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CIN treatment: Excisional procedures: Knife, laser or LEEP? How to minimize damage and optimize outcome

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Principles and techniques of treating CIN

Precancerous cervical lesions are described in three stages; CIN1, 2, and 3 according to the degree of cellular abnormality and extent of epithelial involvement.

The goal of treatment for CIN is to prevent possible **progression** to invasive cancer while **avoiding over-treatment** of lesions that are likely to regress.

CIN1 lesions usually do not require any treatment unless the lesion is persistent beyond two year.

Given the malignant potential of CIN3, there is an international consensus that these lesions should be treated following diagnosis, except in pregnancy.

Darragh TM, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions *Arch Pathol Lab Med* 2012
Partha Basu, et al. Management of cervical premalignant lesions, *Current Problems in Cancer* 2018

Principles and techniques of treating CIN

In recent years, some important distinctions have been discovered regarding CIN2.

Studies have shown that immunohistochemical staining for p16INK4 / Ki67 may provide a useful biomarker for prediction of progression of CIN2.

CIN2 lesions **over expressing p16INK4** are considered as HSIL and need treatment.

CIN2 lesions **not over–expressing p16INK4** are considered as LSIL and can be followed up.

All CIN2 lesions should be treated where such facilities do not exist.

Darragh TM, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions *Arch Pathol Lab Med* 2012
Partha Basu, et al. Management of cervical premalignant lesions, *Current Problems in Cancer* 2018

Three-tiered score for Ki-67 and p16^{ink4a} improves accuracy and reproducibility of grading CIN lesions

Marjolein van Zummeren,[1] Annemiek Leeman,[2] Wieke W Kremer,[1]

- Grading of cervical intraepithelial neoplasia (CIN) by a simple Ki-67 and p16^{ink4a} immunoscore system has a higher accuracy and reproducibility compared with current CIN grading.
- By use of the Ki-67 and p16^{ink4a} immunoscore, most of classical CIN2 can be divided into more accurately graded CIN1 and CIN3.
- Use of the Ki-67 and p16^{ink4a} immunoscore for CIN grading allows better evaluation of the role of new biomarkers in the development of cervical cancer.

van Zummeren M, *et al*. *J Clin Pathol* 2018

Principles and techniques of treating CIN

Excisional treatment of these lesions is not without risk and is associated with a significantly increased risk in subsequent pregnancies.

The obstetrical morbidity related to the excisional treatment **depends on** dimensions of the removed cervical tissue.

The risk of premature delivery following excision **appears to be significant** in women whose **depth of excised** cone is **greater than 10 mm.**

Arbyn M, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ 2008

Kyrgiou M, et al. Obstetrics outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006

Principles and techniques of treating CIN

Margin status also has a crucial importance, incomplete excision is related to a substantial risk of high-grade post-treatment disease.

Therefore, **excisional treatment** should be used only in well-selected women with a clear indication for invasive treatment.

Colposcopy would allow for the optimization of excisional procedures both in terms **of margins status and excised cone dimensions.**

Colposcopy guided excision may lead to significantly smaller cone specimens without compromising margin status.

Carlo A. Liverani, et al. Length but not transverse diameter of the excision specimen for high-grade cervical intraepithelial neoplasia (CIN 2–3) is a predictor of pregnancy outcome. European Journal of Cancer Prevention 2015
Hilal Z, et al . Loop electrosurgical excision procedure with or without intraoperative colposcopy: a randomized trial Am J Obstet Gynecol 2018

Exicisional techniques of treating CIN

- **Cold knife conization**
- **Laser**
- **Electrosurgery**

  Loop Electrosurgical Excision Procedure (LEEP) or

  Large Loop Excision of Transformation Zone (LLETZ)

  Needle Excision of Transformation Zone (NETZ)

Exicisional techniques of treating CIN

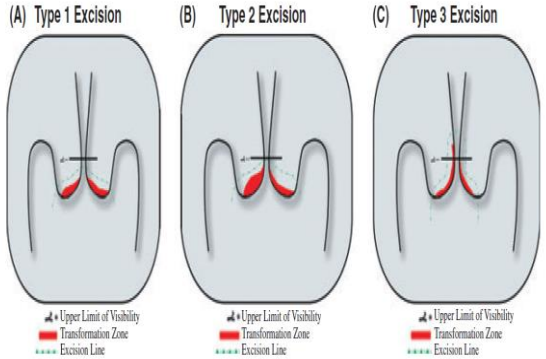


Figure 4. Line drawing of the three types of excision. (A) Excision of a completely ectocervical or type-1 TZ; the LLETZ procedure needs not encroach on the endocervical canal, nor does it need to be greater than 8-mm thick throughout the resection. (B) The type-2 excision has an endocervical component, but is fully visible. (C) The type-3 excision resects a longer and larger volume of tissue; the excision margin is depicted by an interrupted green line.

Treatment of CIN requires excision of the **entire transformation** zone rather than only of the visible abnormality.

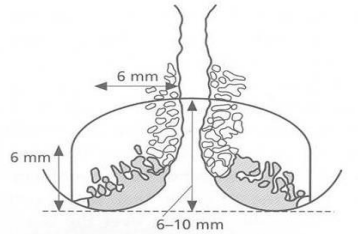
Type I TZ excision : Central cone length must be **8 mm** and not more than 10 mm, **5 mm** peripheral cone length of the transformation zone may be sufficient.

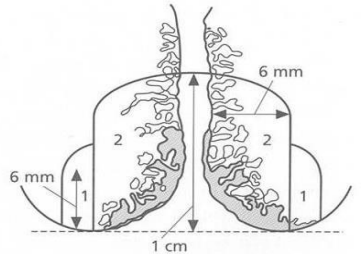
Type 2 TZ excision : not more than 15 mm length of tissue excised (10-15 mm)

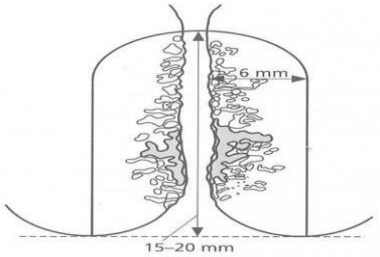
Type 3 TZ excisions : > 15 mm length (15-20 mm).

Should be used for women with:

suspected invasive disease
proven or suspected glandular disease
Type 3 TZ with proven or suspected high-grade disease.







Bornstein J, et al. ***2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy.*** Obstet Gynecol 2012

LEEP (loop electrosurgical excisional procedure)

Loop electrosurgical excision procedure (LEEP) was first demonstrated by Walter Prendiville in 1986.

The majority of patients can be treated under local anesthesia as outpatients, and the excised tissue can be sent for histopathologic evaluation.

