Second generation endometrial ablation

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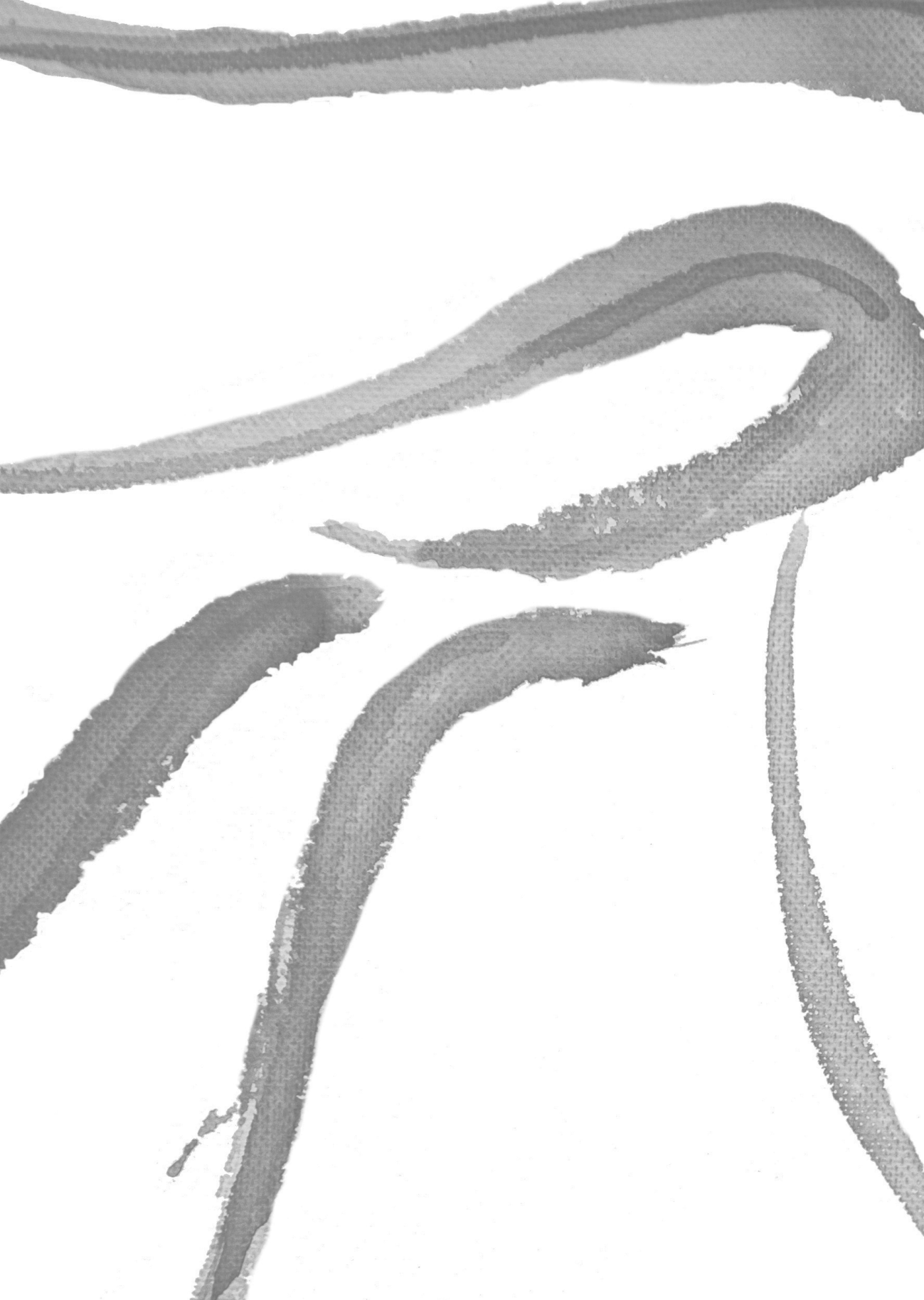

Chapter 1

Introduction

Introduction

Heavy menstrual bleeding, or menorrhagia, is a significant health problem in women of reproductive age. Its incidence varies between 9% and 22%.[1-3] Menorrhagia is defined as a menstruation at regular cycle intervals, but with excessive flow and duration. Clinically, menorrhagia is defined as menstrual blood loss exceeding 80 mL per cycle.[4] In recent years, changes in terminology appeared, because there was a great variation in the way the terms abnormal uterine bleeding, menorrhagia and dysfunctional uterine bleeding were used. It was proposed to use abnormal uterine bleeding as the overarching term to describe all symptomatic blood loss from normal menstruation or the menstrual cycle. Heavy menstrual bleeding (HMB) is a suitable replacement for the term menorrhagia.[5]

HMB has a significant impact on the medical, social economic and psychological well-being of women.[1,6] When medical treatment fails, surgical interventions, like destruction of the endometrium or a hysterectomy can be considered. Hysterectomies are performed in 30-40% of the patients for treatment of severe HMB.[4] Hysterectomy is an effective treatment with good health related quality of life scores.[7] The level of satisfaction with hysterectomy is usually high, but it is a major surgical procedure with a complication rate up to 43%, but only about 4% of these complications are major complications.[8] Patient preference studies show that women place a high value on retaining their uterus and that they have a strong preference for avoiding hysterectomy as a treatment to resolve the problem of HMB, but when they do undergo a hysterectomy they are generally satisfied.[9] Endometrial ablation is an alternative to hysterectomy in women with heavy menstrual bleeding. It is a relatively minor surgical procedure which preserves the uterus yet reduces heavy menstrual bleeding.

Endometrial ablation

Endometrial ablation was introduced in the 1980's. It includes the removal or destruction of the basal layer of the endometrium. This results in an inability of the endometrium to react on hormonal stimuli, and therefore decreases menstrual blood loss.

The first endometrial ablations were performed with direct hysteroscopic vision. They are referred to as first-generation devices. The first-generation devices

were: endometrial laser ablation, transcervical resection of the endometrium and rollerball ablation.[10-13] The introduction of endometrial ablation caused a rapid decrease in the amount of hysterectomies performed.[14] However, the first-generation endometrial ablation techniques involved a long learning curve and had other disadvantages.[7,15,16] Glycine and Sorbitol are both used when performing a hysteroscopic guided endometrial ablation. The risk of absorption of the distension fluid is present and is characterized by hyponatraemia, water intoxication, cerebral edema and cardiac overload, which can result in a fatal hyponatremic encephalopathy.[17,18] Over the past decade, second-generation non-hysteroscopic techniques overcame these disadvantages. Destruction of the endometrium by the 'blind' endometrial ablation is achieved by different methods, the most important being microwave (Microsulis®), high temperature fluids within a balloon (Thermachoice®, Cavaterm®, Thermablate®), bipolar radiofrequency energy (NovaSure®) and free fluid with a high temperature (Hydrothermablator®).[19] The second-generation techniques are safer, technically easier and quicker to perform, and involve shorter hospital stays.[20] Bipolar radiofrequency endometrial ablation (NovaSure®) is reported to be superior over balloon ablation (Thermachoice®).[21] Another second-generation device, the Hydrothermablator®, is applied in the uterus under hysteroscopic view, thus potentially reducing the risk of uterine perforation compared to other second generation techniques. In a randomized multicenter study hydrothermablation was found to be equally effective as rollerball ablation.[19]

The advantages of the endometrial ablation seem to diminish within time. Two years after ablation, 12% of the women had had a hysterectomy and four years after ablation even 30%.[20,22] Nevertheless, most women prefer endometrial ablation over hysterectomy as therapy for menorrhagia.[23]

The indication for ablation could be improved by predicting the probability of success in each particular case. Factors as a young age, a retroverted uterus, an endometrial thickness of at least 4mm and a prolonged duration of menstruation seem to be associated with an increased risk of endometrial ablation treatment failure.[24] However, publications that investigated a relation between a previous Cesarean section and the success of an endometrial ablation are lacking.

When endometrial ablation was introduced, the procedures were performed in theatre with general anesthesia or regional (spinal) anesthesia. Years after, endometrial ablation was also performed at the outpatient clinic with a paracervical block combined with intra-venous sedation. One study compared

intraoperative and postoperative pain between ThermaChoice® and NovaSure® endometrial ablation.[25] The NovaSure® system was associated with significantly lower intraoperative and postoperative pain. These data supported the idea that the NovaSure® procedure could become an office-based procedure with local anesthesia, meaning only a paracervical block. The NovaSure® only takes a maximum of two minutes to perform the ablation. Lately, more endometrial ablation techniques, like Thermablate® and ThermaChoice® III balloon ablation, are developed with a shorter treatment time, which seems better applicable for treatment in the office with local anesthesia.

This thesis deals with the prognostic factors for the success of endometrial ablation and the use of different second-generation endometrial ablation techniques in theatre and in the outpatient clinic with a paracervical block.

Outline of the thesis

This thesis aims to answer the following questions:

1. Which are the prognostic factors for success of endometrial ablation in the treatment of heavy menstrual bleeding?
2. What is the effectiveness of bipolar radiofrequency endometrial ablation in the treatment of heavy menstrual bleeding as compared to hydrothermablation after 12 months and at long-term follow-up in terms of amenorrhea, satisfaction, reinterventions and quality of life?
3. Is it safe and acceptable to perform bipolar radiofrequency endometrial ablation with a paracervical block in the outpatient clinic?
4. What is the effectiveness of bipolar radiofrequency endometrial ablation in the treatment of heavy menstrual bleeding as compared to balloon endometrial ablation in the outpatient clinic in terms of amenorrhea, pain, satisfaction and quality of life?
5. Which endometrial ablation technique(s) is/are preferred in the treatment of heavy menstrual bleeding?

To answer these questions we conducted the following studies, of which the results are presented in this thesis:

Chapter 2 studies a history of Cesarean section and other factors that are potentially associated with endometrial ablation failure in the treatment of heavy

menstrual bleeding. A case-control study was performed, comparing patients who had failed ablation versus successful ablation. Failed ablation was defined as the need for hysterectomy due to persistent heavy menstrual bleeding after ablation. Successful ablation was defined as a satisfied patient who did not need a hysterectomy after ablation for menorrhagia. Both groups, cases and controls, were identified from the surgery registration in the Máxima Medical Center between January 1999 and January 2009.

Chapter 3 presents the results of a double blind randomized controlled trial comparing the effectiveness of two second-generation ablation techniques in the treatment of heavy menstrual bleeding: bipolar radiofrequency impedance-controlled endometrial ablation (NovaSure®) and hydrothermablation (HTA®). Patients were included between March 2005 and August 2007. The primary outcome was amenorrhea at 12 months after treatment. Secondary outcome measures were patient satisfaction and reinterventions.

Chapter 4 evaluates the 5-year follow-up results of the study described in chapter 3, comparing bipolar radiofrequency endometrial ablation with hydrothermablation for the treatment of heavy menstrual bleeding.

Chapter 5 reports the health related quality of life of patients who participated in the randomized controlled trial described in chapter 3 and 4. Health related quality of life was assessed and compared between both groups before randomization and at each follow-up visit at 4 weeks, 6 months, 12 months and 5 years after treatment. The questionnaires that were used were the medical outcomes study Short-Form (SF-36), Euroqol and the menorrhagia multi-attribute scale (Shaw). The menorrhagia outcomes questionnaire (MOQ) was completed at 4 weeks, 6 and 12 months after treatment.

Chapter 6 describes a prospective cohort study to evaluate the safety, feasibility and efficacy of bipolar radiofrequency endometrial ablation with local anesthesia. Women with heavy menstrual bleeding were included to undergo bipolar radiofrequency endometrial ablation with a paracervical block. We measured the acceptability, pain score (visual analog scale), patients' satisfaction during and after the procedure and amenorrhea.

Chapter 7 presents the results of a multi-center double blind randomized controlled trial comparing the effectiveness of two second-generation ablation techniques, bipolar radiofrequency endometrial ablation (NovaSure®) and balloon endometrial ablation (Thermablate®), in the office with a paracervical block in patients with heavy menstrual bleeding. Patients were included between March 2009 and December 2011. The main outcome was amenorrhea at 12 months follow-up. We also measured pain, satisfaction, quality of life and reinterventions.

Chapter 8 reports a systematic review comparing the efficacy, safety and acceptability of methods used to destroy the endometrium in premenopausal women with heavy menstrual bleeding. Randomized controlled trials comparing different endometrial ablation techniques in women with a complaint of heavy menstrual bleeding without uterine pathology were eligible. The outcomes included reduction of heavy menstrual bleeding, improvement in quality of life, operative outcomes, satisfaction with the outcome, complications and need for further surgery or hysterectomy.

Chapter 9 provides a general discussion and implementations for future research.

Chapter 10 summarizes the data presented in this thesis. A Dutch version is included.

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Chapter 2

Prognostic factors for the success of endometrial ablation in the treatment of menorrhagia with special reference to previous Cesarean section

Peeters JA, Penninx JP, Mol BW, Bongers MY

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Abstract

Objective: To assess whether, among other prognostic factors, a history of Cesarean section is associated with endometrial ablation failure in the treatment of menorrhagia.

Study design: We compared women who had failed ablation to women who had successful ablation for menorrhagia in a case-control study. Failed ablation was defined as the need for hysterectomy due to persistent heavy menstrual bleeding after ablation. Successful ablation was defined as an ablation for menorrhagia not needing hysterectomy and the woman being satisfied with the result. Both cases and controls were identified from the surgery registration in the Máxima Medical Center between January 1999 and January 2009. Cases were women that had an endometrial ablation and a hysterectomy, whereas controls only had an endometrial ablation. From the medical files we collected for each patient clinical history, including the presence of a previous Cesarean section, baseline characteristics at the moment of initial ablation, data of the ablation technique and follow-up status. We used univariable and multivariable logistic regression to estimate the risk of failure of endometrial ablation.

Results: We compared 76 cases to 76 controls. Among the cases, 12 women had had a previous Cesarean section versus 15 in the control group (15.8% versus 19.7%; odds ratio (OR) 0.76; 95% confidence interval (CI) 0.3-1.8). Factors predictive for failure of ablation were dysmenorrhea (OR 3.0; 95% CI 1.5-6.1), having a submucous myoma (OR 3.2; 95% CI 1.5–6.8) and uterine depth (per cm OR 1.3; 95% CI 1.0–1.6). Presence of intermenstrual bleeding, sterilization and age were not associated with failure of ablation.

Conclusion: A previous Cesarean delivery is not associated with an increased risk of failure of endometrial ablation, but dysmenorrhea, a submucous myoma and longer uterine depth are. This should be incorporated in the counseling of women considering endometrial ablation.

Introduction

Dysfunctional uterine bleeding is a frequent problem in premenopausal women, as one in 20 women suffer from menorrhagia.[1,2] Menorrhagia has consequences for the general well-being of women. Although a hysterectomy guarantees amenorrhea in all women, it is expensive and has a significant impact on health-related quality of life immediately after surgery.[3,4] The treatment of dysfunctional uterine bleeding by destroying the endometrium without removal of the uterus has become common practice. Compared with hysterectomy, transcervical endometrial ablation techniques initially show similar efficacy with lower costs and less complications.[4,5] These beneficial outcomes, however, seem to diminish with time, as 12% of the women require hysterectomy within 2 years and 30% within 4 years after ablation.[4,5] Nevertheless, most women choose endometrial ablation rather than hysterectomy as therapy for menorrhagia.[6] Despite the willingness to accept potential risk of treatment failure, counseling of women with menorrhagia, who needed surgical treatment, could be improved by predicting the probability of success in each particular case.

Due to the rise in Cesarean sections in the last decade more and more women who will get an endometrial ablation have a Cesarean section. Data are lacking however, on the association between a previous Cesarean section and the success of an endometrial ablation.

The objective of this study was to assess if, among other potential prognostic factors, a Cesarean section could determine the outcome of endometrial ablation in women with menorrhagia.

Materials and Methods

We performed a retrospective case-control study in the Maxima Medical Center (MMC). The MMC is a teaching hospital with 500 beds in the south of The Netherlands. We studied women who had undergone an endometrial ablation between January 1999 and March 2009 for menorrhagia. In our center, endometrial ablation for menorrhagia has been carried out since 1994. In the study period we performed several randomized clinical trials evaluating balloon ablation, NovaSure® and Hydrothermal ablation (HTA). At present, NovaSure® is the treatment of choice due to the results of the RCT's.[7-9]

In this study, we defined cases, i.e. women in whom ablation has failed, as women who underwent a hysterectomy for persistent menorrhagia after an ablation in the period January 1999 until March 2009. Controls were women who had had an ablation without any reintervention. We identified our cases and controls from the electronic operation room planning system. For each included case patient, the next woman with a successful comparable ablation procedure scheduled directly after the index procedure was selected as a control patient. Subsequently we checked the medical records of the selected control patients whether the endometrial ablation had indeed been successful or not. An endometrial ablation was considered to be successful if the patient was satisfied without a reintervention. Information on satisfaction was obtained from the medical chart and by contacting the patient by telephone.

We only included patients with dysfunctional uterine bleeding who had cavity investigation by a saline infusion sonography and/or a hysteroscopy. Submucous myomas, as observed in ultrasound or pre-endometrial ablation hysteroscopy, were defined as partial protrusion of myoma into the cavity. Only women with submucous myomas smaller than 2 cm, or not disturbing the endometrial cavity could undergo endometrial ablation. Exclusion criteria were malignancy of the uterus or cervix, presence of intrauterine adhesions, after assessing by hysteroscopy, and uterine depth more than 12 cm. The use of oral contraceptives, antiprostaglandins and anticoagulants in the previous 3 months before the ablation was not an exclusion criterion.

The three global endometrial ablation methods which were used in MMC during the study period were radiofrequency ablation (NovaSure®), hydrothermal ablation (HTA®) and balloon ablation (Thermachoice®). All three procedures were performed in the operating room under regional or general anesthesia. After 2005 the NovaSure® also was performed in an outpatient setting under local anesthesia. Women who choose the procedure at the outpatient clinic were advised to use an oral nonsteroidal anti-inflammatory drug as a painkiller 12 hours and 1 hour before the procedure. At the beginning a paracervical block with Ultracaine or Prilocaine 1% with or without adrenaline was placed.

The aim of the analysis was to relate potential prognostic factors available before the start of treatment to the occurrence of an adverse outcome. Apart from previous Cesarean section, the case subjects were compared with the control subjects with regard to the occurrence of clinical signs and symptoms, abnormal laboratory tests, medical history and preoperative characteristics. The position

of the uterus was assessed by bimanual examination and confirmed during hysteroscopy. Dysmenorrhea, intermenstrual bleeding and an irregular menstrual cycle were recorded either present or absent and the duration of menstruation was recorded in days.

All data were obtained from patients' medical records. In the cases and controls in which we were not sure about whether a Cesarean delivery had been performed, we contacted the patient. Beside Cesarean delivery we also collected data of preoperative characteristics, medical history and main factors about dysfunctional uterine bleeding. Age was categorized by using two threshold values; one of 40 years and one of 45 years. A 4 mm threshold for endometrial thickness was selected.[7]

Each potential prognostic variable was first evaluated in a univariable logistic regression model. Subsequently variables with a *P*-value ≤ 0.05 were evaluated in a multivariable logistic regression model. Odds ratios (ORs) and 95% Confidence Interval (CI) were presented. All data were analyzed using SPSS 17.0 for Windows.

Results

We identified 890 women who have had an endometrial ablation in the MMC between January 1999 and March 2009. Of these 890 women, 76 had had a hysterectomy after their endometrial ablation as treatment for menorrhagia, and therefore were considered as having experienced the ablation as unsuccessful. These patients were compared to 76 women who had an ablation with a satisfying result. Of the 152 women 110 had a NovaSure®, 36 the HTA and the other 6 the Thermachoice®.

Table 1 shows the clinical characteristics of both the cases and controls. There were a few differences between case and control subjects. Duration of menstruation, intermenstrual bleeding and an age above the 45 years differed significantly (respectively: *P*=.03, *P*=.03 and *P*=.03). In the case subjects, the mean number of months between the endometrial ablation and the hysterectomy was 12.6 months. The mean follow-up of the controls was 54.7 months.

Twelve of the 76 case subjects had had a Cesarean section, as compared with 15 of the 76 control subjects (OR 0.76; 95% CI, 0.3 to 1.8) (Table 2). Table 2 also shows the results of the other potential prognostic factors. Age above 45 years reduced the risk of an adverse outcome (OR 0.47; 95% CI 0.2 to 0.9). On the other

hand, the risk of an adverse outcome increased when women had dysmenorrhea (OR 3.0; 95% CI, 1.5 to 6.1), intermenstrual bleeding (OR 2.1: 95% CI, 1.1 to 4.1), a submucous myoma (OR 3.2; 95% CI, 1.5 to 6.8) or a sterilization in medical history (OR 2.2; 95% CI, 1.1 to 4.2). An uterus in retroversion flexion increased the risk of failure of treatment (OR 2.1; 95 % CI 0.9 to 4.8), whereas endometrial thickness was not associated with the risk of an adverse outcome (1.02; 95% CI 0.9 to 1.1).

Table 1. Baseline characteristics of the cases and controls

	Cases n=76	Controls n=76	*P*-value
Age before treatment (mean ± sd)	42.8	44.1	0.47
	(41.8-43.8)	(43.0-45.2)	
Age 41-45 years (%)	39.5	35.5	0.62
Age ≤ 45 years (%)	56.6	71.1	0.06
Age > 45 years (%)	26.3	43.4	0.03
Previous Cesarean delivery (%)	15.8	19.7	0.52
Parity (mean ± sd)	1.95	2.32	0.42
	(1.71-2.18)	(2.15-2.48)	
Anticoagulance (%)	9.5	2.7	0.09
Dysmenorrhea (%)	60.0	33.3	0.00
Intermenstrual bleeding (%)	45.9	28.9	0.03
Irregular menstrual cycle (%)	25.0	23.9	0.90
Duration (days) bleeding	8	7	0.03
(median + range)	(3-56)	(3-21)	
PBAC-score (median + range)*	17	740	0.12
	(27-3000)	(340-2000)	
Uterus in retroversion flexion (%)	26.8	14.7	0.08
Uterine depth (cm; mean ± sd)	8.77	8.02	0.29
	(8.31-9.23)	(7.61-8.43)	
Endometrial thickness	9.68	9.30	0.12
(cm; mean ± sd)	(8.12-11.23)	(8.14-10.46)	
Endometrial thickness ≥ 4 mm** (%)	87.8	92.6	0.41
Sterilisation (%)	48.7	30.7	0.02
Hemoglobin ((Mmol/l) ***	7.58	7.85	0.03
	(7.27-7.89)	(7.61-8.08)	
Uterus abnormalities			
Uterine polyp (%)	8.5	2.6	0.12
Submucous myoma (%)	39.4	17.1	0.003
Nonsubmucous myoma (%)	5.6	2.6	0.36

* Available for N is 24 (Cases) and 28 (Controls)
** Available for N is 49 (Cases) and 54 (Controls)
*** Available for N is 52 (Cases) and 55 (Controls)

Table 2. Results of the univariable and multivariable analysis of potential prognostic factors for endometrial ablation

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age before treatment	0.94 (0.88-1.01)	0.08		
Age 41-45 years	1.18 (0.61-2.28)	0.62		
Age ≤ 45 years	1.88 (0.96-3.69)	0.07		
Age > 45 years	0.47 (0.24-0.92)	0.03	0.40 (0.15-1.05)	0.06
Previous Cesarean delivery	0.76 (0.33-1.76)	0.53		
Parity	0.61 (0.42-0.90)	0.01	0.79 (0.47-1.34)	0.38
Anticoagulance	3.76 (0.76-18.75)	0.11		
Dysmenorrhea	3.00 (1.47-6.12)	0.03	4.03 (1.58-10.3)	0.004
Intermenstrual bleeding	2.09 (1.06-4.10)	0.03	1.87 (0.72-4.83)	0.20
Irregular menstrual cycle	0.94 (0.44-2.03)	0.88		
Duration (days) bleeding	1.02 (0.88-1.19)	0.81		
PBAC-score	1.00 (1.00-1.00)	0.45		
Uterus in retroversion flexion	2.12 (0.90-4.77)	0.08		
Uterine depth	1.28 (1.04-1.57)	0.02	1.36 (1.05-1.75)	0.02
Endometrial thickness	1.02 (0.94-1.10)	0.69		
Endometrial thickness ≥ 4 mm	0.57 (0.15-2.12)	0.41		
Sterilisation	2.15 (1.10-4.17)	0.03	1.70 (0.68-4.26)	0.26
Hemoglobin (mmol/l)	0.76 (0.51-1.12)	0.17		
Uterus abnormalities				
Uterine polyp	3.42 (0.67-17.51)	0.14		
Submucous myoma	3.16 (1.47-6.77)	0.0003	6.45 (2.11-19.7)	0.001
Nonsubmucous myoma	2.21 (0.39-12.45)	0.37		

OR; odds ratio, CI; Confidence interval.

Beside the univariable results, table 2 also shows the results of the multivariable logistic regression analysis. Dysmenorrhea, uterine depth and a submucous myoma decreased the chance of a successful outcome. All these three associations were statistically significant. However, sterilization, intermenstrual bleeding and age above the 45 years associated with an increased risk in the univariable analysis, had limited impact on the multivariable analysis (respectively: *P*=.26, *P*=.20 and *P*=.06).

Discussion

In this case-control study, we assessed prognostic failures for endometrial ablation in women suffering from menorrhagia. We found that a previous Cesarean section did not affect the success rate of endometrial ablation, but dysmenorrhea (before treatment), uterine depth and a submucous myoma increased the risk of treatment failure. On the other hand we showed that sterilization, intermenstrual bleeding and age equal or above the 45 years had also an effect on the treatment outcome, although this effect was limited in the multivariable analysis. These results are generally in agreement with results of other studies evaluating the outcome of various sorts of endometrial ablation techniques.[4,10-13]

The main limitation of our study was its retrospective character. This resulted in partly precluding some objective pre-operatively factors and objective treatment outcomes, for example the validated pictorial blood loss assessment chart (PBAC) score. Besides that, date of a few potential prognostic factors were partly incomplete. Three pre-operative variables, hemoglobin, endometrial thickness and the PBAC-score were missing data from more than 20% of patients.

Naturally we realized that retrospective data collection is not as reliable as prospective data collection, but we only used properly recorded data of the medical records of our own patients. In this way we tried to avoid any kind of bias related to the retrospective nature of this study. The strength of our study is the long-term outcome, representing the experience of a relatively large geographic region in a specialized medical center, and on the other hand the size and diversity of the population of clinicians and patients.

Predictors of treatment failure included dysmenorrhea, uterine depth and a submucous myoma. The association between the increased risk of treatment failure and dysmenorrhea was described by El Nashar et al. and Bongers et al., although in the study of Bongers et al. the association could not be confirmed in the multivariable analysis.[4,12] An explanation could be that undiagnosed adenomyosis may persist after ablation, which could cause pelvic pain and unsatisfied patients. Unfortunately we could not find enough reliable (histological) information about adenomyosis in the medical records or the operation theatre registration to come to a conclusion or give an explanation for possible failure of any endometrial ablation. At the end, this could require a hysterectomy. Consistent to the result of Gemer et al., Comino and Torrejón and El Nashar et al. a submucous myoma is also a risk factor for hysterectomy.[11-13]

Our result that age above 45 years affected the treatment outcome is consistent with findings from previous studies showing that older women have a better outcome from endometrium ablation than younger women.[4,10,12,14] The reason for the higher observed rate of hysterectomy in women who underwent a sterilization is not clear. There are studies in which a post-ablation tubal sterilization syndrome has been described, characterized by pain from the distention of the proximal end of the fallopian tube. This supposed to be cause by regeneration of the cornual endometrium, intra-uterine adhesions that obstruct the outflow tract and tubal ligation that prevents emptying into the peritoneal cavity.[15]

In this study a retroverted uterus, prolonged duration of menstruation, pretreatment endometrial thickness, parity, PBAC-score, and hemoglobin showed no statistically significant increased risk of treatment failure (OR's respectively, 2.1, 1.0, 0.6, 1.0, 0.8). In contrast, Bongers et al. previously found an association between a retroverted uterus, prolonged duration of menstruation and endometrial thickness with an increased risk of treatment failure using the thermal balloon ablation.[4] The association regarding the retroverted uterus may occur because the posterior wall of a uterus in retroversion will not have as much thermal injury as the posterior wall of an anteverted uterus. However, in our study we used three different endometrial ablation methods, including the NovaSure®, a technique based on radiofrequency ablation which do not use any balloon. Thick endometrium was suggested to prevent a deep intramural thermal effect, so the damage of the basal layer was limited.[4,12] The duration of menstruation before treatment was, in agreement with El Nashar et al., not a significant risk factor for treatment failure.[12] The finding that those last three factors did not affect the outcome of endometrial ablation in our study is consistent with results that were reported in previous studies.[12,16]

Theoretically, a NovaSure® procedure carries the risk of uterine perforation in women with a previous Cesarean section. In our study, we did not observe cases of perforation. Obviously, our sample size was not large enough to rule out a small risk.

In conclusion, the findings of this study show that Cesarean delivery is not associated with an increased risk of endometrial ablation failure in women with menorrhagia, but dysmenorrhea, uterine depth and a submucous myoma can predict treatment failure. Therefore we believe that the data of this study can be used to optimize preoperative patient counseling.

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Chapter 3

Bipolar radiofrequency endometrial ablation versus hydrothermablation for dysfunctional uterine bleeding; a randomized controlled trial

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Obstet Gynecol 2010;116:819-26.

Abstract

Objective: To compare the effectiveness of two second-generation ablation techniques, bipolar radiofrequency impedance-controlled endometrial ablation and hydrothermablation, in the treatment of menorrhagia.

Methods: This study was a double-blind, randomized controlled trial, which took place in a large teaching hospital in The Netherlands with 500 beds. Women with menorrhagia were randomly allocated to bipolar radiofrequency ablation (bipolar group) and hydrothermablation (hydrotherm group). At follow-up, both women and observers remained unaware of the type of treatment that had been performed. The primary outcome was amenorrhea. Secondary outcome measures were patient satisfaction and reintervention.

Results: We included 160 women in the study, of which 82 were allocated to the bipolar group and 78 to the hydrotherm group. No complications occurred in either of the treatment groups. After 12 months the amenorrhea rates were 47% (35 of 75) in the bipolar group and 24% (17 of 71) in the hydrotherm group (relative risk (RR) 2.0, 95% confidence interval (CI) 1.2-3.1). In the bipolar group 87% (65 of 75) of the patients were completely satisfied with the result of the treatment compared with 68% (48 of 71) in the hydrotherm group (RR 1.3, 95% CI 1.03-1.6). The relative risks for a reintervention in the bipolar group compared with the hydrotherm group was 0.29 (95% CI 0.12-0.67), whereas for hysterectomy, this was 0.49 (95% CI 0.15-1.5).

Conclusion: In the treatment of menorrhagia, bipolar radiofrequency endometrial ablation system is superior to hydrothermablation.

Introduction

Excessive menstrual bleeding, or menorrhagia, is a frequent problem in women of reproductive age. The definition of menorrhagia is menstrual blood loss exceeding 80 ml from normal secretory endometrium.[1] Its incidence varies between 9% and 14%.[2] The disorder may cause iron deficiency anemia but also shows a significant impact on the medical, social economic and psychological well-being of women.[3,4] About 30-40% of the hysterectomies are performed for treatment of severe dysfunctional bleeding.[5]

Endometrial ablation is an alternative to hysterectomy in women with dysfunctional bleeding. The first-generation devices for ablation were endometrial laser ablation, transcervical resection of the endometrium and rollerball ablation. These techniques had disadvantages such as fluid overload or water intoxication.[6-10] Second-generation techniques overcame these disadvantages of the first generation techniques. Moreover, these techniques require less skill of the surgeon.[11,12,13]

The NovaSure® endometrial ablation device (bipolar radiofrequency endometrial ablation) is one of the second-generation devices that use bipolar radiofrequency impedance-controlled endometrial ablation to evaporate endometrial tissue. Recently, bipolar radiofrequency endometrial ablation was reported to be superior over balloon ablation, making it the standard of choice in women requesting ablation for dysfunctional uterine bleeding.[14] However, the method also has disadvantages. It is a blind procedure, which is performed without hysteroscopic view. The size and shape of the uterus must be fairly normal in order to use the system, and intracavitary fibroids or large polyps interfere with the placement of the device.

The HydroThermAblator® (hydrotherm endometrial ablation) system is a second-generation technique that is applied under hysteroscopic view, thus potentially reducing the risk of uterine perforation. In a randomized multicenter study hydrothermablation was found to be equally effective as rollerbal ablation.[15] Randomized comparisons between bipolar radiofrequency and hydrotherm endometrial ablation are lacking. In view of this lack of knowledge, we performed a randomized controlled trial comparing these two second-generation endometrial devices in women suffering from menorrhagia.

Material and methods

We performed a randomized controlled trial (RCT) in the Máxima Medical Centre, Veldhoven, The Netherlands. The Máxima Medical Centre is a teaching hospital with 500 beds in the south of The Netherlands. The study was approved by the institutional review board (number 457) and registered in the clinical trial register (ISRCTN23845359). All participants gave written informed consent before enrollment.

Women with menorrhagia were eligible for the trial. Menorrhagia was defined as indicated on the pictorial chart described by Higham et al.[16] During their period, the patient records the use of tampons and towels, and the loss of clots on a scoring system. A lightly stained towel or tampon scored 1 point, a moderately stained towel or tampon 5 points, a towel or tampon which was saturated with blood scored 20 points. A clot the size of 1p scored 1 point, a 50p sized clot scored 5 points and flooding also scored 5 points. One period is counted and a minimum score of 150 points was described as menorrhagia. We did not select the patients with an anemia because women in the Netherlands are seen by their general practitioner first. Most of them were already treated with iron therapy and would not a low hemoglobin and hematocrit in the hospital.

Saline infusion sonography or diagnostic hysteroscopy was required to confirm a normal uterine cavity, with a cavity length of 6 to 12 cm and a histologically benign endometrium. All women underwent a sonography. Patients with minimal intracavitary pathology, such as type 2 fibromas and small polyps (both ≤2cm), were also included. All women had to have a normal Pap smear, a negative Chlamydia test of the cervix, and a premenopausal follicular stimulating hormone (FSH)-level of less than 40 IU/l. Exclusion criteria were the presence of coagulopathies, use of anticoagulants, a desire to preserve fertility, prior uterine surgery (except low segment Caesarean section) and suspected or confirmed uterine malignancy. All women who were included in the study preferred to be treated by endometrial ablation after careful evaluation of the advantages and disadvantages of the other treatment options.

We planned surgery in day 3 to 8 of the menstrual cycle. Both groups received no medical endometrial pre-treatment prior to surgery, because of the side-effects of the medication and the bipolar group would have been treated unnecessarily. All patients had Naproxen 250 mg 12 hours and one hour before treatment. Computer generated randomization was performed by one of the authors (JP or

RE) just before the start of treatment in a 1:1 ratio.

