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Reproductive Outcomes after Local Treatment for Preinvasive Cervical Disease

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This is the second edition of this paper, first published in October 2010 under the title 'Obstetric Impact of Treatment for Cervical Intraepithelial Neoplasia'.

1. Background

The introduction of systematic call and recall screening programmes in the UK has resulted in a profound decrease in the incidence and mortality of invasive cervical cancer.[1] The purpose of the screening programme is to identify preinvasive cervical disease (cervical intraepithelial neoplasia [CIN]). The treatment for CIN is usually excisional with high success rates.[2] In England in 2013–14 3.23 million women aged between 25 and 64 years attended for cervical screening and 22 092 excisional procedures were carried out.[3]

As the mean age of women undergoing treatment for preinvasive cervical disease is similar to the age of women having their first child, the evidence for the impact of cervical treatment on subsequent fertility and pregnancy should be available for effective patient counselling at colposcopy and antenatal clinics.

Clinical practice varies across Europe and beyond, although most countries have moved to less aggressive techniques. In some European countries, knife excision (cold knife conisation [CKC]) is still regularly performed; in others, laser ablation or laser conisation is common practice. In the UK, outpatient large loop excision of the transformation zone (LLETZ) is the preferred treatment, with some units offering ablative treatment. This Scientific Impact Paper attempts to present the current evidence and future research required. The evidence presented is relevant to all treatment settings but is particularly focused on UK practice.

2. Fertility outcomes

Evidence on the impact of treatment on the ability to conceive is limited. Two small case series[4,5] reported that treatment for CIN did not adversely affect the time to conception. A retrospective cohort of 35 000 women, with a follow-up of over 250 000 woman-years, reported higher pregnancy and live birth rates for treated women compared with the reference population.[6] However, another large series reported that women after conisation took longer to conceive than women who attended for colposcopy but did not require treatment, or women without CIN (time to conception greater than 12 months: 16.4% versus 8.6% or 8.4% respectively; $P = 0.039$).[7]

A meta-analysis published in 2014[8] concluded that there was no evidence that local treatment for CIN adversely affects the ability to conceive. The overall pregnancy rate was higher for treated versus untreated women (four studies; 43% versus 38%; relative risk [RR] 1.29, 95% CI 1.02–1.64). The pregnancy rate in women with an intention to conceive was only assessed in two studies which gave similar results (87.9% versus 94.6%; RR 0.93, 95% CI 0.80–1.08). For women requiring more than 12 months to conceive the rates for treated versus untreated women were higher, although the difference was not significant (three studies; 14.7% versus 9.2%; RR 1.45, 95% CI 0.89–2.37). Although this may be due to the impact of treatment on fertility, it may also be explained by clinicians' recommendation to delay conception until after the early post-operative period. Limited published evidence did not permit stratification of the risk according to the length of the cone and the number of treatments. The impact of repeat and proportionally large excisions on fertility remains unclear.

3. Early pregnancy outcomes

The evidence on the impact of treatment for preinvasive cervical disease on early pregnancy outcomes (less than 24 weeks of gestation) is limited.

A systematic review and meta-analysis[8] reported similar rates of overall and first trimester miscarriages for treated and untreated women, although cervical treatment significantly increased the risk of second trimester miscarriage compared with untreated controls (eight studies; 1.6% versus 0.4%; RR 2.6, 95% CI 1.45–4.67). These results were corroborated by a large population-based study[9] of 15 108 treated and 2 164 006 untreated women that reported a four-fold increase in the risk of midtrimester loss after conisation compared with the untreated women (1.5% versus 0.4%; RR 4.0, 95% CI 3.3–4.8).

The meta-analysis[8] also showed that treated women had higher rates of ectopic pregnancy (six studies; 1.6% versus 0.8%; RR 1.89, 95% CI 1.50–2.39) and termination of pregnancy (12.2% versus 7.4%; RR 1.71, 95% CI 1.31–2.22) compared with untreated individuals.

4. Obstetric outcomes

Local treatment of the cervix has been associated with adverse obstetric outcomes. A meta-analysis of 27 retrospective cohort studies[10] demonstrated that excisional treatment increases the risk of preterm birth (less than 37 weeks of gestation; CKC versus no treatment: 14% versus 5%; RR 2.59, 95% CI 1.80–3.72; LLETZ versus no treatment: 11% versus 7%, RR 1.7, 95% CI 1.24–2.35). Low birthweight (less than 2500 g) and preterm prelabour rupture of membranes (pPROM) were also increased after excisional treatment. This analysis did not report an increase in preterm birth in women who previously had had laser ablation, although a more recent systematic review[11] documented that preterm birth may also be increased after some types of ablative treatments. The impact of cold coagulation has never been reported separately.[12]

A subsequent meta-analysis[13] reported that severe adverse obstetric outcomes were more prevalent after excisional treatment techniques. Their frequency and severity increased with treatment methods that remove large amounts of cervical tissue. Women who had undergone CKC were three times more likely to deliver before 32–34 weeks of gestation (severe prematurity), and more than five times more likely to deliver before 28–30 weeks of gestation (extreme prematurity) (4.6% versus 1.6%; RR 2.78, 95% CI 1.72–4.51; and 4.2% versus 0.8%; RR 5.33, 95% CI 1.63–17.40 respectively). Perinatal mortality was also increased after CKC (4.3% versus 0.5%; RR 2.87, 95% CI 1.42–5.81); these severe adverse outcomes were not increased after LLETZ or laser ablation.