The length of the excised cervical cone depends on the type of transformation zone.

Properly performed LEEP causes only minimal thermonecrosis on the surgical resection margin.

Kyrgiou M, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. *BMJ* 2014
Arbyn M, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: metaanalysis. *BMJ* 2008

Loop Electrosurgical Excisional Procedure (LEEP)

Treatment success of LEEP is reported as 91- 98% in non-randomised studies.

Complications have been reported in 7-10% of treated women.

50-70% of these complications are intra or post-operative bleeding. Haemostasis can be achieved easily by application of Monsell's solution.

Other complications are purulent vaginal discharge and pelvic pain.

The risk of cervical incompetence is dependent on the depth of the stromal tissue removed during the procedure.

Cervical stenosis is reported in a small number of cases which may lead to hematometria, infertility and difficulties during subsequent colposcopy.

Murdoch 1992, Prendeville 1989

Cold knife conization (CKC)

Cervical conization with a scalpel is an excisional method generally reserved for treating **adenocarcinoma in situ** and **microinvasive carcinoma**.

CKC avoids the thermal artifact of LEEP and Laser, thus allowing better histopathological assessment of cone margins.

The major **disadvantages of CKC** are that the procedure has to be performed under regional or general anesthesia for which hospitalization will be necessary and complications such as primary and secondary hemorrhage and adverse pregnancy events are higher than LEEP.

Martin-Hirsch PP et al. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev* 2013

Laser conization

This procedure can be performed under general or local analgesia.
A highly focused laser spot is used to make an ectocervical circumferential incision to a depth of 1 cm.

The **major advantages** are accurate tailoring of the size of the cone, low blood loss in most cases, and less cervical trauma **than with knife cut cones**.

D**isadvantage of laser conization** is that the cone biopsy specimen might suffer from thermal damage, making **histological evaluation of margins impossible**.

The treatment success of laser cone biopsy is reported as 93% to 96% in non-randomised studies.

Bostofte 1986, Tabor 1990

Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP

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EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY

Objective: To evaluate the long-term recurrence rates and complication of different techniques of cervical ablation. *Methods*: A randomized trial of three techniques of conization (cold knife, laser, and loop electrosurgical excisional procedure (LEEP)) for cervical intraepithelial neoplasia (CIN) in which 110 patients had been recruited. *Results*: Eighty-six patients were followed-up for more than 3 years. Of these 28 had been treated with the cold knife, 29 with LEEP and 29 by laser. Five recurrences were observed, one in the cold knife group, two in the LEEP group and two in the laser group (P = NS). The only observed complication was cervical stenosis: zero cases in the laser group, one case in the LEEP group and four cases in the cold knife group (laser versus cold knife: $P = 0.03$; LEEP versus cold knife: $P = 0.06$). Fifty pregnancies were observed in 39 patients. First and second trimester outcomes of pregnancy were without complications. One patient treated with the LEEP presented with a premature rupture of membranes and premature labor at 36 weeks. A total of nine cesarean sections were performed with two cases for cervical dystocia. *Conclusion*: There is no major difference in obstetrical outcome between the three techniques.

Table 3
Obstetrical results, first trimester outcome of pregnancies

	Cold knife	Laser	LEEP	Total
Number of pregnancies	13	25	12	50
Early miscarriage	1 (7.7%)	4 (16%)	1 (8.3%)	6 (12%)
Ectopic pregnancy	1 (7.7%)	1 (4%)	0	2 (4%)
Induced abortion	2 (15.4%)	3 (12%)	2 (16.7%)	7 (14%)
Pregnancies >1 trimester	9 (69.2%)	17 (68%)	9 (75%)	35 (70%)

Table 4
Obstetrical results, second and third trimester outcome of pregnancies

	Cold knife	Laser	LEEP	Total
Pregnancies >1 trimester	9	17	9	35
Late miscarriage	0	0	0	0
Threatened preterm delivery	0	2 (11.8%)	1 (11.1%)	3 (8.6%)
Preterm rupture of membrane and preterm delivery	0	0	1 (11.1%)	1 (2.9%)
Cesarean section	2 (22.2%)	4 (23.5%)	3 (33%)	9 (25.7%)

Cochrane Database Syst Rev. 2010

Surgery for cervical intraepithelial neoplasia.

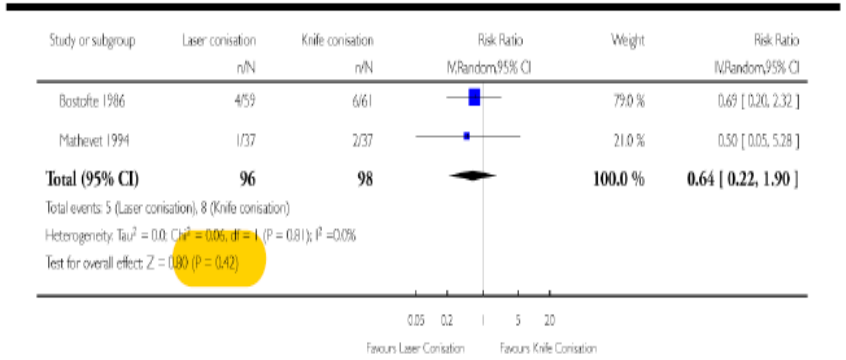
Martin-Hirsch PP

Analysis 3.1. Comparison 3 Laser conisation versus knife conisation, Outcome 1 Residual Disease (All Grades of CIN)

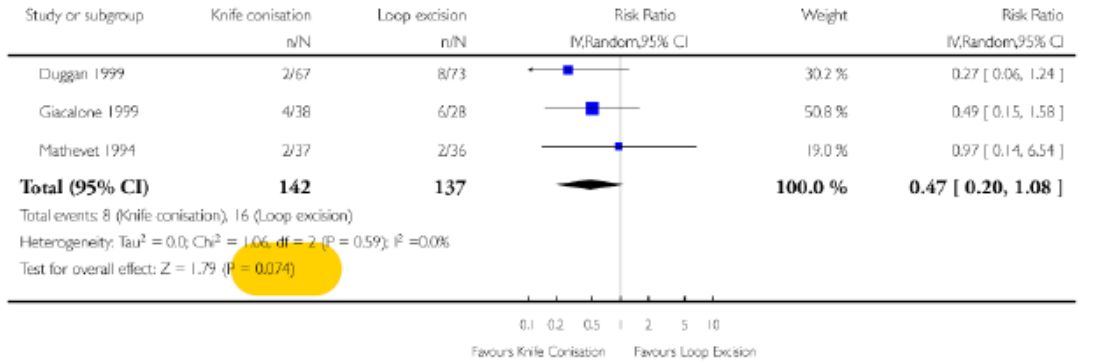
Review: Surgery for cervical intraepithelial neoplasia