Patients and investigating doctors were masked for the randomization allocation, and remained so during the study. The doctors performing the endometrial ablation did know at that moment which device was used. The patient did not know. The physician who saw the patient at the follow-up visits did not know which device was used. At the 12 months follow-up visit the patient was told which device was used for the endometrial ablation. The ablation treatments in both arms were all performed by two gynaecologists (CK or MB), specialized in these ablation techniques. Both surgeons had equal experience with each device.

The bipolar radiofrequency endometrial ablation system consists of a generator and a disposable device. When suction is applied, the endometrial lining is brought into contact with the electrode array. It is suitable for a uterus with a minimum of 2.5 cm cornu-to-cornu distance, and a depth of 6 to 11 cm as measured by uterine sounding.[14]

The hydrothermablation provides controlled endometrial ablation by circulating heated saline in the uterine cavity under hysteroscopic vision. The disposable sheath is inserted into the uterine cavity under direct hysteroscopic vision. A tight seal is necessary to prevent leakage of heated saline through the cervix. First a diagnostic hysteroscopy with room-temperature saline was performed to rule out intracavitary pathology. Continuous-flow circulation is maintained by gravity inflow and an aspiration pump. The fluid pressure is determined by the height of the fluid measurement reservoir and saline bag. The height of the reservoir is 115cm above the patient's uterus; it gives a net pressure of saline into the uterine cavity of 50-55 mmHg, which is well below the 70mmHg at which the tubes are opened. Once the diagnostic hysteroscopy was finished, the ablation treatment was started. The ablating phase starts with heating the saline in the heating canister, the temperature is displayed on the panel. It takes approximately three minutes to heat the saline to 90 degrees. The ablation cycle takes 10 minutes, the timer is set on the display. During heating and treatment cycle, the procedure automatically stops when the fluid loss is 10ml.

We measured the duration of the procedure which was defined as the moment the gynaecologist begun with introduction of a speculum, until the end of the ablation. Patients in both groups were treated in a day-care program, using either spinal or general anaesthesia. Follow-up visits were carried out at the outpatient clinic at four weeks, six months and 12 months after the initial treatment. At these consultations, the patients were seen by a doctor who was

unaware of the treatment that had been performed. At each visit, duration of menstruation, presence of dysmenorrhea and clots were registered. Patients also completed a pictorial chart, and expressed their satisfaction about the treatment result. Level of satisfaction was categorised as; completely satisfied, satisfied, doubtful or not satisfied. Furthermore, we registered whether a reintervention had been performed. Reinterventions considered were the use of oral contraceptives and performed hysterectomies. Menstrual bleeding was quantified using the Pictoral Blood Loss Assessment Chart (PBLAC) of Higham et al. A score of zero (0) operationally defined "amenorrhea".

The primary outcome measure was amenorrhea at 12 months post treatment. Secondary outcome measures were the reduction in bleeding, patient satisfaction, and complications and hysterectomies in both groups.

We anticipated an amenorrhea rate of 30% in the hydrotherm group.[14] Using an equivalence assumption with a 90% success rate for both groups and an acceptable difference of at maximum 15%, we needed 72 women per arm (80% power).[17] Assuming that approximately 90% of enrolled patients would complete the study protocol, a total of 160 patients (hydrotherm:bipolar 1:1) had to be enrolled.

Analysis

The analysis was performed according to the 'intention-to-treat' principle i.e., patients were analysed in the group to which they had been allocated. Patients in whom a hysterectomy was performed for bleeding complaints were considered as being amenorrhoeic.

Repeated measures analysis of variance was used to evaluate changes in effect over time (time effect), differences in effect between both treatment groups (treatment effect), and interaction between changes in effect over time and treatment group (time by treatment effect).[18] Patients with missing measurements were included in the repeated measure analysis if data were available for at least two different time points.[19] P-values less than 0.05 were considered to indicate statistically significant differences. When a statistically significant difference in menstrual pattern and patient satisfaction between both treatment groups or an interaction between changes in menstrual pattern and patient satisfaction over time and treatment group was found, the differences between treatment groups at specific points in time were examined. In case of dichotomous endpoints this was done by calculating relative risks and 95% confidence intervals. For the continuous

outcome duration of menstruation we calculated a difference of the medians with a 95% confidence interval, using a bootstrap procedure.[20] The pictorial chart score were compared using the Wilcoxon test.[21]

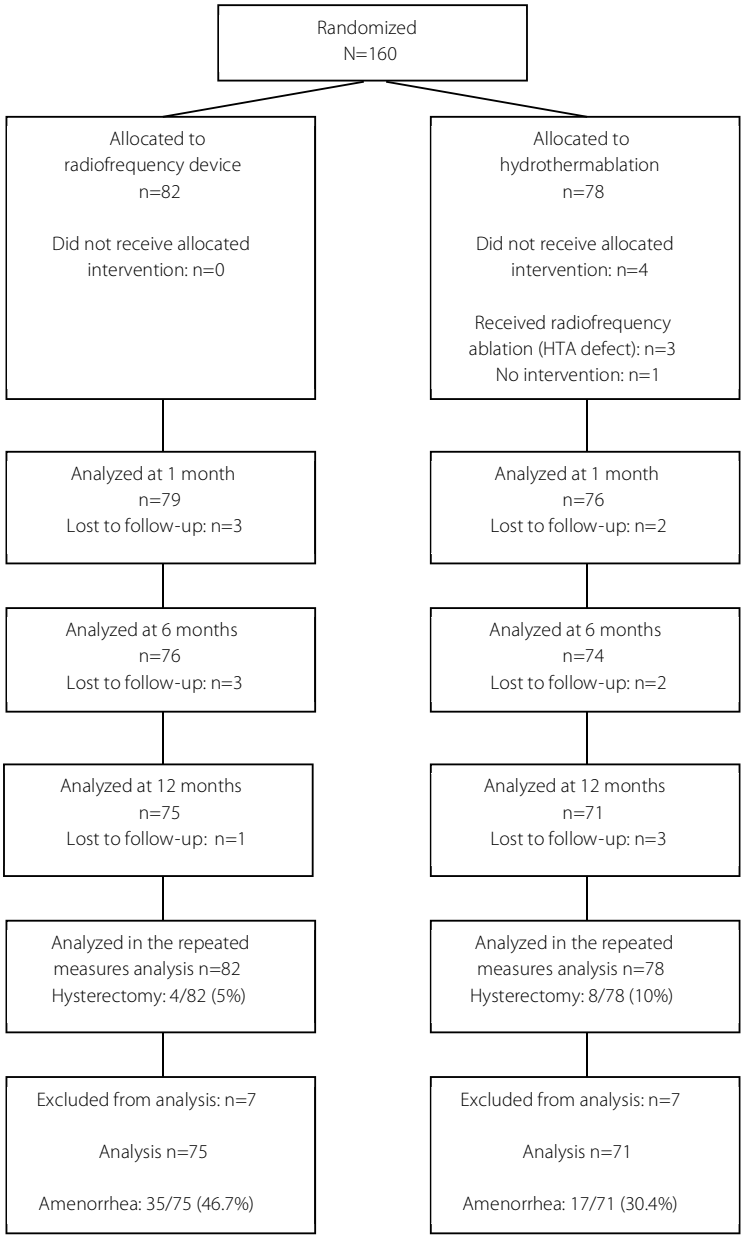

Figure 1. Trial profile. HTA= hydrothermablation

Results

Between March 21st 2005 and August 30th 2007 160 women were included in the study, of which 82 patients were allocated to the bipolar endometrial ablation group and 78 patients to the hydrothermablation group (Figure 1). The baseline characteristics of both groups were comparable (Table 1).

All women included in the study underwent sonography. Furthermore, 59 women in the hydrotherm group and 58 women in the bipolar group had a saline infusion sonography, and in each group 17 patients underwent a hysteroscopy. Three patients (one in the hydrotherm group and two in the bipolar group) decided not to undergo the endometrial ablation after randomization, as they became frightened of the procedure. Three patients in the hydrotherm group underwent bipolar radiofrequency endometrial ablation, because of technical problems with the hydrothermablation device in the operating room at the moment the treatment had to be performed.

The average duration of the bipolar group was 11.8 minutes (range 5 to 40 minutes) compared to 27.8 minutes (range 14 to 55 minutes) for the hydrothermablation group ($P<.001$). In the bipolar group one patient had a perforated uterus. In three patients in the hydrothermablation group leakage of saline was reported, but it was possible to complete the procedure in these three patients. Two of these three women reported to be satisfied with the treatment result at 12 months.

Overall, seven patients in each group were lost to follow up after 12 months

(Figure 1). Baseline characteristics of the patients lost to follow-up were comparable to those included in the study, but numbers were too low to compare this for statistical significance (Table 1).

Table 1. Baseline characteristics

			Loss to follow-up	
	Bipolar group n=82	Hydrotherm group n=78	Bipolar group n=7	Hydrotherm group n=7
Age (years)	44.7 ± 4.8	44.8 ± 4.9	41.2	43.6
Duration of menstruation (days)	8.8 ± 4.9	10.0 ± 4.9	10.1	10.7
Patients with clots	67 (82)	68 (87)	6 (86)	7 (100)
Duration of clots (days)	3.1 ± 2.7	3.5 ± 2.7	2.8	3.8
Pictorial chart score	810 (300-4000)	792 (200-2100)	683 (400-953)	642 (380-855)
Dysmenorrhea				
Moderate	18 (22)	16 (21)	26%	0%
Severe	12 (15)	15 (19)	0%	14%
Uterus				
Anteverted	64 (78)	66 (8)	5 (83)	5 (71)
Midposition	1 (1)	1 (1)	0 (0)	0 (0)
Retroverted	14 (17)	9 (12)	1 (17)	2 (29)
Missing data	3 (4)	2 (2)	1 (14)	0 (0)
Hemoglobin (mmol/L)	8.1 ± 0.8	8.2 ± 0.8	7.5	8.3
FSH (international units/L)	9.6 ± 15.2	12.4 ± 15.5	5.7	4.6
Uterine length (cm)	9.1 ± 1.2	9.1 ± 1.2	9.2	9.1
Endometrial thickness (mm)	7.5 ± 5.8	7.6 ± 5.7	5.9	10.9

Data are mean ± standard deviation or median (minimum-maximum), or n (%). FSH: follicle-stimulating hormone.

Figure 2 shows the patient satisfaction at 4 weeks, and at 6 and 12 months after treatment. Both treatment and time effect of patient satisfaction were statistically significant (P<.001), whereas time by treatment effect showed no significant interaction (P=.06). At 12 months, the patients were more satisfied after bipolar endometrial ablation (RR 1,3, 95% CI 1.0-1.6).

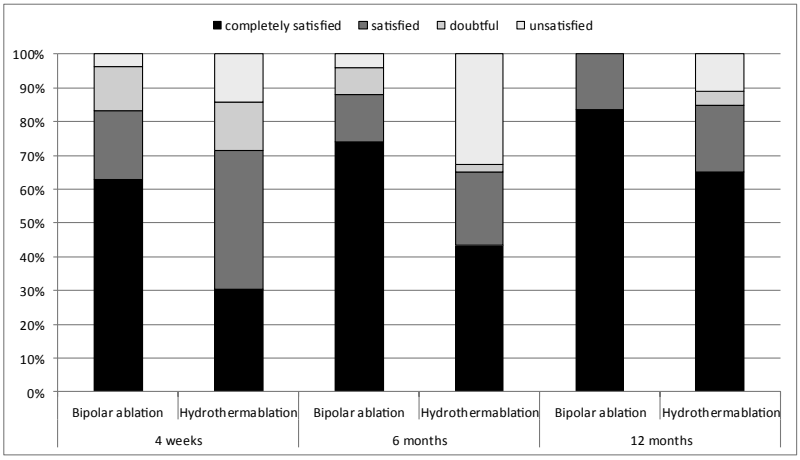

Figure 2. Patient satisfaction at 4 weeks, 6 months, and 12 months after the bipolar or hydrotherm ablation. Repeated measure analysis indicates that both, the treatment effect as well as the effect in time, on patient satisfaction are statistically significant (P<.001)

Figure 3 shows the percentage of women with amenorrhea, absence of dysmenorrhea and absence of clots after bipolar endometrial ablation and hydrothermablation. There were significantly more women reporting amenorrhea at six and 12 months after the procedure in the bipolar group (RR at 12 months 2.0, 95% CI 1.2 to 3.1). A sensitivity analysis showed that when all women that were lost to follow-up after bipolar radiofrequency endometrial ablation would have had amenorrhea, the relative risk at 12 months would have been 2.1 (95% CI 1.3 to 3.3). In contrast, when all women that were lost to follow-up after hydrothermablation would have had amenorrhea, the RR at 12 months would have been 1.7 (95% CI 1.1 to 2.7).

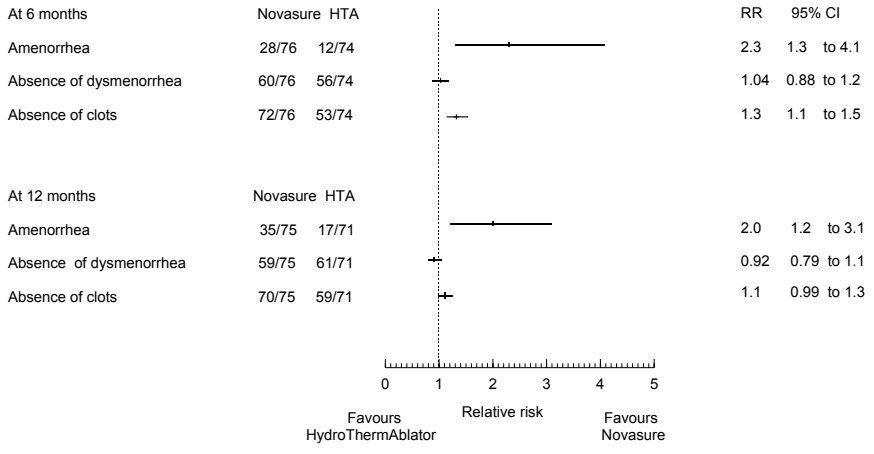

Figure 3. Treatment effect of bipolar and hydrotherm ablation at 6 months and 12 months after treatment. RR, relative risk; CI, confidence interval

There was a significant decrease in duration of menstruation after 6 and 12 months in both groups, as compared to the duration of menstruation at baseline (*P*=.001). The duration of menstruation was significantly shorter in the bipolar group in time, treatment and time by treatment effect (*P*-values <.001). Figure 4 shows the median pictorial chart score in both groups at baseline, 4 weeks, 6 months and 12 months after the procedure.

Six months after the procedure 24 reinterventions had been performed in total, five in the bipolar group compared to 19 in the hydrotherm group. One patient in the bipolar group had bipolar endometrial ablation again, whereas four women had a hysterectomy. In the hydrotherm group, eight patients underwent a bipolar endometrial ablation procedure, three patients started oral contraceptives and eight women underwent a hysterectomy. At 12 months only two more reinterventions were performed. One patient started oral contraceptives in the bipolar group and one patient underwent bipolar endometrial ablation in the hydrothermablation group. All reinterventions were performed because of persisting menorrhagia. Pathologic examination showed normal sized uteri in all cases. At 12 months, six reinterventions had been performed in the bipolar group versus 20 in the hydrotherm group (RR 0.29 (95% CI 0.1 to 0.7)). Furthermore, a total of four patients underwent a hysterectomy in the bipolar group, compared to eight in the hydrotherm group (RR 0.49 (95% CI 0.2 to 1.5)).

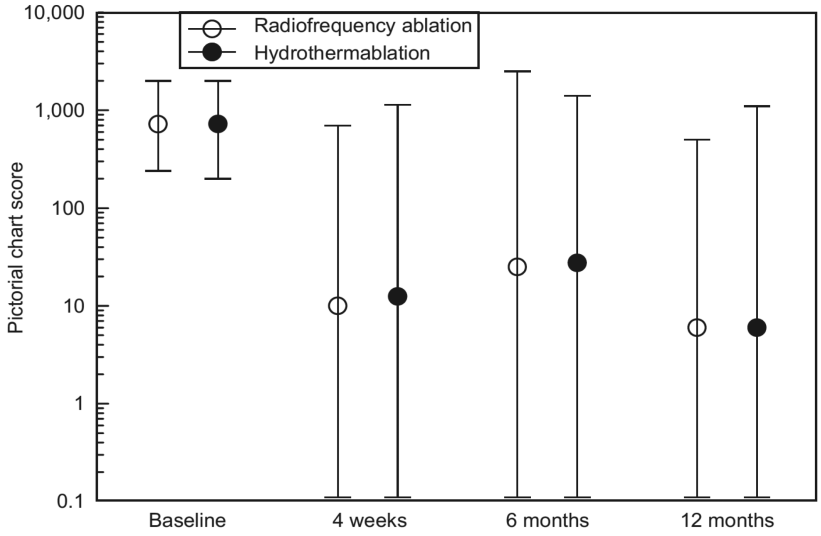

Figure 4. Median pictorial (minimum, maximum) chart score at baseline, 4 weeks, 6 and 12 months after treatment

Discussion

In this randomized clinical trial, we studied two second-generation endometrial ablation techniques during the first year after treatment. The bipolar radiofrequency endometrial ablation device performed better than hydrothermablation in terms of patient satisfaction, amenorrhea, and menstrual bleeding as scored on the mean pictorial chart score.

We analyzed the study according to intention to treat. Three women in the hydrotherm group received the bipolar radiofrequency procedure because of a technical defect of the hydrothermablation device. The most reinterventions were performed after six months. We expect that these reinterventions can influence the results of both groups, but especially the outcome of the hydrotherm group.

The amenorrhea rate of the hydrotherm group is higher than expected probably due to the fact that 35% had a reintervention of which nine hysterectomies were performed. These women were scored as amenorrheal and were satisfied with the result of the reintervention. We choose to consider women who had a hysterectomy as amenorrheal. By doing so, we basically evaluated the effect of two strategies, of which hysterectomy was a part. Alternatively, one could consider patients who had additional hysterectomy as failures. However, in that case one has to make assumptions on the pictorial chart scores, as these women were amenorrheal after their hysterectomy.

As shown in table 1 the average hemoglobin was around 8,1 mmol/L in both groups. The women in the Netherlands are seen by their general practitioner first. When they visited the hospital they were already treated with iron therapy if there was an anemia. These women would not show a low hemoglobin and hematocrit. That is why we did not select the patients with anemia but used the pictorial chart score to select patients.

The operation time for the bipolar endometrial ablation was less than half that of the hydrotherm procedure. This shortens operating room time and may be an important advantage in an outpatient setting. We have not performed an analysis of cost-effectiveness. Hydrothermablation is feasible and acceptable in outpatient setting, but the ablation cycle takes about 10 minutes compared to 90 seconds of the bipolar radiofrequency procedure.[22] The very short ablation procedure of the bipolar radiofrequency device however, makes it a promising ablation technique for outpatient treatment.

The amenorrhea rate of the bipolar group was comparable with previously reported studies (41%-58%).[14,23-24] We expected the hydrotherm group to do better, especially in women with small intracavitary pathology, as the circulating hot water has the possibility to contact the entire endometrial surface regardless of the shape of the uterine cavity. By including women with small intracavitary abnormalities, we suspected the bipolar radiofrequency device to be less successful. However, we found a lower amenorrhea rate in the hydrotherm group compared to the bipolar group, but also lower than reported in previous studies using hydrothermablation and comparing the hydrothermablation to rollerball endometrial ablation (40-44%).[18,25] In most reported studies hydrothermablation is performed after GnRH pretreatment. This treatment thins the endometrial layer and thus might give better treatment results.[18] We wanted to perform an everyday practice study and decided to schedule the procedure just after menstruation.

The patient satisfaction after bipolar radiofrequency endometrial ablation is comparable to other studies (90-92%) and slightly lower in the hydrotherm group (73%).[14,18,26]

There is a high reintervention percentage compared to other studies (5%).[17] The study of Guillot et al. was a retrospective study, it could be that the hysterectomies were underreported. It is possible that GnRH-pretreatment is necessary for an optimal result in the hydrotherm group. This is a disadvantage for the hydrothermablation device in view of the costs and adverse side effects of GnRH. In our study only three patients (4%) in the bipolar group underwent a hysterectomy in the year after treatment, this percentage is lower than presented in previous studies (4,8-8%).[14]

Both second-generation ablation techniques used in this study are safe and easy to perform. However, based on the results of the current randomized trial, bipolar endometrial ablation appears to offer higher patient satisfaction and amenorrhea rates.

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Chapter 4

Five year follow-up after comparing bipolar endometrial ablation with hydrothermablation for menorrhagia

Penninx JPM, Herman MC, Mol BW, Bongers MY

Obstet Gynecol 2011;118:1287-92.

Abstract

Objective: To evaluate the results of a previous study comparing bipolar radiofrequency endometrial ablation with hydrothermablation for the treatment of menorrhagia at 5-year follow-up.

Methods: A double-blind, randomized, controlled trial was performed in a large teaching hospital in the Netherlands between March 2005 and August 2007. One-hundred sixty women with menorrhagia were randomly allocated to bipolar ablation or hydrothermablation. The results of follow-up at 12 months were previously reported. At 4-5 years of follow-up, a questionnaire was sent to all the participants to register amenorrhea rates, reinterventions, and patient satisfaction.

Results: At 5-year follow-up, response rates were 90% and 83% in the bipolar group and hydrotherm group, respectively. Amenorrhea rates were 55.4% and 35.3% in the bipolar group and the hydrotherm group, respectively (relative risk (RR) 1.5, 95% confidence interval (CI) 1.05-2.3). The number of surgical reinterventions was 11 compared with 23 (RR 0.43, 95% CI 0.23-0.80). Overall, more women were satisfied in the bipolar group compared with the hydrotherm group.

Conclusion: After treatment, bipolar radiofrequency endometrial ablation system is more effective at 5 years than hydrothermablation in the treatment of menorrhagia.

Introduction

Heavy menstrual bleeding is a common gynecological problem in women of reproductive age and is one of the most important reasons for consulting a gynecologist.[1,2] Hysterectomy is a definitive solution for the treatment of menorrhagia. Based on cost-effectiveness hysterectomy should be considered as the preferred strategy for the treatment of heavy menstrual bleeding.[3] Nevertheless, it is a major surgical procedure with physical complications and social and economic costs.[4] Many women opt a less invasive treatment, even when they are informed of the fact that success is not always assured.[5] So, further research should focus on different treatment options and need to contain patients preference.

Many endometrial ablation techniques have been evaluated as a treatment for menorrhagia and currently have been established as a common practice. The first-generation techniques (laser, transcervical resection of the endometrium and rollerball) require a hysteroscopy with the use of distension medium and the risk of intravasation with fluid overload. These procedures require skilled surgeons to minimize adverse events. Second-generation techniques have been developed. These techniques are more simple and easy to perform, without the need of a hysteroscopy. Second-generation techniques are at least as effective as first generation techniques, but often are easier to perform.[6] However, 5-year follow-up is frequently limited in most of the second-generation studies. The aim of ablative therapies is to offer patients a desirable and long term solution. Therefore, adequate follow-up of these therapeutic interventions is needed for good evidence-based clinical decision making.

From March 2005 until August 2007, we performed a randomized controlled trial in which we compared the bipolar radiofrequency impedance-controlled endometrial ablation with hydrothermablation. The primary outcome measure was amenorrhea; secondary outcome measures were reintervention and patient satisfaction. We concluded that bipolar endometrial ablation is superior to hydrothermablation in the treatment of menorrhagia within a follow-up of 12 months.[7] This study evaluates the primary and secondary outcomes at 5-year follow-up.

Material and methods

A randomized controlled trial comparing the bipolar radiofrequency impedance-controlled endometrial ablation device (NovaSure®, Hologic) and hydrothermablation (HydroThermAblator® system, Boston Scientific) was performed in the Máxima Medical Centre, a teaching hospital with 500 beds in the south of The Netherlands. The trial has previously been described in detail by Penninx et al.[7] The randomization techniques were performed by the CONSORT guidelines. The individuals gave informed consent at start of the study so we could contact them in future for a follow-up study. The ethics committee of the Máxima Medical Centre in Veldhoven, the Netherlands, approved the study.[7]

Women with menorrhagia as indicated on the pictorial chart described by Higham et al, with a minimum score of 150 points, were eligible for the trial.[8] They were referred by their general practitioner and hormonal treatment was already tried but unsuccessful, or patients were not motivated to use hormonal treatment. During their menstrual period, the patient recorded the use of tampons and towels, and the loss of clots on a scoring system. A lightly stained towel or tampon scored 1 point, a moderately stained towel or tampon 5 points, a towel or tampon which was saturated with blood scored 20 points. A small clot scored 1 point, a moderate clot scored 5 points and flooding also scored 5 points. One menstrual period is counted and a minimum score of 150 points was described as menorrhagia.

Further inclusion criteria were an uterine depth between 6 and 11 cm and a premenopausal state. Patients with minimal intracavitary pathology, such as leiomyomata, of which less than 50% of the myoma was present in the uterine cavity and small polyps (less than 2 cm), were also included. Women with presence of coagulopathies, a desire to preserve fertility and uterine malignancy were excluded.

All participants had to complete a written informed consent form before enrollment. Computer-generated randomization was performed by one of the authors (JP) just before the beginning of treatment, at which 82 women were allocated to the bipolar group and 78 women to the hydrotherm group. Patients and doctors who performed the follow-up visits and telephone calls were masked for the randomization allocation, and remained so during the study. The doctor performing the endometrial ablation did, of course, know at that moment which device was used. The patient did not know. The physician who saw the patient at the follow-up visits was masked and did not know which device was used.

To obtain insight into the 5-year follow-up, postal questionnaires were send from November 2010 until January 2011 (4-5 years of follow-up). The mean follow-up time was 4.5 years after the original procedure (range 3 to 5-6 years). All patients were asked to complete the questionnaires. Outcomes were amenorrhea, reinterventions and patient satisfaction with the result of the treatment, which was similar to what we previously reported at 12 months follow-up. The preablation bleeding was already asked at trial entry.

Patients who did not return the questionnaires received a single reminder after one week. If questionnaires were not returned after this reminder in 4 weeks, we tried to contact the patients by telephone. A simplified questionnaire was used for the telephonic interviews. Women were asked about their menstruation (days, clots and dysmenorrhea), treatment satisfaction and reintervention. We contacted patients' general practitioners if we had missing addresses or phone numbers. In case of lacking information, we searched patients' medical records for information about reinterventions.

The analysis was performed according to the intention-to-treat principle, ie. patients were analyzed in the group to which they had been allocated. We considered women who have undergone a hysterectomy as not having amenorrhea and as being dissatisfied with their ablation treatment. Both hysterectomy and reablation were scored as a surgical reintervention. Time to surgical reintervention was compared with Kaplan Meier analysis. Dichotomous outcomes, such as presence of amenorrhea, absence of clots, absence of dysmenorrhea, and reinterventions were compared by calculating a relative risk (RR) and its 95% confidence interval (CI). Repeated-measures analysis of variance was used to evaluate changes over time (time effect) between both groups (treatment effect) and interaction between changes in effect over time and treatment group (time by treatment effect).

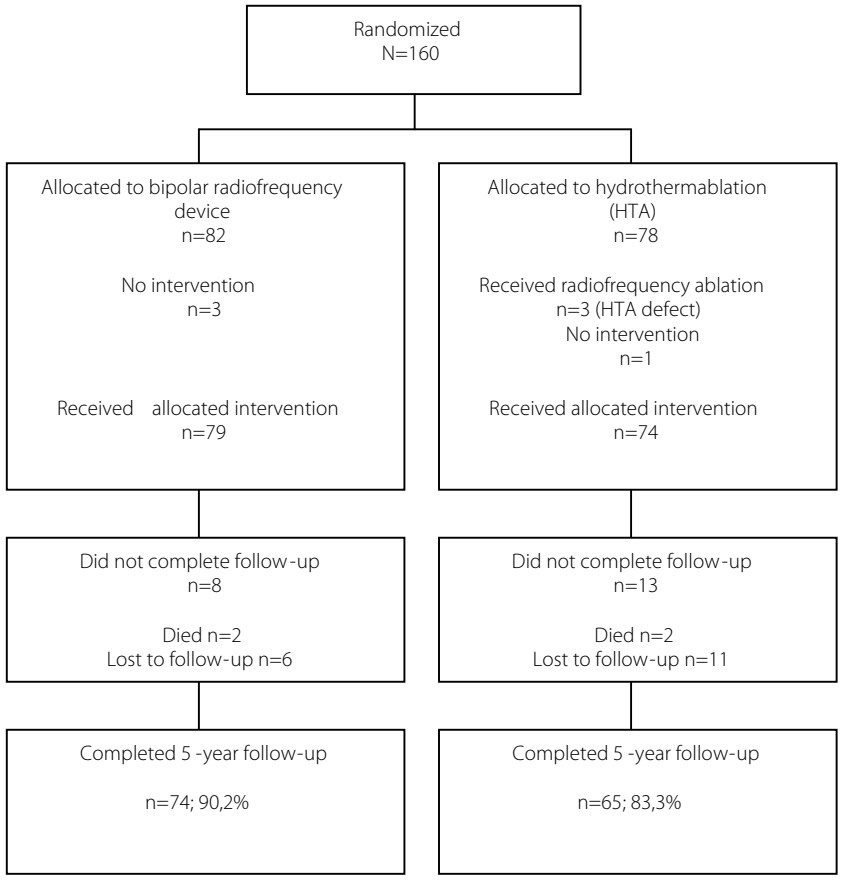

Figure 1. Trial profile

Results

Between March 2005 and August 2007, 160 women were included in the trial, of which 82 women were allocated to the bipolar group and 78 women to the hydrotherm group. In November 2010 we sent questionnaires to all patients, after which 125 women returned the questionnaire. Of the non-responding 35 women, 19 women were contacted by telephone, after which eight women sent the questionnaires, eight women were interviewed by telephone, and three women did not want to participate. Seven women had unknown addresses or telephone numbers (or both), four women died, and five did not answer their telephone

multiple times. Non-response was mostly attributable to the fact that patients had moved houses or changed telephone numbers. Overall, 21 women (eight in the bipolar group and 13 in the hydrotherm group) were lost to follow-up. The 5-year follow-up rate was 90.2% (n=74) in the bipolar group and 83.3% (n=65) in the hydrotherm group (figure 1). The baseline characteristics of both groups were comparable (table 1) and resembled those reported in our previous study.[5]

Table 1. Baseline characteristics at 5-year follow-up

	Bipolar group n=74	Hydrotherm group n=65
Age (years)	49.5 ± 5.0	49.3 ± 4.7
Duration of menstruation (days)	8.6 ± 4.0	9.4 ± 5.2
Duration of clots (days)	3.6 ± 2.7	3.5 ± 2.8
Pictorial chart	825 (240-4,000)	784 (200-2,000)
Dysmenorrhea		
Moderate	15 (20)	14 (22)
Severe	11 (15)	13 (20)

Data are mean ± standard deviation or median (minimum-maximum), or n (%).

After 5-year follow up, the number of patients with amenorrhea in the bipolar endometrial ablation group was 41 of 74 (55.4%), compared to 23 of 65 (35.4%) in the hydrotherm group (RR 1.5, 95% CI 1.1-2.3). Table 2 shows the percentage of women with amenorrhea, absence of dysmenorroe and absence of clots after bipolar endometrial ablation and hydrotherm ablation. A sensitivity analysis showed that when we did consider women who have undergone a hysterectomy as being amenorrhoeic, as we did in our previous study, the relative risk would have been 1.2 (95% CI 0.9-1.5). When we consider all women who were lost to follow-up after the endometrial ablation as nonamenorrhoeic, the RR at 5-year follow-up would have been 1.6 (95% CI 1.1-2.4).

We recorded 43 reinterventions, all because of persisting menorrhagia, 14 in the bipolar group compared to 29 in the hydrotherm group (RR 0.43, 95% CI 0.25-0.74). Two patients in the bipolar group had undergone bipolar endometrial ablation again, whereas nine women had a hysterectomy, two women got a levonorgestrel intrauterine device, and one patient underwent a hysteroscopy. In the hydrotherm group, 10 patients underwent bipolar endometrial ablation, 13 patients underwent a hysterectomy, four patients started oral hormonal

therapy and two patients had a levonorgestrel intrauterine device placed. When reintervention was limited to surgical procedures, 11 women in the bipolar group had a surgical reintervention compared to 23 women in the hydrotherm group (RR 0.43 (95% CI 0.23-0.80)). When we consider the women who were lost to follow-up as having had a reintervention, the RR at 5-year follow-up would have been 0.52 (95% CI 0.34-0.80). The life table analysis is shown in figure 2.

Table 2. Comparison of bipolar and hydrotherm endometrial ablation at 1-year and 5-year follow-up

	Bipolar group	Hydrotherm group	RR (95% CI)
1 year	n=75	n=71	
5 year	n=74	n=65	
Amenorrhea			
1 year	35 (47)	17 (24)	2.0 (1.2-3.1)
5 year	41 (55)	24 (37)	1.5 (1.1-2.3)
Absence of dysmenorrhea			
1 year	59 (79)	61 (86)	0.9 (0.8-1.1)
5 year	51 (69)	34 (52)	1.3 (0.96-1.7)
Absence of clots			
1 year	70 (93)	59 (83)	1.1 (0.99-1.3)
5 year	65 (88)	48 (74)	1.1 (0.97-1.3)

RR, relative risk, CI, confidence interval. Data are n or n (%).

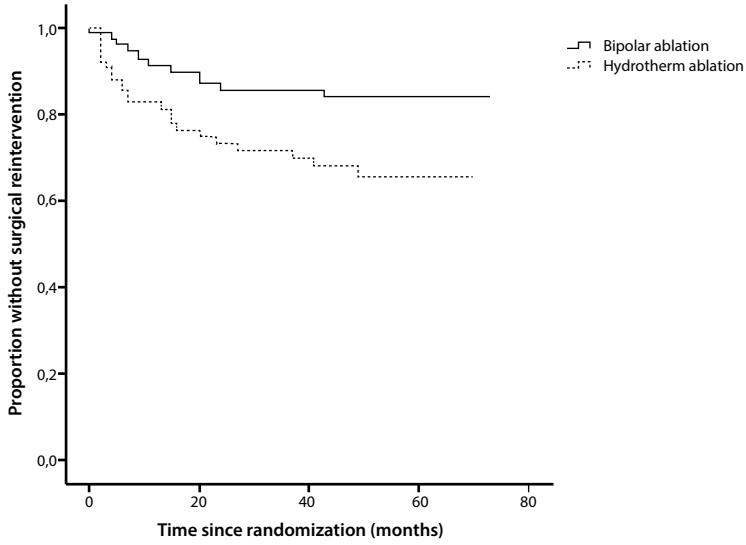

Figure 2. Percentage of women after bipolar or hydrotherm endometrial ablation without a reintervention in months after randomization

Pathologic examination of the hysterectomy specimens in the bipolar group showed adenomyosis (n=2), leiomyomata (n=4) and no abnormalities (n=3). In the hydrotherm group, pathologic examination showed adenomyosis (n=2), leiomyomata (n=5), a combination of adenomyosis and leiomyomata (n=3) and no abnormalities (n=3).

