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Systematic review

Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review

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Background Cold coagulation is an ablative method for treatment of cervical intraepithelial neoplasia (CIN). Despite reports of efficacy against all grades of CIN (CIN1-3), cold coagulation has been infrequently used since the 1980s, and was absent from the recent Cochrane review on CIN treatment.

Objectives To provide a systematic review of cold coagulation efficacy and acceptability for CIN treatment through meta-analysis of clinical reports and a randomised control trial.

Search strategy A literature search in PubMed, Web of Science, EMBASE, and regional databases yielded 388 papers. Title, abstract and/or reference list review identified 22 papers describing cold coagulation treatment of CIN, with 13 providing adequate data for inclusion in the meta-analysis.

Selection criteria Publications or conference abstracts describing original data (number of women treated, followed up and cured, provider type, cure definition) were retained. No language or publication date limitations were imposed.

Data collection and analysis Data extracted from 13 studies were pooled, and statistical analyses of proportion cured were conducted with data stratified by lesion grade and study region.

Main results Among 4569 CIN patients treated with cold coagulation, summary proportion cured of 96% [95% confidence interval (CI) 92–99%] and 95% (92–98%) were obtained for CIN1 and CIN2-3 disease, respectively. Side-effects and adverse effects were infrequent, and fertility was not impaired.

Conclusions Cold coagulation CIN cure rates were comparable to those of other excisional and ablative methods. Cold coagulation is indicated for all grades of CIN, is safe, quick and acceptable, and may be of particular relevance for use in resource-limited settings.

Keywords Acceptability, cervical intraepithelial neoplasia, cold coagulation, efficacy, pooled analysis.

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Introduction

Several excisional and ablative methods exist for treatment of cervical intraepithelial neoplasia (CIN). Cold knife conisation, large-loop excision of the transformation zone (LLETZ), and laser conisation are effective excisional options indicated for CIN3 disease, but require highly trained personnel and expensive infrastructure, and may impair fertility.[1] As such, more conservative ablative methods may be preferable in resource-limited settings, or in younger patients of child-bearing age. Ablative methods, including cold coagulation, cryotherapy, laser ablation, and electrocoagulation diathermy,[1–6] are generally indicated for CIN1-2 treatment, and can be performed on an out-patient basis.

Our group recently published a meta-analysis on the efficacy of cryotherapy as an ablative procedure of relevance in resource-limited settings. Cryotherapy ablates cervical tissues by freezing with compressed refrigerant gas. This method demonstrates high cure rates across world regions (94% for CIN1, 92% for CIN2, and 85% for CIN3), and can be effectively performed by mid-level providers.[7] However, cryotherapy poses challenges in certain regions, given the limited availability of refrigerant gas.[8] In these contexts, cold coagulation may constitute a more feasible treatment option for CIN.

The Semm cold coagulator – developed by Kurt Semm in 1966[9] – has been used worldwide, but most notably in the UK in the 1980s.[4,10] This method utilises electricity to heat a thermosound to temperatures of 100–120°C, allowing for ablation of cervical lesions by 'boiling'.[1,3,11] Cold coagulation is indicated for non-pregnant women of any age with CIN1-3 when the entire transformation zone is visible, when there is no suspicion of endocervical involvement or of micro-invasive, invasive, or glandular disease, and when the transformation zone has not previously been treated.[1,3–5,11–13] The procedure is fast (20–45 seconds per application) and achieves a treatment depth of 4–7 mm.[14] Anaesthesia can be avoided in most patients, and complications and adverse effects are minimal.[3,4,15–19] Of particular relevance for resource-limited or field settings, the instrument is small, self-sterilises by heating, has minimal infrastructural requirements, and can be used by mid-level providers.[3,18]

Cold coagulation is infrequently used at present,[12,20] and is often substituted by excisional methods, which have the added advantage of allowing for a histology exam. This method was also absent from the recent Cochrane review on CIN surgical techniques.[5] The aim of the current systematic review was to provide a comprehensive literature search and meta-analysis of randomised control trials and clinical reports, in order to report on the summary efficacy and acceptability of cold coagulation for CIN treatment.

Methods

Literature search strategy and inclusion criteria

With assistance from a medical librarian, an electronic literature search was performed through PubMed, Web of Science, EMBASE, and regional databases. Given the diversity in terminology used to describe cold coagulation in the literature, our search employed a broad range of keywords. A preliminary search in PubMed using the keywords 'Cervical Intraepithelial Neoplasia' [MeSH] OR 'Cervical Intraepithelial Neoplasia' (tiab) OR CIN (tiab) AND 'cold coagulation' (tiab) OR 'thermosurgery' (tiab) yielded only 18 papers, so a more comprehensive search was attempted by adding 'electrocautery' (tiab), 'Semm' (tiab), 'electrocoagulation' (tiab), 'electrocoagulation' (MeSH), and 'ablative' (tiab) to the search terms. This second attempt yielded 245 papers in PubMed. In Web of Science, keywords were 'Cervical Intraepithelial Neoplasia' OR CIN AND 'cold coagulation' OR 'thermosurgery', yielding 17 papers. In EMBASE, keywords were: 'Cervical Intraepithelial Neoplasia' or CIN AND 'cold coagulation' or 'thermosurgery', yielding 125 papers. To include research from resource-limited regions, regional databases were also queried for 'Cervical Intraepithelial Neoplasia' and 'cold coagulation', including the African Index Medicus (AIM), Caribbean Health Sciences Literature (MedCarib), Index Medicus for South-East Asia Region (IMSEAR), Index Medicus for Eastern Mediterranean Region (IMEMR), Indian Medlars National Informatics Centre (IndMed), and Latin American and Caribbean Center on Health Sciences Information (LILACS) databases. Only one paper was retrieved from a regional database (IMSEAR) with these search terms. This search strategy retrieved 388 papers in total (Figure 1).