Comparison: 3 Laser conisation versus knife conisation

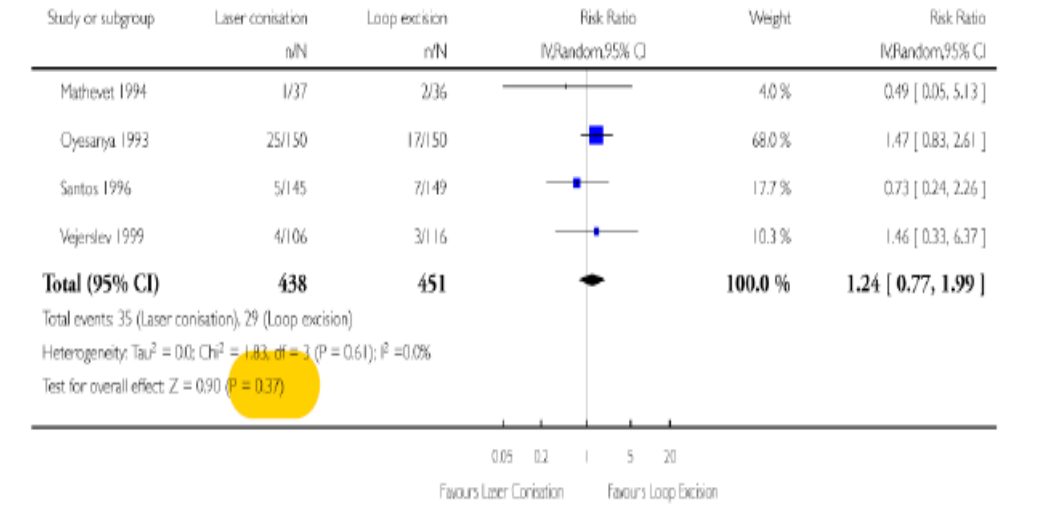
Outcome: 1 Residual Disease (All Grades of CIN)



Analysis 7.1. Comparison 7 Knife conisation versus loop excision, Outcome 1 Residual Disease



Analysis 5.1. Comparison 5 Laser conisation versus loop excision, Outcome 1 Residual Disease

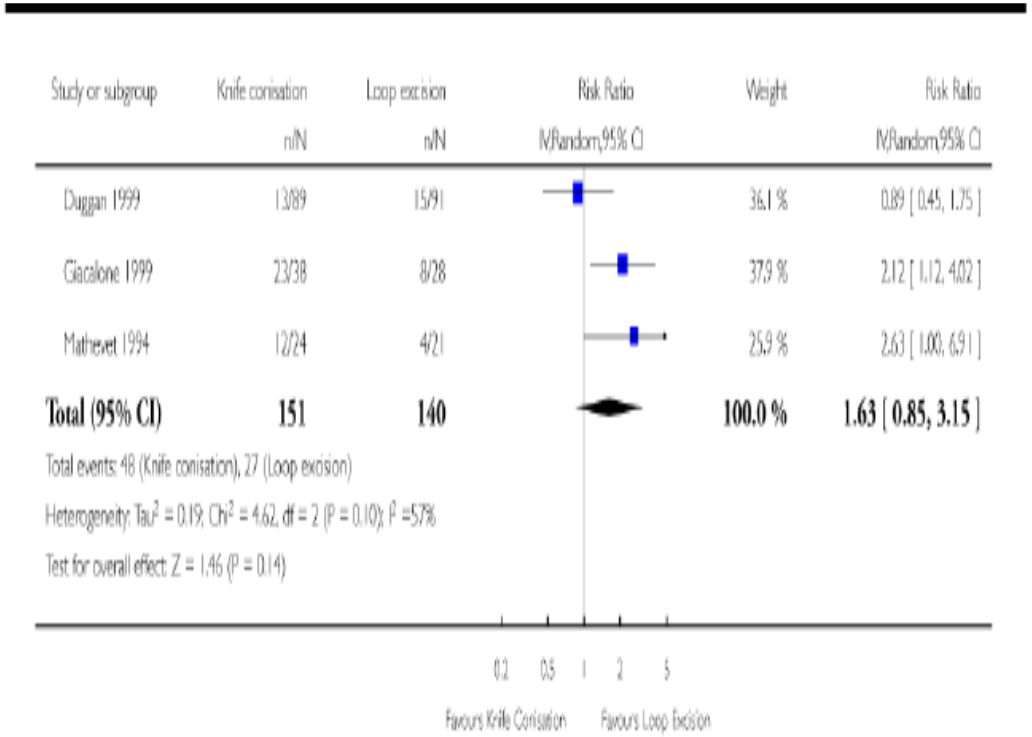


Cochrane Database Syst Rev. 2010

Surgery for cervical intraepithelial neoplasia.

Martin-Hirsch PP

Analysis 7.3. Comparison 7 Knife conisation versus loop excision, Outcome 3 Inadequate Colposcopy at Follow-up

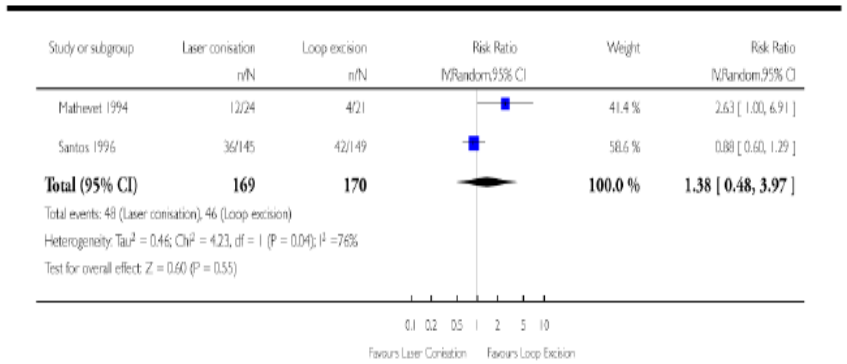


Analysis 5.8. Comparison 5 Laser conisation versus loop excision, Outcome 8 Inadequate Colposcopy

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 5 Laser conisation versus loop excision

Outcome: 8 Inadequate Colposcopy



GYNECOLOGY

Loop electrosurgical excision procedure with or without intraoperative colposcopy: a randomized trial

Check for updates

2018

Ziad Hilal, MD; Günther A. Rezniczek, PhD; Ferizan Alici, MD; Anne Kumpernatz, MD; Askin Dogan, MD; Lale Alieva, MD; Clemens B. Tempfer, MD, MBA

BACKGROUND: Loop electrosurgical excision procedure is the standard surgical treatment for cervical dysplasia. Loop electrosurgical excision procedure is advised to be performed under colposcopic guidance to minimize adverse pregnancy outcomes. To date, there is no evidence from randomized trials for this recommendation.

