

## Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years experience

HELEN K. GORDON, IAN D. DUNCAN

**Summary.** A total of 1628 women with CIN 3 treated with the Semm cold coagulator between 1975 and 1989 was followed primarily by cytology. The standard suitability criteria for ablation were adhered to except that patients were treated at their first visit when the colposcopist expected that the diagnosis would be no worse than CIN 3. Overall 97% of the women were treated at their first visit. In 30 women (2%) the histology was glandular or worse than expected, but 22 of these showed no persistent cervical disease subsequently. Follow-up was achieved for 87% at 10 years. In actuarial terms the primary success rate was 95% at 1 year and 92% at 5 years, it was similar for all age groups. Repeat cold-coagulation for persistent/recurrent CIN 3 was less successful and is not advised. The outcome for 226 pregnancies established after treatment is known. The rates for miscarriage, preterm or operative delivery were not increased. Cold-coagulation of CIN 3 at 100°C as performed by us is as effective as any other treatment and calls into question the need for more expensive practices.

Cervical intraepithelial neoplasia (CIN) is one of the most common gynaecological conditions encountered today. It is dealt with in a variety of ways either by excision or more frequently by destruction. A recent survey by the British Society for Colposcopy and Cervical Pathology (reported by H. Kitchener at their Annual Scientific Meeting in 1990) found that the cold coagulator was second only to the carbon dioxide laser as the most commonly used method. In marked contrast to laser treatment, very little has been published about cold coag-

ulation which despite its name uses temperatures of up to 120°C.

The apparatus was initially introduced by Semm (1966) for the destruction of benign cervical conditions. Its applicability was tested in the cervix clinic of Ninewells Hospital and Medical School, Dundee in three patients in 1975 and since 1978 it has been the standard form of treatment for all CIN suitable for destruction. This is the longest running series in the United Kingdom and comes from an area where the incidence of invasive squamous cervical cancer continues to fall (Fig. 1).

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Department of Obstetrics and Gynaecology,  
University of Dundee Medical School, Ninewells  
Hospital, Dundee DD1 9SY.

H. K. GORDON  
I. D. DUNCAN

Correspondence: Helen K. Gordon, MRCOG.

### Subjects and methods

Women are seen for colposcopy at the Ninewells Clinic if they have had two smears showing mild dyskaryosis or atypia or one smear showing moderate or severe dyskaryosis or cells suspi-

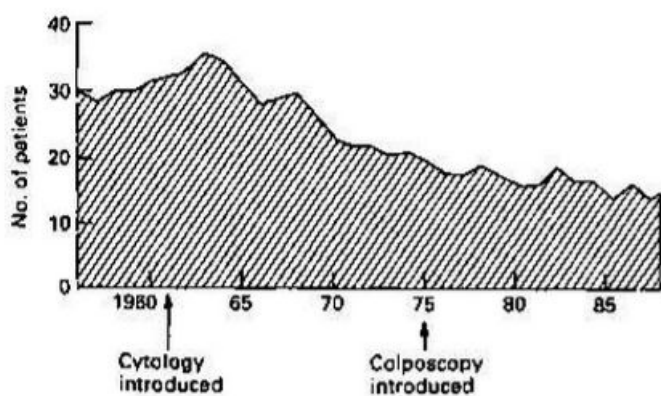


Fig. 1. Running 3-year averages of patients with invasive carcinoma of the cervix in the Dundee laboratories catchment area.

cious of invasion. Colposcopy was performed using 3% acetic acid. If early invasion or glandular abnormality was suspected from the cytological or colposcopic appearances or if the squamocolumnar junction was hidden up the canal, then the transformation zone was excised. If colposcopically overt invasive carcinoma was seen, then treatment was given after confirmatory histology. In all other patients, two to four directed punch biopsies were taken. Immediately thereafter the transformation zone including the lower endocervix was destroyed at 100°C by overlapping 20-s applications of the thermoprobes. Usually between two and five applications were sufficient, taking less than 2 min and haemostasis was achieved by the very nature of the procedure. The woman was given a supply of triple sulphonamide cream for routine intravaginal use for the next week but normal sexual activity was not restricted. Follow-up was by cervical smears and colposcopy was only repeated if the original cytological criteria for referral were found again. The histological diagnosis was used to determine the frequency and duration of smear follow-up. Patients with a pre-treatment diagnosis of CIN 3 have smears repeated in the clinic at 4, 8, 12, 18 and 24 months. They are then seen by their general practitioners for annual smears for a further 8 years before reverting to the normal screening programme.