The title and/or abstract of each article was reviewed, and peer-reviewed publications or conference abstracts with original qualitative or quantitative data were retained. Reviews of previously published data, and studies in which cold coagulation treatment was provided in combination with another method, were excluded from the analysis. No language or publication date limitations were imposed. Finally, reference lists of eligible publications were reviewed to ascertain additional relevant papers. The breakdown of papers retrieved and included through our search strategy

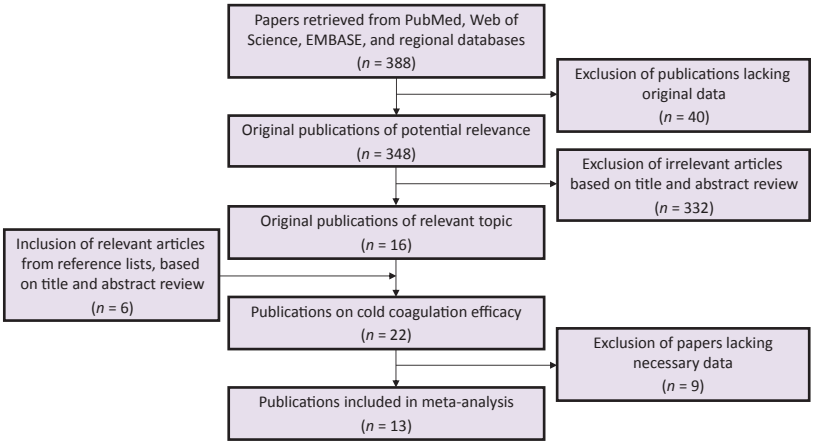

Figure 1. Flowchart summarising inclusion and exclusion criteria used in literature search strategy.

is shown in Figure 1. Overall, 22 studies on cold coagulation treatment of CIN were identified, with 13 being eligible for inclusion in the meta-analysis. Studies were excluded when the follow-up information was missing and consequently the cure could not be verified; studies with a treatment outcome other than CIN or cold coagulation used in combination with another treatment were also excluded.

Data extraction

Data from each study were extracted into a Microsoft EXCEL spread sheet, corresponding to the following categories: year of publication; world region; study period; study setting; study design; patient age (range and/or mean); case definition; biopsy confirmation; endocervical involvement of lesion; performer; treatment procedure (e.g. temperature, duration, and number of applications); duration of follow up; type of examination at follow up; number of patients treated; patients lost to follow up; patients with persistent or recurrent disease at follow up; definitions of cure and treatment failure (successful treatment was defined as a negative cytology at the follow-up visit, from at least 4–6 months following treatment); and information on complications (safety) or adverse effects (acceptability). Some authors were also contacted when relevant information was missing in studies published within the last 2 years. All extracted data were independently verified by two researchers (LD; CS).

Assessment of study quality

The 13 studies eligible for inclusion in the meta-analysis were assessed for quality of study design and data reporting, using a modified 27-item quality assessment checklist created by Downs and Black (Table S1).[21] Each article was assigned points in the areas of quality of reporting, external validity, internal validity (bias and confounding), and study power (based on sample size), to a maximum score of 28. Study power was estimated according to the sample size of patients followed up; according to quintiles, studies were scored as follows: 0 (≤40 women followed up); 1 (41–62 women followed up); 2 (63–71 women followed up); 3 (72–116 women followed up); 4 (117–924 women followed up); and 5 (>925 women followed up). Based on tertiles, studies receiving a score of <9 were classified as 'poor', 9–19 as 'moderate', and >19 as 'high' quality. A moderate or high quality score was required for inclusion in the meta-analysis.

Statistical analysis

A random effects model using the method of DerSimonian and Laird was used for all the meta-analyses carried out, with the estimate of heterogeneity being taken from the Mantel–Haenszel model. Meta-analyses were conducted on coded data stratified by lesion grade (CIN1-3) and by region of study (North America, Europe or Asia). As few papers provided data on CIN3 disease specifically, we analysed the efficacy of cold coagulation in the treatment of CIN1 and CIN2-3 lesions. CIN2-3 disease cure rates were also assessed by duration of follow up and by treatment provider. Data were graphically displayed in Forest plots, which display point estimates of cure rate within squares of variable size (representative of the weights given to the studies based on the precision of the effect size), with 95% confidence intervals (CI). I^2 statistic values were calculated to quantify degree of heterogeneity among studies, where values of 25–50% represented moderate heterogeneity and values of >50% large heterogeneity among studies.[22] The influence of each study on the overall estimate of the CIN2 or worse disease outcome was assessed. Publication bias was assessed using the Egger's test at the 1% level of significance. All analyses were conducted using STATA version 12.1 (StataCorp, College Station, TX, USA), with the 'metan', 'metareg' and 'metainf' software commands.

Results

Of 388 papers reviewed, 22 papers on treatment of CIN by cold coagulation were identified, with 13 being eligible for inclusion in the meta-analysis (Table 1). These 13 studies represented work conducted primarily in Europe, as well as a single study from North America and two from Asia. No studies from South America or Africa were identified. In total, the 13 papers described the efficacy of cold coagulation as observed among 4569 women with CIN1-3.[4,15–19,23–29] The remaining nine studies were not included in the meta-analyses for the following reasons: cold coagulation was provided in combination with another treatment method ($n = 2$); treatment was for non-CIN cervical anomalies ($n = 1$); data corresponded to safety/acceptability rather than efficacy ($n = 2$); and insufficient data were provided for calculation of cure rates ($n = 4$).[13,20,30–36]

All 13 included studies were scored as having 'moderate' ($n = 9$) or 'high' ($n = 4$) methodological quality (Appendix Table 1). Quality scores ranged from 9 to 21, with lowest scores arising in the categories of sample size (women followed up ranged from 30 to 1453), and internal validity. Poor internal validity scores were most often due to a lack of adequate description of patients lost to follow up. Studies additionally often lacked patient characteristics (such as age), and identification of cold coagulation provider. However, details of patient inclusion criteria and treatment methodology (e.g. temperature, application duration, and number of applications) were consistently reported.

Details of the 13 included studies are given in Table 1. Ten studies (77%) reflected work conducted in Europe, with seven (54%) coming from the UK specifically.

Table 1. Summary of studies on cold coagulation treatment of cervical intraepithelial neoplasia.