OBJECTIVE: We sought to assess the benefits of performing loop

In this randomized trial, they demonstrated that LEEP-DCV leads to significantly smaller cone specimens without compromising margin status.

primary endpoint was resected cone mass; the secondary endpoints were margin status, fragmentation of the surgical specimen, procedure time, time to complete hemostasis, blood loss, and intraoperative and postoperative complications. A sample size of 87 per group (n = 174) was planned (with an assumed type I error of 0.05 and drop-out rate of 5%) to achieve 90% power to detect a 25% reduction in cone mass (with an assumed cone mass of 2.5 ± 1.6 g in the control group) using a nonparametric test (Mann-Whitney *U*).

RESULTS: From October 2016 through December 2017, we randomized 182 women: 93 in the loop electrosurgical excision procedure group and 89 in the loop electrosurgical excision procedure—direct colposcopic vision group. Women undergoing loop electrosurgical excision procedure—direct colposcopic vision had significantly smaller cone specimens than those undergoing loop electrosurgical excision procedure (weight: median 1.86 [interquartile range 1.20–2.72] vs median 2.37 [interquartile range 1.63–3.31] g, respectively, $P = .006$). Secondary outcome measures did not differ significantly between groups: resection margin status involved vs free margin: 12 (13%) vs 75

85

190

290)

08)

loss

(Δhemoglobin): 0.4 (interquartile range 0.2–1.0) and 0.5 (interquartile range 0.1–0.9); complication rate: 6 (6.5%) and 2 (2.2%). In a multivariate analysis, study group allocation ($P = .021$) and parity ($P = .028$), but not age, body mass index, type of transformation zone, and dysplasia degree independently influenced the amount of resected cone mass.

CONCLUSION: Loop electrosurgical excision procedure with intraoperative colposcopy leads to significantly smaller cone specimens without compromising margin status.

Key words: cervical dysplasia, colposcopy, conization, controlled trial, direct colposcopic vision, loop excision, randomized

TABLE 2
Primary and secondary outcome measures

	Group 1 LEEP-DCV	Group 2 LEEP, without colposcope	*P*
N	92	89	
Primary outcome measure			
Resected cone mass, g	1.86 (1.20–2.72) [1]	2.37 (1.63–3.31)	.006[b]
Secondary outcome measures			
Resection margin status	[5]	[3]	
R1 vs R0	12 (13%) vs 75 (82%)	11 (12.4%) vs 75 (84.3%)	.98
Cone dimensions	[1]	[1]	
Base length, mm	23 (20–27)	25 (21–28)	.12
Base width, mm	8 (6–13)	11 (9–15)	<.001[b]
Height, mm	20 (16–23)	20 (17–23)	.45
Volume,[a] cm^3	1.38 (0.67–2.30)	1.76 (1.18–2.56)	.005[b]
No. of fragments			
1 vs >1	85 (92.4%) vs 7 (7.6%)	84 (94.4%) vs 5 (5.6%)	.81
No. of additional resections	2 (1–2.75)	1 (1–2)	.13
Procedure time, s	190 (138–294) [3]	171 (133–290) [3]	.64
TCH, s	61 (31–108) [8]	51 (30–81) [8]	.23
Intraoperative blood loss, Δhemoglobin	0.4 (0.2–1.0) [8]	0.5 (0.1–0.9) [14]	.99
Complications			
Intraoperative	6 (6.5%)	2 (2.2%)	.30
Postoperative	8 (8.7%)	4 (4.5%)	.40

Values are counts (percentage proportions) or medians (interquartile ranges); no. in brackets indicates missing values. *P* values were calculated using Mann-Whitney *U* test for nonnormally distributed data and Fisher exact test for proportions.

DCV, direct colposcopic vision; *LEEP*, loop electrosurgical excision procedure; *R0*, free margin; *R1*, involved margin; *TCH*, time to complete hemostasis.

[a] Cone volume was calculated as length × width × height ÷ 3 (pyramid); [b] Statistically significant.

Hilal et al. Colposcopy-guided conization. Am J Obstet Gynecol 2018.

Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis

Marc Arbyn, Charles W E Redman, Freija Verdoodt, Maria Kyrgiou, Menelaos Tzafetas, Sadaf Ghaem-Maghami, Karl-Ulrich Petry, Simon Leeson, Christine Bergeron, Pekka Nieminen, Jean Gondry, Olaf Reich, Esther L Moss

Summary

Background Incomplete excision of cervical precancer is associated with therapeutic failure and is therefore considered as a quality indicator of clinical practice. Conversely, the risk of preterm birth is reported to correlate with size of cervical excision and therefore balancing the risk of adequate treatment with iatrogenic harm is challenging. We reviewed the literature with an aim to reveal whether incomplete excision, reflected by presence of precancerous tissue at the section margins, or post-treatment HPV testing are accurate predictors of treatment failure.

The risk of residuel or recurrent CIN2+ lesions are increased with positive compared with negative resection margins.
High-risk HPV DNA testing post-treatment, more sensitive and similarly specific compared with the margin status.

meta-analysis of binomial data and analysed using random-effects models.

Findings 97 studies were eligible for inclusion in the meta-analysis and included 44 446 women treated for cervical precancer. The proportion of positive margins was 23·1% (95% CI 20·4–25·9) overall and varied by treatment procedure (ranging from 17·8% [12·9–23·2] for laser conisation to 25·9% [22·3–29·6] for large loop excision of the transformation zone) and increased by the severity of the treated lesion. The overall risk of residual or recurrent CIN2+ was 6·6% (95% CI 4·9–8·4) and was increased with positive compared with negative resection margins (relative risk 4·8, 95% CI 3·2–7·2). The pooled sensitivity and specificity to predict residual or recurrent CIN2+ was 55·8% (95% CI 45·8–65·5) and 84·4% (79·5–88·4), respectively, for the margin status, and 91·0% (82·3–95·5) and 83·8% (77·7–88·7), respectively, for high-risk HPV testing. A negative high-risk HPV test post treatment was associated with a risk of CIN2+ of 0·8%, whereas this risk was 3·7% when margins were free.

