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The risk of preterm birth after treatment for cervical pre-invasive and early invasive disease increases with increasing cone depth: a systematic review and meta-analysis.

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ABSTRACT

Objective: To assess the effect of treatment for CIN on obstetric outcomes and to correlate this to the cone depth and comparison group used.

Methods

Design**:** Systematic review and meta-analysis

Data Sources**:** CENTRAL, MEDLINE, EMBASE searched without language restriction from 1948 to December 2014.

Eligibility Criteria: Studies assessing obstetric outcomes in women with or without a previous local cervical treatment.

Data Extraction & Synthesis**:** Independent reviewers extracted the data and performed quality assessment using the Newcastle-Ottawa criteria. Studies were classified according to method and obstetric endpoint. Pooled risk ratios (RR) were calculated using a random-effect model and inverse variance. Inter-study heterogeneity was assessed with I^2 statistics.

Main outcome(s) and measure(s)**:** Obstetric outcomes; pre-term birth (spontaneous and threatened), premature rupture of the membranes, chorioamnionitis, mode of delivery, length of labour, induction of delivery, oxytocin use, haemorrhage, analgesia, cervical cerclage & cervical stenosis. Neonatal outcomes; birth weight, neonatal intensive care unit admission, stillbirth, APGAR scores and perinatal mortality.

Results: Sixty-nine studies were included (6338982 participants: 63591 treated-6275391 untreated). Treatment significantly increased the risk of overall (<37weeks)(10.8 v 5.5%, RR=1.71[1.52,1.92]), severe (<34/32weeks)(3.5 v 1.4%, RR=2.45[1.96,3.06]) and extreme prematurity (<30/28weeks)(1.0 v 0.3%, RR=2.64[1.81,3.86]). The magnitude of the effect was higher for radical techniques (<37weeks: CKC (RR=2.11[1.24,3.57]), excision NOS (RR=2.13 [1.66,2.74]), LLETZ (RR=1.56[1.36,1.79]), ablation NOS (RR=1.46 [1.27,1.66]).

Repeat treatment multiplied the risk (13.2 v 4.1%, RR=3.78[2.65,5.39]). The risk increased with increasing cone depth (≤10/12mm: 7.1 v 3.4%, RR=1.54[1.09,2.18]; ≥10/12mm: 9.8 v 3.4%, RR=1.93[1.62,2.31]; ≥ 15/17mm: 10.1 v 3.4%, RR=2.77[1.95,3.93]; ≥20mm: 10.2 v 3.4%, RR=4.91[2.06,11.68]). The choice of 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/or pregnancies before treatment had higher risk of preterm birth (PTB) than the general population (5.9 v 5.6%, RR=1.27[1.16,1.39]). Spontaneous PTB, premature rupture of the membranes, chorioamnionitis, low birth weight, neonatal intensive care unit admission and perinatal mortality were also significantly increased after treatment.

Conclusions: Women with CIN have a higher baseline risk for prematurity. Excisional and ablative treatment 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.

INTRODUCTION

The introduction of systematic call and recall screening programmes in the UK over the past 20 years has resulted in a profound decrease in the incidence and mortality from invasive cervical cancer as pre-invasive lesions (cervical intra-epithelial neoplasia; CIN) can be detected by the national screening programme and treated appropriately [1]. In England alone in 2013–14, 3.6 million women aged between 25 and 64 years attended for cervical screening and over 23 800 cervical procedures were carried out[2].

The mean age of women undergoing treatment for preinvasive cervical disease is similar to the age of women having their first child. Local cervical treatment has been correlated to an increased risk of preterm birth, perinatal morbidity and mortality in a subsequent pregnancy [3-8]. The underlying mechanism is unclear; hypotheses include immunomodulation relating to HPV infection affecting parturition pathways, and acquired 'mechanical weakness' secondary to loss of cervical tissue[9].

Since the first documentation of the reproductive risk associated with treatment almost a decade ago [3], more than 50 observational studies have been published confirming [10 11] or disputing these associations [12 13]; some of these reporting data from large population-based datasets. Individual attempts to synthetize parts of this rapidly evolving evidence base in small systematic reviews and meta-analyses reached contradictory conclusions [3-6 14-17] and initiated debates and confusion within the scientific community [4 14-17]. Whether these discrepancies were due to questionable quality of some of these reviews [14-16] or differences in the explored comparisons [6], the field is open to a comprehensive high quality synthesis of the existing evidence that will be highly informative to women, clinicians and policy makers.

Media publicity has heightened public awareness that treatment for cervical precancer is associated with an increased reproductive morbidity. There has been a substantial increase in enquiries from patients and clinicians on the risks associated with different treatment

techniques and cone depths[18 19], and as to how this risk may be managed and prevented. With a rapidly evolving evidence base and lack of a robust synthesis of the published literature, these questions are becoming increasingly difficult to answer.

The aim of this systematic review and meta-analysis is to explore the impact that treatment for cervical pre-invasive and early invasive disease has on obstetric outcomes and to explore how this risk may be modified by the cone depth and comparison group.

MATERIALS AND METHODS

Inclusion Criteria and Outcomes

We included all studies reporting on obstetric outcomes (more than 24 weeks of gestation) in women with a previous local cervical treatment for CIN or microinvasive cervical cancer as compared to women without treatment. Studies reporting on the outcomes following two or more treatment were also included. The interventions included any type of treatment, either excisional (cold knife conisation [CKC]; laser conisation (LC); needle excision of the transformation zone [NETZ], aka straight wire excision [SWETZ]; large loop excision of the transformation zone [LLETZ], aka loop electrosurgical excisional procedure [LEEP]) or ablative (laser ablation [LA]; radical diathermy [RD]; cold coagulation [CC]; cryotherapy [CT]). In studies that reported on the impact of several treatment techniques, we extracted data for each specific method, where possible. If the outcomes were not reported separately for each technique, we analysed the intervention under broader terms, i.e. excisional treatment not otherwise specified (NOS), ablative treatment NOS and treatment NOS.

Women were included irrespective of the grade of the lesion for both squamous and glandular intra-epithelial neoplasia. We excluded studies that did not include an untreated reference population, compared different treatment techniques without an untreated control, and compared outcomes for treatments performed during pregnancy.

Studies were included irrespective of the type of untreated reference population that could have been drawn from one of the following sources: a) External group from general population that was mostly matched or adjusted for confounders; b) Internal group with self-matching of the pregnancies for the same women before and after treatment; c) Internal group with the pre-treatment pregnancies of those women that also delivered before the treatment; d) Women attending colposcopy with or without CIN/biopsy but no treatment; e) Women with high-grade disease but no treatment (high-grade squamous intra-epithelial lesion [HSIL]).

We assessed obstetric outcomes of pregnancies progressing beyond 24 weeks of gestation. We examined both maternal and neonatal outcomes. The maternal outcomes included overall (<37 weeks of gestation), severe (<32/34 weeks) and extreme (<28/30 weeks) prematurity (preterm birth [PTB]); PTB in singleton and multiple pregnancies; spontaneous; PTB in nulliparous and parous women; PTB in single and repeat cones; PTB for different cone depths and volumes; PTB for different comparison groups; overall (<37 weeks of gestation), severe (<32/34 weeks) and extreme (<28/30 weeks) spontaneous prematurity (sPTB); threatened PTB; premature rupture of the membranes (pPROM); chorioamnionitis; mode of delivery (caesarean section, instrumental deliveries); depth of labour (precipitous, prolonged); induction of labour or oxytocin use; haemorrhage (antepartum, postpartum); analgesia (epidural, pethidine, NOS); cervical stenosis; cervical cerclage. The neonatal outcomes included: low birth weight (LBW) at <2500g, <2000g, <1500g and <1000g; neonatal intensive unit (NICU) admission; perinatal mortality; stillbirth; Apgar score.

Literature search, Data extraction and Risk of bias

We searched three electronic databases (CENTRAL, MEDLINE and EMBASE) and targeted reports published between 1948 and December 2014. We used keywords such as ‘cervical intraepithelial neoplasia (CIN)’, ‘cervical cancer’, ‘LLETZ or LEEP’, ‘conisation’, ‘excision’,

'pregnancy', 'obstetric', 'preterm birth', 'prematurity'. The full strategy is included in a supplementary file. In an attempt to identify any articles missed by the initial search or any unpublished data, we hand searched the references of the retrieved articles and meta-analyses and the proceedings of relevant conferences. There was no language restriction.

From each study, we extracted data on the study design and setting, the study population, the interventions examined, the comparison group, the quality of the data and risk of bias and the outcomes assessed. We retrieved from each study and outcome, the number of events in treated and untreated women. If required, authors were contacted to obtain additional data if the numbers provided in the published report did not allow sufficient precision in the data extraction.

We used the Newcastle-Ottawa score to formally assess the quality of non-randomised cohort studies[20], according to the MOOSE checklist[21]. This scoring system assesses the a) cohort selection, b) comparability and c) assessment of outcomes, to give a maximum score of 9 (highest quality).

Two investigators (MK, AA) independently performed the literature search, assessed the eligibility and quality of the retrieved papers and performed the data extraction. The two authors then compared the results and disagreements were resolved by discussion. If required, a consensus was reached with the involvement of a third investigator (MP) if necessary.

Data Synthesis and Assessment of heterogeneity

We calculated the risk ratio (RR) and 95% confidence intervals (95% CI) for each reported outcome in the treated versus untreated women for dichotomous outcomes using the Cochrane Revman 5 software. We used a random-effect model and inverse variance weighting for all meta-analyses [22]. In studies with multiple treatment groups, we proportionally divided the 'shared' comparison group into the number of treatment groups;

we treated comparisons between each treatment group and the split comparison group as independent comparisons. If a study presented data for more than one comparison group, the external comparison group of women with or without disease was used in preference to internal controls. If data were not of suitable quality for meta-analysis, we reported the results as a narrative in the text of the review.

We assessed inter-study heterogeneity with the Cochran Q test, by visual inspection of forest plots [23], by estimation of the percentage of heterogeneity between studies which cannot be ascribed to sampling variation (I^2 statistic) [24], and by a formal test of the significance for heterogeneity[25]. If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

We performed a series of subgroup analyses. We analysed the data separately for each treatment modality, in groups of ablative and excisional techniques, and as a whole irrespective of the type of method used. Given the non-randomised nature of the included studies, we assessed whether the choice of comparison group impacts on the risk estimate for each outcome and over-inflates the effect of treatment that could be partly attributed to other confounders. We therefore distinguished the different untreated comparison groups used across studies and performed subgroup analyses for the risk of PTB for each individual comparator (external; internal (self-matching); internal (pre-treatment pregnancies); colposcopy but no treatment; HSIL but no treatment).

Patient involvement

The research question and outcome measures were developed based on the concerns and priorities of patients seen in the colposcopy clinic and obstetric services. Patients were not involved in the design of the study, interpretation of results or writing of the article. The result will be disseminated to the lay audience through the authors' involvement with various charities and funding bodies.

RESULTS

We identified 381 potentially eligible studies; 69 [7 10-13 26-89] fulfilled the inclusion criteria of this review. No unpublished studies were identified. We excluded studies without an untreated reference population [90-113], studies that included women treated during pregnancy [114 115], studies assessing fertility and early pregnancy outcomes below 24 weeks of gestation [116-121], studies assessing outcomes post-treatment in high-risk populations [122] and studies assessing the impact of CIN on outcomes without information as to whether treatment was performed [123-125]. More details of the literature search and the reasons for exclusion are resented in in the PRISMA flowchart [126] (Figure 1).

The detailed characteristics of the included studies and the outcomes examined are shown in Table 1. The majority of the studies were retrospective with only four prospective reports [69 75 76 78 80]. All were cohort studies, apart from one case-control study by Castanon 2014 [83]. There were no randomised controlled studies. Fourteen studies examined the impact of CKC [11 26-28 30-32 35 58-60 80 85 87], 11 of LC [40 44-47 49 50 54 70 74 76], one of NETZ [11], 35 of LLETZ [11 37-39 42 43 48 53-58 60 61 63-67 70-72 74-76 78-81 84-86 88 89], eight of LA [33 36 37 45 47 52 54 60], one of RD [60], two of CT [29 58], 13 of Excision NOS [7 10 12 13 51 62 68 69 73 77 82 83 88], five of Ablation NOS [10 12 51 68 85], and three of Treatment NOS [34 41 76]. There were five types of untreated comparison groups. Some used an external comparator adjusting for known risk factors related to adverse obstetric sequelae [7 10-13 26 27 31 33-43 46 47 49-53 55-59 62-79 81 84 85 87], others compared to the pre-treatment pregnancies of the treated population (internal) [7 13 28-30 32 43-45 56 71 72 82 89], or used self-matching for women that delivered both before and after treatment (internal) [11 13 41 46 49 62 64], some compared to women that attended colposcopy with or without CIN and/or biopsy but no treatment [13 54 60 61 65 66 75 79 80 82 86 88 89], and some to women with high-grade disease but no treatment [11 51 68]. All studies that used an external comparison group either matched for known risk factors or performed a regression analysis to control for known confounders. Four studies [41 59 63 74] did not include any control for confounders.

The quality assessment for observational studies with the Newcastle-Ottawa score is included in Table 1 and is presented in more details in Supplementary table 1. The majority of the studies scored eight or nine points, ten [28 33 41 43-45 48 59 70 74] scored seven and two [36 63] scored six.

Preterm birth

The risk preterm birth was significantly increased after cervical treatment (Table 2; Figure 2). This was the case for prematurity overall at less than 37 weeks of gestation (57 studies, 5198352 women, 10.8 v 5.5%, RR=1.71 [1.52, 1.92]), for severe prematurity less than 34/32 weeks of gestation (24 studies, 3794833 women, 3.5 v 1.4%, RR=2.45 [1.96, 3.06]) and extreme prematurity less than 30/28 weeks of gestation (eight studies, 3906697 women, 1.0 v 0.3%, RR=2.64 [1.81, 3.86]). The magnitude of the effect of treatment was higher for more radical treatment techniques and for excision rather than ablation. More specifically, the risk of preterm birth at less than 37 weeks of gestation was higher for CKC (RR=2.11 [1.24, 3.57]), excision NOS (RR=2.13 [1.66, 2.74]), LLETZ (RR=1.56 [1.36, 1.79]), ablation NOS (RR=1.46 [1.27, 1.66]). Similar trends were noted for severe and extreme prematurity. Treatment also increased the risk of preterm birth for women with multiple pregnancies for some but not other treatments but the results were inconsistent due to the small number of studies. The impact of treatment was not different for nulliparous and multiparous women. The effect of multiple as opposed to single treatments on the risk of prematurity was substantially higher (repeat treatment: 11 studies, 1317284 women, 13.2 v 4.1%, RR=3.78 [2.65, 5.39]; single treatment: 17 studies, 1367023 women, 7.5 v 4.2%, RR=1.75 [1.49, 2.06]). The relative risk of preterm birth for two excisional treatments was as high as 5.48 [2.68, 11.24] and that of two loop excisions as high as 2.81 [2.33, 3.39].

The analysis of the risk of preterm birth at less than 37 weeks of gestation according to the cone dimensions demonstrated that the risk increases progressively with increasing cone

depth or volume (Table 3; Figure 3). The risk for treated versus untreated women was significantly increased for women with cone depth of less than 10/12mm (eight studies, 550929 women, 7.1 v 3.4%, RR=1.54 [1.09, 2.18] but the magnitude of effect increased with increasing cone depth (≥10/12mm: eight studies, 552711 women, 9.8 v 3.4%, RR=1.93 [1.62, 2.31]; ≥ 15/17mm: four studies, 544248 women, 10.1 v 3.4%, RR=2.77 [1.95, 3.93]; ≥ 20mm: three studies, 543750 women, 10.2 v 3.4%, RR=4.91 [2.06, 11.68]). The trend was similar with increasing cone volume (<6mm: one study, 550 women, 8.1 v 3.6%, RR=2.25 [1.09, 4.66]; >6cc: one study, 284 women, 50.0 v 3.6%, RR=13.9 [5.09, 37.98]).

The comparison of treated women for different cone depths revealed that deep excisions significantly increased the risk of preterm birth (<37 weeks) as opposed to less deep excisions and the magnitude of the effect increased in longer cones (≥10/12mm v ≤12/10mm: eight studies, 6633 women, 12.4 v 7.9%, RR=1.59 [1.28, 1.98]; ≥15/17mm v ≤ 17/15mm: four studies, 4275 women, 10.1 v 5.7%, RR=1.82 [1.47, 2.26]; ≥ 20mm v ≤20mm: four studies, 4011 women, 10.8 v 5.7%, RR=2.90 [1.52, 5.54])(Supplementary table 2; Figure 4). The findings were similar for the comparison of cone volumes (> 3/4cc v < 4/3cc: three studies, 591 women, 16.3 v 7.7%, RR=2.15 [1.03, 4.49]; >6cc v <6cc: two studies, 552 women, 27.1 v 8.1%, RR=4.01 [1.93, 8.33].

The impact that the choice of comparison group may have on the magnitude of effect was assessed by a subgroup analysis that classified different studies according to the comparator used (Table 4). The results suggested that treatment significantly increased the risk of preterm birth at less than 37 weeks of gestation irrespective of the comparison group used. The magnitude of effect was higher when an external comparison group was used (44 studies, 5177986 women, 10.6 v 5.4%, RR=1.96 [1.74, 2.21]), followed by internal comparators (self-matching: seven studies, 3132 women, 10.9 v 7.1%, RR=1.55 [1.2, 1.99]; pre-treatment pregnancies: 13 studies, 83086 women, 14.1 v 6.4%, RR=1.41 [0.98, 2.02]) and ultimately women with disease but no treatment (11 studies, 70061 women, 8.7 v 6.0%,

RR=1.25 [1.11, 1.4]). When women with disease but no treatment and the pregnancies of the same women before treatment were compared to the general population, the risk of preterm birth was significantly increased (16 studies, 4342190 women, 5.9 v 5.6%, RR=1.27 [1.16, 1.39]). These findings suggest that although women with CIN have higher risk of preterm birth than women without the disease, treatment significantly increases that risk further.

