

RESEARCH

Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis



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Abstract

Objective To determine the impact of cervical excision for cervical intraepithelial neoplasia on fertility and early pregnancy outcomes.

Design Systematic review and meta-analysis of cohort studies.

Data sources Medline and Embase.

Eligibility criteria Studies assessing fertility and early pregnancy outcomes in women with a history of treatment for cervical intraepithelial neoplasia versus untreated women. We classified the included studies according to treatment type and fertility or early pregnancy endpoint.

Analysis Pooled relative risks and 95% confidence intervals using a random effect model, and interstudy heterogeneity with I^2 statistics.

Results 15 studies fulfilled the inclusion criteria and were included. The meta-analysis did not provide any evidence that treatment for cervical intraepithelial neoplasia adversely affected the chances of conception. The overall pregnancy rate was higher for treated women than for untreated women (four studies; 43% v 38%, pooled relative risk 1.29, 95% confidence interval 1.02 to 1.64), although the heterogeneity between studies was high ($P < 0.0001$). Pregnancy rates did not differ between women with an intention to conceive (two studies; 88% v 95%, 0.93, 0.80 to 1.08) and the number requiring more than 12 months to conceive (three studies, 15% v 9%, 1.45, 0.89 to 2.37). Although the rates for total miscarriages (10 studies; 4.6% v 2.8%, 1.04, 0.90 to 1.21) and miscarriage in the first trimester (four studies; 9.8% v 8.4%, 1.16, 0.80 to 1.69) was similar for treated and untreated women, cervical

treatment was associated with a significantly increased risk of miscarriage in the second trimester. The rate was higher for treated women than for untreated women (eight studies; 1.6% v 0.4%, 16 558 women; 2.60, 1.45 to 4.67). The number of ectopic pregnancies (1.6% v 0.8%; 1.89, 1.50 to 2.39) and terminations (12.2% v 7.4%; 1.71, 1.31 to 2.22) was also higher for treated women.

Conclusion There is no evidence suggesting that treatment for cervical intraepithelial neoplasia adversely affects fertility, although treatment was associated with a significantly increased risk of miscarriages in the second trimester. Research should explore mechanisms that may explain this increase in risk and stratify the impact that treatment may have on fertility and early pregnancy outcomes by the size of excision and treatment method used.

Introduction

Cervical screening for the early identification and treatment of cervical intraepithelial neoplasia has reduced the incidence and mortality from cervical cancer.¹ As the precancerous lesions and their treatment typically occur in women of reproductive age, the impact of conisation on the outcomes of subsequent pregnancies has been an area of active research for the past decade.

Meta-analyses^{2,3} and large retrospective linkage studies^{4,5} suggest that the excisional methods of treatment (cold knife conisation, large loop excision of the transformation zone (LLETZ), and

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Details of search strategy
Newcastle-Ottawa scores

laser conisation) increase the risk of preterm birth, low birth weight, premature rupture of membranes, and perinatal mortality in subsequent pregnancies; cervical intraepithelial neoplasia itself and other confounders may contribute to that risk.⁶⁻⁸

Although the impact of treatment for cervical precancer on obstetric sequelae has been extensively described, its effect on the ability to conceive and early pregnancy outcomes has been relatively under-reported.⁹⁻¹⁰ Cervical excision removes part of the endocervical canal and as a result the mucus-secreting endocervical glands, which produce secretions facilitating penetration of the sperm and conception. This has been suggested to adversely affect the chances of conception.¹¹ The loss of the normal functional cervical structure and the healing process in the regenerated crater after excision may also induce severe stenosis of the cervical os, which may further inhibit sperm penetration and conception.¹²

Two previous small case series¹³⁻¹⁴ with limited numbers of patients reported that cervical treatment did not adversely affect the time to conception. A retrospective cohort from Finland of 35 000 women with a follow-up of over 250 000 women years assessing total pregnancy and live birth rates among treated and untreated women reported no negative effect from treatment.¹⁵ Treated women were more likely to have more pregnancies and children than the reference population; the pregnancy rates in women with intention to conceive was not reported.¹⁵ Conversely, the assessment of the actual time to conception in another recent large cohort study from the United States reported that after conisation women took longer to conceive than untreated normal women or women attending colposcopy but not treated (time to conception >12 months 16.4% v 8.4%, adjusted odds ratio 2.09, 95% confidence interval 1.26 to 3.46).¹⁶ The impact that treatment may have on conception and child bearing causes anxiety to women requiring conisation. Although the impact of treatment on obstetric outcomes has been the subject of previous reports, there is little evidence on the effect that this has on the ability to conceive and early pregnancy outcomes, particularly the rate of miscarriages in the second trimester. The existing published data are limited, often contradictory, and poorly documented. In this systematic review and meta-analysis we assessed the effect of treatment for cervical intraepithelial neoplasia on fertility and early pregnancy outcomes.

Methods

We included all studies that compared fertility and early pregnancy (<24 weeks' gestation) outcomes in women with or without treatment for cervical intraepithelial neoplasia. We also included all types of treatment, both ablative (laser ablation, cold coagulation, cryotherapy, or radical diathermy) and excisional (cold knife conisation, LLETZ—also known as loop electrosurgical excisional procedure (LEEP), laser conisation, and needle excision of the transformation zone (NETZ)—also known as straight wire excision of the transformation zone (SWETZ)). Studies were included irrespective of the type of untreated reference population—that is, matched or unmatched untreated women, internal self matching with the pregnancies of the same women before treatment, and women attending colposcopy but not receiving treatment. Studies that reported on different treatment methods without specifying the exact type of treatment were also included, even if the outcomes were not reported separately for each treatment modality. 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.

Outcome measures

We included outcome measures related to fertility and early pregnancy outcomes. The fertility outcomes included total pregnancy rates, pregnancy rates in women wishing to conceive in an unspecified period, and time to conception. The early pregnancy outcomes included rates of miscarriage in the first trimester (<12 weeks' gestation) and second trimester (between 12 and 24 weeks), and overall (<24 weeks); the rate of ectopic pregnancies and hydatiform moles; and the rate for termination of pregnancies.

Retrieval and selection of references

A search of two electronic databases (Medline and Embase) was conducted targeting reports published between 1960 and March 2014. There was no language restriction. We used keywords such as “cervical intraepithelial neoplasia”, “cervical cancer”, “fertility”, “pregnancy”, “miscarriage”, “conception”, “LLETZ or LEEP”, “conisation”, “excision”, and “treatment”. The full search 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.

Two independent investigators (MK, AM) performed the literature search, the assessment of eligible reports according to the inclusion and exclusion criteria, and the extraction of data. They then compared the results of the search and data extraction; discrepancies were resolved by consensus, with the involvement of a third investigator (MA) if necessary.

The Newcastle-Ottawa score was used to formally assess the quality of the included studies,¹⁷ according to the MOOSE checklist.¹⁸

Statistical analysis

From each study we retrieved the number of events in treated and untreated women for each outcome of interest. We analysed the data separately for each treatment modality—in groups of ablative and excisional techniques and as a whole, irrespective of the method used. We distinguished the different untreated reference populations across studies (matched to factors in the treated group, women with cervical intraepithelial neoplasia but no treatment, self matching or internal controls=before compared with after treatment). A random effects model was used to pool the data,¹⁹ and Cochrane Revman 5 software to calculate relative risks and 95% confidence intervals. We used the Cochrane's Q test and I² statistic to assess heterogeneity among studies for each outcome, corresponding to the percentage of total variance across studies caused by heterogeneity.²⁰⁻²¹ We planned to assess the possible presence of publication bias with funnel plots and formal testing of small study effects for meta-analyses including at least 10 studies.²²

Results

We identified 167 potentially eligible studies; 15 fulfilled the inclusion criteria.⁴⁻¹³⁻¹⁶⁻²³⁻³² No unpublished studies were identified. All studies were published in English. The details are presented in the PRISMA flowchart³³ together with the reasons for exclusion (fig 1⇓).