Details of the colposcopy, histology and initial follow-up were entered on a punch card and a microcomputer file kept separate from the patient's case notes. Details of follow-up smears were entered into the OCCURS computer (Online Cervical Cytology Update and Recall System). This system currently serves Tayside, Fife and the Central Region of Scotland.

The punch cards were updated manually from the OCCURS computer before analysis. End points included persistent or recurrent histologi-

cal abnormality (CIN 1 or worse), cone biopsy or hysterectomy (even when the histology was entirely benign) or death. Patients were deemed lost to follow-up when six months or more have elapsed since the last smear was due.

### Patients

On 1st January, 1990, there were 1661 patients with CIN 3 treated consecutively with the cold-coagulator who were eligible for follow-up for periods of 4 months to 14 years. Thirty-three women have been lost without any follow-up data whatsoever and they have been excluded. The completeness of follow-up ranged from 98% at 4 months, through 87% at 5 years and 87% at 10 years. All the patients eligible for follow-up at 11 years and later have been seen (Table 1). Of the women lost to follow-up, 169 had normal smears, 94 (56%) of them had three or more normal smears consecutively, six others had had abnormal smears, three had a single mildly dyskaryotic smear and three had moderate dyskaryosis.

Thus 1628 women have been followed up. Their age distribution is shown in Figure 2; 1228 (75%) were <35 years of age, 23 (1.5%) were teenagers and 61 (3.5%) were  $\geq 45$  years. Figure 3 shows the parity distribution, 219 (13%) were nulliparous and 1024 (63%) had had not more than two pregnancies before treatment.

### Results

#### Effectiveness

A single treatment was effective in restoring the cervical cytology to normal in 1518 of 1628 (93%) women followed-up. This is the primary success rate and was similar in the various age groups (Table 2).

Expressed in actuarial terms the primary success rate fell from 96% at 4 months, through 95% at 1 year, 94% at 18 months, 94% at 2 years, 93% at 3 years, 92% at 4 years, 92% at 5 years to 91% at 6 years and thereafter. Most 'recurrences' were probably persistent disease detected in the first 18 months of follow-up. Table 3 details the failures after a single treatment, they include one adenosquamous carcinoma, one squamous carcinoma, two invasive carcinomas (early stromal invasion) one moderate glandular atypia, 62 CIN 3, 19 CIN 2, 19 CIN 1 and abnormal cytology (as yet unresolved) in five women. One of these five women has severe

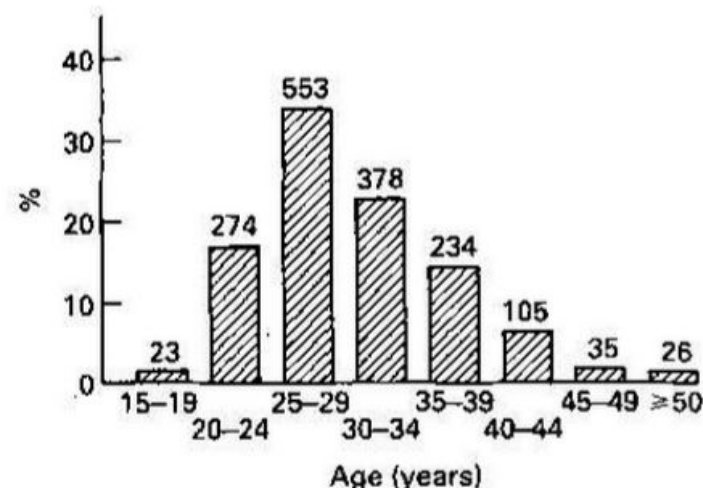
**Table 1.** Completeness of follow-up for 1628 patients with CIN 3 treated with cold-coagulation in Dundee

