J P Daniels, L J Middleton, R Champaneria, K S Khan, K Cooper, B W J Mol, S Bhattacharya on behalf of the International Heavy Menstrual Bleeding IPD Meta-analysis Collaborative Group
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RESEARCH

Second generation endometrial ablation techniques for heavy menstrual bleeding: network meta-analysis


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Abstract

Objective To determine the relative effectiveness of second generation ablation techniques in the treatment of heavy menstrual bleeding.

Design Network meta-analysis on the primary outcome measures of amenorrhoea, heavy bleeding, and patients' dissatisfaction with treatment.

Data sources Nineteen randomised controlled trials (involving 3287 women) were identified through electronic searches of the Cochrane Library, Medline, Embase and PsycINFO databases from inception to April 2011. The reference lists of known relevant articles were searched for further articles. Two reviewers independently selected articles without language restrictions.

Eligibility criteria for selecting studies Randomised controlled trials involving second generation endometrial destruction techniques for women with heavy menstrual bleeding unresponsive to medical treatment.

Results Of the three most commonly used techniques, network meta-analysis showed that bipolar radiofrequency and microwave ablation resulted in higher rates of amenorrhoea than thermal balloon ablation at around 12 months (odds ratio 2.51, 95% confidence interval 1.53 to 4.12, P<0.001; and 1.66, 1.01 to 2.71, P=0.05, respectively), but there was no evidence of a convincing difference between the three techniques in the number of women dissatisfied with treatment or still experiencing heavy bleeding. Compared with bipolar radio frequency and microwave devices, an increased number of women still experienced heavy bleeding after free fluid ablation (2.19, 1.07 to 4.50, P=0.03; and 2.91, 1.23 to 6.88, P=0.02, respectively). Compared with radio frequency ablation, free fluid ablation was associated with reduced rates of amenorrhoea (0.36, 0.19 to 0.67, P=0.004) and increased rates of dissatisfaction (4.79, 1.07 to 21.5, P=0.04). Of the less commonly used devices, endometrial laser intrauterine thermotherapy was associated with increased rates of amenorrhoea compared with all the other devices, while cryoablation led to a reduced rate compared with bipolar radio frequency and microwave.

Conclusions Bipolar radio frequency and microwave ablative devices are more effective than thermal balloon and free fluid ablation in the treatment of heavy menstrual bleeding with second generation endometrial ablation devices.

Introduction

Heavy menstrual bleeding is a common incapacitating problem in women of reproductive age,[1] which can severely affect their quality of life.[2 3] When medical treatments fail to provide adequate relief, surgical interventions, including hysterectomy or destruction of the endometrium, can be considered.[4] Initially, rollerball ablation, transcervical resection, and laser ablation were the predominant endometrial destruction techniques performed under direct hysteroscopic vision. These led to a rapid decrease in the number of hysterectomies performed.[5]

Over the past decade, a second generation of non-hysteroscopic techniques, which are safer, technically easier to perform, involve shorter hospital stays, and can be performed under local anaesthesia, have become dominant.[6 7] These involve devices that are sited and activated to treat the whole endometrial cavity. Destruction is achieved through various methods, the most commonly used[8] being high temperature fluids within a balloon

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Appendix 1: Search strategy
Appendix 2: Characteristics of included studies

(Thermachoice and Cavaterm)[9-11] or application of microwave (Microsulis)[12 13] or bipolar radiofrequency electrical energy (Novasure).[14] Less commonly used ablative techniques include free fluid at high temperature (Hydrothermablator),[15] endometrial laser intrauterine thermotherapy (ELITT),[16] and cryoablation (HerOption).[17] Other than free fluid thermal ablation, these are "blind" techniques. A recent meta-analysis of individual patient data found that second generation techniques were at least as effective, in terms of patients' dissatisfaction, as first generation techniques and, importantly, gave rise to fewer operative complications, were considerably quicker, and were less likely to need to be performed under general anaesthesia.[18] Thus they are clearly preferable to first generation techniques.

When more than two treatments options are available, the use of network meta-analysis, which allows us to combine both direct and indirect estimates for treatment effects, has become increasingly common.[19 20] Randomised comparisons within trials are preserved and the main assumption—that there are no systematic differences between the trials that could bias the indirect measurements—is similar to those underlying any standard meta-analysis.

There have been numerous randomised controlled trials comparing the different second generation techniques with each other or with first generation devices, yet with the sheer number of potential comparisons there are gaps in direct evidence for efficacy of some techniques, while other comparisons have low statistical power because of the small numbers randomised. We carried out a network meta-analysis to assess the relative effectiveness of six second generation techniques to provide both users and recipients of these devices with an improved evidence base to inform their decision making.