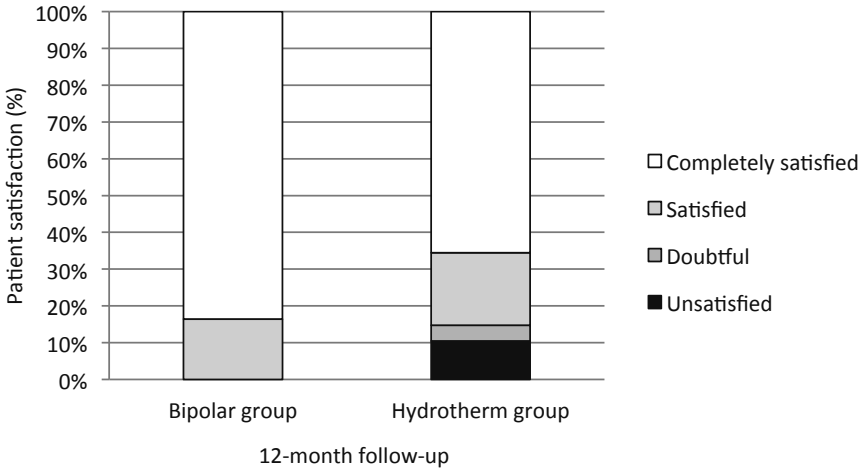

Figure 3A. Patient satisfaction at 12 months of follow-up after bipolar and hydrotherm endometrial ablation

Patients were more often satisfied in the bipolar group compared with those in the hydrotherm group (80.6% versus 48.4%, RR 1.7, 95% CI 1.3-2.2) (Figure 3A en 3B). When we consider the nonresponders as not satisfied, the RR would have been the same 1.7 (CI 95% 1.3-2.2)). Repeated-measures analysis showed a significant treatment effect (P<0.001). Nevertheless, in both groups satisfaction rates were decreased as compared to rates at 12 months (time effect P<0.001); time-by-treatment effect showed no significant interaction (P=0.107).

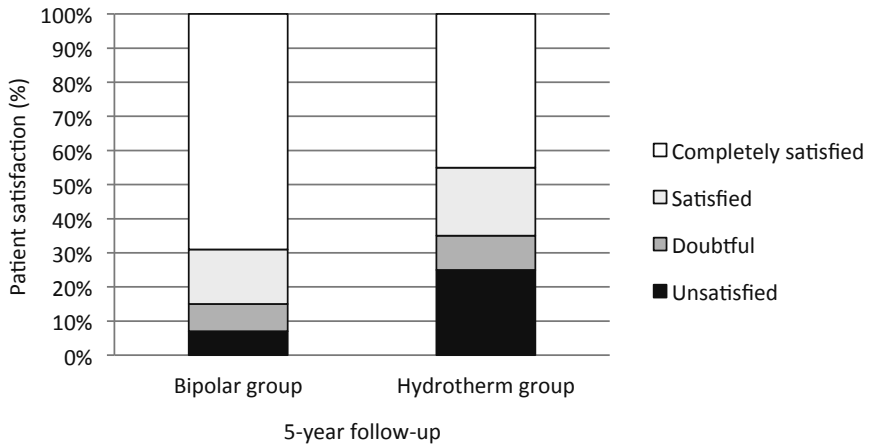

Figure 3B. Patient satisfaction at 5 years of follow-up after bipolar and hydrotherm ablation

Discussion

In this follow-up study, we compared the treatment of two second-generation endometrial ablation techniques in women with menorrhagia 5 years after treatment. Amenorrhea rates were higher in the bipolar group than the hydrotherm group, respectively (55.4% and 35.3%, RR 1.50, 95% CI 1.05-2.3), and the number of surgical reinterventions was lower (11 compared with 23, RR 0.43, 95% CI 0.23-0.80). Overall, more women were satisfied in de bipolar group compared to the hydrotherm group.

We analyzed the study according to the intention-to-treat principle. Unlike our previous study, we evaluated women who had a hysterectomy as being non-amenorrhoeic because of the fact that those women chose this treatment because of their persisting menorrhagia. We considered patients who had an additional hysterectomy as failures of treatment. Scoring hysterectomy as being amenorrhoeic, as in our previous study, would not give direct results on the ablation effect, especially not with this higher number of surgical reinterventions compared with 12-month follow-up.

Compared to the 1-year follow-up, the 5-year follow up showed an increase in amenorrhea rates in both groups. Because the patient characteristics were comparable at the beginning of the randomized controlled trial, we would estimate that by randomization the amount of women who would be postmenopausal would be approximately the same in both groups. The amenorrhea rate of the

bipolar group is comparable with that seen in previously reported long-term follow-up studies (48%-65%).[9,10] Long-term studies of hydrothermablation are limited, and amenorrhea rates differ from 38% to 53%.[11,12] We found lower amenorrhea rates in the hydrotherm group compared with those found in the literature, but this is in line with our previously reported 12-month result.[7] In most studies hydrotherm ablation is performed after gonadotropin-releasing hormone pretreatment. This might give better treatment result because it thins the endometrial layer.[13] In the Netherlands, we do not administer gonadotropin-releasing hormone pretreatment before endometrial ablation; therefore, we scheduled the procedure just after menstruation. Differences in numbers comparing absence of clots and absence of dysmenorroe between 12 months and 5 years were explained by the fact that we considered women with a hysterectomy as being amenorrhoeic at the 12-month follow up.

At 5-year follow up, we see a comparable increase in reinterventions in both groups. We chose to report the surgical reinterventions rather than hysterectomies alone, whereas both hysterectomy and reablation are invasive ways of treatment. At 12-month follow-up, the hydrotherm ablation already showed significantly more reinterventions, and so does this follow-up study for reintervention in total as surgical reintervention.

We observed a high surgical reintervention rate in both groups compared with other studies.[9-14] Kopeika et al reported a hysterectomy rate of 11% for the hydrotherm ablation at a follow-up of 8 years, but this was a retrospective study.[11] As mentioned, it is possible that gonadotropin-releasing hormone pretreatment is necessary for an optimal result in this group.[13] The thickness of the endometrial layer could be a predictor for failure of hydrotherm ablation treatment. As shown in our previous article, there was no difference in baseline endometrial thickness.[7] In the group with reinterventions, the average endometrial thickness was 7,7 in the hydrotherm group and 7,9 in the bipolar group. Comparing pathology of hysterectomy specimens, differences in both ablation groups were not found. Literature reporting on long-term follow-up after bipolar ablation describes hysterectomy rates from 3% to 9.8%.[9,10,14] However, only Kleijn et al reported a patient-blinded and observer-blinded randomized controlled trial, comparable to our study. Because of lack of blinding in previous studies, the hysterectomy rate might have been overstated in earlier studies.

This trial described a high satisfaction level for the bipolar ablation 5 years after the procedure, whereas satisfaction rates for the hydrotherm group were

low. Although we saw an increase in amenorrhea rate in both groups, we also saw a significant reduction in satisfaction level in both groups over time. In literature, a few trials use satisfaction as an outcome measure and because of this, it is difficult to compare these results with other trials. However, Middleton et al describes that more women are dissatisfied after endometrial destruction than after hysterectomy, but the rates of dissatisfaction are still relatively low.[15] They also noticed that absence of leiomyomata, or polyps shows a trend towards reduced dissatisfaction (P=.07).[15] In our study, we did not exclude women with leiomyomata, because we wanted to evaluate the results of ablation in patients with menorrhagia with or without little uterine leiomyomata and in women with menorrhagia without hormonal pretreatment. This could have influenced our results. Data of success, satisfaction and health related quality of life are essential to offer patients a desirable and long-term solution for menorrhagia. Therefore, adequate follow-up of these therapeutic interventions is still needed for clinical decision making and counselling of patients.

The results from this follow-up study showed that bipolar ablation has many advantages over hydrotherm ablation. Higher amenorrhea rate, less reinterventions, and higher levels of satisfaction were shown. So, the bipolar radiofrequency endometrial ablation system is more effective than hydrotherm ablation in the treatment of menorrhagia.

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Chapter 5

Bipolar radiofrequency endometrial ablation compared with hydrothermablation for heavy menstrual bleeding: impact on patients' health related quality of life

Penninx JPM, Mol BW, Kruitwagen RFPM, Bongers MY

Submitted.

Abstract

Objective: We have previously demonstrated that in women with heavy menstrual bleeding bipolar radiofrequency ablation is superior over hydrotherm ablation in terms of amenorrhea rates and patient satisfaction. In the present study, we report health related quality of life after both interventions.

Design: A double blind randomized controlled trial.

Setting: A teaching hospital in the Netherlands.

Population: One hundred and sixty women with heavy menstrual bleeding.

Methods: Women were randomly allocated to bipolar radiofrequency ablation and hydrothermablation. They were asked to complete quality of life questionnaires at baseline, 4 weeks, 6 and 12 months and 5 years after randomization. The menorrhagia multi-attribute scale (Shaw), medical outcomes study Short-Form (SF-36), and EuroqoI before randomization, and at each follow-up visit after randomization, were selected to evaluate quality of life. The menorrhagia outcomes questionnaire (MOQ) was completed at 4 weeks, 6 and 12 months after treatment.

Main outcome measures: Health related quality of life.

Results: Health related quality of life data were available at at least two different time points in 136 patients. Quality of life improved significantly over time in all questionnaires. None of the quality of life dimensions showed a significant effect between both groups, neither was there a significant interaction between time and treatment.

Conclusions: In all generic and disease specific questionnaires treatment of heavy menstrual bleeding improved health related quality of life over time. A treatment effect of amenorrhea and satisfaction did not result in quality of life benefits.

Introduction

Heavy menstrual bleeding (HMB) is a common problem for women in their reproductive age. It has psychosocial effects on women and their environment and can result in work impairment.[1] Heavy menstrual bleeding often is the main reason for consultation of a gynaecologist. The perception of women on the severity of the bleeding often is very important for the evaluation of treatment success.

At present, many studies report on amenorrhea and satisfaction rates after treatment, as these dimensions are considered to be most important for the patient after treatment. Currently, quality of life assessment might potentially also be important, as this is a more objective assessment of the patient's condition. However, little data are available on the impact of treatment of HMB on quality of life. Besides that, there is an increasing demand on long term follow-up studies after treatment.[2,3] We recently reported the results of a randomized controlled trial comparing bipolar radiofrequency endometrial ablation (bipolar group) and HydroThermAblation (hydrotherm group) in women with HMB.[4] At 12-month follow-up the amenorrhea rates were 47% in the bipolar group compared to 24% in the hydrotherm group (relative risk (RR) 2.0, 95% confidence interval (CI) 1.2-3.1). At the same time, 94% (45/48) of the patients in the bipolar group were satisfied with the result versus 80% (36/45) in the balloon group (RR 1.2, 95% CI 1.0 to 1.4). After 5 years, the bipolar group still had higher satisfaction and amenorrhea rates compared to the hydrotherm group in the treatment of HMB.[5]

We concluded that in the treatment of HMB, bipolar radiofrequency endometrial ablation was superior to hydrothermablation. As part of the RCT, we measured health related quality of life. In the present paper, we compare quality of life after bipolar radiofrequency endometrial ablation and hydrothermablation.

Material and methods

We performed a randomized controlled trial in the Máxima Medical Centre, Veldhoven, The Netherlands. Women with HMB, documented by a Highamscore of 150 points or more, were eligible for the trial.[6] The study was approved by the Institutional Review Board (No. 457) and was registered in the international trial register (ISRCTN23845359). All participants provided written informed consent before enrollment.

Computer randomization was performed in a 1:1 ratio. Patients and investigating doctors were masked for the randomization allocation, and remained so during the study. Doctors performing the endometrial ablation obviously did know which device was used, but the physician who saw the patient at the follow-up visits did not know which device had been used. The patient was not informed during the first year of follow-up. Saline infusion sonography or diagnostic hysteroscopy was required to exclude patients with intracavitairy pathology. Women with a normal uterine cavity or minimal intracavitairy pathology, such as type 2 fibromas and small polyps (both ≤ 2cm), were included. All women had to have a histologically benign endometrium and a cavity length of 6-12 cm. Women with HMB were randomly allocated to bipolar radiofrequency ablation and hydrothermablation in a 1:1 ratio.

All patients were asked to complete quality of life questionnaires at baseline, 4 weeks, 6 months, 12 months and 5 years after randomization. The menorrhagia multi-attribute scale (Shaw), medical outcomes study Short-Form (SF-36), and Euroqol before randomization, and at each follow-up visit after randomization were selected to evaluate quality of life.[7] The menorrhagia outcomes questionnaire (MOQ) was completed at 4 weeks, 6 months and 12 months after treatment.

The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. The SF-36 and MOQ have proven their reliability and validity to measure the effects of treatment on quality of life in women suffering from HMB.[8-11]

The menorrhagia outcomes questionnaire (MOQ) was specifically developed as a questionnaire that could be administered following treatment, and therefore it did not needed a pre-treatment assessment for comparison. The MOQ has four score domains: symptoms (2), post-operative complications (3), quality of life (7) and satisfaction with outcome (5). Two summary scores are obtained for Quality of Life/ Satisfaction (12 items) and Global outcome (17 items).[11]

The menorrhagia multi-attribute quality-of-life scale (Shaw) has also proven its validity and acceptability.[12,13] It assesses the effect of HMB on quality of life on six domains: practical difficulties, social life, psychological wellbeing, physical health, work routine and family life. The statement scores derive from a weighting of the domains and a weighting of the statements in level of severity by women in the original study. Scores range from 0 (worst possible state in all domains) to 100 (best possible state in all domains).

To obtain insight in the long term follow-up, postal questionnaires (SF-36, EuroQOL and Shaw) were sent 5 years after the original procedure. All patients were asked to complete the questionnaires. Patients who did not return the questionnaires received a single reminder after one week. If questionnaires were not returned after this reminder in 4 weeks, we tried to contact the patients by telephone.

Analysis

Health related quality of life was studied on an intention to treat basis. Repeated measure analysis of variance was used to establish changes in health related quality of life over time (time effect), differences in health related quality of life between both treatment groups (treatment effect), and interaction between changes in health related quality of life over time and treatment group (time by treatment effect). Patients with missing values were included in the repeated measure analysis if data were available for at least two different time points.[14]

P-values < 0.05 were considered to indicate statistically significant differences. If a statistical difference in health related quality of life between both treatment groups, or an interaction between changes in health related quality of life over time and treatment group was found, Student's t-tests were used to examine differences between time groups at specific time points.

Results

Between March 21st 2005 and August 30th 2007, 160 women were included in the study, of which 82 patients were allocated to bipolar endometrial ablation (bipolar group), and 78 patients to hydrothermablation (hydrotherm group). The number of patients allocated to the bipolar group and the hydrotherm group that completed the questionnaires at separate time points were: 70 versus 65 at baseline, 73 versus 67 at 4 weeks, 57 versus 49 at 6 months, 55 versus 50 at 1 year and 74 versus 65 at 5 years after treatment. The baseline characteristics were comparable in both groups (Table 1).

Table 1. Baseline characteristics

	Bipolar group n=55	Hydrotherm group n=50
Age (years)	44.5 ± 4.5	44.6 ± 4.3
Duration of menstruation (days)	8.6 ± 3.9	9.8 ± 5.8
Number of patients with clots	47 (85)	43 (86)
Duration of clots (days)	3.4 ± 1.6	3.6 ± 2.9
Pictorial chart	745 (240–2000)	809 (250–2005)
Dysmenorrhea		
Moderate	13 (24)	15 (30)
Severe	9 (16)	13 (26)
Uterus		
Anteverted	45 (82)	45 (80)
Midposition	1 (2)	0 (0)
Retroverted	9 (16)	5 (10)
Haemoglobin (mmol/L)	8.0 ± 0.8	8.0 ± 0.8
FSH (International units/L)	8.5 ± 12.0	14.1 ± 17.8

Data are mean ± standard deviation or median (minimum-maximum), or n (%).
FSH: follicle-stimulating hormone.

The results of the comparison between health related quality of life (SF-36) in the bipolar and hydrotherm group are shown in table 2.

It shows no significant effect between both groups nor a significant interaction between time and treatment for the SF-36. However, on all measures there was a significant effect over time for health related quality of life. Health related quality of life improved in all dimensions at 4 weeks, 6 months, 12 months and 5 years after treatment, as compared to the baseline measurements in both, the bipolar group and the hydrotherm group. Figure 1 shows the changes of the SF-36 over time. There were no significant differences between both groups at follow-up, but the physical component of the SF-36 score was significantly lower in the bipolar group at baseline (P=.010). Health related quality of life improved at 4 weeks, 6 months and 12 months after treatment, to decrease again at 5-year follow-up. But still, it remained however as high or higher compared to the reference value of the general population.

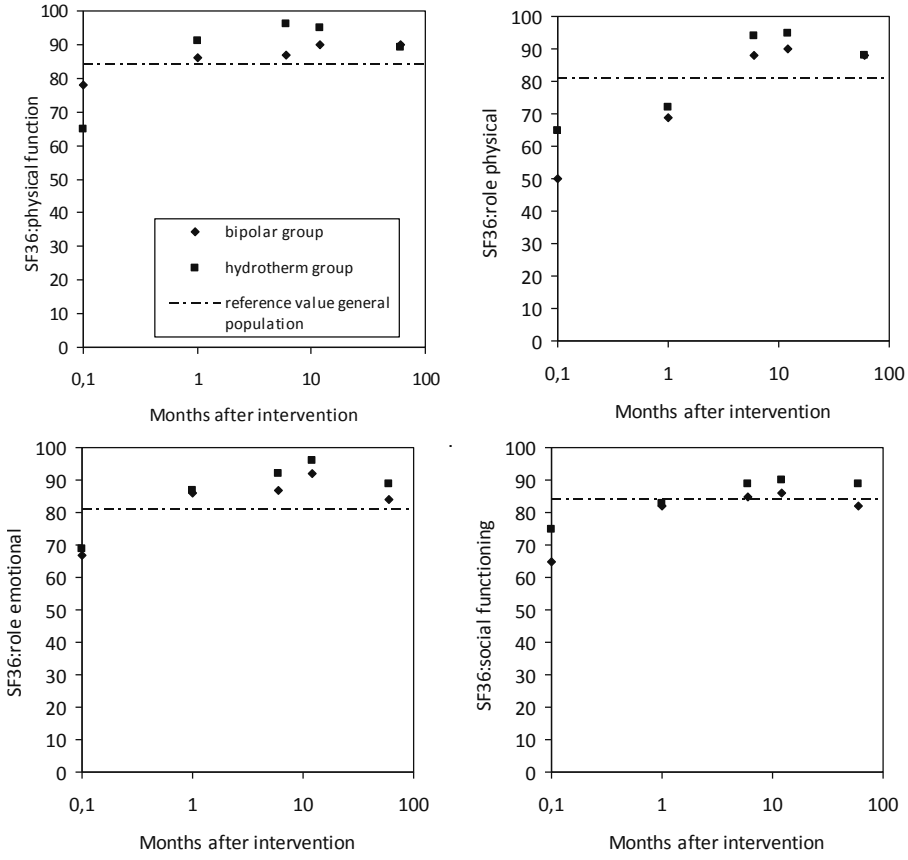
Table 2 shows the results of the EuroQOL with the effect measurement at 1 year and 5 years after treatment. Health related quality of life improved at each follow up moment after treatment as compared to the baseline measurements in both, the bipolar group and the hydrotherm group. Till 12 months after treatment a significant effect over time was found (P=.017). Five years after treatment the time effect was not statistically significant anymore (P=.140). Figure 2 shows the changes of the EuroQOL over time. The quality of life improved at 4 weeks,

Table 2. Patients' health-related quality of life in patients after bipolar endometrial ablation and hydrotherm endometrial ablation

	Treatment	Time points after randomization					Reference	MANOVA *P*-values		
		Intake (n=136)	4 weeks (n=140)	6 months (n=106)	1 year (n=105)	5 years (n=125)		Time effect	Treatment effect	Time by treatment effect
SF-36§										
Physical function	Bipolar	78±43	86±17	87±18	90±16	90±15	85	<0.001	.069	.22
	Hydrotherm	65±42	91±14	96±9	95±9	89±20				
Role physical	Bipolar	50±43	69±41	88±29	90±28	88±29	81	<0.001	.79	.98
	Hydrotherm	65±42	72±41	94±29	95±19	88±31				
Role emotional	Bipolar	67±40	86±25	87±30	92±23	84±46	81	0.005	.11	.12
	Hydrotherm	69±45	87±21	92±32	96±18	89±27				
Social functioning	Bipolar	65±23	82±21	85±24	86±21	82±27	84	<0.001	.63	.72
	Hydrotherm	75±21	83±20	89±28	90±18	89±16				
Mental health	Bipolar	68±18	80±15	77±15	78±17	78±17	81	0.001	.17	.89
	Hydrotherm	73±20	81±16	83±15	85±14	80±18				
Energy/vitality	Bipolar	47±18	62±19	67±19	70±18	66±20	61	<0.001	.87	.70
	Hydrotherm	55±21	63±23	71±18	73±18	68±21				
Pain	Bipolar	60±26	74±22	82±23	82±25	82±20	75	<0.001	1.0	.63
	Hydrotherm	63±25	74±22	81±20	85±18	81±24				
General health	Bipolar	64±21	72±22	72±23	77±20	72±21	72	<0.001	.66	.29
	Hydrotherm	75±20	78±19	82±17	81±17	80±40				
EuroQOL¥	Bipolar	0.81±0.14	0.89±0.13	0.87±0.17	0.89±0.17	0.89±0.20	0.85	0.017[1]	.19[1]	.44[1]
	Hydrotherm	0.88±0.17	0.90±0.14	0.91±0.20	0.93±0.17	0.86±0.20		0.141[2]	.59[2]	.32[2]
Shaw§	Bipolar	41±17	82±21	90±17	88±23	86±19		<0.001[1]	.12[1]	.70[1]
	Hydrotherm	47±21	74±24	78±22	84±21	79±27				
MOQ Quality of life/ Satisfaction‡	Bipolar	-	19±12	14±12	13±11	-		<0.001	.19	.56
	Hydrotherm		22±11	15±13	14±13					
General outcome#	Bipolar	-	28±6	15±13	15±13	-		<0.001	.69	.53
	Hydrotherm		30±6	16±15	15±14					

Results are expressed in mean ±SD. Reference values are general population means.
§ scores could range from 0-100 with higher scores indicating better functioning.
¥scores could range from 0-1 with higher scores indicating better functioning.1=effect till 1 year after randomization, 2=effect till 5 years after randomization.
‡scores could range from 10-46 with lower scores indicating better functioning
scores could range from 11-57 with lower scores indicating better functioning.

6 months and 12 months after treatment in the hydrotherm group, but decreased at 5-year follow-up. In the bipolar group the EuroQOL increased after treatment and stayed the same until 5-year follow-up.



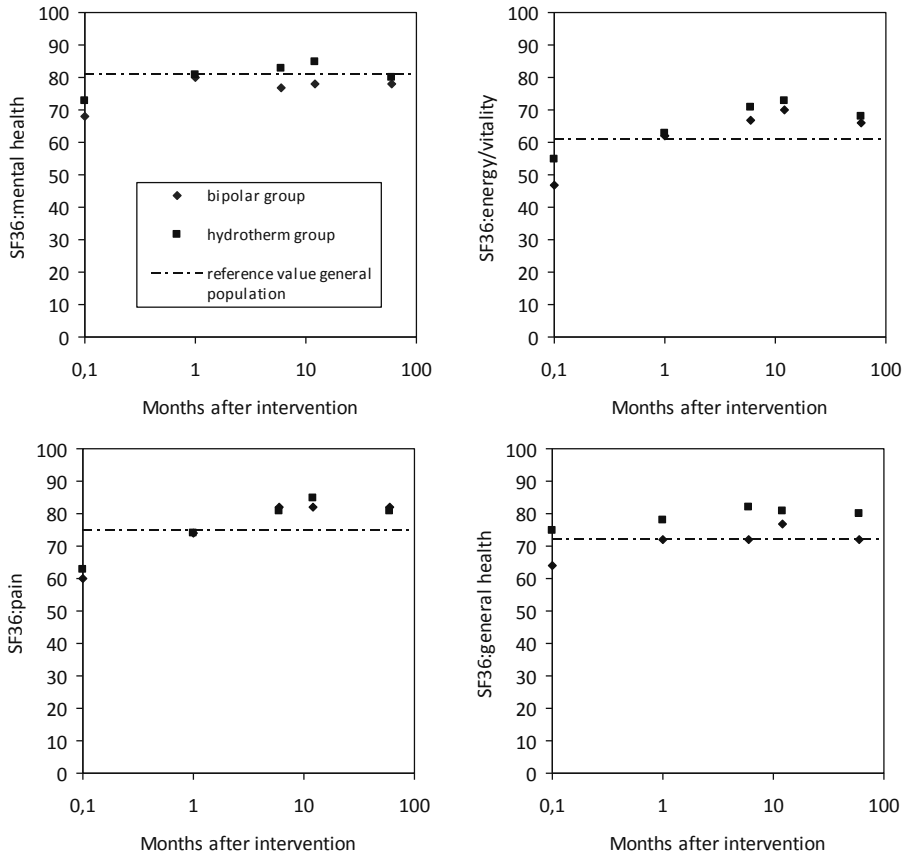


Figure 1. SF-36 quality of life domains, before and after bipolar radiofrequency endometrial ablation and hydrotherm endometrial ablation

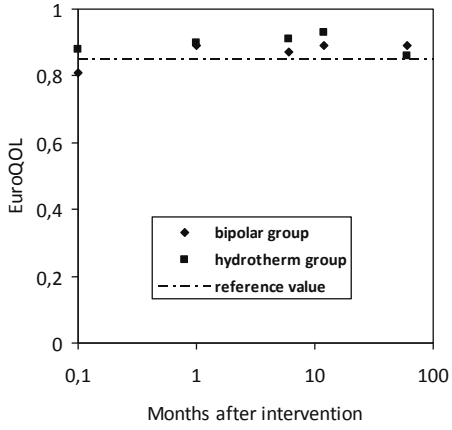


Figure 2. EuroQOL before and after bipolar radiofrequency endometrial ablation and hydrotherm endometrial ablation

Mean scores of the Shaw questionnaire are shown in table 2. There was a significant effect over time for health related quality of life (*P*<.001), but there was neither a significant effect between both groups nor a significant interaction between time and treatment.

Figure 3 shows the Shaw scores at baseline and at follow-up. There was a significant higher Shaw score at baseline in the hydrotherm group (*P*=.042). After treatment, the bipolar group shows higher Shaw scores, but only at six months follow-up the score in the bipolar group was significant higher (*P*=.004).

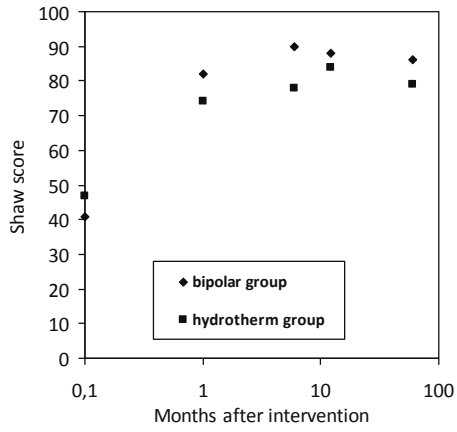


Figure 3. Shaw questionnaire score at baseline, 4 weeks, 6 months, 12 months and 5 years after bipolar radiofrequency endometrial ablation and hydrothermablation

In each separate Shaw domain the score was significantly higher in the bipolar group at six months follow-up, except at domains psychological health and physical health/wellbeing (Figure 4). Table 2 shows the means of the MOQ score, that significantly improved over time (P<.001). Again, there was neither a significant effect between both groups nor a significant interaction between time and treatment (Table 2).

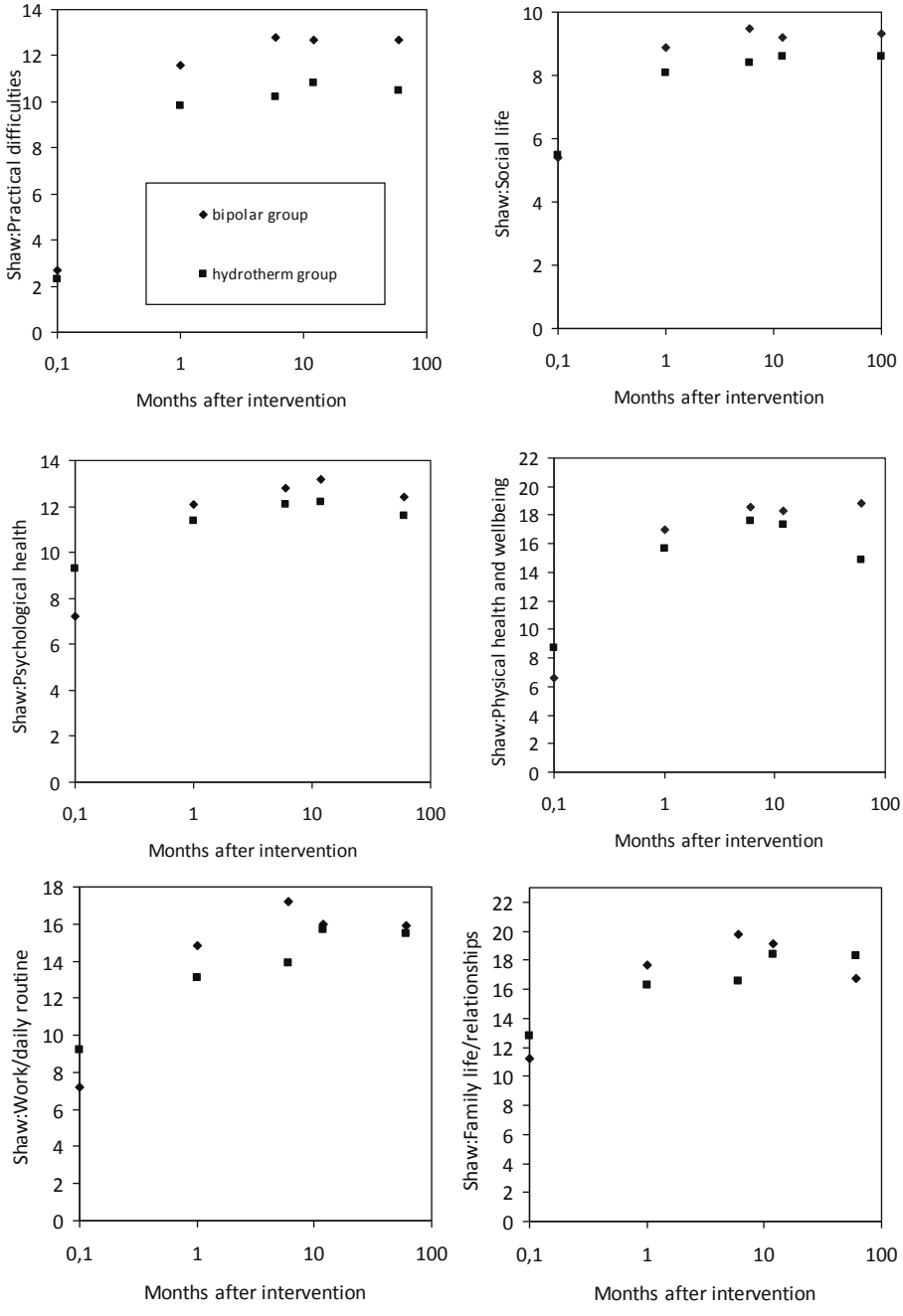


Figure 4. Shaw domains before and after bipolar radiofrequency endometrial ablation and hydrotherm endometrial ablation

Discussion

This randomized clinical trial comparing bipolar radiofrequency endometrial ablation and hydrotherm endometrial ablation in women suffering from dysfunctional uterine bleeding showed a significant improvement of health related quality of life after treatment for a period of at least 5 years after treatment. The generic and disease specific questionnaires gave similar results over time. The differences in amenorrhea rate and satisfaction rate between both ablation techniques, as reported earlier, did not result in a quality of life difference between both treatments.[4]

There are two ways to measure health related quality of life.[15,16] The generic measures can be used for the assessment of a general profile of perceived health, with dimensions such as physical, psychological and social health. These questionnaires allow comparisons among different types of disease, because they are not specific to any particular condition. We used generic quality of life instruments (SF-36 and EuroQOL) to ensure appropriate measurement of quality of life. We found changes in quality of life after treatment in the SF-36. Others also have found the SF-36 to be sensitive for changes in quality of life after treatment in women suffering from HMB.[17-19] Both, the SF-36 and EuroQOL, do contain many items about health problems at a specific moment, which is difficult to answer by women with HMB because they mainly have complaints during their menstruation. Furthermore, these instruments do not determine the specific impact of a disease or condition on quality of life. Disease specific quality of life instruments are designed to measure the specific consequences that a particular disease has on quality of life. Therefore, we combined generic quality of life instruments with disease specific questionnaires (Shaw questionnaire and MOQ).[11-13] Shaw et al. developed the multi-attribute assessment instrument to assess the effect of HMB on quality of life.[7] Especially the domain practical difficulties, relating to sanitary protection, flooding, etc. in the Shaw questionnaire is specific for HMB compared to other quality of life questionnaires.[12] The Shaw questionnaire also showed a significant improvement over time (time-effect), but no difference between the two endometrial ablation techniques (treatment-effect).

The menorrhagia outcome questionnaire (MOQ) was developed to evaluate the outcomes of all surgical interventions for the treatment of HMB.[11] It was specifically developed as a single questionnaire which could be administered once following treatment therefore not needing a pre-treatment assessment

for comparison. The questions are framed to elicit an assessment of the patient's current symptoms and quality of life compared to prior to the operation. Then you have to rely on post-treatment retrospective items.[19]

Sexual health, another important part of woman's quality of life, may also be adversely affected by HMB. Sexual health also should have been assessed before and after treatment, but this was not measured by the quality of life questionnaires used in this trial. Only one question in the MOQ covered the influence of the operation on sexual health. Therefore, sexual health is not extensively measured by the quality of life questionnaires used in this trial.

The improvement in health related quality of life, that was observed in both groups over time, could be affected by the fact that patients knew that they had been treated. As far as we know, all RCTs evaluating the effect of treatment on dysfunctional uterine bleeding have reported an improvement in quality of life after treatment. We are unaware of studies that have included a sham procedure or a control group without intervention. The role of any medical or surgical treatment intervention against no intervention is still an interesting area for research. The review of quality of life instruments in studies of HMB showed the absence of a standardized instrument for measuring outcomes in trials for abnormal uterine bleeding.[20] It would be ideal if a validated measure or set of instruments would be developed that captured all HMB symptoms. This standardized tool could be used in all future trials.