Other Maternal outcomes

Maternal outcomes other than preterm birth were assessed in several studies (Supplementary table 3) and many of these were found to be increased after cervical treatment. This increase was more frequent for excisional as opposed to ablative techniques and with increasing treatment radicality, although the number of studies assessing each individual treatment method was frequently small.

Cervical treatment increased the risk of spontaneous overall, severe and extreme preterm birth (<37 weeks: 14 studies, 1024731 women, 7.0 v 3.7%, RR=1.76 [1.47, 2.11]); <34/32 weeks: seven studies, 655675 women, 1.8 v 0.6%, RR=2.63 [1.91, 3.62]); <28 weeks: two studies, 626670 women, 0.6 v 0.2%, RR=3.18 [1.64, 6.16] and the admissions for threatened preterm birth (five studies, 903 women, 9.1 v 3.2%, RR=2.44 [1.37, 4.33]). The risk (<37 weeks) was higher for CKC (RR=3.53 [2.05, 6.05]) followed by excision NOS (RR=1.70 [1.17, 2.46]), LLETZ (RR=1.60 [1.22, 2.08]) and ablation NOS (RR=1.42 [1.2, 1.7]). NETZ and LA were only assessed in one study, respectively. There was substantial heterogeneity for the comparisons assessing outcomes at less than 32/34 and 28 weeks of gestation (P-value<0.05).

The risk of pPROM (<37 weeks: 21 studies, 477011 women, 6.1 v 3.4%, RR=2.36 [1.76, 3.17]) and chorioamnionitis (four studies, 29198 women, 3.5 v 1.1%, RR=3.43 [1.36, 8.64]) was also increased after treatment. The risk of pPROM was higher for CKC (RR=4.11 [2.05, 8.25])

followed by LLETZ (RR=2.15 [1.48, 3.12]). NETZ was only assessed in one study and LA did not significantly affect the risk but was only assessed in two studies.

The mode of delivery (caesarean section or instrumental delivery), the length of labour (precipitous or prolonged), the use of analgesia (epidural, pethidine or other), the rate of induction of labour (with or without oxytocin), cervical stenosis or haemorrhage (antenatal or postpartum) was not affected by treatment. As expected, the rate of cervical cerclage insertion was higher for treated as opposed to non-treated women (eight studies, 141300 women, 4.0 v 0.7%, RR=14.29 [2.85, 71.65] and more so for CKC (RR=31.42 [2.32, 426.2]), LLETZ (RR=11.0 [0.64, 190]) or excisional treatment not otherwise specified (RR=42.45 [28.99, 62.16]).

Neonatal outcomes

More than 30 studies assessed one or more neonatal outcomes (Supplementary table 4). Cervical treatment (excisional or ablative) was associated with a significant increase in adverse neonatal outcomes as opposed to women having no treatment (comparison group not specified). The association with adverse neonatal events was stronger and more frequent for excisional as opposed to ablative techniques and with increasing treatment radicality, although the number of studies for each individual treatment technique was often limited.

More specifically, cervical treatment overall increased the risk of low birth weight (less than 2500g: 30 studies, 1348206 women, 7.9 v 3.7%, RR=1.81 [1.58, 2.07); less than 1500g: five studies, 76836 women, 2.0 v 0.5%, RR=3.00 [1.54, 5.85]), neonatal intensive unit admission (eight studies, 2533 women, 12.6 v 9.1%, RR=1.44 [1.14, 1.82]) and perinatal mortality (23 studies, 1659183 women, 0.9 v 0.7%, RR=1.55 [1.15, 2.08]). There was significant interstudy heterogeneity for perinatal mortality (P-value=0.03, I^2=38%).

The rate of neonates born with birth weight of less than 2500g was significantly higher for women treated with CKC (five studies, 1348206, RR=2.51 [1.78, 3.53]), LLETZ (12 studies, 3357, RR=2.11 [1.51, 2.94]), excisional (ten studies, 823648, RR=2.01 [1.62, 2.49]) or ablative (four studies, 483402, RR=1.36 [1.19, 1.55]) treatment not otherwise specified but not so for laser ablation (RR=1.07 [0.59, 1.92]), although only four studies with a total of 1104 participants assessed that comparison. The rate of NICU admission was only assessed for excisional techniques and was significantly increased after LLETZ (five studies, 1994 women, RR=1.42 [1.01, 1.99]). Perinatal mortality was significantly increased overall and for excisional technique not otherwise specified (five studies, 820028, RR=1.85 [1.02, 3.36]) but not for the individual techniques possibly due to the limited number of studies and the low prevalence of the outcome. Subgroup analysis according to the different comparison groups or cone depths was not possible due to the limited number of studies assessing each outcome.

DISCUSSION

Main findings

The knowledge that local treatment for cervical precancer, particularly excisional, increases the risk of preterm birth has led to major changes in clinical practice. With a rapidly evolving evidence base and inconsistencies in the published literature [12 13 15 16 64 109], a high quality synthesis of the evidence should be available for effective patient counselling at colposcopy and antenatal clinics.

This meta-analysis documents that any local cervical treatment for cervical pre-invasive or early invasive disease increases the risk of preterm birth and adverse sequelae in a subsequent pregnancy. Cervical treatment was found to be associated with an increased risk of overall, severe and extreme prematurity, spontaneous preterm birth, threatened preterm

labour, pPROM, chorioamnionitis, low birth weight, neonatal admission and perinatal death. As expected the rate of cervical cerclage was substantially increased in treated women as opposed to untreated controls. Treatment equally affected outcomes for nulliparous as well as parous, singleton and multiple pregnancies. The mode of delivery, length of labour, the induction rate, the use of analgesia, the rate of stenosis and haemorrhage were not significantly affected.

The magnitude of the effect of treatment was higher for more radical techniques (ie. CKC followed by LLETZ and LA) and for excision rather than ablation. Multiple conisations increased four-fold the risk of preterm birth as compared to untreated controls overall. Subgroup analyses clearly demonstrated that the risk of preterm birth directly correlates to the cone dimensions (depth/volume) and progressively increases with increasing cone depth ('dose-effect'). Although the risk was increased even for excisions measuring less than 10mm in depth, this was almost two-fold higher for excisions of more than 10mm, three-fold higher for more than 15/17mm and almost five-fold higher for excisions exceeding 20mm in depth.

It has been previously suggested that the impact of treatment on the risk of preterm birth may not be a consequence of treatment but rather a product of other confounders present in women with cervical disease [9 12 13]. Our subgroup analyses that stratified the risk to the comparator used, clearly documents that although the risk of preterm birth is significantly increased after treatment irrespective of the comparison group used, the choice of comparator may over-inflate or under-estimate the effect from treatment. The magnitude of effect was higher when external controls were used, followed by internal control, followed by women that had disease but were not treated. The analyses in women with HSIL but no treatment only included three studies and 3764 participants; we were unable to draw any firm conclusions from this comparison.

Our results also confirm that although women with CIN have a higher baseline risk of prematurity as compared to the general population, cervical treatment and particularly long cones further increase that risk.

Strengths and limitations

This is the first systematic review to demonstrate that any local cervical treatment technique (excisional or destructive) is associated with an increased risk of preterm birth and adverse obstetric sequelae and to document that the risk directly correlates to the cone depth (and volume), the treatment technique (excision more than ablation) and radicality. This meta-analysis included a large number of studies (69 cohorts) with sufficient sample size and power to explore several comparisons of treatment techniques and cone depths. Furthermore, we were able to perform subgroup analyses according to the comparator used and quantify the risk in different clinical groups.

However, the results should be interpreted with caution. Due to the pre-malignant nature of the disease, no randomised studies could be identified. All the included studies were cohorts, in the vast majority retrospective. Such reports are at known risk of recall bias and inadequate adjustment for known and unknown confounders, while some of the outcomes of interest were difficult to objectively measure. Many of the studies relied on data collected from structured interviews and mailed questionnaires and in some of these the response rate was small, increasing also the risk of incomplete outcome data (attrition) and misclassification bias. The studies often had different designs and used comparisons between and amongst women and mixed matching. Although the overall number of studies was large, for some outcomes and comparisons the numbers of studies was small and the analyses did not have sufficient sample sizes to support definite conclusions.

Although the inter-study heterogeneity was not significant for the majority of the analyses, some subgroup analyses did demonstrate variation in the outcomes across studies. This was often in analyses that included small number of studies and participants.

Interpretation in light of other evidence

The knowledge that local treatment for cervical precancer, particularly excisional, increases the risk of preterm birth has led to major changes in clinical practice. With an increasing evidence base suggesting that this risk is higher for more radical techniques, there has been a tendency to use less aggressive treatments. Although it was previously thought that the various techniques had comparable efficacy [127], evidence from a population-based study raised concerns that less radical treatment may increase the risk of post-treatment invasion [128 129]. Additionally, since the first documentation of the reproductive risk associated with treatment almost a decade ago [3], subsequent observational studies and even meta-analyses reached contradictory conclusions [3-6 14-17] and initiated debates within the scientific community. With some authors raising concerns that the progressive reduction in the radicality of treatment has led to increased risk of future of invasion [128 129], and others advocating the move to less radical techniques like laser ablation for the prevention treatment-associated future perinatal morbidity and mortality [130], high quality synthesis of the evidence had become an urgent unmet need.

Preterm birth is a major cause of neonatal death and disability and represents an enormous cost to the health services and the society. While pregnant, these women make up a large proportion of preterm clinics referrals. These referrals have increased from almost none in 1999, to more than 40% in 2012 [131]. Ultrasound-directed surveillance is labour intensive, costly, and may be associated with maternal anxiety, more so because 85% of women post-excision are effectively low risk and will deliver at term [3 6].

With increasing accummulating evidence, there was a clear need to quantify the comparative obstetric morbidity for different treatment techniques and cone depths and assist clinicians decision making and counselling in different clinical groups. With this study findings, patients, clinicians and policy makers will be able to balance the quantified increase in reproductive morbidity with increasing treatment radicality. This study further allows the identification of women at high risk of preterm birth that would benefit from referral and intensive surveillance antenatally and will minimize the unnecessary interventions for those at low risk.

Conclusion

Women with CIN have a higher baseline risk of preterm birth as compared to women from the general population. Local cervical treatment for pre-invasive or early invasive disease further increases the risk more so for excisional but also for ablative techniques. The risk of preterm birth increases with increasing cone depth (and volume) and techniques that remove or destroy larger parts of the cervix.

When deciding to treat young women, every effort should be made to perform a local treatment that will optimise the chances of a healthy pregnancy without compromising the completeness of the local treatment. Quality assurance in treatment of disease should include audit of dimensions of excisional specimens and persistent disease rates to ensure that treatment depth is kept to acceptable parameters.

Future research should investigate if women who have pre-invasive cervical disease are both susceptible to the disease and preterm birth, or whether HPV induced disease alone is the principal factor in increasing premature delivery. It is likely that a combination of immunological and epigenetic factors play a role.

What this study adds

What is already known on this subject

• Local cervical treatment has been correlated to an increased risk of preterm birth, perinatal morbidity and mortality in a subsequent pregnancy which may be associated with depth of excision.

• Discrepancies exist regarding the data regarding the impact of treatment on the risk of subsequent PTB, and whether CIN acts as a confounder, which may be due to the heterogeneity in comparison groups used in previous studies or on how different excision depths and/or treatment techniques are analysed.

What this study adds

• Increased risk of adverse obstetric outcomes correlates directly to the the treatment technique (excision more than ablation) and radically, determined by the depth and dimensions of the cone.

• Choice of comparison group may over-inflate or under-estimate the effect from treatment, due to the background increased risk of PTB in women with CIN. However, the increased risk of PTB remains to be significantly increased after treatment, in spite of the chosen comparator.

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The lead author MK (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: no additional data available.

the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above."

Figure legends

Figure 1: PRISMA flowchart

Figure 2: Meta-analysis on preterm birth (<37weeks) in treated versus untreated women

Figure 3: Meta-analysis on preterm birth (<37 weeks) in treated versus untreated women according to the cone depth a) ≤10/12mm; b) ≥10/12mm; c) ≥15/17mm d) ≥20mm

Figure 4: Meta-analysis on preterm birth (<37 weeks) in women treated with a cone depth a) ≥10/12mm versus ≤10/12mm; b) ≥15/17mm versus ≤17/15mm; c) ≥20mm versus ≤20mm

Table 1: Characteristics of included studies assessing obstetric outcomes for treated versus untreated women

Study (Country)	Study Design	Comparison Group	Procedure	Treated*	Untreated*	Source of data	Outcomes	Newcastle-Ottawa score
Jones 1979 (UK)	Retrospective cohort (population-based)	External: matching for age, parity, social class, delivery date, singleton birth	CKC	66	264	Clinical records from Cardiff Cervical Cytology Study - Cardiff Birth Survey (registry)	PTB (<37w); PTB (<37w)(singleton); sPTB (<37w); CS; ID; PrecL (<2h); ProlL (>12h); LBW (<2500g); PM; SB	9
Weber 1979 (Denmark)	Retrospective cohort (hospital-based)	External: matching for age	CKC	48	48	Hospital records; structured interviews	LBW (<2500g)	8
Buller 1982 (USA)	Retrospective cohort (hospital-based)	Internal (pre-treatment pregnancies)	CKC	47	79	Hospital records	PTB (<37w); tPTL; CS	7
Hemmings-son 1982 (Sweden)	Retrospective cohort (hospital-based)	Internal (pre-treatment pregnancies)	CT	115	65	Hospital records	PTB (<36w); pPROM; CS; stenosis; PM	8
Larsson 1982 (Sweden)	Retrospective cohort (population-based)	Internal (pre-treatment pregnancies) matching for age, parity, socioeconomic status, smoking, treatment, diseases	CKC	197	284	South Swedish Regional Tumour Registry, hospital records	PTB (<37w); PTB (<37w)(singleton); PTB (<37w)(multiple); PM; SB	9

Ludviksson 1982 (Sweden)	Retrospective cohort (hospital-based)	External: matching for age, parity, time of delivery	CKC	83	79	Hospital records	PTB (≤37w); PTB (≤33w); PTB (<30w); PPH; MOH	8
Moinian 1982 (Sweden)	Retrospective cohort (hospital-based)	Internal (pre-treatment pregnancies)	CKC	103	720	Hospital records	PTB (<37w); cerclage	8
Anderson 1984 (UK)	Retrospective cohort (hospital-based)	External: matching for age, race, births, miscarriages/TOPs	LA	68	70	Hospital records; postal questionnaires; obstetricians	PTB (<37w); PTB (<37w)(single); CS; ID; ProlL (>12h); LBW (<2500g)	7
Kristensen 1985 (Denmark)	Retrospective cohort (population-based)	External: matching for age, parity	Treatment NOS	85	12792	Hospital records; questionnaires	PTB (<37w); PTB (<37w)(singleton); LBW (<2500g)	9
Kuoppala 1986 (Finland)	Retrospective cohort (hospital-based)	External: matching for age, parity, date of delivery, singleton birth	CKC	62	62	Hospital records	PTB (<37w); CS; ID; IoL; oxytocin; analgesia; cerclage; PM; SB	9
Saunders 1986 (UK)	Retrospective cohort (hospital-based)	External: matching for age, parity, race, year of delivery, singleton pregnancy	LA	97	97	Hospital records; general practitioners	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); pPROM; CS; ID; LBW (<2500g); PM	6
Gunasekera	Retrospective cohort (hospital-	External: matching for age, parity, race,	LLETZ; LA	140 (LLLETZ=23	140 (LLLETZ=23;	Hospital records	PTB (<37w); CS; ID;	9

1992 (UK)	based)	duration of pregnancy, smoking		; LA=117)	LA=117)		ProlL(>12h)	
Blomfield 1993 (UK)	Retrospective cohort (hospital-based)	External: matching for age, parity, ethnic group	LLETZ	40	80	Hospital records	PTB (<37w); sPTB (<37w); CS; ID; IoL; oxytocin; epidural; LBW (<2500g); NICU; PM	9
Haffenden 1993 (UK)	Retrospective cohort (hospital-based)	External: matching for age, parity	LLETZ	152	152	Hospital records	PTB (<37w); CS; ID; PrecL (<2h); ProlL (>12h); IoL; oxytocin; epidural; LBW (<2500g)	9
Hagen 1993 (Norway)	Retrospective cohort (hospital-based)	External: matching for age, parity; regression for height, marital status, education, smoking, TOP - index pregnancy: hypertension, APH, mode of delivery	LC	56	112	Hospital records	PTB (≤37w); PTB (≤37w)(nulliparous); PTB (≤37w)(parous); PTB (≤37w)(singleton); CS; ID; APH	9
Kristensen 1993 (Denmark)	Retrospective cohort (population-based)	A) External: no matching, no regression B) Internal (self-matching)	Treatment NOS (CKC, laser, electrocaute-ry)	A) 130 B) 62	A) 28124 B) 62	Medical Birth Register; national Register of Hospital Discharges	PTB (<37w); PTB (<37w)(nulliparous); PTB (<37w)(parous); PTB (<37w)(singleton)	7
Braet 1994 (UK)	Retrospective cohort (hospital-based)	External: matching for age, parity, smoking	LLETZ	78	78	Hospital records	PTB (<37w); PTB (<37w)(singleton); pPROM; CS; ID;	9

							APH; LBW (<2500g); PM	
Cruickshank 1995 (UK)	Retrospective cohort (hospital-based)	A) External: age, parity, partner's social class, height, smoking B) Internal (pre-treatment pregnancies)	LLETZ	149	A) 298 B) 133	Aberdeen Maternity and Neonatal Databank; postal questionnaires	PTB (<37w); PTB (<28w); PTB (singleton)(<37w); CS; PrecL (<2h); SB	7
Sagot 1995 (France)	Retrospective cohort (hospital-based)	Internal (pre-treatment pregnancies)	LC	53	59	Hospital records	PTB (<37w); tPTL; pPROM; CS; chorioamnionitis; cerclage	7
Spitzer 1995 (Jamaica)	Retrospective cohort (hospital-based)	Internal (pre-treatment pregnancies) with matching for age, parity	LC; LA	163 (LC=34; LA=129)	112	Hospital/private practice records; questionnaires (by mail, phone or in person)	PTB (<37w)	7
Bekassy 1996 (Sweden)	Retrospective cohort (hospital-based)	A) External: matching for age, parity, time of delivery B) Internal (self-matching)	LC ('miniconisa-tion')	A) 250 B) 148	A) 250 B) 148	National Medical Birth Registry; hospital records	PTB (<37w); PTB (<37w)(nulliparous); PTB (<37w)(parous); PTB (<37w)(single); PTB (<37w)(repeat); CS; ID; ProlL (>12h); stenosis; LBW (<2500g); PM; SB	8
Forsmo 1996 (Norway)	Retrospective cohort	External: age, parity, place of delivery	LC; LA	71 (LC=51;	174	Hospital records, postal questionnaires	LBW (<2500g); LBW (<2000g); LBW (<1500g); PM; SB	8