Methods

The systematic review was conducted based on a protocol designed with widely recommended methods[21 22] that complied with reporting guidelines for meta-analyses.[23]

Literature search and study selection

We carried out an extensive literature search in the Cochrane Library, Medline, Embase, and PsycINFO from inception to April 2011. Our search term combinations consisted of MeSH subheadings, text words and word variations for "heavy menstrual bleeding," and the various types of first and second generation endometrial destruction techniques. This search strategy was adapted to suit each database and was restricted to "humans" and "females" (see appendix 1). Bibliographies of known relevant primary articles and reviews were searched by hand to identify articles missed by the electronic searches. Were also contacted experts in the specialty to uncover any grey literature. A comprehensive database was constructed with Reference Manager 12.0 to store all identified references. No language restriction was applied.

Studies were selected in a two step process. Firstly, we scrutinised the citations identified by the electronic searches and subsequently obtained full manuscripts of citations that met or were thought to have met the predetermined inclusion criteria. We included studies if they recruited women with heavy, abnormal, excessive, or prolonged uterine bleeding that was unresponsive to initial medical treatment and the study design was a randomised controlled trial comparing endometrial ablation methods.

Data collection and study quality assessment

Two reviewers (LJM and RC) independently inspected all the manuscripts to determine if they met the above criteria. When possible we obtained individual patient data from the primary author using methods described in the related meta-analysis.[18] When raw data were not available, two independent reviewers (RC and LJM) used predesigned forms to extract aggregate data from manuscripts. Any disagreements were resolved by consensus or arbitration by a third reviewer (JPD).

Outcome measures used to evaluate the treatments were those most commonly used across studies (table 1⇓): rate of amenorrhoea (converted from a pictorial bleeding assessment score of zero when these data existed, otherwise as reported), rate of heavy bleeding (likewise converted from a pictorial bleeding assessment score of >100[24] when data existed, otherwise as reported), and rate of dissatisfaction with treatment (see related paper for a full description of how dissatisfaction was calculated).[18] We used data at 12 months (the most popular time point) as the focus for analysis or results at two years if 12 month data were not available.

Statistical analysis

For all three outcomes we first assessed direct estimates in individual trials by calculating point estimates and 95% confidence intervals. We then calculated a traditional weighted average meta-analysis yielding a Mantel-Haenszel odds ratio, with heterogeneity investigated with Cochran's Q[25] and I^2 statistics.[26]

We carried out the network meta-analysis by fitting a linear mixed model to the log odds ratio from each trial with the GLIMMIX procedure in SAS, using maximum likelihood to estimate treatment effects. Two models were attempted; the first included a fixed treatment effect and allowed the effect of the study to vary randomly. The second model also included a random effect for the difference in treatment in each trial by including a study by treatment interaction parameter.[27] The inclusion of a random study effect allowed the recovery of any differences between trials, which has greater importance when not all of the treatments are included in every trial, as is the case here.[28] We also included a random effect for treatment pair (that is, to separate those trials comparing different treatments types) in both models to allow for any inconsistency or "incoherence" in the model.[29] This effect (ω, the standard deviation of the random effect) allows for any indirect estimates to be inconsistent with any direct estimates of the same treatments and can be calculated where there any closed "loops" of treatments exist (for instance, A *v* B, B *v* C, A *v* C). Increased incoherence increases standard errors, and hence the size of the confidence interval, of differences between treatments. If large levels of incoherence are present it might not be sensible to combine estimates with this method,[30] analogous to having high levels of heterogeneity in a standard meta-analysis. We used Revman v5.0 (Cochrane Collaboration, Denmark) and SAS v9.2 (SAS Institute, Cary, NC) software for analysis.

Results

Trials and patients

We identified 719 citations through the electronic literature searches (fig 1⇓) and excluded 672 after screening titles and abstracts. A further 28 were excluded for being duplicate publications or not involving direct comparisons of endometrial ablative techniques. After detailed evaluation of the citations, 19 primary articles met the selection criteria and were included

in the network meta-analysis (see appendix 2 for full details of these 19 studies). These consisted of five head to head comparisons of second generation devices[31-35] (744 women) and 14 comparing a second generation device with a first generation (hysteroscopic) device[9 12 14-17 36-43] (2543 women) (fig 2⇓). Table 1 shows further descriptions of device type and the frequencies used in the analysis⇓. As the fixed and random effect network meta-analysis models produced similar results only those from the latter are described here.

Effectiveness in reducing bleeding

Direct comparisons show an increased rate of amenorrhoea with bipolar radio frequency ablation compared with thermal balloon ablation (odds ratio 4.56, 95% confidence interval 2.24 to 9.26; P<0.001) (table 2⇓). Free fluid thermal ablation was associated with reduced rates of amenorrhoea (0.36, 0.18 to 0.73; P=0.005) and increased rates of heavy bleeding (4.88, 1.32 to 18.11; P=0.02, table 3⇓) compared with bipolar radio frequency ablation. We found no other convincing differences. When there was more than one study in a comparison, estimates between studies were highly consistent (all I^2=0% apart from the comparison of amenorrhoea rates with microwave ablation versus first generation techniques where I^2=17%).