This RCT, comparing bipolar radiofrequency ablation and hydrothermablation, showed a significant improvement over time in health related quality of life in the generic and disease specific questionnaires. A treatment effect of amenorrhea and satisfaction did not result in quality of life benefits. The better amenorrhea and satisfaction rates in the bipolar group compared to the balloon group were not accompanied with a difference in quality of life. When looking at the figures 1 till 4, the Shaw questionnaire (Figure 4) seems to show a trend to a higher score in the bipolar group, which corresponds with the higher amenorrhea and satisfaction rate, compared to the other questionnaires, but it only was significant at 6 month follow-up. The discrepancy between clinical outcome and quality of life was also reported in the trial of Clark et al. in which bipolar endometrial ablation was compared with thermal balloon endometrial ablation in the office.[21] They used the same health related quality of life questionnaires as in our trial, and also found a significant time effect, but no significant treatment effect.

The fact that the better amenorrhea and satisfaction rates in the bipolar

group did not result in a difference in quality of life could be explained in two ways. First, the quality of life questionnaires that we used may be not sensitive enough to measure the effects of treatment on quality of life. Second, an explanation for the discrepancy between the similar quality of life scores in spite of different amenorrhea and patients satisfaction rates might be that amenorrhea and patient satisfaction do not affect quality of life. The impact of HMB on quality of life has been reported previously, and therefore it is unlikely that the significant difference in amenorrhea rate and satisfaction rate does not affect health related quality of life.[17,22] But in these studies quality of life was only measured with the generic health related quality of life questionnaire (SF-36).

In conclusion, health related quality of life in the treatment of HMB improved over time in all generic and disease specific questionnaires in both treatment groups. The better amenorrhea and satisfaction rates in the bipolar group compared to the balloon group did not result in quality of life benefits.

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Chapter 6

Endometrial ablation with paracervical block

Penninx JP, Mol BW, Bongers MY

J Reprod Med 2009;54:617-20.

Abstract

Objective: To evaluate the safety, feasibility and efficacy of endometrial ablation under local anesthesia.

Methods: A prospective cohort study was performed at the gynecology department of a large teaching hospital. Women with dysfunctional uterine bleeding were included to undergo NovaSure® endometrial ablation with paracervical block. We measured the acceptability, pain score (visual analog score), amenorrhea, and patients' satisfaction after the procedure.

Results: We treated 33 patients. No complications occurred during the procedure or postoperatively. Of the 33 women, 28 found treatment with NovaSure® endometrial ablation under local anesthetics acceptable. After 24 hours, 23 of 33 women reported to be pain free, whereas 10 women still had mild pain. Twenty women developed amenorrhea (60.6%) and 13 women hypomenorrhea (39.4%). All women were satisfied with the treatment result and would recommend it to a friend.

Conclusion: NovaSure® endometrial ablation performed under local anesthesia is a safe, feasible and efficacious procedure.

Introduction

Menorrhagia is a frequent problem in premenopausal women. Menorrhagia affects 1 in 20 women.[1] If the diagnostic work-up has shown no abnormalities, the menorrhagia is classified as dysfunctional bleeding. In women with dysfunctional bleeding, endometrial ablation is an effective treatment.[2] The NovaSure Endometrial Ablation Device (Hologic, USA) is a bipolar radiofrequency impedance-controlled system to evaporate endometrial tissue.[3] In our clinic, the NovaSure® was performed from 1998 onward with general anesthesia or regional (spinal) anesthesia. The procedure only takes 1 to 2 minutes.[4]

We hypothesized that this short duration of treatment would make this intervention suitable for local anesthesia. We performed a prospective study to assess the feasibility and patient acceptability of NovaSure® endometrial ablation in an outpatient setting under local anesthesia.

Materials and Methods

We performed this prospective study in the Maxima Medical Centre (MMC), Veldhoven, The Netherlands, approved by the institutional review board. The MMC is a teaching hospital with 500 beds. Women suffering from menorrhagia, as indicated by a pictorial chart with a Higham score of ≥ 200 points, were eligible for the study. Only women with dysfunctional bleeding were included after evaluation with saline infusion sonohysterography and hysteroscopy verifying that there were no abnormalities. The women had no desire for another child. After being informed about the study, women gave written informed consent.

In the MMC, endometrial ablation is performed with a NovaSure® device (Hologic, USA). If an ablation treatment of the endometrium was indicated, women were asked if they wanted to undergo the procedure under local anesthesia. The pain score of their menses was noted.

The NovaSure® procedure was scheduled at the outpatient clinic. Women were advised to use an oral nonsteroidal anti-inflammatory drug (Ibuprofen 500mg) as a painkiller 12 hours and 1 hour before the procedure. A paracervical block with Ultracaine or Prilocaine 1% with or without adrenaline was placed. A 12-20 mL amount of the solution was injected just under the epithelium of the cervix, not deeper than 3 mm, at 2, 5, 7 and 10 o'clock.

After placing the paracervical block there was a 3-minute wait time for anesthetic effect before starting the NovaSure® procedure. After the NovaSure® device had been brought into the uterus, suction was applied, the endometrial lining was brought into contact with the electrode array, and the fluid and debris generated during the ablation process were removed. During the procedure, oxygen saturation was observed by a pulse-oximeter. The procedure was only performed by one gynecologist. Four hours after the procedure the patient was advised to take Paracetamol 1,000mg, Naproxen 500mg or, Tramal 100mg.

Visual analog scales (VAS) were used to measure pain when dilating the cervix, during the NovaSure® procedure, and at 4 and 24 hours after the procedure. The VAS is a straight line with the left end of the line representing no pain and the right end of the line representing the worst pain. Patients were asked to mark on the line the painfulness of the procedure.

Follow-up examination was done at 6 weeks after treatment. At this visit the menstruation was scored again on a pictorial chart. Women were also asked if they would be prepared to undergo the procedure again if needed and if they would recommend the procedure to a friend.

Results

From November 2006 until January 2008, 33 women were included in the study. The mean age was 46.7 years, ranging from 33 to 57 years. The average parity was 2.0, with three nulliparas. In all women it was feasible to perform the total NovaSure® procedure with a paracervical block, and premature termination of the procedure was never needed. Four patients developed a vasovagal reaction during the procedure. The average procedure time was 110 seconds (range 63-120). The average probe length was 8.5 cm (range 7-10), the length of the uterine cavity was 4.6 cm (range 3.5- 6), and the intercornual length was 4.1 cm (range 2.0-4.8).

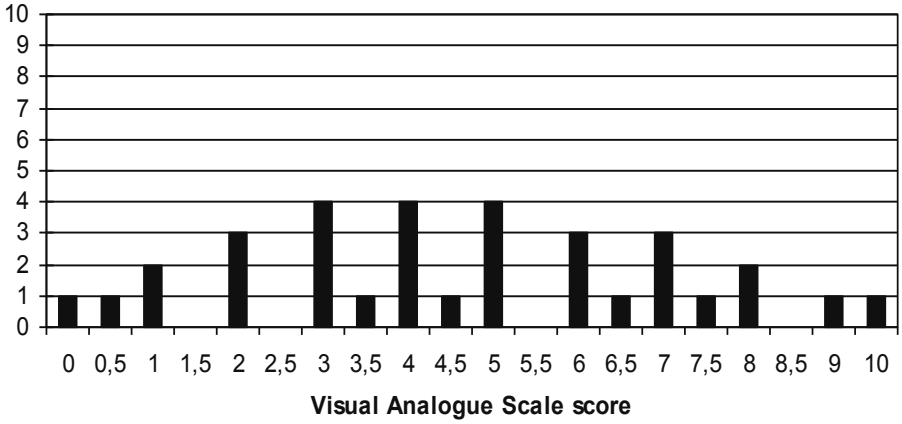

Figure 1. Visual analog scale pain score of the total bipolar ablation procedure

The median pain score during dilatation was 3.0 (range 1.0-7.0). The median pain score for the entire procedure was 5.1 (range 0.0-10.0) (Figure 1). After 24 hours, 23 women had a pain score of 0 points, as shown in Figure 2.

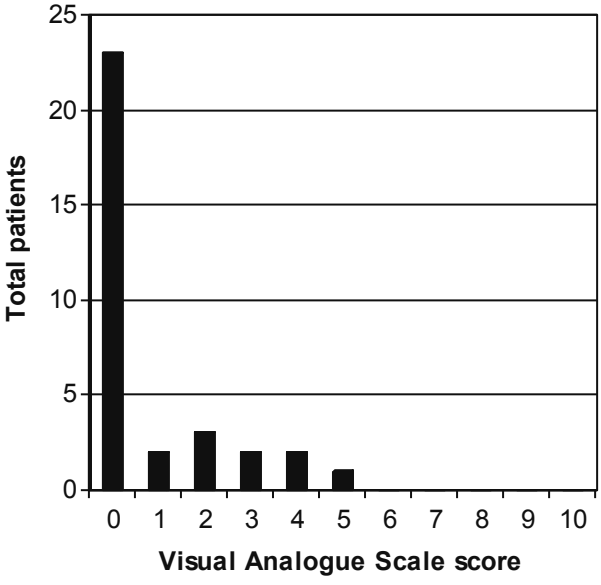

Figure 2. Visual analog scale pain score 24 hours after bipolar ablation treatment

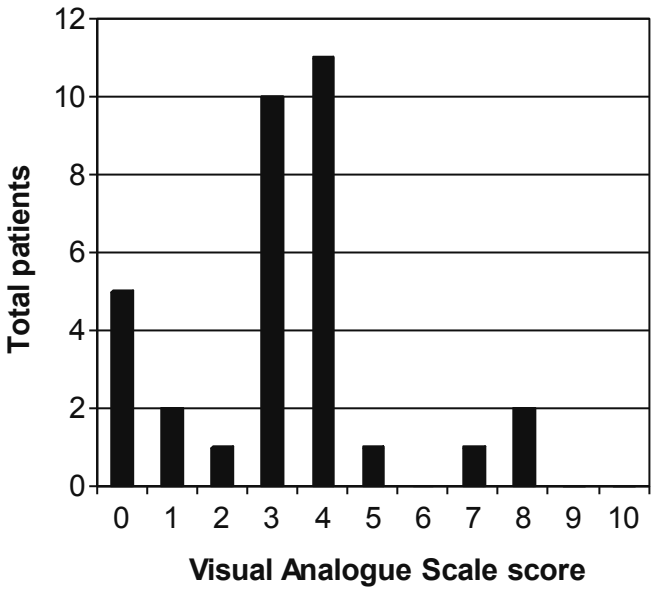

Figure 3. Visual analog scale pain score of dysmenorrhea before treatment

After six weeks 20 women developed amenorrhea (60.6%) and 13 women hypomenorrhea (39.4%). They were all satisfied with the result. Thirty-one patients found the NovaSure® under local anesthetics to be acceptable (94%); only 2 patients would not undergo the procedure again. No complications occurred during the procedure or postoperatively.

Discussion

We used the NovaSure® procedure with local anesthesia in 33 patients, and found it to be a safe and feasible procedure. In the medical literature almost all endometrial ablation procedures are performed at an outpatient clinic or theatre with general or local anesthetics, or paracervical block with intra-venous sedation.

One study compared intraoperative and postoperative pain between ThermaChoice® endometrial ablation and NovaSure® procedure.[5] The NovaSure® system was associated with statistically significant lower intraoperative and postoperative pain than the ThermaChoice® system. Data supported the idea that the NovaSure® procedure could become an office-based procedure.

In 2006, hysteroscopic endometrial ablation using the HydroThermAblator®

was performed under paracervical block without local anesthetics or IV sedation.[6] The patients reported mild pain during the procedure, and most found the procedure acceptable. We confirmed this with our study. The percentage of women with amenorrhea after the NovaSure® varies from 40-60%.[7-10] The finding of an amenorrhea rate of 60% after 6 weeks corresponds with previous results in the literature.

In summary, we successfully performed endometrial ablation under local anesthesia in our clinic setting, reducing operating room utilization and its associated costs and inconveniences. The results of this study support NovaSure® endometrial ablation under local anesthesia as a minimally invasive procedure of choice for women with dysfunctional uterine bleeding. It is a safe, feasible, and efficacious procedure. Whether the procedure is equally effective as treatment under general anesthesia should be evaluated in a larger clinical trial.

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Chapter 7

Bipolar versus balloon endometrial ablation in the office: a randomized controlled trial

Penninx JPM, Herman MC, Kruitwagen RFPM, Ter Haar JF, Mol BW, Bongers MY

Submitted.

Abstract

Objective: To compare the effectiveness of bipolar radiofrequency endometrial ablation (Novasure®) and balloon endometrial ablation (Thermablate®) in the office in patients with heavy menstrual bleeding.

Methods: We performed a multi-center double blind randomized controlled trial in three hospitals in The Netherlands. Women with heavy menstrual bleeding were randomly allocated to bipolar endometrial ablation or balloon endometrial ablation, performed in the office, using a paracervical block. The primary outcome was amenorrhea. Secondary outcome measures were pain, satisfaction, quality of life and reintervention.

Results: We included 104 women of whom 52 were allocated to bipolar ablation and 52 to balloon ablation. Complications did not occur. The mean visual analog pain score of the total procedure was 7.1 in the bipolar group and 7.4 in the balloon group ($P<.577$). Amenorrhea rates were 60% (29/48) in the bipolar group and 27% (12/45) in the balloon group (relative risk (RR) 2.3, 95% confidence interval (CI) 1.3 to 3.9). After 12 months, 94% (45/48) of the patients in the bipolar group were satisfied with the result of the treatment versus 80% (36/45) in the balloon group (RR 1.2, 95% CI 1.0 to 1.4). The reintervention rates were 5/52 (10%) in the bipolar group and 6/52 (12%) in the balloon group (RR 1.02, 95% CI 0.9 to 1.2). The Shaw score, expressing quality of life, improved over time ($P<.001$) and was significantly higher in the bipolar group at 12 months follow-up ($P=.025$).

Conclusion: In the treatment of heavy menstrual bleeding, bipolar radiofrequency endometrial ablation is superior to balloon endometrial ablation.

Introduction

Excessive menstrual bleeding is a significant health problem in women in reproductive age. It can cause anemia and reduce quality of life. The incidence varies between 9 to 22 %.[1-3] About 30-40% of the hysterectomies are performed for treatment of severe dysfunctional bleeding.[4] Hysterectomy is an effective treatment, but it is a major surgical procedure with a complication rate up to 67%.[5]

Endometrial ablation is a less invasive alternative to hysterectomy, and preserves the uterus. The first-generation endometrial ablation techniques were laser ablation, transcervical resection of the endometrium and rollerball ablation. Disadvantages of these techniques were the chance of fluid overload or water intoxication.[6-9] Second-generation techniques overcame these disadvantages as they were technically simpler, quicker to perform and requiring less skills of the surgeon, while satisfaction rates and reduction in heavy menstrual bleeding are similar.[10]

The NovaSure® endometrial ablation device is one of the second-generation devices that uses bipolar radiofrequency impedance-controlled endometrial ablation to evaporate endometrial tissue. Bipolar radiofrequency endometrial ablation was reported to be superior over balloon ablation and hydrothermablation, making it the standard of choice in women requesting ablation for dysfunctional uterine bleeding.[11-13] NovaSure® can be used under local anesthesia in the office.[14]

The majority of women (70%) prefer an outpatient ablation treatment.[15] Spending less time in the hospital, attending for one visit, feeling well directly after treatment and choosing the treatment setting were important factors to the majority of women in this choice. Recently we reported that NovaSure® under local anesthesia in the outpatient setting was a safe, feasible, and efficacious procedure.[14]

The Thermablate® balloon ablation technique is relatively new on the market. It seems perfect for outpatient treatment with local anesthesia because of its small diameter and relatively short treatment time of two and a half minutes and a much higher temperature compared to the Thermachoice® balloon.[16,17] There are no randomized trials comparing Thermablate® with other ablation techniques. In view of this lack of knowledge, we performed a randomized controlled trial comparing these two second-generation endometrial devices with local anesthesia in the office.

Materials and Methods

We performed a multi-centre randomized controlled trial (RCT) in the Máxima Medical Centre Veldhoven, Twee Steden Hospital Tilburg and Zuidoost Clinic Amsterdam, The Netherlands. The study was approved by the local institutional review board (number 813) and registered in the international trial register (ISRCTN17974690). All participants gave written informed consent before enrollment.

Women with heavy menstrual bleeding (HMB) were eligible for the trial. HMB was defined as indicated on the pictorial chart described by Higham et al.[18] One period is counted, and a minimum score of 150 points was described as HMB.

All women underwent a sonography. Women with intracavitairy pathology were excluded, except women with intracavitary polyps less than 1 cm. Saline infusion sonography or diagnostic hysteroscopy was required to confirm a normal uterine cavity, with a cavity length of 6 to 12 cm and a histologically benign endometrium within 6 months of screening. All women had to have a normal Pap smear and a premenopausal follicular stimulating hormone (FSH)-level of less than 40 IU/l. Exclusion criteria were the presence of coagulopathies, use of anti-coagulants, a desire to preserve fertility, prior uterine surgery other than low segment Cesarean section and suspected or confirmed uterine malignancy. All women who were included in the study preferred to be treated by endometrial ablation in the outpatient setting after careful evaluation of the advantages and disadvantages of the other treatment options. The procedure was planned in the postmenstrual phase at day 3-8 of the menstrual cycle. Both groups received no medical endometrial pretreatment prior to surgery.

Eligible and consenting women were randomly allocated to bipolar endometrial ablation or balloon endometrial ablation in the office. Randomization was performed by taking a sealed opaque envelope just before start of treatment in every center in a 1:1 ratio. Patients and investigating doctors were masked for the randomization allocation, and remained so during the study, while obviously the doctors performing the ablation did know at that moment which device was used. The physician who saw the patient at the follow-up visits did not know which device was used.

The bipolar radiofrequency endometrial ablation system (NovaSure®) consists of a generator and a disposable device. After the device is introduced in the uterine cavity, a cavity assessment check has to be completed. When suction is

applied, the endometrial lining is brought into contact with the electrode array. It is suitable for a uterus with a minimum of 2.5 cm cornu-to-cornu distance, and a depth of 6-11 cm as measured by uterine sounding.[19]

The balloon endometrial ablation (Thermablate® EAS system) consists of a hand-held automated Treatment Control Unit (TCU) and a single-use disposable catheter balloon cartridge. The cartridge contains 28 ml of a biocompatible treatment fluid. It is connected to the TCU which heats the fluid to a temperature of 173°C in 8 minutes. This heating process takes place before or during patient preparation. The 6 mm, heat shielded, soft-tipped catheter is brought into the uterine cavity to the predetermined depth. The TCU's pneumatic system transfers the fluid through the catheter, inflating the silicone balloon within the cavity to a set pressure level of 220 mmHg. During treatment, the system performs a depressurization and repressurization cycle 3 times to maintain consistent balloon surface contact with the uterine cavity. This creates uniform temperature of the fluid within the balloon. The treatment time always is 2 minutes and 38 seconds.[17] Before and after the balloon ablation a hysteroscopy was performed, as the balloon procedure itself does not verify cavity integrity before treatment.

All procedures were scheduled at the outpatient clinic. Women used an oral nonsteroidal anti-inflammatory drug (Naproxen 500mg) as a painkiller one hour before treatment. A paracervical block with Ultracain was placed. A 12-20 mL amount of the solution was injected just under the epithelium of the cervix at 2, 5, 7 and 10 o'clock. After placing the paracervical block there was a 3 minute waiting time for the anesthetic effect before starting the dilatation of the cervix. After the procedure the patient was advised to take Paracetamol 1,000mg, Naproxen 500mg or if necessary Tramal 100mg.

Visual analog scales were used to measure pain when dilating the cervix, during the endometrial ablation, and at 1, 4, 12 and 24 hours after the procedure. The visual analog scale is a straight line with the left end of the line representing no pain and the right end of the line representing the worst pain. Patients were asked to mark on the line the painfulness of the procedure which corresponds with a pain score from 0 to 10.

Follow-up visits were carried out at the outpatient clinic or by telephone at 6 weeks, 6 months and 12 months after the initial treatment. At these consultations, the patient had contact with a doctor who was unaware of the treatment that had been performed. At each visit, duration of menstruation, presence of dysmenorrhea and clots were registered. Patients also completed a pictorial chart, and expressed

their satisfaction about the treatment result. Level of satisfaction was categorized as completely satisfied, satisfied, doubtful or not satisfied.

Menstrual bleeding was quantified using the Pictoral Blood loss Assessment Chart (PBAC) of Higham et al. A score of zero (0) operationally defined "amenorrhea". All patients were asked to complete the menorrhagia multi-attribute scale (Shaw questionnaire) at baseline and at each follow-up visit to assess the effects of HMB on quality of life. The scores of the domains were rated with a score of zero points (worst) to 100 points (best).[20,21] Furthermore, we registered whether a reintervention had been performed. Reinterventions considered were the use of oral contraceptives, re-ablation, and performed hysterectomies.

The primary outcome measure was amenorrhea at 12 months post treatment. Secondary outcome measures were pain, reduction in bleeding, patient satisfaction, quality of life and reinterventions.

Based on available information of the Thermablate® and other balloon ablation devices, an amenorrhea rate of 30% is anticipated in the balloon group and 50% in the bipolar group.[11,12,22-25] Using a 1-tailed test of proportions with P=0.05, the proposed sample size of 94 patients has 80% power to detect a treatment difference of 20% or greater. Assuming that approximately 90% of enrolled patients would complete the study protocol, a total of 104 patients (bipolar:balloon 1:1) had to be enrolled.

Analysis

The analysis was performed according to the 'intention-to-treat' principle i.e., patients were analyzed in the group to which they had been allocated. Repeated measures analysis of variance was used to evaluate changes in effect over time (time effect), differences in effect between both treatment groups (treatment effect), and interaction between changes in effect over time and treatment group (time-by-treatment effect). Patients with missing measurements were included in the repeated measure analysis if data were available for at least two different time points.[26]

P-values less than 0.05 were considered to indicate statistical significance. When a statistically significant difference in menstrual pattern, patient satisfaction or multi utility scale score between both treatment groups or an interaction between changes in menstrual pattern and patient satisfaction over time and treatment group was found, the differences between treatment groups at specific points in time were examined. In case of dichotomous endpoints this was done

by calculating relative risks and 95% confidence intervals. The pictorial chart score and VAS score were compared using the Wilcoxon test.[27,28] We calculated treatment satisfaction after treatment with a T test. All data were analyzed using IBM SPSS statistics 20 for Windows.

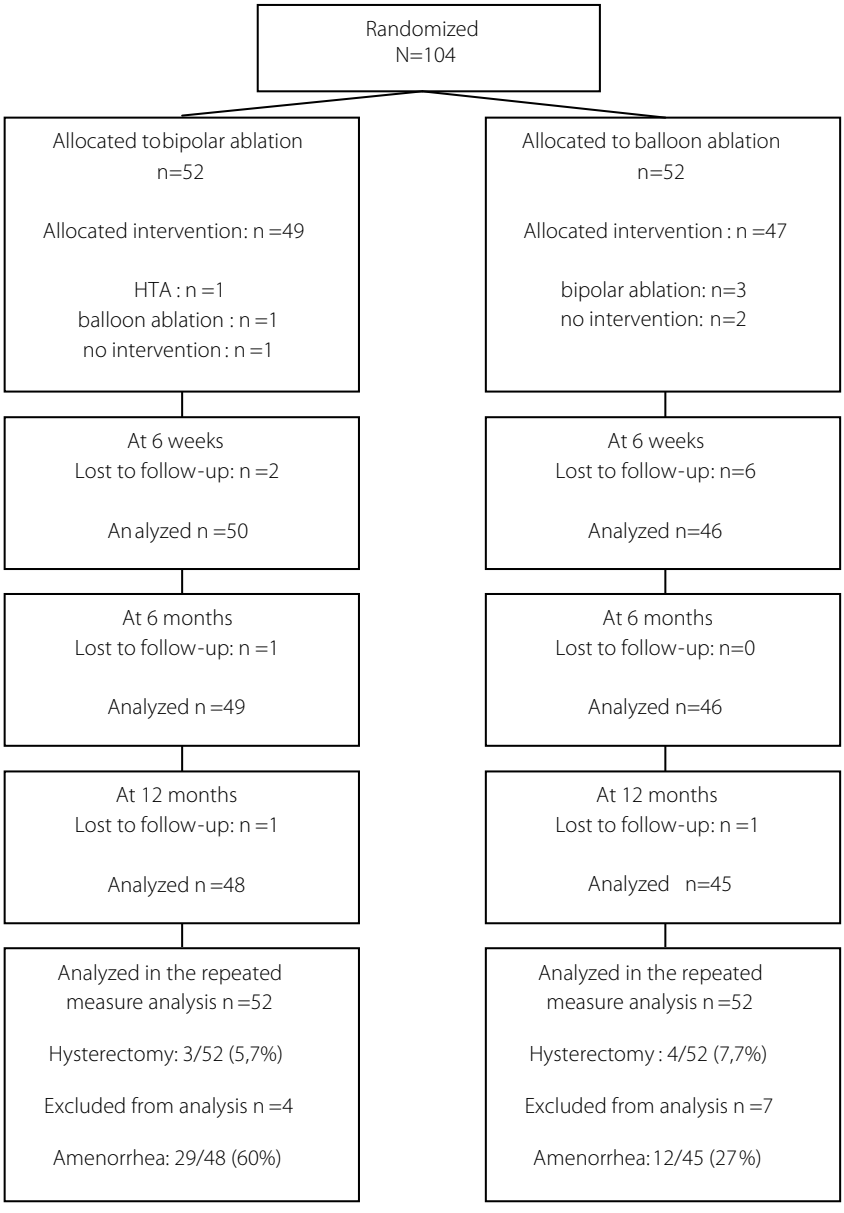

Figure 1. Trial profile. HTA=hydrothermablation

Results

Between March 2009 and December 2011 104 women were included in the study, of whom 52 were allocated to the bipolar group, and 52 were allocated to the balloon group (Figure 1). Ninety-six patients were included in the Máxima Medical Centre in Veldhoven, six patients in the Twee Steden Hospital and two in the Zuidoost Clinic. Table 1 shows the baseline patient characteristics of both groups, these were comparable.

Table 1. Baseline characteristics

	Bipolar group n=52	Balloon group n=52
Age (years)	45.4 ± 4.7	44.1 ± 4.4
Duration of menstruation (days)	9.3 ± 4.9	8.4 ± 4.9
Patients with clots	47 (90)	51 (98)
Duration of clots (days)	3.2 ± 1.6	3.2 ± 1.1
Pictorial chart	979 (300-2400)	931 (452-2500)
Dysmenorrhea		
Moderate	10 (19)	8 (15)
Severe	9 (17)	9 (17)
Uterus		
Anteverted	42 (81)	40 (77)
Midposition	0 (0)	3 (6)
Retroverted	10 (19)	6 (11)
Missing data	0 (0)	3 (6)
Hemoglobin (mmol/L)	7.5 ± 1.1	8.1 ± 0.7
FSH (international units/L)	10.9 ± 13.0	7.9 ± 9.6
Uterine length (cm)	9.0 ± 1.0	9.2 ± 0.9
Endometrial thickness (mm)	7.4 ± 6.5	10.1 ± 7.6

Data are mean ± standard deviation or median (minimum-maximum), or n (%).
FSH: follicle-stimulating hormone.

In the bipolar group 49 patients had the allocated intervention, while 3 did not. One patient decided not to undergo the endometrial ablation, as she became frightened of the ambulant procedure after randomization. One patient underwent balloon endometrial ablation because of technical problems with the bipolar system and one patient had a hydrothermablation because of an uterus subseptus. In two patients in the bipolar group it was not possible to perform the procedure in the office because, in one patient, dilatation of the cervix was too painful, and in one patient stenosis of the cervix made it impossible to introduce the NovaSure®. In both patients the procedure was performed in theatre with spinal analgesia.

In the balloon group, 47 patients had the allocated intervention, while 5 did not. One patient decided not to undergo the endometrial ablation, as she became frightened of the ambulant procedure after randomization. In another patient it was not possible to perform the procedure because of a deformed uterine cavity by myomas, as became apparent during the procedure. Three patients in the balloon group underwent bipolar radiofrequency endometrial ablation, one because of technical problems with the balloon device, while two women persisted on having the bipolar treatment after randomization.

The average treatment duration of the bipolar group was 10.4 minutes (range 6 to 30) compared to 12.1 minutes (range 5 to 45) for the balloon group (*P*=.340). The mean VAS score of the total ablation procedure was 7.1 in the bipolar group compared to 7.4 in the balloon group (*P*<.577). The VAS score showed no significant difference between both groups at all time moments after the procedure at which the VAS was measured (Table 2). No complications occurred in both groups. Overall, four patients in the bipolar group and seven patients in the balloon group were lost to follow-up (Figure 1).

Table 2. Visual analog scale (VAS) pain scores

	Bipolar group n=44	Balloon group n=44	*P*-value
Menstruation	4.8 ± 2.8	5.1 ± 2.4	.742
Total procedure	7.1 ± 2.1	7.4 ± 2.1	.577
1 hour after treatment	4.6 ± 3.1	4.5 ± 2.6	.799
4 hours after treatment	5.7 ± 2.9	5.5 ± 2.4	.826
12 hours after treatment	2.8 ± 2.0	2.5 ± 2.3	.857
24 hours after treatment	1.5 ± 1.8	1.2 ±1.8	.870

Data are presented as mean ± SD.

Figure 2 shows the percentage of women with amenorrhea, dysmenorrhea and patients with clots during their menstruation after bipolar endometrial ablation and balloon ablation.

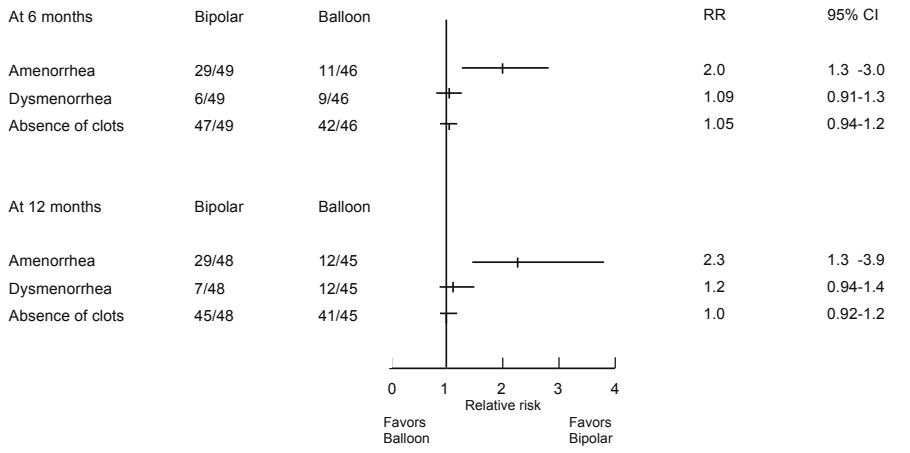

Figure 2. Treatment effects at 6 months and 12 months after treatment.
RR, relative risk; CI, confidence interval.

The number of women reporting amenorrhea at 6 and 12 months after the procedure was 29/49 (59%) and 29/48 (60%) in the bipolar group and 11/46 (24%) and 12/45 (27%) in the balloon group (RR 2.0, 95% CI 1.3-3.0 and RR 2.3, 95% CI 1.3 to 3.9, at 6 and 12 months, respectively). There was a significant decrease in duration of menstruation after 6 and 12 months in both groups, as compared to the duration of menstruation at baseline (*P*=.001). The duration of menstruation was significantly shorter in the bipolar group after 6 months (1.8 vs. 3.4 days, *P*=.039) and 12 months (1.6 vs. 3.4 days, *P*=.003).

Figure 3 shows the median pictorial chart score in both groups at baseline, 6 weeks, 6 months and 12 months after the procedure. There was no significant difference between both groups in median pictorial chart score at baseline (*P*=.48). The pictorial chart score was significantly lower in the bipolar group at 6 months (*P*=.006) and 12 months (*P*<.001).

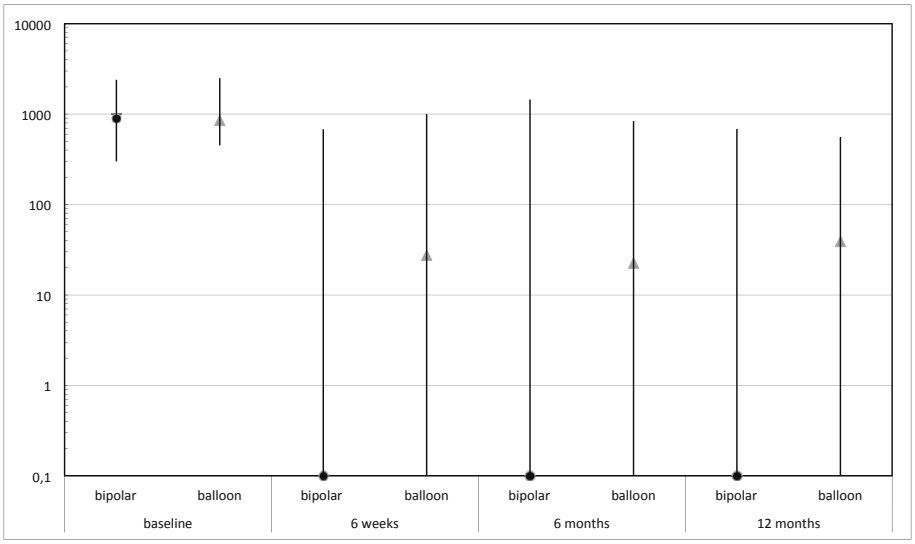

Figure 3. Pictorial chart score (PCAS) (median, minimum and maximum) at baseline, 6 weeks, 6 months, and 12 months after bipolar and balloon endometrial ablation

Figure 4 shows the patient satisfaction at 6 weeks, 6 months and 12 months after treatment. Patient satisfaction did not differ over time (*P*=.470), as did the time-by-treatment effect (*P*=.940). Treatment effect of patient satisfaction showed a significant difference (*P*=.028). After 12 months, 94% (45/48) of the patients in the bipolar group were satisfied with the result of the treatment versus 80% (36/45) in the balloon group (RR 1.2, 95% CI 1.0 to 1.4). At 12 months, more patients were completely satisfied after bipolar endometrial ablation (40/48 (83%) versus 29/45 (64%), RR 1.3, 95% CI 1.0-1.7).