Author, Year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow up	Number of women treated	Number (%) of women followed up	Cure definition
Studies included in the meta-analysis															
Cassidy (1987)	UK (Scotland)	1979–86	IIIry H	Clinical report	–	CIN1-2-3	–	–	–	Gynaecologist	–	–	924	924 (100%)	Response to treatment
de Cristofaro (1990)	Italy	1985–?	IIIry H	Clinical report	–	CIN1-2-3	Yes	No	–	Gynaecologist	–	6–12 months	212	116 (55%)	Absence of CIN at follow-up cytology
Goodman (1991	UK (England)	1987–88	IIIry H	Clinical report	Mean 27	HPV+ or CIN1-2-3	Yes	Yes and no	–	Gynaecologist	–	4 months (83%)	78	62 (79%)	Absence of dyskaryosis at follow-up cytology
Gordon (1991)	UK (Scotland)	1975–89	IIIry H	Clinical report	15 to >50	CIN3	Yes	No	–	Colposcopist	Yes	4 months (98%) to 10 years (87%)	1628	1453 (89%)	Normal cytology at follow up
Grubišić (2010)	Croatia	1999–2000	IIIry H	Clinical report	Mean 30	CIN1-2	Yes	No	–	Gynaecologist	–	–	30	30 (100%)	Normal cytology at follow up
Hussein (1985)	UK (Scotland)	1982–83	IIIry H	Clinical report	–	CIN1-2-3	Yes	No	–	Colposcopist	–	4 months to 2 years	65	65 (100%)	Normal cytology and colposcopy at follow up 4 months after treatment
Javaheri (1981)	USA	1974–79	IIIry H	Clinical report	15 to >50	CIN1-2	Yes	No	–	Physician	–	1–5 years (>50% followed up for 3 years)	43	40 (93%)	Absence of CIN within 1st year follow up (persistence) and after 1st year follow up (recurrence)
Joshi (2013)	India	2010–2011	Iry H	Clinical report	21–60	CIN1-2-3	Yes	No	Yes	Physician	Yes	6–12 months	83	45 (54%)	No evidence of CIN2 or worse at follow up
Loobuyck (1993)	UK (Scotland)	1978–90	IIIry H	Clinical report	–	CIN1-2	Yes	No	–	Colposcopist	Yes	6 months to 11 years (>80% followed up for 3 years)	1165	1104 (95%)	Normal cytology at follow up
Rogstad (1992)	UK (England)	1988–89	IIIry H	Clinical report	–	CIN1-2	Yes	No	–	Physician	–	12–18 months	59	35 (59%)	No persistence or progression of CIN at follow up

Table 1. (Continued)

Author, Year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow up	Number of women treated	Number (%) of women followed up	Cure definition
Singh (1988)	Singapore	1983–88	IIIry H	RCT	Mean 35 (20–53)	CIN1-2-3	Yes	No	–	Colposcopist	–	3 months to 4 years (88% followed up for >1 year)	89	89 (100%)	No evidence of CIN at follow up
Staland (1978)	Sweden	1971–?	IIIry H	Clinical report	–	CIN2-3	No	–	–	Gynaecologist	–	3–4 years (80% followed up for >2 years	71	71 (100%)	Normal colposcopic view
Williams (1993)	UK (England)	1988–89	IIIry H	Clinical report	Mean 25 (16–46)	CIN2-3	Yes	No	–	Physician	–	18 months (78%)	125	125 (100%)	Absence of abnormality at follow-up cytology and colposcopy
Studies excluded due to lack of necessary data															
Allam (2005)	UK (Scotland)	1992–2000	IIIry H	CC combined with another procedure	Mean 33	CIN1-2-3	Yes	No	–	Colposcopist	Yes (in some)	12 months	666	541 (81%)	No persistent CIN in cytology & colposcopy
Duncan (2005)	UK (Scotland)	–	IIIry H	Safety and acceptability RCT	Mean 32	CIN1-2-3	Yes	No	–	Colposcopist	Yes	–	93	–	–
Farquharson (1987)	UK (Scotland)	–	IIIry H	Safety and acceptability clinical report	–	CIN2-3	–	–	–	Colposcopist	No	6 months	714 (laser or CC)	–	–
Fergusson (1974)	UK (England)	–	IIIry H	Cryosurgery or CC clinical report	–	Benign cervical erosion	No	–	–	–	–	2–4 months	24	23 (96%)	No residual erosion
Hughes (1992)	UK (Scotland)	–	IIIry H	CC or laser (combined data given)	–	CIN2-3	Yes	No	–	Colposcopist	–	9 months to 2.5 years	856 (laser or CC)	856 (laser or CC) (100%)	Absence of CIN based on cytology, colposcopy, and biopsy

Table 1. (Continued)

Author, Year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow up	Number of women treated	Number (%) of women followed up	Cure definition
Lee (2009)	Korea	1994–2005	IIIry H	CC combined with another procedure	Median 39 (27–67)	CIN1-2-3	Yes	No	–	–	–	Median 81 months (13–127 months)	70	70 (100%)	Absence of recurrent disease above CIN1
Semple (1999)	UK (England)	1996–97	19 IIIry Hs	Assessing screening and treatment across multiple centers	–	Dyskaryosis or CIN1-2-3	Yes	–	–	Colposcopist or Gynaecologist	Yes (in 41%)	1 year	268	–	Normal cytology and/or colposcopy at follow up
Smart (1987)	UK (Scotland)	1983–?	IIIry H	Comparing laser with CC	–	CIN2-3	Yes	No	–	Colposcopist	–	2 years	1169 (laser or CC)	–	Normal cytology, colposcopy, or biopsy
Zawislak (2003)	N. Ireland	1980–94	IIIry H	Clinical report	Mean 28 (17–52)	CIN 1-2-3	Yes	No	–	Colposcopist	Yes	3 months to 12 years	725	619 (85%)	Absence of persistent or recurrent abnormalities

RCT, randomised control trial; HPV, human papillomavirus; CIN, cervical intra-epithelial neoplasia; IIIry H, tertiary hospital; Iry H, primary hospital; CC, cold coagulation; –, missing data (information not reported or available). ?, unknown.

Reflecting its era of greatest popularity, 11 (85%) studies assessed patients treated with cold coagulation in the 1970s and 1980s. Only one (8%) was a randomised control trial; the remaining studies were prospective or retrospective clinical reports. Eleven (85%) studies reported that CIN disease was confirmed with biopsy, and 10 (77%) reported that cases with endocervical involvement were excluded. Three studies provided immediate cold coagulation treatment as part of a screen-and-treat programme. Duration of follow up ranged from a minimum of 4 months to a maximum of 11 years, and follow up was most often by cytology with colposcopic assessment. Cure was defined as absence of dyskaryosis or CIN at follow up, based on cytology, colposcopy and/or biopsy. Treatment failure was indicated by persistent or recurrent dyskaryosis or CIN at follow up. Treatment recipients were similar across studies, most commonly comprising patients referred for abnormal smears and treated at a tertiary referral hospital, with the exception of the study by Joshi and colleagues,[16] which assessed treatment among HIV-positive women seen at a primary care centre in India.

