

Hysterectomy, endometrial ablation and Mirena® for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis

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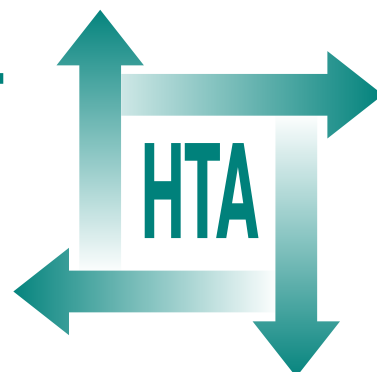


Executive summary

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Executive summary

Background

Heavy menstrual bleeding (HMB) is a common problem that affects approximately 1.5 million women in England and Wales and accounts for 20% of gynaecology outpatient referrals. Although objectively defined as cyclical loss of > 80 ml of blood during each menstrual period, HMB is diagnosed clinically in the presence of excessive menstrual blood loss that interferes with a woman's physical, emotional, social and material quality of life.

Medical treatments for HMB include oral drug regimens, such as tranexamic acid and mefenamic acid, and the combined oral contraceptive pill as well as the levonorgestrel intrauterine system (LNG IUS) (Mirena®, Bayer Healthcare Pharmaceuticals, Pittsburg, PA, USA), which can reduce menstrual loss by local release of progestogen. Surgical treatments include first- (hysteroscopic) and second- (non-hysteroscopic) generation endometrial ablation (EA), which destroys the lining of the cavity of the uterus (endometrium), and hysterectomy (surgical removal of the uterus). First-generation ablation techniques include endometrial laser ablation, transcervical resection of the endometrium and rollerball (RB) ablation. Examples of second-generation ablative techniques are fluid-filled thermal balloon endometrial ablation, radiofrequency (thermoregulated) balloon endometrial ablation, hydrothermal endometrial ablation, microwave EA (MEA) and impedance-controlled bipolar radiofrequency ablation (NovaSure®; Hologic Inc., Bedford, MA, USA).

In 1999–2000, half of the 51,858 hysterectomies performed in the public sector in England were for HMB. In contrast, 7179 hysterectomies were performed for HMB in 2004–5 while 9701 women underwent EA – over half of these (5457) by means of second-generation (non-hysteroscopic) techniques. The use of Mirena has increased concurrently, although its widespread use for contraception across a number of clinical settings in primary and secondary care means that it is difficult to gather accurate data on numbers prescribed for HMB.

Objective

The aim of this project was to determine the clinical effectiveness and cost-effectiveness of hysterectomy, first- and second-generation EA, and Mirena for the treatment of HMB. To address this question, the specific objectives were:

1. To determine, using individual patient data (IPD) meta-analysis of existing randomised controlled trials (RCTs), the short- to medium-term effects of each class of treatment in terms of patient dissatisfaction, time to resumption of normal activities and complication rate, and to explore these outcomes in clinical subgroups.
2. To report, using population-based data from record linkage, the long-term effects of ablative techniques and hysterectomy in terms of failure rates and complications.
3. To inform current treatment policy in this clinical area, while the value of information component serves to highlight future research needs and agendas, and inform possible future research funding decisions.

Design

Systematic review and individual patient data meta-analysis of available evidence

A detailed search was carried out to identify systematic reviews and RCTs involving hysterectomy, EA and Mirena. IPD were sought from RCTs of hysterectomy, EA techniques and Mirena to examine their relative effectiveness. A systematic review was conducted based on a protocol designed using widely recommended methods that complied with meta-analysis reporting guidelines.

Individual patient data on 2814 women were available from 17 of the 30 RCTs identified (14 trials including 2448 women for first- vs second-generation EA; seven trials including 1127 women for hysterectomy vs first-generation EA; five trials including 304 women for second-generation EA vs Mirena; three trials including 190 women for first-generation EA vs Mirena; one trial including 236 women for hysterectomy vs Mirena). Direct and indirect comparisons were made where appropriate to assess the effect of interventions on the primary outcome measure of patient dissatisfaction.

