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Commentary

Risk of preterm birth following surgical treatment for cervical disease: executive summary of a recent symposium

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We report on a symposium held in London, UK, on 16 February 2015 to discuss the association between surgical treatment of cervical intraepithelial neoplasia (CIN) and subsequent preterm birth, and to consider appropriate recommendations for the treatment of CIN and management of treated women during pregnancy. The meeting focused on CIN grades 2 and 3 that have been managed surgically. Clinical practice varies internationally: in some countries knife excision is common; in others, laser ablation is the treatment of choice; and in others, treatment predominantly involves outpatient large loop excision of the transformation zone (LLETZ), also called loop electrosurgical excision procedure (LEEP). The meeting was part of the dissemination strategy of the National Institute for Health Research (NIHR)-funded PaCT study (preterm delivery after treatment of the cervical transformation zone). Around 50 people attended, including gynaecologic oncologists, (nurse and medical) colposcopists, obstetricians, and epidemiologists. The authors of this executive summary include the speakers at the symposium, who are also authors of important papers in the subject area, and the symposium chairs, to provide an independent opinion on the views expressed by the audience. Further details on the expertise of the authors can be found in the contribution to authorship.

Meta-analysis suggested that pregnant women previously treated by LLETZ are at approximately twice the risk of a preterm birth than pregnant women in general.[1–3] A study from England,[4] and a recent meta-analysis,[3] found a much lower relative risk and no association after adjusting for confounding factors. More recent research suggests that the increased risk may be associated with large excisions alone (10–14 mm, and particularly >15 mm), and that the reason for the lack of association in some studies was that the majority of women treated had small excisions.[5] Assuming the observed associations are causal, how should guidelines be modified to minimise the risk of causing preterm deliveries whilst still effectively preventing progression from CIN to invasive cervical cancer? In thinking about the balance between the harms and benefits of treatment it is important to know about the long-term consequences of late preterm deliveries (34–36 weeks of gestation). Even if the association between LLETZ and preterm birth is not causal, having identified a high-risk group there is a question as to how they should be managed obstetrically.

The first part of the meeting focused on the results of international studies on the association between the treatment of CIN and subsequent risk of preterm delivery.

1 There is strong observational (but no experimental) evidence [level 2a[6]] suggesting a causal link between treatment for CIN and subsequent preterm birth, meeting most of the Bradford Hill criteria for causation.

a *Consistency*. There is a strong and consistent association between LLETZ and subsequent preterm birth, summarised in meta-analyses and observed in several countries.[1,7,8]
b *Biological gradient*. More aggressive forms of treatment (e.g. knife cones) are more strongly associated with preterm birth.[1] There is a greater risk of preterm delivery with increasing length/volume of tissue removed.[1,5,9] Ablative treatment, generally reserved for smaller lesions, has not been associated with preterm birth.[1]
c *Temporality*. There is no such gradient when the birth precedes the treatment.[16]
d *Specificity*. Women who receive a diagnostic punch biopsy at colposcopy before delivery have a similar risk as those who have <10 mm (defined as the distance from the distal or external margin to the proximal or internal margin of the excised specimen)[10] of cervical tissue excised.[5]
e *Strength*. The risk of preterm birth per pregnancy increased with increasing length of excision, to around one in six in women who have more than 20 mm of tissue removed.[5]
f *Specificity*. There is evidence that the association is greater when the analysis is restricted to women who have spontaneous onset of labour resulting in a preterm birth. The association also exists for late mid-trimester miscarriages and very preterm births (at 20–31 weeks of gestation).[1,11]
g *Plausibility*. There are three plausible mechanisms by which treatment could increase the risk of preterm birth: a mechanical weakening of the cervix; more subtle histological changes in the healed cervix, affecting the tensile strength; impaired cervical antimicrobial mechanisms, such as mucus plug formation, allowing microbial access to the uterine cavity.[11]

2 There is evidence (level 2b) that it does not hamper conception following treatment.[12,13]
3 There is evidence (level 2b) that the time from treatment to conception does not influence the risk of a preterm birth,[5] provided that conception does not happen within 4 months of treatment.[14,15]
4 There is some evidence (level 2b) to suggest that the age at treatment does not influence the risk of a preterm birth.[16]
5 The increased risk of preterm birth is not limited to the first birth after treatment (level 2b). Even women who have a term birth after a large excision (>15 mm length) are at increased risk of preterm delivery during future pregnancies.[16]

The second part of the meeting aimed to put the evidence regarding the risk of preterm birth in the context of the wider aims of cervical screening (to prevent cervical cancer by appropriate treatment of precancerous lesions). The speakers explored the use of ablative treatment in colposcopy and the need for quality assurance of the programme.

There was consensus (level 5) among the audience on the following points.

1 Quality management of colposcopy is essential.
2 The volume of material excised may often be excessive.
3 It is important to find a way of recording the length of excision in the primary care notes.
4 Excision of high-grade CIN should aim to result in margins that are clear of disease.
5 Complete excision of a CIN grade 3 should not be jeopardised for the sake of reducing the risk of a preterm birth.
6 Ablative treatments, including thermo-coagulation, have an important role in low- and middle-income countries.