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See Comment page 1565

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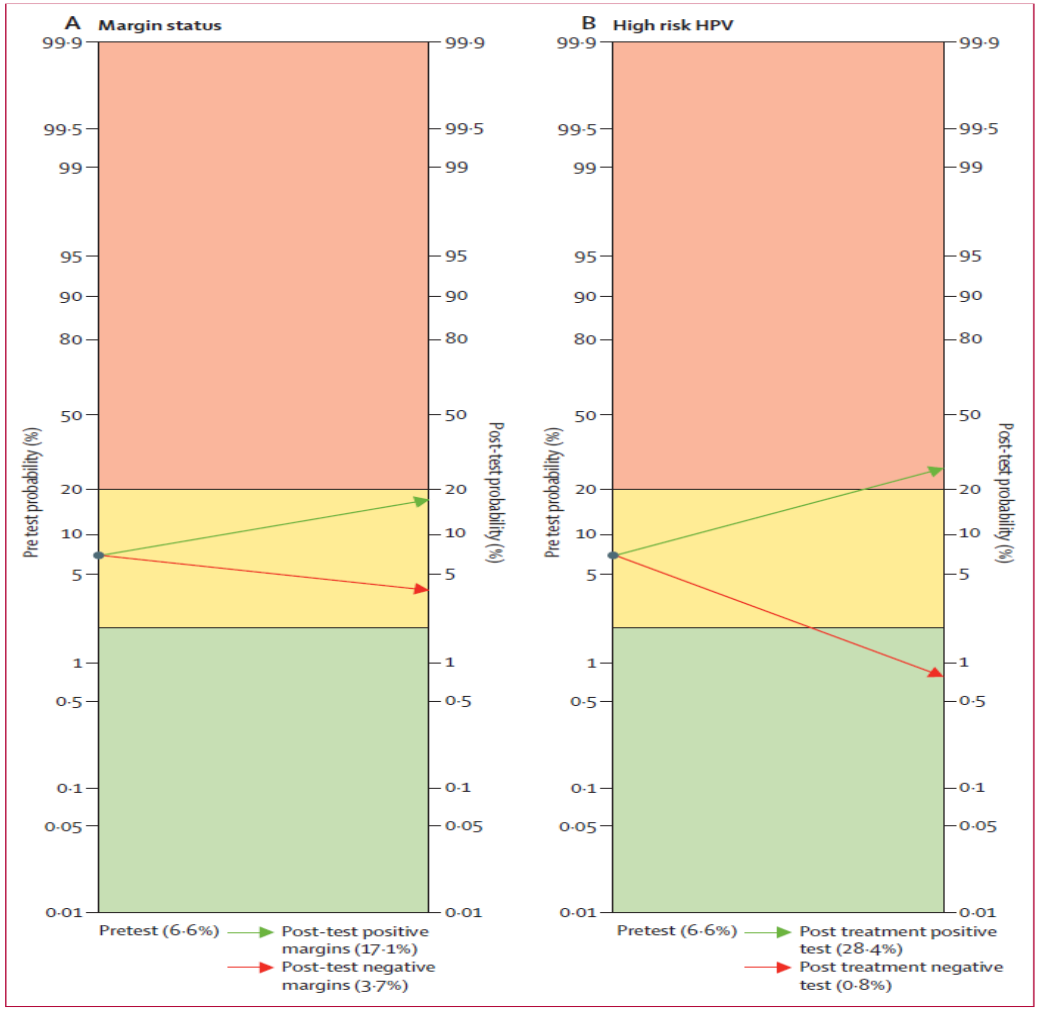

Figure 5: **Pretest and post-test probabilities of residual or recurrent CIN2+ after treatment of CIN2+, assessed by the histological evaluation of the resection margins (A) or by high-risk HPV testing (B) at 3–9 months post-treatment**
The arrows in the PPP plot connect the pretest risk with post-test risk for patients with a positive (red) or negative (green) test result, respectively. Benchmarks are defined at risk levels of 2% and 20%. When post-test risk is >20% (red zone), referral to colposcopy is warranted, whereas when post-test risk is <2% (green zone), release to the routine screening schedule is considered acceptable. When risk of CIN2+ is between 2% and 20% (yellow zone), further surveillance is recommended.[29] CIN2+=cervical intraepithelial neoplasia of grade 2 or worse. HPV=human papillomavirus.

Incomplete Excision of Cervical Intraepithelial Neoplasia as a Predictor of the Risk of Recurrent Disease – a 16 Year Follow-Up Study

Susanna Alder, David Megyessi, Karin Sundström

Journal Pre-proof

Incomplete Excision of Cervical Intraepithelial Neoplasia as a Predictor of the Risk of Recurrent Disease – a 16 Year Follow-Up Study

Susanna Alder, MD, PhD, David Megyessi, MD, Karin Sundström, MD, PhD, Ellinor Östensson, MPH, PhD, Miriam Mints, MD, PhD, Karen Belkić, MD, PhD, Marc Arbyn, MD, PhD, Sonia Andersson, MD, PhD

PII: S0002-9378(19)31056-7

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Objectives: In this study, we examine the long-term risk of residual/recurrent CIN2+ among women previously treated for CIN2 or 3 and how this varies according to margin status (considering also location), as well as comorbidity (conditions assumed to interact with hrHPV acquisition and/or CIN progression), post-treatment presence of hrHPV and other factors.

Study Design: This prospective study included **991 women with histopathologically-confirmed CIN2/3 who underwent conization** in 2000-2007. Information on the primary histopathologic finding, treatment modality, comorbidity, age and hrHPV status during follow-up and residual/recurrent CIN2+ was obtained from the Swedish National Cervical Screening Registry and medical records. Cumulative incidence of residual/recurrent CIN2+ was plotted on Kaplan–Meier curves, with determinants assessed by Cox regression.

Results: During a median of 10 years and maximum of 16 years follow-up, **111 patients were diagnosed with residual/recurrent CIN2+.**

Women with **positive/uncertain margins** had a **higher risk of residual/recurrent** CIN2+ than women with negative margins, adjusting for potential confounders (hazard ratio **(HR)=2.67**; 95% confidence interval (CI): 1.81–3.93).

The risk of residual/recurrent CIN2+ **varied by anatomical localization of the margins** (endocervical: HR=2.72; 95%CI: 1.67–4.41) and both endo- and ectocervical (HR=4.98; 95%CI: 2.85-8.71).

The risk **did not increase** significantly when only **ectocervical** margins were positive/uncertain.

The presence of comorbidity (autoimmune disease, human immunodeficiency viral infection, hepatitis B and/or C, malignancy, diabetes, genetic disorder and/or organ transplant) was also a significant independent predictor of residual/recurrent CIN2+.

In women with **positive hrHPV** findings during follow-up, the HR of positive/uncertain margins **for recurrent/residual CIN2+ increased** significantly compared to women with hrHPV positive findings but negative margins.

Conclusions: Patients with incompletely excised CIN2/3 are at increased risk of residual/recurrent CIN2+.