Follow-up of women following hysterectomy and endometrial ablation by record linkage

Patient-based data for inpatient and day case activity from the whole of Scotland which are routinely collected as Scottish Morbidity Returns (SMR) by the Scottish Information Services Division (ISD) were used for this study. Following linkage with the Scottish Cancer Registry, an anonymised data set containing follow-up hospital data on all women who had undergone either hysterectomy or EA for HMB between 1989 and 2006 was made available to the researchers. Socioeconomic status was assessed using the Carstairs index, which was divided into quintiles for analysis. Descriptive statistics were used to summarise each of the surgical outcomes and potential predictor variables (age, year of procedure and Carstairs quintile). Appropriate univariate analyses across the hysterectomy and EA groups were performed. Cox proportional hazards regression analysis was used to examine the survival experience for different surgical outcomes in the hysterectomy and EA groups and then between different types of hysterectomy following adjustment for age, year of primary operation and Carstairs quintile.

Cost-effectiveness evaluation

The authors developed a state transition (Markov) model using Microsoft EXCEL (Microsoft Corporation, Seattle, WA, USA). The structure was informed by the review of the clinical literature supplemented by clinical input. The model allows a comparison of four hypothetical cohorts of women with HMB who are treated separately by one of four alternative strategies: (1) Mirena coil; (2) first-generation EA techniques; (3) second-generation EA techniques; and (4) hysterectomy. Given the reliance on secondary data and the availability of data, the model-based economic evaluation takes the form of a cost–utility analysis and was carried out from the perspective of the UK NHS in a secondary care setting. The results are reported in terms of incremental cost per quality-adjusted life-year (QALY) gained based on quality of life data available from published sources. The presentation of results in QALYs allows comparison of the results with other available and recently published studies [Garside R, Stein K, Wyatt K, Round A, Price A. The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling. *Health Technol Assess* 2004;8(3)]. Resource use was estimated from the existing published evidence and additional cost data from other sources such as the annual review of unit health and social care costs (Personal Social Services Research Unit) and national schedule for reference costs.

Results

Clinical effectiveness from individual patient data meta-analysis

At around 12 months, 7.3% more women [12.6% (57/454) vs 5.3% (23/432)] were dissatisfied with the outcome of first-generation EA than with hysterectomy [OR (odds ratio) 2.46, 95% confidence interval (CI) 1.54 to 3.93; $p = 0.0002$], but hospital stay [WMD (weighted mean difference) 3.0 days, 95% CI 2.9 to 3.1 days; $p < 0.00001$] and time to resumption of normal activities (WMD 5.2 days, 95% CI 4.7 to 5.7 days; $p < 0.00001$) were longer for hysterectomy. Unsatisfactory outcomes were comparable with first- and second-generation EA techniques [12.2% (123/1006) vs 10.6% (110/1034); OR 1.20, 95% CI 0.88 to 1.62; $p = 0.2$], although second-generation techniques were quicker (WMD 14.5 minutes, 95% CI 13.7 to 15.3 minutes; $p < 0.00001$) and women recovered sooner (WMD 0.48 days, 95% CI 0.20 to 0.75 days; $p = 0.0008$) with fewer procedural complications. Indirect comparison suggested more unsatisfactory outcomes with second-generation EA techniques than with hysterectomy [10.6% (110/1034) vs 5.3% (23/432); OR 2.32, 95% CI 1.27 to 4.24; $p = 0.006$].

Rates of dissatisfaction with Mirena and second-generation EA were similar [18.1% (17/94) vs 22.5% (23/102); OR 0.76, 95% CI 0.38 to 1.53; $p = 0.4$]. Overall rates of dissatisfaction were 17.2% (22/128) for Mirena and 18.2% (25/137) for both first- and second-generation EA. Lack of IPD prohibited any further investigation of subgroups or repeated measures.

