Obstetric complications following conservative treatment of Cervical Intraepithelial Neoplasia

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Abstract

Treatment for cervical intraepithelial neoplasia (CIN) has been correlated with adverse reproductive morbidity in subsequent pregnancies. This review provides a summary of the risks, potential mechanisms and current obstetric management of women previously treated for CIN.

Background

The introduction of an organised screening programme in the UK in 1988 has significantly decreased the incidence and mortality rates of invasive cervical cancer (Quinn et al., 1999) through detection and treatment of the pre-malignant lesions of the uterine cervix, cervical intraepithelial neoplasias (CIN). In 2013-14, 3.4 million women aged between 25-64 years attended cervical screening in England (77.8% of the eligible population), and 199,322 were referred for colposcopy. During the same period almost 22,000 excisional treatments and around 1000 more ablative procedures for CIN were carried out (Health and Social Care Information Centre, 2012).

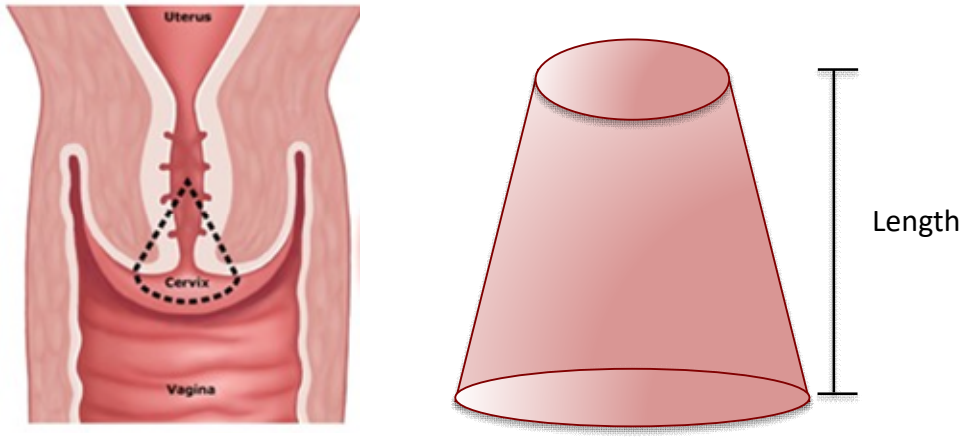
Until recently, local conservative treatment for cervical disease, excisional or ablative, was thought to have minimal complications, mainly related to small risk of haemorrhage and infection. Several studies published in the last decade documented that treatment for CIN adversely affects reproduction and led to major changes in clinical practice. The mean age for having conservative treatment for CIN in England is 30 years, which is also the mean age of mothers giving birth in the UK.

This review will address the current evidence and will summarise risks, potential mechanisms and current obstetric management of women previously treated for CIN, with an emphasis on UK-based practice.

Conservative local treatment for CIN

Excisional and ablative treatment techniques can be employed for the conservative local treatment of CIN. Both are simple and quick to perform, mostly under local anaesthesia in the outpatient clinic. Neither method has been shown to be superior with regard to recurrent CIN or invasive cancer (Martin-Hirsch et al., 2013). Large loop excision of the transformation zone (LLETZ) is the most commonly used technique in the UK, and involves a cone-shaped excision (Figure 1A) containing the whole transformation zone with the affected area of dysplastic cells. Immediate complications are relatively rare, infection and bleeding occurring in around 4 and 5% of cases, respectively (Sutthichon and Kietpeerakool, 2009).

FIGURE 1. Site of cervical cone biopsy (A) and excised tissue (B)



Fertility outcomes

The possible impact on fertility is a major concern for women undergoing conservative treatment for CIN but there has been paucity of data investigating the impact of treatment on the ability to conceive. A large retrospective study from the USA has shown that a greater proportion of treated women took over 12 months to conceive (16.4%), compared to untreated women with CIN (8.6%) or healthy controls (8.4%) [adjusted Odds Ratio (aOR=2.09); *P* = 0.039) (Spracklen et al., 2013). Although this may be attributed to treatment, medical advice may confound this by delaying conception until after the early post-operative period. Several smaller studies comparing pregnancy rates and time to conception did not find the same effect, and a large population-based cohort study in fact showed that treated women had a higher pregnancy rate before and after the treatment than the reference population [Hazard ratios (HRs)=1.15 (p<0.001) and 1.06 (p<0.001), respectively] (Kalliala et al., 2012). A recent meta-analysis of fertility outcomes concluded, however, that the treatment has no impact on pregnancy rates, or time to successful conception (Kyrgiou et al., 2014), although it included only a small number of studies and was not able to account for depth of excision or repeat treatments.

