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[Intervention Review]

Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease

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ABSTRACT

Background

The mean age of women undergoing local treatment for pre-invasive cervical disease (cervical intra-epithelial neoplasia; CIN) or early cervical cancer (stage IA1) is around their 30s and similar to the age of women having their first child. Local cervical treatment has been correlated to adverse reproductive morbidity in a subsequent pregnancy, however, published studies and meta-analyses have reached contradictory conclusions.

Objectives

To assess the effect of local cervical treatment for CIN and early cervical cancer on obstetric outcomes (after 24 weeks of gestation) and to correlate these to the cone depth and comparison group used.

Search methods

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library, 2017, Issue 5), MEDLINE (up to June week 4, 2017) and Embase (up to week 26, 2017). In an attempt to identify articles missed by the search or unpublished data, we contacted experts in the field and we handsearched the references of the retrieved articles and conference proceedings.

Selection criteria

We included all studies reporting on obstetric outcomes (more than 24 weeks of gestation) in women with or without a previous local cervical treatment for any grade of CIN or early cervical cancer (stage IA1). Treatment included both excisional and ablative methods. We excluded studies that had no untreated reference population, reported outcomes in women who had undergone treatment during pregnancy or had a high-risk treated or comparison group, or both



Data collection and analysis

We classified studies according to the type of treatment and the obstetric endpoint. Studies were classified according to method and obstetric endpoint. Pooled risk ratios (RR) and 95% confidence intervals (CIs) were calculated using a random-effects model and inverse variance. Inter-study heterogeneity was assessed with I² statistics. We assessed maternal outcomes that included preterm birth (PTB) (spontaneous and threatened), preterm premature rupture of the membranes (pPROM), chorioamnionitis, mode of delivery, length of labour, induction of delivery, oxytocin use, haemorrhage, analgesia, cervical cerclage and cervical stenosis. The neonatal outcomes included low birth weight (LBW), neonatal intensive care unit (NICU) admission, stillbirth, perinatal mortality and Apgar scores.

Main results

We included 69 studies (6,357,823 pregnancies: 65,098 pregnancies of treated and 6,292,725 pregnancies of untreated women). Many of the studies included only small numbers of women, were of heterogenous design and in their majority retrospective and therefore at high risk of bias. Many outcomes were assessed to be of low or very low quality (GRADE assessment) and therefore results should be interpreted with caution. Women who had treatment were at increased overall risk of preterm birth (PTB) (less than 37 weeks) (10.7% versus 5.4%, RR 1.75, 95% CI 1.57 to 1.96, 59 studies, 5,242,917 participants, very low quality), severe (less than 32 to 34 weeks) (3.5% versus 1.4%, RR 2.25, 95% CI 1.79 to 2.82), 24 studies, 3,793,874 participants, very low quality), and extreme prematurity (less than 28 to 30 weeks) (1.0% versus 0.3%, (RR 2.23, 95% CI 1.55 to 3.22, 8 studies, 3,910,629 participants, very low quality), as compared to women who had no treatment.

The risk of overall prematurity was higher for excisional (excision versus no treatment: 11.2% versus 5.5%, RR 1.87, 95% CI 1.64 to 2.12, 53 studies, 4,599,416 participants) than ablative (ablation versus no treatment: 7.7% versus 4.6%, RR 1.35, 95% CI 1.20 to 1.52, 14 studies, 602,370 participants) treatments and the effect was higher for more radical excisional techniques (less than 37 weeks: cold knife conisation (CKC) (RR 2.70, 95% CI 2.14 to 3.40, 12 studies, 39,102 participants), laser conisation (LC) (RR 2.11, 95% CI 1.26 to 3.54, 9 studies, 1509 participants), large loop excision of the transformation zone (LLETZ) (RR 1.58, 95% CI 1.37 to 1.81, 25 studies, 1,445,104 participants). Repeat treatment multiplied the risk of overall prematurity (repeat versus no treatment: 13.2% versus 4.1%, RR 3.78, 95% CI 2.65 to 5.39, 11 studies, 1,317,284 participants, very low quality). The risk of overall prematurity increased with increasing cone depth (less than 10 mm to 12 mm versus no treatment: 9.8% versus 3.4%, RR 1.93, 95% CI 1.62 to 2.31, 8 studies, 552,711 participants, low quality; more than 15 mm to 17 mm versus no treatment: 10.1 versus 3.4%, RR 2.77, 95% CI 2.06 to 11.68, 3 studies, 544,986 participants, very low quality; CI unditive versus 3.4%, RR 4.91, 95% CI 2.06 to 11.68, 3 studies, 543,750 participants, very low quality). The comparison group affected the magnitude of effect that was higher for external, followed by internal comparators and ultimately women with disease, but no treatment. Untreated women with disease and the pre-treatment pregnancies of the women who were treated subsequently had higher risk of overall prematurity than the general population (5.9% versus 5.6%, RR 1.24, 95% CI 1.14 to 1.34, 15 studies, 4,357,998 participants, very low quality).