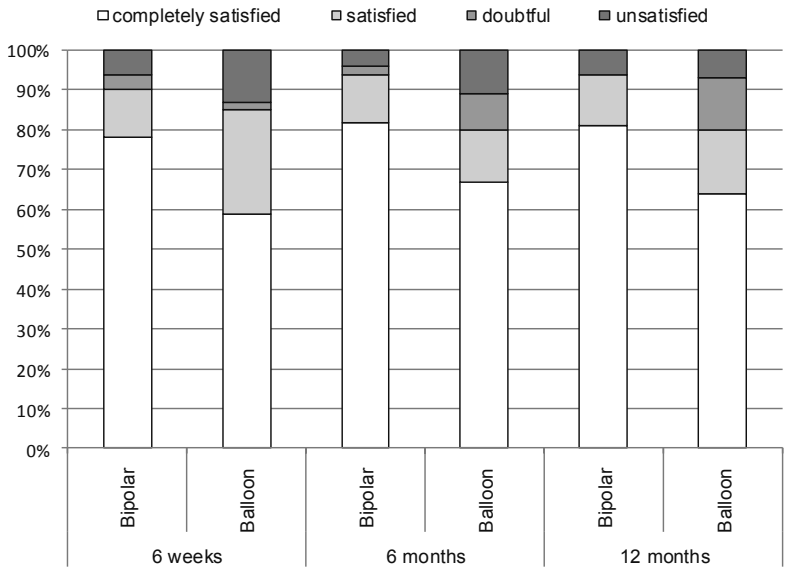

Figure 4. Patient satisfaction 6 weeks, 6 months and 12 months after treatment in the bipolar and balloon group

After 1 year follow-up, there were 5 reinterventions in the bipolar group and 6 in the balloon group (RR 1.02, 95% CI 0.9 to 1.2). All, but one, reinterventions were performed because of persisting HMB. In the remaining patient in the bipolar group a hysterectomy was performed for dysmenorrhea.

In the bipolar group, we performed five reinterventions. Three patients had a hysterectomy, while one patient started oral contraceptives and in one patient a bipolar endometrial ablation was performed. This last patient had a Thermablate® performed before in the bipolar group because of a technical problem with the NovaSure®. In the balloon group, there were six reinterventions performed: four patients had a hysterectomy, while two patients started oral contraceptives.

Table 3. Mean Shaw score expressing quality of life

	Bipolar group n=41	Balloon group n=41	*P*-value	95% CI
baseline	48.9	43.2	.245	-3.7 to 13.9
6 weeks	90.5	84.1	.218	-3.3 to 14.4
6 months	95.7	90.5	.273	-2.7 to 10.9
12 months	95.8	88.3	.025	0.9 to 13.7

Score 0 (worst) to 100 (best). CI, Confidence Interval.

Mean scores of the Shaw questionnaire at baseline, and at 6 weeks, 6 months and 12 months after randomization are shown in table 3. There was a significant effect over time (*P*<.001), with the Shaw score being significantly higher in the bipolar group at 12 month follow-up (*P*=.025). There was neither a significant effect between both groups nor a significant interaction between time and treatment (Figure 5).

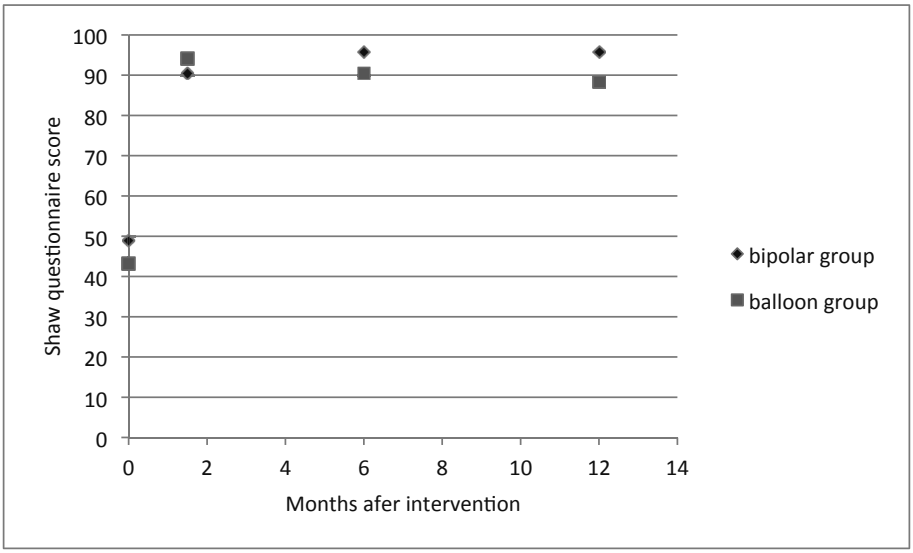

Figure 5. Shaw score, expressing quality of life, at baseline, 6 weeks, 6 months and 12 months after bipolar radiofrequency endometrial ablation and balloon endometrial ablation

Discussion

In this randomized clinical trial, we studied two second-generation endometrial ablation techniques in the outpatient clinic during the first year after treatment. The bipolar radiofrequency endometrial ablation device (NovaSure®) performed better than the balloon endometrial ablation device (Thermablate®) in terms of amenorrhea, duration of menstruation, pictorial chart score, patient satisfaction and the Shaw questionnaire score.

The amenorrhea rate of 60% in the bipolar group and 27% in the balloon group were comparable with previously reported studies (40-56% for the bipolar ablation, and 7-38% for the balloon ablation).[24,25,29] The higher amenorrhea

rate in the bipolar group is according to the network meta-analysis of second-generation endometrial ablation techniques of Daniels et al. in which the bipolar radiofrequency and microwave ablation techniques appeared to be superior over thermal balloon ablation in terms of increased amenorrhea rate in women with heavy menstrual bleeding.[25]

Both office procedures seem acceptable. Our observed pain scores are comparable with a previous reported study of Clark et al. comparing bipolar ablation with thermal balloon ablation (ThermaChoice® III) in the office.[30] Other studies mostly use rescue analgesia by inhaling nitrous oxide or conscious sedation when performing endometrial ablation in the outpatient setting. A disadvantage of the study is that we did not consequently asked women if they experienced the treatment as an acceptable procedure, in the office with local anesthesia, and if they would recommend it to a friend. As reported in our previous prospective cohort study 94% of women found the bipolar endometrial ablation an acceptable procedure.[14] In the study of Clark et al. one-third of women would have preferred a general anesthesia with hindsight. We believe both treatments seem acceptable in the office, but we need to improve pain control.

Similarly, patient satisfaction after bipolar radiofrequency endometrial ablation was comparable to other studies (90-92%), as was the case for balloon endometrial ablation systems (76-77%).[11-13,31,32] A prospective cohort pilot study of the Thermablate® by Karamandis et al. showed a satisfaction rate of 93% at 12 months.[33] We must be aware that satisfaction is a subjective measure that is resulting from subjective expectations and from effectiveness, as women could potentially have been more satisfied in the knowledge that a new endometrial ablation device was used. In a blinded RCT, the effectiveness of Thermablate® will probably decrease.[11,29] Immediately before ablation, thinning of the endometrium was achieved by sharp curettage. It is plausible that this would have resulted in better scores compared to women without pretreatment.

Finally, the hysterectomy rate also was comparable to other studies (2,4-7.3%).[12,30-33]

Both second-generation ablation techniques used in the office with a paracervical block in this study are safe and easy to perform. However, based on the results of the current randomized trial, bipolar endometrial ablation appears to offer higher amenorrhea rates, patient satisfaction and quality of life.

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Chapter 8

Endometrial resection/ablation techniques for heavy menstrual bleeding

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Cochrane Database of Systematic Reviews 2013.

Abstract

Background: Heavy menstrual bleeding (HMB) is a significant health problem in premenopausal women; it can reduce their quality of life and cause anemia. First-line therapy has traditionally been medical therapy but this is frequently ineffective. On the other hand, hysterectomy is obviously 100% effective in stopping bleeding but is more costly and can cause severe complications. Endometrial ablation is less invasive and preserves the uterus, although long-term studies have found that the costs of ablative surgery approach the cost of hysterectomy due to the requirement for repeat procedures. A large number of techniques have been developed to 'ablate' (remove) the lining of the endometrium. The gold standard techniques (laser, transcervical resection of the endometrium and rollerball) require visualization of the uterus with a hysteroscope and, although safe, require skilled surgeons. A number of newer techniques have recently been developed, most of which are less time consuming. However, hysteroscopy may still be required as part of the ablative techniques and some of them must be considered to be still under development, requiring refinement and investigation.

Objectives: To compare the efficacy, safety and acceptability of methods used to destroy the endometrium to reduce HMB in premenopausal women.

Search methods: We searched MEDLINE, EMBASE, CINAHL, PsycInfo, the Cochrane Central Register of Controlled Trials and the Cochrane Menstrual Disorders and Subfertility Group Specialized Register of controlled trials (from inception to July 2012). We also searched trial registers and other sources of unpublished or grey literature, reference lists of retrieved studies, experts in the field and made contact with pharmaceutical companies that manufactured ablation devices.

Selection criteria: Randomized controlled trials comparing different endometrial ablation techniques in women with a complaint of heavy menstrual bleeding without uterine pathology were eligible. The outcomes included reduction of heavy menstrual bleeding, improvement in quality of life, operative outcomes, satisfaction with the outcome, complications and need for further surgery or hysterectomy.

Data collection and analysis: Two review authors independently selected trials for inclusion, assessed trials for risk of bias and extracted data. Attempts were made to contact authors for clarification of data in some trials. Adverse events were only assessed if they were separately measured in the included trials. Comparisons were made with individual techniques and an overall comparison between first and second generation ablation methods was also undertaken.

Main results: Twenty five trials (4040 women with sample sizes ranging from 20 to 372) were included in the review. A majority of the trials had a specified method of randomization, adequate description of dropouts and no evidence of selective reporting. Less than half had adequate allocation concealment and most were unblinded.

There was insufficient evidence to suggest superiority of a particular technique in the pairwise comparisons between individual ablation and resection methods. In the overall comparison of the newer 'blind' techniques (second generation) with the gold standard hysteroscopic ablative techniques (first generation), there was no evidence of overall differences in the improvement in HMB (12 RCTs) or patient satisfaction (11 RCTs).

Surgery was an average of 15 minutes shorter (mean difference (MD) 14.9, 95% CI 10.1 to 19.7; 9 RCTs; low quality evidence), local anesthesia was more likely to be employed (relative risk (RR) 2.8, 95% CI 1.8 to 4.4; 6 RCTs; low quality evidence) and equipment failure was more likely (RR 4.3, 95% CI 1.5 to 12.4; 3 RCTs; moderate quality evidence) with second-generation ablation. Women undergoing newer (second) ablative procedures were less likely to have fluid overload, uterine perforation, cervical lacerations and hematometra than women undergoing the more traditional type of ablation and resection techniques (RR 0.18, 95% CI 0.04 to 0.79, 4 RCTs; RR 0.32, 95% CI 0.1 to 1.0, 8 RCTs; RR 0.22, 95% CI 0.08 to 0.61, 8 RCTs and RR 0.32, 95% CI 0.12 to 0.85, 5 RCTs, all moderate quality evidence, respectively). However, women were more likely to have nausea and vomiting and uterine cramping (RR 2.0, 95% CI 1.3 to 3.0, 4 RCTs and RR 1.2, 95% CI 1.0 to 1.4, 2 RCTs, both moderate quality evidence, respectively). The risk of requiring either further surgery of any kind or hysterectomy specifically was reduced with second generation ablative methods compared to first generation

ablation up to 10 years after surgery (RR 0.69, 95% CI 0.48 to 0.99, 1 RCT and RR 0.60, 95% CI 0.38 to 0.96, 1 RCT, both moderate quality evidence, respectively), but not at earlier follow up. Additional research is required to confirm this finding.

Authors' conclusions: Endometrial ablation techniques offer a less invasive surgical alternative to hysterectomy. The rapid development of a number of new methods of endometrial destruction has made systematic comparisons between individual methods and with the 'gold standard' first generation techniques difficult. Most of the newer techniques are technically easier than traditional hysteroscopy-based methods to perform but technical difficulties with new equipment need to be ironed out. Overall, the existing evidence suggests that success and satisfaction rates and complication profiles of newer techniques of ablation compare favorably with hysteroscopic techniques.

Plain language summary

Endometrial destruction techniques for heavy menstrual bleeding using the newer global ablation techniques and more established hysteroscopic techniques.

Drugs or hysterectomy (removing the uterus) used to be the main option for women having problems with heavy menstrual bleeding. In the last few decades, surgical techniques have been developed that remove only the lining of the uterus (endometrium). These techniques involve either cutting out the endometrium (resection) or destroying it with thermal energy from a laser, electric instruments or other devices.

This review identified 25 randomized controlled trials undertaken in 4040 women. Most of the women knew which treatment they were receiving, which may have influenced their judgment about menstrual blood loss and satisfaction. Other aspects of study quality varied among the trials. The review has not found that any of these procedures is better than any other in reducing heavy menstrual bleeding and satisfaction was high with all procedures. The more modern devices (second generation ablation) took less time to perform than the older first generation devices and were more likely to be performed under local anesthesia when the woman is awake. Side effects were generally similar and mostly mild.

Background

Description of the condition

Heavy menstrual bleeding (HMB), or menorrhagia, is a significant cause of ill health in premenopausal women and can significantly affect their quality of life.[1] It is clinically defined as blood loss greater than or equal to 80 ml per menstrual cycle.[2,3] With a monthly blood loss of greater than 50 to 60 ml per cycle, most women consuming an average Western diet will develop a negative iron balance (Rybo 1966). However, it is the woman's perception of her own menstrual loss that is the key determinant in her referral and, indeed, subsequent treatment. One in 20 women in the UK aged between 30 and 49 years of age consult their general practitioner (GP) each year with HMB and the condition affects about 22% of otherwise healthy premenopausal women aged more than 35 years.[4,5] A comparable prevalence rate is likely in other Western countries. In New Zealand,

for example, it is estimated that 2.3% of GP consultations for women less than 50 years are for heavy menstrual bleeding.[6] In the majority of cases no pathology (abnormality) is found to explain HMB.[1] The causes of HMB, where there is no endometrial pathology, remain poorly understood and this has been a barrier to the development of new non-surgical therapies.

First-line therapy is usually with drugs prescribed by general practitioners; in 1993 in the UK, 345,225 women were given 821,700 medical prescriptions, which cost the UK National Health Service over £7 million, to control their heavy menstrual bleeding.[1,7] However, efficacy is variable and at best medication reduces menstrual blood loss by only 50%. The levonorgestrel-releasing intrauterine system, on the other hand, is more effective and reduces HMB by as much as 94% at three months.[8] Nevertheless, HMB accounts for 12% of all gynaecology referrals in the UK.[9] A similar rate of referral (11%) is found in New Zealand and is likely to be similar in other Western countries.[10]

Surgical treatment of HMB often follows failed or ineffective medical therapy, although it is also used as a first-line therapy. Hysterectomy has traditionally been regarded as the definitive surgical treatment for heavy menstrual bleeding but, in spite of a 100% success rate (complete cessation of menstruation) and high levels of satisfaction, it is a major surgical procedure with significant physical complications and social and economic costs.[11] These include a high rate of major and minor post-operative complications (up to 67%) and a long recovery time.[12] Almost half of the hysterectomies performed worldwide were carried out for HMB.[13] However, many women prefer less invasive surgical treatment even when they are made aware that the success of the treatment is not always assured.[14]

Description of the intervention

Endometrial destruction techniques, which aim to destroy or remove endometrial tissue, have become increasingly popular less invasive alternatives in the last two decades and, as a result, the number of hysterectomies in the United Kingdom declined by 64% between 1995 and 2002.[15] The first effective ablation of the endometrium under hysteroscopic vision for the treatment of heavy menstrual bleeding was performed using laser photovapourisation.[16] Rollerball ablation (RB) with simple and cheap electrosurgical equipment rather than expensive lasers was performed a few years later.[17,18] A method to excise rather than ablate the endometrium using an unmodified resectoscope (an instrument used for resection (excision)) was also developed and good results were reported.[19,20]

The technique transcervical resection of the endometrium (TCRE) is often used in conjunction with rollerball ablation. These methods of ablation, also termed first generation methods, were the most commonly used and were widely regarded as the gold standard for endometrial ablation.[21] They all require direct visualization by hysteroscope (an instrument for examining the uterine cavity), which may confer the additional advantage of diagnosis of polyps. Endometrial destruction techniques in use in the UK by 1995 included electrocautery (either loop or rollerball) (80%), laser (18%) and radiofrequency (a procedure using electromagnetic energy) (2%).[22]

The expectation was that these first generation ablation methods would become an alternative to hysterectomy but, at least initially, the total number of operations for HMB increased.[23] More recent figures in the UK suggest that the rate of surgery for menorrhagia (based on data from 2004 to 2006) is 143 procedures per 100,000 premenopausal women, of which approximately 60% are endometrial ablations.[24] However, analyses of recent hospital statistics in the UK suggest that first generation endometrial ablation has failed to have an impact on hysterectomy numbers.[25]

The drawbacks of these first generation ablation techniques are the expertise needed and patient morbidity. A prospective national audit of hysteroscopic endometrial ablation and resection (10,686 cases) in England and Wales between 1993 and 1994 assessed the incidence of complications and reported a total complication rate of 4.4%.[26] Endometrial ablation by laser and rollerball were significantly safer than endometrial resection; the risk of immediate haemorrhage was three times greater and the risk of uterine perforation was four times greater with resection than with ablation. These complications are thought to be avoidable with good surgical technique and adequate training. However, hysteroscopic endometrial ablation requires an operating room environment, a skilled surgeon and general or regional anaesthesia.

Subsequently, second generation non-hysteroscopic techniques have been developed, which are considered easier to perform, equally effective and safe.[27] All of these techniques, with the exception of hydrothermal ablation and endometrial laser intrauterine thermal therapy, involve performing surgery without direct visualization through a hysteroscope. They can potentially be used in outpatient settings and include cryoablation[28], hot saline solution irrigation[29], diode laser hyperthermy (heating)[30], microwave ablation[31], a heated balloon system[32] and photodynamic therapy (intrauterine light delivery)[33]. Economic modelling also

suggests that second generation techniques may be more cost effective than first generation methods.[34]

How the intervention might work

Endometrial destruction involves the removal of endometrial tissue. The endometrium has great powers of regeneration and to suppress menstruation successfully it is essential to remove the full thickness of this lining together with the superficial myometrium (wall of the uterus), including the deep basal glands. The latter are believed to be the primary foci for endometrial regrowth. This tissue may be removed under direct hysteroscopic view either by excision with an electrosurgical loop or by ablating the endometrium with some form of thermal energy of sufficient power to produce necrosis (cell death) of the full thickness of the endometrium when applied to its surface.

Why it is important to do this review

There is a wide range of available techniques for ablating and destroying the endometrium to reduce HMB and it is not clear which techniques offer the best option in terms of effectiveness and safety. The aim of this review is to assess the efficacy, safety and acceptability of all methods both by comparing individual techniques pairwise and making overall comparisons with first and second generation techniques. Other Cochrane reviews have compared endometrial ablation with hysterectomy for HMB and endometrial ablation with medical therapies.[35,36]

Objectives

To compare the effectiveness, safety and acceptability of endometrial destruction techniques for heavy menstrual bleeding.

Methods

Criteria for considering studies for this review

Types of studies

All randomized controlled comparisons of techniques for the destruction of the endometrium and comparisons of endometrial destruction techniques for the reduction of HMB.

Types of participants

Source of recruitment:

- primary care, family planning or specialist clinics.

Inclusion criteria:

- women of reproductive years with regular heavy periods measured either objectively or subjectively.

Exclusion criteria:

- postmenopausal bleeding (more than one year from the last period);
- irregular menstruation and intermenstrual bleeding;
- pathological causes of HMB (for example uterine cancer);
- iatrogenic causes of HMB (for example intrauterine coil devices).

Types of interventions

Endometrial resection and ablation techniques (TCRE, laser ablation, rollerball ablation, saline irrigation, microwave ablation, radiofrequency ablation, heated balloon, photodynamic therapy, cryoablation and any other endometrial destruction techniques) compared to each other or grouped in the broad categories of first or second generation techniques and used to reduce heavy menstrual bleeding.

Types of outcome measures

The assessment of most of the following outcomes was related to the duration of follow up after the initial surgical procedure. As the aim of endometrial resection and ablation therapies is to offer women a permanent solution to their bleeding problems, long term follow up of these treatments is needed to enable informed decision making between surgical options. Thus, for the following outcomes, evaluation at different time points is considered important to assess effects over

time: six months, 12 months, two years, two to five years and more than five years. Where trials measured outcomes at two different follow up times within the categories (e.g. at three and five years), the longer follow up time only was recorded in the category, two to five years.

Primary outcomes

1. Menstrual bleeding:
    - an objective assessment of improvement in menstrual blood loss (measured by the modified alkaline hematin method: modified by Newton 1977 from the original technique of Hallberg 1964);[37,38]
    - a semi-objective or subjective assessment of improvement in menstrual blood loss (measured by the pictorial chart method (PBAC) or women's perception of improvement).[39]

2. Rate of satisfaction with the outcome of the procedure (this outcome was moved from the position as secondary outcome to primary outcome in the 2009 update)

Secondary outcomes

1. Operative outcomes:
    a. Duration of surgery (min's)
    b. Operative difficulties (such as difficulty of surgery, technical complications, abandoning procedure)
    c. Proportion having local rather than general anaesthesia.
2. Recovery:
    a. Length of hospital stay.
    b. Time or ability to return to normal activities or work.
3. Quality of life:
    Women's perceived change in quality of life where this has been recorded in a reproducible and validated format.
4. Improvement in menstrual symptoms, such as premenstrual syndrome (PMS) and dysmenorrhea.
5. Complication rate, the frequency of specific adverse events both before and after discharge from hospital.
6. Requirement for further surgery for menstrual symptoms (by duration of follow-up)
7. Mortality as a direct result of surgery.

Search methods for identification of studies

Electronic searches

The Menstrual Disorders and Subfertility Group Trials Search Coordinator searched the following electronic databases from inception to 7 July 2012: MEDLINE, EMBASE, CINAHL, PsycInfo, the Cochrane Central Register of Controlled Trials and the MDSG Specialised Register of Controlled Trials.

The MEDLINE search was combined with Cochrane highly sensitive search strategy for identifying randomized trials, which appears in the searching chapter of The Cochrane Handbook of Systematic Reviews of Interventions.[40]

The EMBASE search was combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2008).

For the other database searches, filters were modified from those used for the MEDLINE and EMBASE searches.

The principal author of the review (AL) searched other electronic sources (trial registers and web sites) to identify additional studies. These sources were:

- Trial registers for ongoing and registered trials - 'Current Controlled Trials' (http://www.controlled-trials.com/), 'ClinicalTrials.gov'
- a service of the US National Institutes of Health (http://clinicaltrials.gov/ct2/home) and 'The World Health Organisation International Trials Registry Platform search portal' (http://www.who.int/trialsearch/Default.aspx)
- Citation indexes – (http://scientific.thomson.com/products/sci/)
- Conference abstracts in the ISI Web of Knowledge (http://isiwebofknowledge.com/)
- LILACS database, as a source of trials from the Portuguese and Spanish speaking world (http://bases.bireme.br/cgi- bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F)
- ClinicalStudyResults for clinical trial results of marketed pharmaceuticals (http://www.clinicalstudyresults.org/)
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) - the random control filter for PubMed will be taken from the searching chapter of The Cochrane Handbook of Systematic Reviews of Interventions
- OpenSIGLE database(http://opensigle.inist.fr/) and Google for grey literature

Searching other resources

The reference lists of articles retrieved by the search were hand searched. Some of the newer second generation techniques are undergoing development and rigorous testing. Expert researchers in the field and companies that manufacture the newer devices were contacted to try and locate ongoing trials and unpublished data. Two experts in the field were contacted about ongoing research on endometrial ablation techniques: Dr David Parkin (Aberdeen Royal Infirmary, UK) and Dr Jed Hawe (South Cleveland Hospital, UK). A number of ongoing trials were described but insufficient details were provided to enable the review authors to initiate contact. Novasure, a company that manufactures the bipolar device Novacept, was also contacted but no reply was received. No new trials were identified from these methods.

Data collection and analysis

Data collection and analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[40]

Selection of studies

One review author (AL) screened the abstracts of all publications which were obtained by the search strategy for eligible RCTs; for the 2009 and 2012 updates, this process was undertaken by two reviewers (either AL and JB or AL and JP). Where the screened abstract was a potential RCT, the full article was obtained and inspected to assess its relevance to this review based on the criteria for inclusion. Uncertainty over eligibility was clarified by discussion between AL and either MH, JB or JP. Disagreements as to study eligibility were resolved by consensus and it was not necessary to involve a third author to arbitrate over selection

Data extraction and management

Data extraction

Data extraction was performed independently by the two review authors (AL and either MH or JP), using forms designed according to Cochrane guidelines.
The following details were collected:

Trial characteristics:
1. method of randomization;
2. presence or absence of blinding to treatment allocation;
3. quality of allocation concealment;

4. number of women randomized, excluded or lost to follow up;
5. whether an intention-to-treat analysis was done;
6. whether a power calculation was done;
7. duration, timing and location of the study;
8. source of funding.

Characteristics of the study participants:
1. age and any other recorded characteristics of women in the study;
2. other inclusion criteria;
3. exclusion criteria.

Interventions used:
1. type of endometrial destruction technique.

Outcomes:
1. methods used to measure menstrual blood loss;
2. methods used to evaluate participant satisfaction, change in quality of life and menstrual symptoms.

Data management
Additional information on trial methodology and trial results was sought from the corresponding authors of some trials which appeared to meet the eligibility criteria. This was when aspects of methodology were unclear or where the data were in a form unsuitable for meta-analysis. Authors of the following trials provided extra information: Abbott 2003; Soysal 2001; Gynecare (pharmaceutical company providing funding for Boujida 2002; Meyer 1998; Perino 2004; van Zon-Rabelink2003).[41-46] One of the authors (JP) provided additional information for Penninx 2010.[47]

Assessment of risk of bias in included studies
Two independent reviewers (AL and JP) assessed risk of bias of each study, using the risk of bias tool developed by the Cochrane Collaboration.[40] The following domains were assessed:
1) sequence generation (whether the allocation sequence was adequately generated, for example, random number table, computer random number generator, coin tossing, throwing dice)

2) allocation concealment (whether the allocation was adequately concealed, for example, sequentially numbered containers of identical appearance, central allocation, sequentially numbered, opaque sealed envelopes)
3) blinding of participants, personnel and outcome assessors (whether knowledge of the allocated intervention was adequately prevented during the study, for example, by ensuring blinding or participants and key personnel or, where there is no blinding, knowledge of the intervention is not likely to influence the outcomes)
4) incomplete outcome data (whether incomplete outcome data were adequately addressed, for example, missing data balanced in numbers across intervention groups, proportion of missing outcomes insufficient to affect estimates, reasons for missing data unlikely to be related to the outcomes)
5) selective outcome reporting (whether the reports of the study were free of suggestion of selective outcome reporting, for example, previous publication of a study protocol, other evidence that the study contains all of the prespecified outcomes)
6) other sources of bias (whether the study was apparently free of other problems that could put it at a high risk of bias, e.g. baseline imbalance, bias related to study design, early termination of study).

These domains were scored as either:

- Criterion met, i.e. low risk of bias
- Unclear, i.e. uncertain risk of bias
- Criterion not met, i.e. high risk of bias

Measures of treatment effect

Almost all of the outcomes were measured by either dichotomous or continuous data. Two authors extracted data to enable calculation of relative risks (RRs) for dichotomous data and mean differences (MDs) for continuous data, together with 95% confidence intervals (CIs). Some outcomes, such as satisfaction with treatment, were measured by ordinal data. These data were dichotomised to represent satisfaction (highly satisfied and satisfied combined) vs no satisfaction (doubtful or dissatisfied) with surgery by collapsing categories. Continuous data were inspected for evidence of skew, where possible, according to guidance in the Cochrane Handbook, by calculating the observed mean minus the lowest (or highest) possible value divided by the standard deviation.

Assessment of heterogeneity

Differences between studies in terms of methodological factors and variations between participants, interventions and outcomes were analysed to determine whether it was appropriate to combine the studies in meta-analysis. If they were sufficiently homogeneous to consider pooling, statistical heterogeneity between the results of different studies were examined by inspecting the scatter in the data points on the graphs, the overlap in their confidence intervals and, more formally, by checking the results of the chi squared tests (with P value <0.1 considered evidence of significant heterogeneity) and the I squared quantity. The I squared quantity is a measure of the consistency between trials in a meta-analysis.[40] As a general rule, I squared values of up to 25% are evidence of low heterogeneity, values from 25% to 50% are considered moderate heterogeneity and 75% or above is considered substantial heterogeneity.

Assessment of reporting biases

A comprehensive search was undertaken, along with careful inspection of the search results to identify duplicates, in order to reduce the risk of reporting bias. If sufficient trials were identified, it was planned to investigate publication bias by undertaking funnel plots of study results.

Data synthesis

Where there was no evidence of clinical heterogeneity between the studies and no evidence of major skew in the data, the outcomes were pooled statistically in a meta-analysis using RevMan software. Relative risks and 95% CIs were combined for meta-analysis using the Peto-modified Mantel-Haenszel method. For some dichotomous outcomes (for example, the proportion of participants requiring further surgery), a higher proportion represented a negative consequence of that treatment and for other outcomes (for example proportion with improvement in menstrual blood loss), a higher proportion was considered a benefit of treatment. This discrepancy between the categorizing of outcomes should be noted when the summary graphs for the meta-analysis are viewed for the assessment of the benefits as opposed to the harms of treatment. Thus, for some of the dichotomous outcomes a treatment benefit is displayed as RR and CIs to the left of the centre line while for others a treatment benefit is displayed to the right of the centre line. The forest plot for each outcome is labeled clearly for clarification.

Mean differences and 95% CIs were combined for meta-analysis using the

inverse variance method. For all continuous outcomes in this review, a high value represents a negative consequence of treatment, for example duration of surgery, amount of fluid deficit (difference between input and output fluid during surgery), pictorial menstrual blood loss assessment chart (PBAC) score. Thus, in the evaluation of the summary graphs means and confidence intervals to the left are considered a benefit of the experimental or comparative treatment.

A fixed effect approach was used to calculate summary effect measures. Where there was substantial statistical heterogeneity, results from the fixed effects model were compared with those from a random effects model to determine whether results were altered substantially by choice of model. A priori, it was expected that two of the outcomes, regardless of comparison, duration of surgery and proportion having local instead of general anaesthesia, would have heterogeneous results. For these comparisons a random effects model was initially used. For all overall comparisons where first generation methods were compared with second generation methods, a random effects model was used because of the expected clinical heterogeneity between trials.

Where there was evidence of skewed data in the measurement of outcomes (for example, summary trial results were expressed as a median and range), the data for these outcomes were not pooled in the meta-analysis but included in table format.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned for different times of follow up after surgery, in particular for amenorrhea rates, satisfaction and requirement for additional surgery. These outcomes were collected at six months, one, two, two to five years and greater than five years after surgery.

Sensitivity analysis

A priori, it was intended that sensitivity analysis would be performed to test the robustness of pooled results in the meta- analysis based on:

(1) trials with good methodology (evidence of adequate allocation concealment and intention-to-treat analysis) versus all included trials;
(2) trials with and without power calculations for sample size;
(3) trials with participants who had confirmed objective heavy menstrual blood loss (more than 80 ml per cycle) versus all included trials;
(4) trials with participants who had initially failed medical treatment for HMB versus all included trials.

For most comparisons there was an insufficient number of included studies to be able to perform any of these sensitivity analyses.

Overall quality of the body of evidence

A summary of findings table for the overall outcome of first generation versus second generation ablation techniques was generated using GRADEPRO software (Summary of findings, Table 1). This table evaluates the overall quality of the body of evidence for each of the main review outcomes, using GRADE criteria (study limitations (ie. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about the evidence quality (high, moderate, low or very low) have been documented and incorporated into the reporting of results for each outcome.

Results

Description of studies

Results of the search

2005 update: Twenty three studies were considered potentially eligible to be included in the review in the 2005 update and full copies of the papers retrieved for closer inspection. One study was excluded because it compared two types of balloon ablation, Menotreat and Cavaterm.[48] Three other studies were later publications of trials that were already included in the review.[44,49,50] Thus, 19 studies, some of which had a number of different publications describing longer follow up or different outcomes, met the inclusion criteria of the review for the 2005 update.

2009 update: A further six potential studies were considered potentially eligible for the 2009 update and full copies of the papers retrieved for closer inspection. One conference abstract and one Chinese trial are waiting assessment because it is unclear whether the two comparative groups were randomised. Of the remaining four studies, two were later publications of trials already included in the review. One of these studies was a five year follow up of a trial comparing bipolar radiofrequency ablation to balloon ablation and the other was 10 year follow up of a trial comparing TCRE with rollerball ablation.[43,51] Two new RCTs (21 studies overall) were eligible for the 2009 update.[52,53]

2012 update: An additional seven studies were considered potentially eligible for the 2012 update and full copies of the papers were retrieved for closer

inspection. Two were excluded; one because it compared different wave forms for rollerball ablation (Chang 2009) and the other because it was not randomized (El-Nashar 2009). One other trial was a 10 year follow up, comparing long term outcomes, of a study already included in the review.[49] Four new trials, one of which had two publications were included in the 2012 update.[47,54-56]

Thus, 25 studies (4040 women, with sample sizes ranging from 20 to 372) were eligible for the review. Full details of the studies can be found in the corresponding article at the Cochrane library.

Study design

All of the trials had a parallel group design. Six large trials were multicentre, each with 200 to 300 participants and one smaller multicentre trial had 62 participants. Eighteen of the trials were single-centre studies (one each from Germany, Australia, Egypt and Denmark; two from Turkey; three from the Netherlands and Italy; and six from the UK). Six of the seven multicentre trials were based in the USA, with three having additional centers in Canada, UK or Australia and one multicentre trial had 6 centres all based in France.

Few of the studies had strict intention to treat analyses or specified methods to deal with missing data. Twelve trials did not report an intention-to-treat (ITT) analysis. Seven trials claimed that ITT analysis was performed but over time a percentage of participants was lost to follow up so the claim of ITT was misleading. However, ITT analysis was usually performed when assessing outcomes such as complication rates in these studies. Four trials had true ITT analysis and one trial had no reported dropouts. One other trial did not report ITT analysis and replaced dropouts with new cases. Seventeen trials reported either pharmaceutical or medical equipment company partial or complete funding or had authors with a conflict of interest.

Participants

The 25 included studies contained 4056 premenopausal participants, mostly within the age range 30 to 50 years. In all of the studies women, with a complaint of heavy menstrual bleeding were recruited from secondary or tertiary referral centres or clinics.

Presence of fibroids was an exclusion criterion in twelve studies and all trials required that the uterine cavity be normal in size with no uterine pathology. One trial required women to have myoma-induced menorrhagia but excluded women with submucous fibroids greater than 3 cm or less than 50% intramural extension.[42]

One other trial excluded only submucous fibroids and one trial excluded both submucous fibroids and extra cavity fibroids >3 cm.[52,54] In one trial, 637 women with self-assessed HMB were screened but, after the application of exclusion criteria, less than half (n = 276) were enrolled and randomized.[57] Almost half of the excluded women had uterine pathology in the form of fibroids or polyps.

