NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endometrial cryotherapy for menorrhagia

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2005.

Procedure name

- Endometrial cryotherapy for menorrhagia
- Endometrial cryoablation for menorrhagia
- Endometrial cryosurgery for menorrhagia

Specialty societies

- Royal College of Obstetrics and Gynaecologists
- British Society of Gynaecological Endoscopy

Description

Indications

Heavy menstrual bleeding (menorrhagia) due to benign causes.

Menorrhagia is heavy cyclical menstrual bleeding over several consecutive cycles in a woman of reproductive years. Menorrhagia can be defined objectively or subjectively. Objectively, menorrhagia is defined as a total menstrual blood loss of more than 80 ml per menstruation. Subjectively, menorrhagia is excessive menstrual blood loss as determined by the patient occurring over several consecutive cycles .

Menorrhagia has adverse implications for quality of life. Women with menorrhagia may have difficulties with daily activities such as work, family life and social activities. Many women report anxiety, depression, embarrassment and problems in their sex lives as a result of menorrhagia. Anaemia is also common among women with menorrhagia, and this may further impair quality of life.

Current treatment and alternatives

Patients with menorrhagia are usually treated with medication before undertaking surgery. Medications may be administered either orally or released into the lining of the uterus (endometrium) by a special intrauterine device. If a woman fails to respond adequately to medical treatment, surgery may be considered. Historically, hysterectomy has been the standard surgical option for women with menorrhagia who no longer desire to maintain fertility. Alternatives to hysterectomy are minimally invasive procedures that may or may not be performed using a hysteroscope (a thin telescope-like instrument inserted through the cervix to look inside the uterus). These procedures involve destroying the endometrium and may reduce complications and recovery times compared with hysterectomy. Hysteroscopic procedures include transcervical endometrial resection or destroying the endometrium with lasers, electrocautery, radiofrequency waves or heated saline. Non-hysteroscopic procedures include destroying the endometrium using heated saline, heated balloons, lasers, radiofrequency waves or microwaves. Non-hysteroscopic procedures are often carried out on a day admission under local anaesthesia.

What the procedure involves

Endometrial cryotherapy (or cryoablation) is a non-hysteroscopic procedure that uses cold temperatures to freeze and destroy the endometrium. It can be performed under general, regional or local anaesthesia, although sometimes no anaesthesia is required. Prior to the procedure, the uterus is sounded and the cervix is dilated, if required, to insert a cryoprobe into the top part (fundus) of the uterus. A small amount of saline solution may be injected into the uterus to enhance freezing. The cryoprobe is cooled by perfusing it with either liquid nitrogen or a compressed gas mixture. The tip of the probe is the site of freezing and is placed in one cornu of the uterus followed by the opposite cornu of the uterus. This generates an iceball in the uterus which destroys the endometrial tissue. Each freeze cycle is followed by a heat (thaw) cycle which allows the probe to be removed. Ultrasound is used to monitor the position of the probe and depth of tissue freezing. Additional freeze/thaw cycles may be repeated if necessary.

Claimed advantages of endometrial cryotherapy over other endometrial ablation approaches are that it is easy to learn and quicker to perform, possibly safer (lower risk of uterine perforation) due to direct ultrasound visualisation of the depth of ablation, requires less anaesthesia due to the analgesic effect of cold temperatures, requires less cervical dilatation, and has the potential for use in the outpatient setting.

Efficacy

Efficacy is based on the results of one randomised controlled trial[1,2,3] comparing endometrial cryotherapy with rollerball electroablation, and one prospective case series[4]. Different primary efficacy outcomes were reported in the two studies.

In the randomised controlled trial, treatment success as assessed by the reduction of menstrual bleeding to a pictorial blood loss assessment chart (PBAC) score of 75 or less in the absence of retreatment at 12 months was 67.4%(130/193) and 73.3%(63/86) by intention to treat analysis in the cryotherapy and electroablation groups, respectively. Bleeding rates at 12 months (not analysed by intention to treat) in the cryotherapy and electroablation groups, respectively, were 12.2% and 6.9% for menorrhagia (PBAC greater than 100), and 27.6% and 55.6% for amenorrhoea (PBAC score 0). In the case series, none of the 67 patients were amenorrhoeic at over 3 months (and up to 18 months) of follow-up.

Absence of abnormal uterine bleeding was achieved in 88% and 93% of women at 12 months, and 94% and 93% of women at 24 months, in the cryotherapy and electroablation groups, respectively, in the randomised controlled trial.