A potential problem with these associations is that of confounding factors, since both preterm birth and CIN are known to be more prevalent in smokers and women of lower socio-economic class. CIN and/or risk factors associated with the disease increase the risk of preterm birth even without treatment.[11,14] It is therefore plausible that studies that used as comparators women without the disease adjusted for known confounders may have overinflated the estimate of risk caused by treatment due to the presence of other unknown confounders in women with CIN .

There is increasing evidence that the amount of cervix excised or destroyed and the cone length/volume appear to be predictors for subsequent prematurity.[10,15,16] The meta-analysis by Kyrgiou et al.[10] reported that excisional treatment which exceeded 10 mm in length increased prematurity (RR 2.61, 95% CI 1.28–5.34), while less deep excisions did not. A case–control study nested within a record linkage cohort study[16] from the UK reported that the absolute risk of preterm birth for small excisional treatments (less than 10 mm in length) was similar to that of a diagnostic punch biopsy only (7.5% versus 7.2%). This risk increased progressively with deeper cones: absolute risk was 9.6% for medium-size cones (10–14 mm), 15.3% for large cones (15–19 mm) and 18% for very large cones (20 mm or greater). Another series[17] reported that the risk of preterm birth increased three-fold when the excision volume exceeded 6 cm^3 and/or the length

exceeded 12 mm. Noehr et al.[15] estimated that every millimetre of cone length increased by 6% the risk of preterm birth. Other authors have further suggested that the proportion of cervical volume/length removed may correlate more accurately to outcomes rather than the absolute excision length since the pretreatment cervical dimensions may vary substantially.[18,19]

5. Potential biological mechanisms for reproductive morbidity

The mechanism that accounts for the increased risk of second trimester loss and preterm birth associated with CIN and its treatment is not yet clarified. It has been postulated that local cervical treatment might remove sufficient mucus-secreting endocervical glands to adversely affect sperm motility,[20,21] while severe cervical os stenosis may further inhibit conception.[22] While acquired mechanical weakness of the cervix secondary to surgery might seem a logical assumption, more subtle mechanisms may be involved. Although the midtrimester mean cervical length is shorter for women with previous cervical treatment,[23] only 28% have a length of less than 25 mm, while there is evidence that the cervix regenerates after treatment.[24–26] Histological changes in the healed cervix affecting the tensile strength or changes in the innate immune system and the vaginal microenvironment may also be involved.

Ascending infection from the vagina into the fetoplacental unit and associated inflammation are presumed to be causative in preterm labour. The uterus in pregnancy is protected by the cervix via its mucous plug, the local synthesis of antimicrobial peptides and proteins, and by a 'benign' *Lactobacillus*-dominated vaginal microflora.[27] Lactobacilli inhibit pathogen growth by maintaining a hostile pH and secrete species-specific metabolites and bacteriocins that limit the growth of other organisms. Removing part of the cervix or simply being infected with human papillomavirus (HPV) may impair the host's defence mechanisms, change the chemical microenvironment and prevent a pregnancy being maintained to full term. Conversely, it may be that women at risk have intrinsic compromised defences that promote the persistence of oncogenic HPV infections and the development of ascending infections during pregnancy.

Future research should explore the mechanisms that lead to adverse reproductive outcomes in this population. A better understanding of pathogenic factors may enable identification of women at risk and help avert these outcomes through the development of cause-directed treatments.

6. Obstetric management of women with a history of treatment for preinvasive cervical disease

Although the risk of preterm birth after cervical treatment is only in the order of 15%,[10] it represents a major contributor to the overall burden of prematurity. Women with a previous cervical treatment represent at least 5% of the obstetric population.[28] Until recently in the UK, only women with a history of preterm birth or midtrimester loss attended the high-risk obstetric prematurity surveillance clinics. In many hospitals, the majority of these referrals now include women who have had a previous cervical treatment; a category virtually undetectable in 1999 increasing to more than 40% in 2012.[28] These clinics are only available in certain units and provide a package of care that can include serial transvaginal cervical length measurements, fetal fibronectin screening and, if the woman screens positive, preventive treatments such as cervical cerclage, progesterone and antenatal corticosteroid therapy. Clinical management across the UK is inconsistent and largely unit- or clinician-dependent.[29] There is limited evidence from observational studies that a strategy of performing cervical cerclage in women whose cervix is 25 mm or less reduces the risk of preterm birth, however the value of this approach has not been tested prospectively. Vaginal but not systemic progesterone reduces the risk of preterm birth in women with a short cervix in general,[30,31] but it is not known whether this is specific to women with prior cervical treatment. This reflects the limited evidence of the value of these interventions in women after cervical treatment and our inability to stratify women into low or high risk.