Nineteen trials required women to have completed their families and fourteen trials included women who previously had not tolerated or had had ineffective medical therapy for their heavy bleeding. Twelve trials objectively confirmed the women's complaint of excessive bleeding by requiring them to record their blood loss. This was prior to surgery and before entry into the trial. Nine trials required women to have pictorial blood loss chart measurements of 150 or greater prior to entry, two trials required women to have PBAC measurements of 100 or greater prior to entry, one trial required a blood loss score of more than 185 and one trial included women only if their blood loss exceeded 70 ml per cycle (as measured by the alkaline haematin method.[38,39] All but one trial had comparable demographic characteristics between comparison groups at baseline; in the Brun trial women undergoing balloon ablation had significantly more heavy blood loss than those undergoing TCRE.[52]

Interventions

Most of the studies (particularly, first generation techniques) had some kind of pretreatment prior to surgery. In thirteen of the trials, participants had preoperative GnRH (gonadotropin-releasing hormone) analogues to prepare and thin the endometrium prior to surgery, although in one of these studies pretreatment was given only to the TCRE group and not to the balloon group. Three months, 14 or 7 days of preoperative treatment with progestogens was also used in three trials. One trial required two months of oral contraceptive therapy prior to surgery to ensure that women were scheduled at a similar time in their cycle. One trial required a dilation and curettage procedure prior to ablation surgery. Four other trials used NSAIDs (non-steroidal anti-inflammatory drugs) to prevent uterine cramping. The remaining three trials had no preoperative therapy.

Five trials compared first generation ablation methods: two compared laser ablation with TCRE (one argon laser, the other Nd:YAG (neodymium yttrium aluminium garnet)), one compared a vaporising electrode procedure with TCRE, and two compared rollerball with TCRE. All of the TCRE comparison groups also had rollerball ablation to treat the uterine cornua (a horn-like area in the uterus)

and fundus (body of the uterus). It was claimed that the vaporising electrode (unlike rollerball) could be used to treat submucous fibroids. Another fourteen trials compared second generation methods with first generation methods: four compared balloon ablation (three with Thermachoice, one with Cavaterm) with rollerball, one compared the Vesta system with rollerball, two compared microwave ablation with TCRE and rollerball, one compared heated saline (Hydro Thermablator) with rollerball, one compared cryoablation with rollerball, one compared thermal laser with TCRE, two compared electrode ablation with TCRE plus rollerball, one compared balloon (Cavaterm) with laser (Nd:YAG), and two compared balloon (Cavaterm) with TCRE plus rollerball. Five trials compared second generation techniques: bipolar electrode ablation (Novasure) with either balloon or hydrotherm ablation or microwave compared with balloon ablation. All of the first generation techniques (laser, rollerball, vaporising electrode and transcervical resection), which use the hysteroscope, were then combined and compared with all the second generation techniques (balloon, microwave, Vesta system, cryoablation, thermal laser, bipolar electrode ablation and hydrothermal ablation), which are blind techniques. An additional trial compared overcurettage with ablative curettage.[56]

Outcomes

Most of the trials assessed amenorrhea (some included 'light' or 'normal' bleeding), satisfaction rates and frequency of complications. Eighteen trials compared the duration of surgery; nineteen trials compared menstrual blood scores on the PBAC chart or success of treatment; twelve assessed the frequency of any additional surgery after treatment; fifteen trials compared hysterectomy rates after treatment; thirteen trials assessed quality of life measures such as SF36, improvement in dysmenorrhea or PMS symptoms; and a few trials measured ability to work, difficulty of surgery, rate of acceptability, degree of fluid deficit and duration of hospital stay. The types of anaesthesia used ('local' versus 'general') were compared between first and second generation techniques.

One trial assessed outcomes only after six months follow up. Eight trials assessed outcomes one year after surgery. Six trials assessed outcomes at both six-months and one-year follow up. Three trials assessed outcomes at both one and two years follow up and the remaining trials had longer term follow up: at either 3, 5 or 10 years follow up. Two trials did not specify the time at which postoperative outcomes were assessed.

Risk of bias in included studies

The risk of bias in the included studies is summarized in Figure 1 and Table 1.

Allocation (selection bias)

Sixteen studies had adequate randomization methods, either computer generated or lists of random numbers. In four studies, no details were provided on the randomization method. One study gave details of an inadequate randomization method; participants were allocated to treatment in the order in which they came into clinic.[53] Ten studies provided evidence of adequate allocation concealment, either sequentially numbered opaque envelopes or central method for allocation to groups. Ten studies did not provide any details as to whether allocation was concealed and the remaining study was scored as having no concealment.

Blinding (performance bias and detection bias)

In most of the trials, blinding was either specifically denied or not reported; for all these trials, blinding was unlikely due to the nature of the interventions. Two trials that compared second generation techniques (bipolar radiofrequency vs balloon)[41,51] and one other comparing balloon with laser[58] had triple blinding (patients, investigators and assessors), and three other second generation trials had double blinding (patients and assessors) (although in the Clark trial, women were likely to have guessed allocation).[47,54,55]

Incomplete outcome data (attrition bias)

Eight trials did not report any dropouts after treatment (five of these had dropouts ranging from 1% to 4% after randomization and before treatment). The remaining trials had dropout rates ranging from 3% to 18% after one-year follow up, from 9% to 17% after two-years follow up, from 2% to 16% after 5 years follow up and from 6% to 28% after 10 years follow up. In one of these trials, with a 9% dropout rate, one arm of the trial (the hydro thermoblator (HTA) group) had a higher dropout rate than the other arm, due to equipment failure.[50] In another trial, 18% of the study population were excluded from the study after randomization and before treatment in unequal numbers per group, making randomization unbalanced.[52]

In assessments regarding incomplete outcome data, sixteen trials were scored as having adequately addressed their missing data (if any), either because there were no reported dropouts, missing data was balanced between groups or there

was minimal loss to follow up that was unlikely to affect the calculation of estimates. For five studies, it was unclear whether their missing data could cause bias and for three studies, missing data was highly likely to bias the estimates, two because of substantial loss to follow up and the other because there were imbalances in the loss of missing data between groups. One other trial had dropouts which were replaced by other cases, which is likely to also cause major bias.[56]

Selective reporting (reporting bias)

There were insufficient trials identified to undertake funnel plot analysis for publication bias or small study bias. Most trials were scored as at low risk of reporting bias as a result of selective reporting of outcomes. In these trials, all prespecified outcomes were reported in the results sections.

Other potential sources of bias

Most studies had no evidence of any other potential source of bias. Three studies had potential sources of bias; one recruited participants over two different time periods and comparison of the two groups indicated substantial differences, one study used denominators for the outcomes that did not correspond to the denominators originally specified and in another study, the numbers in the 2 randomized groups differed substantially with no explanation given.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abbott 2003	+	+	+	+	+	+	?
Clark 2011	+	+	-	-	-	+	?
Bongers 2004	+	+	+	+	+	?	?
Boujida 2002	+	+	-	-	+	+	+
Brun 2006	+	+	-	-	-	+	-
Clark 2011	+	+	?	?	-	+	+
Cooper 1999	+	+	-	-	+	+	?
Cooper 2002	+	?	-	-	?	+	?
Cooper 2004	+	?	-	-	+	+	?
Corson 2000	+	+	-	-	?	+	?
Corson 2001	+	?	-	-	?	+	?
Duleba 2003	?	?	-	-	?	+	?
Hawe 2003	+	+	+	+	+	+	?
McClure 1992	?	?	-	-	+	+	+
Meyer 1998	+	?	-	-	+	+	?
Onuglu 2007	-	-	-	-	+	-	+
Pellicano 2002	+	?	-	-	?	+	?
Penninx 2010	+	+	?	+	+	?	+
Perino 2004	+	?	-	-	+	+	+
Romer 1998	?	?	-	-	+	?	+
Sambrook 2009b	+	+	?	+	+	+	+
Soysal 2001	+	+	-	-	+	+	?
Thabet 2010	?	?	-	-	-	+	?

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality for each included study

Table 1. Summary of findings

Second generation compared to first generation endometrial ablation for heavy menstrual bleeding

Patient or population:patients with heavy menstrual bleeding
Settings: **Intervention:** second generation endometrial ablation
Comparison: first generation endometrial ablation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	First generation	Second generation			
Amenorrhoea rate-At 1 year follow up usually by questionnaire	**376 per 1000**	**353 per 1000** (278 to 451)	**RR 0.94** (0.74 to 1.2)	2085 (12 studies)	+ **very low[1,2]**
Satisfaction rate – At 1 year follow up patient questionnaire	**884 per 1000**	**884 per 1000** (858 to 902)	**RR 1** (0.97 to 1.02)	1690 (11 studies)	+++ **moderate[3]**
Success of treatment (PBAC < 75 or acceptable improvement)-At 12 months follow up	**808 per 1000**	**824 per 1000** (783 to 872)	**RR 1.02** (0.97 to 1.08)	1375 (6 studies)	++++ **high**
Duration of operation (mins) Measured in various ways by clinicians		Mean duration in intervention groups **14.86 lower** (19.68 to 10.05 lower)		1762 (9 studies)	++ **low[4]**
Proportion having local aneaesthesia (%)	**208 per 1000**	**578 per 1000** (366 to 915)	**RR 2.78** (1.76 to 4.4)	1434 (6 studies)	++ **low[5]**
Operative or postoperative complicartion rate-perforation	**13 per 1000**	**4 per 1000** (1 to 13)	**RR 0.32** (0.1 to 1.01)	1885 (8 studies)	+++ **moderate[6]**
Requirement for any additional surgery-> 5 years follow up	**381 per 1000**	**263 per 1000** (183 to 377)	**RR 0.69** (0.48 to 0.99)	263 (1 study)	+++ **moderate[7]**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval, **RR:**Risk ratio. PBAC:Pictorial Blood Assessment Chart
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes
[1] Substantial heterogeneity (I square=74%) that could not be explained.
[2] Most studies had relatively small sample sizes and effects had wide confidence intervals
[3] As most trials were unblended, participant knowledge of the treatment they received could bias their assessments of satisfaction
[4] Substantial heterogeneity (I square=97%) that is likely to be due to different methods of measuring the time taken in surgery, differing expertise of surgeons, and numerous other factors
[5] Subtantial heterogeneity (I square=85%) which is likely to be explained by different methods being pooled under the general headings of first and second generation ablation
[6] Few events and wide confidence intervals
[7] Based on only one trial using specific types of first and second generation ablative devices

Effects of interventions

First generation technique comparisons

1. Laser versus transcervical resection of the endometrium (TCRE) (Comparison 1):
   PRIMARY OUTCOMES: There was no evidence of significant differences between groups in the primary outcomes measured: amenorrhea rate, combined amenorrhea/hypomenorrhoea rate, menstrual blood loss at six months or satisfaction at 12 months.
   SECONDARY OUTCOMES: Duration of laser surgery was an average of nine minutes longer than for TCRE (mean difference (MD) 9.15, 95% CI 7.2 to 11.1). The risk of equipment failure and fluid overload were also greater among women who had laser ablation when compared with TCRE (risk ratio (RR) 5.5, 95% CI 1.7 to 18.6; RR 4.9, 95% CI 1.4 to 16.6, respectively). There was no evidence of significant differences between laser ablation and TCRE for the other secondary outcomes: other types of operative difficulties, improvement in symptoms, improvement in dysmenorrhea, requirement for further surgical treatment, other complications and general health after treatment.

2. Vaporising electrode ablation versus TCRE (Comparison 2):
   PRIMARY OUTCOMES: There was no evidence of significant differences between TCRE and vaporising electrode ablation for measurement of bleeding or satisfaction: amenorrhea or hypomenorrhoea (scanty menstruation) rate, pictorial chart method (PBAC) score at 12 months and satisfaction with treatment.
   SECONDARY OUTCOMES: The odds of 'difficult' surgery (assessed subjectively into three categories by surgeons) were less likely with vaporising electrode ablation when compared with TCRE (RR 0.29, 95% CI 0.10 to 0.82). The amount of fluid deficit was greater (MD 258 ml, 95% CI 173.9 to 342.1) and the duration of surgery longer (MD =1.5 min, 95% CI 0.35 to 2.65) in the TCRE group when compared with vaporising electrode ablation.

3. Rollerball versus TCRE (Comparison 3):
   PRIMARY OUTCOMES: There were no primary outcomes measured in the included studies. SECONDARY OUTCOMES: There was no evidence of significant differences between these two first generation ablation methods, rollerball and TCRE, in the proportion requiring either hysterectomy or any surgical

intervention after two, five and ten years follow up or in the complication rates measured (fluid deficit ad perforation). Non-parametric analysis confirmed that the duration of surgery was significantly shorter with rollerball than with TCRE in one trial (median 13 minutes with rollerball versus 20 minutes with TCRE, P value < 0.05) but this was not confirmed by another small trial that assessed mean difference between groups.

Second generation first generation technique comparisons

4. Thermal laser versus TCRE (Comparison 4):
   PRIMARY OUTCOMES: The odds of amenorrhea at one and three years after surgery was significantly greater for women in the thermal laser group when compared with women in the TCRE group (RR 2.5, 95% CI 1.5 to 4.0; OR 2.5, 95% CI 1.5 to 4.2, respectively) in one study with 111 participants. There was no evidence of statistical differences in the satisfaction rates between groups.
   SECONDARY OUTCOMES: Mean length of surgery was an average of nine minutes shorter for women in the thermal laser group when compared with women in the TCRE group (MD 9.3, 95% CI 11.4 to 7.2). However, women appeared to experience more pain with thermal laser treatment (MD 0.7 units on pain scale, 95% CI 0.02 to 1.4), which just reached significance (P value 0.05). There was no evidence of differences in the requirement for more surgical intervention or complication rates (urinary tract infection) between the groups.

5. Hydro thermoblator (HTA) versus rollerball (Comparison 5):
   PRIMARY OUTCOMES: There was no evidence of significant differences between groups in amenorrhea rate, other menstrual loss outcomes or success of treatment.
   SECONDARY OUTCOMES: The chance of having local rather than general anaesthesia was increased twofold for women having HTA ablation (RR 2.0, 95% CI 1.3 to 3.1). Women in the HTA group were also less likely to experience the adverse event of hematometra (haemorrhage in the uterus) from surgery (RR 0.18, 95% CI 0.04 to 0.93) but more likely to experience abdominal pain (RR 1.4, 95% CI 1.0 to 1.9) and nausea and vomiting after surgery (OR 3.1, 95% CI 1.4 to 7.0). There was no evidence of significant differences between groups for the other outcomes: need for further surgery and other operative adverse events.

6. Cryoablation versus rollerball (Comparison 6):
   PRIMARY OUTCOMES: Women having cryoablation were less likely to have amenorrhea one year after surgery than women having rollerball treatment (OR 0.5, 95% CI 0.36 to 0.69). There was no evidence of significant differences between groups for satisfaction with treatment at one or two years follow up.
   SECONDARY OUTCOMES: Women having cryoablation were more likely to have local rather than general anaesthesia when compared with women having rollerball ablation (RR 6.6, 95% CI 3.2 to 13.6). There was no evidence of significant differences between groups for the other secondary outcomes measured: requirement for further surgery or hysterectomy alone two years after ablation treatment and rates of intraoperative complications.

7. Electrode ablation (balloon or mesh) versus TCRE (Comparison 7):
   PRIMARY OUTCOMES: There was no evidence of significant differences between groups for any of the primary outcomes measured: amenorrhea rate, PBAC score <75, PBAC score or satisfaction rate.
   SECONDARY OUTCOMES: The duration of the procedure was significantly longer for women having TCRE compared with VESTA or Novasure (MD 18.7 mins, 95% CI 16.8 to 20.7). Women undergoing electrode ablation were also more likely to have local rather than general anaesthesia than women having TCRE (RR 3.9, 95% CI 2.9 to 5.0). Perforation and cervical tears or lacerations were less likely with electrode ablation than with TCRE (RR 0.13, 95% CI 0.02 to 1.0; RR 0.11, 95% CI 0.01 to 0.9). There was no evidence of significant differences between groups for the other secondary outcomes compared: other complication rates or requirement to have hysterectomy after two years follow up.

8. Microwave versus TCRE plus rollerball (Comparison 8):
   PRIMARY OUTCOMES: There was no evidence of significant difference between groups in the primary outcomes measuring menstrual blood loss: amenorrhea rate or success of treatment, measured by PBAC < 75, or the rates of satisfaction one or up to 10 years after surgery. However, with the follow up at two years, there was a significant benefit for microwave ablation in terms of satisfaction with treatment when compared with TCRE (RR 1.2, 95% CI 1.0 to 1.4) and this benefit was maintained at five years (RR 1.2, 95% CI 1.0 to 1.4) but not at longer follow up in the same trial.
   SECONDARY OUTCOMES: In one study, the duration of the procedure was

significantly shorter with microwave when compared with TCRE (MD -3.6 mins, 95% CI -5.7 to -1.4). In one study, the risk of equipment failure was higher in the microwave group when compared with the TCRE group (RR 3.8, 95% CI 1.1 to 13.3). Vomiting and uterine cramping were more likely with microwave treatment than with TCRE (RR 3.6, 95% CI 1.3 to 10.0: RR 1.2, 95% CI 1.0 to 1.4, respectively). Patients undergoing microwave ablation were more likely to have local anaesthesia than those undergoing TCRE (RR 2.5, 95% CI 1.7 to 3.7). At 10 year follow up, the risk of further surgery or hysterectomy was marginally reduced with microwave ablation (any surgery: RR 0.7, 95% CI 0.5 to 1.0; hysterectomy: RR 0.6, 95% CI 0.4 to 1.0). For all other secondary outcomes, there was no evidence of significant differences between groups: rate of other complications, abandoning the procedure, postoperative analgesia, improvement in dysmenorrhea, change in change in most SF 36 scores (Short Form 36 scale, a generic measure of subjective health), duration of hospital stay, requirement for further surgery at other time points, inability to work, or improvement in symptoms.

9. Balloon versus rollerball (Comparison 9:)
   PRIMARY OUTCOMES: Amenorrhea was less likely after balloon ablation than after rollerball ablation at one year follow up (RR 0.63, 95% CI 0.41 to 0.97; three studies) but there were no significant differences between groups two and up to five years after treatment, although a strong trend was shown in favor of rollerball ablation. There was no evidence of significant differences between groups for the other outcomes assessing menstrual blood loss: satisfaction, rate of amenorrhea and hypomenorrhoea combined, success of treatment and PBAC score at one year, although one trial found a significantly lower PBAC score at two years in women having balloon ablation which was not confirmed by other trials assessing PBAC score at one year.
   SECONDARY OUTCOMES: The mean difference between duration of surgery for women in the balloon group and women in the rollerball group was 21 minutes (MD -20.9, 95% CI -19.3 to -22.5; three studies). There was no evidence of significant differences between groups for the other secondary outcomes compared: complication rates, inability to work, improvement in dysmenorrhea or premenstrual syndrome (PMS), technical complication rate or requirement for further surgery or hysterectomy.

10. Balloon versus laser (Comparison 10):
    PRIMARY OUTCOMES: There was no evidence of statistical differences in the amenorrhea or satisfaction rates or in the PBAC score after treatment between groups.
    SECONDARY OUTCOMES: Most outcomes were not significantly different between treatment groups. However, women having balloon treatment had a significantly greater pain score than women in the laser group (MD 32.7, 95% CI 23.7 to 41.7; one study). At 12 months after treatment, women in the balloon group had higher scores on the Euroquol 5D VAS than women in the laser group (MD 10.1, 95% CI 2.4 to 17.8; one study), which was not found at earlier follow up or for other quality of life scores.

11. Balloon versus TCRE (Comparison 11):
    PRIMARY OUTCOMES: There was no evidence of a difference in amenorrhea rates at 6 and 12 months follow up after surgery between groups. Satisfaction with treatment was greater in the balloon group than in the TCRE group two years after surgery (RR 1.4, 95% CI 1.1 to 1.7; one study) but this difference was not found 6 months or one year after surgery.
    SECONDARY OUTCOMES: Duration of surgery was significantly shorter (35%) with balloon than with TCRE treatment in one trial (MD 13 min, 10.8 to 15.2) but this finding was not confirmed by another trial which could not be pooled in the forest plot.[52] Mean intraoperative blood loss (measured in ml) was significantly less for balloon treatment compared to laser treatment in one small trial (MD -81.8, 95% CI -70.3 to -93.3). Postoperative pain (as measured by a continuous VAS scale) was significantly higher for women in the TCRE group than for women in the balloon group in one small trial (MD 0.6 points, 95% CI 0.3 to 0.9) which was confirmed by another trial that could not be included in the forest plot.[52] Recovery, as measured by stay in hospital and return to normal activities, was faster for women in the balloon group than for those in the TCRE group in one small trial (MD 0.3 of a day, 95% CI 0.1 to 0.5; MD 2.1 days, 95% CI 0.8 to 3.4, respectively); another trial which could not be included in the forest plot confirmed the finding that balloon surgery was associated with a shorter hospital stay but there was no evidence of a difference in return to normal activities in this trial.[52] There was no evidence of differences between groups for the other secondary outcomes: other complication rates, equipment failure or requirement for further surgery.

2nd generation ablation comparisons

12. Bipolar electrode ablation versus balloon (Comparison 12):
    PRIMARY OUTCOMES: Amenorrhea was more likely for women in the electrode ablation group than those in the balloon group both at six months and 12 months after treatment (RR 4.4, 95% CI 2.0 to 9.7, two studies and RR 3.8, 95% CI 2.1 to 6.9, two studies); at five years follow up, a small trial did not find significant differences between treatment groups in amenorrhea rates but a non-significant trend favored bipolar ablation. One trial at 12 months follow up did not find a difference in the PBAC score after treatment between groups. There was no evidence of significant differences between groups in rates of satisfaction after treatment, although a trend at 12 months follow up favored bipolar ablation.
    SECONDARY OUTCOMES: Duration of procedure time was from 5 minutes to 19 minutes shorter with bipolar ablation when compared with balloon ablation in three trials (two of which recorded significant differences). For most of the quality of life scores, there was no evidence of significant differences between groups. However, women having balloon ablation had significantly higher scores on the SF35 emotional role domain than women having bipolar ablation five years after their treatment (MD -9.0 points, 95% CI -3.6 to -14.5), but not at other follow up times. Results were inconsistent for rates of dysmenorrhea and PMS: two trials found no evidence of a difference in dysmenorrhea rates between groups and one trial found no evidence of a difference in premenstrual syndrome symptoms. However, another trial found that bipolar ablation was associated with improved dysmenorrhea and PMS symptoms (summary figures not provided). There was no evidence of significant differences between groups for the other secondary outcomes: technical complication rate or requirement for further surgery.

13. Microwave ablation versus balloon ablation (Comparison 13):
    PRIMARY OUTCOMES: Amenorrhea rates were significantly higher with microwave ablation than balloon ablation at 6 months follow up (RR 1.5, 95% CI 1.1 to 2.1) but not at 12 months follow up. PBAC scores and satisfaction rates were not significantly different between groups at 12 months follow up.
    SECONDARY OUTCOMES: Operation time was reduced by almost seven minutes with microwave ablation when compared to balloon ablation (MD

-6.6 minutes, 95% CI -5.8 to -7.4) and the microwave device was less likely to fail (RR 0.1, 95% CI 0.01 to 0.7). There was no evidence of significant differences between groups for the other secondary outcomes: other device difficulties, proportion choosing local anaesthesia, quality of life scores, requirement for analgesia, overnight stay, need for further surgery or pain scores.

14. Bipolar electrode ablation versus hydrothermal ablation (Comparison 14):
    PRIMARY OUTCOMES: Amenorrhea rates were significantly increased with bipolar ablation when compared to hydrothermal ablation at all time points (6 months: RR 2.3, 95% CI 1.3 to 4.1; 12 months: RR 2.0, 95% CI 1.2 to 3.2; 5 years: RR 1.6, 95% CI 1.1 to 2.3) and satisfaction rates were significantly increased (RR 1.3, 95% CI 1.1 to 1.5).
    SECONDARY OUTCOMES: There was a greater chance of eliminating dysmenorrhea symptoms with bipolar ablation when compared to hydrothermal ablation (RR 1.3, 95% CI 1.0 to 1.7) at 5 years follow up but not at 12 months follow up. The duration of the procedure was significantly shorter with bipolar ablation (11.8 minutes with bipolar versus 27.8 minutes with hydrothermal ablation). There was a significantly reduced risk of requiring any surgery with bipolar when compared to hydrothermal ablation both at 12 months and up to 5 years follow up (12 months: RR 0.3, 95% CI 0.1 to 0.7; 5 years: RR 0.4, 95% CI 0.2 to 0.8). There was no evidence of significant differences between groups for the other secondary outcomes: complications or future hysterectomy.

15. Ablative curettage versus overcurettage (Comparison 15):
    PRIMARY OUTCOMES: Ablative curettage resulted in significantly higher rates of amenorrhea than overcurettage (RR 4.5, 95% CI 2.3 to 8.7) and rates of amenorrhea and normal menses combined (RR 1.9, 95% CI 1.3 to 2.7). The authors stated that these outcomes were measured 3 years after surgery.
    SECONDARY OUTCOMES: Bleeding complications were significantly less likely with ablative curettage than overcurettage (RR 0.21, 95% CI 0.07 to 0.70) and failure rates of the procedure were less likely (RR 0.29, 95% CI 0.12 to 0.74). Overcurettage was associated with a significantly reduced hospital stay in comparison to ablative curettage (MD 1.6 days, 95% CI 1.2 to 2.0). There was no evidence of significant differences between groups for the other secondary outcomes: other complications and requirement for further surgery.

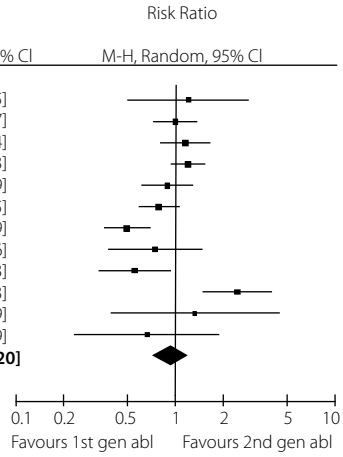
16. Second generation ablative techniques versus first generation ablation techniques (overall):
    PRIMARY OUTCOMES: There was no evidence of significant differences in the rates of amenorrhea or successful treatment at any follow up time, from six months to ten years after surgery. There was also no evidence of significant differences in satisfaction rates at any time point.
    SECONDARY OUTCOMES: On average, first generation ablation techniques required an extra 15 minutes treatment time when compared with second generation techniques (MD -14.9, 95% CI -10.1 to -19.7). There was also a greater risk of equipment failure with second generation devices (RR 4.3, 95% CI 1.5 to 12.4) and greater chance of using local rather than general anaesthesia with second generation devices (RR 2.8, 95% CI 1.8 to 4.4). Regarding complications, women undergoing second generation ablation procedures were less likely to have fluid overload, perforation, cervical lacerations and hematometra as a result of their surgery than women undergoing first generation ablation (RR 0.2, 95% CI 0.04 to 0.8; RR 0.3, 95% CI 0.1 to 1.0; RR 0.2, 95% CI 0.08 to 0.6; RR 0.3, 95% CI 0.1 to 0.9, respectively). They had a significantly greater risk of having nausea and vomiting and uterine cramping (RR 2.0, 95% CI 1.3 to 3.0; RR 1.2, 95% CI 1.0 to 1.4, respectively). There was no evidence of significant differences for the other secondary outcomes compared: inability to work, other complication rates and requirement for any additional surgery or hysterectomy. The main outcomes for this overall comparison can be viewed in the Summary of findings (Table 1).

Analysis 16.1. Second generation endometrial ablation compared to first generation endometrial ablation for heavy menstrual bleeding.

Outcome 1: **Amenorrhea rate** at 1-year follow-up.

Study or Subgroup	Second generation Events	Total	First generation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.1 At 1 year follow up						
Brun 2006	10	28	5	17	4.8%	1.21 [0.50, 2.95]
Cooper 1999	46	116	49	124	10.8%	1.00 [0.73, 1.37]
Cooper 2002	63	154	29	82	10.4%	1.16 [0.82, 1.64]
Cooper 2004	119	215	49	107	11.7%	1.21 [0.95, 1.53]
Corson 2000	38	122	39	112	10.1%	0.89 [0.62, 1.29]
Corson 2001	67	167	42	83	11.2%	0.79 [0.60, 1.05]
Duleba 2003	43	156	40	72	10.6%	0.50 [0.36, 0.69]
Hawe 2003	10	34	13	33	6.6%	0.75 [0.38, 1.46]
Meyer 1998	19	125	31	114	8.3%	0.56 [0.34, 0.93]
Perino 2004	35	56	14	55	8.5%	2.46 [1.50, 4.03]
Romer 1998	4	10	3	10	3.1%	1.33 [0.40, 4.49]
Soysal 2001	5	45	8	48	3.9%	0.67 [0.24, 1.89]
Subtotal (95% CI)		**1228**		**857**	**100.0%**	**0.94 (0.74, 1.20]**
Total events	459		322			

Heterogeneity: $TaU^2 = 0.1\ 2$; $Chi^2 = 41\_76$, df= 11 (P < 0.0001); 12 = 7 4%
Test for overall effect: Z= 0.50 (P = 0.61)

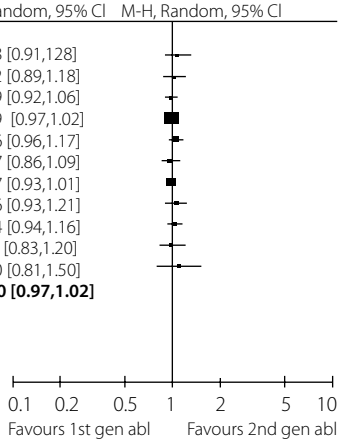


Analysis 16.2. Second generation endometrial ablation compared to first generation endometrial ablation for heavy menstrual bleeding.

Outcome 2: **Satisfaction rate** at 1-year follow-up

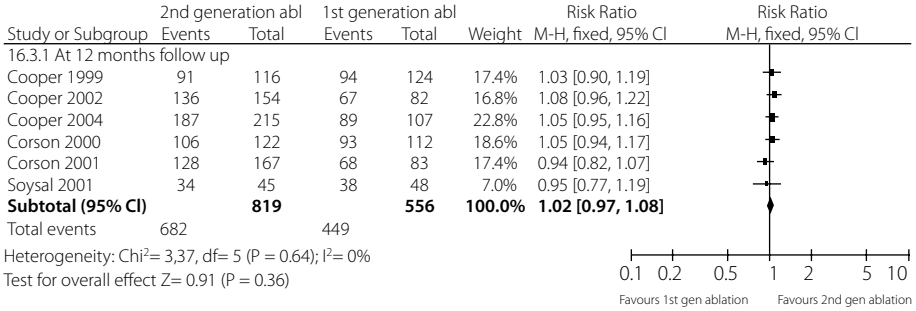
Study or Subgroup	Second generation Events	Total	First generation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.2 At 1 year follow up						
Brun 2006	27	28	17	19	1.6%	10.8 [0.91,128]
Cooper 1999	89	116	93	124	2.3%	1.02 [0.89,1.18]
Cooper 2002	143	154	77	82	8.9%	0.99 [0.92,1.06]
Cooper 2004	193	196	96	97	45.6%	0.99 [0.97,1.02]
Duleba 2003	176	193	74	86	5.0%	1.06 [0.96,1.17]
Hawe 2003	28	30	26	27	3.1%	0.97 [0.86,1.09]
Meyer 1998	120	125	113	114	24.8%	0.97 [0.93,1.01]
Pellicano 2002	35	37	34	38	2.6%	1.06 [0.93,1.21]
Perino 2004	53	56	50	55	4.2%	1.04 [0.94,1.16]
Romer 1998	10	10	10	10	1.4%	100 [0.83,1.20]
Soysal 2001	30	45	29	48	0.5%	1.10 [0.81,1.50]
Subtotal (95% CI)		**990**		**700**	**100.0%**	**1.00 [0.97,1.02]**
Totalevents	904		619			

Heterogeneity: Tau^2=0.00; Chi^2=10.55, df=10 (P=0.39); I^2=5%
Test foroverall effect: Z=0.36 (P=0.72)



Analysis 16.3. Second generation endometrial ablation compared to first generation endometrial ablation for heavy menstrual bleeding

Outcome 3: **Satisfaction of treatment** (PBAC < 75 or acceptable improvement) at 1-year follow-up



Heterogeneity

1. Specific types of endometrial resection or ablation:

Most of the forest plots comparing specific types of endometrial ablation were comparisons between groups in individual trials or pooled two or three studies at most, and there was little evidence of statistical heterogeneity. However, substantial statistical heterogeneity (I2 >50%) was found for the following forest plots:

Comparison 1.5: duration of operation (laser versus TCRE)

Comparison 7.5: duration of operation (electrode ablation versus TCRE + RB)

Comparison 9.8: duration of operation (balloon versus RB)

Comparison 9.14: requirement for further surgery (two year follow up) (balloon versus RB)

Comparison 12.3: satisfaction rate (six months follow up) (bipolar RF ablation versus balloon)

Comparison 12.33: requirement for further surgery (bipolar RF versus balloon)

Duration of operation is affected by numerous confounding factors, such as expertise of individual surgeons, hospital type and procedures and differences between groups of women. For the comparison, laser versus TCRE, the Bhattacharya study[59] did not include the total time spent in theatre and the McClure study[60] recorded the induction and reversal of anaesthesia in the estimate of operation time which resulted in much larger estimates. In this latter trial, temporary laser malfunction prolonged two laser cases to 240 minutes. For the comparison, electrode ablation versus TCRE + rollerball, differences between studies are likely to

be explained by the two different systems used; the Corson study[61] used the Vesta balloon ablation and the Cooper study used Novasure.[62] In the comparison, balloon vs rollerball, all three pooled studies used the Thermachoice balloon system. The operation time recorded for the rollerball ablation was similar in the three trials but times differed between studies for balloon ablation. The Meyer study had no preoperative treatment to thin the endometrium whereas the other two studies had two months of GnRHa pretreatment.[44] In the Soysal study[42], participants had both myomas and heavy menstrual bleeding. Other factors such as cavity length were correlated with operation time and it is not clear whether these were similarly distributed between the participants in the three trials. Another major confounding factor was the ability to use local rather than general anaesthesia which was more likely in the trials comparing second generation ablation to first generation ablation methods.