Early pregnancy outcomes (<24 weeks of gestation)

Around 20% of pregnancies end in miscarriage, and the vast majority of these (80%) occur in the first trimester (≤12 weeks). Between 50 and 85% are caused by fetal chromosomal abnormalities, with inherited thrombophilia, uterine malformation, uncontrolled diabetes and thyroid disease cited as less common causes. In the recent meta-analysis, treatment for CIN did not increase the risk of pregnancy loss in the first trimester (Kyrgiou et al., 2014).

Second trimester miscarriage (12-24 weeks gestation) may be associated with cervical incompetence and infection, in addition to the causes of early miscarriage. Women treated for cervical disease were shown to have a 2.60 greater relative risk of second trimester miscarriage compared to untreated controls in the same meta-analysis of 2,165,710 women (Kyrgiou et al., 2014). It is plausible that this phenomenon is a continuum of the factors causing preterm birth (PTB) in this patient group.

Ectopic pregnancy is another complication of early pregnancy, and higher rates have been observed in women treated for CIN (Kyrgiou et al., 2014). This is likely to be confounded by sexual and behavioural factors, predisposing to both CIN and ectopic pregnancy.

Obstetric outcomes

Numerous retrospective cohort studies and subsequent meta-analyses have documented the link between treatment for CIN and PTB (less than 37 weeks of gestation), along with other serious adverse obstetric outcomes including preterm pre-labour rupture of membranes (pPROM), low-birth weight and neonatal morbidity and mortality (Bruinsma and Quinn, 2011, Arbyn et al., 2008, Kyrgiou et al., 2006).

The risk of PTB appears to correlate with the length of the cone (Figure 1B), which can cause a dilemma for clinicians aiming for complete excision to ensure good oncological outcomes (Arbyn et al., 2014), yet balance reproductive wishes of the patient. A nested case-control study of women who underwent treatment for CIN in the UK showed that excision to a depth of 9mm or less does

not appear to significantly increase the risk of PTB compared to the general population (9%), but at longer lengths, however, the risk increased linearly: between 10-14mm, the risk was increased to 9.6% (relative risk (RR) 1.28, 95% CI 0.98 to 1.68), 15-19mm to 15.3% (RR 2.04, 95% CI 1.41 to 2.96) and 20mm or greater to 18.0% (RR 2.40, 95% CI 1.53 to 3.75) (Castanon et al., 2014). The same study showed a similar pattern with increasing volume of excised cervical tissue with volumes greater than 2.66cm^3 doubled the risk of PTB. This has been replicated by other studies (Khalid et al., 2012, Kyrgiou et al., 2015), and yet still debated by some (Kitson et al., 2014). The proportion of excision, rather than absolute length/volume may play a more important role as the length of the cervix may vary between individuals. Cold knife conisation has been shown to remove a significantly greater volume of healthy stromal tissue compared to LLETZ (Grimm et al., 2013), and it is therefore unsurprising that this technique is associated with the highest risk of PTB. Ablative treatments, particularly laser ablation are related to less frequent, if any adverse complications (Arbyn et al., 2008, Bruinsma and Quinn, 2011, Kyrgiou et al., 2006).

There does not appear to be a correlation between time interval from treatment to conception and risk of PTB (Castanon et al., 2014, Khalid et al., 2012). Furthermore, the increased risk does not appear to be restricted to the first birth after treatment, but applies to all subsequent pregnancies (Castanon et al., 2015).