Summary estimates of cold coagulation cure rates obtained from the 13 studies are shown for CIN1 (Figure 2), and CIN2-3 (Figure 3), stratified by world region. Proportion cured of 96.0% (95%CI 92–99%; 593 women cured/620 women treated with a follow-up visit) and 95.0% (95%CI 92–98%; 1019/1070) were achieved for CIN1 and CIN2-3 disease, respectively. The overall efficacy of cold coagulation against all grades of CIN (CIN1-3) was 94.0% (95%CI 91–96%; 3912/4159) (data not shown). I^2 statistics ranged from 41.3% (CIN1) to 84.2% (CIN2-3), suggesting a high degree of heterogeneity among studies on high-grade disease in particular. None of the studies included in the final analysis had a significant influence on the overall estimate of the CIN2 or worse disease outcome. Egger's test showed that there was no publication bias (P-value = 0.715). Proportion-cured estimates for CIN2-3 disease were additionally stratified by duration of patient follow up and by treatment provider (Table 2); estimates were similar for follow-up periods of ≤2 years and of >2 years, and when treatment was provided by colposcopists, physicians or gynaecologists.

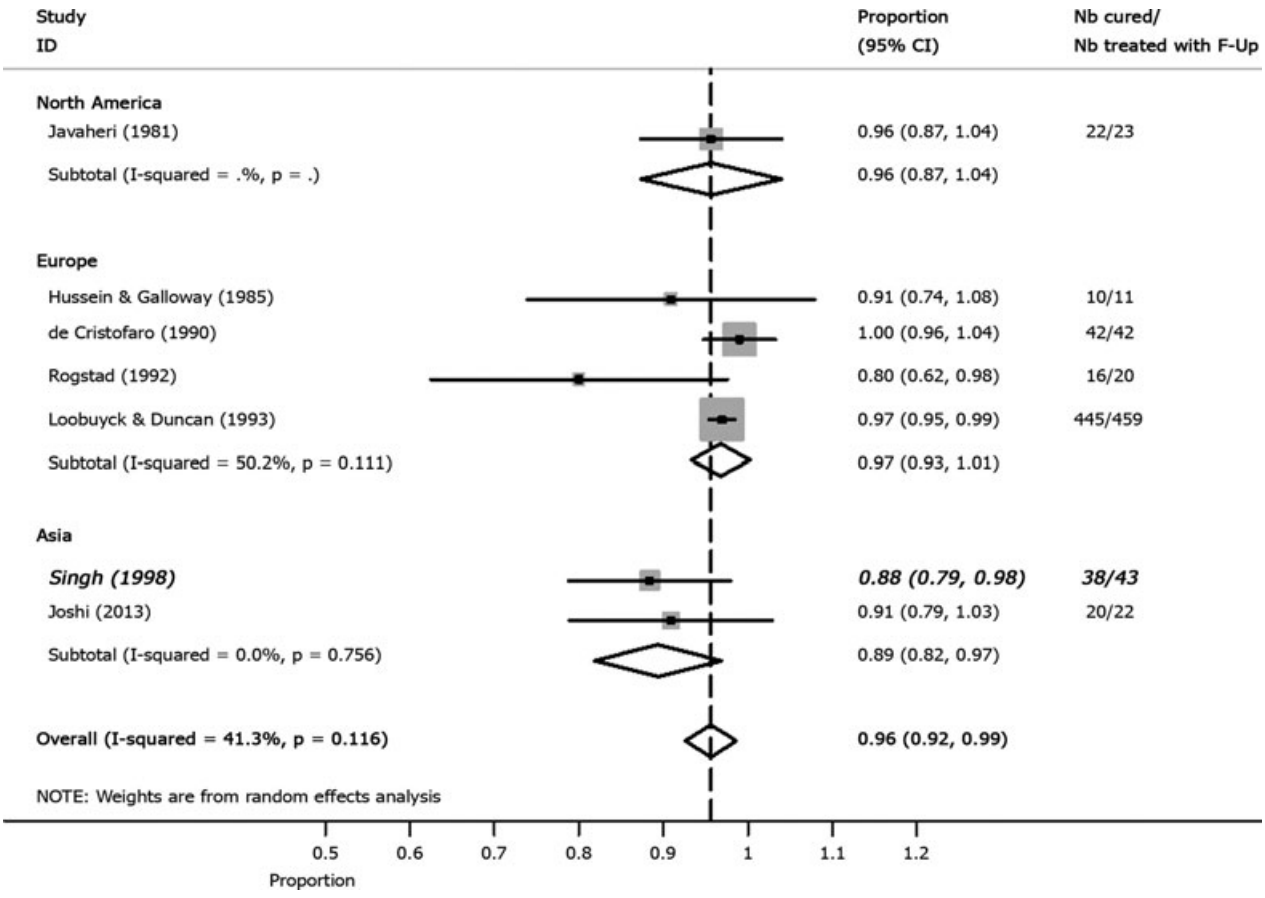

Figure 2. Proportion-cured estimates associated with cold coagulation treatment for CIN1 disease, by world region.