Results from the network meta-analysis (tables 2 and 3 and fig 3⇓) concurred with the results of the direct evidence, with an increased rate of amenorrhea with bipolar radio frequency ablation compared with thermal balloon ablation (2.51, 1.53 to 4.12; P<0.001). Results were also similar for the comparison between free fluid thermal ablation and bipolar radio frequency ablation for amenorrhoea (0.36, 0.19 to 0.67; P=0.004) and heavy bleeding (2.19, 1.07 to 4.50; P=0.03). There was an increase in the rate of amenorrhoea with radio frequency ablation compared with cryoablation in the indirect comparison (0.20, 0.09 to 0.49; P=0.002). Microwave ablation was associated with an increased rate of amenorrhoea compared with thermal balloon ablation (1.66, 1.01 to 2.71; P=0.05) and cryoablation (0.31, 0.13 to 0.74; P=0.01) and some reduction in the rate of heavy bleeding compared with free fluid ablation (2.91, 1.23 to 6.88; P=0.02). The endometrial laser intrauterine thermotherapy (ELITT) was associated with increased rates amenorrhoea compared with all the other devices, with wide confidence intervals reflecting the small number of women evaluated with this device in randomised controlled trials (table 2⇓). No other compelling differences between devices were noted. There were relatively low but variable rates of heavy bleeding across the studies (such as 0-32% for thermal balloon ablation and 8-18% for bipolar radiofrequency ablation).

Effectiveness in reducing dissatisfaction with treatment

Direct comparisons showed some evidence of reduced rates of dissatisfaction with bipolar radio frequency ablation compared with thermal balloon ablation (0.39, 0.16 to 0.91; P=0.03) (table 4⇓), though this difference was not as convincing in the network meta-analysis (0.56, 0.28 to 1.09; P=0.09). Increased dissatisfaction was seen with free fluid thermal ablation compared with bipolar radio frequency (9.40, 1.14 to 77.18; P=0.04) and a similar result was seen in the network meta-analysis (4.79, 1.07 to 21.48; P=0.04). There were no other obvious differences. Direct estimates between studies were also consistent for dissatisfaction where more than one study in a comparison existed (0%<I^2<4%). Overall rates of dissatisfaction were generally low (such as 0-7% for bipolar radiofrequency ablation).

Incoherence

Estimates of incoherence, ω, from the network model of amenorrhoea rate were relatively high at 0.23 compared with other studies that have used this technique to evaluate multiple treatments simultaneously.[19 30 44] When we removed the single trial comparing microwave ablation with thermal balloon ablation,[33] this estimate was reduced to 0.13. This trial's direct estimate yielded no significant difference between treatments (1.13, 0.70 to 1.82; P=0.6), which conflicted with the estimate expected by any indirect comparison where the network analysis favoured microwave ablation (1.66, 1.01 to 2.71; P=0.05). A sensitivity analysis of the network analysis with this trial excluded produced a higher estimate in favour of microwave ablation (2.23, 1.21 to 4.09; P=0.02), with some other minor adjustments to the other estimates (free fluid ablation was now associated with a lower amenorrhoea rate also compared with microwave ablation: 0.45, 0.21 to 0.97; P=0.04). Incoherence parameters for heavy bleeding and dissatisfaction, along with the interaction parameter for study by treatment, were estimated to be so close to zero that they were negligible and so effectively did not contribute to any estimates.

Discussion

Main findings

Of the three most popular second generation endometrial ablation devices (thermal balloon, bipolar radio frequency, and microwave) examined in this network meta-analysis, bipolar radio frequency and microwave ablation techniques seem to have an advantage over thermal balloon ablation in terms of increased amenorrhea rate in women with heavy menstrual bleeding. Compared with free fluid ablation, both bipolar radio frequency and microwave ablation techniques were associated with a reduction in the number of women still experiencing heavy bleeding. Radio frequency ablation was also associated with an increased amenorrhoea rate and a reduced number of women dissatisfied with treatment compared with free fluid ablation. Endometrial laser intrauterine thermotherapy (ELITT) was also associated with high rates of amenorrhoea compared with hysteroscopic ablation in the small single study that evaluated this technique. Not surprisingly this translated to estimates of amenorrhoea higher than the other devices when we combined results in the network meta-analysis. Conversely, cryoablation was associated with lower rates of amenorrhoea compared with bipolar radio frequency and microwave ablative techniques. Rates of dissatisfaction with treatment or ongoing heavy bleeding were generally low across all studies. Apart from the comparison of microwave ablation versus thermal balloon ablation, estimates from the network meta-analysis were consistent with available direct estimates between second generation devices in terms of direction and significance of treatment effect. The implication of this inconsistency from this one comparison is unclear.

Strengths and limitations of the review

We used the relatively new approach of network meta-analysis to synthesise data, and this provided effect estimates when direct comparisons were not available. We used optimal methods, complying with guidelines on reporting of systematic reviews and meta-analyses.[23] We carried out an extensive literature search, with no language restrictions, minimising the risk of missing information. The collection of individual patient data from some studies improved estimates.