Indirect estimates suggest that hysterectomy is also preferable to second-generation EA (OR 2.32, 95% CI 1.27 to 4.24; $p = 0.006$) in terms of patient dissatisfaction. This is confirmed by the repeated measures analysis over all three time points, which only include IPD (OR 3.06, 95% CI 1.59 to 5.90; $p = 0.0008$). The evidence to suggest that hysterectomy is preferable to Mirena was weaker (OR 2.22, 95% CI 0.94 to 5.29; $p = 0.07$), but given the lack of precision from Mirena comparisons this was not a surprising result.

Medium- to long-term surgical outcomes following endometrial ablation and hysterectomy for heavy menstrual bleeding

Between 1989 and 2006, 37,120 Scottish women underwent hysterectomy and 11,299 had EA as a primary surgical procedure for HMB. The median [interquartile range (IQR)] duration of follow-up was 6.2 (2.7–10.8) and 11.6 (7.9–14.8) years, respectively, in the EA and hysterectomy cohorts.

A total of 2779 women in the original EA group went on to have a hysterectomy and were excluded from further analysis.

Of the remaining women originally treated by EA, 962 (8.5%) underwent further gynaecological surgery. While the risk of adnexal surgery was similar in both groups, women who had undergone hysterectomy were more likely to need further surgery for stress urinary incontinence. Vaginal hysterectomy was associated with a significantly higher chance of further surgery for urinary incontinence and pelvic floor repair than hysterectomy carried out through the abdominal route. The incidence of endometrial cancer following endometrial ablation was low at 0.02%.

Cost-effectiveness

The results of the cost-effectiveness model show that the strategy of hysterectomy is the most cost-effective. Hysterectomy dominates the first-generation EA strategy and, although more expensive, produces more QALYs than the other strategies of second-generation EA and Mirena. The incremental cost-effectiveness ratios for hysterectomy compared with Mirena and

hysterectomy compared with second-generation ablation are £1440 per additional QALY and £970 per additional QALY, respectively.

Discussion

Strengths and limitations of the analysis

For the systematic review, an extensive literature search was conducted, with no language restrictions, minimising the risk of missing information.

A limitation of the systematic review was the unavailability of IPD from at least 35% of randomised women, which could not be accessed as a number of triallists did not agree to collaborate or could not be contacted. Received data were sometimes incomplete and, on occasions, failed quality checks, and so were unusable. The review's inferences are also limited by the inconsistent outcome measure used across trials; studies involving endometrial destruction (ED) and Mirena focused on comparing reduction in bleeding, while hysterectomy trials focused on patient satisfaction and quality.

The follow-up study on women who had undergone hysterectomy or EA is, to our knowledge, the first large population-based study to use national data. Use of the *International Classification of Diseases* codes allowed us to define both the cause of HMB as well as the nature of surgery, but, as the diagnosis of dysfunctional uterine bleeding was performed by a process of exclusion, it is possible that the hysterectomy cohort could have included a few women with other causes of HMB. As a retrospective observational study, it is not free from problems of bias and confounding. The analysis was compromised by the limited availability of key socioeconomic as well as clinical variables. Although the numbers of women in the hysterectomy and ablation cohorts were large, a major drawback was our inability to discriminate between the individual types of first- and second-generation EA or adjust for the experience of the operator as has been done in previous national audits. We were also unable to analyse the long-term outcomes following laparoscopic hysterectomy as numbers were small and these were grouped with abdominal hysterectomy.

The major strength of the economic component of this study is that it was based on a state-of-the-art Markov model which was informed by data from an IPD meta-analysis of randomised trials. A multidisciplinary team including economists, expert clinicians and statisticians provided input into the model structure, primarily based on the evidence in the literature. All assumptions used in the model were made a priori, and were based on the best available evidence.