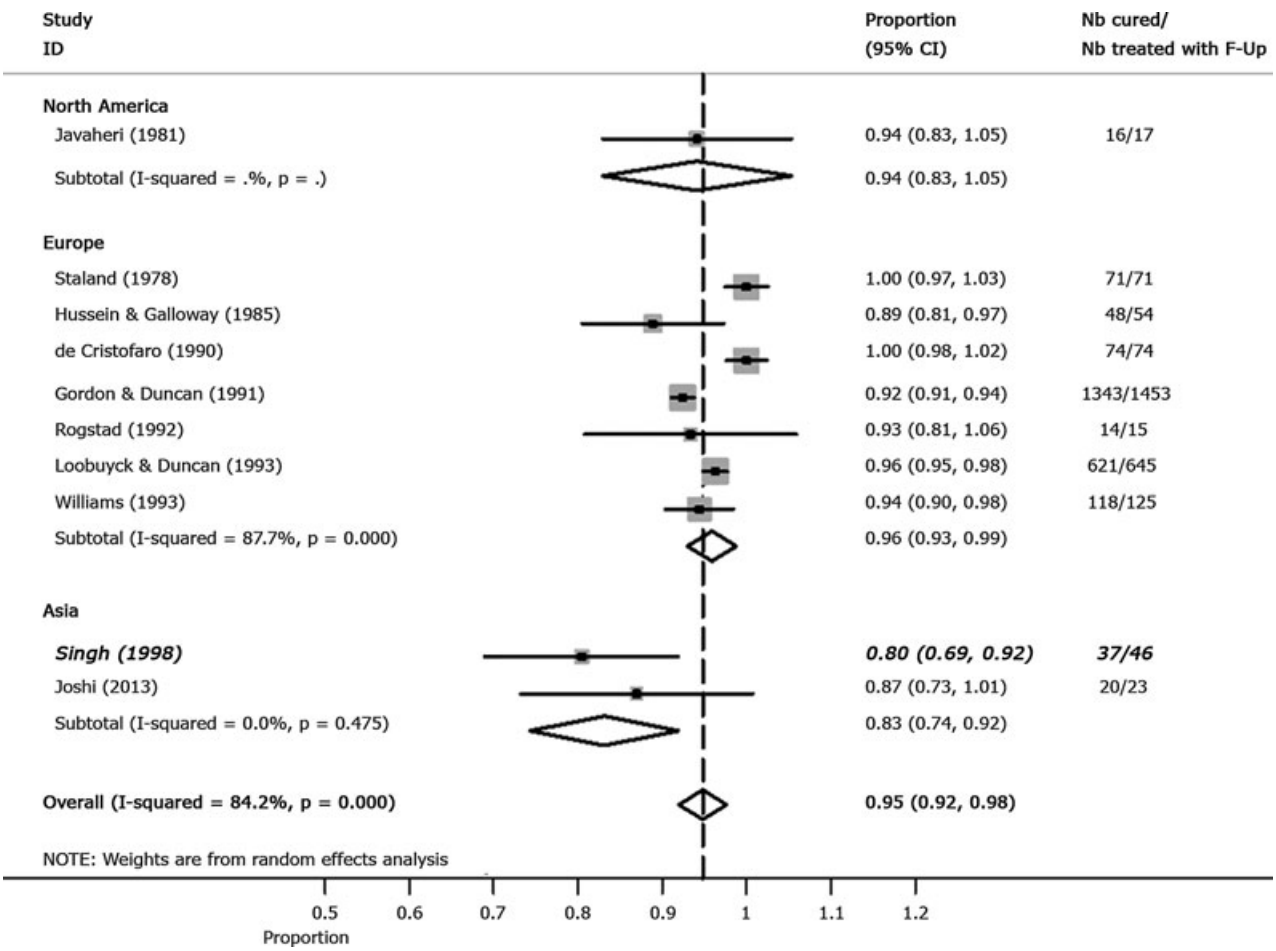

Figure 3. Proportion-cured estimates associated with cold coagulation treatment for CIN2-3 disease, by world region.

Table 2. CIN2-3 proportion cured according to potential determinants

Predictor	No. of studies that included the predictor	Proportion cured (%)	95% confidence interval	I^2 statistic	*P*-value
Duration of follow-up					
≤2 years	5	94	89–99	69.3	0.011
>2 years	5	95	91–98	89.4	<0.001
Overall	10	95	92–98	84.2	<0.001
Provider					
Colposcopist	4	92	89–96	85.9	<0.001
Gynaecologist	2	100	98–102	0.0	1.000
Physician	4	94	90–97	0.0	0.791
Overall	10	95	92–98	84.2	<0.001

Side-effects (representative of life-threatening events) and adverse effects (representative of acceptability) were infrequently reported across the 13 studies, being mentioned in only eight papers (61.5%). Among these eight studies, five reported an absence of side-effects during treatment, and two reported an absence of post-treatment adverse effects. In the remaining papers, side-effects during treatment included mild cramping in up to 25.0%,[15,16] moderate pain

in 10.5%,[24] severe pain in 3.5%,[24] mild bleeding in <1.0%,[16] and fainting attacks in <1.0%.[16] After treatment, adverse effects included watery or foul-smelling vaginal discharge in <2.5%,[16,17,25] pain after treatment in <1.0–5.0%,[16,25] cervical stenosis requiring dilation in <1.0%,[17,23] vaginal bleeding in 1.5%,[17] and local cervical infection in 1.1%.[18] Pain during treatment did not appear to limit practice, as only two studies routinely provided local anaesthesia to all treated patients, either by injection[25] or by spray.[27] In six studies, no analgesia was provided for all or the majority of patients undergoing cold coagulation.[4,15–19]

There were no demonstrable adverse effects on fertility and delivery in pregnancies conceived after cold coagulation, according to long-term follow-up studies. For instance, among 226 pregnancies conceived after CIN3 treatment in one cohort, no increases in miscarriage rates or preterm deliveries were observed: nine had a first trimester miscarriage, three had ectopic pregnancies, and three had preterm deliveries, with the remainder proceeding to term.[4] Among six patients analysed by Williams and colleagues after CIN2-3 treatment, all had normal pregnancies with vaginal deliveries at term.[19] Cassidy and colleagues analysed nine pregnancies conceived after CIN1-3 treatment, and reported that all proceeded to term (beyond 35 weeks) with normal fetal outcomes.[23] Treatment during pregnancy is not advised,[3,13,31] but the procedure can be performed on women with an intrauterine device (IUD) in place, as the operating temperature does not damage the threads.[17]

Discussion

Main findings

Of 22 studies on cold coagulation treatment, 13 studies described its efficacy in 4569 women with CIN1-3. These studies primarily described European patients, most of whom received treatment at tertiary hospitals from colposcopists, physicians or gynaecologists. Summary proportion-cured estimates of 96.0 and 95.0% were reported for CIN1 and CIN2-3, respectively, and no influence of treatment provider or duration of follow up on estimates was observed. The 13 studies displayed heterogeneity in terms of study quality, sample size, duration of follow up, and definition of cure.

Strengths and weaknesses

Cure rate estimates from this meta-analysis are, to our knowledge, derived from all applicable existing studies on cold coagulation efficacy. However, estimates are subject to limitations. Research on cold coagulation efficacy is scarce, and the literature search is hindered by the diversity of terminologies used to refer to cold coagulation, including moderate heat thermosurgery,[29] low heat electrocautery,[27,33] and electrocoagulation.[26] Only a single study was available on treatment in a primary care centre of a low-income country,[16] and as this cohort comprised HIV-positive women, resulting cure rates may underestimate what is achievable in non-immunocompromised women in similar settings. Additionally, several factors were difficult to account for in analysis. Loss of patients to follow up was frequent across studies, and this could have variable impacts on reported cure rates: failure to return due to remission of symptoms could contribute to underestimation of cure rate, and failure to return due to low socio-economic status could contribute to overestimation of cure, as such patients are at higher risk of treatment failure.[7]

Interpretation

The current meta-analysis suggests that cold coagulation cure rates are comparable with those of other excisional and ablative methods.[5] Among excisional methods, cure rates of CINs confirmed by biopsy range from 90–94% with knife cone biopsy, 91–98% with LLETZ, and 93–96% with laser conisation.[5] Among ablative techniques on CIN1 and worse lesions confirmed by biopsy, cryotherapy cure rates reached 85–94%,[7] and laser ablation achieved cure rates of 95–96%.[5] As mentioned in the Cochrane review, this evidence suggests that there is no one superior method of CIN treatment,[5] and our meta-analysis shows that cold coagulation is on a par with these techniques.