Patient satisfaction ranged from 66.6% (22/33) at over 3 months (and up to 18 months) of follow-up in the case series to 91% at 24 months in the randomised controlled trial.

Improvements in quality of life as measured by the SF-36 questionnaire were similar in patients treated with cryotherapy (1.3 ±0.7) and rollerball electroablation (1.3 ±0.9) in the randomised controlled trial.

Retreatment rate at 24 months was reported in 9.7% (18/186) of patients in the randomised controlled trial: 7% (13/186) by hysterectomy and 2.7% (5/186) by repeat ablation.

The Specialist Advisors stated that there is little randomised controlled trial evidence. Published amenorrhoea rates for endometrial cryotherapy are lower than for other endometrial ablation procedures.

Safety

In the randomised controlled trial[3], the respective adverse events reported during and within 24 hours of the procedure, and at follow-up (3–12 months) included uterine cramping 8% (15/186) and 4% (7/186), other abdominal or pelvic pain/cramping 15% (27/186) and 14% (26/186), nausea and vomiting 2% (4/186) and 0.5% (1/186), and hot flushes 1%(2/186) and 2% (3/186). Other adverse events included uterine perforation during sounding prior to treatment 0.5% (1/186), and vaginal infection 4% (7/186) and urinary tract infection 1% (2/186) at follow-up (3–12 months). Three serious adverse events occurring more than 15 days after the procedure (and within 12 months) were reported in the trial: these were severe abdominal cramping (2 patients) and severe vaginal bleeding (1 patient).

In the prospective case series[4], typical adverse events reported immediately after the procedure included urinary frequency, urgency and pain, pelvic pain and vaginal discharge. Other less commonly reported adverse events were prolonged tiredness and perimenopausal symptoms.

Reported adverse events found in the US Food and Drug Administration (FDA) Centre for Devices and Radiological Health (CDRH) MAUDE database[6] were few and included excessive bleeding, stenosis of the cervix, uterine perforation and bowel injury.

The Specialist Advisors stated that the procedure appears to be safe, but there are no data available on the incidence of major complications. Theoretical adverse events include thermal injury to the cervix and vagina. Anecdotal adverse events include persistent discharge and endometritis.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endometrial cryotherapy for menorrhagia. Searches were conducted via the following databases, covering the period from their commencement to May 2005: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See Appendix B for details of the search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1. Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with menorrhagia due to benign causes.
Intervention/test	Endometrial cryotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to safety and/or efficacy.
Language	Non-English language articles were excluded unless they were thought to add substantively to the English language evidence base.

List of studies included in the overview

This overview is based on one randomised controlled trial comparing endometrial cryotherapy with rollerball electroablation[1-3], and one prospective case series[4].

The randomised controlled trial has been reported in two articles[1,2], one with 1 year of follow-up and the other with 2 years of follow-up. In addition, 1-year results of the trial have been published by the US FDA CDRH[3].

In the prospective case series[4], results of the first 18 patients have been reported in an earlier article. This article has not been included in the main extraction table (Table 2), but has been listed in Appendix A.

The two studies included in this overview used different cryotherapy devices, although both devices were cooled by compressed gas mixtures.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) have been listed in Appendix A.

Existing reviews on this procedure

Interventional procedures guidance documents have been previously issued for the treatment of menorrhagia using the following endometrial ablation approaches: microwave (IPG007), photodynamic therapy (IPG047), thermal balloon therapy (IPG006), thermal free-fluid therapy (IPG051) and impedance-controlled bipolar radiofrequency (IPG104).

The literature search also identified three Cochrane systematic reviews[7-9] that looked at surgical treatments (including endometrial destruction approaches) for heavy menstrual bleeding. The reviews did not find any randomised controlled trials for endometrial cryotherapy at the time.

Table 2. Summary of key efficacy and safety findings on endometrial cryotherapy for menorrhagia

Abbreviations used: AUB, abnormal uterine bleeding; CI, confidence interval; PBAC, pictorial blood loss assessment chart.

