Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis


CRD summary
This review evaluated perinatal mortality, preterm delivery and low birth weight associated with previous treatment for precursors of cervical cancer. Cold knife conisation and probably laser conisation and radical diathermy were associated with increased risk of perinatal mortality and other serious outcomes. Due to methodological and reporting weaknesses these conclusions may not be reliable.

Authors' objectives
To evaluate the relative risk of perinatal mortality, severe preterm delivery and low birth weight associated with previous treatment for precursors of cervical cancer.

Searching
MEDLINE and EMBASE were searched between 1960 and November 2007 without language restrictions. Search terms were reported. References of retrieved articles and conference proceedings were also searched for relevant studies.

Study selection
Controlled studies of women treated for cervical intraepithelial neoplasia that provided data on subsequent severe obstetric or neonatal outcomes were eligible for inclusion. Severe obstetric or neonatal events were perinatal mortality, severe (<32/34 weeks gestation) and extreme (<28/30 weeks) preterm delivery and severe low birth weight (<2000g, <1500g and <1000g). Retrospective matched cohort, matched registry based cohort and population based cohort study designs and one prospective cohort study were included. The types of treatment eligible for inclusion and included were excisional procedures (cold knife conisation, large loop excision of the transformation zone and laser conisation) and ablative procedures (laser ablation, cryotherapy and diathermy).

Studies were selected independently by three reviewers and disagreements resolved by consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The total number of pregnant women that were treated and not treated for cervical intraepithelial neoplasia and the number of adverse obstetric or neonatal events was extracted or calculated. Authors were contacted to obtain data on outcomes by specific treatment if the information was not available in the report. Relative risks (RRs) were calculated for each adverse pregnancy outcome in the treated versus untreated groups.

The authors did not state how the data were extracted for the review or how many reviewers performed the data extraction.

Methods of synthesis
Studies were grouped by type of treatment (excisional or ablative), then specific treatment procedure. RRs and corresponding 95% confidence intervals (CIs) were pooled in a random effects meta-analysis, weighted by control group size according to the size of the corresponding treated groups for studies that contributed data for multiple procedures. To test for robustness several methods were used for pooling (fixed and random effects models, Poisson regression), weighting of the study estimates (Mantel-Haenszel, reciprocal of study variance) and continuity correction values. Studies with no events in treatment or control group were excluded. Statistical heterogeneity was investigated using Cochrane's Q test and the I² test. If significant heterogeneity was present for severe adverse pregnancy outcomes
the results were not pooled. Number needed to treat to harm (NNTH) was also calculated.

**Results of the review**

Twenty-one studies were included in the review (n=496,129); one prospective cohort study (n=213) and 20 retrospective cohort studies (n=495,916).

Statistically significant heterogeneity was found for the risk of perinatal mortality when all procedures were pooled (p=0.031), and in studies of laser conisation ($I^2=67\%$, p=0.082) which were not pooled. The same was noted for risk of extreme preterm delivery following large loop excision of the transformation zone (results not shown) which were not pooled.

All models and continuity corrections had similar pooled estimates.

Cold knife conisation was associated with a significantly increased risk of perinatal mortality (seven studies) RR 2.87 (95% CI: 1.42, 5.81), severe preterm delivery (gestation <32/34 weeks) RR 2.78 (95% CI: 1.72, 4.51, five studies), extreme preterm delivery (gestation <28/30 weeks) RR 5.33 (1.63, 17.40, four studies) and low birth weight <2000g RR 2.86 (95% CI: 1.37, 5.97, one study).

Laser conisation was described in one study. This was associated with a significantly increased risk of low birth weight <1500g RR 10 (95% CI: 1.19, 83.84) and <2000g RR 3.50 (95% CI: 1.06, 11.53). Ablation by radical diathermy (one study) was significantly associated with severe preterm delivery RR 2.54 (95% CI: 1.65, 3.89) and extreme preterm delivery RR 2.15 (95% CI: 1.11, 4.18) and low birth weight <1500g RR 2.53 (95% CI: 1.62, 3.95) and <2000g RR 2.04 (95% CI: 1.45, 2.87).

Serious adverse pregnancy outcomes were not significantly associated with large loop excision of the transformation zone or ablative treatment with cryotherapy or laser.

Previous treatment with cold knife conisation, laser conisation or diathermy was estimated to result in approximately one perinatal death in 70 pregnancies and large loop excision with two deaths in 1000 pregnancies.

After cold knife conisation and diathermy, the NNTH was often <60 for severe and extreme preterm delivery and low birth weight. After large loop excision, the NNTH was greater than 100 for delivery <32-34 weeks and birth weight <2000g; and for a birth weight <1500g, the NNTH was greater than 500.

**Authors' conclusions**

Cervical intraepithelial neoplasia treatments of cold knife conisation and probably laser conisation and radical diathermy are associated with an increased risk of perinatal mortality and other serious pregnancy outcomes. Large loop excision of the transformation zone cannot be considered free of adverse outcomes.

**CRD commentary**

The review question was clear with inclusion criteria for participants, intervention, study design and outcomes. Published and unpublished sources were searched in all languages, reducing the risk of publication and language bias. Studies were selected independently by multiple reviewers, reducing the risk of reviewer error and bias, however, it is not clear whether similar steps had been taken in the data extraction process. Statistical heterogeneity was assessed and the studies were not pooled if the differences were significant, which was appropriate. However, the authors did not report that they assessed methodological quality of the primary studies, therefore the reliability of the results of these studies and their synthesis cannot be determined. Few details of the participants were presented, so the clinical differences between primary studies could not be assessed. Also, the number of included studies was unclear as this differed between the text and tables. As there were a number of reporting and methodological weaknesses the authors' conclusions may not be reliable.

**Implications of the review for practice and research**

Practice: The authors stated that testing for human papillomavirus can help with the follow-up of women after treatment for cervical intraepithelial neoplasia. However, optimal triage and diagnostic procedures should be developed that select only those progressing cases that need aggressive treatment.
Research: The authors stated that further work is needed to discover whether there is a critical threshold in the amount of tissue excised or destroyed that determines obstetric morbidity and success of treatment in terms of recurrent cervical intraepithelial neoplasia or cancer.

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