Table 1⇓ shows the characteristics of the included studies and the outcomes examined. We identified 15 studies assessing

fertility and early pregnancy outcomes in treated and non-treated women. Apart from one prospective study,²⁶ the remainder were described as retrospective cohort studies. There were no randomised controlled studies. Three studies examined the impact of cold knife conisation on the studied outcomes,^{14 24 27} six on large loop excision of the transformation zone (LLETZ),^{13 23 25 26 31 32} one on laser conisation,²⁸ and the remaining five on multiple treatment techniques.^{4 15 16 29 30} Some studies adjusted the untreated population for known risk factors for adverse reproductive outcomes,^{13 14 23 25 31} some included women with cervical intraepithelial neoplasia who received no treatment,³² some did not match for any confounders,²⁶ others used internal controls (outcomes in the same women before and after treatment),^{24 27 28 30} whereas some performed a logistic regression to control for known confounders.^{4 15 16 29} Two of the studies using internal controls also matched for known confounders such as age and parity.^{27 30} The data were retrieved from hospital records, questionnaires, and national registries. The number of participants in the treated and untreated groups ranged from 21 to 15 108 and from 20 to 2 164 006, respectively (table 1).

Table 1 shows the Newcastle-Ottawa scores for quality assessment of the observational studies. All the studies scored at least 7. A more detailed assessment is included in the supplementary file.

Table 2 show the fertility and early pregnancy outcomes assessed in each of the included studies. Tables 3 and 4 show the pooled results.

Fertility outcomes

The meta-analysis did not provide any evidence to suggest that treatment for cervical intraepithelial neoplasia adversely affects the chances of conception (table 3 and fig 2).

The results of the individual studies on the overall pregnancy rate varied. Two studies did not report any significant differences,^{13 32} whereas the remaining two described significantly higher overall pregnancy rates for the treated population.^{13 30} Specifically, one study³⁰ reported that women treated with laser conisation or ablation had high pregnancy rates (277/433; 64%) compared with untreated women (177/433; 41%) (relative risk 1.56, 95% confidence interval 1.37 to 1.79). Similarly, another study¹⁵ reported higher pregnancy rates for treated women (multiple methods: cold knife conisation, LLETZ, laser conisation, laser ablation, cryotherapy) compared with untreated women (2578/6179; 41.7% v 11642/30463; 38.2%, respectively) (1.09, 1.06 to 1.13). The pooled analysis for the overall pregnancy rate assessed in four studies was higher for treated women than for untreated women (43% and 38%) (1.29, 1.02 to 1.64), although heterogeneity in the studies was high ($P<0.0001$, fig 2).

Two small studies assessed the pregnancy rate in women with an intention to conceive,^{14 32} and in both the result was no different between treated and untreated women. The pooled meta-analysis also confirmed that treated and untreated women did not differ significantly (two studies; relative risk 0.93, 95% confidence interval 0.80 to 1.08, fig 3).

Three small studies described the time needed to conceive.^{13 14 16} Two of them^{13 14} reported non-significant differences, although one¹⁶ suggested that the proportion of women who required more than 12 months to conceive was significantly higher for treated women (all methods, not specified) (25/152; 16%) than for all untreated women (86/1021; 8.4%) (relative risk 1.95, 95% confidence interval 1.29 to 2.95) or compared with non-treated women attending for colposcopy (13/151; 9%) (1.91,

1.02 to 3.59). The pooled meta-analysis suggested that treatment did not adversely affect the proportion of women who required more than 12 months to conceive (three studies; 14.7% v 9.2%, 1.45, 0.89 to 2.37, $P=0.14$, fig 3). The remaining intervals to conception that were assessed were also not significantly affected ($P>0.05$).

Early pregnancy outcomes

Early pregnancy outcomes were assessed in 14 studies. Table 4 and figures 4 and 5 present the results of the meta-analysis on the early pregnancy outcomes.

All studies reporting on the overall rate for miscarriage,^{13-15 24 26-28 31 32} apart from one,³⁰ reported no significant differences between treated and untreated populations. One study³⁰ reported a protective effect for treated women compared with untreated controls (11.4% and 18.6%) (relative risk 0.60, 95% confidence interval 0.38 to 0.94, $P=0.03$). The pooled analysis for the total rate for miscarriage between treated and untreated women was not significantly different (10 studies; 4.6% v 2.8%, 1.04, 0.90 to 1.21) for any of the methods assessed (fig 4).

Four studies reported on miscarriage rates in the first trimester, separately^{14 24 27 28}; the included studies did not differ significantly. The pooled meta-analysis for miscarriage rates in the first trimester showed no significant differences (9.8% v 8.4%; 1.16, 0.80 to 1.69) (fig 5).

Eight studies reported on miscarriage rates in the second trimester.^{4 14 23-25 27-29} Seven did not report significant differences, whereas one with a large sample size⁴ showed that treated women had a significantly higher rate of miscarriage in the second trimester (226/15 108; 1.5%) when compared with untreated (8501/2 164 006; 0.4%, 3.81, 3.34 to 4.34) or internal controls (209/57136; 0.4%, 4.09, 3.39 to 4.93). In the pooled meta-analysis, we found that cervical treatment significantly increased the risk of miscarriage in the second trimester. This outcome was assessed in eight studies and 16 558 treated women. The rate was higher for treated than for untreated women (1.6% and 0.4%, 2.60, 1.45 to 4.67, fig 5). There was no significant interstudy heterogeneity.

The rate of ectopic pregnancy was also higher for treated than for untreated women (1.6% and 0.8%) (six studies, 1.89, 1.50 to 2.39), whereas the rate for molar pregnancy did not differ ($P>0.05$). The termination of pregnancy rate was higher in women with a history of treatment than in untreated controls (12.2% and 7.4%) (seven studies, 1.71, 1.31 to 2.22).

Given the low number of studies included in each of the meta-analyses, the risk of publication bias and the potential sources of heterogeneity could not be assessed formally.

Discussion

Cervical treatment has been associated with an increased risk of adverse obstetric sequelae and preterm birth in subsequent pregnancies.^{2 3 7 34} More recent data suggest that cervical intraepithelial neoplasia itself may partly contribute to that risk,⁶ while there seems to be a “dose-response” effect documented for treatment; the larger the excision or proportion of cervix removed, the larger and more serious the effect may be from treatment.^{5 7 35-38}

It has been suggested that cervical treatment may impair future fertility for women as a result of cervical stenosis and the reduction of cervical glands and mucus.^{10 11} Similarly, concerns have been raised that the rate of miscarriages in the second trimester is also increased in treated populations. To date, the

impact on fertility and early pregnancy outcomes has not been systematically assessed in the published literature.

This systematic review and meta-analysis demonstrates that there is no evidence to support that treatment for cervical precancer adversely affects fertility outcomes and the chances to conceive. Although the pregnancy rate in women with an intention to conceive was no different, the overall pregnancy rate was higher for women who received treatment than for untreated controls; the heterogeneity across studies was significant. The higher pregnancy rate in the treated population may be explained by sexual and behavioural characteristics in women with cervical precancer or their increased anxiety for their future fertility after treatment. The time required to conceive was overall similar among the compared populations. There was a trend towards longer conception time for treated women, but the differences were not significant. Although this may hint at an impact of treatment on fertility, it may also be explained by clinicians' recommendation to avoid conception during the early postoperative period and until the first follow-up assessment confirms the absence of residual disease.