pPROM (6.1% versus 3.4%, RR 2.36, 95% CI 1.76 to 3.17, 21 studies, 477,011 participants, very low quality), low birth weight (7.9% versus 3.7%, RR 1.81, 95% CI 1.58 to 2.07, 30 studies, 1,348,206 participants, very low quality), NICU admission rate (12.6% versus 8.9%, RR 1.45, 95% CI 1.16 to 1.81, 8 studies, 2557 participants, low quality) and perinatal mortality (0.9% versus 0.7%, RR 1.51, 95% CI 1.13 to 2.03, 23 studies, 1,659,433 participants, low quality) were also increased after treatment.

Authors' conclusions

Women with CIN have a higher baseline risk for prematurity. Excisional and ablative treatment appears to further increases that risk. The frequency and severity of adverse sequelae increases with increasing cone depth and is higher for excision than it is for ablation. However, the results should be interpreted with caution as they were based on low or very low quality (GRADE assessment) observational studies, most of which were retrospective.

PLAIN LANGUAGE SUMMARY

Obstetric outcomes after conservative treatment for cervical intraepithelial lesions

The issue

Cervical intra-epithelial neoplasia (CIN) is a pre-cancerous lesion of the cervix uteri (neck of the womb) caused by human papillomavirus (HPV), which may develop into cervical cancer, if not treated. Local treatment involves destroying or removing the abnormal area of the cervix, leaving most of the cervix, and the uterus in place maintaining the ability to become pregnant in the future, if desired. Certain types of local treatment may also be suitable for very early cervical cancer (stage IA1) if the tumour is very small and very unlikely to have spread beyond the cervix. There are many studies investigating whether the local treatment for CIN and early cervical cancer increases the risk of preterm birth (PTB) in subsequent pregnancies. However, there is no definite conclusion and this creates confusion for both the medical staff and women who may be recommended treatment, but also want to have children in the future.

The aim of the review

We aimed to assess whether the local conservative treatment techniques for cervical precancer (CIN) and early cervical cancer increased the risk of complications for mother and baby during pregnancy occurring after treatment, and especially whether treatment is associated with an increase in the risk of PTB. We also studied whether the risk of PTB increases with increasing amount of cervical tissue removed.

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Selection criteria

We included all studies that investigated the effect of treatment of CIN and early cervical cancer on late pregnancy outcomes (beyond 24 weeks of gestation) in women who had been treated previously for CIN and early cervical cancer, as compared to women who had not been treated. We excluded studies that had no untreated comparison group, reported pregnancy outcomes in women who had undergone treatment during pregnancy, or had a high-risk treated, comparison group or both.

What are the main findings?

We included 69 studies (6,357,823 pregnancies: 65,098 pregnancies of treated and 6,292,725 pregnancies of untreated women). Treatment was associated with an increased risk of PTB before 37 pregnancy weeks, as well as an increased risk of severe PTB (less than 32 to 34 pregnancy weeks), extreme PTB (less than 28 to 30 pregnancy weeks) and pPROM (premature preterm rupture of the membranes) as compared to untreated women. The risk of overall PTB was higher for women treated by excisional methods (where tissue is cut away) than by ablative treatments (where tissue is destroyed instead of being cut away). Multiple treatments, as well as increasing amounts of tissue removed at the time of treatment, were associated with an increased risk of overall PTB. However, women with CIN who were not treated also had a higher risk of overall PTB than the general population. Low birth weight (LBW) < 2500g), neonatal intensive care unit (NICU) admission and perinatal mortality rates were also found to be increased after treatment.

What is the quality of the evidence?

Due to the nature of the intervention and outcomes studied, we were only able to include observational studies, of which the majority were retrospective. These types of studies are of low quality with a high level of variability between the studies, therefore the level of evidence for most outcomes can only be considered to be of low or very low quality.

What are the conclusions?

Women with CIN have a higher baseline risk for PTB than the general population and the treatment for CIN probably increase this risk further. The risk for PTB is probably higher when excisional techniques are used than for ablative treatments. Also, the risk of PTB appears to increase with multiple treatments and increasing amounts of tissue removed. However, these results should be interpreted with caution due to the low and very low quality of the included studies.