	(hospital-based)			LA=20)				
Turlington 1996 (USA)	Retrospective cohort (hospital-based)	Biopsy but no treatment: regression for age	LLETZ	15	15	Hospital records; telephone interviews/mail-in questionnaires	SB	7
Raio 1997 (Switzeland)	Retrospective cohort (hospital-based)	A) External: matching for age, parity, marital status, social class, smoking, PTB B) Internal (self-matching)	LC	A) 64 B) 26	A) 64 B) 26	Hospital records	PTB (<37w); PTB (<37w)(singleton); PTB (<37w)(D<10mm); PTB (<37w)(D≥10mm); pPROM	9
Andersen 1999 (Denmark)	Retrospective cohort (hospital-based)	External: matching for age, parity	LC	75	150	Hospital records	PTB (≤37w); PTB (≤37w)(D<15mm); PTB (≤37w)(D=15-20mm); PTB (≤37w)(D>20mm); pPROM; CS; PM; SB	9
El-Bastawissi 1999 (USA)	Retrospective cohort (population-based)	A) External: matching for age, country B) HSIL but no treatment Both regression for parity, race, smoking, marital status, TOPs	Excision NOS (CKC, LC, LLETZ); Ablation NOS (LA, CT)	1096	A) 9201 B) 330	Cancer Surveillance System (a population-based cancer registry); Birth Certificates (from the Department of Health in Washington state)	PTB (<37w); PTB (<37w)(singleton); CS; LBW (<2500g)	9
van Rooijen 1999	Retrospective	External: matching for age, parity, year	LA	236	472	Hospital records	PTB (<37w); PTB (<37w)(single); CS;	9

(Sweden)	cohort (hospital-based)	of delivery					APH; LBW (<2500g); LBW (<2000g); LBW (<1500g); LBW (<1000g)	
Paraskevai-dis 2002 (Greece)	Retrospective cohort (hospital-based)	External: matching for age, parity, smoking, multiple pregnancies, PTBs	LLETZ (for microinva-sion)	28	28	Hospital records	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); sPTB; CS; PrecL (<2h); LBW (<2500g); NICU	9
Sadler 2004 (New Zealand)	Retrospective cohort (hospital-based)	Colposcopy but no treatment: regression for age, ethnicity, socioeconomic status, smoking, obstetric history, transfer to hospital, APH	LC; LLETZ; LA	652	426	Hospital records	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); PTB (<37w)(singleton); PTB (<37w)(D≤10mm); PTB (<37w)(D=11-16mm); PTB (<37w)(D≥17mm); PTB (<32w); sPTB (<37w); pPROM	9
Tan 2004 (UK)	Retrospective cohort (hospital-based)	External: matching for age, parity	LLETZ	119	119	Hospital records	PTB (<37w); CS; ID; ProlL (>12h); IoL; oxytocin; epidural; pethidine	8
Acharya 2005 (Norway)	Retrospective cohort (hospital-based)	A) External: matching for age, parity, date of delivery, smoking, obstetric history B) Internal (pre-	LLETZ	79	A) 158 B) 45	Hospital records	PTB (<37w); tPTL; chorioamnionitis; IoL; LBW (<2500g); PM	9

		treatment pregnancies)						
Samson 2005 (Canada)	Retrospective cohort (hospital-based)	External: matching for age, parity, smoking status, year of delivery	LLETZ	571	571	Registries	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); PTB (<37w)(singleton); PTB (<37w)(multiple); PTB (<34w); PTB (<34w)(multiple); pPROM; CS; IoL; oxytocin; LBW (<2500g); NICU; PM; SB	9
Crane 2006 (Canada)	Retrospective cohort (hospital-based)	External: regression for age, gestation at USS, parity, smoking, APH, sPTB	CKC; LLETZ; CT	132 (CKC=21; LLETZ=75; CT=36)	81	Hospital records	sPTB (<37w); sPTB (<37w)(singleton); sPTB (<34w); CS; IoL; APH; LBW (<2500g); NICU; PM; Apgar (<7)(5min)	8
Klaritsch 2006 (Austria)	Retrospective cohort (hospital-based)	External: no matching, no regression	CKC	76	29711	Hospital records	PTB(<37w); PTB (<37w)(single); PTB (<37w)(singleton); PTB(<34w); pPROM; CS; chorioamnionitis; LBW (<2500g); PM	7
Bruinsma 2007	Retrospective cohort (hospital-	A) Colposcopy before pregnancy but no	CKC; LLETZ; LA; RD	1951	A) 2294	Hospital records and registries	PTB (<37w); PTB (<37w)(singleton); PTB (<32w); PTB	9

(Australia)	based)	treatment B) Colposcopy during pregnancy but no treatment Both regression for age, drug use, marital status, medical conditions, TOPs, miscarriages, PTBs, treatment			B) 1303		(<28w); sPTB; pPROM; CS; ID; LBW (<2500g); PM; SB	
Himes 2007 (USA)	Retrospective cohort (hospital-based)	Biopsy but no treatment – no matching, regression	LLETZ	114	962	Hospital records	PTB (<37w); PTB (<37w)(singleton); sPTB; pPROM	8
Jakobsson 2007 (Finland)	Retrospective cohort (population-based)	External: regression for age, parity, smoking	Excision NOS (CKC, LC, LLETZ); Ablation NOS (LA, CT, electrocoa-gulation)	8422 (Excision NOS=4846; Ablation NOS=3576)	1056855	National registers	PTB (<37w); PTB (<28w); LBW (<2500g); PM	9
Sjoborg 2007 (Norway)	Retrospective cohort (population-based)	A) External: matching for age, parity, plurality B) Internal (self-matching) Both regression for smoking, marital	Excision NOS (LC, LLETZ)	A) 742 (LC=609; LLETZ=133) B) 419	A) 742 B) 419	Hospital records	PTB (<37w); PTB (<32w); PTB (<28w); pPROM; LBW (<2500g); LBW (<1500g); LBW (<1000g); PM	8

		status, education						
Albrechtsen 2008 (Norway)	Retrospective cohort (population-based)	A) External B) Internal (pre-treatment pregnancies) Both regression for age, birth order	Excision NOS (CKC, LC, LLETZ)	14882	A) 2155505 B) 56927	National registries	PTB (<37w); PTB (<33w); PTB (<28w)	9
Parikh 2008 (USA)	Retrospective cohort (hospital-based)	External: no matching, no regression	LLETZ	87	18042	Hospital records	PTB (≤34w)	6
Jakobsson 2009 (Finland)	Retrospective cohort (hospital-based)	A) External: no matching B) Internal (self-matching) Both regression for age, parity, or both	LLETZ	A) 624 B) 258	A) 554507 B) 258	National registers and hospital records	PTB (<37w)(nulliparous); PTB (<37w)(parous)	8
Noehr 2009 (singletons) (Denmark)	Retrospective cohort (population-based)	A) External B) Biopsy but no treatment Both regression for age, year of delivery, smoking, marital status	LLETZ; Ablation NOS	10207 (LLETZ=8180; Ablation NOS=2027)	A) 510841 B) 31630	National registries	sPTB (<37w); sPTB (<37w)(D≤12mm); sPTB (<37w)(D=13-15mm); sPTB (<37w)(D=16-19mm); sPTB (<37w)(D≥20mm); sPTB (<37w)(single); sPTB (<37w)(repeat); sPTB (<37w)(singleton);	9

							sPTB (<32w); sPTB (<28w)	
Noehr 2009 (twins) (Denmark)	Retrospective cohort (population-based)	External: regression for age, year of delivery, smoking, marital status, IVF	LLETZ	166	9702	National registries	sPTB (<37w)(multiple); sPTB (<32w)(multiple); sPTB (<28w)(multiple)	9
Shanbhag 2009 (UK)	Retrospective cohort (population-based)	A) External B) CIN3 but no treatment Both regression for age, smoking, socioeconomic status, year of delivery, birth weight, malpresentation, sPTB, pPROM	Excision NOS (CKC, LC, LLETZ); Ablation NOS (LA, CC, diathermy coagulation)	1388 (Excision NOS=1103; Ablation NOS=285)	A) 119216 B) 87	National registries	PTB (<37w); sPTB (<37w); pPROM; CS; LBW (<2500g); PM	8
Fischer 2010 (USA)	Prospective cohort study (hospital-based)	External: matching for age, race, vaginal deliveries, gestational age at USS	Excision NOS (CKC, LLETZ)	85 (CKC=48; LLETZ=68; both=2)	85	Hospital records	PTB (<37w); PTB (<37w)(singleton); PTB (<34w); CS; cerclage	8
Ortoft 2010 (Denmark)	Retrospective cohort (hospital-based)	A) External B) HSIL but no treatment Both regression for	CKC; NETZ; LLETZ	A/B) 746 [single cone=710 (CKC=67; NETZ=71;	A) 72899 B) 383 C) 170	National registries, hospital records, questionnaires	sPTB (<37w); sPTB (<37w)(single); sPTB (<37w)(repeat); sPTB (<37w)(singleton);	9

		age, parity, smoking, education, marital status C) Internal (self-matching)		LLETZ=572) repeat cones=36] C) 170			sPTB (<32w); sPTB (<28w); pPROM (<37w); pPROM (<32w); pPROM (<28w); LBW (<2500g); LBW (<2000g); LBW (<1500g); PM; PM (<37w); PM (<32w); PM (<28w)	
van de Vijner 2010 (Belgium)	Retrospective cohort (hospital-based)	External: matching for age, parity, year of delivery	LC; LLETZ	55 (LC=5; LLETZ=50)	55	Hospital records and questionnaires	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); PTB (<37w)(singleton); PTB (<37w)(multiple); PTB (<34w); tPTL; pPROM; CS; ID; IoL; oxytocin; LBW (<2500g); NICU; PM; SB	7
Werner 2010 (USA)	Retrospective cohort (hospital-based)	A) External B) Internal (pre-treatment pregnancies) Both regression for age, parity, race	LLETZ	551	A) 240348 B) 842	Hospital records	PTB (<37w); PTB (nulliparous)(<37w); PTB (singleton)(<37w); sPTB (<37w); pPROM; PM; SB	9
Andia 2011 (Spain)	Retrospective, cohort (population-	A) External B) Internal (pre-	LLETZ	189	A) 189	Hospital records and registries	PTB (<37w); PTB (<37w)(nulliparous); PTB (<37w)(parous);	9

	based)	treatment pregnancies) Both regression for age, parity, smoking			B) 189		PTB (<37w)(singleton); PTB (<35w); PTB (<32w); CS; LBW (<2500g); LBW (1500g)	
Armarnik 2011 (Israel)	Retrospective cohort (hospital-based)	External: regression for age, birth order, year of delivery, smoking, cervical cerclage	Excision NOS (CKC, LC, LLETZ, other)	53	104617	Hospital records	PTB (<34w); CS; epidural; cerclage; PM	9
Lima 2011 (Portugal)	Retrospective cohort (hospital-based)	External: no matching, no regression	LC; LLETZ	29 (LC= 11; LLETZ=18)	58	Hospital records	PTB (<37w); PTB (<37w)(D≤10mm); PTB (<37w)(D>10mm); CS; LBW (<2500g); Apgar (<7)(5min)	7
Castanon 2012 (& 2014) (UK)	Retrospective cohort (hospital-based)	A) External (general population) B) Biopsy no treatment C) Internal (pre-treatment pregnancies) D) Internal (self-matching)	Excision NOS (CKC, LC, LLETZ, other)	4776	A) 510660 B) 7263 C) 1173 D) 372	Hospital records and national registries	PTB (<37w); PTB (<37w)(D<10mm); PTB (<37w)(D≥10mm); PTB (<37w)(singleton); PTB (<33w)	8
Poon 2012 (UK)	Prospective cohort (hospital-	External: regression for parity, race, smoking, cervical	LLETZ	473	25772	Hospital records, private practice records,	sPTB (<37w); sPTB (<34w)	8

	based)	length, PTB, miscarriage, LLETZ				questionnaires		
Reilly 2012 (UK)	Retrospective cohort (population-based)	A) External negative smear B) Colposcopy +/- biopsy Both regression for age, social deprivation, smoking, time to conception, obstetric history	Excision NOS (CKC, LLETZ); Ablation NOS (LA, CC, CT)	2162 (single excision= 1546; single ablation=53; multiple=82)	A) 38983 B) 2534	National registries	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); PTB (<37w)(singleton); PTB (<32w); PTB (<28w); LBW (<2500g)	9
Simoens 2012 (Belgium)	Prospective cohort (hospital-based)	External: matching for hospital; regression for age, parity, ethnicity, smoking, education, HIV	LC; LLETZ; Treatment NOS [only Excision NOS (CKC, LC, LLETZ) or Excision + Ablation NOS (LA, CC, CT)]	97 [Excision=81 (CKC=8; LC=24; LLETZ=53; unknown=4); Ablation=8 (LA=6; CC=1; CT=1); both=8]	194	Hospital records; questionnaires and medical records	PTB (<37w); PTB (<37w)(D≤10mm); PTB (<37w)(D>10mm); PTB (<37w)(singleton); PTB (<32w); sPTB (<37w); sPTB (<32w); CS; LBW (<2500g)	9
Van Hentenryck 2012 (Belgium)	Retrospective cohort (hospital-based)	External: matching for age, parity, smoking, HIV	Excision NOS (CKC, LC, LLETZ)	106	212	Hospital records	PTB (<37w); PTB (<34w); tPTL; pPROM; chorioamnionitis; CS; ID; IoL; LBW (<2500g); NICU	9

Frega 2013 (Italy)	Prospective cohort (population-based)	External: matching for parity (nulliparous only), race (white only)	LLETZ	406	379	Hospital records	PTB (<37w); PTB (<37w)(nulliparous); PTB (<37w)(single); PTB (<37w)(singleton)	9
Frey 2013 (USA)	Retrospective cohort (hospital-based)	A) External with smear B) Biopsy but no treatment matching for age, year of treatment; regression for age, parity, race, diabetes, BMI, birth weight, CS	LLETZ	598	A) 588 B) 552	Hospital records and structured phone interviews	PTB (<37w); CS; IoL	8
Heinonen 2013 (Finland)	Retrospective cohort (population-based)	External: regression for age, socioeconomic status, marital status, urbanism, time to conception, PTB	LLETZ	7636	658179	National registers	PTB (<37w); PTB (<37w)(single); PTB (<37w)(repeat); PTB (<37w)(singleton)	9
Guo 2013 (China)	Prospective cohort (hospital-based)	Biopsy +/- CIN but no treatment: matching for smoking (non-smokers only)	CKC; LLETZ	84 (CKC=36; LLETZ=48)	68	Hospital records	PTB (<37w); PTB (<37w)(single); PTB (<34w); pPROM; CS; PrecL (<2h); ProlL (>12h); LBW (<2500g); Apgar (<7)(1min)	8
Wuntakal 2013 (UK)	Retrospective cohort (hospital-	A) Biopsy but no treatment	Excision NOS (CKC, LC,	261	A) 257	Hospital records	PTB (<37w)(single); PTB (<37w)(repeat);	9

	based)	B) Internal, (pre-treatment pregnancies) Both regression for parity, ethnicity, deprivation	LLETZ)		B) 181		pPROM; CS; ID; LBW (<2500g)	
Ciavattini 2014 (Italy)	Retrospective cohort (hospital-based)	External: matching for age, parity, BMI, smoking, hormonal contraception, PTB, cervical incompetence	LLETZ	7	21	Hospital records	sPTB (<36w)(multiple)	8
Ehsanipoor 2014 (USA)	Retrospective cohort (hospital-based)	External: regression for age, parity, race, PTB, smoking, drug use, chorionicity	CKC; LLETZ; Ablation NOS (LA, CT)	110 (CKC=10; LLETZ=36; Ablation NOS=64)	766	Hospital records	PTB (<37w)(multiple); PTB (<34w)(multiple); PTB (<28w)(multiple)	9
Kitson 2014 (UK)	Retrospective cohort (hospital-based)	Biopsy but no treatment: matching for age, parity, smoking	LLETZ	278	278	Hospital records	PTB (<37w); PTB (<37w)(singleton); PTB (<34w); sPTB; pPROM; CS; ID; LBW (<2500g); NICU	9
Sozen 2014 (Turkey)	Retrospective cohort (hospital-based)	External: matching for age, parity, obstetric history	CKC	15	24	Hospital records	PTB (<37w); pPROM; NICU	9
Martyn 2015 (Ireland)	Retrospective cohort (hospital-based)	Colposcopy but no treatment: matching for age	LLETZ; Excision NOS (CKC, repeat	297 (LLETZ=278; Excision	204	Hospital records and postal questionnaires	PTB (<37w); PTB (<37w)(single)	8

			LLETZ)	NOS=19)				
Stout 2015 (USA)	Retrospective cohort (hospital-based)	A) Cytology/biopsy but no treatment: matching for age, hospital, year B) Internal (pre-treatment pregnancies)	LLETZ	598	A) 1129 B) 598	Hospital records and structured phone interviews	sPTB (<37w); sPTB (<37w)(singleton); sPTB (<34w)	9