Although the rates for miscarriage overall and in the first trimester did not differ, this meta-analysis suggests that treatment for cervical intraepithelial neoplasia increases the risk of miscarriage in the second trimester, possibly as a result of cervical incompetence after proportionally large excisions. The incidence of miscarriages in the second trimester is low and therefore individual small cohorts often failed to reach significant results previously. This is the first meta-analysis combining multiple studies to show statistically significant differences. Although the results of the analysis are dominated by one large study,⁴ this is not an outlier, and exclusion of this study from the analysis yielded similar results. This study included various treatment modalities (knife, laser, and LLETZ) and the outcomes for each individual technique were not available from the registry linkage. Most deliveries (87%) were after the 1990s and the introduction of LLETZ, although the timing of treatment was unclear. The higher number of ectopic pregnancies and terminations in the treated population possibly reflects the characteristics of women with cervical precancer, who are known to be at a higher risk of sexually transmitted disease and unplanned pregnancies and not related to cervical intraepithelial neoplasia treatment. It may also be that a dysfunction in the immune defences and the protective mechanisms makes some women more prone to ascending infections and also persistence of human papillomavirus and cervical precancer. Conversely, human papillomavirus infection itself may have an effect on antimicrobials in the cervical mucus.

Strengths and limitations of this review

This is the first systematic review to show that fertility is probably not impaired after treatment. The results, however, should be interpreted with caution. The included studies were heterogeneous for study design, included populations, matching for confounders, length of follow-up, and outcome verification. The number of studies and the study size were often small for many of the reported outcomes and the outcomes of interest were difficult to objectively measure. Although the interstudy heterogeneity was not significant for all outcomes apart from one, the number of studies was small and the analysis could be affected by the addition of further studies. The effect was not significantly changed by sensitivity analysis excluding some of the largest studies. All studies apart from one²⁶ described retrospective cohorts and are prone to possible bias. The data were derived from self reporting, clinic datasets, telephone contacts, and postal questionnaires or national registries and

may represent incomplete and selected data. Early pregnancy outcomes are often less well reported than outcomes in the third trimester. The level of over-reporting or under-reporting may be different for treated and untreated women and the impact of this is difficult to assess. Reporting may be better in the treated group owing to easier access to gynaecological services or, conversely, may be lower in women with cervical intraepithelial neoplasia, who often belong to lower socioeconomic classes that are likely to be less compliant with recommended medical care. Studies that assess fertility outcomes post-treatment are difficult owing to the multifactorial nature of the condition (for example, male, lifestyle). It is often difficult to design such a study and yet eliminate all of the confounding variables.

The analysis included studies with different designs, using comparisons between and among women and mixed matching. It was not possible to carry out subgroup analyses for the different comparison groups because of the limited number of studies in each group. It is unlikely that the use of different comparison groups generated bias because the studies using different comparators showed similar direction and magnitude of effect. Four studies used comparisons of the same women before and after treatment; two of these also matched for known confounders. A sensitivity analysis that excluded the four studies using internal comparators and a sensitivity analysis that excluded old or poor quality studies did not significantly change the direction or the magnitude of the effect of the meta-analysis.

A separate analysis for different treatment modalities was done, but the power to identify significant findings was limited owing to the lack of large studies. An analysis that would stratify according to the depth of the cone or parity was also not feasible, as these data were not reported by the individual studies. It is likely that the risk increases with greater proportions of the cervix removed. Future studies should try to stratify the risk of miscarriages in the second trimester and the chances of conception according to the depth and proportion of cervix excised. Inability to adjust for size of excision and treatment technique may mask the true effect that deep conisations could have on fertility and, conversely, the lack of effect that small excisions (<10 mm) may have on the risk of miscarriages in the second trimester.

Possible mechanisms

The exact mechanism that explains the increased risk of miscarriages in the second trimester and preterm birth associated with cervical intraepithelial neoplasia and its treatment is unclear. Although most obstetricians would think that this increase in risk is due to a simple lack of mechanical support, histological changes in the healed cervix affecting the tensile strength³⁹ or changes in the innate immune system and the vaginal microenvironment probably also make an important contribution. The uterus in pregnancy is protected from ascending infection by the cervix, its mucous plug, and its synthesis of antibacterial compounds, and by a "benign" lactobacillus dominated vaginal microflora.⁴⁰ There is a clear link between infection or inflammation and preterm birth. Removing part of the cervix or simply being infected with human papillomavirus may impair the host's defense mechanisms and change the chemical microenvironment and as a result affect the vaginal microbiome or the production of natural antimicrobials by the cervix.⁴¹ It may also be that some women share immunological variations and other factors that co-associate with both cervical intraepithelial neoplasia and preterm birth and that make them susceptible to not only persistent infections with human papillomavirus but also ascending infections and preterm birth when pregnant. A better

understanding of these factors may enable selection of women at risk and prevention with cause directed strategies.⁴²⁻⁴⁶ It may be possible to manipulate the vaginal microbiota through microbiome gene regulations and probiotic and prebiotic treatments to establish a healthy environment, combat disease, and improve health.⁴²⁻⁴³

Conclusion and policy implications

Despite the limitations of this meta-analysis, we found no evidence to suggest that fertility is affected by treatment for cervical intraepithelial neoplasia, although the risk of miscarriages in the second trimester was significantly increased. The risk of second trimester miscarriages with less aggressive treatment, such as LLETZ, particularly for small excisions, or the risk for reduced fertility in proportionally large conisations, remains unclear. Future large, well designed studies are required to carefully explore possible associations between treatment for cervical intraepithelial neoplasia and subsequent fertility and early and late pregnancy outcomes, stratifying by the size of excision and treatment technique. The exact mechanism and the extent of excision that increase the risk remain unknown. Caution should prevail when considering treatment in young women who may want future pregnancies. Until more evidence becomes available, it is important to remove as little tissue as possible, especially in nulliparous women with a small cervix, without compromising the eradication of the disease. More sensitive tests such as those for human papillomavirus DNA should be used to improve the detection of residual or recurrent lesions after treatment and to minimise the risk of future cancer in young women.⁴⁷ Every effort should be made to optimise both reproductive and oncological outcomes for women requiring treatment.³⁷⁻⁴⁸

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Data sharing: No additional data available.

Transparency: 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.

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What is already known on this topic

Treatment for cervical intraepithelial neoplasia increases the risk of preterm birth and this risk increases with increasing depth of excision
A large retrospective cohort reported that treated women had higher pregnancy rates than the untreated population¹⁵
However, another recent large series reported that women after conisation take longer to conceive than untreated normal women or women attending colposcopy but not treated¹⁶

What this study adds

There is no evidence to support that fertility is affected after treatment for cervical precancer, although the rate of miscarriages in the second trimester was increased
Future studies should carefully explore associations between treatment and subsequent reproductive outcomes stratifying by the size of excision and treatment technique

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Tables

Table 1 | Characteristics of included studies comparing fertility and early pregnancy outcomes with untreated women