Follow-up (years)	Number	(%)
0.3	1628/1661	(98.0)
1	1362/1424	(95.6)
1.5	1196/1250	(95.7)
2	1061/1121	(94.6)
3	813/878	(92.6)
4	641/720	(89.0)
5	523/604	(86.6)
6	409/474	(86.3)
7	318/377	(84.4)
8	213/244	(87.3)
9	126/149	(84.6)
10	53/61	(86.9)
11	14/14	
12	2/2	
13	2/2	
14	1/1	

dyskaryosis, but has refused further investigation, four have moderate dyskaryosis (one declined further surgery and three have emigrated). Three women who were lost to follow-up after a single mildly dyskaryotic smear have not been considered as failures.

The adequacy of cold-coagulation could be assessed histologically in hysterectomy or cone biopsy obtained subsequently from 99 patients; a lesion was suspected in 59 of them but was only confirmed in 42 (71.2%). Of 40 patients who had hysterectomies for unrelated conditions one had a focus of CIN 3, two of CIN 2, three of CIN 1, and 34 (85%) were clear.

Twenty-six patients with recurrent CIN 3 were treated on a second occasion with the cold coagulator (Table 4). This resulted in five failures

**Fig. 2.** Age distribution in 1628 patients with CIN 3 treated with cold-coagulation in Dundee.

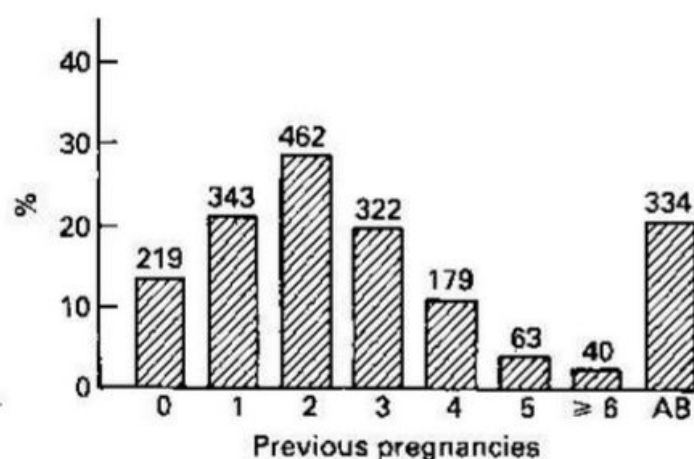
(19%) comprising one adenosquamous carcinoma, one squamous carcinoma, one CIN 3 and adenocarcinoma *in situ* combined, one CIN 2 and one CIN 1. This adds credence to the belief that skip lesions can occur in a cervix that has been treated previously. We therefore consider that repeat treatment by this method is inadvisable and recommend excisional treatment if persistent or recurrent CIN 3 is suspected.

#### Subsequent pregnancy

We know of 243 pregnancies among the treated women and the outcome in 226. Forty women (18%) had a legal abortion; nine (4%) had a first trimester miscarriage and three had ectopic pregnancies. The other 174 pregnancies resulted in deliveries. Three were preterm (two singletons at 35 weeks and one twin pregnancy at 27 weeks). The remainder went to term. Overall the caesarean section rate was 9% and the forceps rate 9%. Earlier in our series, we found that 94 of 101 women (94%) conceived within 2 years after treatment. Thus, the evidence is that cold-coagulation has no adverse effects on fertility or pregnancy outcome.

#### Inadvertent and possibly inappropriate treatment

Our policy of treating at the first assessment visit those women in whom colposcopically directed biopsies were expected to show CIN 3 at the worst differs from standard teaching. We are open to the criticism that we may treat glandular atypia, microinvasion and invasive carcinoma not suspected by the colposcopist both inadver-

**Fig. 3.** Distribution by number of previous pregnancies in 1628 patients with CIN 3 treated with cold-coagulation in Dundee. AB = abortions.