*Numbers refer to women or pregnancies

APH: antepartum haemorrhage; BMI: body mass index; CC: cold coagulation; CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; CS: caesarean section; CT: cryotherapy; D: depth; HSIL: high-grade squamous intraepithelial lesion; ID: instrumental deliveries (ventouse/forceps); IoL: induction of labour; LA: laser ablation; LBW: low birthweight; LC: laser conisation; LLETZ: large loop excision of the transformation zone; MOH: massive obstetric haemorrhage; NETZ: needle excision of the transformation zone; NICU: neonatal intensive care unit admission; NOS: not otherwise specified; PM: perinatal mortality; PPH: postpartum haemorrhage; pPROM: preterm premature rupture of membranes; PreL: precipitous labour; ProlL: prolonged labour; PTB: preterm birth; RD: radical diathermy; SB: stillbirth; sPTB: spontaneous preterm birth; (s)PTB (single): (spontaneous) preterm birth (single cone); (s)PTB (repeat): (spontaneous) preterm birth (repeat cones); (s)PTB (singleton): (spontaneous) preterm birth (singleton pregnancies); (s)PTB (multiple): (spontaneous) preterm birth (multiple pregnancies); TOP: termination of pregnancy; tPTL: threatened preterm labour; USS: ultrasound scan;

Table 2: Preterm birth for treated versus untreated women and also according to parity, number of fetuses and treatments*

Preterm birth outcome	Studies	Total N	Treated n/N (%)	Untreated n/N (%)	Effect Estimate RR (95% CI)	Heterogeneity - p value (I^2%)
PTB						
PTB (<37w)						
All Treatment types	57	5198352	6334/58867 (10.8)	280421/5139485 (5.5)	1.71 [1.52, 1.92]	0 (90)
CKC	12	39102	126/844 (14.9)	2321/38258 (6.1)	2.70 [2.14, 3.4]	0.62 (0)
LC	9	1464	96/672 (14.3)	58/792 (7.3)	2.11 [1.24, 3.57]	0.02 (56)
NETZ	1	7399	17/71 (23.9)	301/7328 (4.1)	5.83 [3.8, 8.95]	N/E (N/E)
LLETZ	26	1445228	1724/21318 (8.1)	66593/1423910 (4.7)	1.56 [1.36, 1.79]	0 (69)
LA	7	4710	168/1867 (9.0)	242/2843(8.5)	1.04 [0.86, 1.26]	0.48 (0)
CT	2	238	4/151 (2.6)	2/87 (2.3)	1.02 [0.22, 4.77]	0.67 (0)
RD	1	2150	109/760 (14.3)	123/1390 (8.8)	1.62 [1.27, 2.06]	N/E (N/E)
Excisional Treatment NOS	13	3088392	3632/26487 (13.7)	182009/3061905 (5.9)	2.13 [1.66, 2.74]	0 (95)
Ablative Treatment NOS	5	595272	430/6482 (6.6)	26804/588790 (4.6)	1.46 [1.27, 1.66]	0.22 (30)
Treatment NOS	2	14397	28/215 (13.0)	1968/14182 (13.9)	0.54 [0.05, 5.53]	0 (97)
PTB (<34/32w)						
All Treatment types	24	3794833	1367/39386 (3.5)	53828/3755447 (1.4)	2.45 [1.96, 3.06]	0 (82)
CKC	5	36979	15/283 (5.3)	920/36696 (2.5)	3.07 [1.72, 5.49]	0.65 (0)
NETZ	1	7399	5/71 (7.0)	49/7328 (0.7)	10.53 [4.33, 25.65)	N/E (N/E)
LLETZ	11	791554	237/11569 (2.0)	9504/779985 (1.2)	2.13 [1.66, 2.75]	0.08 (40)
CT	1	58	1/36 (2.8)	0/22 (0.0)	1.86 [0.08, 43.87]	N/E (N/E)
Excisional Treatment NOS	9	2831594	992/22301 (4.4)	42591/2809293 (1.5)	3.40 [2.12, 5.43]	0 (91)
Ablative Treatment NOS	2	120762	26/2549 (1.0)	686/118213 (0.6)	1.59 [1.08, 2.35]	0.92 (0)
Treatment NOS	2	6487	91/2577 (3.5)	78/3910 (2.0)	1.65 [1.13, 2.42]	0.25 (24)
PTB (<30/28w)						

All Treatment types	8	3906697	374/37229 (1.0)	12857/3869468 (0.3)	2.64 [1.81, 3.86]	0 (81)
CKC	2	7118	2/150 (1.3)	19/6968 (0.3)	4.52 [0.83, 24.54]	0.74 (0)
NETZ	1	7399	3/71 (4.2)	21/7328 (0.3)	14.74 [4.5, 48.32]	N/E (N/E)
LLETZ	3	502778	59/8899 (0.7)	1224/493879 (0.2)	2.57 [1.97, 3.35]	0.9 (0)
Excisional Treatment NOS	4	2821185	287/21984 (1.3)	9854/2799201 (0.4)	2.90 [1.52, 5.52]	0 (88)
Ablative Treatment NOS	3	568217	23/6125 (0.4)	1739/562092 (0.3)	1.38 [0.81, 2.36]	0.21 (35)
Singleton/Multiple pregnancies						
PTB (<37w) & Singleton pregnancies						
All Treatment types	30	2170822	2777/31839 (8.7)	109868/2138983 (5.1)	1.80 [1.59, 2.03]	0 (78)
CKC	6	37759	83/495 (16.8)	2286/37264 (6.1)	2.89 [2.22, 3.77]	0.62 (0)
LC	4	545	52/249 (20.9)	24/296 (8.1)	2.54 [1.24, 5.2]	0.08 (55)
NETZ	1	7399	17/71 (23.9)	301/7328 (4.1)	5.83 [3.8, 8.95]	N/E (N/E)
LLETZ	18	1444175	1660/20812 (8.0)	66533/1423363 (4.7)	1.61 [1.39, 1.87]	0 (76)
LA	3	3420	129/1325 (9.7)	188/2095 (9.0)	1.10 [0.75, 1.62]	0.18 (42)
CT	1	58	1/36 (2.8)	0/22 (0.0)	1.86 [0.08, 43.87]	N/E (N/E)
RD	1	2150	109/760 (14.3)	123/1390 (8.8)	1.62 [1.27, 2.06]	N/E (N/E)
Excisional Treatment NOS	5	524094	599/5777 (10.4)	34775/518317 (6.7)	1.68 [1.08, 2.62]	0.03 (63)
Ablative Treatment NOS	2	110091	99/2099 (4.7)	3670/107992 (3.4)	1.14 [0.56, 2.32]	0.2 (40)
Treatment NOS	2	41131	28/215 (13.0)	1968/40916 (4.8)	2.57 [1.39, 4.77]	0.1 (64)
PTB (<37w) & Multiple pregnancies						
All Treatment types	6	10825	138/299 (46.2)	3585/10526 (34.1)	1.13 [0.95, 1.34]	0.25 (23)
CKC	2	84	5/13 (38.5)	37/71 (52.1)	0.95 [0.49, 1.83]	1 (0)
LLETZ	4	10227	98/219 (44.7)	3308/10008 (33.1)	1.26 [1.08, 1.46]	0.44 (0)
Excisional Treatment NOS	1	4	3/3 (100.0)	0/1 (0.0)	3.5 [0.31, 39.71]	N/E (N/E)
Ablative Treatment NOS	1	510	32/64 (50.0)	240/446 (53.8)	0.93 [0.72, 1.2]	N/E (N/E)
PTB (<34/32w) & Multiple pregnancies						
All Treatment types	3	10789	38/286 (13.3)	715/10503 (6.8)	1.68 [0.95, 2.98]	0.08 (52)
CKC	1	80	4/10 (40.0)	8/70 (11.4)	3.5 [1.29, 9.52]	N/E (N/E)

LLETZ	3	10199	28/212 (13.2)	658/9987 (6.6)	1.76 [0.88, 3.5]	0.21 (36)
Ablative Treatment NOS	1	510	6/64 (9.4)	49/446 (11.0)	0.85 [0.38, 1.91]	N/E (N/E)
PTB (<28w) & Multiple pregnancies						
All Treatment types	2	10744	12/276 (4.3)	237/10468 (2.3)	2.43 [1.4, 4.22]	0.88 (0)
CKC	1	80	0/10 (0.0)	1/70 (1.4)	2.15 [0.09, 49.56]	N/E (N/E)
LLETZ	2	10154	10/202 (5.0)	230/9952 (2.3)	2.45 [1.34, 4.47]	0.42 (0)
Ablative Treatment NOS	1	510	2/64 (3.1)	6/446 (1.3)	2.32 [0.48, 11.26]	N/E (N/E)
Parity						
PTB (<37w) & Nulliparous						
All Treatment types	6	245707	111/1080 (10.3)	11325/244627 (4.6)	1.92 [1.23, 2.98]	0.01 (67)
LC	2	267	19/123 (15.4)	12/144 (8.3)	2.18 [1.09, 4.37]	0.3 (7.52)
LLETZ	3	231344	86/923 (9.3)	10611/230421 (4.6)	1.51 [0.76, 3.02]	0 (83)
Treatment NOS	1	14096	6/34 (17.6)	702/14062 (5.0)	3.53 [1.7, 7.33]	N/E (N/E)
PTB (<37w) & Multiparous						
All Treatment types	5	339507	69/573 (12.0)	15532/338934 (4.6)	2.05 [0.95, 4.43]	0 (83)
LC	2	401	22/183 (12.0)	15/218 (6.9)	2.82 [0.16, 49.84]	0 (91.76)
LLETZ	2	324948	34/294 (11.6)	15006/324654 (4.6)	1.20 [0.22, 6.65]	0.01 (86)
Treatment NOS	1	14158	13/96 (13.5)	511/14062 (3.6)	3.73 [2.23, 6.22]	N/E (N/E)
Number of treatments						
PTB (<37w) & Single treatment						
All Treatment types	17	1367023	1519/20302 (7.5)	56185/1346721 (4.2)	1.75 [1.49, 2.06]	0 (79)
CKC	3	36783	38/179 (21.2)	2250/36604 (6.1)	2.89 [2.08, 4.03]	0.42 (0)
LC	2	657	34/335 (10.1)	29/322 (9.0)	1.06 [0.54, 2.09]	0.17 (48)
NETZ	1	7399	17/71 (23.9)	301/7328 (4.1)	5.83 [3.8, 8.95]	N/E (N/E)
LLETZ	9	1277874	1139/16755 (6.8)	51075/1261119 (4.0)	1.74 [1.45, 2.1]	0 (75)
LA	4	1421	58/624 (9.3)	68/797 (8.5)	1.07 [0.66, 1.74]	0.17 (40)
Excisional Treatment NOS	3	32106	197/1816 (10.8)	1840/30290 (6.1)	1.88 [1.2, 2.93]	0.1 (57)
Ablative Treatment NOS	1	10783	36/522 (6.9)	622/10261 (6.1)	1.14 [0.82, 1.57]	N/E (N/E)

PTB (<37w) & Repeat treatment						
All Treatment types	11	1317284	191/1442 (13.2)	54142/1315842 (4.1)	3.78 [2.65, 5.39]	0 (75)
CKC/LA	1	99	2/2 (100.0)	6/97 (6.2)	12.56 [5.11, 30.87]	N/E (N/E)
LC/LC	1	270	6/20 (30.0)	20/250 (8.0)	3.75 [1.7, 8.27]	N/E (N/E)
LLETZ/ LLETZ	4	1202174	139/1195 (11.6)	48586/1200979 (4.0)	2.81 [2.33, 3.39]	0.35 (9)
LLETZ/ Treatment NOS	1	298	9/41 (22.0)	6/257 (2.3)	9.40[3.53, 25.03]	N/E (N/E)
Excisional Treatment NOS/ Excisional Treatment NOS	3	73651	17/57 (29.8)	3034/73594 (4.1)	5.48 [2.68, 11.24]	0.16 (45)
Treatment NOS/ Treatment NOS	2	40792	18/127 (14.2)	2490/40665 (6.1)	1.71 [1.1, 2.67]	0.85 (0)

*If a study had more than one comparison groups, we used external groups (external general, external untreated women that had colposcopy+/-CIN+/-biopsy, women with HSIL but no treatment) in preference to internal comparators (self-matching or pre-treatment pregnancies).

CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; CT: cryotherapy; HSIL: high-grade squamous intraepithelial lesion; LA: laser ablation; LC: laser conisation; LLETZ: large loop excision of the transformation zone; N/E: not eligible; NETZ: needle excision of the transformation zone; NOS: not otherwise specified; PTB: preterm birth; RD: radical diathermy

Table 3: Preterm birth (<37 weeks) for treated women verses untreated women according to the cone dimensions (length/volume)

Treated Group	Studies	Total N	Treated n/N (%)	Untreated n/N (%)	Effect Estimate RR (95% CI)	Heterogeneity - p value (I^2%)
Cone Length						
Cone Length ≤ 10/12mm						
All Treatment types	8	550929	293/4105 (7.1)	18720/546824 (3.4)	1.54 [1.09, 2.18]	0 (67)
LC	1	105	1/41 (2.4)	3/64 (4.7)	0.52 [0.06, 4.83]	N/E (N/E)
LLETZ	3	544907	98/1600 (6.1)	18448/543307 (3.4)	2.01 [1.28, 3.15]	0.13 (51)
Excisional Treatment NOS	4	5917	194/2464 (7.9)	269/3453 (7.8)	1.20 [0.78, 1.85]	0.15 (44)
Cone Length ≥ 10/12mm						
All Treatment types	8	552711	571/5845 (9.8)	18723/546866 (3.4)	1.93 [1.62, 2.31]	0.13 (37)
LC	1	87	5/23 (21.7)	3/64 (4.7)	4.64 [1.2, 17.88]	N/E (N/E)
LLETZ	3	546134	193/2827 (6.8)	18448/543307 (3.4)	2.29 [1.57, 3.34]	0.2 (37.23)
Excisional Treatment NOS	4	6490	373/2995 (12.5)	272/3495 (7.8)	1.68 [1.41, 1.99]	0.37 (5.32)
Cone Length ≤ 15/17mm						
All Treatment types	4	545939	149/2614 (5.7)	18493/543325 (3.4)	1.36 [1.15, 1.61]	0.61 (0)
LC	1	164	0/14 (0.0)	7/150 (4.7)	0.67 [0.04, 11.18]	N/E (N/E)
LLETZ	2	545119	117/2370 (4.9)	18434/542749 (3.4)	1.42 [1.18, 1.7]	0.41 (0)
Excisional Treatment NOS	1	656	32/230 (13.9)	52/426 (12.2)	1.14 [0.76, 1.72]	N/E (N/E)
Cone Length ≥ 15/17mm						
All Treatment types	4	544986	167/1661 (10.1)	18493/543325 (3.4)	2.77 [1.95, 3.93]	0.1 (53)
LC	1	211	14/61 (23.0)	7/150 (4.7)	4.92 [2.09, 11.59]	N/E (N/E)
LLETZ	2	544248	128/1499 (8.5)	18434/542749 (3.4)	3.16 [1.54, 6.48]	0.08 (67)
Excisional Treatment NOS	1	527	25/101 (24.8)	52/426 (12.2)	2.03 [1.33, 3.1]	N/E (N/E)
Cone Length ≤ 20mm						

All Treatment types	3	545992	174/3093 (5.6)	18441/542899 (3.4)	1.60 [1.38, 1.87]	0.62 (0)
LC	1	183	2/33 (6.1)	7/150 (4.7)	1.30 [0.28, 5.97]	N/E (N/E)
LLETZ	2	545809	172/3060 (5.6)	18434/542749 (3.4)	1.61 [1.38, 1.87]	0.35 (0)
Cone Length ≥ 20mm						
All Treatment types	3	543750	87/851 (10.2)	18441/542899 (3.4)	4.91 [2.06, 11.68]	0.01 (77)
LC	1	192	12/42 (28.6)	7/150 (4.7)	6.12 [2.57, 14.57]	N/E (N/E)
LLETZ	2	543558	75/809 (9.3)	18434/542749 (3.4)	4.72 [1.25, 17.8]	0.01 (83)
Cone Length = 10/13-15/16mm						
All Treatment types	3	544534	75/1359 (5.5)	18486/543175 (3.4)	1.32 [1.04, 1.66]	0.82 (0)
LLETZ	2	543994	57/1245 (4.6)	18434/542749 (3.4)	1.32 [1.02, 1.72]	0.53 (0)
Excisional Treatment NOS	1	540	18/114 (15.8)	52/426 (12.2)	1.29 [0.79, 2.12]	N/E (N/E)
Cone Length = 15/16-19/20mm						
All Treatment types	3	543608	55/709 (7.8)	18441/542899 (3.4)	2.24 [1.73, 2.91]	0.42 (0)
LC	1	169	2/19 (10.5)	7/150 (4.7)	2.26 [0.5, 10.08]	N/E (N/E)
LLETZ	2	543439	53/690 (7.7)	18434/542749 (3.4)	2.53 [1.42, 4.51]	0.19 (43)
Cone Volume						
Cone Volume < 3cc						
All Treatment types (Volume<3cc)	1	496	16/218 (7.3)	10/278 (3.6)	2.04 [0.94, 4.41]	N/E (N/E)
LLETZ	1	496	16/218 (7.3)	10/278 (3.6)	2.04 [0.94, 4.41]	N/E (N/E)
Cone Volume > 3cc						
All Treatment types (Volume>3cc)	1	338	9/60 (15.0)	10/278 (3.6)	4.17 [1.77, 9.82]	N/E (N/E)
LLETZ	1	338	9/60 (15.0)	10/278 (3.6)	4.17 [1.77, 9.82]	N/E (N/E)
Cone Volume < 6cc						
All Treatment types	1	550	22/272 (8.1)	10/278 (3.6)	2.25 [1.09, 4.66]	N/E (N/E)
LLETZ	1	550	22/272 (8.1)	10/278 (3.6)	2.25 [1.09, 4.66]	N/E (N/E)
Cone Volume > 6cc						
All Treatment types	1	284	3/6 (50.0)	10/278 (3.6)	13.9 [5.09, 37.98)	N/E (N/E)
LLETZ	1	284	3/6 (50.0)	10/278 (3.6)	13.9 [5.09, 37.98]	N/E (N/E)

Cone Volume = 3-6cc						
All Treatment types	1	332	6/54 (11.1)	10/278 (3.6)	3.09 [1.17, 8.14]	N/E (N/E)
LLETZ	1	332	6/54 (11.1)	10/278 (3.6)	3.09 [1.17, 8.14]	N/E (N/E)

*If a study had more than one comparison groups, we used external groups (external general, external untreated women that had colposcopy+/-CIN+/-biopsy, women with HSIL but no treatment) in preference to internal comparators (self-matching or pre-treatment pregnancies).

CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; CT: cryotherapy; HSIL: high-grade squamous intraepithelial lesion; LA: laser ablation; LC: laser conisation; LLETZ: large loop excision of the transformation zone; N/E: not eligible; NETZ: needle excision of the transformation zone; NOS: not otherwise specified; PTB: preterm birth; RD: radical diathermy

Table 4: Preterm birth (<37 weeks) for treated and untreated women according to the comparison group.

Comparison Group 1	Comparison Group 2	Studies	Total N	Treated n/N (%)	Untreated n/N (%)	Effect Estimate RR (95% CI)	Heterogenei - p value (I^2%
All Treatment types	**Untreated External**	**44**	**5177986**	**5758/54308 (10.6)**	**278047/5123678 (5.4)**	**1.96 [1.74, 2.21]**	**0 (90)**
CKC		7	37370	62/390 (15.9)	2263/36980 (6.1)	3.28 [2.44, 4.42]	0.99 (0)
LC		6	1126	68/480 (14.2)	46/646 (7.1)	2.39 [1.24, 4.61]	0.02 (63)
NETZ		1	7361	17/71 (23.9)	300/7290 (4.1)	5.82 [3.79, 8.94]	N/E (N/E)
LLETZ		20	1415006	1513/19934 (7.6)	65080/1395072 (4.7)	1.69 [1.46, 1.97]	0 (68)
LA		4	1258	37/510 (7.3)	50/748 (6.7)	1.27 [0.67, 2.4]	0.19 (38)
CT		1	58	1/36 (2.8)	0/22 (0.0)	1.86 [0.08, 43.87]	N/E (N/E)
Excision NOS		11	3085727	3602/26190 (13.8)	181806/3059537 (5.9)	2.15 [1.68, 2.76]	0 (96)
Ablation NOS		5	588949	430/6482 (6.6)	26534/582467 (4.6)	1.45 [1.26, 1.67]	0.19 (35)
Treatment NOS		2	41131	28/215 (13.0)	1968/40916 (4.8)	2.57 [1.39, 4.77]	0.1 (64)
All Treatment types	**Internal (pre-Tx pregnancies)**	**13**	**83086**	**3075/21860 (14.1)**	**3930/61226 (6.4)**	**1.41 [0.98, 2.02]**	**0 (89)**
CKC		3	1430	39/347 (11.2)	38/1083 (3.5)	1.79 [0.81, 3.95]	0.15 (47)
LC		2	161	8/87 (9.2)	3/74 (4.1)	1.65 [0.11, 23.58]	0.06 (7)
LLETZ		5	3331	192/1524 (12.6)	178/1807 (9.9)	1.21 [0.73, 2.01]	0 (77)
LA		1	226	16/129 (12.4)	10/97 (10.3)	1.20 [0.57, 2.53]	N/E (N/E)
CT		1	180	3/115 (2.6)	2/65 (3.1)	0.85 [0.15, 4.94]	N/E (N/E)
Excision NOS		2	77758	2817/19658 (14.3)	3699/58100 (6.4)	1.69 [0.77, 3.73]	0 (98)
All Treatment types	**Internal (self-matching)**	**7**	**3132**	**166/1526 (10.9)**	**114/1606 (7.1)**	**1.55 [1.2, 1.99]**	**0.33 (12)**
LC		2	354	12/177 (6.8)	9/177 (5.1)	1.3 [0.56, 3.06]	0.42 (0)
LLETZ		1	516	31/258 (12.0)	17/258 (6.6)	1.82 [1.04, 3.21]	N/E (N/E)
Excision NOS		3	1922	104/961 (10.8)	72/961 (7.5)	1.46 [0.89, 2.39]	0.08 (60)
Treatment NOS		1	340	19/130 (14.6)	16/210 (7.6)	1.92 [1.02, 3.59]	N/E (N/E)
All Treatment types	**Untreated Colposcopy+/-Biopsy**	**11**	**70061**	**1877/21506 (8.7)**	**2900/48555 (6.0)**	**1.25 [1.11, 1.4]**	**0 (58)**

CKC		2	265	25/107 (23.4)	18/158 (11.4)	1.76 [1.01, 3.08]	0.83 (0)
LC		1	177	20/105 (19.0)	9/72 (12.5)	1.52 [0.74, 3.15]	N/E (N/E)
LLETZ		9	39249	877/10441 (8.4)	1511/28808 (5.2)	1.33 [1.11, 1.6]	0.02 (55)
LA		2	3326	115/1228 (9.4)	182/2098 (8.7)	1.05 [0.84, 1.31]	0.45 (0)
RD		1	2150	109/760 (14.3)	123/1390 (8.8)	1.62 [1.27, 2.06]	N/E (N/E)
Excision NOS		3	15424	600/6316 (9.5)	742/9108 (8.1)	1.16 [1.05, 1.29]	0.4 (0)
Ablation NOS		2	9470	131/2549 (5.1)	315/6921 (4.6)	1.00 [0.74, 1.36]	0.18 (45)
All Treatment types	**Untreated HSIL**	**3**	**3764**	**364/3022 (12.0)**	**58/742 (7.8)**	**1.37 [0.85, 2.19]**	**0.05 (53)**
CKC		1	103	7/67 (10.4)	1/36 (2.8)	3.76 [0.48, 29.39]	N/E (N/E)
NETZ		1	109	17/71 (23.9)	2/38 (5.3)	4.55 [1.11, 18.66]	N/E (N/E)
LLETZ		1	881	55/572 (9.6)	12/309 (3.9)	2.48 [1.35, 4.55]	N/E (N/E)
Excision NOS		2	2275	247/1955 (12.6)	38/319 (11.9)	1.06 [0.71, 1.59]	0.24 (28)
Ablation NOS		2	397	38/357 (10.6)	5/40 (12.5)	0.68 [0.28, 1.68]	0.87 (0)
Untreated population	**General Population**	**16**	**4342190**	**6064/102637 (5.9)**	**236298/4239553 (5.6)**	**1.27 [1.16, 1.39]**	**0 (71)**
Pre-treatment pregnancies		12	3134087	3893/60543 (6.4)	176453/3073544 (5.7)	1.26 [1.08, 1.45]	0.03 (49)
Untreated Colposcopy+/-Biopsy		3	1029651	2113/41352 (5.1)	48741/988299 (4.9)	1.27 [1.17, 1.37]	0.08 (60)
Untreated HSIL		3	178452	58/742 (7.8)	11104/177710 (6.2)	1.40 [0.94, 2.1]	0.08 (59)

CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; CT: cryotherapy; HSIL: high-grade squamous intraepithelial lesion; LA: laser ablation; LC: laser conisation; LLETZ: large loop excision of the transformation zone; N/E: not eligible; NETZ: needle excision of the transformation zone; NOS: not otherwise specified; PTB: preterm birth; RD: radical diathermy

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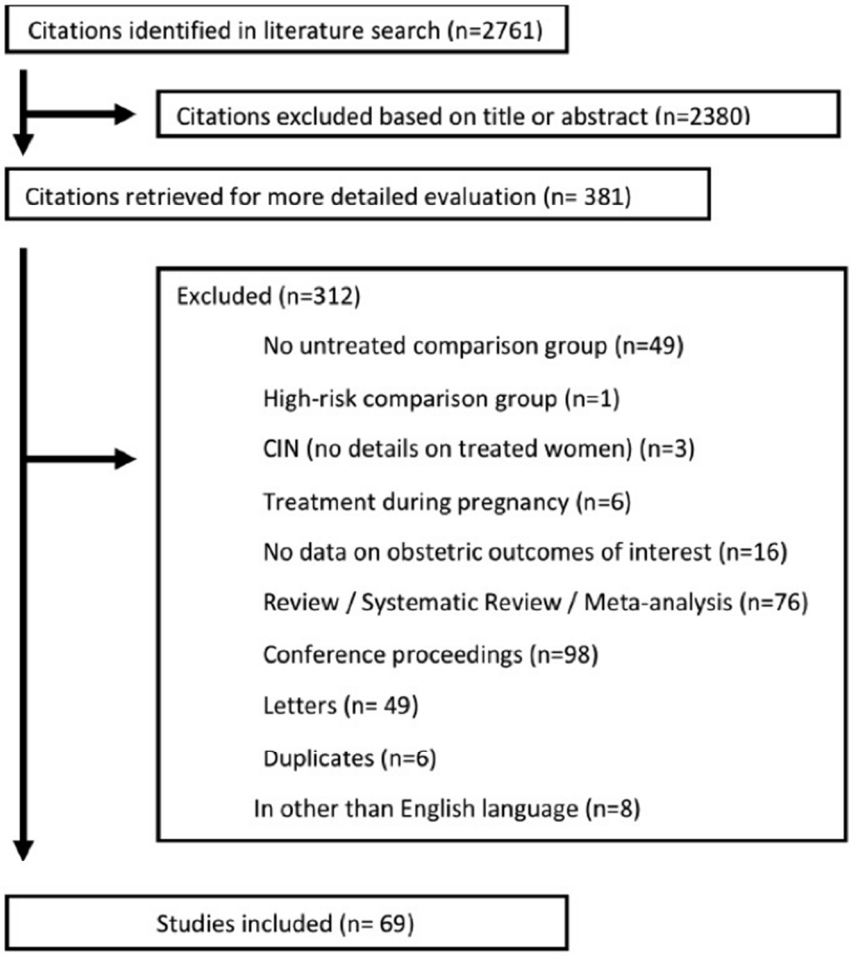

PRISMA flowchart
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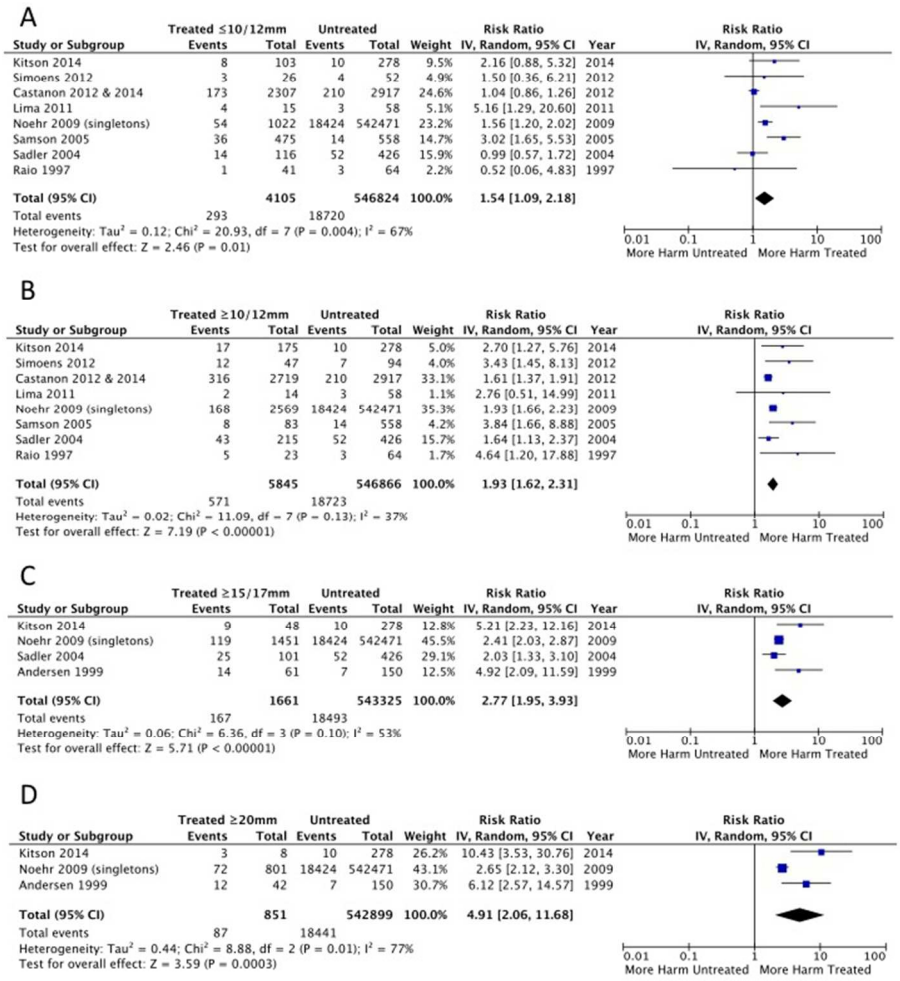

Meta-analysis on preterm birth (<37weeks) in treated versus untreated women
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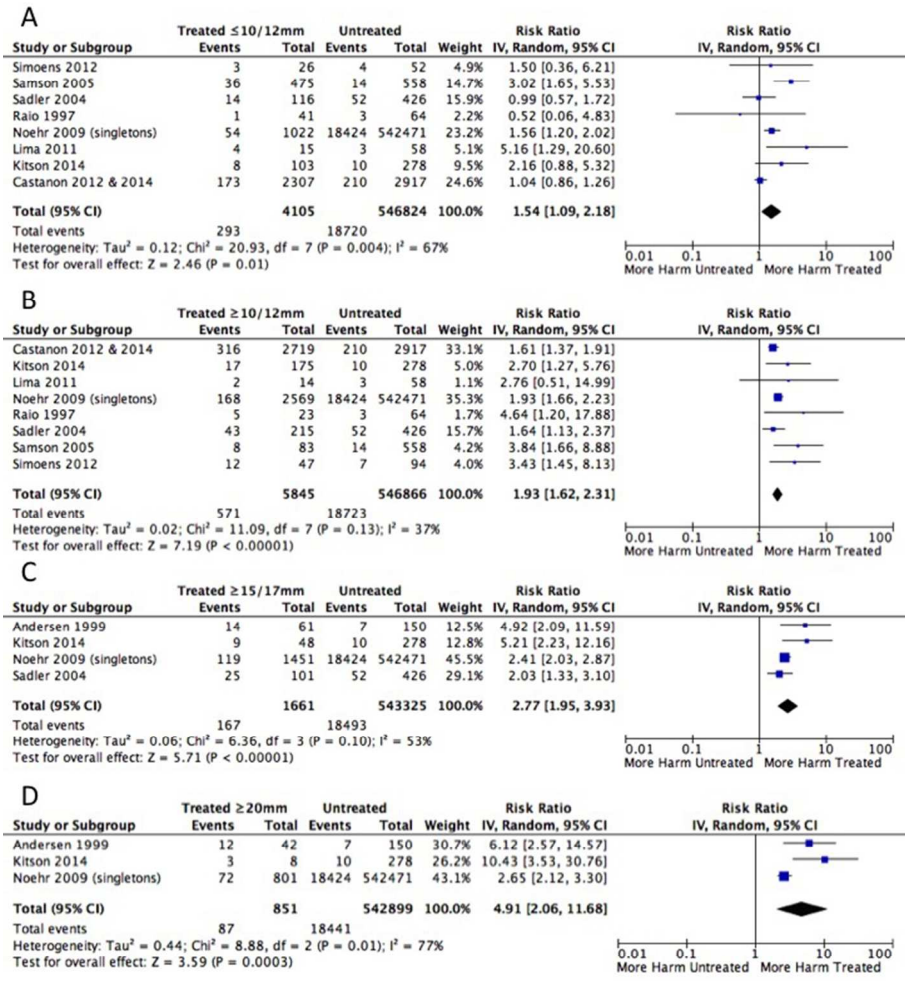
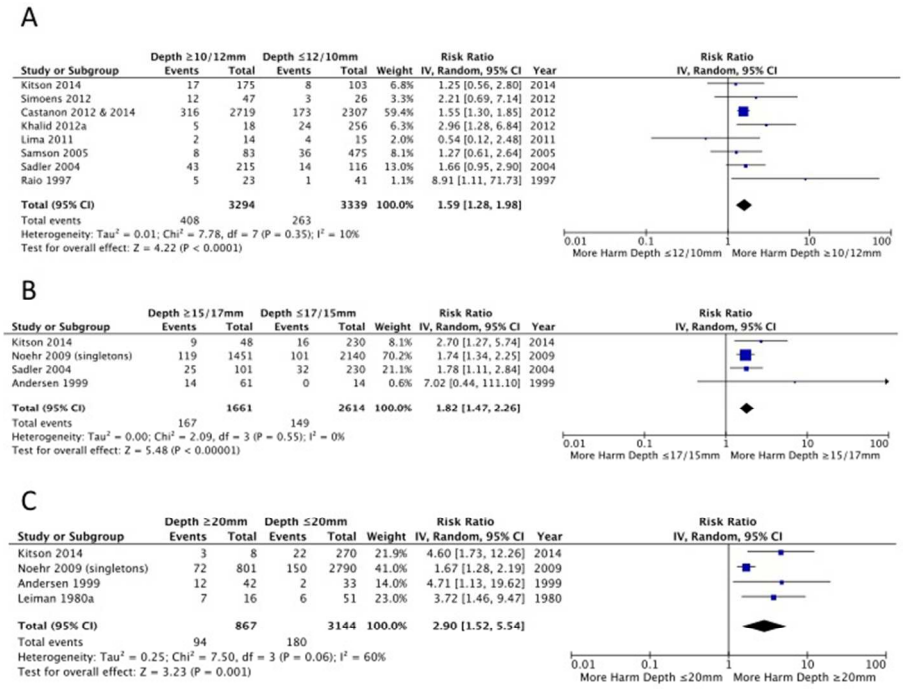


Meta-analysis on preterm birth (<37 weeks) in treated versus untreated women according to the cone depth
a) ≤10/12mm; b) ≥10/12mm; c) ≥15/17mm d) ≥20mm
254x338mm (72 x 72 DPI)



Meta-analysis on preterm birth (<37 weeks) in women treated with a cone depth a) ≥10/12mm versus ≤10/12mm; b) ≥15/17mm versus ≤17/15mm; c) ≥20mm versus ≤20mm
254x338mm (72 x 72 DPI)

Supplementary Table 1: Newcastle-Ottawa quality assessment of the included studies