Many obstetricians believe that preterm labour following cervical treatment is a result of 'cervical weakness', which can be corrected by cerclage. However, cerclage for all women with prior cervical treatment is inappropriate since approximately 85% of them will deliver at term. Serial measurement of cervical length on transvaginal ultrasound to detect cervical shortening has been proven to predict preterm labour in the general population,[32] specifically in women with prior cervical treatment.[23,24] Poon et al.[33] showed that individual cervical length has the same predictive value in women with cervical cone as in the general population, for whom a cut-off of 25 mm is usually used to target treatment.

In the overall obstetric population, cervical cerclage does not reduce the risk of preterm labour where the only risk factor is a short cervix discovered incidentally in the second trimester, but does reduce the risk in women with a short cervix who have a history of midtrimester losses or preterm births.[32,34] Consequently, women with prior local cervical treatment but no other obstetric history fall between these two groups. Since cervical treatment may mechanically damage the cervix, it is plausible that cerclage will be of benefit in some women. However, either CIN itself or the effects of 'foreign' material (cervical stitch) may affect the vaginal microenvironment and the immune defence system, such that the risk of preterm labour could plausibly be unaffected or worsened by cervical cerclage.[35] Progesterone may be of value as it has been found to decrease the risk of preterm birth in women with a short cervix.[30]

Some National Health Service (NHS) hospitals have already introduced a strategy of cervical length-indicated cerclage post conisation, even though the associated risks and benefits have not yet been fully assessed in properly designed studies. This strategy may become a 'standard of care' without strong evidence of benefit but may also lead to worse outcomes, as discussed above. Women after cervical treatment represent a discrete group with known aetiology for preterm birth (either CIN or the effects of treatment for CIN), albeit with yet unclear pathogenic pathways. Future research should assess the value of antenatal interventions in this distinct group and devise a logical prevention strategy that can be tested and then applied across the NHS and beyond.

7. Oncological outcomes

When considering the impact of treatment on fertility, the influence of the type and radicality of the treatment on the chances of recurrence or the risk of future invasive disease should be carefully balanced. A population-based study from Sweden[36] reported an increase in the rate of invasive disease after local cervical treatment, which may be partially explained by the use of less aggressive treatment techniques.[37]

Excisional techniques, particularly LLETZ, have largely replaced destructive techniques in developed countries. This is because the resulting specimen provides important prognostic information on the grade, the completeness of the excision (excision margins[38]), the absence of (micro)invasion and the stratified risk for future prematurity according to the specimen's length. Despite these advantages of excision, the risk of precancerous[2,39] or invasive recurrence[40,41] on long-term follow-up is no different among different treatment techniques, with the exception of cryotherapy.

Ang et al.[42] demonstrated that in women with a fully visible transformation zone, there is little to be gained from LLETZ to a length greater than 10 mm in line with NHS Cancer Screening Programmes[43] and European[44] guidelines. However, 52% of women aged 35 or under in this study had a cone length that exceeded 11 mm.[42] Repeat excisions multiply the frequency and severity of the adverse reproductive sequelae. The colposcopist is therefore obliged to optimise treatment after detailed colposcopy at the first attempt as margins substantially increase the risk of high-grade recurrence (18% versus 3%).[38] Colposcopists should audit their treatment outcomes, and units should benchmark their practice in terms of mean depth/volume, single/multiple specimens, excisional marginal status and failure rates.

8. Opinion

Women with CIN have a higher baseline risk for preterm birth. Local cervical treatment further increases that risk. Small conisations of less than 10 mm in length do not appear to confer additional risk, although deeper and repeat excisions progressively increase the frequency and severity of adverse reproductive outcomes. The risk of second trimester miscarriage is also increased after treatment, although there is no evidence that fertility is compromised.

Colposcopists should alert women receiving proportionally large or repeat excisions that in the event of a future pregnancy they should be considered at high risk of preterm delivery. There is no robust evidence to suggest that antenatal surveillance and interventions have any benefit; further research is required.

Until new data become available, caution should prevail when considering treatment in nulliparous women. Treatment should always be tailored to treat disease effectively, and at the same time minimise reproductive sequelae. New HPV biomarkers may allow the selection of women that are at risk of developing cancer and would benefit from treatment and, in contrast, the identification of those at low risk who could be managed by observation. HPV vaccination should reduce the incidence of preinvasive lesions requiring treatment and further reduce adverse reproductive sequelae.

Ideally, professional bodies should agree on the histological reporting of excisional specimens, which should include standardised measurement of dimensions. This would facilitate audit of practice and future research. It would also allow obstetricians to triage women at risk of preterm birth and develop strategies to reduce adverse outcomes.

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