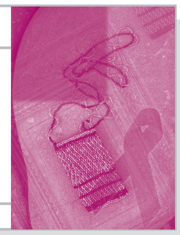
REVIEW ARTICLE

Cervical conisation and reproductive outcome



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According to the International Agency for Research on Cancer (IARC), cervical cancer accounts for 23% of all new cancers diagnosed in South Africa annually.[1] The age-standardised incidence rate for cervical carcinoma in southern Africa is approximately 35 per 100 000 women-years. This is one of the highest incidence rates in the world. In 2002 cervical cancer was the cause of an estimated 3 700 deaths in South Africa.

Screening for cervical carcinoma in well-organised programmes has been shown to be effective in reducing the incidence of and death rates due to the disease.[2] The aim of a cervical cytology screening programme is to detect pre-malignant lesions on the transformation zone of the cervix. Those patients with abnormal cytological results are then referred for further management. In South Africa the cytological screening programme is not always well organised.[3] However, many screening smears are performed. Patients with abnormal cytological results are referred for further management, usually at dedicated colposcopy clinics. The current referral criteria are a single smear with a high-grade squamous intra-epithelial lesion (HSIL) or two low-grade squamous intra-epithelial lesion (LSIL) smears. The aim of colposcopy is to detect the most abnormal area on the cervix and to direct the clinician to the area of biopsy.

In many clinics a 'see-and-treat' approach is used and a patient with an abnormal smear often receives treatment at her first visit to the colposcopy clinic.[4] The rationale may be that, in the public sector at least, follow-up rates are poor and transport to and from clinics is difficult. However, one has to caution against blanket treatment of all patients purely on the basis of cytological results. Certain authors have shown that between 5% and 40% of all patients with abnormal cytology results might not have histological abnormality on large loop excision of the transformation zone (LLETZ) cone biopsy.[5] It is therefore necessary to do a thorough colposcopic evaluation and to treat only those patients with a recognisable abnormality. If there is doubt about the severity of the abnormality, a biopsy should confirm a cervical intraepithelial neoplasia (CIN) II lesion or higher to justify treatment by destruction or resection of the transformation zone. Over-treatment may jeopardise a patient's future reproductive performance.

The anatomy of the cervix is an important consideration when we discuss potential longer-term side-effects of cervical conisation. The cervix has an epithelial layer that is very important to both the cytopathologist and the gynaecologist. All investigations and treatments are aimed at the transformation zone, i.e. the area between the original squamo-columnar junction and the current squamo-columnar junction. This area is very susceptible to the oncogenic effects of the human papillomavirus. On histological examination the transformation zone consists of ectocervical squamous epithelium covering the underlying stroma with glandular components. The endocervical glands may be involved with intra-epithelial neoplasia and may lie as deep as 7 mm from the surface epithelium. Treatment for intra-epithelial neoplasia should be at least 1 cm deep to include these crypts.

When treatment is planned for intra-epithelial neoplasia, the treatment should include the whole lesion as visible on colposcopy. It should also include the upper border of the metaplastic epithelium. That might be slightly higher up in the endocervical canal, particularly in postmenopausal patients. The squamo-columnar junction might not be visible during colposcopy (incomplete colposcopy). In order to achieve complete excision of the transformation zone in those cases it is necessary to aim treatment even higher up in the endocervical canal. A LLETZ cone biopsy should be of adequate size to achieve disease-free margins and include the whole transformation zone. It has been shown that incomplete excision margins may lead to a higher rate of treatment failure.[4]

Since 1965 it has been shown that locally destructive techniques might be as effective as hysterectomy in preventing a CIN lesion from subsequently becoming cancerous. These techniques include cryotherapy, coagulation, conisation and laser treatment. In the late 1980s Prendiville *et al.*[6] popularised the concept of large loop excision of the transformation zone although it had first been described by another author a few years previously. The principle of a LLETZ is that a high current is used in a very thin wire loop, which then produces a steam envelope in tissue that has a high water content. This steam envelope cuts the tissue with minimal thermal damage to the surrounding tissue. It is important that the sample produced after a LLETZ cone biopsy has as little thermal damage as possible. Thermal damage adversely affects histological examination of the specimen. In their original work Prendiville *et al.*[6] suggested that the depth of the cervical cone be between 0.7 and 1.5 cm.