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
Jones 1979	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age, parity, social class, date of delivery and singleton birth	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective
Weber 1979	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Structured interview	*Yes	*External: matching for age	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Buller 1982	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Internal (pre-treatment pregnancies)	*Secure record - hospital records	*Yes	*Internal (pre-treatment pregnancies)	*Record linkage	*Yes - retrospective	Inadequate: 27% lost to follow-up – no description of those lost
Hemmingsson 1982	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Internal (pre-treatment pregnancies)	*Secure record - hospital records	*Yes	*Internal (pre-treatment pregnancies)	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Larsson 1982	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Internal (pre-treatment pregnancies)	*Secure record - registry	*Yes	**Internal (pre-treatment pregnancies) with matching for age, parity, socioeconomic status, smoking, surgical interventions and various diseases	*Record linkage	*Yes – retrospective	*Complete follow-up – retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
Ludviksson 1982	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community.	no description of the derivation of the non exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age, parity and time of delivery	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective
Moinian 1982	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Internal (pre-treatment pregnancies)	*Secure records – hospital records	*Yes	*Internal (pre-treatment pregnancies)	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective
Anderson 1984	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: matching for age, race, births and miscarriages/TOP	Self-report	*Yes - retrospective	Inadequate: 25% lost to follow-up – no description of those lost
Kristensen 1985	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age and parity	*Record linkage (questionnaires for a minority that moved away)	*Yes - retrospective	*Complete follow up - retrospective
Kuoppala 1986	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age, parity and date of delivery	*Record-linkage	*Yes - retrospective	*Complete follow up - retrospective
Saunders 1986	6	*Somewhat representative of the average pregnant woman with a previous history of	*drawn from the same community as the exposed cohort	Hospital case notes and contact with local general practitioners	*Yes	**External: matching for age, parity, race, year of delivery and singleton pregnancy	Hospital case notes and contact with local general practitioners	*Yes - retrospective	No description

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		treatment for CIN in the community							
Gunasekera 1992	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record-hospital records	*Yes	**External: matching for age, parity, race, duration of pregnancy and smoking habit	*Record linkage	*Yes-retrospective	*Complete follow up - retrospective
Blomfield 1993	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: matching for age, parity and ethnicity	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Haffenden 1993	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age and parity	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Hagen 1993	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community.	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age and parity; regression analysis for maternal height, marital status, level of education, smoking, previous TOP, and, in the index pregnancy, occurrence of gestational hypertension or antepartum haemorrhage and the mode of delivery	*Record linkage	*Yes - retrospective	*Subjects lost to follow up (1.7%) unlikely to introduce bias
Kristensen 1993	7	*Truly representative of the average	*A) External: drawn from	*Secure record - registry	*Yes	A) External: no matching, no	*Record linkage	*Yes - retrospective	*Complete follow-up –

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		pregnant woman with a previous history of treatment for CIN in the community	the same community as the exposed cohort B) Internal (self-matching)			regression analysis B) Internal (self-matching)			retrospective
Braet 1994	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age, parity and smoking	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Cruickshank 1995	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record – registry	*Yes	**A) External: matching for maternal age, parity, husband's or partner's social class, height and daily cigarette consumption B) Internal (pre-treatment pregnancies)	Record linkage but also self-report	*Yes - retrospective	Inadequate: 34.7% did not respond to the questionnaire – no description of those lost
Sagot 1995	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community.	*Internal (pre-treatment pregnancies)	*Secure record - hospital records	*Yes	*Internal (pre-treatment pregnancies)	*Record linkage	*Yes - retrospective	Inadequate: 21.6% could not be recontacted – no description of those lost
Spitzer 1995	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Internal (pre-treatment pregnancies)	*Secure record – hospital/private practice records	*Yes	**Internal (pre-treatment pregnancies) with matching for age and parity	Self-report	*Yes - retrospective	Inadequate: 47.9% lost to follow-up – no description of those lost
Bekassy 1996	8	*Somewhat representative of the average pregnant	A) External: drawn from a different	*Secure record - hospital records	*Yes	**A) External: matching for age, parity and time of	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		woman with a previous history of treatment for CIN in the community	source B) Internal (self-matching)			delivery B) Internal (self-matching)			
Forsmo 1996	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*drawn from a same area & period but may be other institutions	*Secure record - hospital records	*Yes	**External: matching for age, parity and place of delivery	Self-report & record linkage for some outcomes	*Yes - retrospective	*Subjects lost to follow-up (3.4%) unlikely to introduce bias
Turlington 1996	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**Women with colposcopically directed biopsy: regression analysis for age	Self-report	*Yes - retrospective	Inadequate: 29.7% did not respond - no description of those lost
Raio 1997	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External: drawn from the same community as the exposed cohort B) Internal (self-matching)	*Secure record - hospital records	*Yes	**A) External: matching for age, parity, marital status, social class, smoking habits and previous PTB B) Internal (self-matching)	*Record linkage	*Yes - retrospective	*Subjects lost to follow-up (11.4%) unlikely to introduce bias
Andersen 1999	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age and parity	*Record-linkage	*Yes - retrospective	*Complete follow up - retrospective
El-Bastawissi 1999	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIS in the community	*Drawn from the same community as the exposed cohort	*Secure record – population-based cancer registry and birth certificates	*Yes	**A) External: matching for age and country of origin B) Women with untreated HSIL: no matching	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
						Both had regression analysis for parity, race, maternal smoking, marital status and history of TOPs			
van Rooijen 1999		*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same source as the treated group	*Secure record - hospital records	*yes	**External: matching for age, parity and year of delivery	*Record linkage	*Yes - retrospective	*Subjects lost to follow-up (16.5%) unlikely to introduce bias
Paraskevaidis 2002	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for IA1 cervical carcinoma in the community	*drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age, parity, smoking, multiple pregnancies and history of previous PTBs	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective
Sadler 2004	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**Women with colposcopy: regression analysis for age, ethnicity, socioeconomic status, smoking in pregnancy, previous obstetric history, transfer to the National Women's Hospital and antepartum hemorrhage	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Tan 2004	8	*Somewhat representative of the average woman with CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age and parity	*Record linkage	*Yes - retrospective	Inadequate: in 29.7% incomplete retrieval of data

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
Acharya 2005	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record – hospital records	*Yes	**A) External: matching for age, parity, date of delivery, smoking and previous obstetric history B) Internal (pre-treatment pregnancies)	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Samson 2005	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – official databases	*Yes	**External: matching for age, parity, smoking status, year of delivery	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Crane 2006	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	no description	*Yes	**External: regression analysis for maternal age, gestational age at the time of transvaginal ultrasonography, parity, smoking, antepartum bleeding after 20 weeks of gestation and previous sPTB	*Record-linkage	*Yes - retrospective	*Complete follow-up – retrospective
Klaritsch 2006	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	External: no matching, no regression analysis	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Bruinsma 2007	9	*Somewhat representative of the average pregnant	*Drawn from the same community as	*Secure record - hospital records	*Yes	**Women with colposcopy but no treatment: regression	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		woman with a previous history of treatment for CIN in the community	the exposed cohort			analysis for for age, illicit drug use during pregnancy, delivery at the RWH, marital status, maternal medical condition, previous TOP, previous miscarriage, previous PTB and previous treatment			
Himes 2007	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	*Women with colposcopic biopsy but no treatment – no matching, no regression analysis	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Jakobsson 2007	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – national registers	*Yes	**External: regression analysis for age, parity and smoking	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Sjoborg 2007	8	*Somewhat representative of the average pregnant woman with a	*A) External: drawn from the same community as	*Secure record – hospital records	*Yes	**A) External: matching for age, parity and plurality B) Internal (self-	*Record linkage	*Yes - retrospective	Inadequate: 69% of the women did not respond or did

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		previous history of treatment for CIN in the community	the exposed cohort B) Internal (self-matching)			matching) Both had regression analysis for smoking, marital status and education			not give their consent – no description of those lost
Albrechtesen 2008	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record - national registries	*Yes	**A) External B) Internal (pre-treatment pregnancies) Both had regression analysis for age and birth order	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Parikh 2008	6	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	No description	*Yes	External: No matching, no regression analysis	*Record linkage	*Yes - retrospective	*Subjects lost to follow-up (10.3%) unlikely to introduce bias
Jakobsson 2009	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	A) External: treated group drawn from hospital while controls from population-based registry B) Internal (self-matching)	*Secure record – national registers and hospital records	*Yes	**A) External: no matching B) Internal (self-matching) Both had regression analysis for age, parity, or both	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective
Noehr 2009 (singletons)	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – national registries	*Yes	**A) External B) Women with biopsy but no treatment Both had regression analysis for age, year of delivery, smoking during pregnancy and	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
						marital status during pregnancy			
Noehr 2009 (twins)	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – national registries	*Yes	**External: regression analysis for age, year of delivery, smoking during pregnancy, marital status during pregnancy and IVF	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Shanbhag 2009	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN3 in the community	*Drawn from the same community as the exposed cohort	*Secure record – national registries	*Yes	**A) External B) Women with untreated CIN 3 Both had regression analysis for maternal age at delivery, smoking, socioeconomic status, year of delivery, birth weight, malpresentation, sPTB and pPROM	*Record linkage	*Yes - retrospective	Inadequate: for 69% of the treated population the type of treatment was not known – no description of those lost
Fischer 2010	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	No description	*Yes	**External: regression analysis for age, race, the number of prior vaginal deliveries at ≥20 weeks and gestational age at the time of cervical sonography	*Record linkage	*Yes	*Complete follow-up
Ortoft 2010	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External B) Women with untreated HSIL Both were drawn from the same community as the exposed cohort C) Internal	*Secure record – national registries	*Yes	** A) External B) Women with untreated HSIL Both had regression analysis for age, parity, smoking status, educational level and marital status C) Internal (self-matching)	*Record linkage (but questionnaires for the outcomes of previous pregnancies when internal matching (self-matching) was used)	*Yes - retrospective	*Complete follow-up

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
			(self-matching)						
Van de Vijner 2010	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: matching for age, parity and year of delivery	Self-report	*Yes - retrospective	No statement
Werner 2010	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record – hospital records	*Yes	**A) External B) Internal (pre-treatment pregnancies) Both had regression analysis for age, parity and race	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Andia 2011	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	A) External: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record – hospital records	*Yes	**A) External B) Internal (pre-treatment pregnancies) Both had regression analysis for age, parity and smoking	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Armarnik 2011	9	*Somewhat representative of the average pregnant women with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: regression analysis for age, birth order, year of delivery, smoking and cervical incompetence with cerclage	*Record linkage	*Yes - retrospective	*Subjects lost to follow-up (7%) unlikely to introduce bias
Lima 2011	7	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	No matching, no regression analysis	*Record linkage	*Yes - retrospective	*Complete follow-up – retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		the community							
Castanon 2012 (& 2014)	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) External (general population) B) Women with punch biopsy C) Internal (pre-treatment pregnancies) D) Internal matching (self-matching)	*Secure record – hospital records	*Yes	**A) General population B) Women with punch biopsy C/D) Internal controls Regression analysis for age parity and study site for a variant of the groups that we used	*Record linkage	*Yes - retrospective	Inadequate: 29.9% lost to follow-up because of unknown gestational age – no description of those lost
Poon 2012	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	Written self-report (questionnaires)	*Yes	**External: regression analysis for parity, race, smoking, cervical length, previous delivery at term, previous PTB, previous miscarriage and previous LLETZ (for the prediction of sPTB)	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Reilly 2012	9	*Truly representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – national registries	*Yes	**A) External B) Women with colposcopy +/- punch biopsy Both had regression analysis for maternal age at birth, social deprivation, smoking status, time interval between screening/colposcopy /treatment and conception, any history of a previous adverse pregnancy outcome (and	*Record linkage	*Yes - retrospective	*Subjects lost to follow-up (10.6%) unlikely to introduce bias

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
						gestational age for LBW outcome)			
Simoens 2012	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – questionnaires in combination with checking of medical files	*Yes	**External: matching for admittance in the same maternity ward; regression analysis for age, parity, ethnicity, smoking, education, HIV status	*Record linkage	*Yes	*Complete follow-up
Van Hentenryck 2012	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: matching for age at delivery, parity, smoking, history of gestation and HIV status	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Frega 2013	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: women of the same parity (only nulliparous) and race (only white)	*Record linkage	*Yes	*Subjects lost to follow up (4.1%) unlikely to introduce bias
Frey 2013	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**A) External B) Women with punch biopsy Both had matching for age and year of treatment, and regression analysis for age, parity, race, maternal diabetes, maternal BMI, neonate birth weight and prior CS	*Record linkage (structured phone interviews and then confirmation from medical files)	*Yes - retrospective	No statement
Heinonen 2013	9	*Truly representative of the average pregnant woman with a previous history of	*Drawn from the same community as the exposed	*Secure record – hospital records	*Yes	**External: regression analysis for maternal age, socioeconomic status, marital status,	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		treatment for CIN in the community	cohort			urbanism, time since LLETZ and previous PTBs			
Guo 2013	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**Women with colposcopic biopsy +/- CIN: all were non-smokers	*Record linkage	*Yes	No statement
Wuntakal 2013	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) Women with biopsy: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record – hospital records	*Yes	**A) Women with biopsy B) Internal (pre-treatment pregnancies) Both had regression analysis for parity, ethnicity and deprivation	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Ciavattini 2014	8	Selected group of users (twin deliveries after assisted reproduction techniques)	*Drawn from the same community as the exposed cohort	*Secure record - hospital records	*Yes	**External: matching for age, parity, BMI, tabagism, previous hormonal contraception, previous PTB and cervical incompetence at 1st trimester	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Ehsanipoor 2014	9	*Somewhat representative of the average pregnant woman (with a twin pregnancy) with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: regression analysis for age, parity, race, history of PTB, history of tobacco use, history of drug use and chorionicity	*Record linkage	*Yes - retrospective	*Complete follow-up - retrospective
Kitson 2014	9	*Somewhat representative of the	*Drawn from the same	*Secure record – hospital records	*Yes	**Women with punch biopsy: matching for	*Record linkage	*Yes - retrospective	*Complete follow-up -

		Selection				Comparability	Outcome		
Reference	Score	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
		average pregnant woman with a previous history of treatment for CIN in the community	community as the exposed cohort			age, parity and smoking			retrospective
Sozen 2014	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record – hospital records	*Yes	**External: matching for age, parity and obstetric history	*Record linkage	*Yes - retrospective	*Complete follow up - retrospective
Martyn 2015	8	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*Drawn from the same community as the exposed cohort	*Secure record - questionnaires which were then confirmed from hospital records	*Yes	**Women with colposcopy: matching for age	Self-report	*Yes - retrospective	*Complete follow up - retrospective
Stout 2015	9	*Somewhat representative of the average pregnant woman with a previous history of treatment for CIN in the community	*A) Women with cervical cytology/punch biopsy: drawn from the same community as the exposed cohort B) Internal (pre-treatment pregnancies)	*Secure record – hospital records	*Yes	**A) Women with cervical cytology/punch biopsy: matching for age, hospital site and calendar year of cervical procedure B) Internal (pre-treatment pregnancies)	*Structured phone interviews which were then confirmed from medical files	**Yes - retrospective	*Subjects lost to follow up (<6%) unlikely to introduce bias

Supplementary Table 2: Preterm birth (<37 weeks) for treated versus treated women for various cone dimensions (length/volume).

Comparison Group 1	Comparison Group 2	Studies	Total N	Treated n/N (%)	Untreated n/N (%)	Effect Estimate RR (95% CI)	Heterogeneity - p value (I^2%)
Cone Length							
Cone Length ≥ 10/12mm	**Cone Length ≤ 12/10mm**						
All Treatment types	All Treatment types	8	6633	408/3294 (12.4)	263/3339 (7.9)	1.59 [1.28, 1.98]	0.35 (10)
LC	LC	1	64	5/23 (21.7)	1/41 (2.4)	8.91 [1.11, 71.73]	N/E (N/E)
LLETZ	LLETZ	3	1110	30/276 (10.9)	68/834 (8.2)	1.64 [0.95, 2.81]	0.24 (29)
Excision NOS	Excision NOS	4	5459	373/2995 (12.5)	194/2464 (7.9)	1.55 [1.31, 1.83]	0.52 (0)
Cone Length ≥ 15/17mm	**Cone Length ≤ 17/15mm**						
All Treatment types	All Treatment types	4	4275	167/1661 (10.1)	149/2614 (5.7)	1.82 [1.47, 2.26]	0.55 (0)
LC	LC	1	75	14/61 (23.0)	0/14 (0.0)	7.02 [0.44, 111.1]	N/E (N/E)
LLETZ	LLETZ	2	3869	128/1499 (8.5)	117/2370 (4.9)	1.86 [1.36, 2.55]	0.28 (14)
Excisional Treatment NOS	Excisional Treatment NOS	1	331	25/101 (24.8)	32/230 (13.9)	1.78 [1.11, 2.84]	N/E (N/E)
Cone Length ≥ 20mm	**Cone Length ≤20mm**						
All Treatment types	All Treatment types	4	4011	94/867 (10.8)	180/3144 (5.7)	2.90 [1.52, 5.54]	0.06 (60)
CKC	CKC	1	67	7/16 (43.8)	6/51 (11.8)	3.72 [1.46, 9.47]	N/E (N/E)
LC	LC	1	75	12/42 (28.6)	2/33 (6.1)	4.71 [1.13, 19.62]	N/E (N/E)
LLETZ	LLETZ	2	3869	75/809 (9.3)	172/3060 (5.6)	2.47 [0.94, 6.51]	0.05 (74)
Cone Length ≥ 15/17mm	**Cone Length ≤ 12/10mm**						
All Treatment types	All Treatment types	3	2841	153/1600 (9.6)	76/1241 (6.1)	1.70 [1.31, 2.22]	0.52 (0)
LLETZ	LLETZ	2	2624	128/1499 (8.5)	62/1125 (5.5)	1.63 [1.21, 2.19]	0.36 (0)
Excisional Treatment NOS	Excisional Treatment NOS	1	217	25/101 (24.8)	14/116 (12.1)	2.05 [1.13, 3.73]	N/E (N/E)
Cone Length ≥ 20mm	**Cone Length ≤ 12/10mm**						
All Treatment types	All Treatment types	2	1934	75/809 (9.3)	62/1125 (5.5)	2.49 [0.93, 6.66]	0.08 (67)
LLETZ	LLETZ	2	1934	75/809 (9.3)	62/1125 (5.5)	2.49 [0.93, 6.66]	0.08 (67)