The disease itself may be a confounding and contributing factor to PTB after treatment. Bruinsma et al. first demonstrated this in a meta-analysis by using internal untreated controls with CIN and external disease-free controls, where the former group had a smaller, yet still significantly increased risk of PTB compared to the latter. Castanon et al. further showed that the risk of PTB in women with CIN without treatment was 9% compared to 6.7% in the general population at the same time (Kyrgiou et al., 2012, Castanon et al., 2012). Smoking and lower socioeconomic status are associated with both PTB and CIN, and both possible attributable confounding factors, even though regression analysis has shown the association between untreated CIN and PTB remains once they are accounted for.

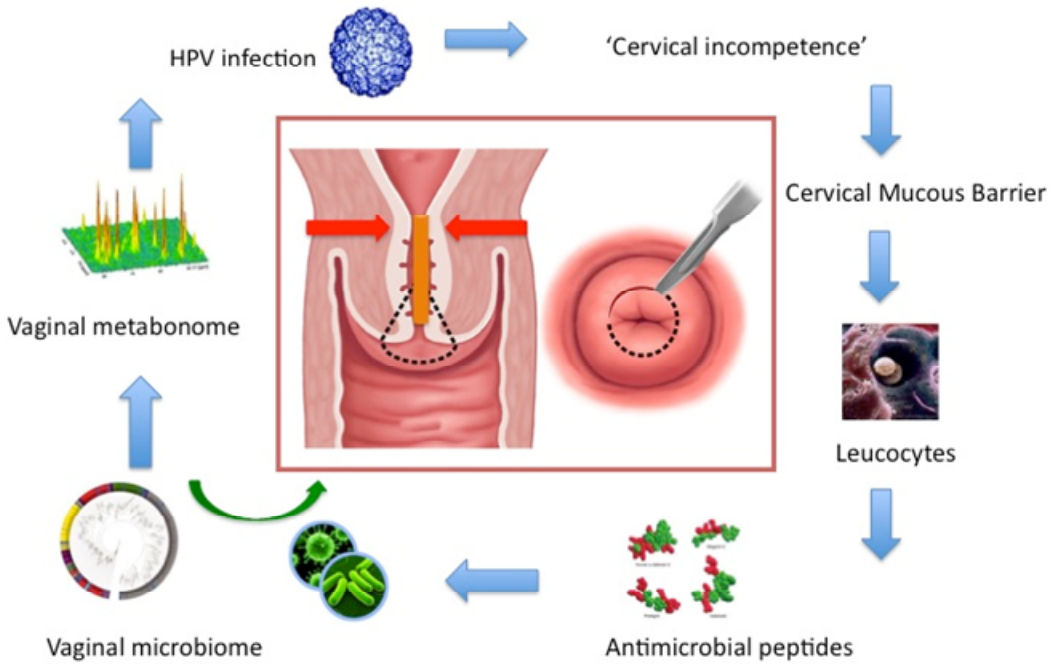
Mechanisms of adverse reproductive outcomes

Cervical stenosis is a known complication of treatment, with increasing risk associated with increased depth of excision (Mossa et al., 2005). Furthermore, treatment involves removal or destruction of cervical mucus secreting glands, which are necessary to facilitate passage of sperm through the cervical canal. Both stenosis and a reduction in secretions may account for the suggestion that fertility may be hindered after treatment.

The mechanisms associating PTB with cervical excision are currently unknown and should be the focus of future research to enable clinicians to identify and provide targeted treatment to the women at greatest risk. Figure 2 shows the possible underlying factors that still require further investigation in determining the aetiology and causality. Cervical regeneration after treatment is reported to be inversely proportional to the percentage of cervix excised (Papoutsis et al., 2012, Founta et al., 2010) and this regenerated tissue may furthermore be of inferior quality due to changes in collagen expression in the regenerated tissue (Phadnis et al., 2011). The inconsistency in the data regarding association with the length of cone, and particularly the volume excised, however, indicates that the underlying mechanism is not purely mechanical or anatomical.