Study Details	Key efficacy findings	Key safety findings	Comments
Duleba AJ et al (2003)[1] Randomised controlled trial Enrolment period May 1998 to Nov 1999 Multicentre (10 centres), USA Device: Her Option cryotherapy system 279 women with menorrhagia due to benign causes randomised in a ratio of 2:1 and stratified by age (≤ 40 years, > 40 years): • n = 193 cryotherapy (mean age 41.2 ±5.1 years) • n = 86 rollerball electroablation (mean age 41.1 ±4.8 years) **Screening criteria** Inclusion criteria: Premenopausal women age 30-50 years; in good general health; documented history of excessive menstrual bleeding for at least 3 months; failed traditional medical therapy; no women desired future fertility. Exclusion criteria: Uterine volume > 300 ml; uterine cavity sounding > 10 cm; clotting deficit or bleeding disorders; active pelvic inflammatory disease; abnormal cervical cytology within the past year, unless appropriately treated; history of gynaecologic malignancy within past 5 years; intramural myomas > 2 cm diameter; submucous myomas or endometrial polyps; septate uterus; previous endometrial ablation or other surgery in which thinning of uterine wall may occur; malignant pathology or hyperplasia as documented by endometrial biopsy; pregnancy. **Enrolment criteria** Prospectively documented PBAC score > 150 during menstrual cycle before procedure (number of patients enrolled not specified) 12 months follow-up Disclosure of interest: study sponsored by the manufacturer of the cryotherapy device.	[a]Number of patients completed 12 months follow-up [b]Success defined as a reduction of menstrual bleeding to PBAC score ≤ 75 in the absence of retreatment at 12 months Menstrual bleeding at 12 months: Cryotherapy n = 156[a] / Rollerball n = 72[a] Success[b]: 84.6% / 88.9% Amenorrhoea (PBAC 0): 27.6% / 55.6% Spotting (PBAC 1-15): 16% / 15.3% Hypomenorrhoea (PBAC 16-75): 41% / 18% Eu-menorrhoea (PBAC 76-100): 3.2% / 4.2% Menorrhagia (PBAC >100): 12.2% / 6.9% Success rates differ between treatments by less than 20% (p = 0.0067) At 12 months: Reductions in: Cryotherapy / Rollerball • menstrual bleeding by diary score: 92% / 94% • severe to very severe menses-related pain: 88% / 72% • moderate to severe symptoms of premenstrual syndrome: 60% / 55% • mood affected by bleeding: 94% / 91% • interference with normal social activities: 97% / 83% Improvement in moderate to extreme interference with quality of life: 94% / 91%	**Immediately after procedure** Cryotherapy: • typical side effects were mild cramping, mild vaginal discharge. • 1 serious adverse event – "difficulty recovering from spinal anaesthesia". Rollerball: • 1 serious adverse event – uterine perforation during procedure. **More than 15 days after procedure** Cryotherapy: • 3 serious adverse events: 2 severe abdominal cramping, 1 severe vaginal bleeding. Rollerball: • 2 serious adverse events: 1 persistent urinary tract infection, 1 severe pelvic pain (probable haematometra) requiring prolonged hospitalisation (174 days). **Other Findings:** **Sedation or anaesthesia during procedure** General anaesthesia: Cryotherapy: 46%(85/186) Rollerball: 92%(79/86) Paracervical block with conscious sedation, from FDA (2001)[3]: Cryotherapy: 39%(72/186) Rollerball: 1%(1/86) **Cervical dilatation during procedure** Cryotherapy: 11% Rollerball: 100% (difference, p = 0.0003)	Prospective randomised controlled trial Patients randomised to cryotherapy or rollerball electroablation in ratio of 2:1, stratified by age and using sealed envelopes – it was not stated if this was done centrally or by centre. Statistical basis for unequal randomisation was also not specified. Results by age stratification was not reported. Number of patients enrolled/treated was not specified. From Townsend (2003)[2], there were 272 patients (186 cryotherapy, 86 rollerball). Raw figures were not reported, only percentages (except for adverse events). Intention to treat analysis was not performed for efficacy outcomes. Number of cases were reported for adverse events. Efficacy and safety were reported incompletely. No retreatment rates were reported. Discrepancies were found in the success rates reported in the abstract section (cryotherapy 77.3%, rollerball 83.8%) and in the results section (cryotherapy 84.6%, rollerball 88.9%) of the article. The latter has been taken to be correct. Quality of life assessed by a version of the Dartmouth COOP assessment questionnaire was stated in the article but not reported. Cryotherapy was given using a fixed treatment protocol for all patients. Changes to the protocol may possibly improve outcomes. More women receiving cryotherapy had heavier pretreatment bleeding. This may have had a negative effect on the success rate. The form of sedation or anaesthesia given was not randomly assigned but left to the discretion of surgeons and anaesthesiologists. All patients received hormonal pretreatment with leuprolide acetate.

