Obstetric complications after treatment of cervical intraepithelial neoplasia

The introduction of an organized 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. In 2014–15, 3.12 million women aged between 25–64 years attended cervical screening in England (73.5% of the eligible population), and 198 216 were referred for colposcopy. During the same period almost 22 000 excisional treatments and around 1000 more ablative procedures for cervical intraepithelial neoplasia were carried out (Health and Social Care Information Centre, 2015).

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

This review addresses the current evidence and summarizes risks, potential mechanisms and current obstetric management of women previously treated for cervical intraepithelial neoplasia, with an emphasis on UK-based practice.

Conservative local treatment for cervical intraepithelial neoplasia

Excisional and ablative treatments can be used for the conservative local treatment of cervical intraepithelial neoplasia. Both are simple and quick to perform, mostly under local anaesthesia in the outpatient clinic. Neither method is superior with regard to recurrent cervical intraepithelial neoplasia or invasive cancer (Martin-Hirsch et al, 2013). Large loop excision of the transformation zone 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).

Fertility outcomes

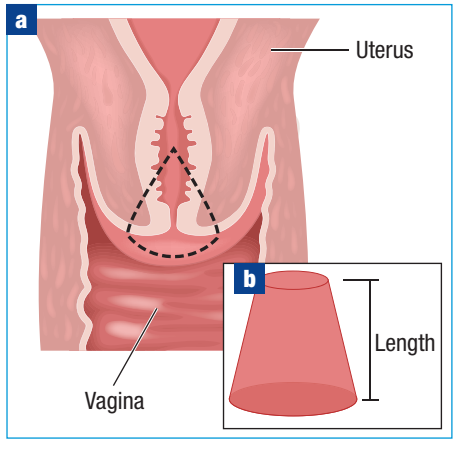
The possible impact on fertility is a major concern for women undergoing conservative treatment for cervical intraepithelial neoplasia but there has been a paucity of data investigating the impact of treatment on the ability to conceive. A large retrospective study from the USA has shown that a greater proportion of treated women took over 12 months to conceive (16.4%), compared to untreated women with cervical intraepithelial neoplasia (8.6%) or healthy controls (8.4%) (adjusted odds ratio=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 postoperative 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=1.15 (P<0.001) and 1.06 (P<0.001) respectively) (Kalliala et al, 2012). However, a meta-analysis of fertility outcomes concluded 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

Figure 1. **a.** Site of cervical cone biopsy and **(b)** excised tissue.



thrombophilia, uterine malformation, uncontrolled diabetes and thyroid disease cited as less common causes. Kyrgiou et al (2014) found that treatment for cervical intraepithelial neoplasia did not increase the risk of pregnancy loss in the first trimester.

Second trimester miscarriage (at 12–24 weeks' gestation) may be associated with cervical incompetence and infection, in addition to causes of early miscarriage. Women treated for cervical disease had 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). This phenomenon may be a continuum of the factors causing preterm birth in this patient group.

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

Obstetric outcomes

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

The risk of preterm birth 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), while balancing the reproductive wishes of the patient. A nested case-control study of women who underwent treatment for cervical intraepithelial neoplasia in the UK showed that excision to a depth of 9 mm or less does not appear to significantly increase the risk of preterm birth compared to the general population (9%), but at longer lengths the risk increased linearly: between 10–14 mm the risk was increased to 9.6% (relative risk 1.28, 95% confidence interval 0.98–1.68), 15–19 mm to 15.3% (relative risk 2.04, 95% confidence interval 1.41–2.96) and 20 mm or greater to 18.0% (relative risk 2.40, 95% confidence interval 1.53–3.75) (Castanon et al, 2014). The same study showed a similar pattern with increasing volume of excised cervical tissue with volumes greater than 2.66 cm^3 doubled the risk of preterm birth.

This has been replicated by other studies (Khalid et al, 2012; Kyrgiou et al, 2015), and yet is still debated by some (Kitson et al, 2014). The proportion of excision, rather than absolute length or volume, may play a more important role as the length of the cervix may vary between individuals. Cold knife conisation removes a significantly greater volume of healthy stromal tissue than large loop excision of the transformation zone (Grimm et al, 2013), so it is unsurprising that this technique is associated with the highest risk of preterm birth. Ablative treatments, particularly laser ablation, have less frequent if any adverse complications (Kyrgiou et al, 2006; Arbyn et al, 2008; Bruinsma and Quinn, 2011).

There does not appear to be a correlation between time interval from treatment to conception and risk of preterm birth (Khalid et al, 2012; Castanon et al, 2014). 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).