Of interest for resource-limited settings, seven of the 22 retrieved studies provided cold coagulation treatment through a 'screen-and-treat' strategy. Screen-and-treat programmes provide visual assessment of cervical anomalies or rapid HPV-DNA testing, followed by immediate treatment at the same visit. In cryotherapy studies, this strategy has been shown to increase treatment adherence rates, particularly in settings where patients are less likely to return for a second appointment.[37] Among three studies, cure rates were 92–97% for CIN1-3 in Europe,[4,17] and exceeded 85% for CIN1-3 cases among HIV-positive women treated in India.[16] As such, cold coagulation may be an effective therapeutic option in screen-and-treat programmes, particularly in low socio-economic settings where patients are less likely to return for treatment. Cold coagulation may also be preferable to cryotherapy in these settings, as the most economical cryotherapy gas tanks are large and heavy (10–15 kg), difficult to move, and require refilling.[8]

Nine studies on cold coagulation treatment of CIN were excluded from meta-analyses (Table 1). Two of these studies assessed cold coagulation when used in combination with another procedure. Among 666 CIN1-3 cases treated with LLETZ in combination with cold coagulation, 0.6% of high-grade and no low-grade patients had abnormal cytology at 1 year post-treatment. The authors suggested that such a combined approach might be of benefit in

environments in which follow-up compliance is low.[30] In the second study, 85 patients with CIN1-3 or microinvasive cancer (stage IA1) were treated with electrosurgical conisation and cold coagulation.[35] Cold coagulation was used to achieve haemostasis and to destroy residual lesions at resection margins. Over a median follow-up period of 81 months, 1.2% displayed recurrent disease. Hughes and colleagues assessed persistence in 856 CIN2-3 patients treated by either CO_2 laser, or cold coagulation.[34] A total of 130 patients (15%) presented with persistent CIN over 9–30 months' follow up. Although data were not segregated by treatment method, the authors commented that 'no demonstrable difference' was observed in detection of persistent CIN between laser and cold coagulation patients. Finally, Smart and colleagues randomised 1169 CIN2-3 patients to laser or cold coagulation treatment.[13] In their preliminary data on 589 patients followed for at least 12 months, the treatment failure rates for cold coagulation and laser were not significantly different (10 and 11.5%, respectively).

Cold coagulation also constitutes a safe and acceptable procedure, as side-effects among analysed studies were infrequent and of low or moderate severity. Farquharson and colleagues randomised 714 CIN2-3 patients to treatment with either cold coagulation or CO_2 laser, and observed statistically significant differences between procedures: patients treated with cold coagulation reported lower pain scores, and only 8% requested local analgesia during treatment, relative to 21% in the laser treatment group.[32] After treatment, a significantly lower proportion of cold coagulation patients experienced bleeding, and significantly fewer required hospital attention for bleeding events. Patients in both arms of the study had pain after treatment (in 30%), and vaginal discharge lasting longer than 1 week (in 35%). Smart and colleagues also randomised 1169 CIN2-3 patients to cold coagulation or CO_2 laser treatment, and observed significantly shorter treatment times among cold coagulation patients (median time of 3 minutes) compared with laser patients (median time of 12 minutes).[13] Fergusson and Craft contrasted 24 cold coagulation patients with 27 cryosurgery patients and found that whereas pain during treatment occurred exclusively in cold coagulation patients (affecting 21%), watery discharge after treatment was much more common among cryosurgery patients (93%) than cold coagulation patients (17%).[33] Finally, in the majority of studies, local analgesia was not required during cold coagulation treatment. This is consistent with the results of a recent randomised placebo-controlled trial in which 44.7% of patients receiving cold coagulation treatment experienced only mild or no pain in the absence of local anaesthesia. However, local anaesthesia may be advisable as it significantly reduced the incidence of severe pain, which affected 19.1% of cold coagulation patients not receiving anaesthesia in that study.[31]

Finally, the analysed studies reported an absence of adverse events on fertility, consistent with previous reports of a 94% conception rate among CIN1-3 patients within 2 years of cold coagulation treatment. Investigators reported that women had normal post-treatment pregnancies, likely due to the minimal scarring with this procedure.[3]

Conclusions

Our comprehensive meta-analysis has demonstrated that cold coagulation generates cure rates comparable to other excisional and ablative methods in use worldwide. Despite its efficacy and acceptability, cold coagulation has progressively been replaced by excisional methods, such as LLETZ, since the 1980s.[12,20] Low rates of use may stem from availability, as only a single manufacturer exists at present. As relatively few studies (and almost no randomised control trials) have analysed cold coagulation efficacy, cure rates should be further assessed in large cohorts with consistent, long-term follow up of patients. In particular, research is needed on the cure rates achievable in resource-limited settings with mid-level treatment providers, where patients have never been or are not often screened. Overall, this systematic review has demonstrated that cold coagulation may be indicated for all grades of CIN, and is safe, quick, and acceptable as an outpatient procedure. Cold coagulation may be of particular relevance for use in resource-limited settings, when access to cryotherapy gas is limited.

Disclosure of interests

The authors have no conflicts of interest.

Contribution to authorship

L.D.: literature search and review; data extraction; data interpretation; drafting the manuscript. C.S.: study initiation and design; data extraction; data interpretation; drafting the manuscript. R.M.: statistical analysis; data interpretation. R.S.: data interpretation; participation in final manuscript. All authors reviewed and approved the final version of the paper.

Details of ethics approval

Not applicable.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Scoring of methodological quality of studies on cold coagulation efficacy. ■

References

1 Prendiville W, de Camargo MJ. Treatment of cervical intraepithelial neoplasia. In: Bosze P, Luesley DM, editors. *European Academy of Gynaecological Cancer Course Book on Coloposcopy*. Chapter 12. Budapest: Prime-X Press; 2003. pp. 106–17.

2 Chanen W, Rome RM. Electrocoagulation diathermy for cervical dysplasia and carcinoma *in situ*: a 15-year survey. *Obstet Gynecol* 1983;61:673–9.