Abbreviations used: AUB, abnormal uterine bleeding; CI, confidence interval; PBAC, pictorial blood loss assessment chart.

Study Details	Key efficacy findings	Key safety findings	Comments

Townsend DE et al (2003)[2]
Randomised controlled trial
Enrolment period May 1998 to Nov 1999
Multicentre (10 centres), USA
 	
Device: Her Option cryotherapy system
 	
272 patients underwent ablation
• Cryotherapy: 186
• Rollerball: 86
 	
Inclusion and exclusion criteria as described in Duleba (2003)[1]
 	
At 12 months follow-up:
228 evaluable patients,comprising 84% of patients treated and 88% of patients not undergoing retreatment.
• Cryotherapy: 156
• Rollerball: 72
 	
At 24 months follow-up:
137 evaluable patients, comprising 50% of patients treated and 56% of patients not undergoing retreatment.
• Cryotherapy: 94
• Rollerball: 43
 	
24 months follow-up
 	
Disclosure of interest: study sponsored by the manufacturer of the cryotherapy device.
	Absence of AUB (Method of assessing AUB was not specified):
	
	Cryotherapy / Rollerball
	At 12 months: 88% / 93%
	At 24 months: 94% / 93%
	
	Of the evaluable patients with data at both 12 and 24 months of follow-up:
	
	Cryotherapy n = 90 / Rollerball (patient number not specified)
	At 12 months: 93% / 92%
	At 24 months: 94% / 92%
	
	Menstrual pain absent or much improved at 24 months:
	• Cryotherapy: 77%
	• Rollerball: 81%
	
	Premenstrual syndrome absent/mild at 24 months:
	• Cryotherapy: 67%
	• Rollerball: 79%
	
	Patients very/extremely satisfied at 24 months:
	• Cryotherapy: 91%
	• Rollerball: 88%
	
	Retreatment at follow-up:
	• Cryotherapy:
	Total: 9.7%(18/186)
	  • Hysterectomy: 7% (13/186)
	  • Repeat ablation: 2.7% (5/186)
	• Rollerball:
	Total: 9.3%(8/86)
	  • Hysterectomy: 8.1% (7/86)
	  • Repeat ablation: 1.2% (1/86)
	
	Estimated retreatment rate at 30 months (no significant difference, p = 0.999):
	• Cryotherapy: 12.9% (95% CI: 8.2 to 20.6%)
	• Rollerball: 14% (95% CI: 7 to 26.9%)
	
	Median time at risk for retreatment = 20.7 months (range 0.5–31.3 months)
		No safety findings reported.	The article reports 2-year results of the randomised controlled trial in Duleba (2003)[1]
			
			Raw figures for efficacy outcomes (except for retreatment) not provided; only the percentages.
			
			Intention to treat analysis not performed, except for retreatment rates.
			
			Patients with favourable outcomes may have been preferentially retained in the evaluable population. This is particularly important at the 24-month follow-up where only about half of the patients enrolled in each treatment group were evaluable. Results at 24 months follow-up should therefore be interpreted with caution.
			
			The main efficacy outcome was the absence of AUB, but the definition and method of assessing AUB were not specified.
			
			Reporting of efficacy outcomes was incomplete and no adverse events were reported.
			
			Quality of life assessed by SF-36 was stated in the article, but no results were reported.
			
			Many of the efficacy outcomes described in Duleba (2003)[1] were not reported in this paper. It is uncertain if any of those efficacy measures were assessed at 24 months.

Abbreviations used: AUB, abnormal uterine bleeding; CI, confidence interval; PBAC, pictorial blood loss assessment chart.

Study Details

Food and Drug Administration (2001)[3]
Randomised controlled trial
Enrolment period May 1998 to Nov 1999
Multicentre (10 centres), USA

Device: Her Option cryotherapy system

279 patients randomly enrolled in a ratio of 2:1 (193 cryotherapy, 86 rollerball)

272 patients underwent ablation
(186* cryotherapy, 86 rollerball)

* Includes cryo equipment malfunctions. Two patients were later treated with cryo.