There was a lack of consensus regarding ablative treatment. The majority view was that ablative treatment is not, at this time, an appropriate alternative to LLETZ in established cervical screening programmes in high-income countries. Concern was raised regarding the risk of invasive cancer after destructive treatments.[17,18] Others felt that ablative treatment is safe for CIN2 and for type–I transformation zone (defined as completely ectocervical and fully visible),[19] and was less likely to result in over treatment (and increased risk of preterm birth) when carried out by a less experienced colposcopist. The counter argument was that without measurements of the volume of tissue destroyed, and without evidence of whether there were clear margins or occult invasive cancer, it was impossible to quality assure ablative treatment. The majority view was that ablative treatments are acceptable for CIN2, provided the whole lesion is visualised.

Although a randomised controlled trial of ablative treatment versus excision for type–I lesions was proposed, it was agreed that any such trial would need to be extremely large and to have long-term follow-up. The majority view was that such a trial was not justified, taking into account that small excision appears to be safe and that the future demand for treatment of CIN3 will be dramatically reduced by human papilloma virus (HPV) vaccination.

Finally, the meeting focused on the long-term impact of preterm birth and the obstetric management of high-risk pregnancies. There is growing evidence of small effects on health and behaviour in children born late preterm compared with those born at 40 weeks of gestation (level 2b). For instance, 16.6% of infants born at 33–34 weeks of gestation and 13.5% of infants born at 35–36 weeks of gestation had an emergency hospital admission for respiratory

disease by the age of 1 year, compared with 7.8% of those born at 40–42 weeks of gestation.[20] Similarly, children born at 33–36 weeks of gestation were 50% more likely to have special educational needs than those born at 40 weeks of gestation.[21] The impact of moderate and late preterm birth even continues into adulthood. A large study from Sweden found that those born at 33–36 weeks of gestation were 50% (95% confidence interval, 95% CI 30–70%) more likely to receive a sickness pension, handicap allowance, or disability assistance than those born at 39–41 weeks of gestation, after adjusting for several risk factors.[22]

A number of studies have shown short cervical length measured by ultrasound during pregnancy (16–24 weeks of gestation) to be predictive of spontaneous preterm (and in particular early preterm) delivery in women previously treated by LLETZ (level 2b), but it is uncertain whether LLETZ (particularly >20 mm in length) confers additional risk after accounting for cervical length.[23,24]

High levels of fetal fibronectin, an extracellular matrix glycoprotein found in cervicovaginal secretions, from 22 weeks of gestation are strongly associated with early (<30 weeks of gestation) preterm delivery (level 2b). Its role in predicting late preterm delivery is less clear.

Various interventions have been shown to prevent preterm delivery in women with a short cervix (≤25 mm). The level of evidence for interventions to prevent preterm birth in very high-risk women is strong, but none have specifically studied women whose increased risk was a consequence of previous LLETZ. Cervical cerclage does not reduce the risk of singleton preterm labour when the only risk factor is a short cervix discovered incidentally, but benefit has been reported in a subgroup of high-risk women (those with cervical lengths of <15 mm).[25] An individual patient data meta-analysis including five small trials of mid-trimester vaginal progesterone treatment showed a reduction in preterm birth <35 weeks of gestation (relative risk 0.69; 95% CI 0.55–0.88).[26] The results of randomised studies of cervical pessary in the prevention of preterm birth are inconsistent.[27]

The consensus is outlined as follows.

1 Predictors of preterm birth, including cervical length and fetal fibronectin, can be used to ascertain risk in women following surgical treatment of high-grade CIN (grade C).
2 There is no evidence to suggest that cerclage, vaginal pessary, or progesterone are less effective in women treated by LLETZ.
3 Women who have had a large excision (>15 mm in length) of their cervical transformation zone should be identified during pregnancy and managed in the knowledge that they are at moderately increased risk of a preterm delivery (grade D).
4 Research into the management of women in pregnancy with prior LLETZ is required, including risk thresholds and types of prophylactic interventions that are efficacious.

Overall, the participants made the following recommendations.

1 Basic research is required to better understand the mechanism by which excision is associated with preterm births (grade D).
2 Publications on this topic should use the following categories for the length of the excised cone (measured on pathology): 1–9, 10–14, 14–19, and ≥20 mm (grade D).
3 Excisions of less than 10 mm in length appear to have, at most, minimal affect on the risk of preterm births (grade B).
4 Auditing standards are needed for the length of excision in cervical screening programmes. We suggest the following guidelines.
   a When treating a type–I transformation zone (defined as completely ectocervical and fully visible, it may be small or large) in a woman of childbearing age, 80% of excisions should be <10 mm and 95% should be <15 mm (grade C).
   b When treating a type–II transformation zone (i.e. including an endocervical component, fully visible, and may have an ectocervical component that may be small or large) in a woman of childbearing age, 50% of excisions should be <10 mm and 80% should be <15 mm (grade C).
5 CIN2 (particularly if p16-negative) in a woman of childbearing age should not automatically be treated but should be discussed at the multidisciplinary team meeting (grade D).

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

PS confirms that this is an honest, accurate, and transparent account of the meeting being reported. AC organised the meeting. PS wrote the first draft of the report. AC, HK, MK, RL, LCP, WP, MQ, AS, PS, and TFW presented data to the meeting. AH, JP, DP, and WPS chaired and directed discussion during the meeting. All authors (PS, AC, RL, MK, HK, MQ, LCP, AS, AH, WPS, TFW, DP, WP, and JP) contributed to the discussion, edited the report, and approved the final version. We would particularly like to acknowledge P. Martin-Hirsch, E. Paraskevaidis, P. Bennett, J. Tidy, S. Leeson, and T. Ind for their contribution to the discussion undertaken at the symposium. ■

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