Margin status combined with hrHPV results and consideration of comorbidity may increase the accuracy for predicting treatment failure.

Journal Pre-proof

Incomplete Excision of Cervical Intraepithelial Neoplasia as a Predictor of the Risk of Recurrent Disease – a 16 Year Follow-Up Study

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PII: S0002-9378(19)31056-7

DOI: https://doi.org/10.1016/j.ajog.2019.08.042

Table 5: Cox regression model for residual/recurrent CIN2+ according to follow-up hrHPV status

	hrHPV positive (Number = 84)		hrHPV negative (Number = 105)	
	Adjusted HR (95% CI)	P-value	**Adjusted HR** (95% CI)	P-value
Margin status		0.031		0.455
Negative	1		1	
Not applicable: No dysplasia on cone biopsy	**18.74 (1.57-220.40)**		0.90 (0.05-15.22)	
Positive/ uncertain	**2.56 (1.17-5.62)**		1.18 (0.40-3.49)	

Margin status combined with hrHPV results may increase the accuracy for predicting treatment failure.

Table 4: Cox regression model for residual/recurrent CIN2+

	Adjusted HR	95% CI	P-value
Margin status			<0.001
Negative	1		
Not applicable	1.94	0.51-7.43	
Positive/uncertain	**2.67**	**1.81-3.93**	
Positive/uncertain: ectocervical	0.96	0.38-2.42	
Positive/uncertain: uncertain which	**2.84**	**1.39-5.81**	
Positive/uncertain: endocervical	**2.72**	**1.67-4.41**	
Positive/uncertain: both	**4.98**	**2.85-8.71**	
Comorbidity			0.002
No comorbidity	1		
Comorbidity	**2.23**	**1.36-3.66**	
Age at surgery			0.866
19-39	1		
40+	1.04	0.68-1.58	
Diagnosis in baseline cone biopsy			0.269
CIN1/no dysplasia	1		
CIN2	1.27	0.43-3.76	
CIN3+	1.77	0.65-4.88	
Treatment modality			0.656
Loop electrosurgical excision (LEEP) or electrosurgery by diathermy needle	1		
Laser	1.21	0.81-1.82	
Ultrasound knife	0.00	0.00-1.07E+161	
Previous conization			0.031
No	1		
Yes	**2.29**	**1.08-4.87**	

Pregnancy outcomes

OBJECTIVE: To investigate the association between cone depth of the loop electrosurgical excision procedure (LEEP) of the cervix and subsequent risk of spontaneous preterm delivery.

METHODS: The study included all deliveries in Denmark over a 9-year period, 1997–2005, with information obtained from various public health registries. Of the 552,678 singleton deliveries included in the study, 19,049 were preterm and 8,180 were subsequent to LEEP. Of the 8,180 deliveries with prior LEEP, 273 were subsequent to two or more LEEPs. Of the deliveries subsequent to only one LEEP, we extracted information about cone depth on 3,605 deliveries, of which 223 were preterm (6.2%). Logistic regression analyses were used to evaluate association between cone characteristics and the subsequent risk of pr taneous adjustment for potent

More than 15 mm

RESULTS: Increasing cone depth was associated with a significant increase in the risk of preterm delivery, with an estimated 6% increase in risk per each additional millimeter of tissue excised (odds ratio 1.06, 95% confidence interval 1.03–1.09). Severity of the cone histology and time since LEEP were not associated with the risk of preterm delivery. Having had two or more LEEPs increased the risk almost fourfold for subsequent preterm delivery when compared with no LEEP before delivery, and almost doubled the risk when compared with one LEEP before delivery.

CONCLUSION: Increasing cone depth of LEEP is directly associated with an increasing risk of preterm delivery, even after adjustment for several confounding factors.

(Obstet Gynecol 2009;114:1232–8)

LEVEL OF EVIDENCE: II

Depth of Cervical Cone Removed by Loop Electrosurgical Excision Procedure and Subsequent Risk of Spontaneous Preterm Delivery

Bugge Noehr, MD, Allan Jensen, MSc, PhD, Kirsten Frederiksen, MSc, PhD, Ann Tabor, MD, DMSc, and Susanne K. Kjaer, MD, DMSc

Table 3. Deliveries With Prior Loop Electrosurgical Excision Procedure: Association Between Loop Electrosurgical Excision Procedure Characteristics and Subsequent Risk of Preterm Delivery

	n	% Preterm Deliveries	OR*	95% CI	OR†	95% CI
Cone depth (mm)						
12 or less	1,022	5.3	1.00	–	1.00	–
13–15	1,118	4.4	0.82	0.55–1.23	0.82	0.55–1.23
16–19	650	7.2	1.44	0.96–2.16	1.45	0.97–2.19
20 or more	801	9.0	1.76	1.21–2.55	1.79	1.23–2.60
Linear (per mm)	3,591	6.2	1.05	1.03–1.08	1.06	1.03–1.09
Histologic findings in cone						
Normal	203	5.9	0.68	0.33–1.41	0.70	0.34–1.45
CIN 1	331	6.3	1.17	0.74–1.85	1.24	0.78–1.96
CIN 2	657	6.0	1.09	0.77–1.56	1.16	0.81–1.66
CIN 3	2,400	6.5	1.00	–	1.00	–
Time since last LEEP (y)						
Less than 1	1,111	6.6	0.96	0.63–1.45	0.94	0.62–1.42
1–2	799	7.1	1.20	0.78–1.83	1.20	0.78–1.85
2–4	1,005	5.7	1.04	0.69–1.58	1.03	0.68–1.57
More than 4	676	5.9	1.00	–	1.00	–
Linear (per y)	3,591	6.3	1.00	0.93–1.08	1.00	0.93–1.08

OR, odds ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure.

* Adjusted for maternal age, year of delivery, smoking during pregnancy, and marital status.

† Mutually adjusted and further adjusted for maternal age, year of delivery, smoking during pregnancy, and marital status.

Deliveries after LEEP with no information on cone depth (n=4,302), deliveries after two or more LEEPs (n=273), and LEEPs with missing diagnosis (n=14) are not included in the model.