The review was not intended to be a comprehensive review of all facets of these devices, and we focused only on outcomes of bleeding after treatment reported by patients and patients' dissatisfaction with treatment. Many other factors, such as ease of use and safety of device, are taken into account in the decision regarding a particular device. For example, the time to complete treatment is significantly shorter with bipolar radiofrequency ablation, and it results in greater coverage of the endometrial surface than thermal balloon ablation, in an outpatient setting.[31]

Because of the limited amount of data (several comparisons consisted of only one trial) and the fact that the traditional meta-analysis did not show any evidence of heterogeneity between estimates (I^2 was generally 0% and never greater than 17%) we did not attempt to further subgroup results by manufacturer or type (Thermachoice, Cavaterm, and the discontinued Vesta all are types of thermal balloon ablative device). This consistency could have occurred by chance, and there could be some differences because of the design of similar products. This could be reasonably evaluated only should more data become available. We considered that the first generation ablative techniques of transcervical endometrial resection and rollerball electrocoagulation were equivalent so we used them as a generic intermediate comparator.[45 46]

Estimates of incoherence were relatively high for the analysis of amenorrhoea rate (less when we omitted one of the studies in a sensitivity analysis), though how this impacts on adjusted estimates is debatable, given that confidence intervals of estimates were increased as a result. Like all meta-analysis, we must consider limitations with combining estimates from different studies because of clinical heterogeneity such as differences in populations of patients, even with statistical adjustments in the analysis. For example, the small study that compared endometrial laser intrauterine thermotherapy (ELITT) with first generation techniques seemed to show a large treatment effect. Given that none of the other studies has shown a comparable effect, there could be something particular about this study, such as the lower rate of amenorrhoea for the first generation comparator, that separates it from the rest, but in the absence of raw data, we were unable to investigate this further. Conversely, the absence of a significant difference does not necessarily mean that techniques are comparable but could be a consequence of small underpowered trial populations. This is reflected in wide confidence intervals for some of the estimates. We did not take into account quality of study in these analyses; the only requirement was that the study needed to be randomised in a specified population of patients.

The usefulness of the network meta-analysis in this setting was highlighted during the course of this review when we updated the analysis to include the results of the most recent study of bipolar radio frequency and free fluid endometrial ablation[32]; the first to compare these two treatments directly. Results from this study for the primary outcome measure of amenorrhoea rate at 12 months suggested improvements with radio frequency, with an odds ratio of 0.36 (0.17 to 0.73). Before inclusion of this later study, our original estimated odds ratio from the network meta-analysis was 0.33, which is similar albeit with a slightly wider confidence interval (0.11 to 0.98). Such an accurate estimate could of course occur by chance, but it does show how useful this analytical method could be where direct head to head assessments of treatments are not available.

Interpretation

Rates of dissatisfaction and heavy bleeding are consistently low for second generation techniques, which, as a group, represent an excellent conservative alternative to hysterectomy. It is clear from the results of our review that bipolar radiofrequency and microwave ablation technique are associated with higher amenorrhea rates than other methods, although it should be reiterated that only hysterectomy can guarantee complete cessation of menstrual bleeding. Endometrial laser intrauterine thermotherapy (ELITT) was associated with highly significant improvements in amenorrhea rates compared with all other methods, albeit from one small study, but this device is no longer marketed (C Dunn, Karl Storz, personal communication).

Data from UK hospital episode statistics show a significant increase in the overall number of inpatient endometrial ablative techniques (fig 4⇓), though radiofrequency ablation techniques are recently the most rapidly rising techniques used. These data do not include ambulatory procedures, which are also increasing rapidly but not adequately coded in the hospital episode data. More recently, the microwave endometrial ablation system from Microsulis has been withdrawn from the European market after Hologic acquired the intellectual property for the device (Microsulis Medical, press release, 2011). Ambiguous categorisation of first generation techniques in the episode data precludes comparison of relative rates, but consensus is that such techniques have rapidly been superseded.

With respect to costs and cost effectiveness, one study has directly compared thermal balloon and microwave ablative techniques.[47] The mean total health service cost per patient was £181 (£70 to £434) more (equivalent to about €219, $287) for the thermal balloon system than for the microwave ablative device (at 2010 costs), though the study found no significant differences between the total non-health costs and health benefits of the two devices. The incremental cost effectiveness ratio showed microwave ablation, on average, dominated thermal balloon ablation at one year after the procedure.

Our previous review indicated that levels of dissatisfaction with second generation techniques, as a class of procedure, were slightly lower than those associated with first generation techniques. Second generation techniques were also quicker, associated with faster recovery times and fewer adverse procedural events, and could be carried out under local anaesthesia.[18] Thus they should be offered when no structural or histological abnormality is present and the woman wants to retain her uterus. While chances of pregnancy are reduced after endometrial ablation, they can occur and such pregnancies have a high risk of adverse outcomes, hence continued contraception is strongly advised.[48]

As to the question of the best second generation technique, bipolar radiofrequency ablation seems to offer benefits over thermal balloon in terms of amenorrhea rates and is procedurally quicker than thermal balloon and microwave ablation.[31 33-35]. Any impact on other outcomes was not significant in either direct comparisons or network meta-analysis. Only two studies have evaluated the use of these three devices under local anaesthesia,[31 33] so while outpatient hysteroscopic treatment is feasible, it would be premature to state any advantage for either anaesthetic approach. The decision should be left to the women's preference and the operator's experience, though the withdrawal of the microwave ablation device reduces available choices.