Excluded patients:

- cryotherapy: 7 patients
  - withdrew consent (n = 3)
  - failed inclusion/exclusion criteria (n = 1)
  - cryo. equipment malfunctions precluding treatment (treated by rollerball) (n = 3)
- rollerball: 0 patients

Age:
- cryotherapy: mean 41.2 ±5.1 years
- rollerball: mean 41.1 ±4.8 years

Pretreatment PBAC scores:
- cryotherapy: mean 570 ±441 (median 453)
- rollerball: mean 474 ±374 (median 356.5)

(mean difference statistically different, p = 0.0223)

Inclusion and exclusion criteria as described in Duleba (2003)[1]

12 months follow-up

Lost to follow-up:
- cryotherapy: 15 patients
- rollerball: 9 patients

Disclosure of interest: not applicable

Key efficacy findings

Success defined as a reduction of menstrual bleeding to PBAC score ≤ 75 in the absence of retreatment at 12 months.

Based on intention to treat population (all patients lost to follow-up were considered as treatment failures):

	Cryotherapy n = 193	Rollerball n = 86
Success (PBAC ≤ 75)	130 (67.4%)	63 (73.3%)
Amenorrhoea (PBAC 0):	43 (22.2%)	40 (46.5%)

Other outcomes:

	Cryotherapy n = 157	Rollerball n = 73
QOL improvement (assessed by SF-36):	1.3 ±0.7	1.3 ±0.9
Patients very or extremely satisfied	86%	88%
Patients recommend to a friend	98%	95%
Patients report time lost from work or other activities. Pre-operative: Post-operative:	 74% 6%	 71% 7%

Hysterectomy prior to 12-month follow-up:

Reasons:	Cryotherapy	Rollerball
Cramping/PMS	1	0
Cramping/ bleeding	3	1
Bleeding	2	1
Pain	0	1
Total	**6**	**3**

6 hysterectomies in women < 40 years (4 cryotherapy, 2 rollerball) and 3 in women > 40 years (2 cryotherapy, 1 rollerball)

Key safety findings

During procedure & within 24 hours postoperatively:

	Cryotherapy n = 186	Rollerball n = 86
Uterine cramping	15 (8%)	4 (5%)
Other abdominal or pelvic pain/cramping	27 (15%)	10 (12%)
Nausea & vomiting	4 (2%)	4 (5%)
Hot flushes	2 (1%)	0 (0%)
Hyponatraemia/ fluid overload	0 (0%)	3 (3%)
Perforation**	1 (0.5%)	1 (1%)
Cervical/vaginal laceration	0 (0%)	1 (1%)

**Cryotherapy perforation occurred during sounding prior to treatment. Rollerball perforation occurred during treatment.

At 2 weeks:

	Cryotherapy n = 186	Rollerball n = 86
Uterine cramping	5 (3%)	0 (0%)
Other abdominal or pelvic pain/cramping	7 (4%)	8 (9%)
Urinary tract infection	5 (3%)	3 (3%)
Hot flushes	6 (3%)	3 (3%)
Vaginal infection	2 (1%)	1 (1%)
Nausea & vomiting	2 (1%)	1 (1%)

At 3, 6 and 12 months:

	Cryotherapy n = 186	Rollerball n = 86
Uterine cramping	7 (4%)	5 (6%)
Other abdominal or pelvic pain/cramping	26 (14%)	16(19%)
Vaginal infection	7 (4%)	1 (1%)
Hot flushes	3 (2%)	7 (8%)
Urinary tract infection	2 (1%)	3 (3%)
Nausea & vomiting	1 (0.5%)	1 (1%)

(Note: the article reports 1% nausea and vomiting in the cryotherapy group.)

In the cryotherapy group, no serious device-related adverse events were reported. Other adverse events in ≤ 1% of patients included severe bleeding, difficulty recovering from anaesthesia and pregnancy (one patient).

Comments

FDA summary of the 1-year results of the randomised controlled trial in Duleba (2003)[1]

Intention to treat analysis was not performed for efficacy outcomes, except for the primary measure of success (PBAC scores).

7 patients, all from the cryotherapy group, were excluded from the per protocol analysis.

Results by age stratification were not reported.

Device malfunctions was experienced in 26% (49/189) of cases: 13 did not preclude completing treatment, 5 resulted in acute treatment failure.

Modifications were made to the Her Option cryotherapy system after the study to address reliability issues. The modified device may have improved outcomes.