Ascending vaginal infection leading to chorioamnionitis may cause up to 40% of cases of PTB and pPROM. Colonisation by pathogenic bacteria activates inflammatory pathways, which result in untimely onset of cervical remodeling and uterine contraction. The glandular cervical tissue provides an important innate immunological barrier during pregnancy, through production of mucus rich in cytokines and antimicrobial peptides. Changes in the character of cervical mucus may also be associated with pre-term birth (Critchfield et al., 2013), thus removal of a proportion of the cervix and its mucus-secreting glands may promote these deleterious changes. Notably many studies assessing the cervico-vaginal immune system have excluded patients with a previous history of cervical pathology and treatment, highlighting the need for research in this area. Indeed in animal models, viral infection of the cervix itself was shown to predispose to ascending viral infections in pregnancy (Racicot et al., 2013), which may also account for the increased risk of PTB seen in women with untreated CIN. Furthermore, these women may have an intrinsic immune abnormality, which not only puts them at risk of persistent HPV infection leading to development of CIN, but also results in a higher propensity to deliver preterm.

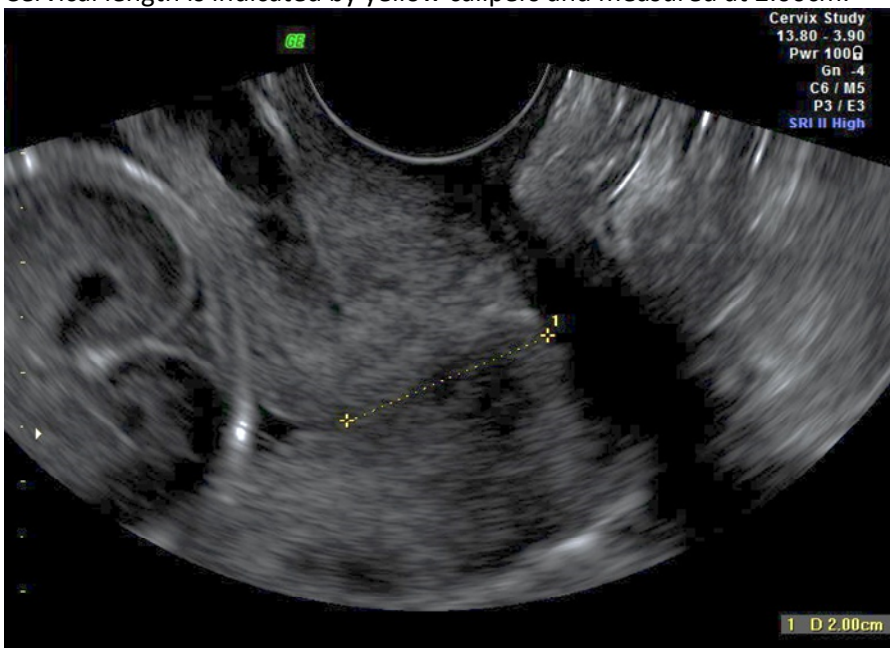
Figure 2. Proposed mechanisms of pre-term birth following excisional treatment for CIN.



In order for pathogenic bacteria to ascend, they must first colonise the vagina, which is usually inhibited by the healthy *Lactobacillus* spp. dominant vaginal microbiome. If the cervico-vaginal microenvironment is disturbed, for example by excisional treatment, the vaginal microbiome may also be disturbed, resulting in depletion of *Lactobacillus* spp. and overgrowth of anaerobic, bacterial vaginosis-associated species which has been associated with adverse obstetric outcomes (Hyman et al., 2014). Such species may also play a role in acquisition and persistence of HPV infections (Brotman et al., 2014) and furthermore, women with HPV have been shown to have significantly less *Lactobacillus* spp. compared to uninfected women (Lee et al., 2013). Increasing CIN severity has recently been associated with increased prevalence of high-diversity, *Lactobacillus* spp.-deplete

microbiomes (Mitra et al., 2015), which may go some way to explain the elevated risk of PTB seen in women with untreated CIN. These factors suggest a complex relationship between the vaginal microbiome, HPV/CIN and its treatment, and warrants further investigation. In particular, the microbiome dynamics can change during pregnancy (MacIntyre et al., 2015), which should also be studied in this discrete group. Microbiome modulation using probiotics could represent a future therapeutic adjunct in this group of women when pregnant.

