Obstetric Impact of Treatment for Cervical Intraepithelial Neoplasia
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1. Background

In countries like the UK, where a cervical screening programme has been successfully applied, the incidence and mortality from cervical cancer has significantly decreased. However, there is increasing evidence that resultant excisional procedures for treatment of cervical intraepithelial neoplasia (CIN) are associated with preterm delivery\(^1\) and might be associated with perinatal mortality.\(^2\)

2. Current treatments for CIN

The mean age of women identified as having CIN and requiring treatment is around 30 years and it is now common that this is before women are starting their families. Therefore, there is a need to consider local treatment for CIN. Treatment of CIN should not be compromised in terms of efficacy and should be as efficient as possible but should not lead to long-term effects on future fertility and pregnancy outcome. Excisional techniques are usually performed under local anaesthesia in an outpatient setting and are easy to perform.

The consensus view is that excisional techniques are superior to destructive ones, as they allow a comprehensive histological evaluation of the excised tissue with precise evaluation of excision margins and possible adjustment of follow up. Large-loop excision of the transformation zone (LLETZ) is by far the most popular treatment. This is because LLETZ combines all the advantages of the excisional techniques: a relatively short duration, low cost, good compliance, simplicity and an easier learning curve. Destructive techniques have similar advantages, are usually performed under local anaesthesia in an outpatient setting and are easy to perform. However, destructive techniques destroy the transformation zone epithelium and preclude histological evaluation. Destructive techniques therefore demand accurate pretreatment biopsy at a separate visit with all the disadvantages this implies: the excision margins and the exact histology of the lesions following treatment are not known, leading in several cases to a rather more intensive follow-up strategy. Despite the theoretical advantages of the excisional techniques, the published evidence shows that all these methods, be they excisional or destructive, have similar efficacy in terms of eradicating intraepithelial lesions.\(^3,4\) The current literature also shows that the risk of invasive disease after the detection and treatment of intraepithelial lesions remains four to five times higher than that of the general population\(^5,6\) and this risk remains stable for 20 years.\(^7\) It is notable that this risk is similar irrespective of the method used for the treatment of the intraepithelial lesions.\(^5,6\) However, colposcopists need to be mindful that, in well-defined clinical scenarios such as the management of glandular disease, incomplete colposcopy or suspected or confirmed microinvasive disease, excisional treatment is mandatory. Colposcopists should always have adequate clinical training to make such decisions.

3. Obstetric complications following treatment for CIN

Since risk of invasive cervical cancer following treatment is similar whichever treatment method is used, the question arises as to whether there are similarly clear and conclusive data regarding future fertility and pregnancy outcomes.

A meta-analysis by Kyrgiou \textit{et al.}\(^1\) analysed a total of 27 retrospective cohort studies of women with CIN, published over the previous three decades. Cold-knife and laser conisation and LLETZ were all significantly associated with increased risk of preterm birth and low birth weight, while no statistically significant difference was found in perinatal mortality. This lack of effect on perinatal mortality was thought to be due to low sample size.\(^1\) Cold-knife conisation was also found to be associated with an increased rate of cesarean section.\(^1\) In contrast, laser vaporisation was not associated with adverse
obstetric outcomes. The surprising finding of this meta-analysis was the adverse effect of laser conisation and LLETZ, which had not been seen in the individual small primary studies. Meta-analysis of three studies revealed a consistent, significantly increased risk for preterm delivery if the depth of the excision exceeded a cut-off point of 10 mm, while for less deep excisions the data of the individual studies were contradictory and heterogeneous.¹

Many large studies were consistent with this meta-analysis and strengthened these initial findings.⁸⁻¹⁰ This led to the question of whether the colposcopists actually dismissed ablative treatment too soon from colposcopy practice.¹¹ To answer this question, analysis of perinatal mortality, the most important of all the outcomes clinically, was needed. A new meta-analysis revealed a significantly increased perinatal mortality for excisional techniques that reflected the increased preterm delivery rate.² The same analysis on the ablative techniques did not reveal increased risk in perinatal mortality.² A single treatment with cold-knife conisation or laser conisation resulted in about one perinatal death in every 70 pregnancies.² LLETZ was associated with a lesser risk of two perinatal deaths in 1000 pregnancies.² Radical diathermy, as opposed to tailored superficial destruction of the transformation zone performed by inserting a ‘needle’ into the cervix to a distance greater than 1 cm, also seemed to cause adverse obstetric outcomes.¹⁰ Severe and extreme preterm delivery (less than 32 weeks) and low birth weight (less than 2000 g) were common after cold-knife conisation and diathermy but rare after large-loop excision.²

