannot be visualised
3. The best way to treat an extensive carcinoma-in-situ of the cervix in which colposcopic examination is satisfactory is:
 - a) LLETZ
 - b) Total hysterectomy
 - c) Modified radical hysterectomy
 - d) Cryotherapy
 - e) Radical trachelectomy
4. In performing ablative therapy for CIN lesions, care must be taken to:
 - a) Ablate only the abnormal areas
 - b) Destroy up to 3 mm depth from the surface as the CIN lesion cannot be thicker than this
 - c) Perform the procedure under colposcopic guidance
 - d) Perform the procedure under aseptic condition in the operating theatre
 - e) Destroy the entire endocervical canal to ensure high cure rate
5. One of the followings is true about risk factors for CIN and cervical cancer:
 - a) HPV types 6 and 11 are important oncogenic viruses for cervical cancer
 - b) Almost all patients with HPV infection will get cervical cancer
 - c) More than 90% of patients with cervical cancer have associated HPV infection
 - d) Chlamydia infection is a well established cause of cervical cancer
 - e) High socio-economic status and nulliparity are important risk factors

ANSWER SHEET

Continuing Professional Development:
Management of Premalignant Lesions of the Cervix

Question 1

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 2

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 3

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 4

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 5

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

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