Length but not transverse diameter of the excision specimen for high-grade cervical intraepithelial neoplasia (CIN 2–3) is a predictor of pregnancy outcome

Carlo A. Liverani[a], Jacopo Di Giuseppe[b], Nicolò Clemente[b],

The objective of this study was to analyze the impact of cone characteristics (depth, transverse diameter, and volume) on subsequent pregnancies after the loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN 2–3). Pregnancy outcomes (preterm birth, gestational age at birth, mode of delivery, and birth weight) of 501 women with singleton gestations and no previous preterm birth or history of late miscarriage, who had previously undergone a single LEEP for CIN 2–3, were retrospectively analyzed with respect to length, transverse diameter, and volume of the excision specimen. The overall incidence of preterm birth was 2.4%. The rate of preterm birth in women with length greater than 20 mm or volume greater than 2.5 cm^3 was significantly higher than that in women with length between 15 and 19 mm (15.6 vs. 3.9%, $P = 0.02$) or women with volume between 2.0 and 2.4 cm^3 (5.8 vs. 1.6%, $P = 0.04$). A linear inverse correlation ($r = -0.3$, $P < 0.001$) between gestational age at birth and length, but not volume ($r = 0.0$, $P = 0.9$) or transverse diameter ($r = 0.2$, $P < 0.0001$), emerged. The mode of delivery was not affected by cone characteristics. Length, but not transverse diameter and volume, of the excised specimen seems to be related to a lower gestational age at birth. When excisions are performed under strict colposcopic guidance, with a correct modulation of cone length, the risk for preterm birth and cesarean delivery in subsequent pregnancies is not increased. *European Journal of Cancer Prevention* 00:000–000

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Keywords: cesarean section, cervical conization, loop electrosurgical excision procedure, preterm delivery

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Table 3 Multivariable logistic regression of risk factors for preterm birth in the study population

Characteristics	Preterm birth ($n = 12$) (2.4%)	Term birth ($n = 489$) (97.6%)	Adjusted odds ratio (95% CI)	*P*-value
Tobacco use before pregnancy	2 (16.6)	80 (16.3)	0.8 (0.1–10.6)	0.91
Tobacco use in pregnancy	–	31 (6.3)	–	0.99
Clinical chorioamnionitis	3 (25)	39 (8)	1.8 (0.2–15.8)	0.58
Diabetes	1 (8.3)	40 (8.2)	0.5 (0–14.7)	0.67
Hypertensive disorders	–	21 (4.3)	–	0.99
Intrauterine growth restriction	1 (8.3)	23 (4.7)	3.3 (0.1–121.4)	0.5
Polyhydramnios	1 (8.3)	5 (1)	1.8 (0–63.5)	0.72
Placental abruption	–	5 (1)	–	0.99
Depth (mean ± SD) (mm)	12.1 ± 3.8	11.9 ± 0.4	49.8 (0.8–3054.1)	0.05
Transverse diameter (mean ± SD) (mm)	19.0 ± 5.8	19.3 ± 0.6	0.0004	0.03
Volume (mean ± SD) (cm^3)	2.2 ± 0.3	2.2 ± 0.3	0.26 (0–22.6)	0.55

Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis

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Pierre Martin-Hirsch,[4,5] Marc Arbyn,[6] Phillip Bennett,[1,2] Evangelos Paraskevaidis[3]

RESULTS

71 studies were included (6 338 982 participants: 65 082 treated/6 292 563 untreated). Treatment significantly increased the risk of overall (<37 weeks; 10.7% *v* 5.4%; relative risk 1.78, 95% confidence interval 1.60 to 1.98), severe (<32-34 weeks; 3.5% *v* 1.4%; 2.40, 1.92 to 2.99), and extreme (<28-30 weeks; 1.0% *v* 0.3%; 2.54, 1.77 to 3.63) preterm birth. Techniques removing or ablating more tissue were associated with worse outcomes. Relative risks for delivery at <37 weeks were 2.70 (2.14 to 3.40) for cold knife conisation, 2.11 (1.26 to 3.54) for laser conisation, 2.02 (1.60 to 2.55) for excision not otherwise specified, 1.56 (1.36 to 1.79) for large loop excision of the transformation zone, and 1.46 (1.27 to 1.66) for ablation not otherwise specified. Compared with no treatment, the risk of preterm birth was higher in women who had undergone more than one treatment (13.2% *v* 4.1%; 3.78, 2.65 to 5.39) and with increasing cone depth (≤10-12 mm; 7.1% *v* 3.4%; 1.54, 1.09 to 2.18; ≥10-12 mm: 9.8% *v* 3.4%, 1.93, 1.62 to 2.31; ≥15-17 mm: 10.1% *v* 3.4%; 2.77, 1.95 to 3.93; ≥20 mm: 10.2% *v* 3.4%; 4.91, 2.06 to 11.68). The choice of comparison group affected the magnitude of effect. This was higher for external comparators, followed by internal comparators, and ultimately women with disease who did not undergo treatment. In women with untreated CIN and in pregnancies before treatment, the risk of preterm birth was higher than the risk in the general population (5.9% *v* 5.6%; 1.24, 1.14 to 1.35). Spontaneous preterm birth, premature rupture of the membranes, chorioamnionitis, low birth weight, admission to neonatal intensive care, and perinatal mortality were also significantly increased after treatment.

Table 1 | Preterm birth in women with cervical intraepithelial neoplasia (CIN) for treated versus untreated women*