Two further publications in 2009 studying large numbers of women also reported a two- to three-fold increase in risk of preterm delivery associated with LLETZ.¹²,¹³ Thus, these two large meta-analyses corroborate the conclusion that laser ablation does not affect obstetric outcomes.¹² The differences in the seriousness of adverse effects noted between cold-knife conisation and LLETZ might be related to variations in the amount of tissue removed. Knife cones, by definition, excise more tissue than loop, while loop cones might vary significantly from small to average or large. Something similar might explain the differences in terms of premature birth between laser ablation and loop excision, as the laser beam allows more accurate destruction with possibly less damage of redundant healthy cervical tissue. Although the recent meta-analysis did not confirm a significant increase of more severe outcomes with LLETZ, it is important to consider that even non-severe prematurity has implications in terms of admission to special care units, health resources and cost, and maternal anxiety.¹⁴

4. Biological mechanism

The mechanism by which the association between treatment for CIN and preterm delivery occurs is not yet clarified. Women with previous excisional cervical treatment were found to have a shorter mid-trimester mean cervical lengths⁹ but a length below 2.5 cm occurred in only 28% of women with previous cervical surgery,¹⁵ suggesting that more subtle mechanisms than mechanical weakness are involved.

A potential problem with the reported association between cervical surgery for CIN and preterm birth is that of confounding factors since both preterm birth and CIN are known to be more prevalent in smokers and women of poor social economic class.¹⁶ A recent publication accounted for these confounding factors in a regression analysis but found that the association between conisation and preterm delivery remained.¹⁷ The same authors compared pregnancy outcomes in the same women before and after cervical treatment and still found an increased risk of preterm birth after surgery, again attributing the association with preterm birth to the treatment rather than any confounding factors.¹⁷

Ascending infection, from the vagina into the fetoplacental unit is commonly seen and presumed to be causative in preterm labour. The cervix is thought to be an important physical and immunological barrier to ascending infection,¹⁸ hence any weakening of the cervical barrier could increase the risk of infection and preterm labour and delivery. The association of LLETZ with preterm prelabour premature rupture of the membranes¹² supports the concept of a weakened defence against infection as the pathophysiological basis for the reported association.
5. Obstetric management of women with a history of treatment for CIN

Until different research aspects are investigated and new data published, women receiving treatment for high-grade lesions with a proportionally large excision should be alerted by their colposcopist that in the event of a future pregnancy, they should be considered at high risk of preterm delivery. This is particularly relevant for women who have had two excision treatments, as they are particularly at risk of preterm delivery (estimated to be up to ten times the background risk) and for those who have had treatment by knife conisation. Warning women of an increased risk of preterm birth may increase their anxiety but may also increase the likelihood that they seek medical help should symptoms of preterm labour occur.

The question arises as to how obstetricians should manage the subsequent pregnancies of women who have had excisional cervical treatment for CIN. The increased risk of preterm delivery in women who have had destructive treatment for CIN is very similar to that of women with a past history of previous preterm birth. In current UK obstetric practice, women with a past history of preterm birth are treated as high-risk patients and referred to high-risk antenatal clinics. The clinics provide a package of care that can include serial transvaginal cervical scanning and/or fetal fibronectin screening and, if the woman screens positive, preventative treatments such as cervical cerclage, progesterone and antenatal corticosteroid therapy. The problem with this ‘screen and treat’ approach is that it has not been shown to improve pregnancy outcome and is probably not cost effective. Further research in this area has been recommended.

Mid-trimester cervical shortening was found to predict preterm birth in women with previous excisional cervical surgery. Furthermore, progesterone, but not cervical cerclage, was found to reduce the rate of preterm birth in women with a short cervix. However, the issue of trying to prolong pregnancy is complicated by the lack of trials of preterm labour prevention that include long-term paediatric outcomes. There is a concern that prolonging pregnancy in women at risk of preterm delivery may simply keep the fetus in an unfavourable intrauterine environment and thereby increase paediatric morbidity. Hence, further research is required to determine the optimal management of pregnancy in women with a history of excisional cervical surgery for CIN.

6. Health services and organisational implications

Treatment for CIN has obstetric consequences that should be considered in young women. Policies of ‘see and treat’ may have been attractive in organisational terms as they involve the minimum number of outpatient attendances. However, a more conservative approach should be the best way forward if we are to minimise the damage to future pregnancy outcomes. This conservative approach could include observational management of low-grade disease in young women, adoption of ‘select and treat’ management protocols and consideration of ablative techniques in histologically proven persistent low-grade disease, in preference to excisional treatment, and possible consideration of ablative treatment in high-grade squamous disease when there is no evidence of invasive disease when colposcopy has been performed by experienced practitioners.

7. Opinion

Colposcopists need to be mindful when planning treatment to the cervix for preinvasive disease that excessive excisional treatment might result in higher risks of obstetric morbidity in subsequent pregnancies. Treatment should always be conducted not only to minimise failure rates but to minimise possible subsequent obstetric morbidity. Gynaecologists should give additional information to the patient as to the amount of cervical tissue removed and the damage to the endocervical canal. Further research is required to predict which women are at risk in subsequent pregnancies and to define antenatal interventions that might reduce such risks.
References