**Table 2.** Simple failure rates for cold-coagulation therapy in 1628 patients with CIN 3 by age group

Age (years)	Number (%)
15-19	1/23 (4.3)
20-24	12/274 (4.4)
25-29	36/553 (6.5)
30-34	30/378 (7.9)
35-39	16/234 (6.8)
40-44	9/105 (8.6)
45-49	3/35 (8.6)
> 50	3/26 (11.5)
Total	110/1628 (6.8)

tently and inappropriately. Overall we treated 1584 of the 1628 women (97%) at their first visit and in 30 of them (2%) the lesion was more advanced than had been suspected (Table 5). The colposcopically directed punch biopsies revealed 14 squamous lesions including 12 microinvasive and two invasive carcinomas and 16 lesions with a glandular component, one of which was invasive. Further investigation showed that cold-coagulation, although inadvertent, had effectively destroyed the lesion in 22 of these 30 women. Residual disease was found in eight women whose management had not been compromised by their possibly inappropriate initial treatment. Unsupervised, inexperienced colposcopists should not treat patients at the first assessment visit, but we have demonstrated that the grounds for fearing that competent colposcopists should not do so are more imagined than real, provided that this is not done when the squamocolumnar junction is not visible, nor

**Table 3.** Diagnoses in 110 failures of a single cold-coagulation treatment in 1628 patients with CIN 3

Diagnosis	Number
Severe dyskaryosis	1
Mod. dyskaryosis	4
CIN 1	19
CIN 2	19
CIN 3	62
GIN 2	1
Early stromal invasion	2
Squamous carcinoma	1
Adenosquamous carcinoma	1
Total	110/1628 (6.8%)

CIN = cervical intraepithelial neoplasia.  
GIN = glandular intraepithelial neoplasia.

when glandular, microinvasive or invasive disease is suspected.

## Discussion

The stability of the local population and the efficiency of the OCCURS system affords an excellent opportunity for longitudinal study. Even those patients deemed to have been 'lost', to follow up tend to reappear, e.g., 117 (70%) of 192 patients 'lost' on 1st January, 1987 were retraced by 1st January, 1990.

Relatively few women (4-5%) are service women or partners of servicemen or undergraduates who leave the area after temporary residence and are lost without trace, but this is unlikely to invalidate the findings from the vast majority who have been followed up.

Our overall primary success rate of 93% with a single treatment compares favourably with other reported centres using the same technique: 94-97% for 924 CIN 1-3 (Cassidy *et al.* 1987); 90% for CIN 2-3 (Smart *et al.* 1987); 97% for 71 CIN 2-3 (Staland 1978). Chanen & Rome (1983) have the longest running series of patients treated with electrocoagulation diathermy. Their primary success rate was 97% in 1864 patients with CIN (about 65% had CIN 3). Similarly 259 women with CIN 3 treated with cryosurgery had a primary success rate of 82%, this improved to 93% after a second treatment (Creasman *et al.* 1984).

Initially tissue destruction with the CO<sub>2</sub> laser was too superficial and good results depended on repeated treatments (Burke 1982). In a series of 40 patients with CIN 3, the primary success rate of 77.5% rose to 85% after a second treatment.

In a series of 419 patients with CIN 3 treated

**Table 4.** Diagnoses in five failures of secondary cold-coagulation treatment in 26 patients with recurrent CIN 3

Diagnosis	Number
CIN 1	1
CIN 2	1
CIN 3 + GIN 3	1
Sq. Ca.	1
Adeno Sq. Ca.	1
Total	5/26 (19%)

CIN = cervical intraepithelial neoplasia.  
GIN = glandular intraepithelial neoplasia.  
Sq. Ca. = squamous carcinoma.