3 Duncan ID. The Semm cold coagulator in the management of cervical intraepithelial neoplasia. *Clin Obstet Gynecol* 1983;26:996–1006.

4 Gordon HK, Duncan ID. Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100 degrees C using the Semm cold coagulator: 14 years experience. *BJOG* 1991;98:14–20.

5 Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO, Keep SL. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev* 2010;6:CD001318.

6 Singer A, Walker P. The treatment of CIN: conservative methods. *Clin Obstet Gynaecol* 1985;12:121–32.

7 Sauvaget C, Muwonge R, Sankaranarayanan R. Meta-analysis of the effectiveness of cryotherapy in the treatment of cervical intraepithelial neoplasia. *Int J Gynaecol Obstet* 2013;120:218–23.

8 Sankaranarayanan R, Muwonge R. Visual inspection with acetic acid (VIA) screening and colposcopic triage. In: Frega A, Gentili C, Biamonti A, Di Renzi F, editors. *Colposcopia*. Rome: Verduci Editore; 2014. (Forthcoming).

9 Semm K. New apparatus for the 'cold-coagulation' of benign cervical lesions. *Am J Obstet Gynecol* 1966;95:963–6.

10 Duncan ID. Destruction of cervical intraepithelial neoplasia at 100°C with the Semm coagulator. In: Heintz APM, Griffiths CT, Trimbos JB, editors. *Surgery in Gynecological Oncology*. The Hague: Martinus Nijhoff Publisher; 1984. pp. 71–85.

11 Duncan ID. Cold coagulation. *Baillieres Clin Obstet Gynaecol* 1995;9:145–55.

12 O'Dwyer V, Madden M, Hickey K. Cold coagulation to treat cervical intraepithelial neoplasia. *BJOG* 2013;120:510.

13 Smart GE, Livingstone JRB, Gordon A, Bain SHH, Fletcher J, West C, et al. Randomised trial to compare laser with cold coagulation therapy in the treatment of CIN II and III. *Colposcopy Gynecol Laser Surg* 1987;3:48.

14 Haddad NG, Hussein IY, Blessing K, Kerr-Wilson R, Smart GE. Tissue destruction following cold coagulation of the cervix. *Colposcopy Gynecol Laser Surg* 1988;4:23–7.

15 Hussein IY, Galloway RK. Use of cold coagulator in the treatment of cervical intraepithelial neoplasia. *J Obstet Gynaecol* 1985;6:62–4.

16 Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. *AIDS* 2013;27:607–15.

17 Loobuyck HA, Duncan ID. Destruction of CIN 1 and 2 with the Semm cold coagulator: 13 years' experience with a see-and-treat policy. *BJOG* 1993;100:465–8.

18 Singh P, Loke K-L, Hii JHC, Sabaratnam A, Lim-Tan SK, Sen DK, et al. Cold coagulation versus cryotherapy for treatment of cervical intraepithelial neoplasia: results of a prospective randomized trial. *Colposcopy Gynecol Laser Surg* 1988;4:211–21.

19 Williams OE, Bodha M, Alawattegama AB. Outcome of cold coagulation for the treatment of cervical intraepithelial neoplasia in a department of genitourinary medicine. *Genitourin Med* 1993;69:63–5.

20 Semple D, Saha A, Maresh M. Colposcopy and treatment of cervical intra-epithelial neoplasia: are national standards achievable? *BJOG* 1999;106:351–5.

21 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377–84.

22 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

23 Cassidy LJ, Mathers A, Kennedy JH. Cold coagulation revisited. *Colposcopy Gynecol Laser Surg* 1987;3:232.

24 de Cristofaro D, Trioni G, Pezzoli C. Treatment of CIN with cold coagulation. *J Exp Clin Cancer Res* 1990;9:133.

25 Goodman JD, Sumner D. Patient acceptability of laser and cold coagulation therapy for pre-malignant disease of the uterine cervix. *BJOG* 1991;98:1168–71.

26 Grubisic G, Vukosavic-Cimic B, Kraljevic Z, Pirkic A, Grbavac I, Bolanca I. Cytologic follow-up in patients with CIN treated by LLETZ, Cold knife Conization and Semm's cold coagulation. *Coll Antropol* 2010;34:13–17.

27 Javaheri G, Balin M, Meltzer RM. Role of cryosurgery in the treatment of intraepithelial neoplasia of the uterine cervix. *Obstet Gynecol* 1981;58:83–7.

28 Rogstad KE, Dixon CA, Ahmed IH. The management of subclinical wart virus infection of the cervix in a genitourinary clinic. *Genitourin Med* 1992;68:307–8.

29 Staland B. Treatment of premalignant lesions of the uterine cervix by means of moderate heat thermosurgery using the Semm coagulator. *Ann Chir Gynaecol* 1978;67:112–16.

30 Allam M, Paterson A, Thomson A, Ray B, Rajagopalan C, Sarkar G. Large loop excision and cold coagulation for management of cervical intraepithelial neoplasia. *Int J Gynaecol Obstet* 2005;88:38–43.

31 Duncan ID, McKinley CA, Pinion SB, Wilson SM. A double-blind, randomized, placebo-controlled trial of prilocaine and felypressin (Citanest and Octapressin) for the relief of pain associated with cervical biopsy and treatment with the Semm coagulator. *J Low Genit Tract Dis* 2005;9:171–5.

32 Farquharson DIM, West CP, Prescott RC, Smart GE. The patient acceptability of laser and cold coagulation therapy to the cervix for treatment of cervical intra-epithelial neoplasia (CIN) 2-3. *Colposcopy Gynecol Laser Surg* 1987;3:49.

33 Fergusson IL, Craft IL. A new 'Cold coagulator' for use in the outpatient treatment of cervical erosion. *J Obstet Gynaecol Br Commonw* 1974;81:324–7.

34 Hughes RG, Haddad NG, Smart GE, Colquhoun M, McGoogan E, MacIntyre CC, et al. The cytological detection of persistent cervical intraepithelial neoplasia after local ablative treatment: a comparison of sampling devices. *BJOG* 1992;99:498–502.

35 Lee SJ, Kim WY, Lee JW, Kim HS, Choi YL, Ahn GH, et al. Conization using electrosurgical conization and cold coagulation for

international federation of gynecology and obstetrics stage IA1 squamous cell carcinomas of the uterine cervix. *Int J Gynecol Cancer* 2009;19:407–11.

36 Zawislak A, Price JH, McClelland HR, Storey RG, Caughley L. Efficacy of cervical intraepithelial neoplasia (CIN) treatment by cold coagulation. *Ulster Med J* 2003;72:10–15.