Further large scale rigorous randomised trials to compare existing and emerging ablative techniques should use meaningful and standardised measures of satisfaction and menstrual bleeding and be run independently from the manufacturers of the devices. Trials incorporating different anaesthetic approaches will also help to refine the evidence available to women and gynaecologists. Concerns with regard to the safety of the "blind"

techniques with respect to extrauterine injury should lead to further evaluation of visual ablative techniques such as the next generation of free fluid ablation. Adequate assessment of relatively rare adverse events, however, would require large cohorts similar to the MISTLETOE study.[49]

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Members of Collaborative Group

The following authors provided us with individual patient data from their trials for this review: J Abbott, University of New South Wales, Sydney, Australia; M Y Bongers, Maxima Medical Centre, Veldhoven, Netherlands; J-L Brun, Hopital Universitaire Pellegrin, Bordeaux, France; T J Clark, Birmingham Women's Hospital, Birmingham, UK; J Cooper (2004 trial), data supplied by Microsulis Medical, Hampshire, UK; K G Cooper, Aberdeen Royal Infirmary, Aberdeen, UK; S L Corson (2001 trial), data supplied by Boston Scientific Corporation, Marlborough, US; J Hawe, Countess of Chester Hospital, Chester, UK; W R Meyer; data supplied by Ethicon, NJ, US; J P M Penninx, Maxima Medical Centre, Veldhoven, Netherlands; A M Sambrook, Aberdeen Royal Infirmary, Aberdeen, UK; I A van Zon-Rabelink, Medical Spectrum Twente, Enschede, Netherlands.

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What is already known on this topic

Second generation endometrial ablation techniques are preferable to first generation techniques in the treatment of heavy menstrual bleeding

Bipolar radiofrequency, thermal balloon, and microwave ablation techniques are the most commonly used and can safely be offered under local anaesthesia but there are insufficient data to recommend any particular technique

What this study adds

Bipolar radiofrequency endometrial ablation shows significant benefit in terms of amenorrhea rates compared with thermal balloon ablation, as does microwave ablation, but there is no evidence of any benefit of bipolar radiofrequency over microwave ablation

There is no evidence of greater dissatisfaction with any treatment in comparisons of bipolar radiofrequency, thermal balloon, or microwave ablation

Other and emerging methods of second generation endometrial ablation require more rigorous evaluation

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Tables

Table 1| Characteristics of included trials and event rates for amenorrhoea, heavy bleeding, and dissatisfaction in systematic review and network meta-analysis of second generation endometrial destruction techniques for heavy menstrual bleeding

Study	Primary outcome measure	Treatment device (manufacturer/trade name)	Amenorrhoea rate		Heavy bleeding rate		Dissatisfaction rate	
			2nd generation	1st generation	2nd generation	1st generation	2nd generation	1st generation
Studies comparing second generation treatments								
Clark 2011[31]	Amenorrhoea rate	Bipolar radio frequency (NovaSure)	14/25	—	2/25	—	2/28	—
		Thermal balloon (Thermachoice)	6/26	—	6/26	—	6/32	—
Penninx 2010[32]	Amenorrhoea rate	Bipolar radio frequency (NovaSure)	35/75	—	8/75	—	1/75	—
		Free fluid (BEI Medical Systems)	17/71	—	10/71	—	10/71	
Sambrook 2009[33]	Satisfaction rate	Microwave (Microsulis)	61/149	—	6/149	—	35/144	—
		Thermal balloon (Thermachoice)	51/134	—	7/134	—	31/134	—
Bongers 2004[34]	Amenorrhoea rate	Biploar radio frequency (NovaSure)	34/79	—	14/79	—	8/83	—
		Thermal balloon (Thermachoice)	3/38	—	7/38	—	8/43	—
Abbott 2003[35]	Amenorrhoea rate	Biploar radio frequency (NovaSure)	16/37	—	5/37	—	0/34	—
		Thermal balloon (Cavaterm)	2/17	—	0/17	—	1/15	—
Studies comparing second generation treatments with first generation hysteroscopic devices								
Brun 2006[36]	Amenorrhoea rate	Thermal balloon (Cavaterm)	11/30	5/17	2/30	2/17	2/21	3/16
Cooper 2004[37]	Heavy bleeding rate	Microwave (Microsulis)	120/194	49/96	5/194	5/96	3/196	1/97
Perino 2004[16]	Amenorrhoea rate	Laser (ELITT)	35/56	14/55	2/56	4/55	3/56	5/55
Duleba 2003[17]	Heavy bleeding rate	Cryoablation (HerOption)	43/156	40/72	19/156	5/72	16/156	10/72
Hawe 2003[38]	Amenorrhoea rate	Thermal balloon (Cavaterm)	10/30	13/28	1/30	1/28	2/30	1/28
Van Zon-Rabelink 2003[39]	Heavy bleeding rate	Thermal balloon (Thermachoice)	6/74	4/55	23/74	19/55	15/75*	13/58*
Cooper 2002[14]	Heavy bleeding rate	Biploar radio frequency (NovaSure)	63/154	29/82	14/154	10/82	11/154	5/82
Pellicano 2002[40]	Satisfaction rate	Thermal balloon (Cavaterm)	NA	NA	NA	NA	7/37	14/38
Corson 2001[15]	Heavy bleeding rate	Free fluid (BEI Medical Systems)	65/172	43/83	31/172	12/83	NA	NA
Soysal 2001[41]	Heavy bleeding rate	Thermal balloon (Thermachoice)	5/45	8/48	11/45	10/48	15/45	19/48
Corson 2000[42]	Heavy bleeding rate	Thermal balloon (Vesta)	38/122	39/112	16/122	19/112	NA	NA
Cooper 1999[12]	Satisfaction rate	Microwave (Microsulis)	46/116	48/124	9/116	11/124	27/116	32/124
Meyer 1998[9]	Heavy bleeding rate	Thermal balloon (Thermachoice)	18/122	32/117	18/122	13/117	5/122	1/116
Romer 1998[43]	Not stated	Thermal balloon (Cavaterm)	4/10	3/10	0/10	0/10	NA	NA