**Table 5.** Details of 30 patients who received inadvertant possibly inappropriate cold-coagulation treatment

<b>Squamous lesions</b>	
Microinvasive (n = 12)	1 invasion to 5 mm on radical hysterectomy, nodes negative, a & w 1 CIN 3 on LLETZ 1 CIN 3 on cone 1 CIN 1 on cone 7 NAD on conc 1 NAD on smear follow-up
Invasive Sq Ca (n = 2)	2 invasion on radical hysterectomy, nodes negative, a & w
<b>Glandular lesions</b>	
GIN 3 (n = 5)	1 GIN 3 on LLETZ-GIN 1 on hysterectomy 1 NAD on hysterectomy 1 NAD on cone 2 NAD on smear follow-up
GIN 1/2 (n = 5)	5 NAD on smear follow-up
CIN 1/2+GIN 1 (n = 4)	4 NAD on smear follow-up
CIN 3+GIN (unspec.) (n = 1)	12 persistent CIN 3
Invasive adeno Ca (n = 1)	1 NAD on radical hysterectomy, nodes negative, a & w

CIN = cervical intraepithelial neoplasia.  
GIN = glandular intraepithelial neoplasia.  
Ca = carcinoma.  
NAD = no evidence of disease.  
a & w = alive and well.  
LLETZ = large loop excision of the transformation zone.

by CO<sub>2</sub> laser vaporization, Anderson (1982) reported a primary success rate of only 74.4%, he suspected that the treatment had been too shallow. Later in the series the success rate improved to 81% with deeper treatment for various grades of CIN.

Subsequent series involving CO<sub>2</sub> laser vaporization to a depth up to 7 mm had more favourable results. Wright & Riopelle (1982) treated a series of 110 women with CIN 3 by CO<sub>2</sub> laser ablation and reported a primary success rate of 93% which improved to 99% after a second treatment. In a series of 129 patients with CIN 3, Jordan *et al.* (1985) reported a primary success rate of 88% in those treated to a depth of

5-7 mm. In a series of 1281 patients with CIN 3 treated over a period of 10 years, Baggish (1989) reported a primary success rate of 96%.

Cold-coagulation has been criticised on the basis of inadequate depth of destruction. Measurement of the depth of destruction is extremely difficult when the surface has been blistered off and the underlying tissue shrivelled by desiccation. Semm (1966) using the cold coagulator at 80-90°C for 15-25 s found that one application could achieve a destruction of 4 mm. De Cristofaro *et al.* (1988) showed that the depth of destruction ranged from 2.5 mm to 4 mm or more after treatment at 100°C for 30 s and always exceeded 4 mm after treatment at 120°C for 30 s. Haddad *et al.* (1988) found that the mean depth of tissue destruction ranged from 2.6 mm (100°C for 20 s) to 3.5 mm (120°C for 30 s).

If this were the case, then 4 mm depth of destruction would rarely be achieved in practice, yet this is the depth recommended by Anderson and Hartley (1980) based on their finding in 343 cone biopsies that the mean depth of involved crypts was 1.24 mm, thus destruction to a depth of 2.92 mm would eradicate all involved crypts in 95% and destruction to 3.80 mm in 97.7%. The difficulties in achieving accurate measurements of tissue destruction may account for any difference between the theoretical and the observed success of this instrument.

Clearly the cold-coagulator effectively destroyed CIN 3 in most of our patients but a few have progressed to microinvasive or invasive cancer. Microinvasion developed in two patients after a single treatment (one squamous and one adenosquamous cancer) and one squamous and one adenosquamous cancer occurred after repeated treatment. The cervical screening programme is aimed at preventing squamous rather than adenocarcinoma. Again the cold-coagulator is comparable with other treatment methods in this respect. Pearson *et al.* (1989) reported the development of invasive cancer in four of 2193 patients with CIN 3 treated by laser ablation (three squamous carcinoma and one adenocarcinoma) and four others developed microinvasion. Townsend *et al.* (1981) reported a survey of the Society of Gynecologic Oncologists which identified 20 patients who had developed invasive cancer after cryosurgery or hot cautery after colposcopically directed biopsy. Cone biopsy and even hysterectomy for CIN 3 do not always prevent the subsequent development of invasive

cancer. Webb (1985) reported the development of invasion in 34 of 5616 (0.6%) women from collected series of patients treated by cone biopsy compared with 19 of 5200 (0.4%) women treated by hysterectomy.

