Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis

CRD summary
This review concluded that excisional treatments for cervical intraepithelial neoplasia are associated with small risks of pregnancy-related morbidities. It is difficult to comment on the strength of the evidence since the quality of the included studies was not assessed and limited study details were reported. In addition, as some studies might have been missed, the reliability of the authors’ conclusions is also weakened.

Authors' objectives
To assess the effects of conservative methods to treat cervical intraepithelial neoplasia and microinvasive cervical cancer on subsequent fertility and pregnancy outcomes.

Searching
MEDLINE and EMBASE were searched from 1960 to 2004; the keywords were reported. Conference proceedings and the reference lists of identified articles were checked for additional publications. No language restrictions were applied.

Study selection

Controlled observational studies were eligible for inclusion; studies without an untreated control group were excluded.

Specific interventions included in the review
Studies that compared conservative treatments of cervical intraepithelial neoplasia or stage I A1 cervical cancer with an untreated control group were eligible for inclusion. Conservative methods included laser ablation, cold knife conisation, large loop excision of the transformation zone (LLETZ) and laser conisation. The characteristics of the patients in the included studies were not reported.

Participants included in the review
Studies of pregnant women who had undergone treatment prior to pregnancy were eligible for inclusion. Studies of treatment undertaken during pregnancy were excluded from the review.

Outcomes assessed in the review
Studies of obstetric outcomes that were reported separately for each treatment group were eligible for inclusion. The fertility outcomes included conception rates, number of pregnancies and time to conception. Pregnancy outcomes were defined as either maternal or foetal. The maternal outcomes included pre-term delivery (defined as less than 37 weeks), Caesarean section rates, precipitous labour (defined as less than 2 hours) and pre-term spontaneous rupture of membranes (pPROM). The foetal outcomes included low birth weight (defined as less than 2.5 kg), perinatal mortality and neonatal intensive care unit admission.

How were decisions on the relevance of primary studies made?
Two reviewers independently applied the inclusion and exclusion criteria. Any disagreements were resolved by consultation with a third reviewer.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Two reviewers independently extracted the data and a third reviewer was consulted in the event of any discrepancies. Data were extracted on the numbers of cases and controls for every outcome, and relative risks (RRs) with corresponding 95% confidence intervals (CIs) were calculated.

Methods of synthesis
How were the studies combined?
Pooled RRs with 95% CIs were calculated for every outcome using random-effects models. The presence of publication bias was assessed using funnel plots and the trim-and-fill method.

How were differences between studies investigated?
The studies were categorised by type of treatment and heterogeneity was formally assessed using the Cochran Q test. To assess the possibility of confounding by differences in the study populations, subgroup meta-analyses were performed on relevant studies with matching for at least three factors (age, parity and smoking), studies that applied self-matching, studies without matching or matching for less than three factors, and studies after the exclusion of those that had used self-matching. Further subgroup analyses of the dimensions and depth of the excised tissue and risk of pre-term delivery were also conducted.

Results of the review
Twenty-seven retrospective cohort studies, with at least 3,302 treated women and 30,597 untreated women, met the inclusion criteria.

LLETZ (10 studies).
LLETZ was associated with a significant increase in the risk of pre-term birth (RR 1.70, 95% CI: 1.24, 2.35), low birth weight (RR 1.82, 95% CI: 1.09, 3.06) and pPROM (RR 2.69, 95% CI: 1.62, 4.46) compared with no treatment. There were no statistically significant differences between treatment groups for any of the other outcomes and no statistical heterogeneity was identified for any of the outcomes of interest.

Cold knife conisation (10 studies).
Cold knife conisation was associated with a statistically significant increase in pre-term delivery (RR 2.59, 95% CI: 1.80, 3.72), low birth weight (RR 2.53, 95% CI: 1.19, 5.36) and Caesarean section (RR 3.17, 95% CI: 1.07, 9.40). Some heterogeneity was identified between the studies in terms of low birth weight outcomes (P=0.054) and Caesarean delivery outcomes (P=0.075). There were no statistically significant differences between the treatment groups for any of the other outcomes of interest.

Laser treatment.
There were no statistically significant differences between laser conisation (7 studies) compared with no treatment and laser ablation (4 studies) compared with no treatment for any of the outcomes of interest. Significant heterogeneity was identified between the laser conisation studies, which was attributed to one study.

In general, the subgroup meta-analyses did not significantly alter any of the results. The exception was LLETZ studies matching for age, parity and smoking, which showed a higher RR for pre-term delivery (RR 2.10, 95% CI: 1.34, 3.29) than unmatched studies (RR 1.17, 95% CI: 0.74, 1.86). There were limited data available on the excisional methods with respect to the dimensions of the tissue removed. However, data from 3 studies suggested that the risk of pre-term delivery was significantly increased if the depth of the LLETZ or laser conisation was greater than 10 mm: the RRs were 1.45 (95% CI: 0.55, 3.86) and 2.61 (95% CI: 1.28, 5.34) for cone depths of less than or greater than 10 mm, respectively. Four studies reported results relating fertility outcomes, none of which suggested any effect of conservative treatments on fertility. No evidence of publication bias was identified from the funnel plots. The trim-and-fill method suggested that the potential existence of 3 studies of LLETZ could alter the significance of pre-term delivery.
Authors' conclusions
Excisional treatment of cervical intraepithelial neoplasia is associated with a small but real risk of pregnancy-related morbidity.

CRD commentary
The review question was clear in terms of the interventions, outcomes and participants that were eligible for inclusion. The search for primary studies was likely to have been adequate for the avoidance of language bias, although some potential publication bias was identified. The methods used to select studies and extract the data were appropriate and reduced the threat of reviewer bias and error. The methodological quality of the included studies was not assessed. Brief details of the included studies were reported and some heterogeneity was identified, which makes it difficult to assess the appropriateness of the meta-analyses. It is difficult to comment on the strength of the evidence that underpins the authors' conclusions, as the quality of the included studies was not assessed and limited study details were reported.

Implications of the review for practice and research
Practice: The authors recommended caution in the treatment of young women with mild cervical abnormalities. Treatment should always be undertaken by experienced clinicians to achieve the best balance between maximum eradication rates and minimum deficit and disruption of cervical anatomy. Women should be warned of a small risk of pregnancy-related morbidity after excisional treatment for cervical intraepithelial neoplasia.

Research: The authors stated that a search for the specific aspects of excisional treatment that could predispose to pregnancy-related morbidity is required. Further research into the proportion of excised tissue and wound management could also be useful, as could further research into the pregnancy-related consequences of cryocautery and cold coagulation.

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