NA=not applicable (outcome not measured).

*Data from 24 months after randomisation but considered as 12 month data. All other data are follow-up data at 12 months after randomisation.

Table 2| Amenorrhoea rate at 12 months: results from direct comparisons and network meta-analysis. Figures are odds ratios (95% confidence intervals) for device in column compared with device in row. Odds ratio >1 indicate increased rate with device in column

	Thermal balloon	Bipolar radio frequency	Microwave	Cryoablation	Free fluid	Laser
First generation device						
Direct	0.72 (0.52 to 1.01); P=0.06*	1.27 (0.73 to 2.20); P=0.4†	1.28 (0.90 to 1.83); P=0.2‡	0.30 (0.17 to 0.55); P<0.001†	0.57 (0.33 to 0.96); P=0.03†	4.88 (2.17 to 11.00); P<0.001†
Network	0.69 (0.49 to 0.97); P=0.03	1.73 (1.07 to 2.78); P=0.03	1.14 (0.73 to 1.79); P=0.5	0.35 (0.17 to 0.75); P=0.01	0.62 (0.34 to 1.13); P=0.1	4.36 (1.82 to 10.44); P=0.002
Thermal balloon						
Direct	—	4.56 (2.24 to 9.26); P<0.001*	1.13 (0.70 to 1.82); P=0.6†	NA	NA	NA
Network	—	2.51 (1.53 to 4.12); P<0.001	1.66 (1.01 to 2.71); P=0.05	0.51 (0.23 to 1.17); P=0.1	0.91 (0.48 to 1.73); P=0.7	6.34 (2.50 to 16.07); P<0.001
Bipolar radio frequency						
Direct	—	—	NA	NA	0.36 (0.18 to 0.73); P=0.005†	NA
Network	—	—	0.66 (0.36 to 1.21); P=0.2	0.20 (0.09 to 0.49); P=0.002	0.36 (0.19 to 0.67); P=0.004	2.52 (0.95 to 6.71); P=0.06
Microwave						
Direct	—	—	—	NA	NA	NA
Network	—	—	—	0.31 (0.13 to 0.74); P=0.01	0.55 (0.27 to 1.13); P=0.09	3.82 (1.46 to 10.01); P=0.009
Cryoablation						
Direct	—	—	—	—	NA	NA
Network	—	—	—	—	1.77 (0.69 to 4.58); P=0.2	12.37 (3.96 to 38.59); P<0.001
Free fluid						
Direct	—	—	—	—	—	NA
Network	—	—	—	—	—	6.98 (2.48 to 19.69); P<0.001

NA=not available.

*I^2=0%.

†I^2=not applicable, only one study in comparison.

‡I^2=17%.

Table 3| **Heavy bleeding rate at 12 months: results from direct comparisons and network meta-analysis. Figures are odds ratios (95% confidence intervals) for device in column compared with device in row. Odds ratio >1 indicate increased rate with device in column**