37 Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, et al. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer* 2007;96:738–43.

There is still some heat in the cold coagulator

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Mini commentary on 'Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review'

In the 1970s and 1980s a variety of techniques were available to ablate cervical intraepithelial neoplasia (CIN), including radical electrodiathermy, laser, cryosurgery, and the quirkily named 'cold coagulator' (CC), which comprised a hot thermaprobe applied at 100–120°C.

Following the report of 'large loop' excision of the transformation zone (LLETZ) (Prendiville et al. BJOG 1989;96:1054–60), ablative methods yielded significantly to a technology that helped to avoid inadvertent and, potentially inadequate, treatment of occult invasive cancer and glandular disease (representative reference: Alvarez et al. Gynecol Oncol 1994;52:175–9). However, for all the benefits of LLETZ (or LEEP: loop electrosurgical excision procedure as it became known in the USA) it is relatively expensive and involves multiple additional resources that are not readily available in the parts of the world where the burden of cervical cancer is greatest: developing nations.

This systematic review by Dolman and colleagues from the International Agency for Research on Cancer was stimulated by interest in implementing treatment methods most applicable to such resource-limited settings. Meta-analysis of data on the use of CC to treat over 4500 women with CIN, mostly from two to three decades ago, revealed estimated cure rates for CIN1 of 96% and CIN2-3 of 95%. It is no surprise that CC would be effective, as both Semm[1] and later Haddad demonstrated that the necessary depth of tissue destruction could be achieved. As with cryosurgery, CC is well tolerated, often without local anaesthetic and with minimal short-term complications.[2,3] Although data on pregnancy outcomes is incomplete, morbidity would be expected to be low based on a meta-analysis of perinatal and obstetric outcomes that included other forms of ablation. (Arbyn et al. BMJ 2008;337:a1284).

Reported experience with CC in resource-limited settings has lagged behind that for cryotherapy, which has been evaluated in programmes utilising mid-level providers in the community.[4] There would seem no reason that CC might not be delivered in such situations but with the added advantages of easier use and without reliance on refrigerant gas. Although a few cases of early invasive carcinoma of the cervix would inevitably be missed with ablation of CIN, this would likely be trumped by the overwhelming need for cervix cancer prevention in populations in developing nations.

This report is valuable in reminding us of the efficacy and side-effect profile of a technology that has gone largely out of fashion. The authors are to be commended for having the vision to see its potential to help treat women with CIN in developing nations. Kurt Semm as a pioneer and those who promoted the use of CC, principally in the UK, should be recognised. This systematic review should stimulate further research on CC. In areas of the world where resources are limited but need is great, this might take the form of a comprehensive 'modern era' RCT of CC versus cryotherapy for all grades of CIN. Closer to home, it might even generate more interest in CC, possibly including a trial of CC versus LLETZ for those with CIN involving type 1 transformation zones (Prendiville. BJOG. 2013; 120:510–1).

Disclosure of interests

I have no conflicts of interest. ■

References

1 Semm K. New apparatus for the 'cold-coagulation' of benign cervical lesions. *Am J Obstet Gynecol* 1966; 95:963–6.

2 Duncan ID, McKinley CA, Pinion SB, Wilson SM. A double-blind, randomized, placebo-controlled trial of prilocaine and felypressin (Citanest and Octapressin) for the relief of pain associated with cervical biopsy and treatment with the Semm coagulator. *J Low Genit Tract Dis* 2005;9:171–5.

3 Farquharson DI, West CP, Prescott RC, Smart GE. The patient acceptability of laser and cold coagulation therapy to the cervix for treatment of cervical intra-epithelial neoplasia (CIN) 2-3. *Colp Gynecol Laser Surg* 1987;3:49.

4 Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, et al. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer* 2007;96:738–43.

Pregnancy outcomes following cold coagulation for CIN have not yet been reported

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Mini commentary on 'Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review'

The meta-analysis of 13 studies published by Dolman et al. (BJOG) in this month's *BJOG* concludes that cure rates for high-grade CIN treated by cold coagulation are high (95%) and comparable to those reported for other excisional or ablative techniques (Martin-Hirsch et al. Cochrane Database Syst Rev 2010;6:CD001318). Although most of the included studies were conducted nearly two decades ago, the reported outcomes are likely to be applicable to contemporary settings.

The systematic review included only non-controlled observational studies and therefore the level of derived evidence must be considered to be low. Moreover, none of the included studies was conducted in developing countries, where cold coagulation might have the most utility, given its ease of application. The systematic review considered absence of cytological lesions as evidence for treatment success, but as cytology is only moderately sensitive for predicting recurrent or residual high-grade CIN (Arbyn et al. Vaccine 2012;30 S 5:F88–99), it is likely that treatment failure is underestimated in this study.

Excisional techniques, particularly LLETZ, have largely replaced ablative techniques for the treatment of CIN in developed countries. This is because LLETZ is cheap, quick, easy to perform and readily available. The resulting cone specimen provides information about the grade of disease, the presence or absence of microinvasive disease and the completeness of excision. These data provide important prognostic information.

The obstetric consequences of excisional treatment are now widely recognised (Kyrgiou et al. Lancet;367:489–98). It appears that the amount of cervical tissue removed is important and studies suggest a dose–response effect (Arbyn et al. 2008;18;337:a1284): the deeper the cone (>10 mm) or greater amount of tissue removed, the higher the risk of premature delivery in subsequent pregnancies.

By contrast, there is no evidence for adverse pregnancy outcomes after laser ablation (Kyrgiou et al. Lancet;367:489–98). This may be because the laser beam can be directed with some accuracy at the abnormal areas on the cervix, thereby avoiding unnecessary destruction of healthy tissue (Martin-Hirsch et al. Cochrane Database Syst Rev 2010;6:CD001318).

The obstetric effects of cold coagulation have not yet been studied. Different ablative techniques (laser ablation, radical diathermy and cold coagulation) may result in different risks of prematurity because the precision of destruction caused by each technique varies. Large and extensive ablations may still result in higher risk of preterm labour than smaller treatments, although the destruction

caused by ablation is difficult to quantify. A return to ablation by colposcopists would prevent accurate assessment of the amount of cervical tissue removed, which in turn would limit our ability to provide individualised risk stratification following treatment for CIN for women who desire future pregnancies.

The effects of cold coagulation on future pregnancies have never been investigated. More research is needed on both the obstetric and oncological consequences of cold coagulation, especially in developing countries.

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