Primary success rates are fundamentally important. Our failure to eradicate disease in 5 of 26 patients treated on a second occasion highlights not so much a failing of the technique, but rather an important difference between an untreated and a previously-treated cervix. In the former, skip lesions are assumed to occur rarely if ever but may well be present in the latter. We would advise excision of the transformation zone in a patient with persistent or recurrent CIN 3 rather than repeat destruction.

The value of any treatment is measured not only by its success but also by its acceptability which depends on various factors including side effects and complications. We did not assess these formally but patients volunteered very few. In women treated for cervical erosions (Ferguson & Craft 1974), pain was experienced by 5 of 24 treated by cold-coagulation, but by none of 27 treated by cryosurgery, a watery discharge was experienced by only four of the former compared with 25 of the latter. Farquharson *et al.* (1987) randomized 714 patients with CIN 2 or 3 to treatment by cold-coagulation or laser vaporization and found that cold-coagulation was significantly shorter, less painful, and less likely to produce secondary haemorrhage.

The most important determinant of unimpaired cervical function is fertility and pregnancy outcome. Duncan (1983) reported a conception rate of 94% within 2 years of treatment. We now have records of 226 pregnancies in women who were treated by cold-coagulation for CIN 3 and their outcome was as good as in untreated women.

Most women with an abnormal smear experience anxiety which is at its peak when awaiting colposcopy and only marginally less so when awaiting treatment (Posner & Vessey 1989). These women benefit greatly from treatment at the first visit. We believe that competent examiners can distinguish almost always between microinvasive or invasive cancer where destruction is inappropriate, and the cervix containing CIN or viral changes. Our experience, in a clinic where 20 operators have been trained by one consultant during 14 years, would support this assertion. All patients (including CIN 1 and 2 and less severe lesions) are treated with a simple

uncomplicated technique which does not compromise the cervix in any recognizable way. Only 44 (3%) of our 1628 patients had to endure an anxious wait for histology which then proved to be normal. This seems to us to be a very large plus to set against the 0.5% of women with CIN 3 whose initial treatment was perhaps inappropriate. Considering we treated a large number of women with lesions less severe than CIN 3, inappropriate treatment was only given to a fraction of 0.5% and in none of them was the definitive treatment compromised.

Costing much the same as a small cryosurgical unit, the Semm coagulator runs conveniently and inexpensively on mains electricity. Small and light, it is readily portable. Its operation is silent and the treatment temperature of 100°C is insufficient to produce charring. The consequent absence of smoke and smell avoids the additional cost of smoke extraction and contributes to a high acceptability by patient and doctor alike. Because of the extremely short duration of the treatment, most women find the associated discomfort tolerable; 1550 of 1628 women (95%) has no anaesthesia whatsoever. The variety of thermoprobes allows uniform treatment of lesions regardless of size or shape provided they meet the generally accepted criteria for local destruction. Post-operative discharge and bleeding are not a problem for most patients. Fertility and the outcome of subsequent pregnancy are not adversely affected.

Our carefully audited experience over many years has convinced us that cold-coagulation is the most cost effective method for the destruction of CIN 3. Our results are as good as those published for any method of treating CIN 3. We treat most women at their first visit and reserve follow-up colposcopy for those with abnormal smears. Salfield & Sharp (1989) attempted to quantify colposcopic requirements assuming that treatment is not given at the first colposcopic assessment and that colposcopy is used routinely on the follow-up of treated patients. Lopes *et al.* (1990) questioned the value of routine colposcopy follow-up. Our study calls into question not only the excessive demands that colposcopy is making upon current resources, but also the need for more expensive forms of treatment.

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