Satisfaction is also likely to vary because of different methods of measurement. In the comparison, bipolar RF ablation vs balloon, satisfaction rates at 6 months in the small Abbott trial may have been related to a technical failure rate of the Novasure procedure, but rates at 12 months follow up were similar and not significantly different at 12 months follow up.[63]

Significant heterogeneity was also found for the outcome, requirement for further surgery, in the comparison of balloon with rollerball and bipolar electrode ablation versus balloon. The different results in the two pooled trials for either comparison could not be explained by examination of their characteristics. Neither trial reported a significant difference in the outcome by ablation technique.

2. Overall analyses comparing first and second generation techniques:
Substantial heterogeneity was displayed for many of the outcomes where first generation procedures were compared with second generation procedures (comparison 16); in particular, amenorrhea rate, duration of operation, and proportion having local as opposed to general anaesthesia. The value for the outcome, amenorrhea at one year after surgery was 74%, at two years 50% and at three years 80%. The rates of amenorrhea ranged widely in the included trials and no statistical difference was reported between groups. Estimates calculated with the fixed effects model were compared with estimates calculated with a random effects model; the estimates did not change markedly but the confidence intervals were wider with the latter approach. There was thus no evidence that amenorrhea rates varied according to whether first or second generation techniques were

used to ablate the endometrium.

The forest plots of the outcomes, duration of surgery and local versus general anaesthesia also indicated substantial heterogeneity. Since these two categories are very broad and they include a number of different ablative techniques, heterogeneity was expected and a random effects model was used to display results. As previously explained, apart from differences between techniques, duration of surgery is likely to be affected by extraneous factors such as skill and expertise of the surgeon, hospital policy and the operating environment. However, each of the included trials reported separately that second generation techniques took significantly less time to perform than first generation techniques, regardless of the procedures compared. A random effects approach indicated significantly less time required for second generation procedures; each of the trials individually indicated a statistically significant difference. The other comparison, proportion of women having local as opposed to general anaesthesia, also indicated highly significant heterogeneity. In all trials in the meta-analysis, the proportion of women undergoing ablation with first generation techniques using local anaesthesia (either: TCRE plus RB or RB alone) ranged from 8% to 23% while the proportion undergoing second generation ablation using local anaesthesia (Vesta, HTA, Novasure, cryoablation or microwave) ranged from 45% to 86%. All trials separately reported large significant differences between first and second generation techniques. A random effects model confirmed these differences in the pooled result.

To sum up, random effects analyses confirmed the following:

(1) There was no evidence of a difference in the amenorrhea when first generation techniques are compared with second generation techniques.
(2) Duration of surgery with second generation techniques overall was less than with first generation techniques. Because of heterogeneity, which is probably explainable by other factors such as experience of surgeons, the difference of fifteen minutes between procedures represents an average which is not informative and this difference is unlikely to be clinically significant.
(3) Women undergoing ablation with second generation techniques are more likely to have local anaesthesia compared to those having ablation with first generation techniques.

Sensitivity analyses

Sensitivity analyses were performed only on the comparisons where five or more

trials were pooled, specifically for the comparison of satisfaction and amenorrhea rates at one-year follow up between first and second generation ablation. There were no significant differences reported between randomized groups and the planned sensitivity analyses did not substantially change the results of all included trials, although heterogeneity was reduced.

Discussion

Summary of main results

A significant number of women with heavy menstrual bleeding (HMB) who seek treatment will not benefit from, or will not wish to continue with, medical treatment and are keen to preserve their uterus. Thus, there appears to be a distinct role for an effective, relatively minor surgical procedure such as endometrial ablation or resection which preserves the uterus yet reduces heavy menstrual bleeding. This review has assessed a wide range of efficacy, satisfaction and safety outcomes relating to different methods of ablating the endometrium for women who complain of excessive menstrual bleeding.

Comparison of different types of first generation techniques

The first generation ablation techniques have been traditionally acknowledged as the "gold standard" by which other, newer procedures are judged. Improvement in menstrual bleeding and satisfaction seems to be similar. The complication profile for the four techniques is slightly different; for example, fluid overload was more likely with laser ablation when compared to TCRE and also more likely with TCRE when compared to vaporizing electrode. However, it is likely that operator safety is a much more important arbiter of patient safety than the instrument itself. Duration of surgery was longer with laser when compared to TCRE and was longer with TCRE when compared to vaporizing electrode ablation. Equipment failure was more likely with laser ablation when compared to TCRE and more difficult with TCRE when compared to vaporizing electrode ablation.

Comparison of different types of first generation with second generation techniques

With reference to the comparisons of the different types of second generation techniques with first generation techniques, thermal laser was more effective than

TCRE at reducing blood loss (as measured by amenorrhea rates) but this did not result in any difference in the satisfaction that the women felt with their surgery. Although rollerball was more likely to result in amenorrhea when compared to cryoablation, there was also no evidence that women were more satisfied. Similarly, the finding that rollerball was associated with significantly more amenorrhea when compared to balloon ablation at some time points, but not at others, is not useful as there was no evidence that this benefit was confirmed by other bleeding outcomes of importance to women, such as PBAC score or scanty menstruation. Patients appeared to be more satisfied with microwave than TCRE at 2 and 5 years after surgery, but these findings were not significant at other time points.

With regards to secondary outcomes, duration of surgery was consistently shorter with second generation ablation and local anaesthesia was more likely to be given. Pain was also more likely with some types of second generation technique, such as thermal laser, balloon and HTA but this outcome was not measured by all trials. The intra- and post-operative complication rates are summarized below.

Comparison of different types of second generation techniques

Bipolar radiofrequency ablation was associated with significantly more amenorrhea than balloon ablation but this was not confirmed by a comparison of PBAC scores or the extent to which women were satisfied with their surgery. Surgery was shorter with bipolar ablation and PMS scores reduced. There was no evidence that bipolar radiofrequency ablation resulted in less re-operation as a result of dissatisfaction with surgery. Bipolar ablation also increased amenorrhea and satisfaction rates when compared with hydrothermal ablation. The procedure time was shorter with bipolar ablation and women were less likely to require additional surgery at later follow up. Amenorrhea rates appeared to be increased with microwave when compared with balloon but no differences were found in PBAC scores or satisfaction. Operation time was also reduced with microwave ablation.

Comparison of curettage techniques

One small trial found advantages for an ablative curettage (devised by the author of the trial) over overcurettage (where the curettage is continued beyond the gritty sensation felt at the basal endometrium) in terms of improved amenorrhea and normal menstruation rates and reduced failure rate and bleeding complications, but longer hospital stay. The objective of the study was to find effective techniques for developing countries which may not have the resources and skills to undertake

other types of ablation discussed in this review, but the authors acknowledged that curettage may only have a temporary role.

Overall comparison of first generation with second generation techniques

Regarding the overall comparison of second generation with first generation techniques, there is no evidence that either broad category is more effective than the other in reducing heavy menstrual bleeding and there was no evidence that rates of satisfaction differed significantly. Overall, second generation techniques were at least as effective as first generation methods but were often easier to perform with shorter surgery times and the ability to use local rather than general anaesthesia. Some types of intra and postoperative complications, such as fluid overload, perforation, cervical lacerations and hematometra, were more common with first generation ablation and other types of complication, nausea and vomiting and uterine cramping and pain, were more common with second generation techniques. Concerns about these 'blind' methods leading to bowel injuries from undetected uterine perforations did not seem to be confirmed in the published studies. However, there are many anecdotal examples that such events can occur and great care must be taken to minimize the risk of such potentially serious complications. There was no evidence that rates of re-intervention, either repeat ablation and/or hysterectomy, differed between first and second generation ablation. A recurrent comment about the newer techniques which rely on 'devices' inserted into the uterine cavity to destroy the endometrium was the incidence of equipment failure. This may represent expected 'teething problems' associated with new equipment. However, since the older methods are extremely simple (a loop, laser or diathermy to destroy the endometrium below it) and the newer techniques are potentially quite complex (microwaves, bags of fluid etc) the potential remains for mechanical breakdown to occur. In addition, considerable experience in intrauterine cavity assessment and manipulation is required to safely use any of these devices. There are potential disadvantages to stressing how little operator skill is required for a device which has the capacity to cause extensive intra-abdominal trauma.

Overall completeness and applicability of evidence

A perennial and unresolved problem in the assessment of any treatment for HMB is the accuracy of the original diagnosis and the quandary that many women who complain of excessive bleeding will be shown to have menstrual losses (MBL)

within normal population limits when blood loss is objectively measured.[64,65] The 'gold standard' technique for the measurement of MBL involves the collection of all menstrual pads and tampons as well as clots and other blood lost, which is impractical for many women. Also, the assessment of blood loss (via the alkaline hematin method) is a time consuming and laborious task, although objective data are helpful in the research setting. Consequently, a number of more pragmatic alternatives have been suggested to attempt to objectively assess MBL in a normal clinical setting, such as the pictorial blood loss assessment chart (PBAC). Unfortunately, none of these alternatives have been shown to reliably correlate with the gold standard. Some authors have accepted that it is the woman's subjective complaint of HMB which is of primary importance in directing intervention in a clinical setting. However, this subjectivity raises problems when used for the comparison of one treatment method with another and in assessing outcome over time. Participants in the trials included in this review all had complaints of heavy menstrual bleeding but there is likely to be a large variation in the extent of the problem because of the subjective nature of the condition.

To make matters more confusing, evidence from a large cross-sectional survey suggests that whilst many women are referred with menorrhagia, many of these women do not complain of HMB when directly questioned; suggesting a tendency for broad menstrual complaints to be reframed as excessive bleeding at referral and during management.[66] As the authors concluded, this is likely to result in women receiving inappropriate care and will also influence the actual and perceived efficacy of treatment modalities for HMB.

The published literature on endometrial destruction techniques for HMB covers a wide range of surgical methods and uses a variety of outcome measures to assess treatment success, making clear comparisons between studies difficult. The participant groups were varied and often potentially important clinical factors, such as the presence of uterine fibroids or a perimenopausal state, were not mentioned in the inclusion or exclusion criteria. This is particularly important with longer follow-up studies. Current clinical approaches to HMB advise that medical therapy should be offered in the first instance and it would be unusual in normal practice to advise endometrial resection or ablation without trying any medical therapies. Indeed, since medical treatment with the levonorgestrel-releasing intrauterine system (Mirena, Schering) reduces MBL by 94% at three months, and has been shown to be as effective as endometrial ablation,[67,68] it could be argued that endometrial surgery is only appropriate for those who are unsuitable or do

not wish to have treatment with the intrauterine system.[8] Fourteen published studies focused on women with failed medical management of HMB and there were insufficient studies within each comparison to determine whether women in these studies differed systematically in their response to treatment than other women. Many researchers are aware of the difficulties in recruitment to randomized clinical trials and the need to obtain sufficient participants to meet the requirements of power calculations. However, the inclusion of unsuitable or unrepresentative participants in trials does not add to our understanding of the role of new therapies in normal clinical practice.

The published studies show a wide variation in the outcome criteria used in assessing endometrial destruction techniques. Since HMB is the main indication for this procedure, we were surprised to find that only one trial objectively measured MBL.[60] Several studies used the pictorial blood loss assessment chart (PBAC) which does not correlate well with objective measurement.[39,69] In addition, the entry criteria for PBAC score varied widely between studies. However, if comparisons are made between studies of changes in PBAC scores following endometrial destruction, few differences were seen between treatment modalities. Some variations were seen in the number of women with amenorrhea following treatment, but since menstrual destruction methods cannot guarantee amenorrhea they are generally not suitable for women who feel strongly that they do not want any more bleeding. A number of studies attempted to quantify participant satisfaction with the procedure but used a variety of different measurements to do so, limiting comparisons between studies. Overall, participant satisfaction was high with most procedures and differences found were unlikely to be clinically significant. Large study numbers would be needed in order to demonstrate a significant difference in satisfaction between different methods of endometrial destruction.

Quality of the evidence

The evidence base on which this review is based was of variable quality. In particular, few studies were blinded and in most of the comparisons between individual techniques, a limited number of studies provided data. Lack of blinding is likely to influence more subjective outcomes, such as satisfaction rates so findings of these types of outcomes should be viewed with caution.

Substantial heterogeneity was identified in some of the outcomes of the overall comparison between first and second generation techniques, and the quality of the evidence has been downgraded to reflect the uncertainty around

the summary effect estimates. See Summary of findings table 1.

Potential biases in the review process

A comprehensive search for relevant studies together with duplicate and independent study selection, data extraction and quality assessment of studies has minimized the chance of potential bias in the review process.

Agreements and disagreements with other studies or reviews

Surprisingly, although there have been numerous RCTs and observational studies of specific types of endometrial ablation techniques, there have been few systematic reviews identified that have made overall comparisons of the specific endometrial ablation techniques for the reduction of HMB. Numerous narrative reviews have been published together with comprehensive audits for first generation techniques. Comparing the first generation methods of endometrial ablation versus resection, the MISTLETOE study concluded that the methods produced similar outcomes in terms of bleeding and participant satisfaction, but that resection methods have significantly more complications, suggesting that ablation should be used in all women with a non-fibroid uterus.[26]

Systematic reviews, one with individual patient data, have not been able to determine major differences between first and second generation techniques in terms of effectiveness or satisfaction with treatment.[11,70] However, Middleton has confirmed the results of this review that second generation techniques are faster, local anaesthesia is more likely to be used and some complications less frequent. The suggestion in this review that additional surgery may be less likely with second generation techniques at longer follow up (10 years) is based on only one trial and needs confirmation from further research.

Of the second generation techniques, the most studied have been Novasure, balloon and microwave ablation.[71] A recent network meta-analysis has reported that bipolar radiofrequency and microwave ablation resulted in higher rates of amenorrhea than thermal balloon ablation at 12 months after treatment but there was no evidence of a convincing difference between the three techniques in satisfaction rates or the number of women still experiencing heavy bleeding and other outcomes were not assessed.[72] However, the lack of a consistent measure of effectiveness has made it difficult to adequately compare techniques and reach conclusions over the technique of choice. Other authors have suggested that there might be commercial resistance to comparing devices, given the likely effect

on the market share for the inferior treatment.[73] It has also been suggested that a potential limitation of second generation devices are the restrictions relating to one or a combination of the size and configuration of the endometrial cavity that may prevent general application of any device to the HMB population.[74] Many of the included studies in this review that evaluated these devices had fairly strict inclusion criteria, limiting the applicability of results to women with large or distorted uteri. Thus, not all women with HMB may be candidates for second generation ablation and it has been suggested that gynaecologists should retain their skills in hysteroscopic surgery for certain types of intrauterine pathology.[75]

An additional issue is the role of patient preferences in decision making on treatments for heavy menstrual bleeding. A recent review suggested that reaching a decision on a "one size fits all" approach may be elusive and that eliciting patient preferences, based on the evidence, is required to reach the decision on the "best" approach.[7]

Author's conclusions

Implications for practice

Endometrial destruction by first or second generation techniques should be considered for all women with normal uteri who wish to reduce their heavy menstrual bleeding and wish to retain their uterus.

The potential for second generation methods to be performed under local anaesthesia is a considerable advantage and should be considered in cases where general anaesthetic may confer particular risk.

There is sufficient evidence to confirm that, on average, second generation techniques are technically simpler and quicker to perform than first generation techniques while satisfaction rates and reduction in heavy menstrual bleeding are similar. However, technical difficulties have not yet been completely resolved.

Implications for research

Future studies should aim to include women in whom medical treatment for heavy menstrual bleeding has been ineffective.

Menstrual blood loss should be objectively or semi-objectively measured in all comparative studies (by the alkaline hematin method or the PBAC), although the assessment of the woman in the clinical setting is nearly always based on more

subjective criteria, such as perception of heavy bleeding.

Amongst first generation techniques for endometrial destruction, there are good data to support the use of endometrial ablation rather than resection.[26] There is a need to systematically compare first generation ablation methods with second generation techniques using standardized criteria of participant satisfaction and quality of life and objectively measured menstrual blood loss in order to establish which of the newer methods has an established role and when they should be the instruments of choice. This may require referral to another unit where such techniques are available. There was insufficient evidence in this review to determine the superiority of one type of second generation technique over another. Equipment reliability for the second generation techniques needs to be established.

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Chapter 9

General discussion

Discussion

Heavy menstrual bleeding (HMB) is a significant health problem in women in reproductive age. The incidence varies between 9 to 22 %.[1,2] Before, HMB was named menorrhagia. Lately, changes in terminology have been introduced because there was a great variation in the way the terms abnormal uterine bleeding, menorrhagia and dysfunctional uterine bleeding were used. It was proposed to use abnormal uterine bleeding as the overarching term to describe all symptomatic flow of normal menstruation or the menstrual cycle. HMB is a suitable replacement for menorrhagia.[3] HMB is defined as cyclical blood loss of >80ml during each menstrual period.[4] However, the amount of blood loss is difficult to objectify. The amount of menstrual blood loss can also be scored on the pictorial blood loss assessment chart (PBAC), described by Higham et al.[5] One period is counted and a minimum score of 150 points is described as HMB.

Only about half the women with HMB who turn to healthcare providers indeed have blood loss greater than the traditional threshold of 80 mL per menstrual cycle.[6] Nevertheless, the diagnosis is often based on the subjective impression of the patient. Regardless of the exact amount of blood loss assistance may be needed when women feel that their everyday activities are affected.[6,7] This corresponds with the description of health by the WHO, formulated in 1948: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[8] Recently, Huber et al. proposed the formulation of health as the ability to adapt and to self-manage.[9] That is why clinical guidelines propose a shift in emphasis from the amount of menstrual blood loss to the more patient centered definition of HMB that interferes with woman's physical, emotional and social life.[10,11]

Women included in our studies had HMB scored >150 points on a PBAC. We have not experienced that a significant part of women with heavy menstrual bleeding in fact did have less than 150 points on their pictorial chart score. This may be explained by the fact that women in the Netherlands are often first seen by their general practitioner before they are referred to a gynecologist.

Why and when do women perceive menstrual bleeding as a problem?

The fact that only half of the women who turn to healthcare providers with HMB objectively do have blood loss >80 mL or scored > 150 points on a PBAC, raises the question why some women perceive a 'normal' menstruation as heavy

while others do not. There is evidence that in such cases a lack of understanding between patients with HMB and their doctors is present.[7,12] Women with HMB were interviewed and they had a precise understanding of their complaint. The problem for many women was the change of their cycle, without reference to outside criteria. Women attached the most importance to how they felt and to their ability to function and they rejected the medical emphasis on blood loss evaluation. Many women were dissatisfied with the consultation and experienced their doctors as being dismissive of their problem. They were seeking an explanation for the fact that their periods had changed and had concerns relating to their understanding of menstrual bleeding.[11] O'Flynn proposed that the disease model should be replaced by illness models.[12] This could suggest that women should be helped by clinicians listening to women's accounts of their menstrual problems in their broadest sense, clarifying presenting symptoms and their impact on everyday life, and offering help and advice for these problems. If women do receive inappropriate care, this will also influence the actual and perceived efficacy of treatment modalities for HMB. This could be the reason why women remain unsatisfied with the result after treatment and will only be satisfied after a hysterectomy has been performed. It would be interesting to study possible correlations between absolute pictorial chart scores and pictorial chart score changes before and after therapy with satisfaction:

- Does satisfaction correlate best with a certain decrease in pictorial chart score after therapy or with an absolute pictorial chart score?
- Is there a difference in satisfaction between women with high versus relatively low pictorial chart scores before treatment?

Is it necessary to screen women with HMB for bleeding disorders?

In the majority of cases no abnormality is found to explain HMB when women are referred for menorrhagia.[13] Nevertheless, systemic problems such as platelet and coagulation disorders as well as hepatic disease, may cause HMB. In women with HMB, inherited coagulopathy is the underlying cause in 10% to 20% of white women and 1% to 2% of black women.[14,15] Platelet dysfunction and deficiency of von Willebrand factor (vWF) are the two most common coagulation disorders observed in HMB.[16] Approximately 74% to 92% of women with deficiency of vWF experience HMB.[17] Among women with deficiencies in factor I, XI, or XIII, HMB prevalence ranges from 35% to 70%.[18] Carriers of haemophilia are more likely to have a better outcome in treating their HMB with gynaecological or surgical

management compared with medical management.[19] Despite these figures, only one third of interviewed fellows of the American College of Obstetricians and Gynecologists would consider bleeding disorders as a cause for HMB in reproductive aged women.[20] According to the ACOG, blood collection to screen for hematologic disorders should be performed before initiating treatment in women who have had heavy menstrual bleeding since menarche and have personal or family history suggesting a coagulation disorder.[10,21] Most studies comparing endometrial ablation, including our own, do not mention if they excluded women with a bleeding disorder.

The optimal treatment of HMB in women with bleeding disorders is not yet known, illustrating the need for better information concerning the influence of von Willebrand Factor (vWF) levels and levels of factor XI on the treatment effect of resp. the LNG-IUS and endometrial ablation. The MIRA study (LNG IUS versus endometrial ablation) will measure factor XI and von Willebrand factor and investigate their influence on the treatment effect of LNG-IUS and endometrial ablation. We have to wait for the results of this study.

What treatment options are available for heavy menstrual bleeding?

Not that long ago women presenting with HMB for whom oral drug regimens did not help, had a hysterectomy performed. In the last decades treatment of HMB has changed. The levonorgestrel intrauterine system (LNG IUS) and endometrial ablation became alternatives. A recent study of Gupta et al. concluded that in women with HMB who turned to primary care providers, the LNG IUS was more effective than usual medical treatment in reducing the effect of heavy menstrual bleeding on quality of life.[22] Nonetheless, at two years, 36% of women in the levonorgestrel-IUS group had the system removed, generally because of lack of effectiveness or irregular or prolonged bleeding. High satisfaction rates (85-90%) with significant decrease in blood loss (80-90%) are shown after endometrial ablation. Results of randomized controlled trials, comparing the effectiveness of the LNG-IUS and endometrial ablation in the treatment of heavy menstrual bleeding, are lacking. We will have to wait for the results of the Dutch MIRA study, which is a randomized controlled trial comparing the costs and effects of the levonorgestrel IUS and endometrial ablation in women with heavy menstrual bleeding.

As shown in our randomized controlled trials, comparing three second-generation endometrial ablation techniques (Chapter 3 and 7), bipolar ablation seems superior in the treatment of HMB. This corresponds with the network

meta-analysis of second-generation ablation techniques of Daniels et al., which also includes our trial comparing bipolar ablation and HTA.[23] They concluded that bipolar radiofrequency and microwave ablative devices are more effective than thermal balloon and free fluid ablation in the treatment of HMB with second-generation endometrial ablation devices. When comparing first-generation and second-generation endometrial ablation devices (Chapter 8), the existing evidence suggests that success and satisfaction rates and complication profiles of newer techniques compare favorably with hysteroscopic first-generation techniques. The newer techniques are technically easier to perform. However, technical difficulties with new equipment need to be ironed out. As implicated for further research in chapter 8, there is a need to systematically compare first-generation ablation methods with second-generation techniques using standardized criteria of participant satisfaction and quality of life and objectively measured menstrual blood loss in order to establish which of the newer methods has an established role and when they should be the instruments of choice. However, we do believe it is not reasonable to perform a randomized controlled trial comparing a first and second-generation ablation device, because severe intra and postoperative complications, such as fluid overload, perforation, cervical lacerations and hematometra, were more common with first generation ablation (Chapter 8). Another disadvantage would be that the first-generation techniques are only used by a few gynecologists, which are specialized in performing these techniques, this can potentially bias the results of the first-generation technique and it may require referral to another unit where such techniques are available.

Is it acceptable to perform an endometrial ablation in the office?

Second generation non-hysteroscopic techniques are considered easier to perform, with shorter treatment time and are equally effective and safe as first-generation endometrial ablation techniques.[24] Along with an advanced technology, ablations are performed more often in the office instead of in the operating room. It appears that with proper patient selection, equipment and anesthesia techniques endometrial ablation can be performed safely and effectively in an office setting. Whereas initially endometrial ablations were performed with local anesthesia combined with conscious sedation, recently studies have been performed only using a paracervical block.[25,26] As shown in chapter 6 and 7, endometrial ablation with a paracervical block seems acceptable and feasible, but discomfort during office surgery remains the main obstacle to more widespread implementation.

Further work is required to improve the identification of women likely to tolerate the procedure well, to improve the patient experience and to minimize pain while maintaining a simple and safe procedure.

Which measures should be used to assess the success of endometrial ablation?
Published literature on endometrial destruction techniques for menorrhagia covers a wide range of surgical methods and uses a variety of outcome measures to assess treatment success. Amenorrhea, satisfaction and re-intervention rates are often used as outcome measures, but besides these measures, it seems important to measure quality of life by validated questionnaires when comparing treatment for HMB.

HMB can cause significant distress to women by affecting their performance at work as well as their social activities, and leads to a measurable reduction in quality of life.[27] Measurement of quality of life might give a better presentation of the effectiveness of the treatment for women compared to the amount of patients with amenorrhea. Quality of life improves after any endometrial ablation procedure, but a discrepancy between clinical outcome in different endometrial ablation techniques and quality of life was found in most randomized studies.[28-31] This was also present in our study, assessing health related quality of life after bipolar endometrial ablation and hydrothermablation (chapter 5). We concluded that in all generic and disease specific questionnaires treatment of HMB improved health related quality of life over time, but the treatment effect of amenorrhea and satisfaction did not result in quality of life benefits.

The pictorial chart score and quality of life scores are never analyzed to answer the question: What is clinical relevant decrease of blood loss in women with heavy menstrual bleeding?'. Besides this, the question arises if women would prefer a return to eumenorrhea rather than amenorrhea. In case of eumenorrhea quality of life and satisfaction should be the primairy outcome of trials comparing endometrial ablation techniques. If they prefer amenorrhea this could explain why they are more satisfied after a hysterectomy. A preference study could determine this problem.

What is the benefit of treatment by endometrial ablation in perimenopausal women?

Most women who are seeking help for HMB are perimenopausal. These women often ask how long their complaints will persist, that is, when they will become postmenopausal. A recent study analyzed the spontaneous resolution of heavy menstrual bleeding in the premenopausal years. When the heaviness of menstrual bleeding interfered with the quality of life of women, the overall rate of resolution without recurrence of heavy menstrual bleeding in naturally menstruating women was around 10% till two years follow up.[32]

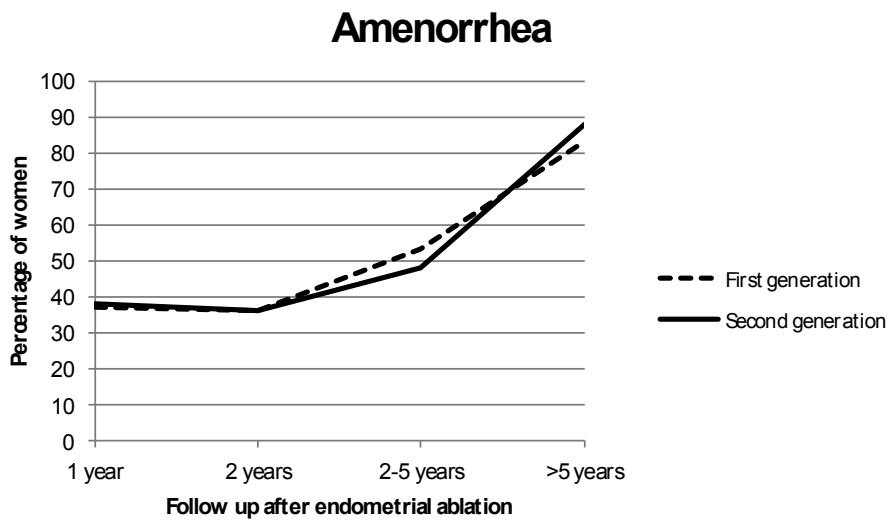

Figure 1. Percentage of women with amenorrhea after first- and second-generation endometrial ablation

Figure 1 shows the amenorrhea rate from long-term follow-up studies after endometrial ablation. The amenorrhea rate starts to increase two years after treatment and even becomes significant after five years, which could be explained by the fact that most women became postmenopausal.[24] This corresponds with the fact that the average age of participants at recruitment of the studies was 40-45 years, and the average age of the menopause in developing countries is 51 years.[33] If we will inform women that the chance of getting postmenopausal will probably be within 2-5 years, they will possibly not have the endometrial ablation performed.

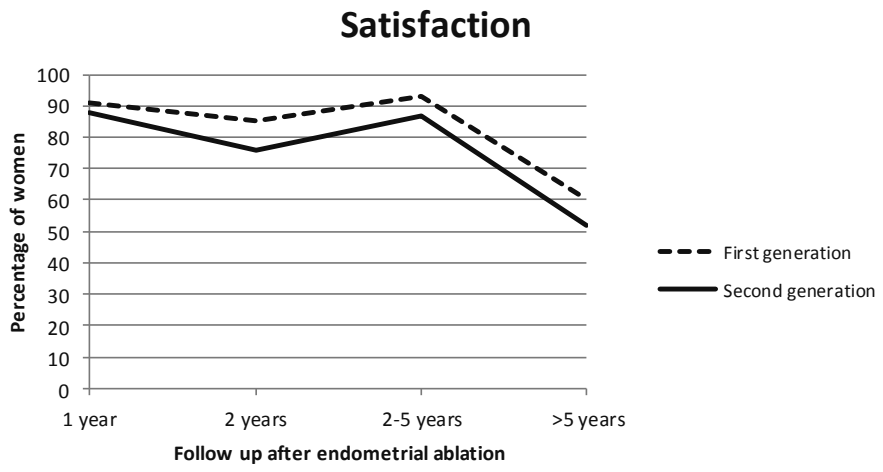

Figure 2. Percentage of women being satisfied with the result of endometrial ablation after first- and second-generation endometrial ablation

Remarkable is the decrease in percentage of women being satisfied more than 5 years after treatment (Figure 2). Whereas the amenorrhea rate increases, the satisfaction rate decreases during time. An explanation could be that a few years after treatment women forget how the HMB interfered with their life before and answer that they are less satisfied. Another explanation could be that satisfaction is not the correct outcome measure evaluating the effect of endometrial ablation at long term follow up. A third explanation could be that women are less satisfied because they are peri- or postmenopausal and do experience physical changes as hot flushes, irregular bleeding and vaginal dryness can appear, or mental changes as mood swings, depressive feelings or insomnia. Long term studies evaluating success, satisfaction and health related quality of life are essential to offer patients information with respect to a desirable and long term solution for heavy menstrual bleeding.

What are the long term risks of endometrial ablation?

At long term follow up, unknown morbidity may become apparent, especially endometrial carcinoma. As endometrial ablation is a relatively new therapy with a variety of techniques, data on incidence of long-term follow-up problems, i.e. endometrial cancer after endometrial ablation are lacking. It is suggested that the incidence of endometrial cancer after endometrial ablation is reduced in case of maximal destruction of the endometrium.[34] However, some evidence

suggests that incidence of endometrial cancer is unchanged after endometrial ablation with first generation techniques. So far, most cases are reported after first generation techniques. The diagnosis of endometrial carcinoma may be delayed after ablation, because adhesions or scars could mask the symptoms of the disease. If postmenopausal bleeding occurs, interpretation of the thickness of the endometrium and hysteroscopy can be difficult to perform because of the anatomical distortion of the uterine cavity. The next decade will provide us with data, because women treated with the first generation endometrial ablation devices are 50-60 years of age, being the age with the highest prevalence of endometrial cancer. Therefore, adequate follow-up of these therapeutic interventions is still needed for clinical decision making and counselling of patients.

In conclusion, my suggestions for future research would be:

- to evaluate the patient preference in treatment of heavy menstrual bleeding.
- to study if there is a relationship between the decrease of pictorial chart score and satisfaction and if we could tell at which pictorial chart score women will be satisfied.
- to study how to improve the patient experience with endometrial ablation in the office and how to identify those women likely to tolerate the procedure well. Trials incorporating different anaesthetic approaches on how to minimize pain would help to refine the evidence available to women and gynaecologists.
- to continue long term follow up studies, especially focusing on endometrial cancer.

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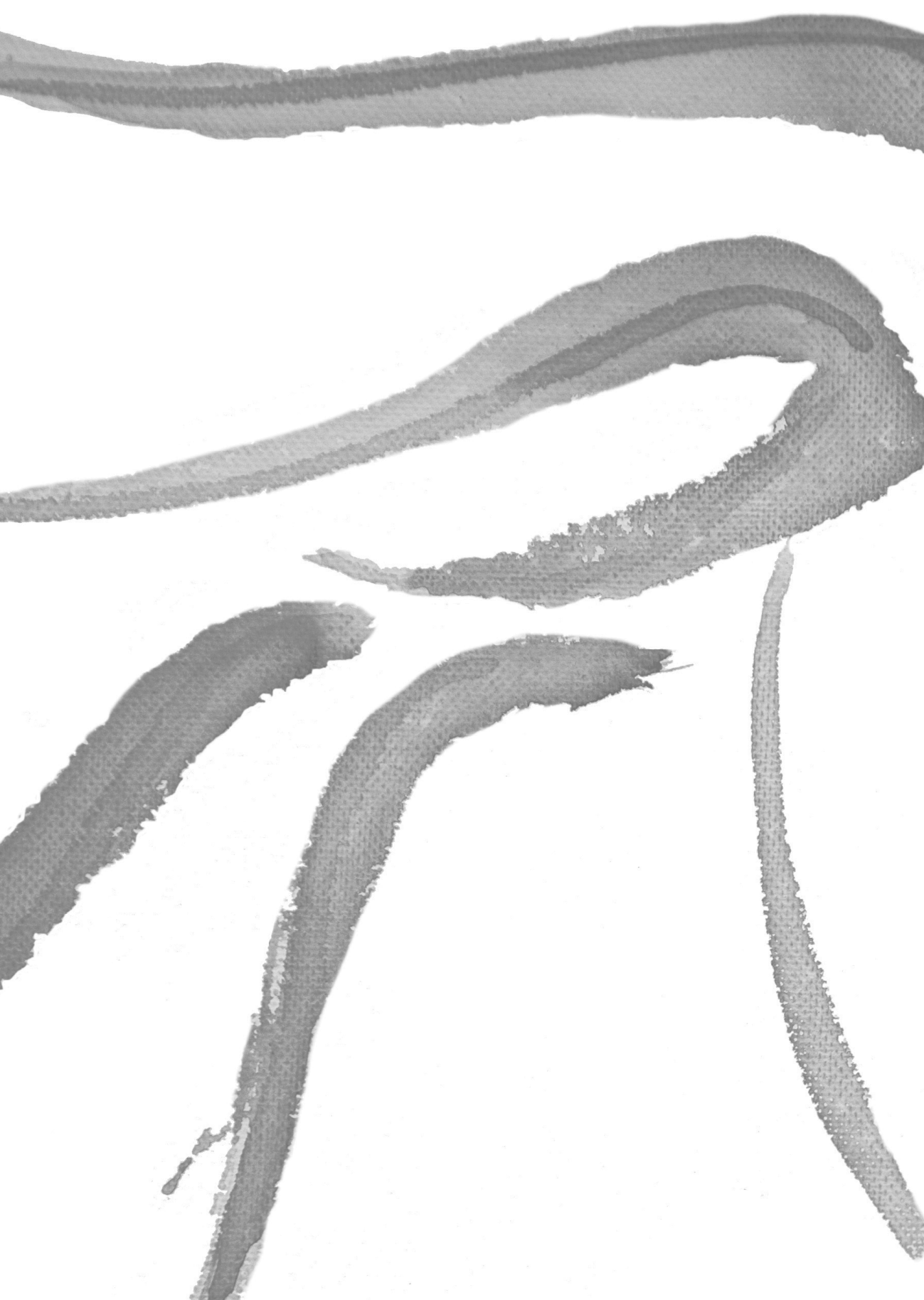

Chapter 10

Summary

Summary

Heavy menstrual bleeding is a significant health problem in women of reproductive age. Its incidence varies between 9% and 22%. Menorrhagia is defined as a menstruation at regular cycle intervals, but with excessive flow and duration. Clinically, menorrhagia is defined as menstrual blood loss exceeding 80 mL per cycle. In recent years changes in terminology appeared, because there was a great variation in the way the terms abnormal uterine bleeding, menorrhagia and dysfunctional uterine bleeding were used. It was proposed to use abnormal uterine bleeding as the overarching term to describe all symptomatic blood loss from normal menstruation or the menstrual cycle. Heavy menstrual bleeding (HMB) is a suitable replacement for term for menorrhagia.