Study	Matching factors	Procedure	Treated	Untreated	Source of data	Outcomes	Newcastle-Ottawa score*
Weber et al 1979 ¹⁴	Partly age and partly internal matching†	Cold knife conisation	21	20	Interview, postal questionnaire	Pregnancy rates in women wishing to conceive; conceptions within given time; miscarriages (total, first and second trimester); terminations	8
Larsson et al 1982 ²⁷	Internal*; comparable for age, parity, socioeconomic status, smoking, surgical interventions, various diseases	Cold knife conisation	294	341	Hospital records	Miscarriages (total, first and second trimester); ectopic pregnancies; terminations	9
Buller et al 1982 ²⁴	Internal†	Cold knife conisation	88	106	Hospital records	Miscarriages (total, first and second trimester); ectopic pregnancies; molar pregnancies; terminations	8
Blomfield et al 1993 ²³	Age, parity, ethnicity	LLETZ	40	80	Hospital records	Miscarriages (second trimester)	9
Biggig et al 1994 ¹³	Age, geographical area; all controls had negative smear test results	LLETZ	76 to 229	66 to 299‡	Telephone interview, postal questionnaire	Total pregnancy rates; conceptions within given time; miscarriages (total); ectopic pregnancies	7
Cruikshank et al 1995 ²⁵	Age, parity, height, smoking status, and partner's social class	LLETZ	149	298	Postal questionnaire (treated); maternity databank (untreated)	Miscarriages (second trimester)	8
Sagot et al 1995 ²⁸	Internal†	Laser conisation	71	82	Hospital records	Miscarriages (total, first and second trimester); ectopic pregnancies; molar pregnancies; terminations	8
Spitzer et al 1995 ³⁰	Internal†; matched for age and parity with population from pretreatment interval of same patients	Laser conisation; laser ablation	433	433	Telephone interview, questionnaire	Total pregnancy rates; miscarriages (total); ectopic pregnancies; terminations	8
Turlington et al 1996 ³²	Untreated women had colposcopy and biopsy but no treatment	LLETZ	54	57	Telephone interview, mail questionnaire	Total pregnancy rates; pregnancy rates in women wishing to conceive; miscarriages (total); terminations	7
Tan et al 2004 ³¹	Age, parity, period of delivery	LLETZ	119	119	Hospital records	Miscarriages (total)	9
Sjoberg et al 2007 ²⁹	Age, parity, plurality, and regression analysis for smoking status, marital status, and education	Laser conisation; LLETZ	742	742	National registry	Miscarriages (second trimester)	8
Albrechtsen et al 2008 ⁴	Unmatched—regression analysis for age and birth order	Cold knife conisation; laser conisation; LLETZ	15 108	2 164 006	National registry	Miscarriages (second trimester)	9
Kalliala et al 2012 ¹⁵	Unmatched—regression analysis for number of pregnancies and children, age, municipality	LLETZ; cold knife conisation; cryotherapy; laser conisation; laser ablation	6179	30 436	Hospital records, national registries	Total pregnancy rates	9
Frega et al 2013 ²⁶	Unmatched but only nulliparous, white ethnic group included	LLETZ	1329	462	Prospective records	Miscarriages (gestation not specified)	8

Table 1 (continued)

Study	Matching factors	Procedure	Treated	Untreated	Source of data	Outcomes	Newcastle-Ottawa score*
Spracklen et al 2013 ¹⁶	Unmatched—regression analysis for age, education, income, race, parity, body mass index, smoking status, cervical surgery, case status	Cold knife conisation; LLETZ; cryotherapy; laser ablation	152	151 colposcopy only; 1021 untreated	Birth registries, telephone interview	Conceptions within given time	8

LLETZ=large loop excision of the transformation zone.

All study designs were retrospective cohort, except for Frega et al,²⁶ which was a prospective cohort design.

*Score for quality assessment in observational studies: maximum 9, minimum 0 (see supplementary appendix 2).

†Self matching is comparison of pregnancies in same woman before and after treatment.

‡Different number of cases and controls for every outcome in same study.

Table 2| Reported individual outcomes in included studies assessing fertility and early pregnancy outcomes between treated and untreated women

	No with outcome/No in group (%)		
Treatment and fertility outcomes	Treated group	Untreated group	Relative risk (95% CI)
Weber et al 1979 ¹⁴			
Cold knife conisation:	n=21	n=20	
PRIC	18 (86)	18 (90)	0.95 (0.76 to 1.20)
Time to conception (months):			
0-3	10 (48)	9 (45)	1.06 (0.55 to 2.05)
0-6	12 (57)	11 (55)	1.04 (0.60 to 1.79)
0-9	14 (67)	13 (65)	1.03 (0.66 to 1.59)
0-12	14 (67)	14 (70)	0.95 (0.63 to 1.44)
0-24	18 (86)	18 (90)	0.95 (0.76 to 1.20)
Miscarriages:	n=66	n=55	
Total	12 (18)	6 (11)	1.67 (0.67 to 4.15)
First trimester	8 (12)	5 (9)	1.33 (0.46 to 3.84)
Second trimester	4 (6)	1 (2)	3.33 (0.38 to 28.96)
Termination of pregnancy	5 (8)	1 (2)	4.17 (0.50 to 34.61)
Buller et al 1982 ²⁴			
Cold knife conisation:	n=88	n=106	
Miscarriages:			
Total	11 (12.5)	10 (9)	1.20 (0.53 to 2.76)
First trimester	9 (10)	8 (7.5)	1.36 (0.55 to 3.36)
Second trimester	1 (1)	2 (2)	0.60 (0.06 to 6.53)
Ectopic pregnancy	3 (3)	1 (1)	3.61 (0.38 to 34.13)
Molar pregnancy	0 (0)	1 (1)	0.4 (0.02 to 9.88)
Termination of pregnancy	24 (27)	15 (14)	1.93 (1.08 to 3.44)
Larsson et al 1982 ²⁷			
Cold knife conisation:	n=294	n=341	
Miscarriages:			
Total	40 (14)	37 (11)	1.25 (0.82 to 1.91)
First trimester	24 (8)	25 (7)	1.11 (0.65 to 1.91)
Second trimester	16 (5)	12 (3.5)	1.55 (0.74 to 3.22)
Ectopic pregnancy	10 (3)	1 (0.3)	11.60 (1.49 to 90.07)
Termination of pregnancy	47 (16)	19 (6)	2.87 (1.72 to 4.78)
Blomfield et al 1993 ²³			
LLETZ:			
Second trimester miscarriages	2/40 (5)	1/80 (1)	4.00 (0.37 to 42.80)
Bigrigg et al 1994 ¹³			
LLETZ:			
Pregnancy rates	76/229 (33)	66/229 (29)	1.15 (0.88 to 1.51)
Time to conception (months):	n=72	n=62	
0-3	36 (50)	36 (58)	0.86 (0.63 to 1.18)
0-6	61 (86)	51 (82)	1.03 (0.89 to 1.19)
0-12	67 (93)	55 (89)	1.05 (0.94 to 1.17)
>12	7 (10)	12 (20)	0.50 (0.21 to 1.20)
>36	4 (5.5)	5 (8)	0.69 (0.19 to 2.45)
Total miscarriages	5/76 (7)	6/66 (9)	0.72 (0.23 to 2.26)
Ectopic pregnancy	2/76 (3)	2/66 (3)	0.87 (0.13 to 6.00)
Cruikshank et al 1995 ²⁵			
LLETZ:			

Table 2 (continued)