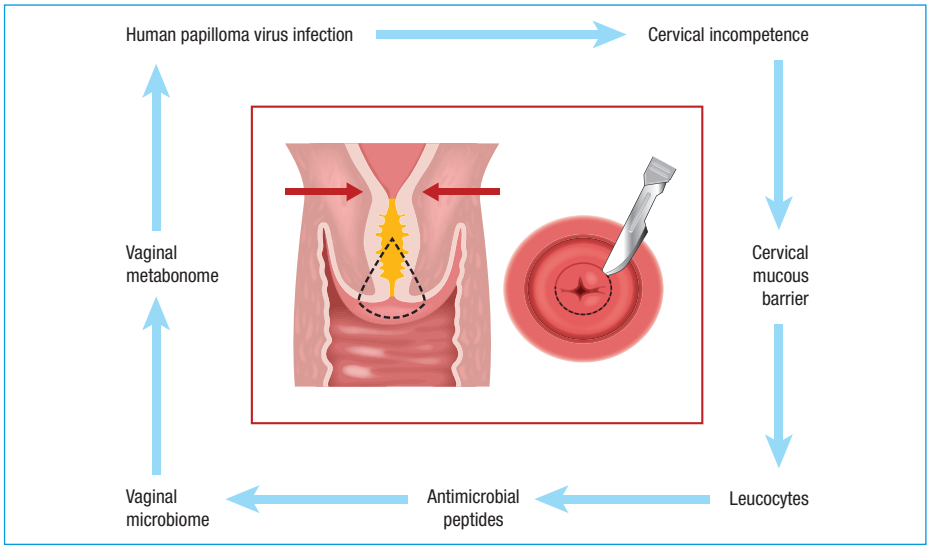
The disease itself may be a confounding and contributing factor to preterm birth after treatment. Bruinsma and Quinn (2011) first demonstrated this in a meta-analysis by using internal untreated controls with cervical intraepithelial neoplasia and external disease-free controls, where the former group had a smaller, yet still significantly increased risk of preterm birth compared to the latter. Castanon et al (2012) further showed that the risk of preterm birth in women with cervical intraepithelial neoplasia without treatment was 9% compared to 6.7% in the general population at the same time (Kyrgiou et al, 2012). Smoking and lower socioeconomic status are associated with both preterm birth and cervical intraepithelial neoplasia, and both possible attributable confounding factors, even though regression analysis has shown the association between untreated cervical intraepithelial neoplasia and preterm birth 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 preterm birth 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

Figure 2. Proposed mechanisms of pre-term birth following excisional treatment for cervical intraepithelial neoplasia.



reported to be inversely proportional to the percentage of cervix excised (Founta et al, 2010; Papoutsis et al, 2012) and this regenerated tissue may be of inferior quality because of 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 preterm birth and preterm pre-labour rupture of membranes. Colonization by pathogenic bacteria activates inflammatory pathways, which result in untimely onset of cervical remodelling 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 preterm birth (Critchfield et al, 2013), thus removal of a proportion of the cervix and its mucus-secreting glands may promote these deleterious changes. 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. 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 preterm birth seen in women with untreated cervical intraepithelial neoplasia. Furthermore, these women may have an intrinsic immune abnormality, which not only puts them at risk of persistent human papilloma virus infection leading to development of cervical intraepithelial neoplasia, but also results in a higher propensity to deliver preterm.

In order for pathogenic bacteria to ascend, they must first colonize 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 have been associated with adverse obstetric outcomes (Hyman et al, 2014). Such species may also play a role in acquisition and persistence of human papilloma virus infections (Brotman et al, 2014) and women with human papilloma virus have significantly fewer *Lactobacillus* spp. than uninfected women (Lee et al, 2013). Increasing cervical intraepithelial neoplasia severity has 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 preterm birth seen in women with untreated cervical intraepithelial neoplasia.

These factors suggest a complex relationship between the vaginal microbiome, human papilloma virus, cervical intraepithelial neoplasia 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.

Obstetric management of women with a history of cervical treatment

A 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 a significantly shorter cervix at 20–22 weeks than untreated women (32 *vs* 34 mm, measured with vaginal ultrasonography) (*Figure 3*), with serial scans increasing the 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 25 mm and below. However, it would be inappropriate to recommend cervical cerclage for all previously treated women, given that around 85% will deliver at term. While the technique can delay or prevent preterm birth 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 preterm birth (Conde-Agudelo et al, 2013). Kindinger et al (2016) 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).

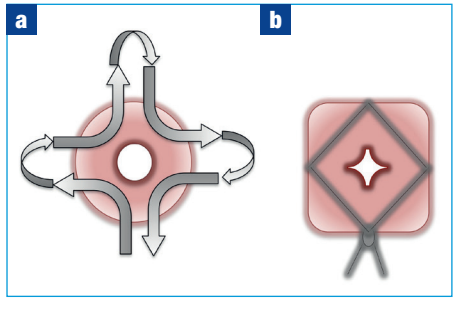
Progesterone supplementation is effective in reducing the risk of preterm birth in women with a short cervix on mid-trimester ultrasound who have had a previous preterm birth (Conde-Agudelo et al, 2013), but there is currently no evidence to suggest this intervention to be effective women who have had a previous treatment for cervical intraepithelial neoplasia.

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

Conclusions

Women with cervical intraepithelial neoplasia have an increased risk of preterm birth compared to the background population, which may be the result of an intrinsic abnormality that links susceptibility to both conditions or other confounding factors. Having an excisional treatment for cervical intraepithelial neoplasia significantly increases the risk as compared to having cervical intraepithelial neoplasia only in a step-wise fashion according to depth of tissue removed and number of treatments performed, which probably arises through damaged cervical

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



architecture and altered cervicovaginal microenvironment, both of which are necessary to maintain a pregnancy to term.

There does not appear to be an increased risk of early pregnancy complications, although 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. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Women with untreated cervical intraepithelial neoplasia are at increased risk of preterm birth compared to the general population. Excisional treatment for cervical intraepithelial neoplasia further increases this risk, proportionally to the length and volume of cone excised.
- The increased risk is not isolated to the first pregnancy after treatment, and is not dependent on the 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 an increase in fertility or early pregnancy complications following treatment, but there is a significantly increased risk of second trimester miscarriage.
- There is a lack of consensus about how these patients should be managed in pregnancy, highlighting the need for further research to determine the exact cause and develop cause-directed strategies.