There was variability in success rates across centres. Placement of probe, lack of adherence to treatment protocol and level of competence needed for using ultrasound intraoperatively were cited as possible reasons.

The Advisory Panel recommendations included standardising the procedure and conducting a post-market analysis of the standardised technique.

Potential adverse events considered were endometritis, difficulty with defaecation or micturition, haematometra, haemorrhage, thermal injury to adjacent tissue, and post-ablation tubal sterilisation syndrome.

Many of the efficacy outcomes reported in Duleba (2003)[1] and Townsend (2003)[2] were not reported in the FDA summary.

For more information, see summary tables for Duleba (2003)[1] and Townsend (2003)[2].

Abbreviations used: AUB, abnormal uterine bleeding; CI, confidence interval; PBAC, pictorial blood loss assessment chart.

Study Details	Key efficacy findings	Key safety findings	Comments
Pittrof R et al (1994)[4] Prospective case series Until Dec 1993 (start date not specified) UK Device: not specified – compressed gas-cooled system (manufactured by Spembly Medical, UK.) 67 women who would have otherwise undergone hysterectomy for prolonged menorrhagia (mean 6 years, range 1–25 years) Mean age 34 (range 28–50) years Inclusion criteria: • heavy menstrual loss unresponsive to medical treatment as determined by the patient • use of a permanent method of contraception or sterilisation prior to procedure • patients have completed their family Exclusion criteria: • significant endometrial or uterine pathology (except for one patient who had a tamoxifen-associated endometrial polyp which was removed at the time of cryotherapy) Patients were followed up to 18 months or until the patient requested hysterectomy. 60 patients were followed for > 3 months. No patients were lost to follow-up. Disclosure of interest: not specified.	**Patient satisfaction** Of the 19 patients ('working' device) treated until 1 Oct 1992 (3 excluded for protocol violations): At 3 months: • satisfied: 100%(16/16) At 18 months: • satisfied: 62.5% (10/16) • not satisfied: 37.5% (6/16). Of the 21 patients ('non-working' faulty device) treated between 1 Oct 1992 and 18 Mar 1993: At 3 months or more: • satisfied: 14.2%(3/21) at 8–10 months • not satisfied: 85.7%(18/21) (All unsatisfied patients opted for hysterectomy.) Of the 27 patients ('working' device) treated with a new cryoprobe and console after 18 Mar 1993 (3 excluded for protocol violations and 7 for follow-up < 3 months). At 3 months or more: • satisfied: 70.6%(12/17) at 3–8 months • not satisfied: 29.4%(5/17) at 3 months. Patients satisfied with treatment at > 3 months according to working/non-working device: • working device: 66.7% (22/33) (63.6% was also stated in the article) • non-working device: 14.3% (3/21). Amenorrhoea at > 3 months: 0 patients Improvement of menstrual symptoms at 3–18mths: 63% patients In the first 18 patients, frequency of sexual intercourse, dysmenorrhoea and premenstrual tension were unaffected or improved after the procedure (time assessed and patient numbers not specified). Patients returned to normal social and sexual activity within 3 months (mean 2 weeks, range 1–12 weeks). Retreatment following failed cryotherapy: • Hysterectomy: 22 patients • Repeat ablation: - patient numbers not specified (2/18 patients from Pittrof (1993)[5])	All patients and their general practitioners were asked to report any complications. During operation: • no surgical complications in all patients • no tubal leakage of uterine distension fluid in the 31 patients who underwent simultaneous laparoscopic sterilisation. Post-operative complications: • all patients had urinary frequency/urgency • moderate pelvic pain (patient numbers not reported) Vaginal discharge and dysuria were also reported in all 18 patients in Pittrof (1993)[5]. At follow-up: • no intrauterine adhesions among patients in whom cryotherapy failed • no vaginal discharge. Prolonged tiredness (4 patients) and perimenopausal symptoms (1 patient) were also reported in Pittrof (1993)[5].	Prospective case series. Results of the first 18 patients have been reported in Pittrof (1993)[5]. The device was found to be faulty ('non-working') during the study. 21 patients were considered to be affected but the exact number of patients was uncertain. The authors suggested that these patients could serve as a control group since neither surgeon nor patient were aware of the problem at the time. The first 19 and last 27 patients (total 46 patients) were analysed as one group ('working' device). But outcomes of the two patient series may differ as improvements were made to the device in the latter group. Intention to treat analysis was not performed. 19.4%(13/67) patients were excluded from analysis for protocol violation (n = 6) and for not yet reaching 3-month follow-up (n = 7). Treatment failed in 7.5% (5/67) of the patients excluded. If these patients were included in the analysis, patient satisfaction rates would be lower. Endometrial thickness > 5mm (n = 4) and absence of pre-operative preparation (n = 1) were described as protocol violations but not specified as exclusion criteria. Pretreatment data for menorrhagia duration, age and time to normal social and sexual activity correspond to those in Pittrof (1993)[5]. Data for the complete cohort (67 patients) may be different. Efficacy and safety were incompletely reported. There may be recall bias in the patient-reported pretreatment menses-related symptoms as these were obtained retrospectively. Method of assessing patient satisfaction and other patient-reported outcomes was not specified. General anaesthesia and cryotherapy using a fixed protocol were given to all patients. More patients pretreated with luteinising hormone-releasing hormone were satisfied compared to those pretreated with Danazol.