Cone Length ≥ 20mm	Cone Length ≤ 15mm						
Comparison Group 1	**Comparison Group 2**	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity - p value (I^2%)**
All Treatment types	All Treatment types	3	3240	87/856 (10.2)	117/2384 (4.9)	3.07 [1.27, 7.45]	0.1 (57)
LC	LC	1	61	12/47 (25.5)	0/14 (0.0)	7.81 [0.49, 124.3]	N/E (N/E)
LLETZ	LLETZ	2	3179	75/809 (9.3)	117/2370 (4.9)	2.85 [1.06, 7.69]	0.05 (73)
Cone Length > 20mm	**Cone Length = 15/16-19/20mm**						
All Treatment types	All Treatment types	3	1560	87/851 (10.2)	55/709 (7.8)	1.46 [0.95, 2.23]	0.33 (11)
LC	LC	1	61	12/42 (28.6)	2/19 (10.5)	2.71 [0.67, 10.96]	N/E (N/E)
LLETZ	LLETZ	2	1499	75/809 (9.3)	53/690 (7.7)	1.40 [0.84, 2.36]	0.26 (22)
Cone Length = 11/13-15/16mm	**Cone Length < 12/10mm**						
All Treatment types	All Treatment types	3	2600	75/1359 (5.5)	76/1241 (6.1)	0.92 [0.67, 1.25]	0.48 (0)
LLETZ	LLETZ	2	2370	57/1245 (4.6)	62/1125 (5.5)	0.83 [0.58, 1.17]	0.97 (0)
Excisional Treatment NOS	Excisional Treatment NOS	1	230	18/114 (15.8)	14/116 (12.1)	1.31 [0.68, 2.5)	N/E (N/E)
Cone Length = 15/16-19/20mm	**Cone Length ≤ 12/10mm**						
All Treatment types	All Treatment types	2	1815	53/690 (7.7)	62/1125 (5.5)	1.43 [1, 2.04]	0.53 (0)
LLETZ	LLETZ	2	1815	53/690 (7.7)	62/1125 (5.5)	1.43 [1, 2.04]	0.53 (0)
Cone Length = 15/16-19/20mm	**Cone Length ≤ 15mm**						
All Treatment types	All Treatment types	3	3093	55/709 (7.8)	117/2384 (4.9)	1.62 [1.18, 2.2]	0.66 (0)
LC	LC	1	33	2/19 (10.5)	0/14 (0.0)	3.75 [0.19, 72.49]	N/E (N/E)
LLETZ	LLETZ	2	3060	53/690 (7,7)	117/2370 (4.9)	1.6/1.17 (2.19)	0.48 (0)
Cone Volume							
Cone Volume > 3/4cc	**Cone Volume < 4/3cc**						
All Treatment types (Volume> 3/4cc)	All Treatment Types	3	591	31/190 (16.3)	31/401 (7.7)	2.15 [1.03, 4.49]	0.17 (44)
CKC	CKC	1	39	7/15 (46.7)	1/24 (4.2)	11.2 [1.53, 82.22]	N/E (N/E)
LLETZ	LLETZ	2	552	24/175 (13.7)	30/377 (8.0)	1.71 [1.03, 2.85]	0.54 (0)
Cone Volume > 6cc	**Cone Volume < 6cc**						
All Treatment types	All Treatment types	2	552	13/48 (27.1)	41/504 (8.1)	4.01 [1.93, 8.33]	0.19 (42)

LLETZ	LLETZ	2	552	13/48 (27.1)	41/504 (8.1)	4.01 [1.93, 8.33]	0.19 (41)

*If a study had more than one comparison groups, we used external groups (external general, external untreated women that had colposcopy+/-CIN+/-biopsy, women with HSIL but no treatment) in preference to internal comparators (self-matching or pre-treatment pregnancies).
CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; CT: cryotherapy; HSIL: high-grade squamous intraepithelial lesion; LA: laser ablation; LC: laser conisation; LLETZ: large loop excision of the transformation zone; N/E: not eligible; NETZ: needle excision of the transformation zone; NOS: not otherwise specified; PTB: preterm birth; RD: radical diathermy

Supplementary Table 3: Maternal outcomes other than preterm birth comparing cervical treatment techniques to no treatment*.

Maternal Outcomes	Studies	Total N	Treated n/N (%)	Untreated n/N (%)	Effect Estimate RR (95% CI)	Heterogeneity – p value (I^2%)
sPTB						
sPTB (<37w)						
All Treatment types	14	1024731	1181/16849 (7.0)	37257/1007882 (3.7)	1.76 [1.47, 2.11]	0 (76.02)
CKC	3	7320	22/154 (14.3)	291/7166 (4.1)	3.53 [2.05, 6.05]	0.38 (0)
LC	2	222	7/112 (6.3)	7/110 (6.4)	1.40 [0.51, 3.81]	0.7 (0)
NETZ	1	7399	17/71 (23.9)	301/7328 (4.1)	5.83 [3.8, 8.95]	N/E (N/E)
LLETZ	11	773123	798/10890 (7.3)	25998/762233 (3.4)	1.60 [1.22, 2.08]	0 (77)
LA	1	356	8/208 (3.8)	6/148 (4.1)	0.95 [0.34, 2.68]	N/E (N/E)
CT	1	58	1/36 (2.8)	0/22 (0.0)	1.86 [0.08, 43.87]	N/E (N/E)
Excisional Treatment NOS	2	95985	115/1115 (10.3)	5453/94870 (5.7)	1.70 [1.17, 2.46]	0.29 (9)
Ablative Treatment NOS	2	134720	121/2312 (5.2)	5071/132408 (3.8)	1.42 [1.2, 1.7]	0.51 (0)
Treatment NOS	1	5548	92/1951 (4.7)	130/3597 (3.6)	1.30 [1, 1.69]	N/E (N/E)
sPTB (<34/32w)						
All Treatment types	7	655675	225/12486 (1.8)	3787/643189 (0.6)	2.63 [1.91, 3.62]	0.01 (58]
CKC	2	6990	2/88 (2.3)	47/6902 (0.7)	4.38 [1.08, 17.65]	1 (0)
NETZ	1	7399	5/71 (7.0)	49/7328 (0.7)	10.53 [4.33, 25.65]	N/E (N/E)
LLETZ	6	530985	197/10176 (1.9)	3113/520809 (0.6)	2.37 [1.82, 3.08]	0.16 (37)
CT	1	58	1/36 (2.8)	0/22 (0.0)	1.86 [0.08, 43.87]	N/E (N/E)
Excisional Treatment NOS	1	264	3/88 (3.4)	0/176 (0.0)	13.92 [0.73, 266.6]	N/E (N/E)
Ablative Treatment NOS	1	109979	17/2027 (0.8)	578/107952 (0.5)	1.57 [0.97, 2.53]	N/E (N/E)

sPTB (<28w)						
Maternal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity – p value (I^2%)**
All Treatment types	2	626670	65/10917 (0.6)	1523/615753 (0.2)	3.18 [1.64, 6.16]	0.02 (68)
CKC	1	6956	1/67 (1.5)	19/6889 (0.3)	5.41 [0.74,39.84]	N/E (N/E)
NETZ	1	7399	3/71 (4.2)	21/7328 (0.3)	14.74 [4.5, 48.32]	N/E (N/E)
LLETZ	2	502336	55/8752 (0.6)	1221/493584 (0.2)	2.57 [1.96, 3.36]	0.66 (0)
Ablative Treatment NOS	1	109979	6/2027(0.3)	262/107952 (0.2)	1.22 [0.54, 2.74]	N/E (N/E)
Threatened PTB						
All Treatment types	5	903	31/340 (9.1)	18/563 (3.2)	2.44 [1.37, 4.33]	0.43 (0)
CKC	1	126	5/47 (10.6)	6/79 (7.6)	1.40 [0.45, 4.34]	N/E (N/E)
LC	1	112	7/53 (13.2)	5/59 (8.5)	1.56 [0.53, 4.62]	N/E (N/E)
LLETZ	1	237	4/79 (5.1)	2/158 (1.3)	4.00 [0.75, 21.37]	N/E (N/E)
Excisional Treatment NOS	2	428	15/161 (9.3)	5/267(1.9)	4.51 [1.68, 12.06]	0.52 (0)
pPROM						
pPROM (<37w)						
All Treatment types	21	477011	485/7903 (6.1)	15970/469108 (3.4)	2.36 [1.76, 3.17]	0 (79)
CKC	4	36733	28/194 (14.4)	930/36539 (2.5)	4.11 [2.05, 8.25]	0.12 (49)
LC	4	635	43/292 (14.7)	25/343 (7.3)	1.89 [0.97, 3.66]	0.21 (34)
NETZ	1	7279	14/71 (19.7)	161/7208 (2.2)	8.83 [5.39, 14.46]	N/E (N/E)
LLETZ	8	302974	124/2428 (5.1)	7619/300546 (2.5)	2.15 [1.48, 3.12]	0.09 (43)
LA	2	548	18/307 (5.9)	9/241 (3.7)	1.62 [0.74, 3.55]	0.64 (0)
CT	1	180	4/115 (3.5)	2/65 (3.1)	1.13 [0.21, 6]	N/E (N/E)
Excisional Treatment NOS	5	98372	162/2260 (7.2)	5680/96112 (5.9)	2.66 [1.13, 6.24]	0 (84)
Ablative Treatment NOS	1	24742	25/285 (8.8)	1458/24457 (6.0)	1.47 [1.01, 2.15]	N/E (N/E)

Treatment NOS	1	5548	67/1951 (3.4)	86/3597 (2.4)	1.44 [1.05, 1.97]	N/E (N/E)
Maternal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity – p value (I^2%)**
pPROM (<32w)						
All Treatment types	1	72788	12/710 (1.7)	202/72078 (0.3)	8.30 [2.03, 33.98]	0.01 (78)
CKC	1	6842	1/67 (1.5)	19/6775 (0.3)	5,32 [0.72, 39.19]	N/E (N/E)
NETZ	1	7279	5/71 (7.0)	20/7208 (0.3)	25.38 [9.8, 65.74]	N/E (N/E)
LLETZ	1	58667	6/572 (1.0)	163/58095 (0.3)	3.74 [1.66, 8.41]	N/E (N/E)
pPROM (<28w)						
All Treatment types	1	72788	4/710 (0.6)	70/72078 (0.1)	9.09 [1.04, 7.18]	0.03 (72)
CKC	1	6842	0/67 (0.0)	7/6775 (0.1)	6.64 [0.38, 115.2]	N/E (N/E)
NETZ	1	7279	3/71 (4.2)	7/7208 (0.1)	43.51 [11.48, 164.9]	N/E (N/E)
LLETZ	1	58667	1/572 (0.2)	56/58095 (0.1)	1.81 [.,25, 13.08]	N/E (N/E)
Chorioamnionitis						
All Treatment types	4	29198	11/314 (3.5)	316/28884 (1.1)	3.43 [1.36, 8.64]	0.74 (0)
CKC	1	28531	2/76 (2.6)	313/28455 (1.1)	2.39 [0.61, 9.43]	1 (0)
LC	1	112	1/53 (1.9)	0/59 (0.0)	3.33 [0.14, 80.11]	N/E (N/E)
LLETZ	1	237	5/79 (6.3)	1/158 (0.6)	10.0 [1.19, 84.15]	N/E (N/E)
Excisional Treatment NOS	1	318	3/106 (2.8)	2/212 (0.9)	3.00 [0.51, 17.68]	N/E (N/E)
Mode of Delivery						
Caeserean Section						
All Treatment types	35	272090	1748/8807 (19.8)	46886/263283 (17.8)	1.06 [0.99, 1.15]	0.16 (18)
CKC	6	30462	54/308 (17.5)	3698/30154 (12.3)	1.24 [0.91, 1.68]	0.36 (9)
LC	5	1038	57/445 (12.8)	63/593 (10.6)	1.38 [0.9, 2.11]	0.23 (29)
LLETZ	14	5436	509/2363 (21.5)	672/3073 (21.9)	1.04 [0.94, 1.15]	0.71 (0)

LA	4	1258	50/510 (9.8)	86/748 (11.5)	0.86 [0.61, 1.2]	0.62 (0)
Maternal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity – p value (I^2%)**
CT	2	238	24/151 (15.9)	5/87 (5.7)	2.47 [1.02, 6.01]	0.32 (0)
Excisional Treatment NOS	7	202971	600/2616 (22.9)	36625/200355 (18.3)	1.07 [0.89, 1.29]	0.03 (56)
Ablative Treatment NOS	2	24848	71/366 (19.4)	5103/24482 (20.8)	1.38 [0.42, 4.58]	0.17 (48)
Treatment NOS	2	5839	383/2048 (18.7)	634/3791 (16.7)	1.12 [1, 1.26]	0.54 (0)
Instrumental Deliveries (ventouse/ forceps)						
All Treatment types	16	9588	484/3773 (12.8)	793/815 (13.6)	0.97 [0.88, 1.08]	0.72 (0)
CKC	2	454	10/128 (7.8)	24/326 (7.4)	1.33 [0.66, 2.7]	0.4 (0)
LC	2	668	21/306 (6.9)	22/362 (6.1)	1.16 [0.65, 2.07]	0.66 (0)
LLETZ	6	1418	85/689 (12.3)	98/729 (13..4)	0.89 [0.68, 1.17]	0.7 (0)
LA	3	550	39/274 (14.2)	42/276 (15.2)	0.94 [0.62, 1.41]	0.37 (0)
Excisional Treatment NOS	3	950	33/425 (7.8)	68/525 (13.0)	0.71 [0.46, 1.1]	0.32 (11)
Treatment NOS	1	5548	296/1951 (15.2)	539/3597 (15.0)	1.01 [0.89, 1.15]	N/E (N/E)
Length of Labour						
Precipitous Labour (<2h)						
All Treatment types	5	1059	34/397 (8.6)	43/662 (6.5)	1.26 [0.8, 1.96]	1 (0)
CKC	2	289	5/71 (7.0)	15/218 (6.9)	1.24 [0.47, 3.27]	1 (0)
LLETZ	4	770	29/326 (8.9)	28/444 (6.3)	1.26 [0.76, 2.08]	1 (0)
Prolonged Labour (>12 h)						
All Treatment types	7	1854	76/859 (8.8)	75/995 (7.5)	1.25 [0.92, 1.69]	0.59 (0)
CKC	2	325	8/91 (8.8)	15/234 (6.4)	1.99 [0.89, 4.45]	0 (100)
LC	1	500	11/50 (4.4)	12/50 (4.8)	0.92 [0.41, 2.04]	N/E (N/E)
LLETZ	4	673	22/341 (6.5)	23/332 (6.9)	0.96 [0.55, 1.7]	0.48 (0)

LA	2	356	35/177 (19.8)	25/179 (14.0)	1.41 [0.88, 2.26]	0.6 (0)
Maternal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity – p value (I^2%)**
Induction of Labour						
All Treatment types	11	4668	477/1971 (24.2)	638/2697 (23.7)	1.01 [0.89, 1.15]	0.34 (10)
CKC	2	137	14/73 (19.2)	10/64(15.6)	1.11 [0.54, 2.29]	0.75 (0)
LLETZ	8	4056	421/1712 (24.6)	551/2344 (23.5)	0.99 [0.82, 1.2]	0.13 (38)
CT	1	58	6/36 (16.7)	6/22 (27.3)	0.61 [0.22, 1.66]	N/E (N/E)
Excisional Treatment NOS	2	417	36/150 (24.0)	71/267 (26.6)	0.90 [0.64, 1.28]	0.79 (0)
Oxytocin Use						
All Treatment types	6	2006	166/978 (17.0)	180/1028 (17.5)	0.90 [0.64, 1.26]	0.04 (58)
CKC	1	103	19/52 (36.5)	19/51 (37.3)	0.98 [0.59, 1.63]	N/E (N/E)
LLETZ	4	1804	131/882 (14.9)	144/922 (15.6)	0.76 [0.43, 1.34]	0.01 (74)
Excisional Treatment NOS	1	99	16/44 (36.4)	17/55 (30.9)	1.18 [0.67, 2.05]	N/E (N/E)
Haemorrhage						
Antepartum Haemorrhage						
All Treatment types	4	1245	24/502 (4.8)	21/743 (2.8)	1.11 [0.4, 3.12]	0.03 (59)
CKC	1	34	4/21 (19.0)	2/13 (15.4)	1.24 [0.26, 5.83]	N/E (N/E)
LC	1	168	4/56 (7.1)	0/112 (0.0)	17.84 [0.98, 325.7]	N/E (N/E)
LLETZ	2	277	10/153 (6.5)	15/124 (12.1)	0.52 [0.16, 1.67]	0.15 (53)
LA	1	708	4/236 (1.7)	1/472 (0.2)	8.00 [0.9, 71.18]	N/E (N/E)
CT	1	58	2/36 (5.6)	3/22 (13.6)	0.41 [0.07, 2.25]	N/E (N/E)
Postpartum Haemorrhage (>600ml)						
All Treatment types	1	149	14/75 (18.7)	3/74 (4.1)	4.60 [1.38, 15.36]	N/E (N/E)
CKC	1	149	14/75 (18.7)	3/74 (4.1)	4.60 [1.38, 15.36]	N/E (N/E)

Massive Obstetric Haemorrhage (>1000ml)						
Maternal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity – p value (I^2%)**
All Treatment types	1	149	4/75 (5.3)	1/74 (1.4)	3.95 [0.45, 34.48]	N/E (N/E)
CKC	1	149	4/75 (5.3)	1/74 (1.4)	3.95 [0.45, 34.48]	N/E (N/E)
Analgesia						
Epidural Use						
All Treatment types	5	105488	87/442 (19.7)	23205/105046 (22.1)	1.02 [0.68, 1.53]	0.02 (64)
LLETZ	4	818	66/389 (17.0)	85/429 (19.8)	0.86 [0.64, 1.16]	0.86 (0)
Excisional Treatment NOS	1	104670	21/53 (9.6)	23120/104617 (22.1)	1.79 [1.29, 2.5]	N/E (N/E)
Pethidine Use						
All Treatment types	2	394	61/197 (31.0)	64/197 (32.5)	0.94 [0.72, 1.24]	0.62 (0)
LLETZ	2	394	61/197 (31.0)	64/197 (32.5)	0.94 [0.72, 1.24]	0.62 (0)
Analgesia use NOS						
All Treatment types	1	103	17/52 (32.7)	15/51 (29.4)	1.11 [0.62, 1.98]	N/E (N/E)
CKC	1	103	17/52 (32.7)	15/51 (29.4)	1.11 [0.62, 1.98]	N/E (N/E)
Cervical cerclage						
All Treatment types	8	141300	97/2416 (4.0)	932/138884 (0.7)	14.29 [2.85, 71.65]	0 (93)
CKC	3	30744	41/246 (16.7)	71/30498 (0.2)	31.42 [2.32, 426.2]	0.07 (62)
LC	1	112	6/53 (11.3)	1/59 (1.7)	6.68 [0.83, 53.69]	N/E (N/E)
LLETZ	1	56	5/28 (17.9)	0/28 (0.0)	11.0 [0.64, 190]	N/E (N/E)
Excisional Treatment NOS	2	104840	18/138 (13.0)	837/104702 (0.8)	42.45 [28.99, 62.16]	1 (0)
Treatment NOS	1	5548	27/1951 (1.4)	23/3597 (0.6)	2.16 [1.24, 3.76]	N/E (N/E)
Cervical stenosis						
All Treatment types	2	680	2/365 (0.5)	0/315 (0.0)	2.26 [0.24, 21.59]	0.81 (0)

LC	1	500	1/250 (0.4)	0/250 (0.0)	3.00 [0.12, 73.29]	N/E (N/E)
Maternal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity – p value (I^2%)**
CT	1	180	1/115 (0.9)	0/65 (0.0)	1.71 [0.07, 41.31]	N/E (N/E)

*If a study had more than one comparison groups, we used external groups (external general, external untreated women that had colposcopy+/-CIN+/-biopsy, women with HSIL but no treatment) in preference to internal comparators (self-matching or pre-treatment pregnancies).