	Thermal balloon	Bipolar radio frequency	Microwave	Cryoablation	Free fluid	Laser
First generation device						
Direct	0.97 (0.66 to 1.41); P=0.9*	0.72 (0.30 to 1.70); P=0.5†	0.71 (0.34 to 1.50); P=0.4*	1.86 (0.67 to 5.19); P=0.2†	1.30 (0.63 to 2.69); P=0.5†	0.47 (0.08 to 2.69); P=0.4†
Network	0.98 (0.69 to 1.39); P=0.9	0.95 (0.56 to 1.62); P=0.8	0.59 (0.32 to 1.09); P=0.09	1.55 (0.63 to 3.81); P=0.3	1.37 (0.74 to 2.51); P=0.3	0.39 (0.07 to 2.09); P=0.3
Thermal balloon						
Direct	—	1.02 (0.46 to 2.29); P=1.0*	0.76 (0.25 to 2.32); P=0.6†	NA	NA	NA
Network	—	0.82 (0.47 to 1.44); P=0.5	0.62 (0.32 to 1.18); P=0.1	1.62 (0.62 to 4.24); P=0.3	1.80 (0.90 to 3.57); P=0.09	0.41 (0.07 to 2.27); P=0.3
Bipolar radio frequency						
Direct	—	—	NA	NA	4.88 (1.32 to 18.11); P=0.02†	NA
Network	—	—	0.75 (0.34 to 1.66); P=0.5	1.98 (0.70 to 5.60); P=0.2	2.19 (1.07 to 4.50); P=0.03	0.50 (0.09 to 2.89); P=0.4
Microwave						
Direct	—	—	—	NA	NA	NA
Network	—	—	—	2.63 (0.89 to 7.78); P=0.08	2.91 (1.23 to 6.88); P=0.02	0.66 (0.11 to 3.96); P=0.6
Cryoablation						
Direct	—	—	—	—	NA	NA
Network	—	—	—	—	1.11 (0.37 to 3.29); P=0.9	0.25 (0.04 to 1.70); P=0.2
Free fluid						
Direct	—	—	—	—	—	NA
Network	—	—	—	—	—	0.23 (0.04 to 1.36); P=0.1

NA=not available.

*I^2=0%.

†I^2=not applicable, only one study in comparison.

Table 4| **Dissatisfaction rate at 12 months: results from direct comparisons and network meta-analysis. Figures are odds ratios (95% confidence intervals) for device in column compared with device in row. Odds ratio >1 indicate increased rate with device in column**

	Thermal balloon	Bipolar radio frequency	Microwave	Cryoablation	Free fluid	Laser
First generation device						
Direct	0.80 (0.50 to 1.27); P=0.3*	1.18 (0.40 to 3.53); P=0.8†	0.90 (0.51 to 1.60); P=0.7‡	0.71 (0.30 to 1.65); P=0.4†	NA	0.57 (0.13 to 2.49); P=0.5†
Network	0.91 (0.61 to 1.36); P=0.6	0.51 (0.25 to 1.01); P=0.05	0.93 (0.59 to 1.47); P=0.7	0.93 (0.59 to 1.47); P=0.7	3.14 (0.66 to 14.83); P=0.1	0.54 (0.12 to 2.43) P=0.4
Thermal balloon						
Direct	—	0.39 (0.16 to 0.91); P=0.03‡	1.07 (0.61 to 1.86); P=0.8†	NA	NA	NA
Network	—	0.56 (0.28 to 1.09); P=0.09	1.02 (0.65 to 1.60); P=0.9	0.79 (0.31 to 2.05); P=0.6	2.66 (0.55 to 12.96); P=0.2	0.59 (0.12 to 2.78); P=0.5
Bipolar radio frequency						
Direct	—	—	NA	NA	9.40 (1.14 to 77.18); P=0.04†	NA
Network	—	—	1.83 (0.85 to 3.95); P=0.1	1.42 (0.47 to 4.29); P=0.5	4.79 (1.07 to 21.48); P=0.04	1.06 (0.20 to 5.51); P=0.9
Microwave						
Direct	—	—	—	NA	NA	NA
Network	—	—	—	0.78 (0.29 to 2.07); P=0.6	2.62 (0.52 to 13.23); P=0.2	0.58 (0.12 to 2.79); P=0.5
Cryoablation						
Direct	—	—	—	—	NA	NA
Network	—	—	—	—	3.37 (0.56 to 20.39); P=0.2	0.74 (0.13 to 4.25); P=0.7
Free fluid						
Direct	—	—	—	—	—	NA
Network	—	—	—	—	—	0.22 (0.03 to 1.95); P=0.2

NA=not available

*I^2=4%

†I^2=not applicable, only one study in comparison.

‡I^2 =0%.

Figures

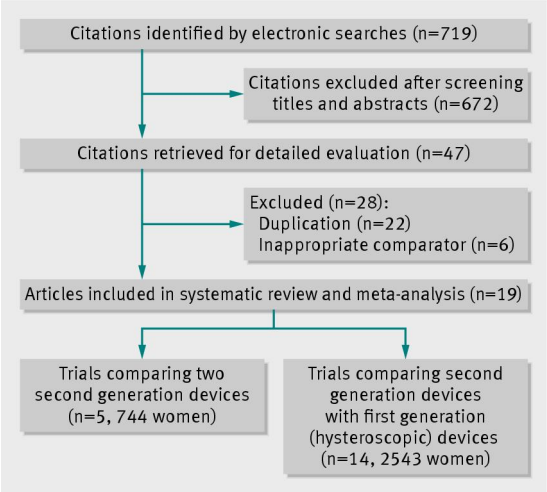

Fig 1 Study selection process for systematic review and network meta-analysis of second generation endometrial destruction techniques for heavy menstrual bleeding