Treatment and fertility outcomes	No with outcome/No in group (%)		Relative risk (95% CI)
	Treated group	Untreated group	
Second trimester miscarriages	2/149 (1)	3/298 (1)	1.33 (0.23 to 7.89)
Sagot et al 1995²⁸			
Laser conisation:			
Miscarriages:	n=71	n=82	
Total	10 (14)	11 (13)	1.05 (0.47 to 2.33)
First trimester	10 (14)	11 (13)	1.05 (0.47 to 2.33)
Second trimester	0 (0)	0 (0)	NE
Ectopic pregnancy	2 (3)	2 (2)	1.15 (0.17 to 7.99)
Termination of pregnancy	6 (8.5)	10 (12)	0.69 (0.27 to 1.81)
Spitzer et al 1995³⁰			
Laser conisation, laser ablation:			
Pregnancy rate:			
Laser conisation	67/100 (67)	28/100 (28)	2.39 (1.70 to 3.37)
Laser ablation	210/333 (63)	149/333 (45)	1.41 (1.22 to 1.63)
All laser	277/433 (64)	177/433 (41)	1.56 (1.37 to 1.79)
Total miscarriages:			
Laser conisation	7/67 (10)	7/28 (25)	0.42 (0.16 to 1.08)
Laser ablation	24/210 (11)	26/149 (17)	0.65 (0.39 to 1.09)
All laser	31/277 (11)	33/177 (19)	0.60 (0.38 to 0.94)
Ectopic pregnancy:			
Laser conisation	3/67 (4.5)	2/28 (7)	0.63 (0.11 to 3.55)
Laser ablation	5/210 (2)	2/149 (1)	1.77 (0.35 to 9.02)
All laser	8/277 (3)	4/177 (2)	1.28 (0.39 to 4.18)
Termination of pregnancy:			
Laser conisation	23/67 (34)	4/28 (14)	2.40 (0.91 to 6.31)
Laser ablation	52/210 (25)	24/149 (16)	1.54 (0.99 to 2.38)
All Laser	75/277 (27)	28/177 (16)	1.71 (1.16 to 2.53)
Turlington et al 1996³²			
LLETZ:			
Pregnancy rate	15/54 (28)	21/57 (37)	0.75 (0.44 to 1.30)
PRIC	11/12 (92)	17/17 (100)	0.95 (0.76 to 1.20)
Total miscarriages	0/15 (0)	3/21 (14)	0.20 (0.01 to 3.54)
Termination of pregnancy	0/15 (0)	2/21 (9.5)	0.28 (0.01 to 5.35)
Tan et al 2004³¹			
LLETZ			
Total miscarriages	14/119 (12)	11/119 (9)	1.27 (0.60 to 2.69)
Sjoberg et al 2007²⁹			
laser conisation, LLETZ			
Second trimester miscarriages	7/742 (1)	0/742 (0)	15.00 (0.86 to 262.16)
Albrechtsen et al 2008⁴			
Cold knife conisation, laser conisation, LLETZ:			
Second trimester miscarriages	226/15 108 (1.5)	8501/2 164 006 (0.4) (untreated)	3.81 (3.34 to 4.34) (untreated)
Second trimester miscarriages	226/15 108 (1.5)	209/57136 (0.4) (internal)	4.09 (3.39 to 4.93) (internal)
Kalliala et al 2012¹⁵			
All treatments*:	n=6179	n=30 463	
Pregnancy rate	2578 (42)	11 642 (38)	1.09 (1.06 to 1.13)
Total miscarriages	159 (3)	707 (2)	1.11 (0.93 to 1.31)

Table 2 (continued)

Treatment and fertility outcomes	No with outcome/No in group (%)		Relative risk (95% CI)
	Treated group	Untreated group	
Ectopic pregnancy	89 (1)	229 (1)	1.91 (1.50 to 2.44)
Molar pregnancy	50 (1)	225 (1)	1.10 (0.81 to 1.49)
Termination of pregnancy	695 (11)	2245 (7)	1.52 (1.41 to 1.65)
Frega et al 2013²⁶			
LLETZ:			
Total miscarriages	69/475 (14.5)	62/441 (14)	1.03 (0.75 to 1.42)
Spracklen et al 2013¹⁶			
All treatments*:			
Time to conception (months):			
>12	25/152 (16)	Untreated 86/1021 (8)	1.95 (1.29 to 2.95)
>12	25/152 (16)	Colposcopy only 13/151 (9)	1.91 (1.02 to 3.59)
All treatments*†:			
All excisional	15/91 (16.5)	51/611 (8)	1.97 (1.16 to 3.36)
All ablative	10/61 (16)	35/410 (8.5)	1.92 (1.00 to 3.68)
LLETZ	8/45 (18)	25/302 (8)	2.15 (1.03 to 4.47)
Cold knife conisation	7/46 (15)	26/309 (8)	1.81 (0.83 to 3.93)
Cryotherapy	6/44 (14)	25/295 (8.5)	1.61 (0.70 to 3.70)
Laser ablation	4/17 (23.5)	10/115 (9)	2.71 (0.95 to 7.67)

LLETZ=large loop excision of the transformation zone; NA=not available; NE=not estimable; NPIC=number of pregnancies in women with intention to conceive; PRIC=pregnancy rates in women with an intention to conceive.

*LLETZ, cold knife conisation, cryotherapy, laser conisation, and laser ablation.

†Compared with untreated women.

Table 3| Meta-analysis of studies comparing fertility in women after treatment for cervical intraepithelial neoplasia versus untreated controls

Fertility outcomes and treatment	Untreated group	No of studies	No of women	No with outcome/No in group (%)		Effect estimate relative risk (95% CI)	Heterogeneity, P value (I ² %)
				Treated group	Untreated group		
Total pregnancy rate							
LLETZ	No treatment	2	569	91/283 (32.2)	87/286 (30.4)	1.00 (0.67 to 1.48)	0.18 (45)
Laser conisation	No treatment	1	200	67/100 (67.0)	28/100 (28.0)	2.39 (1.70 to 3.37)	NE (NE)
Laser ablation	No treatment	1	666	210/333 (63.0)	149/333 (44.7)	1.41 (1.22 to 1.63)	NE (NE)
Treatment NS	No treatment	1	36 615	2578/6179 (41.7)	11 642/30 436 (38.3)	1.09 (1.02 to 1.64)	NE (NE)
All treatment types	No treatment	4	38 050	2946/6895 (42.7)	11 906/31 155 (38.2)	1.29 (1.02 to 1.64)	<0.0001 (88)
Pregnancy rate in women with intention to conceive							
All treatment types	No treatment	2	70	29/33 (87.9)	35/37 (94.6)	0.93 (0.80 to 1.08)	0.77 (0)
Time to conception (months):							
0-3	No treatment	2	175	46/93 (49.5)	45/82 (54.9)	0.89 (0.67 to 1.19)	0.58 (0)
0-6	No treatment	2	175	73/93(78.5)	62/82 (75.6)	1.03 (0.89 to 1.19)	0.97 (0)
0-9	No treatment	1	41	14/21 (66.7)	13/20 (65.0)	1.03 (0.66 to 1.59)	NE (NE)
0-12	No treatment	2	175	81/93 (87.1)	69/82 (84.1)	1.04 (0.94 to 1.16)	0.62 (0)
0-24	No treatment	1	41	18/21 (85.7)	18/20 (90.0)	0.95 (0.76 to 1.20)	NE (NE)
Conception >12 months:							
Cold knife conisation	No treatment	2	396	11/67 (16.4)	30/329 (9.1)	1.51 (0.78 to 2.92)	0.39 (0)
LLETZ	No treatment	2	481	15/117 (12.8)	37/364 (10.2)	1.06 (0.25 to 4.47)	0.01 (84)
Laser ablation	No treatment	1	132	4/17 (23.5)	10/115 (8.7)	2.71 (0.95 to 7.67)	NE (NE)
Cryotherapy	No treatment	1	339	6/44 (13.6)	25/295 (8.5)	1.61 (0.70 to 3.70)	NE (NE)
Excisional treatment	No treatment	3	877	26/184 (14.1)	67/693 (9.7)	1.03 (0.40 to 2.65)	0.03 (73)
Ablative treatment	No treatment	1	471	10/61 (16.4)	35/410 (8.5)	1.92 (1.00 to 3.68)	NE (NE)
All treatment types	No treatment	3	1348	36/245 (14.7)	102/1103 (9.2)	1.45 (0.89 to 2.37)	0.10 (46)
Conception >12 months:							
Cold knife conisation	Colposcopy only	1	91	7/46 (15.2)	4/45 (8.9)	1.71 (0.54 to 5.45)	NE (NE)
LLETZ	Colposcopy only	1	90	8/45 (17.8)	4/45 (8.9)	2.00 (0.65 to 6.17)	NE (NE)
Laser ablation	Colposcopy only	1	34	4/17 (23.5)	1/17 (5.9)	4.00 (0.50 to 32.20)	NE (NE)
Cryotherapy	Colposcopy only	1	88	6/44 (13.6)	4/44 (9.1)	1.50 (0.45 to 4.95)	NE (NE)
Excisional treatment	Colposcopy only	1	181	15/91 (16.5)	8/90 (8.9)	1.85 (0.83 to 4.16)	NE (NE)
Ablative treatment	Colposcopy only	1	122	10/61 (16.4)	5/61 (8.2)	2.00 (0.73 to 5.51)	NE (NE)
All treatment types	Colposcopy only	1	303	25/152 (16.4)	13/151 (8.6)	1.88 (0.99 to 3.55)	0.88 (0)
Conception >36 months:							
All treatment types	No treatment	1	134	4/72 (5.5)	5/62 (8.0)	0.69 (0.19 to 2.45)	NE (NE)

LLETZ=Large Loop Excision of the Transformation Zone; NS=not specified; NE=not estimable.