HMB has a significant impact on the medical, social economic and psychological well-being of women. When medical treatment fails surgical interventions, like destruction of the endometrium or a hysterectomy, can be considered. Hysterectomies are performed in 30-40% of the patients for treatment of severe HMB. The level of satisfaction with hysterectomy is usually high with good health related quality of life scores, but it is a major surgical procedure with a complication rate up to 43%. Patient preference studies show that women place a high value on retaining their uterus and that they have a strong preference for avoiding hysterectomy as a treatment to resolve the problem of HMB, but when they do undergo a hysterectomy they are generally satisfied. Endometrial ablation is an alternative to hysterectomy in women with heavy menstrual bleeding. It is a relatively minor surgical procedure which preserves the uterus yet reduces heavy menstrual bleeding.

Endometrial ablation

Endometrial ablation was introduced in the 1980's. Endometrial ablation removes or destroys the basal layer of the endometrium. This results in an inability of the endometrium to react on hormonal stimuli, and therefore decreases menstrual blood loss. The first endometrial ablations were performed under direct hysteroscopic vision. They are referred to as first-generation devices. The first-generation devices were; endometrial laser ablation, transcervical resection of the endometrium and rollerball ablation. The introduction of endometrial ablation caused a rapid decrease in the amount of hysterectomies performed. However, the first-generation endometrial ablation techniques involved a long learning curve and had the risk of absorption of the distension fluid (Glycine or Sorbitol).

This is characterized by hyponatraemia, water intoxication, cerebral edema and cardiac overload, which can result in a fatal hyponatremic encephalopathy. Over the past decade, second-generation non-hysteroscopic techniques overcame these disadvantages. Destruction of the endometrium by the 'blind' endometrial ablation methods is achieved by different methods, the most important being microwave (Microsulis®), high temperature fluids within a balloon (Thermachoice®, Cavaterm®, Thermablate®), bipolar radiofrequency energy (NovaSure®) and free fluid with a high temperature (Hydrothermablator®). The second-generation techniques are safer, technically easier and quicker to perform, and involve shorter hospital stays. When endometrial ablation was introduced, the procedures were performed in theatre with general anesthesia or regional (spinal) anesthesia. Years after, endometrial ablation was also performed at the outpatient clinic with a paracervical block combined with intra-venous sedation. One study compared intraoperative and postoperative pain between ThermaChoice® and NovaSure® endometrial ablation. The NovaSure® system was associated with significantly lower intraoperative and postoperative pain. These data supported the idea that the NovaSure® procedure could become an office-based procedure with local anesthesia, meaning only a paracervical block.

This thesis deals with the prognostic factors for the success of endometrial ablation and the use of different second-generation endometrial ablation techniques in theatre and in the outpatient clinic with a paracervical block.

Chapter 1 outlines the aim of the thesis, and is formulated into five questions. This thesis aims to answer the following questions:

1. Which are the prognostic factors for success of endometrial ablation in the treatment of heavy menstrual bleeding?
2. What is the effectiveness of bipolar radiofrequency endometrial ablation in the treatment of heavy menstrual bleeding as compared to hydrothermablation after 12 months and at long term follow-up in terms of amenorrhea, satisfaction, reinterventions and quality of life?
3. Is it safe and acceptable to perform bipolar radiofrequency endometrial ablation with a paracervical block in the outpatient clinic?
4. What is the effectiveness of bipolar radiofrequency endometrial ablation in the treatment of heavy menstrual bleeding as compared to balloon endometrial ablation in the outpatient clinic in terms of amenorrhea, pain, satisfaction and quality of life?

5. Which endometrial ablation technique(s) is/are preferred in the treatment of heavy menstrual bleeding?

Chapter 2 studies a history of Cesarean section and other factors that are potentially associated with endometrial ablation failure in the treatment of heavy menstrual bleeding and answers the first question:

Which are the prognostic factors for success of endometrial ablation in the treatment of heavy menstrual bleeding?

We compared women who had failed ablation to women who had successful ablation for heavy menstrual bleeding in a case-control study. Failed ablation was defined as the need for hysterectomy due to persistent HMB after ablation. Successful ablation was defined as a satisfied patient who did not need a hysterectomy after ablation for HMB. Both groups, cases and controls were identified from the surgery registration in the Máxima Medical Center between January 1999 and January 2009. Cases were women that had an endometrial ablation and a hysterectomy, whereas controls only had an endometrial ablation. From the medical files we collected clinical history, including the presence of a previous Cesarean section, baseline characteristics at the moment of initial ablation, data of the ablation technique and follow-up status for each patient.

We compared 76 cases to 76 controls. Among the cases, 12 women had had a previous Cesarean section versus 15 in the control group (15.8% versus 19.7%; odds ratio (OR) 0.76; 95% confidence interval (CI) 0.3–1.8). Factors predictive for failure of ablation were dysmenorrhea (OR 3.0; 95% CI 1.5–6.1), having a submucous myoma (OR 3.2; 95% CI 1.5–6.8) and uterine depth (per cm OR 1.3; 95% CI 1.0–1.6). Presence of intermenstrual bleeding, sterilization and age were not associated with failure of ablation.

In conclusion, a previous Cesarean delivery is not associated with an increased risk of failure of endometrial ablation, but dysmenorrhea, a submucous myoma and longer uterine depth are. This should be incorporated in the counseling of women considering endometrial ablation.

What is the effectiveness of bipolar radiofrequency endometrial ablation in the treatment of heavy menstrual bleeding as compared to hydrothermablation after 12 months and at long-term follow-up in terms of amenorrhea, satisfaction, reinterventions and quality of life?

Chapters 3, 4 and **5** focused on this second question.

Chapter 3 presents the results of a double blind randomized trial comparing the effectiveness of two second-generation ablation techniques in the treatment of heavy menstrual bleeding: bipolar radiofrequency impedance-controlled endometrial ablation (NovaSure®) and hydrothermablation (HTA®). Patients were included between March 2005 and August 2007. The primary outcome was amenorrhea at four weeks, six months and twelve months after treatment. Secondary outcome measures were patient satisfaction and re-intervention.
We included 160 women in the study, of which 82 were allocated to the bipolar group and 78 to the hydrotherm group. No complications occurred in either of the treatment groups. After 12 months the amenorrhea rates were 47% (35/75) in the bipolar group and 24% (17/71) in the hydrotherm group (relative risk (RR) 2.0, 95% CI 1.2-3.1). In the bipolar group 87% (65/75) of the patients was completely satisfied with the result of the treatment, against 68% (48/71) in the hydrotherm group (RR 1.3, 95% CI 1.03-1.6). The relative risk for a re-intervention in the bipolar group compared to the hydrotherm group was 0.29 (95% CI 0.12 to 0.67), whereas for hysterectomy this was 0.49 (95% CI 0.15-1.5).

In the treatment of heavy menstrual bleeding, the bipolar radiofrequency endometrial ablation system is superior to hydrothermablation

Chapter 4 evaluates the 5-year follow-up results of the study described in chapter 3, comparing bipolar radiofrequency endometrial ablation with hydrothermablation for the treatment of HMB. At 5-year of follow-up, a questionnaire was sent to all the participants to register amenorrhea rates, reinterventions, and patient satisfaction.

At 5-year follow-up, response rates were 90% in the bipolar group and 83% in the hydrotherm group. Amenorrhea rates were 55.4% and 35.3% in the bipolar group and the hydrotherm group, respectively (RR 1.5, 95% CI 1.1-2.3). The number of surgical reinterventions was 11 compared with 23 (RR 0.43, 95% CI 0.2-0.8). Overall, more women were satisfied in the bipolar group compared with the hydrotherm group.

The results from this follow-up study showed that bipolar ablation has advantages over hydrothermablation. Higher amenorrhea rate, less re-interventions, and high levels of satisfaction were shown. So, the bipolar radiofrequency endometrial ablation system is more effective than hydrothermablation in the treatment of HMB.

Chapter 5 reports the health related quality of life of patients who participated in the randomized controlled trial described in chapter 3 and 4. Health related quality of life was assessed and compared between both groups. Patients were asked to complete quality of life questionnaires at baseline, 4 weeks, 6 and 12 months and 5 years after randomization. The medical outcomes study Short-Form (SF-36), Euroqol and menorrhagia assessment scale (Shaw), before randomization and at each follow-up visit were selected to evaluate quality of life. The menorrhagia outcomes questionnaire (MOQ) was completed at 4 weeks, 6 months and 12 months after treatment.

Quality of life improved significantly over time in all questionnaires. None of the quality of life dimensions showed a significant effect between both groups, neither was there a significant interaction between time and treatment. In all generic and disease specific questionnaires treatment of HMB improved health related quality of life over time. A treatment effect of amenorrhea and satisfaction did not result in quality of life benefits.

Chapter 6 describes a prospective cohort study to evaluate the safety, feasibility and efficacy of bipolar radiofrequency endometrial ablation under local anesthesia, which answers the third question:

Is it safe and acceptable to perform bipolar radiofrequency endometrial ablation with a paracervical block in the outpatient clinic?

Women with HMB were included to undergo bipolar radiofrequency endometrial ablation with a paracervical block. We measured the acceptability, pain score (visual analog scale) and patients' satisfaction during and after the procedure and amenorrhea at 6 weeks follow-up.

We treated 33 patients. No complications occurred during the procedure or postoperatively. Of the 33 women, 28 (85%) did found treatment with bipolar radiofrequency endometrial ablation under local anesthetics acceptable. After 24 hours, 23 of 33 (70%) women reported to be pain free, whereas 10 women

still had mild pain. Twenty women developed amenorrhea (61%) and 13 women hypomenorrhea (39%). All women were satisfied with the treatment result and would recommend it to a friend.

Bipolar radiofrequency endometrial ablation performed under local anesthesia seems a safe, feasible and efficacious procedure.

What is the effectiveness of bipolar radiofrequency endometrial ablation in the treatment of heavy menstrual bleeding compared to balloon endometrial ablation in the outpatient clinic in terms of amenorrhea, pain, satisfaction and quality of life?

Chapter 7 presents the results of a multi-center double blind randomized trial comparing the effectiveness of two second-generation ablation techniques, bipolar radiofrequency endometrial ablation (NovaSure®) and balloon endometrial ablation (Thermablate®), in the office with a paracervical block in patients with heavy menstrual bleeding. Patients were included between March 2009 and December 2011. Women with HMB were randomly allocated to bipolar or balloon endometrial ablation, performed in the office, using a paracervical block. The primary outcome was amenorrhea. Secondary outcome measures were pain, satisfaction, quality of life and re-interventions.

We included 104 women, of whom 52 were allocated to bipolar ablation and 52 to balloon ablation. Complications did not occur. The mean visual analog scale pain score of the total procedure was 7.1 in the bipolar group and 7.4 in the balloon group ($P<.577$). Amenorrhea rates were 60% (29/48) in the bipolar group and 27% (12/45) in the balloon group (RR 2.3, 95% CI 1.3 to 3.9) a 12-month follow-up. 94% (45/48) of the patients in the bipolar group were satisfied with the result of the treatment versus 80% (36/45) in the balloon group (RR 1.2, 95% CI 1.0 to 1.4). The reintervention rates were 5/52 (10%) in the bipolar group and 6/52 (12%) in the balloon group (RR 1.02, 95% CI 0.9 to 1.2). The Shaw score, expressing quality of life, improved over time ($P<.001$) and was significantly higher in the bipolar group at 12 months follow-up ($P=.025$).

Both second-generation ablation techniques used in the office with a paracervical block in this study are safe and easy to perform. However, based on the results of the current randomized trial, bipolar endometrial ablation appears to offer higher amenorrhea rates, patient satisfaction and quality of life.

Which endometrial ablation technique(s) is/are preferred in the treatment of heavy menstrual bleeding?

Chapter 8 reports a systematic review to compare the efficacy, safety and acceptability of methods used to destroy the endometrium in premenopausal women with heavy menstrual bleeding. Randomized controlled trials comparing different endometrial ablation techniques in women with a complaint of heavy menstrual bleeding without uterine pathology were eligible. The outcomes included reduction of heavy menstrual bleeding, improvement in quality of life, operative outcomes, satisfaction with the outcome, complications and need for further surgery or hysterectomy. Twenty five trials (4040 women with sample sizes ranging from 20 to 372) were included in the review.

In conclusion, the rapid development of a number of new methods of endometrial destruction has made systematic comparisons between individual methods and with the 'gold standard' first generation techniques difficult. Most of the newer techniques are technically easier than traditional hysteroscopy-based methods to perform but technical difficulties with new equipment need to be ironed out. Overall, the existing evidence suggests that success and satisfaction rates and complication profiles of newer techniques of ablation compare favorably with hysteroscopic techniques.

Chapter 9 provides a general discussion and implementations for future research.

Hoofdstuk 10

Samenvatting

Samenvatting

Hevig menstrueel bloedverlies is een belangrijk gezondheidsprobleem voor premenopauzale vrouwen. De incidentie varieert van 9% tot 22%. Menorragie wordt gedefinieerd als een regelmatige cyclus met hevig bloedverlies tijdens de menstruatie in combinatie met een lange duur van de menstruatie. Klinisch wordt menorragie gedefinieerd als maandelijks meer dan 80 ml bloedverlies. De afgelopen jaren heeft er een verandering plaats gevonden in terminologie, omdat er sprake was van een grote variatie waarin de termen abnormaal uterien bloedverlies, menorragie en dysfunctioneel uterien bloedverlies werden gebruikt. Er werd voorgesteld om abnormaal uterien bloedverlies als overkoepelende term te gebruiken, om alle vormen van symptomatisch bloedverlies tijdens de menstruatie of tijdens de menstruatiecyclus te beschrijven. Hevig menstrueel bloedverlies (HMB) werd voorgesteld al een geschikte vervanger van de term menorragie.

HMB heeft grote invloed op het fysieke, sociaal economisch en psychologisch welzijn van de vrouw. Wanneer de medicamenteuze behandeling niet helpt of een vrouw dit niet wenst, kunnen chirurgische interventies, zoals een endometriumablatie of een uterusextirpatie worden overwogen. Bij 30-40% van de patiënten wordt ter behandeling van het HMB een uterusextirpatie verricht. De tevredenheid na een uterusextirpatie is meestal hoog met hoge scores op kwaliteit van leven, maar het blijft een grote chirurgische behandeling met een complicatierisico tot 43%. Patiënt preferentie studies laten zien dat vrouwen het belangrijk vinden om hun uterus te behouden. Ze hebben een sterke voorkeur om een uterusextirpatie te voorkomen, maar wanneer zij een uterusextirpatie hebben gehad zijn ze meestal wel tevreden. Een alternatief voor een uterusextirpatie in de behandeling van HMB is een endometriumablatie. Het is een relatief kleine chirurgische procedure waarbij de uterus behouden blijft, maar toch het menstrueel bloedverlies wordt gereduceerd.

Endometriumablaties

De endometriumablatie werd geïntroduceerd in de jaren tachtig. Tijdens een endometriumablatie wordt de basale laag van het endometrium verwijderd of beschadigd. Het endometrium kan dan niet meer reageren op hormonale stimuli en hierdoor reduceert het menstrueel bloedverlies. De eerste endometriumablaties werden verricht met behulp van een hysteroscopie. Zij worden eerste generatie

endometriumablaties genoemd. De eerste generatie endometriumablatie technieken waren, laserablatie, transcervicale resectie van het endometrium (TCRE) en de rollerball ablatie. Na de introductie van de endometriumablatie was er een sterke reductie in het aantal verrichte uterusextirpaties. Maar de eerste generatie endometriumablatie technieken vereisen training en hebben een lange leercurve. Daarnaast hebben zij nog een ander groot nadeel. Glucose en Sorbitol worden beiden gebruikt als distensievloeistof tijdens de hysteroscopische endometriumablatie. Daarbij is een risico op absorptie van de distensievloeistof aanwezig. Als gevolg hiervan kan hyponatriemie, waterintoxicatie, cerebraal oedeem of overvulling ontstaan wat kan leiden tot een fatale hyponatremische encefalopathie. Daarom werden het afgelopen decennium tweede generatie niet-hysteroscopische technieken ontwikkeld, die deze nadelen niet hadden. Destructie van het endometrium bij de belangrijkste 'blinde' endometriumablatie methoden wordt bereikt door radiogolven (Microsulis®), hete vloeistof in een ballon (Thermachoice®, Cavaterm®, Thermablate®), bipolaire radiofrequente weerstand gecontroleerde energie (NovaSure®) en vrije vloeistof met een hoge temperatuur (Hydrothermablator®). De tweede generatie endometriumablatie technieken zijn veiliger, technisch simpeler en sneller te verrichten dan de eerste generatie technieken en omvatten een kortere opname in het ziekenhuis.

Na introductie van de endometriumablatie werd deze verricht op de operatiekamer met algehele anesthesie of spinaalanesthesie. Jaren later werd de endometriumablatie ook op de poliklinische operatiekamer verricht met een paracervicaal block, maar wel gecombineerd met intraveneuze sedatie. In één studie, waarin de ThermaChoice® en NovaSure® werden vergeleken, werd de intra-operatieve en postoperatieve pijn gemeten. Tijdens en na de behandeling met de NovaSure® gaven patiënten significant lagere pijnscores dan na de ThermaChoice®. Deze data ondersteunden het idee dat deze procedure een poliklinische behandeling zou kunnen worden met alleen lokaalanesthesie (paracervicaal block).

In dit proefschrift zullen de prognostische factoren voor het succes van een endometriumablatie worden behandeld, tevens worden de resultaten van verschillende tweede generatie endometriumablatie technieken, verricht op de operatiekamer en polikliniek, beschreven.

In **hoofdstuk 1** staat het doel van dit proefschrift beschreven. Dit doel is aan de hand van vijf vragen geformuleerd:

1. Wat zijn de prognostische factoren aan de hand waarvan het succes van een endometriumablatie kan worden voorspeld in de behandeling van hevig menstrueel bloedverlies?
2. Wat is de effectiviteit van bipolaire endometriumablatie in de behandeling van hevig menstrueel bloedverlies in vergelijking met hydrothermablatie, voor wat betreft amenorroe, tevredenheid, het aantal re-interventies en kwaliteit van leven na 12 maanden en 5 jaar follow-up?
3. Is het veilig en acceptabel om een bipolaire endometriumablatie op de polikliniek te verrichten met een paracervicaal block?
4. Wat is effectiviteit van bipolaire endometriumablatie in vergelijking met ballon endometriumablatie, in de behandeling van hevig menstrueel bloedverlies, voor wat betreft amenorroe, pijn, tevredenheid en kwaliteit van leven?
5. Welke endometriumablatie techniek(en) heeft/hebben de voorkeur in de behandeling van hevig menstrueel bloedverlies?

Hoofdstuk 2 onderzoekt factoren die invloed kunnen hebben op het slagen van de endometriumablatie in de behandeling van HMB, met speciale aandacht voor de sectio Caesarea in de anamnese.

Wat zijn de prognostische factoren aan de hand waarvan het succes van een endometriumablatie kan worden voorspeld in de behandeling van hevig menstrueel bloedverlies?

In een patiënt-controle studie werden patiënten vergeleken waarbij het resultaat van de endometriumablatie was geslaagd met patiënten waarbij de endometriumablatie niet was geslaagd. Patiënten met een niet geslaagde ablatie werden geïncludeerd als er een uterusextirpatie was verricht in verband met persisterend HMB na de endometriumablatie. Een succesvolle ablatie werd gedefinieerd als een ablatie voor HMB waarna geen uterusextirpatie werd verricht en de patiënt tevreden wat met het resultaat. De patiënten en controles werden geïdentificeerd uit het chirurgisch registratiesysteem in het Máxima Medisch Centrum, tussen januari 1999 en januari 2009. De patiënten waren vrouwen die een endometriumablatie en een uterusextirpatie hadden ondergaan. De controles hadden alleen een endometriumablatie gehad. Uit de medische status werd de klinische voorgeschiedenis achterhaald, de patiënt karakteristieken op het moment van de endometriumablatie, gegevens van de endometriumablatie en de follow-up van elke patiënt.

We vergeleken 76 patiënten met 76 controles. Binnen de patiënten hadden 12 vrouwen een sectio Caesarea in de anamnese versus 15 in the controle groep (15.8% versus 19.7%; odds ratio (OR) 0.76; 95% CI 0.3–1.8). Voorspellende factoren voor het falen van de endometriumablatie waren de aanwezigheid van dysmenorroe (OR 3.0; 95% CI 1.5–6.1), een submuceus myoom (OR 3.2; 95% CI 1.5–6.8) en de uteruslengte (per cm OR 1.3; 95% CI 1.0–1.6).

De aanwezigheid van tussentijds vaginaal bloedverlies, een sterilisatie in de voorgeschiedenis en de leeftijd waren niet geassocieerd met het falen van de endometriumablatie.Concluderend lijkt de sectio Caesarea in de voorgeschiedenis niet geassocieerd met een hogere kans op falen van de endometriumablatie, maar de aanwezigheid van dysmenorroe voor de behandeling, een submuceus myoom en een grote sondelengte zijn wel geassocieerd met een hogere kans op falen van de endometriumablatie. Dit is belangrijk om mee te nemen in de counseling van de patiënt die een endometriumablatie overweegt.

Wat is de effectiviteit van bipolaire endometriumablatie, in vergelijking met hydrothermablatie, in de behandeling van hevig menstrueel bloedverlies, voor wat betreft amenorroe, tevredenheid, het aantal re-interventies en kwaliteit van leven, na 12 maanden en 5 jaar follow-up?

De **hoofdstukken 3, 4** en **5** bespreken het antwoord op deze tweede vraag.

In **Hoofdstuk 3** worden de resultaten van een dubbelblinde gerandomiseerde studie gepresenteerd waarin de effectiviteit van twee tweede generatie endometriumablatie technieken wordt vergeleken in de behandeling van HMB, de bipolair radiofrequente weerstand gecontroleerde endometriumablatie (NovaSure®) en de hydrothermablatie (HTA®). Patiënten werden geïncludeerd tussen maart 2005 en augustus 2007. De primaire uitkomst was amenorroe. Secundaire uitkomsten waren tevredenheid en het aantal re-interventies.

Er werden 160 vrouwen geïncludeerd in de studie, 82 vrouwen werden gerandomiseerd voor een bipolaire ablatie en 82 voor een hydrothermablatie. Er traden geen complicaties op. Na 12 maanden was het percentage patiënten met een amenorroe 47% (35/75) in de bipolaire groep en 24% (17/71) in de hydrotherm groep (RR 2.0, 95% CI 1.2-3.1). In de bipolaire groep was 87% (65/75) van de patiënten zeer tevreden met het resultaat van de behandeling, vergeleken met 68% (48/71) in de hydrotherm groep (relatief risico (RR) 1.3, 95% CI 1.03-1.6).

Het relatief risico om een re-interventie te moeten ondergaan in de bipolaire groep vergeleken met de hydrotherm groep was 0.29 (95% CI 0.12 to 0.67), voor een uterusextirpatie was het relatief risico 0.49 (95% CI 0.15-1.5).

Concluderend geeft het bipolaire endometriumablatie systeem betere resultaten dan de hydrothermablatie in de behandeling van hevig menstrueel bloedverlies. De bipolaire groep heeft namelijk een hoger percentage amenorroe, minder re-interventies en meer patiënten zijn tevreden met het resultaat van de behandeling.

Hoofdstuk 4 evalueert de 5-jaars follow-up van de studie beschreven in hoofdstuk 3, waarin de bipolaire endometriumablatie en hydrothermablatie worden vergeleken in de behandeling van HMB. Vijf jaar na de behandeling werd een vragenlijst naar alle deelnemers verstuurd om het percentage amenorroe, re-interventies en patiënt tevredenheid te registreren.

Vijf jaar na de endometriumablatie had 90% van de vrouwen in de bipolaire groep de vragenlijst ingevuld versus 83% in de hydrotherm groep. Het percentage amenorroe was 55% in de bipolaire groep en 35% in de hydrotherm groep (RR 1.5, 95% CI 1.05-2.3). Het aantal re-interventies was 11 versus 23 (RR 0.43, 95% CI 0.23-0.80). In de bipolaire groep waren significant meer vrouwen tevreden met het resultaat van de behandeling dan in de hydrotherm groep.

De resultaten van deze follow-up studie laten zien dat bipolaire ablatie voordelen heeft ten opzichte van hydrotherm ablatie. De bipolaire groep heeft namelijk een hoger percentage amenorroe, minder re-interventies en meer patiënten zijn tevreden met het resultaat van de behandeling vijf jaar na de endometriumablatie. De bipolaire ablatie is dus effectiever in de behandeling van HMB dan de hydrothermablatie.

Hoofdstuk 5 rapporteert de kwaliteit van leven van de patiënten uit de gerandomiseerde studie zoals beschreven in hoofdstuk 3 en 4. De kwaliteit van leven werd beoordeeld en vergeleken tussen beide groepen. Patiënten vulden verschillende kwaliteit van leven vragenlijsten in voor de behandeling, en 4 weken, 6 maanden, 12 maanden en 5 jaar na randomisatie. De algemene gezondheidstoestand vragenlijst (SF-36), Euroqol en de menorragie vragenlijst (Shaw) werden voor randomisatie, en tijdens elk follow-up bezoek ingevuld om de kwaliteit van leven te evalueren. De menorragie uitkomst vragenlijst (MOQ) werd ingevuld 4 weken, 6 maanden en 12 maanden na de behandeling.

De kwaliteit van leven liet een significant tijdseffect zien in alle vragenlijsten, zowel de algemene als ziektespecifieke vragenlijsten. Geen van de kwaliteit van leven dimensies liet een significant behandeleffect tussen de groepen zien, of een interactie tussen tijd en behandeling. Een behandeleffect, dus een hoger percentage amenorroe en tevredenheid, liet geen kwaliteit van leven voordelen zien.

Hoofdstuk 6 beschrijft een prospectieve cohort studie die de veiligheid en geschiktheid van de bipolaire endometriumablatie met lokaalanesthesie onderzoekt. Dit beantwoord de derde vraag.

Is het veilig en acceptabel om een bipolaire endometriumablatie op de polikliniek te verrichten met een paracervicaal block?

Vrouwen die een bipolaire endometriumablatie (NovaSure®) wilden ondergaan op de poliklinische operatiekamer (POK) met een paracervicaal block, werden geïncludeerd in de studie. Wij registreerden de pijnscore (visueel analoge schaal), patiënt tevredenheid tijdens en na de behandeling, of patiënten de behandeling op de POK acceptabel vonden en het percentage amenorroe 6 weken na de behandeling.

Er werden 33 patiënten behandeld met de bipolaire endometriumablatie. Er traden geen complicaties op tijdens de procedure of postoperatief. Van de 33 patiënten vonden 28 patiënten (85%) de ablatie met lokaalanesthesie op de POK acceptabel. Vierentwintig uur na de behandeling rapporteerden 23 van de 33 patiënten (70%) dat zij pijn vrij waren en 10 patiënten hadden milde pijn. Twintig vrouwen hadden een amenorroe (61%) en 13 een hypomenorroe (39%). Alle patiënten waren tevreden met het resultaat van de behandeling en zouden het aanraden aan een vriendin.

Hieruit concluderend lijkt de bipolaire endometriumablatie verricht met lokaalanesthesie op de POK een veilige en werkzame procedure.

Wat is effectiviteit van de bipolaire endometriumablatie in vergelijking met ballon endometriumablatie, in de behandeling van hevig menstrueel bloedverlies, voor wat betreft amenorroe, pijn, tevredenheid en kwaliteit van leven?

Hoofdstuk 7 presenteert de resultaten van een multicenter dubbel blind gerandomiseerde studie waarin de effectiviteit van twee tweede generatie

endometriumablatie technieken wordt vergeleken, bipolaire radiofrequente endometriumablatie (NovaSure®) en ballon endometriumablatie (Thermablate®).

Patiënten werden geïncludeerd van maart 2009 tot december 2011. Vrouwen met HMB werden willekeurig gepland voor een bipolaire of een ballon endometriumablatie. De procedure werd verricht op de POK met een paracervicaal block. De primaire uitkomst was amenorroe. De secundaire uitkomsten waren pijn tijdens en na de behandeling, tevredenheid, kwaliteit van leven en het aantal re-interventies.

Er werden 104 vrouwen geïncludeerd, 52 ondergingen de bipolaire ablatie en 52 de ballon ablatie. Er traden geen complicaties op. De gemiddelde pijnscore (visueel analoge schaal) van de totale procedure was 7.1 in de bipolaire groep en 7.4 in de ballon groep ($P<.577$). Na 12 maanden was het percentage amenorroe 60% (29/48) in de bipolaire groep en 27% (12/45) in de ballon groep (RR 2.3, 95% CI 1.3 tot 3.9). 94% (45/48) van de patiënten in de bipolaire groep was tevreden met het resultaat van de behandeling versus 80% (36/45) in de ballon groep (RR 1.2, 95% CI 1.0 tot 1.4). Het aantal re-interventies was 5/52 (10%) in de bipolaire groep en 6/52 (12%) in de ballon groep (RR 1.02, 95% CI 0.9 tot 1.2). De kwaliteit van leven werd berekend met behulp van de menorragie vragenlijst score (Shaw). Er werd een significant tijdseffect gevonden ($P<.001$). De Shaw score was significant hoger in de bipolaire groep 12 maanden na de behandeling. ($P=.025$).

Beide tweede generatie endometrium ablatie technieken verricht in deze studie zijn veilig en makkelijk uit te voeren op de POK met een paracerviaal block. Maar, gebaseerd op de resultaten van deze gerandomiseerde studie, blijkt de bipolaire endometriumablatie een hoger percentage amenorroe, patient tevredenheid en een hogere score op kwaliteit van leven te geven.

Welke endometriumablatie techniek(en) heeft/hebben de voorkeur in de behandeling van hevig menstrueel bloedverlies?

In **Hoofdstuk 8** wordt een systematische review gerapporteerd waarin de werkzaamheid, veiligheid en aanvaardbaarheid van verschillende methoden om het endometrium te beschadigen worden vergeleken, in premenopauzale vrouwen met HMB. Voor deelname aan de review kwamen gerandomiseerde gecontroleerde studies in aanmerking waarin verschillende endometriumablatie technieken werden vergeleken bij vrouwen met HMB zonder intra-uteriene afwijkingen. De uitkomsten waren reductie van HMB, verbetering van kwaliteit van

leven, tevredenheid met het resultaat, complicaties en re-interventies zoals verdere chirurgische behandeling (incl. uterusextirpatie). Vijfentwintig studies (4040 vrouwen met een studiegrootte variërend van 20 tot 372) werden geïncludeerd in de review.

Concluderend is het systematisch vergelijken van verschillende individuele endometriumablatie methoden met de 'gouden standaard' eerste generatie technieken moeilijk. Dit komt door de snelle ontwikkeling van nieuwe methoden van endometriumdestructie. De meeste nieuwe technieken zijn technisch makkelijker te verrichten dan de hysteroscopische methoden, maar technische problemen met de nieuwe apparatuur moeten nog opgelost worden.
De bestaande studies laten wel zien dat het aantal geslaagde ablaties, de tevredenheid en complicaties van de nieuwe technieken vergelijkbaar zijn met de hysteroscopische technieken.

Hoofdstuk 9 tenslotte geeft een algemene beschrijving van de resultaten uit dit proefschrift, beschrijft de klinische implicaties en bevat aanbevelingen voor toekomstig onderzoek.

Chapter 11

Dankwoord

Dankwoord

Wat een fantastisch gevoel, mijn proefschrift is klaar! Het laatste half jaar heb ik fulltime de tijd gehad om aan mijn proefschrift te werken en daardoor is het ineens snel gegaan. Een proefschrift schrijven doe je niet alleen, maar met de hulp en steun van velen. Daarom wil ik graag iedereen bedanken die een bijdrage heeft geleverd aan mijn proefschrift, maar een aantal personen wil ik afzonderlijk bedanken.

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Curriculum Vitae

Josien Penninx werd geboren op 15 september 1980 te Nijmegen. Zij behaalde haar VWO diploma in 1999 aan de Scholengroep Cambium te Zaltbommel. Hetzelfde jaar startte zij met de opleiding Geneeskunde aan de Universiteit van Maastricht. In 2005 haalde zij Cum Laude haar artsexamen. Hierna werkte zij als ANIOS gynaecologie/obstetrie in het Orbis Medisch Centrum te Sittard, waarna ze in april 2007 begon als ANIOS gynaecologie/obstetrie in het Máxima Medisch Centrum te Veldhoven. Tijdens dit assistentschap startte ze, onder leiding van dr. M.Y. Bongers, met het onderzoek zoals beschreven in dit proefschrift. In januari 2010 werd zij aangenomen voor de opleiding tot gynaecoloog in Veldhoven.

Josien Penninx woont samen met Mathijs van Ballegooijen. Ze zijn de trotse ouders van hun zoon Joep (2 jaar) en dochter Roos (10 maanden).

Josien Penninx was born on the 15th of September 1980 in Nijmegen, The Netherlands. After finishing secondary school at the 'Scholengemeenschap Cambium' in Zaltbommel in 1999, she started her medical study at Maastricht University. In 1995 she graduated Cum Laude from medical school. After this, she worked as a resident at the department of Obstetrics and Gynecology in the Orbis Medical Centre in Sittard. In 2007 she continued her residency in the Máxima Medical Centre in Veldhoven/Eindhoven. During this period she started the PhD research, which resulted in this thesis under supervision of Dr. M.Y. Bongers. She started her specialist training on the first op January 2010 in Veldhoven. Josien Penninx lives together with Mathijs van Ballegooijen, they are the parents of their son Joep and daughter Roos.