Validity and generalisability of the studies

- This overview is based on only two studies: one randomised controlled trial with 2 years of follow-up and one case series with up to 18 months of follow-up. Efficacy and safety outcomes in these studies were poorly reported.
- Intention to treat analysis was not performed for efficacy outcomes in both studies, except for treatment success measured by PBAC score in the randomised controlled trial that was published by the FDA. This is important as success rates are lower when analysed by intention to treat.
- Measures of success were based on subjective patient-reported outcomes, which may vary widely in different patient populations and different treatment settings (for example, hospitalised or outpatient settings).
- Comparison of efficacy outcomes between studies was not possible as the primary measures of treatment success varied between studies.
- The randomised controlled trial was sponsored by the manufacturer of the Her Option cryotherapy device.
- In the randomised controlled trial, only about half of the patients enrolled in each treatment group were evaluable at 24 months of follow-up. Furthermore, patients with favourable outcomes may have been preferentially retained in the evaluable population. The results at 24 months of follow-up should therefore be interpreted with caution.
- Patients in the randomised controlled trial were allocated to either cryotherapy or rollerball electroablation treatment in a ratio of 2:1, respectively. No statistical rationale was described in the article. Care may need to be taken in comparing the outcomes of the two treatments.
- In the case series, the cryotherapy device was determined to be faulty during the study. Patients designated to the 'working' device group included those who were treated with the original device (before the fault was discovered) and those who were treated with a modified device (after the fault was discovered). Patients using the modified device may have better outcomes than those using the original device without the modifications.
- Endometrial cryotherapy was performed according to a fixed treatment protocol in both studies. Improvements in outcomes may potentially be achieved using a different protocol.
- Different aspects of the procedure varied between the two studies (and sometimes within a study) including the type of cryotherapy device used, duration of freeze/thaw cycles, temperature of the freezing zone, type of pre-treatment hormonal therapy used, treatment setting, concurrent procedures, and method of sedation or anaesthesia (if used). These may need to be taken into consideration when comparing between studies.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr E Downes**,** Mr K Edmonds, Mr D Parkin

- Evidence for endometrial cryotherapy from randomised controlled trials is limited.
- Endometrial cryotherapy should be compared with transcervical endometrial resection or balloon endometrial ablation.
- There are no data available on the incidence of major complications.
- Physicians need to be experienced in performing ultrasound scanning intra-operatively, as well as be able to dilate and manipulate the uterus.
- The technique will not be suitable for all women as the procedure cannot be used for patients who have significant fibroids or large intrauterine cavities.
- The procedure is not suitable for the outpatient setting if general anaesthesia is required.
- It is important to collect data on the use of cryotherapy in the outpatient setting as this may have some practical advantages.
- The manufacturer of the Her Option® cryoablation therapy system is evaluating its treatment protocol. It is important that this trial is completed before clear protocols are given to maximise the efficacy of endometrial cryotherapy.

Issues for consideration by IPAC

- Endometrial cryotherapy is an evolving technology.
- A study to evaluate the effectiveness of extended treatment regimens with the Her Option cryoablation therapy system for treatment of menorrhagia is currently being conducted with expected completion in March 2008. (www.clinicaltrials.gov/ct/show/NCT00094536)
- Medical device safety notices[10,11] on "endometrial ablation achieved by thermal means" have been issued by the UK Medicines and Healthcare products Regulatory Agency (MHRA). Serious adverse incidents of uterine perforation and injury to adjacent organs, particularly the bowel and bladder have been reported. It was not stated if the adverse incidents were reported for cryotherapy. However these incidents have been reported for cryotherapy elsewhere.