Not all abbreviations mentioned NE to termination of pregnancy.

Table 4| Meta-analysis of studies comparing early pregnancy outcomes in women after treatment for cervical intraepithelial neoplasia versus untreated controls

Early pregnancy outcomes by treatment group	Untreated group: No of studies	No of women	No with outcome/No in group (%)		Effect estimate relative risk (95% CI)	Heterogeneity: P value (I ² %)
			Treated group	Untreated group		
Miscarriage rates						
Total miscarriages:						
Cold knife conisation	3	950	62/448 (13.8)	53/502 (10.6)	1.30 (0.92 to 1.83)	0.84 (0)
LLETZ	4	1332	88/685 (12.8)	82/647 (12.7)	1.03 (0.77 to 1.36)	0.58 (0)
Laser conisation	2	248	17/138 (12.3)	18/110 (16.4)	0.69 (0.28 to 1.69)	0.14 (53)
Laser ablation	1	359	24/210 (11.4)	26/149 (17.4)	0.65 (0.39 to 1.09)	NE (NE)
Excisional treatment	9	2530	167/1271 (13.1)	153/1259 (12.2)	1.07 (0.87 to 1.31)	0.50 (0)
Ablative treatment	1	359	24/210 (11.4)	26/149 (17.4)	0.65 (0.39 to 1.09)	NE (NE)
Treatment NS	1	36 615	159/6179 (2.6)	707/30 436 (2.3)	1.11 (0.93 to 1.31)	NE (NE)
All treatment types	10	39 504	350/7660 (4.6)	886/31 844 (2.8)	1.04 (0.90 to 1.21)	0.36 (9)
First trimester miscarriages:						
Cold knife conisation	3	950	41/448 (9.2)	38/502 (7.6)	1.20 (0.78 to 1.83)	0.91 (0)
Laser conisation	1	153	10/71 (14.1)	11/82 (13.4)	1.05 (0.47 to 2.33)	NE (NE)
Excisional treatment	4	1103	51/519 (9.8)	49/584 (8.4)	1.16 (0.80 to 1.69)	0.97 (0)
Second trimester miscarriages:						
Cold knife conisation	3	950	21/448 (4.7)	15/502 (3.0)	1.55 (0.79 to 3.01)	0.58 (0)
LLETZ	2	567	4/189 (2.1)	4/378 (1.1)	1.98 (0.48 to 8.21)	0.47 (0)
Laser conisation	1	153	0/71 (0)	0/82 (0)	NE	NE (NE)
Excisional treatment NS	2	2 180 598	233/15 850 (1.5)	8510/2 164 748 (0.4)	3.82 (3.35 to 4.35)	0.34 (0)
Excisional treatment	8	2 182 268	258/16 558 (1.6)	8520/2 165 710 (0.4)	2.60 (1.45 to 4.67)	0.12 (41)
Ectopic pregnancy						
Cold knife conisation	2	388	13/282 (3.4)	2/447 (0.4)	6.83 (1.50 to 31.02)	0.44 (0)
LLETZ	1	142	2/76 (2.6)	2/66 (3.0)	0.87 (0.13 to 6.00)	NE (NE)
Laser conisation	2	248	5/138 (3.6)	4/110 (3.6)	0.82 (0.23 to 2.99)	0.64 (0)
Laser ablation	1	359	5/210 (2.4)	2/149 (1.3)	1.77 (0.35 to 9.02)	NE (NE)
Excisional treatment	5	1219	20/596 (3.4)	8/623 (1.3)	1.77 (0.59 to 5.27)	0.19 (35)
Ablative treatment	1	359	5/210 (2.4)	2/149 (1.3)	1.77 (0.35 to 9.02)	NE (NE)
Treatment NS	1	36615	89/6179 (1.4)	229/30 436 (0.8)	1.91 (1.50 to 2.44)	NE (NE)
All treatment types	6	38193	114/6985 (1.6)	239/31 208 (0.8)	1.89 (1.50 to 2.39)	0.44 (0)
Molar pregnancy						
Cold knife conisation	1	194	0/88 (0)	1/106 (0.9)	0.40 (0.02 to 9.88)	NE (NE)
Treatment NS	1	36 615	50/6179 (0.8)	225/30 436 (0.7)	1.10 (0.81 to 1.49)	NE (NE)
All treatment types	2	36 809	50/6267 (0.8)	226/30 542 (0.7)	1.08 (0.80 to 1.47)	0.54 (0)
Termination of pregnancy						
Cold knife conisation	3	950	76/448 (17.0)	35/502 (7.0)	2.45 (1.68 to 3.58)	0.53 (0)
LLETZ	1	36	0/15 (0)	2/21 (9.5)	0.28 (0.01 to 5.35)	NE (NE)
Laser conisation	2	248	29/138 (21.0)	14/110 (12.7)	1.29 (0.38 to 4.37)	0.07 (69)
Excisional treatment	6	1234	105/601 (17.5)	51/633 (8.1)	1.87 (1.12 to 3.11)	0.11 (44)
Laser ablation	1	359	52/210 (24.8)	24/149 (16.1)	1.54 (0.99 to 2.38)	NE (NE)
Ablative treatment	1	359	52/210 (24.8)	24/149 (16.1)	1.54 (0.99 to 2.38)	NE (NE)
Treatment NS	1	36 615	695/6179 (11.2)	2245/30 436 (7.4)	1.52 (1.41 to 1.65)	NE (NE)
All treatment types	7	38 208	852/6990 (12.2)	2320/31 218 (7.4)	1.71 (1.31 to 2.22)	0.10 (41)

LLETZ=large loop excision of the transformation zone; NS=not specified; NE=not estimable.