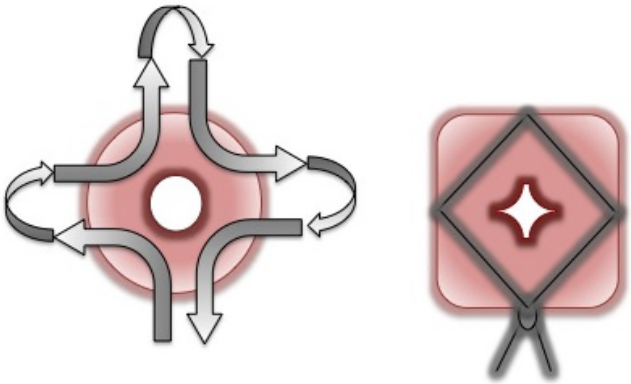
Figure 3. Transvaginal cervical length measurement.
Cervical length is indicated by yellow calipers and measured at 2.00cm.



Current obstetric management of women with a history of cervical treatment

A recent survey highlighted the lack of consensus in UK practice for diagnosis and treatment of women at risk of preterm birth (Stock et al., 2015). Treated women have been shown to have a significantly shorter cervix at 20-22 weeks than untreated women (32 vs 34mm, measured with vaginal ultrasonography) (Figure 3), with serial scans shown to increase sensitivity and specificity of predicting those at greatest risk of preterm birth (Poon et al., 2012). Cervical cerclage (Figure 4) is the insertion of a purse-string suture into the cervix to provide mechanical support, and can be offered to women with a cervical length of 25mm and below. It would however be inappropriate to recommend a cervical cerclage for all previously treated women, given that around 85% will deliver at term. Whilst the technique has been shown to delay or prevent PTB where there is demonstrable cervical shortening (Poon et al., 2012), there is increasing evidence that a suture is of no benefit to many women and may even increase the risk of PTB (Conde-Agudelo et al., 2013). A recent study by Kindinger et al. highlighted the effect of suture material choice, with patients in whom a non-absorbable nylon suture was used having significantly fewer preterm births, compared to those with a braided, polyfilament cerclage (15% vs 40%, p=0.008) (Kindinger et al., 2015). Progesterone supplementation has been shown to be effective in reducing the risk of PTB in women with a short cervix on mid-trimester ultrasound, who have had a previous preterm birth (Conde-Agudelo et al., 2013), however, this is currently no evidence to suggest this intervention to be effective in this discrete group of patients.

Figure 4. Cervical cerclage
Non-absorbable suture material is inserted transvaginally (A) either at the cervicovaginal junction (McDonald's technique) or at the level of the cardinal ligaments (Shirodkar's technique) and tied in a purse-string fashion (B). The knot is usually positioned posteriorly to prevent bladder erosion.
A **B**



Summary
Women with CIN have an increased risk of PTB compared to the background population, which may be due to an intrinsic abnormality that links susceptibility to both conditions or other confounding factors. Having an excisional treatment for CIN significantly increases the risk as compared to having CIN only in a step-wise fashion according to depth of tissue removed and number of treatments performed, which probably arises through damaged cervical architecture and altered cervicovaginal microenvironment, both of which are necessary for maintaining a pregnancy to term. There does not appear to be an increased risk of early pregnancy complications, however there is an increased risk of second trimester miscarriage, preterm rupture of membranes, preterm birth and perinatal morbidity and mortality. Further research is required to determine the mechanisms in order to determine which patients are at the highest risk, and to develop directed treatment strategies.

KEY POINTS

- **Women with untreated CIN are at an increased risk of PTB compared to the general population. Excisional treatment for CIN further increases this risk. The increased risk is proportional to the length and volume of the cone excised.**
- **The increased risk is not isolated to the first pregnancy after treatment, and is not dependent on time interval between excision and pregnancy.**
- **A change in cervical architecture and the cervicovaginal microenvironment are likely to be involved in the aetiology, although further research is required.**
- **There is no strong evidence to suggest and increase in fertility or early pregnancy complications following treatment, however there is a significantly increased risk of second trimester miscarriage.**
- **There is a lack of consensus regarding how this patient group should be managed in pregnancy, highlighting the need for further research to determine the exact cause in order to develop cause-directed strategies.**

Conflict of interest – the authors have no conflict of interest to declare.

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