References

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Appendix A: Additional papers on endometrial cryotherapy for menorrhagia not included in summary Table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table. It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non inclusion in Table 2
Davies WAR, Pollard W, Basterfield P. (1985) Reduction of menstrual blood loss with endometrial cryosurgery. *Journal of Obstetrics and Gynaecology* 6(2):119.	49 women with dysfunctional uterine bleeding Follow-up was not reported in abstract Device: not reported in abstract	Menstrual blood loss assessment: • subjective: 38 patients • objective: 11 patients Significant reduction ($p < 0.01$) in mean duration of bleeding and mean number of tampons, pads or both used by subjective assessment Significant reduction ($p < 0.05$) in blood loss in 72.7% (8/11) by objective measurements	Old case series reported in 1985.
Dobak JD, Willems J, Howard R et al. (2000) Endometrial cryoablation with ultrasound visualization in women undergoing hysterectomy. *Journal of the American Association of Gynecologic Laparoscopists* 7(1):89–93.	10 women scheduled for hysterectomy No follow-up Device: First Option system	Preliminary experience with First Option device (original name for the Her Option device) and ultrasound monitoring appears feasible and safe	Small case series, unlicensed device
Kumar S, Suneetha PV, Dadhwal V, et al. (2002) Endometrial cryoablation in the treatment of dysfunctional uterine bleeding. *International Journal of Gynecology and Obstetrics* 76:189–190	27 women with dysfunctional uterine bleeding for whom medical treatment has failed Mean follow-up 8.6 (3–16) months Mean age 32.8 years Device: Cryosuper AA-4 device	Non-responders: 29.6% (8/27) At 3 months follow-up: • eumenorrhoea: 40.74% (11/27) • hypomenorrhoea: 22.22% (6/27) • amenorrhoea: 7.44% (2/27)	Small case series, unlicensed device

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non inclusion in Table 2
Pittrof R, Majid S, Murray A. (1993) Initial experience with transcervical cryoablation of the endometrium using saline as a uterine distension medium. *Minimally Invasive Therapy* 2:69–73.	18 women with menorrhagia >3 months follow-up Device: gas-cooled system (name not specified). Manufactured by Spembly Medical, UK	Prospective study: initial experience using saline as a uterine distension medium Patients satisfied at ≥ 3 months 67%(8/12) No operative complications or leakage of distension fluid on laparoscopic exam	Small case series Results of study have been included in Pittrof (1994)[3]
Rutherford TJ, Rutherford TJ, Zreik TG et al. (1998) Endometrial cryoablation, a minimally invasive procedure for abnormal uterine bleeding. *Journal of the American Association of Gynecologic Laparoscopists* 5(1):23–28.	15 women with metrorrhagia or menorrhagia 22 months follow-up Median age 47years (range 31–78 years) Device: CMS 450 AccuProbe system	Prospective pilot study 16 procedures were performed, 1 repeated Amenorrhoea rates by life table analysis: • 75.5% at 6 months • 50.3% at 22 months All patients had serosanguineous discharge 4–8 weeks post-op No rehospitalisation due to procedure	Small case series

Appendix B: Literature search for endometrial cryotherapy for menorrhagia

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	Issue 2, 2005	16.5.2005
CRD	April 2005	16.5.2005
Embase	1980 to 2005 Week 20	16.5.2005
Medline	1966-May Week 1, 2005	16.5.2005
Premedline	May 13, 2005	16.5.2005
CINAHL	1982-May Week 1, 2005	16.5.2005
British Library Inside Conferences (limited to current year only)	2004-2005	16.5.2005
National Research Register	Issue 2, 2005	16.5.2005
Controlled Trials Registry	N/A	16.5.2005

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

```
1    exp MENORRHAGIA/
2    menorrhagia.tw.
3    (heavy menstru$ bleed$ or HMB).tw.
4    exp ENDOMETRIUM/
5    or/1-4
6    (endometri$ adj3 (cryo$ or crymo$ or freez$ or sub-zero)).tw.
7    (uter$ adj3 (cryo$ or crymo$ or freez$ or sub-zero)).tw.
8    Her option.tw.
9    exp CRYOSURGERY/
10    or/6-9
11    5 and 10
12    limit 11 to humans
```