Figures

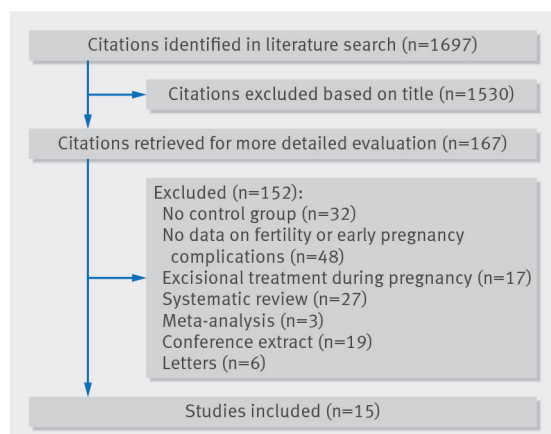


Fig 1 PRISMA flowchart

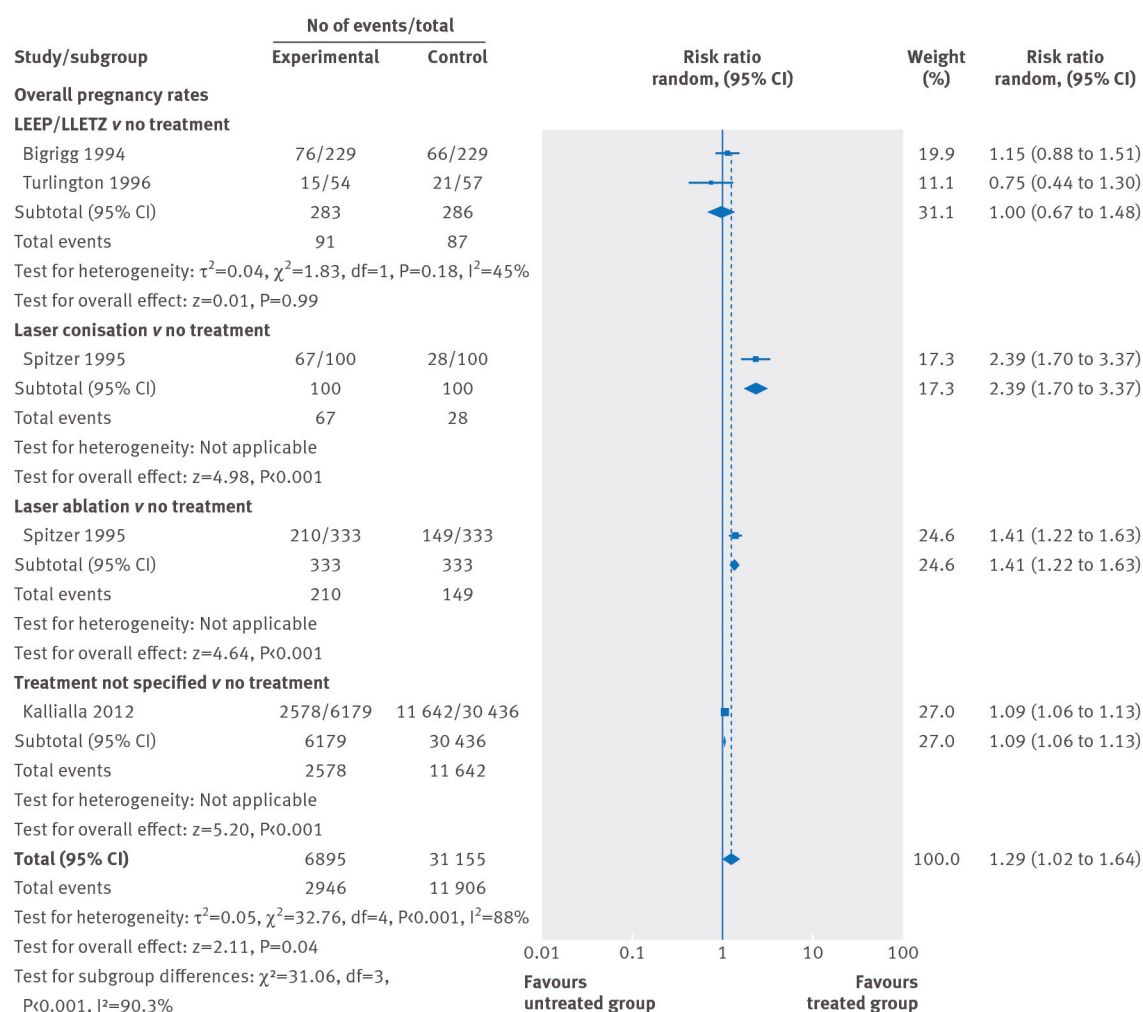


Fig 2 Meta-analysis on overall pregnancy rates in treated versus untreated women. LLETZ=large loop excision of the transformation zone; LEEP=loop electrosurgical excisional procedure

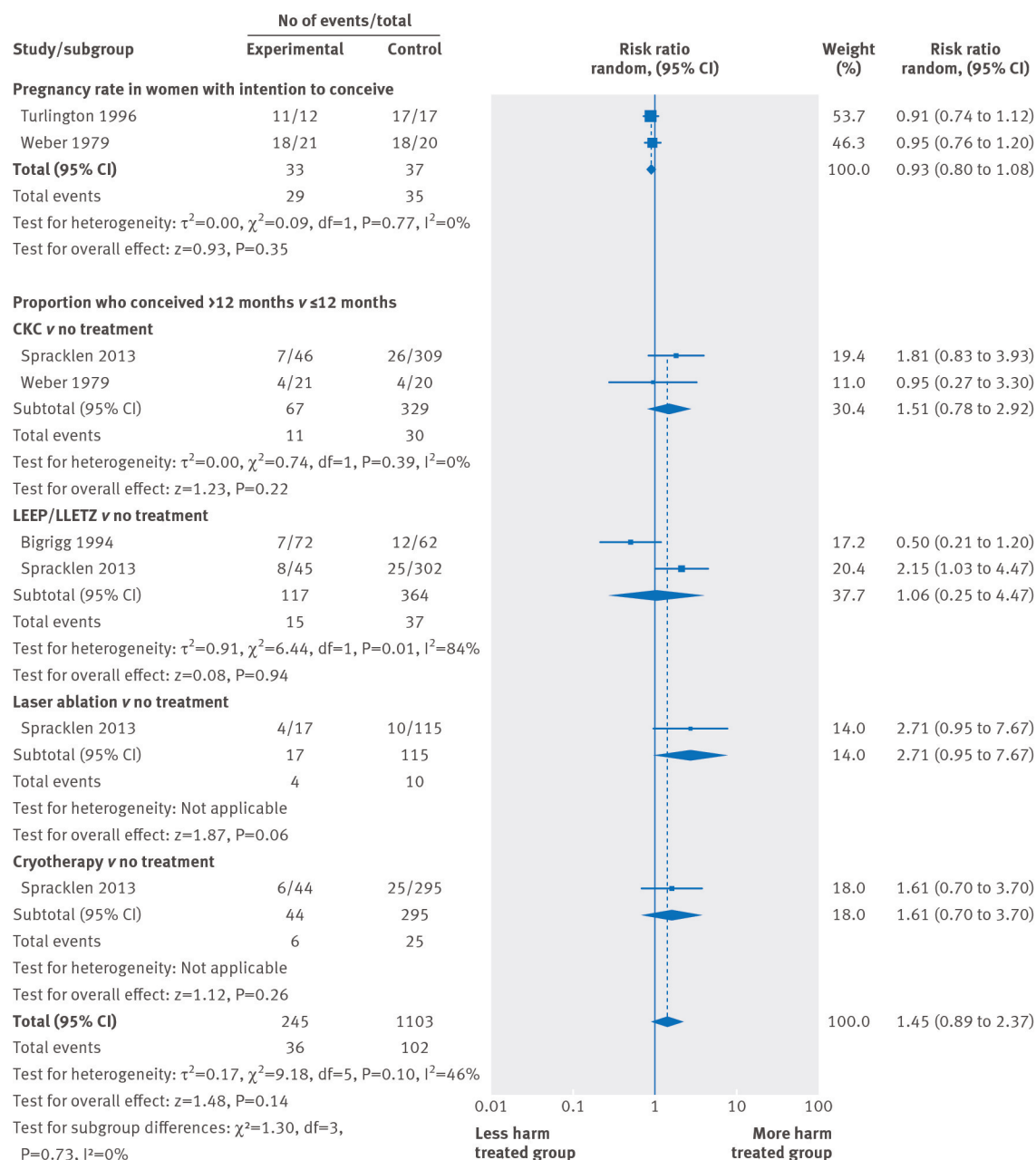


Fig 3 Meta-analysis on pregnancy rates in women with an intention to conceive, and time to conception greater than 12 months in treated versus untreated women. CKC=cold knife conisation; LLETZ=large loop excision of the transformation zone; LEEP=loop electrosurgical excisional procedure