A cold knife cone biopsy has the potential advantage of a very clear surgical margin. This makes histological examination much more accurate. A cold knife cone biopsy can sample higher up in the canal without damaging the histological sample. It is therefore preferred in some situations. Because of the more invasive nature of a cold knife cone it might cause more long-term morbidity. Whenever the underlying stroma of the cervix is included in the biopsy the remaining cervix is shortened and the supportive tissue is potentially less capable of supporting an intra-uterine pregnancy.

Reproductive outcome

CIN is most often diagnosed in women of reproductive age.[7] When treatment for a CIN lesion is considered it would be prudent to take note of a patient's future reproductive wishes and to be aware of any adverse effects that cervical conisation might have on her future fertility and obstetric outcome. Cervical conisation could theoretically have an adverse effect on a patient's fertility and lead to an increase in the incidence of miscarriage, premature rupture of membranes, premature labour, cervical distocia and precipitate labour.

Infertility

There is limited information in the literature on the effect of cervical conisation on fertility. Buller and Jones[8] found no evidence of secondary infertility in a group treated with cold knife conisation. Keijser *et al.*[9] Turlington *et al.*[10] Bigrigg *et al.*[11] and Cruikshank *et al.*[12] did retrospective cohort studies on the effect of LLETZ conisation on subsequent pregnancy outcome. They could show no decrease in pregnancy rate in the treatment groups compared with the cohorts. Similarly, Ferenczy *et al.*,[13] in a prospective cohort study of patients treated with LLETZ, demonstrated no deleterious effect on fertility. In an excellent meta-analysis Kyrgiou *et al.*[14] concluded: '... despite these difficulties, the available evidence suggests that fertility is not impaired after treatment for cervical intraepithelial neoplasia'.

These studies provide some reassurance that cervical conisation is not a major cause of infertility. Unfortunately they do not have sufficient power to exclude any subtle influence of cervical conisation on fertility.

Cervical conisation might lead to infertility by causing cervical stenosis or a decrease in the production of cervical mucus. Very rarely an ascending infection, caused by the conisation, might lead to tubal damage. There have been case reports of women presenting with secondary infertility due to cervical stenosis and amucorrea post LLETZ.[15] Cervical stenosis seems to occur more often after cold knife cone biopsy than after laser conisation or LLETZ. With all modalities, a higher cone is associated with a greater occurrence of cervical stenosis.[16,17]

It is important to remember that the patient who presents with a CIN lesion is also at risk for tubal damage because of other sexually transmitted diseases.[8] This will need to be taken into account when any conclusions are drawn regarding the effect of cervical conisation on fertility.

Miscarriage

Cervical conisation has not been shown to have any effect on the occurrence of first-trimester miscarriages. Midtrimester miscarriages do seem to be significantly more common after cold knife conisation. Moinian and Andersch[18] compared pregnancies in a group of 414 patients before and after cold knife conisation. They found late spontaneous miscarriages to be seven times more frequent after cold knife conisation than before. This complication increases in proportion to the size of the cone biopsy.[19]

Laser conisation and LLETZ do not seem to cause an increase in the incidence of mid-trimester miscarriages. This is possibly because of the smaller amount of cervical tissue removed by these methods when compared with cold knife conisation. In a prospective study of 50 pregnancies in 86 patients treated using cold knife conisation, LLETZ or laser conisation, Mathevet *et al.*[16] observed no late miscarriages. In a group of 54 women treated with laser conisation, Sagot noted no late spontaneous abortions in 71 pregnancies following conisation.[20] Similarly, Althuisius found no second-trimester abortions in 56 women delivering after LLETZ.[21] These studies were unfortunately not large enough to detect less overt effects of conisation on the incidence of miscarriage. Nevertheless, it would seem prudent to do a LLETZ or laser conisation unless a cold knife conisation is specifically indicated.