CKC: cold knife conisation; CT: cryotherapy; g: grams; LA: laser ablation; LBW: low birth weight; LC: laser conisation; LLETZ: large loop excision of the transformation zone; min: minute; N/E: not eligible; NETZ: needle excision of the transformation zone; NICU: neonatal intensive care unit; NOS: not otherwise specified; pPROM: preterm premature rupture of membranes PTB: preterm birth; sPTB: spontaneous preterm birth; w: weeks

Supplementary Table 4: Fetal outcomes comparing cervical treatment techniques to no treatment*.

Fetal Outcomes	Studies	Total N	Treated n/N (%)	Untreated n/N (%)	Effect Estimate RR (95% CI)	Heterogeneity - p value (I^2%)
Birth weight						
LBW (<2500g)						
All Treatment types	30	1348206	1542/19489 (7.9)	48632/1328717 (3.7)	1.81 [1.58, 2.07]	0 (63)
CKC	5	30304	49/246 (19.9)	2308/30058 (7.7)	2.51 [1.78, 3.53]	0.79 (0)
LC	4	786	29/336 (8.6)	30/450 (6.7)	1.76 [0.72, 4.35]	0.04 (63)
LLETZ	12	3357	157/1605 (9.8)	83/1752 (4.7)	2.11 [1.51, 2.94]	0.13 (32)
LA	4	1104	29/421 (6.9)	42/683 (6.1)	1.07 [0.59, 1.92]	0.29 (20)
CT	1	58	6/36 (16.7)	1/22 (4.5)	3.67 [0.47, 28.47]	N/E (N/E)
Excisional Treatment NOS	10	823648	840/10416 (8.1)	29739/813232 (3.7)	2.01 [1.62, 2.49]	0 (78)
Ablative Treatment NOS	4	483402	220/4478 (4.9)	16140/478924 (3.4)	1.36 [1.19, 1.55]	0.88 (0)
Treatment NOS	1	5547	212/1951 (10.9)	289/3596 (8.0)	1.35 [1.14, 1.6]	N/E (N/E)
LBW (<2000g)						
All Treatment types	3	74981	50/1053 (4.7)	788/73928 (1.1)	2.49 [0.97, 6.36]	0.01 (72)
LC	1	181	7/51 (13.7)	4/130 (3.1)	4.46 [1.36, 14.59]	N/E (N/E)
LA	2	772	7/256 (2.7)	15/516 (2.9)	0.95 [0.39, 2.29]	0.89 (0)
Excisional Treatment NOS	1	74028	36/746 (4.8)	769/73282 (1.0)	4.60 [3.32, 6.37]	N/E (N/E)
LBW (<1500g)						
All Treatment types	5	76836	39/1977 (2.0)	390/74859 (0.5)	3.00 [1.54, 5.85]	0.24 (26)
LC	1	181	5/51 (9.8)	1/130 (0.8)	12.75 [1.53, 106.4]	N/E (N/E)
LLETZ	1	378	3/189 (1.6)	0/189 (0.0)	7.00 [0.36, 134.6]	N/E (N/E)
LA	2	772	2/256 (0.8)	7/516 (1.4)	0.68 [0.16, 2.8]	0.97 (0)
Excisional Treatment NOS	2	75505	29/1481 (2.0)	382/74024 (0.5)	3.34 [2.02, 5.54]	0.61 (0)
LBW (<1000g)						
All Treatment types	2	2185	11/971 (1.1)	4/1214 (0.3)	2.09 [0.06, 74.71]	0.05 (75)

LA	1	708	0/236 (0.0)	3/472 (0.6)	0.29 [0.01, 5.50]	N/E (N/E)
Fetal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity - p value (I^2%)**
Excisional Treatment NOS	1	1477	11/735 (1.5)	1/742 (0.1)	11.10 [1.44, 85.79]	N/E (N/E)
NICU Admission						
All Treatment types	8	2533	155/1226 (12.6)	119/1307 (9.1)	1.44 [1.14, 1.82]	0.64 (0)
CKC	2	47	6/35 (17.1)	6/12 (50.0)	0.60 [0.04, 8.73]	1 (0)
LLETZ	5	1994	110/991 (11.1)	81/1003 (8.1)	1.42 [1.01, 1.99]	0.36 (8)
CT	1	58	4/36 (11.1)	1/22 (4.5)	2.44 [0.29, 20.49]	N/E (N/E)
Excisional Treatment NOS	2	434	35/164 (21.3)	31/270 (11.5)	1.76 [1.13, 2.75]	0.85 (0)
Perinatal Mortality						
Perinatal mortality overall						
All Treatment types	23	1659183	149/15817 (0.9)	11687/1643366 (0.7)	1.55 [1.15, 2.08]	0.03 (38)
CKC	7	50588	16/573 (2.8)	945/50015 (1.9)	1.46 [0.83, 2.57]	0.93 (0)
LC	3	656	6/376 (1.6)	5/280 (1.8)	5.10 [0.96, 26.98]	0 (100)
NETZ	1	7399	3/71 (4.2)	31/7328 (0.4)	9.99 [3.13, 31.92]	N/E (N/E)
LLETZ	7	302271	17/1925 (0.9)	2430/300346 (0.8)	1.53 [0.88, 2.67]	0.93 (0)
LA	2	258	1/117 (0.9)	0/141 (0.0)	3.00 [0.12, 72.74]	1 (0)
CT	2	258	0/151 (0.0)	1/87 (1.1)	0.19 [0.01, 4.59]	1 (0)
Excisional Treatment NOS	5	820028	63/6792 (0.9)	5427/813236 (0.7)	1.85 [1.02, 3.36]	0.08 (56)
Ablative Treatment NOS	2	472197	16/3861 (0.4)	2798/468336 (0.6)	0.69 [0.42, 1.13]	0.77 (0)
Treatment NOS	1	5548	27/1951 (1.4)	50/3597 (1.4)	1.00 [0.63, 1.58]	N/E (N/E)
Perinatal Mortality (<37w)						
All Treatment types	1	73992	6/710 (0.8)	98/73282 (0.1)	9.40 [2.01, 43.89]	0.06 (65)
CKC	1	6956	0/67 (0.0)	9/6889 (0.1)	5.33 [0.31, 90.71]	N/E (N/E)
NETZ	1	7399	3/71 (4.2)	10/7328 (0.1)	30.96[8.71, 110.1]	N/E (N/E)
LLETZ	1	59637	3/572 (0.5)	79/59065 (0.1)	3.92 [1.24, 12.38]	N/E (N/E)
Perinatal Mortality (<32w)						

All Treatment types	1	73992	6/710 (0.8)	71/73282 (0.1)	12.77 [2.51, 64.99]	0.05 (67)
Fetal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity - p value (I^2%)**
CKC	1	6956	0/67 (0.0)	7/6889 (0.1)	6.75 [0.39, 117.1]	N/E (N/E)
NETZ	1	7399	3/71 (4.2)	7/7328 (0.1)	44.23 [11.67, 167.6]	N/E (N/E)
LLETZ	1	59637	3/572 (0.5)	57/59065 (0.1)	5.43 [1.71, 17.3]	N/E (N/E)
Perinatal Mortality (<28w)						
All Treatment types	1	73992	5/710 (0.7)	57/73282 (0.1)	13.76 [2.37, 79.89]	0.05 (67)
CKC	1	6956	0/67 (0.0)	5/6889 (0.1)	9.21 [0.51, 165]	N/E (N/E)
NETZ	1	7399	3/71 (4.2)	6/7328 (0.1)	51.61 [13.17, 202.3]	N/E (N/E)
LLETZ	1	59637	2/572 (0.3)	46/59065 (0.1)	4.49 [1.09, 18.45]	N/E (N/E)
Stillbirth						
All Treatment types	12	249855	28/3920 (0.7)	1376/245935 (0.6)	0.98 [0.63, 1.52]	0.8 (0)
CKC	3	935	5/325 (1.5)	5/610 (0.8)	1.61 [0.48, 5.4]	0.66 (0)
LC	2	725	1/325 (0.3)	3/400 (0.8)	0.33 [0.03, 3.18]	1 (0)
LLETZ	4	242473	7/1244 (0.6)	1332/241229 (0.6)	1.42 [0.62, 3.26]	0.84 (0)
LA	1	64	0/20 (0.0)	0/44 (0.0)	0.00 [0, 0]	N/E (N/E)
Treatment NOS	1	5548	15/1951 (0.8)	36/3597 (1.0)	0.77 [0.42, 1.4]	N/E (N/E)
Excisional Treatment NOS	1	110	0/55 (0.0)	0/55 (0.0)	0.00 [0, 0]	N/E (N/E)
Apgar score						
Apgar score (≤5)(1min)						
All Treatment types	1	225	2/75 (2.7)	7/150 (4.7)	0.57 [0.12, 2.68]	N/E (N/E)
LC	1	225	2/75 (2.7)	7/150 (4.7)	0.57 [0.12, 2.68]	N/E (N/E)
Apgar score (<7)(1min)						
All Treatment types	1	152	2/84 (2.4)	3/68 (4.4)	0.63 [0.07, 5.71]	0.24 (28)
LLETZ	1	87	0/48 (0.0)	2/39 (5.1)	0.16 [0.01, 3.30]	N/E (N/E)
CKC	1	65	2/36 (5.6)	1/29 (3.4)	1.61 [0.15, 16.9]	N/E (N/E)
Apgar score (<7)(5min)						

All Treatment types	2	297	4/159 (2.5)	3/138 (2.2)	0.82 [0.19, 3.59]	0.8 (0)
Fetal Outcomes	**Studies**	**Total N**	**Treated n/N (%)**	**Untreated n/N (%)**	**Effect Estimate RR (95% CI)**	**Heterogeneity - p value (I^2%)**
CKC	1	32	0/20 (0.0)	0/12 (0.0)	0.00 [0, 0]	N/E (N/E)
LLETZ	1	120	3/74 (4.1)	2/46 (4.3)	0.93 [0.16, 5.37]	N/E (N/E)
CT	1	58	1/36 (2.8)	1/22 (4.5)	0.61 [0.04, 9.28]	N/E (N/E)
Excisional Treatment NOS	1	87	0/29 (0.0)	0/58 (0.0)	0.00 [0, 0]	N/E (N/E)

*If a study had more than one comparison groups, we used external groups (external general, external untreated women that had colposcopy+/-CIN+/-biopsy, women with HSIL but no treatment) in preference to internal comparators (self-matching or pre-treatment pregnancies).

CKC: cold knife conisation; CT: cryotherapy; g: grams; LA: laser ablation; LBW: low birth weight; LC: laser conisation; LLETZ: large loop excision of the transformation zone; min: minute; N/E: not eligible; NETZ: needle excision of the transformation zone; NICU: neonatal intensive care unit; NOS: not otherwise specified; w: weeks

Supplementary file 5. Search strategy

Medline Ovid

1 exp Uterine Cervical Neoplasms/

2 (cervi* and (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom*)).mp.

3 exp Cervical Intraepithelial Neoplasia/

4 CIN.mp.

5 (cervi* and (intraepithel* or epithel* or dysplasia or pre-cancer* or precancer*)).mp.

6 or/1-5

7 exp Conization/

8 (conisation or conization).mp.

9 exp Laser Therapy/

10 laser.mp.

11 exp Cryotherapy/

12 cryotherapy.mp.

13 cold coagulation.mp.

14 exp Diathermy/

15 diatherm*.mp.

16 cone biopsy.mp.

17 loop.mp.

18 LLETZ.mp.

19 LEEP.mp.

20 ablat*.mp.

21 excision*.mp.

22 transformation zone.mp.

23 (CKC or LA or LC or CC or RD or TZ).mp.

24 (conservative and (method* or treatment* or intervention* or management)).mp.

25 or/7-24

26 6 and 25

27 exp Premature Birth/

28 (preterm or premature).mp.

29 exp Infant, Low Birth Weight/

30 birth weight.mp.

31 Perinatal Mortality/

32 perinatal mortality.mp.

33 exp Intensive Care, Neonatal/

34 (neonatal and intensive care).mp.

35 exp Fertility/

36 fertil*.mp.

37 conception.mp.

38 exp Pregnancy/

39 pregnancy.mp.

40 gestation*.mp.

41 exp Abortion, Spontaneous/

42 miscarriage*.mp.

43 exp Cesarean Section/

44 (cesarean or caesarean).mp.

45 exp Obstetric Labor, Premature/

46 exp Labor, Obstetric/

47 (labor or labour).mp.

48 Fetal Membranes, Premature Rupture/

49 pPROM.mp.

50 or/27-49

51 26 and 50

key:

mp=title, original title, abstract, name of substance word, subject heading word

Embase Ovid

1 exp uterine cervix tumor/

2 (cervi* and (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom*)).mp.

3 uterine cervix carcinoma in situ/

4 CIN.mp.

5 (cervi* and (intraepithel* or epithel* or dysplasia or pre-cancer* or precancer*)).mp.

6 or/1-5

7 uterine cervix conization/

8 (conisation or conization).mp.

9 low level laser therapy/

10 laser.mp.

11 exp cryotherapy/

12 cryotherapy.mp.

13 cold coagulation.mp.

14 diathermy/

15 diatherm*.mp.

16 cone biopsy.mp.

17 loop.mp.

18 LLETZ.mp.

19 LEEP.mp.

20 ablat*.mp.

21 excision*.mp.

22 transformation zone.mp.

23 (CKC or LA or LC or CC or RD or TZ).mp.

24 (conservative and (method* or treatment* or intervention* or management)).mp.

25 or/7-24

26 6 and 25

27 prematurity/

28 (preterm or premature).mp.

29 exp low birth weight/

30 birth weight.mp.

31 perinatal mortality/

32 perinatal mortality.mp.

33 newborn intensive care/

34 (neonat* and intensive care).mp.

35 female fertility/

36 fertil*.mp.

37 conception/

38 conception.mp.

39 exp pregnancy/

40 pregnancy.mp.

41 gestation*.mp.

42 spontaneous abortion/

43 miscarriage*.mp.

44 cesarean section/

45 (cesarean or caesarean).mp.

46 premature labor/

47 (labor or labour).mp.

48 premature fetus membrane rupture/

49 pPROM.mp.

50 or/27-49

51 26 and 50

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

CENTRAL

#1 MeSH descriptor **Uterine Cervical Neoplasms** explode all trees

#2 cervi* and (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom*)

#3 MeSH descriptor **Cervical Intraepithelial Neoplasia** explode all trees

#4 CIN

#5 cervi* and (intraepithel* or epithel* or dysplasia or pre-cancer* or precancer*)

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 MeSH descriptor **Conization** explode all trees

#8 conisation or conization

#9 MeSH descriptor **Laser Therapy** explode all trees

#10 laser

#11 MeSH descriptor **Cryotherapy** explode all trees

#12 cryotherapy

#13 cold coagulation

#14 MeSH descriptor **Diathermy** explode all trees

#15 diatherm*

#16 cone biopsy

#17 loop

#18 LLETZ

#19 LEEP

#20 ablat*

#21 excision*

#22 transformation zone

#23 CKC or LA or LC or CC or RD or TZ

#24 conservative and (method* or treatment* or intervention* or management)

#25 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)

#26 (#6 AND #25)

#27 MeSH descriptor **Premature Birth** explode all trees

#28 preterm or premature

#29 MeSH descriptor **Infant, Low Birth Weight** explode all trees

#30 birth weight

#31 MeSH descriptor **Perinatal Mortality** explode all trees

#32 perinatal mortality

#33 MeSH descriptor **Intensive Care, Neonatal** explode all trees

#34 neonat* and (intensive care)

#35 MeSH descriptor **Fertility** explode all trees

#36 fertil*

#37 conception

#38 MeSH descriptor **Pregnancy** explode all trees

#39 pregnancy

#40 gestation*

#41 MeSH descriptor **Abortion, Spontaneous** explode all trees

#42 miscarriage*

#43 MeSH descriptor **Cesarean Section** explode all trees

#44 cesarean or caesarean

#45 MeSH descriptor **Obstetric Labor, Premature** explode all trees

#46 MeSH descriptor **Labor, Obstetric** explode all trees

#47 labor or labour

#48 MeSH descriptor **Fetal Membranes, Premature Rupture** explode all trees

#49 pPROM

#50 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49)

#51 (#26 AND #50)