Preterm birth	No of studies	Total No of women	No (%) of women		Effect estimate RR (95% CI)	P value for heterogeneity (I^2%)
			Treated	Untreated		
<37 weeks' gestation						
All treatment types	60	5 244 560	6506/60 619 (10.7)	281 575/5 183 941 (5.4)	1.78 (1.60 to 1.98)	<0.001 (88)
CKC	12	39 102	126/844 (14.9)	2321/38 258 (6.1)	2.70 (2.14 to 3.40)	0.62 (0)
LC	9	1464	96/672 (14.3)	58/792 (7.3)	2.11 (1.24 to 3.57)	0.02 (56)
NETZ	1	7399	17/71 (23.9)	301/7328 (4.1)	5.83 (3.80 to 8.95)	N/E
LLETZ	26	1 445 341	1724/21 318 (8.1)	66 607/1 424 023 (4.7)	1.56 (1.36 to 1.79)	<0.001 (69)
LA	7	4710	168/1867 (9.0)	242/2843 (8.5)	1.04 (0.86 to 1.26)	0.48 (0)
CT	2	238	4/151 (2.6)	2/87 (2.3)	1.02 (0.22 to 4.77)	0.67 (0)
RD	1	2150	109/760 (14.3)	123/1390 (8.8)	1.62 (1.27 to 2.06)	N/E
Excisional treatment NOS	15	3 107 438	3788/28 104 (13.4)	183 133/3 079 334 (5.9)	2.02 (1.60 to 2.55)	<0.001 (95)
Ablative treatment NOS	5	595 272	430/6482 (6.6)	26 804/588 790 (4.6)	1.46 (1.27 to 1.66)	0.22 (30)
Treatment NOS	3	41 401	44/350 (12.6)	1979/41 051 (4.8)	2.20 (1.28 to 3.78)	0.07 (62)
<32-34 weeks' gestation						
All treatment types	25	3795 351	1375/39 647 (3.5)	53 835/3755 704 (1.4)	2.40 (1.92 to 2.99)	<0.001 (82)
CKC	5	36 979	15/283 (5.3)	920/36 696 (2.5)	3.07 (1.72 to 5.49)	0.65 (0)
NETZ	1	7399	5/71 (7.0)	49/7328 (0.7)	10.53 (4.33 to 25.65)	N/E
LLETZ	11	791 554	237/11 569 (2.0)	9504/779 985 (1.2)	2.13 (1.66 to 2.75)	0.08 (40)
CT	1	58	1/36 (2.8)	0/22 (0.0)	1.86 (0.08 to 43.87)	N/E
Excisional treatment NOS	10	2 832 112	1000/22 562 (4.4)	42 598/2 809 550 (1.5)	3.05 (1.95 to 4.78)	<0.001 (91)
Ablative treatment NOS	2	120 762	26/2549 (1.0)	686/118 213 (0.6)	1.59 (1.08 to 2.35)	0.92 (0)
Treatment NOS	2	6487	91/2577 (3.5)	78/3910 (2.0)	1.65 (1.13 to 2.42)	0.25 (24)
<28-30 weeks' gestation						
All treatment types	9	3 912 106	403/39 154 (1.0)	12 887/3 872 952 (0.3)	2.54 (1.77 to 3.63)	<0.001 (81)
CKC	2	7118	2/150 (1.3)	19/6968 (0.3)	4.52 (0.83 to 24.54)	0.74 (0)
NETZ	1	7399	3/71 (4.2)	21/7328 (0.3)	14.74 (4.50 to 48.32)	N/E
LLETZ	3	502 778	59/8899 (0.7)	1224/493 879 (0.2)	2.57 (1.97 to 3.35)	0.9 (0)
Excisional treatment NOS	4	2 821 185	287/21 984 (1.3)	9854/2 799 201 (0.4)	2.90 (1.52 to 5.52)	<0.001 (88)
Ablative treatment NOS	3	568 217	23/6125 (0.4)	1739/562 092 (0.3)	1.38 (0.81 to 2.36)	0.21 (35)
Treatment NOS	1	5409	29/1925	30/3484	1.75 (1.05 to 2.91)	N/E

CKC=cold knife conisation; CT=cryotherapy; LA=laser ablation; LC=laser conisation; LLETZ=large loop excision of transformation zone; N/E=not eligible; NETZ=needle excision of transformation zone; NOS=not otherwise specified; RD=radical diathermy.
*If study had more than one comparison groups, we used external groups (external general, external untreated women who had colposcopy+/-CIN+/-biopsy, women with HSIL but no treatment) in preference to internal comparators (self matching or pregnancies before treatment).
†In cases of heterogeneity in cut-offs used for classification of prematurity, these were grouped together when possible (for instance, 32-34 or 28-30 weeks included both cut offs).

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ORIGINAL ARTICLE

Effects of cervical conisation on pregnancy outcome: a meta-analysis

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ABSTRACT

To assess the effect of cervical conisation on pregnancy outcome, a literature search strategy was conducted to identify all of the references lists of the relevant studies. The fixed or random effect model was used to calculate pooled RRs on the basis of heterogeneity. Twenty-seven publications with *n* cases and *m* controls were included in the meta-analysis. The results showed that conisation was associated with a higher risk of a preterm delivery ($p = .010$), PROM ($p = .008$), and a lower birth weight ($p < .001$) in overall effect. The subgroup analysis showed that CKC was associated with a significantly increased risk of a preterm delivery ($p < .001$), and a lower birth weight ($p < .001$). LLETZ was associated with preterm delivery ($p = .004$) and a lower birth weight ($p = .020$). The results suggested that cervical conisation increases the risk of a preterm delivery, PROM, and a lower birth weight, especially in a CKC and LLEETZ procedure.

Table 3. Effects of different procedures on the preterm delivery.

	Heterogeneity		Overall effect	
Outcomes	*p*	I^2	RR with 95% CI	*p*
CKC	.003	72.1	2.310 (1.459–3.657)	.000
LLETZ	.609	0.0	1.511 (1.138–2.005)	.004
Laser	.629	0.0	1.373 (0.980–1.925)	.066
LEEP	.000	95.8	1.048 (0.597–1.840)	.870

Table 4. Effects of different procedures on the perinatal death or still birth.

	Heterogeneity		Overall effect	
Outcomes	*p*	I^2	RR with 95% CI	*p*
CKC	.237	28.4	0.922 (0.176–4.822)	.923
LLETZ	.592	0.0	0.779 (0.281–2.159)	.630
Laser	.082	67.0	2.131 (0.186–24.406)	.543
LEEP	.008	79.3	0.999 (0.056–17.925)	1.000

Table 5. Effects of different procedures on the PROM.

	Heterogeneity		Overall effect	
Outcomes	*p*	I^2	RR with 95% CI	*p*
CKC	.633	0.0	1.743 (1.287–2.361)	.000
Laser	.515	0.0	1.190 (0.642–2.203)	.581
LEEP	.050	74.0	0.570 (0.034–9.500)	.696

Table 6. Effects of different procedures on the lower birth weight.

	Heterogeneity		Overall effect	
Outcomes	*p*	I^2	RR with 95% CI	*p*
CKC	.695	0.0	2.531 (1.712–3.743)	.000
LLETZ	.222	33.5	2.314 (1.144–4.680)	.020
Laser	.041	75.9	1.234 (0.387–3.935)	.722
LEEP	.015	76.2	1.605 (0.685–3.761)	.276

Take home messages

CIN1 lesions usually do not require any treatment unless the lesion is persistent beyond two years.

CIN2 lesions over-expressing p16INK4 need treatment while those negative on these tests can be followed up.

There is international consensus that CIN3 lesions should be treated following diagnosis, except in pregnancy.

The obstetrical morbidity related to CIN excisional treatment depends on the **dimensions of the** removed **cervical tissue**.

The risk of premature delivery following excision appears to be significant in women whose **depth of excised** cone is **greater than 10 mm.**

Take home messages

Excisional treatment should be used only in well-selected women with a clear indication and should be guided by colposcopy.

Margin status also appears to be of crucial importance, positive margin exposes patient to a substantial risk of high grade post-treatment disease.

Colposcopy would allow for the optimization of excisional procedures both in terms **of margin status and excised cone dimensions.**

Margin status combined with hrHPV results may increase the accuracy for predicting residuel/recurrent lesions.

Cold knife conisation should be reserved for treating **adenocarcinoma in situ** and **microinvasive carcinoma**.

LEEP should be the first line procedure in women with fertility concerns.