Pre-term premature rupture of membrane and premature labour

In any study of the effect of cone biopsy on preterm premature rupture of membranes (PPROM) and preterm labour, it is important to bear in mind that CIN lesions have risk factors such as smoking, multiple sex partners and sexually transmitted diseases in common with both PPROM and premature labour.[22] There are a number of mechanisms whereby a prior cone biopsy could lead to PPROM and preterm labour. The structural change in the cervix after a cone biopsy is important. The cervix might be shortened and the collagen formed in the scar tissue could be more fragile and react in a different manner from normal tissue to the hormonal changes of pregnancy. Especially with the larger cones that remove endocervical glands, the formation of cervical mucus may be impaired. The protective mucus plug and local immunological mechanisms are compromised. This might lead to ascending infections, the release of prostaglandins and PPROM or premature labour.[22]

Kristensen *et al.*[22] examined a cohort of 14 233 women, of whom 170 had a cervical conisation. Women who had cone biopsies for CIN lesions had a significantly increased risk of premature labour before 37 weeks compared with the general population. This risk is increased before conisation, but even more so after conisation. The authors postulate that the same risk factors that predispose patients to develop CIN lesions are also associated with premature labour, but that cervical conisation has an additive effect.

Other earlier studies also found cold knife and laser cervical conisation to be associated with delivery before 37 weeks' gestation.[23-25] However a number of studies found cold knife or laser conisation and LLETZ not to be associated with preterm delivery or PPROM.[8,12,16,20,21,26] These conflicting results can be explained by the generally small size of the study groups and the resultant lack of power to detect significant differences in the incidence of preterm birth.

Crane[27] did a systematic review on the effect of LLETZ on subsequent pregnancy outcomes. She found LLETZ to be significantly associated with preterm birth before 37 weeks' gestation. In a retrospective cohort study of 571 women who delivered after a LLETZ, Samson *et al.*[28] found LLETZ to be associated with low birth weight, PPROM and preterm delivery before 37 weeks. The increase in delivery before 34 weeks was not significant.

Sadler *et al.*[29] found both laser conisation and LLETZ to be associated with a significantly increased risk of PPROM and subsequent preterm delivery. This effect was more marked with increasing cone height.

In a recent meta-analysis there was a statistically significant association between cold knife conisation and LLETZ with preterm delivery and low birth weight.[14] LLETZ was also statistically significantly associated with preterm delivery (RR 1.70 (1.24 - 2.35)) and low birth weight (RR 1.82 (1.09 - 3.06)). Laser procedures, both ablation and conisation, were not associated with preterm delivery or low-birth-weight infants.

While it seems clear that cervical conisation results in a greater risk of PPROM and preterm delivery and that this effect increases with increasing size of the cone, most women will have uncomplicated pregnancies following cervical conisation. It remains to identify those at increased risk of having a complicated pregnancy after cervical conisation. Berghella *et al.*[30] found a cervical length on ultrasound of less than 25 mm to be predictive of preterm birth in patients with prior cone biopsy. It is unfortunately not yet clear how best to manage these patients. Prophylactic cerclage does not appear to prevent preterm labour in patients with prior cervical conisation.[31]

Precipitate labour and cervical distocia

Cervical conisation disturbs the structural integrity of the cervix. The resultant scar tissue might not respond appropriately to the hormonal changes of parturition and result in an abnormal pattern of labour. It has been shown that neither precipitate nor prolonged labour is more common after cervical conisation.[24,27] However there is a small increase in the number of caesarean sections done for cervical distocia.[18-20]

Conclusion

Cervical conisation is an indispensable tool in the management of cervical intraepithelial neoplasia, but it is not without risks. The risk of intra-operative complications is low and significant postoperative bleeding is rare. It may, however, have long-term adverse effects on a patient's future fertility and obstetric outcome. Cervical conisation is associated with a small but significant increase in the incidence of PPROM and premature labour. The greater the amount of tissue removed by the cone, the greater this effect. In isolated cases cervical conisation might cause cervical stenosis and amucorrea which could lead to infertility.

It is important to be aware of these possible complications and to counsel patients appropriately before they undergo treatment. The indications for conisation should be sound and should be based on a careful colposcopic examination of the cervix. This would make unnecessary surgical intervention a rare event. It would seem prudent to remove as little cervical tissue as will treat the CIN lesion. During pregnancy the patient should be monitored carefully. Measurement of cervical length during the second trimester will identify those at higher risk of premature labour, but it is not yet clear how best to manage those patients. The role of prophylactic cerclage in the patient with a shortened cervix following conisation needs to be elucidated.

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