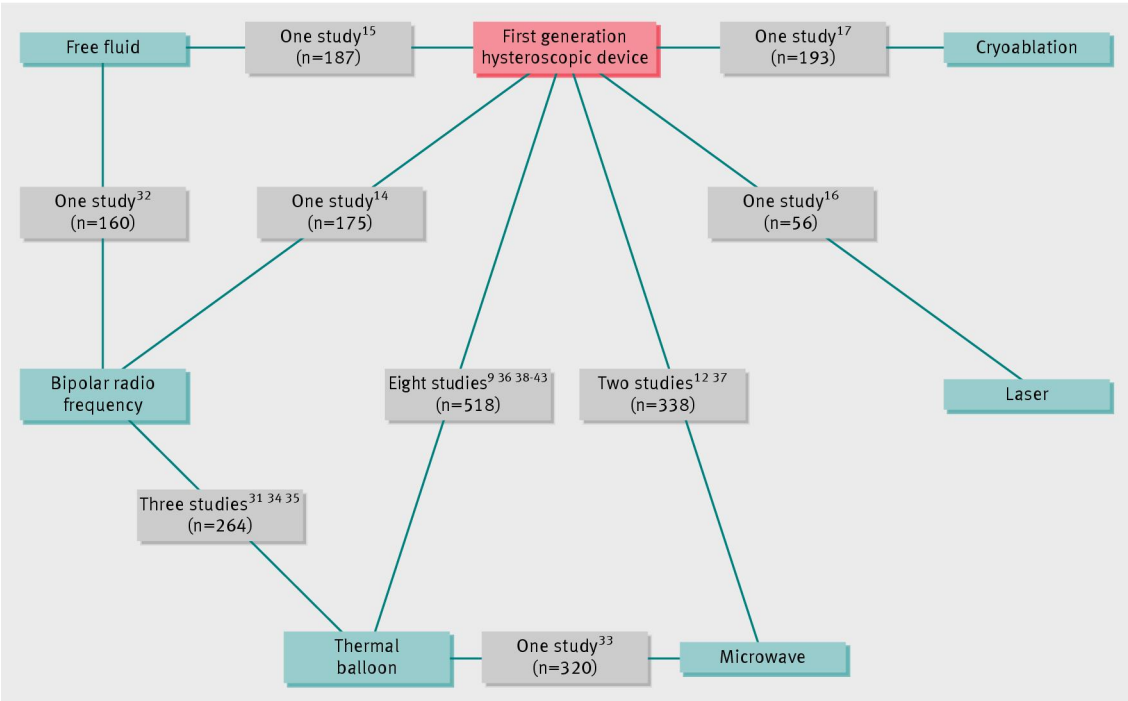

Fig 2 Network of studies evaluating second generation endometrial destruction devices for treatment of heavy menstrual bleeding. Number of women randomised to second generation treatment are shown in parentheses

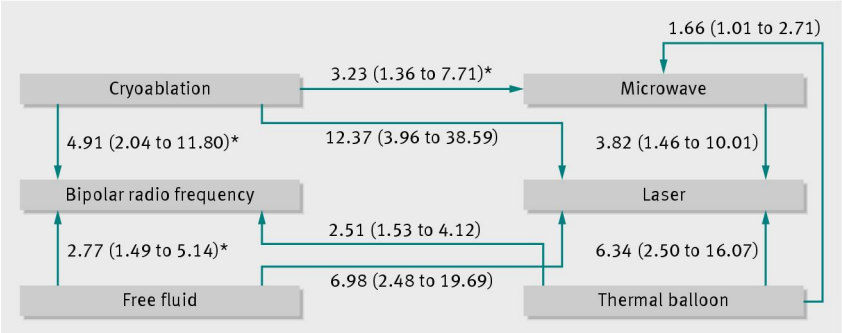

Fig 3 Amenorrhoea rate at 12 months from network meta-analysis (odds ratio and 95% confidence intervals). Results reflect those in table 2 (*indicates reversed ratios so all are pointing in direction of increased amenorrhoea rate). Only results with P≤0.05 are shown

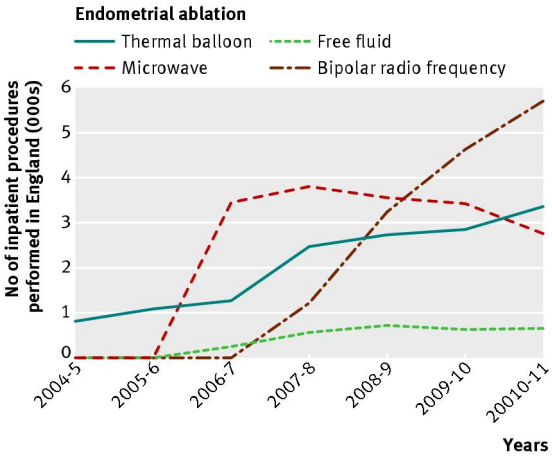

Fig 4 Trends in types of endometrial ablation procedures performed in England, 2004-11 (data from hospital episode statistics)