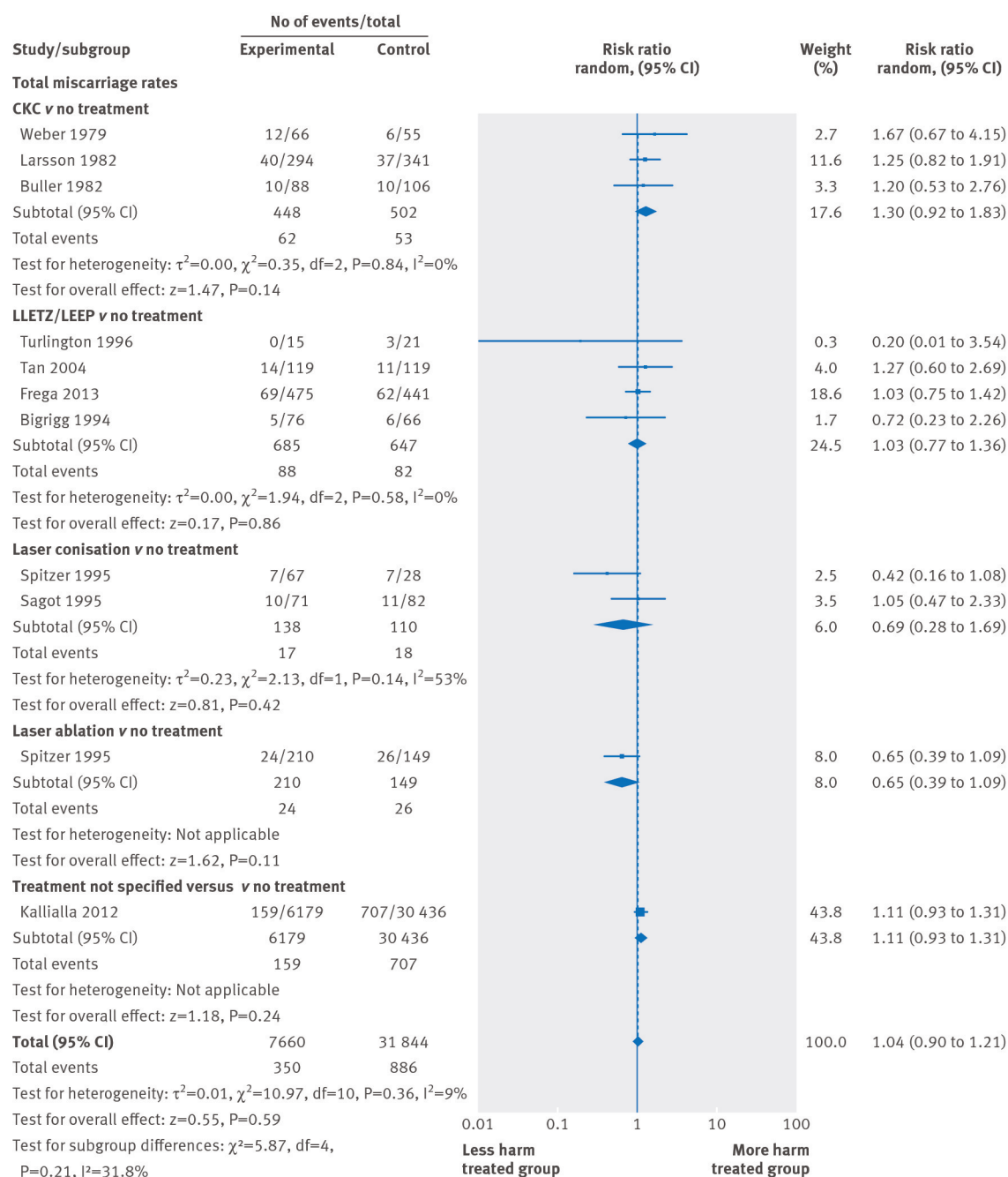


Fig 4 Forest plots from meta-analysis on rates for total miscarriage in treated versus untreated women. CKC=cold knife conisation; LLETZ=large loop excision of the transformation zone; LEEP=loop electrosurgical excisional procedure

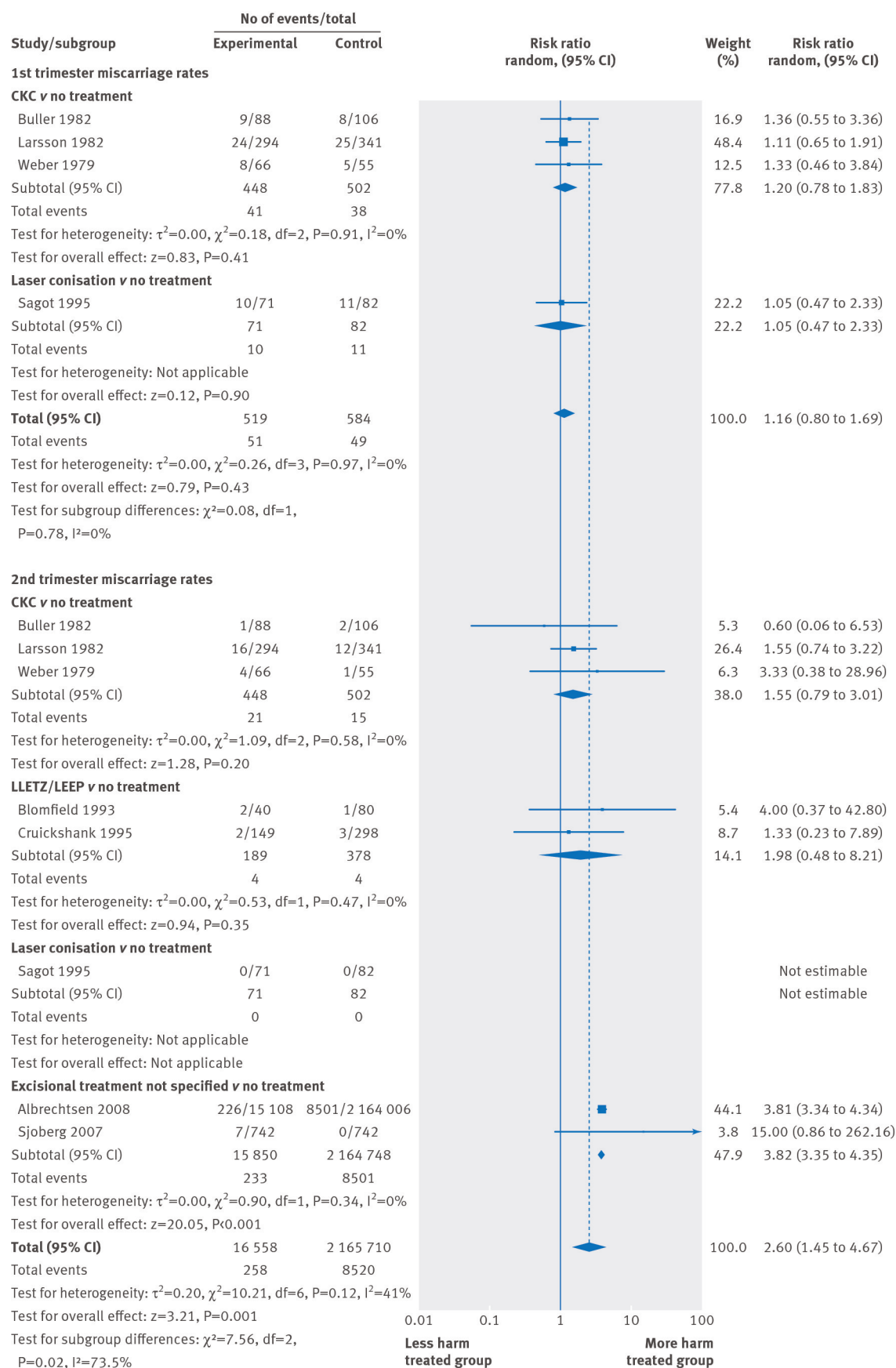


Fig 5 Forest plots from the meta-analysis on rates for miscarriage in first and second trimesters in treated versus untreated women. CKC=cold knife conisation; LLETZ=large loop excision of the transformation zone; LEEP=loop electrosurgical excisional procedure