Hysterectomy, endometrial ablation and Mirena[®] for heavy menstrual bleeding: a systematic review of clinical effectiveness and costeffectiveness analysis

S Bhattacharya, LJ Middleton, A Tsourapas, AJ Lee, R Champaneria, JP Daniels, T Roberts, NH Hilken, P Barton, R Gray, KS Khan, P Chien, P O'Donovan, KG Cooper and the International Heavy Menstrual Bleeding Individual Patient Data Meta-analysis Collaborative Group



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Abstract

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

S Bhattacharya,^{1*} LJ Middleton,² A Tsourapas,² AJ Lee,¹ R Champaneria,² JP Daniels,² T Roberts,² NH Hilken,² P Barton,² R Gray,² KS Khan,² P Chien,³ P O'Donovan,⁴ KG Cooper⁵ and the International Heavy Menstrual Bleeding Individual Patient Data Meta-analysis Collaborative Group[†]

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Objective: The aim of this project was to determine the clinical effectiveness and costeffectiveness of hysterectomy, first- and second-generation endometrial ablation (EA), and Mirena[®] (Bayer Healthcare Pharmaceuticals, Pittsburgh, PA, USA) for the treatment of heavy menstrual bleeding.

Design: Individual patient data (IPD) meta-analysis of existing randomised controlled trials to determine the short- to medium-term effects of hysterectomy, EA and Mirena. A population-based retrospective cohort study based on record linkage to investigate the long-term effects of ablative techniques and hysterectomy in terms of failure rates and complications. Cost-effectiveness analysis of hysterectomy versus first- and second-generation ablative techniques and Mirena.

Setting: Data from women treated for heavy menstrual bleeding were obtained from national and international trials. Scottish national data were obtained from the Scottish Information Services Division.

Participants: Women who were undergoing treatment for heavy menstrual bleeding were included.

Interventions: Hysterectomy, first- and second-generation EA, and Mirena. **Main outcome measures:** Satisfaction, recurrence of symptoms, further surgery and costs.

Results: Data from randomised trials indicated that at 12 months more women were dissatisfied with first-generation EA than hysterectomy [odds ratio (OR): 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 associated with first- and second-generation

techniques were comparable [12.2% (123/1006) vs 10.6% (110/1034); OR 1.20, 95% CI 0.88 to 1.62; p = 0.2). 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]. Indirect estimates suggested that hysterectomy was also preferable to second-generation EA (OR 2.32, 95% CI 1.27 to 4.24; p = 0.006) in terms of patient dissatisfaction. 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). In women treated by EA or hysterectomy and followed up for a median [interquartile range (IQR)] duration of 6.2 (2.7-10.8) and 11.6 (7.9-14.8) years, respectively, 962/11,299 (8.5%) women originally treated by EA underwent further gynaecological surgery. While the risk of adnexal surgery was similar in both groups [adjusted hazards ratio 0.80 (95% CI 0.56 to 1.15)], women who had undergone ablation were less likely to need pelvic floor repair [adjusted hazards ratio 0.62 (95% CI 0.50 to 0.77)] and tension-free vaginal tape surgery for stress urinary incontinence [adjusted hazards ratio 0.55 (95% CI 0.41 to 0.74)]. Abdominal hysterectomy led to a lower chance of pelvic floor repair surgery [hazards ratio 0.54 (95% CI 0.45 to 0.64)] than vaginal hysterectomy. The incidence of endometrial cancer following EA was 0.02%. Hysterectomy was the most cost-effective treatment. It dominated first-generation EA and, although more expensive, produced more quality-adjusted life-years (QALYs) than second-generation EA and Mirena. The incremental cost-effectiveness ratios for hysterectomy compared with Mirena and hysterectomy compared with second-generation ablation were £1440 per additional QALY and £970 per additional QALY, respectively.

Conclusions: Despite longer hospital stay and time to resumption of normal activities, more women were satisfied after hysterectomy than after EA. 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 second-generation techniques. Owing to a paucity of trials, there is limited evidence to suggest that hysterectomy is preferable to Mirena. The risk of pelvic floor surgery is higher in women treated by hysterectomy than by ablation. Although the most cost-effective strategy, hysterectomy may not be considered an initial option owing to its invasive nature and higher risk of complications. Future research should focus on evaluation of the clinical effectivesness and cost-effectiveness of the best second-generation EA technique under local anaesthetic versus Mirena and types of hysterectomy such as laparoscopic supracervical hysterectomy versus conventional hysterectomy and second-generation EA.

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Glossary

Adenomyosis The presence of endometrium in the myometrium. Can cause heavy menstrual bleeding and pain.

Amenorrhoea Absence of periods.

Cervix The lower, narrower end of the uterus.

Cornua The horn-shaped top of the uterus leading to the fallopian tubes.

Cystometry A method for measuring the pressure-volume relationship of the bladder.

Diathermy Use of a high-frequency electrical current to produce heat that destroys tissues through cutting or electrocoagulation. The patient's body forms part of the circuit.

Dysmenorrhoea Painful periods.

Electrocautery Cauterisation of tissue using an electric current to generate the heat. Cauterisation destroys the tissue and causes scarring.

Endometriosis A condition where tissue resembling the endometrium occurs outside the uterus. The tissue responds to the menstrual cycle causing internal bleeding and pain.

Endometrium The inner lining of the uterus that thickens and sloughs off during the menstrual cycle.

Fibroids Benign smooth muscle tumours of the uterus.

Fundus The higher, wider end of the uterus.

Haematometra A collection of blood and other menstrual fluids in the uterus, which causes it to distend.