The quality of the health economic model was affected by the paucity of good-quality data such as those related to adverse outcomes following some types of EA and follow-up data on Mirena use. In addition, the complexity of the model meant a long running time, which inevitably affected the number and nature of additional sensitivity analyses undertaken.

Interpretation of available evidence and consensus regarding treatment

More women were dissatisfied following EA than hysterectomy. However, dissatisfaction rates were low after all treatments and hysterectomy was associated with an increased hospital stay and recovery period. The paucity of suitable trials means that definitive evidence on the effectiveness of Mirena compared with more invasive procedures is lacking. Hysterectomy would be considered the most cost-effective strategy in the light of the acceptable thresholds used by the National Institute for Health and Clinical Excellence (NICE). The results concur with those of other studies, but are sensitive to utility values used in the analysis.

A summary of the results on the clinical effectiveness and cost-effectiveness of Mirena, EA and hysterectomy was sent electronically to 15 national experts (gynaecological surgeons) along with a short questionnaire to encourage rapid response. After two mailings, responses were received from 10 clinicians, 9 of whom indicated that having considered effectiveness, cost-effectiveness and invasiveness/risks they would favour HMB LNG IUS (Mirena), second-generation EA techniques and hysterectomy as first-, second- and third-line approaches to HMB resistant to oral medication. This view was endorsed by three consumers who highlighted the need for a degree of flexibility in order to accommodate the preferences of individual women.

Conclusion

Although hospital stay and time to resumption of normal activities were longer, more women were satisfied after hysterectomy than after first-generation EA. In the absence of head-to-head trials, indirect estimates suggest that hysterectomy is also preferable to second-generation EA in terms of patient satisfaction. Dissatisfaction rates were comparable between first- and second-generation techniques, although second-generation techniques were cheaper, quicker and associated with faster recovery and fewer complications. There are few comparisons of Mirena with more invasive procedures.

The few data available suggest that Mirena is potentially cheaper and more effective than first-generation ablation techniques with rates of satisfaction that are similar to those of second-generation techniques. Owing to a paucity of trials, there is limited evidence to suggest that hysterectomy is preferable to Mirena. Hysterectomy is considered the most cost-effective strategy, but, owing to its invasive nature and higher risk of complications, is considered a final option by gynaecological experts and consumers.

Implications for service provision

Our review provides evidence that hysterectomy reduces dissatisfaction compared with EA, and this information could contribute to a consultation with women making a choice about treatment options when initial drug treatment fails to control HMB. EA is satisfactory for a very high proportion of women, but, if complete cessation of bleeding is sought, then hysterectomy may be offered. A decision to opt for hysterectomy needs also to take into account the invasive nature of the procedure and its potential for short- and long-term morbidity in some women.

Although conclusive evidence from randomised trials is still awaited, the evidence from our review is consistent with a recent NICE recommendation that women should be offered Mirena before more invasive procedures. This view reflects the minimally invasive nature of the intervention as well as the ability to offer it in primary care. This piece of research has highlighted the benefits and risks associated with the three broad strategies for the treatment of HMB and, while supportive of the existing NICE guideline on this subject, our results underline the need for a degree of flexibility in accommodating women's preferences.

Need for further research

This project has uncovered a number of areas for future research. These include:

- evaluation of the clinical effectiveness and cost-effectiveness of the best second-generation EA technique under local anaesthetic versus Mirena
- exploring the safety of second-generation EA and Mirena through a national audit
- longer term follow-up of randomised cohorts of women treated for HMB

- evaluation of the clinical effectiveness and cost-effectiveness of hydrothermablator (HA, the second-generation EA device which can be used under direct vision) against other second-generation techniques
- trials assessing conservative and less morbid types of hysterectomy such as laparoscopic supracervical hysterectomy versus conventional hysterectomy and second-generation EA.

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Publication

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NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/45/02. The contractual start date was in September 2007. The draft report began editorial review in February 2010 and was accepted for publication in September 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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