Hyperplasia The abnormal increase in the number of normal cells in a tissue.

Hysterectomy The surgical removal of the uterus; may include removal of the cervix.

Hegar A German gynaecologist who gave his name to a series of graduated cylindrical instruments used to dilate the cervix.

Hysteroscope An instrument using fibre optic technology that allows direct visualisation of the uterine cavity. Channels in the instrument allow it to be inserted to perform ablations.

Iatrogenic An adverse effect inadvertently induced through treatment.

Laparoscope A device used in surgery that allows visualisation through the use of fibre optics.

Leiomyomas Fibroids.

Menopause Cessation of menstruation, usually around age 50 years.

Menometrorrhagia Frequent, excessive menstrual bleeding.

Menorrhagia Heavy menstrual bleeding, clinically defined as more than 80 ml of blood per cycle, but more usually defined subjectively by the woman.

Menstruation The cyclic physiological discharge of blood and mucosal tissues through the vagina from the non-pregnant uterus. It is under hormonal control and recurs at approximately 4-week intervals.

Metrorrhagia Irregular, sometimes prolonged, menstrual bleeding.

Myometrium The outer muscular layer of the uterus.

Necrosis Cell death.

Oligomenorrhoea Few or scanty periods.

Pelvic inflammatory disease An inflammatory process that may be caused by sexually transmitted infection, ovarian cystic disease or infections after childbirth.

Perimenopausal Around the time of the menopause.

Polyp A mass of tissue on the mucosal lining, in this case in the uterus.

Post-ablation sterilisation syndrome In previously sterilised women, accumulation of the blood in the fallopian tubes, which may cause severe pelvic pain.

Pre-menstrual syndrome A combination of emotional and physical features that occur cyclically in women. May include mood changes, bloating, breast tenderness, fatigue and other symptoms.

Pyrexia Fever.

Salpingo-oophorectomy Surgical removal of the fallopian tubes and the ovaries.

Uterus The womb. A hollow, muscular pear-shaped organ in which the embryo is nourished.

List of abbreviations

AD	aggregate data
CEAF	cost-effectiveness acceptability frontier
CLAI	confidence interval
CUA	cost–utility analysis
DUB	dysfunctional uterine bleeding
ELA	endometrial laser ablation
ELA	endometrial ablation
ED	endometrial destruction
EQ-5D EVPI	European Quality of Life-5 Dimensions
GA	expected value of perfect information general anaesthetic
GI	gastrointestinal
GnRH	0
GIRT	gonadotrophin-releasing hormone
HMB	general practitioner
НА	heavy menstrual bleeding
ICD	hydrothermablator International Classification of Diseases
ICD ICD-9	
ICD-9 ICD-10	International Classification of Diseases, Ninth Edition
	International Classification of Diseases, Tenth Edition
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
IQR	interquartile range Information Services Division
ISD	
ITT	intention to treat
IUD	intrauterine device
IUS	intrauterine system
LA	local anaesthetic
LNG	levonorgestrel
MEA	microwave endometrial ablation
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PBAC	pictorial blood loss assessment chart
PICOS	participants, interventions, comparisons, outcomes and study design
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RB	rollerball
RBEA	rollerball endometrial ablation
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
SMD	standardised mean difference
SMR	Scottish Morbidity Returns

TBEA	thermal balloon endometrial ablation
TCRE	transcervical resection of the endometrium
TVT	tension-free vaginal tape
UTI	urinary tract infection
VAS	visual analogue scale
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or at the end of the table.

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 modelbased 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-ofthe-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

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- 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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Chapter 1

Background

Heavy menstrual bleeding (HMB) is a common problem¹ which affects approximately 1.5 million women in England and Wales.² The condition causes 1 in 20 women of reproductive age to consult their general practitioners (GPs) and accounts for 20% of gynaecology outpatient referrals. 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 (QoL).³ Surgery has been traditionally used as the definitive treatment of HMB such that, in the past, by the age of 55 years one in five women in the UK had a hysterectomy,⁴ over half of which were for HMB.⁵

Definition of heavy menstrual bleeding

Although objectively defined as the loss of >80 ml of blood per cycle,⁶ such measurement is impractical in most clinical settings. Between 35% and 60% of women who present with a subjective complaint of HMB have been shown to have normal levels of blood loss.^{7,8} Conversely, many women with objectively demonstrable high blood loss do not seek help for associated symptoms.⁹

Of various methods used to measure menstrual blood loss, the alkaline haematin technique has been considered to be the gold standard.¹⁰ Despite the introduction of modifications in an effort to simplify it,¹¹ this method remains laborious and involves extraction of haemoglobin from used sanitary wear. As such, it is unsuitable for regular clinical use.

A more practical method of assessing menstrual blood loss is the pictorial blood loss assessment chart (PBAC).¹² This takes into account the number of items of sanitary wear used and the degree of staining, which are in turn converted into a score. This technique is now more widely used than the alkaline haematin method although the correlation between actual measured blood loss and the PBAC score has been questioned.¹³ Another indirect method for estimating menstrual blood loss is the 'menstrual pictogram',¹⁴ which is similar to the PBAC but additionally requires women to comment on the absorbency of the towel or tampon and any extraneous blood loss.

From a clinical perspective, HMB is defined as excessive menstrual blood loss which interferes with a woman's physical, emotional, social and material QoL, and which can occur alone or in combination with other symptoms.¹⁵

Causes of heavy menstrual bleeding

Possible causes of HMB are shown in *Table 1*. In most cases a definite cause is not found and the condition is labelled as dysfunctional uterine bleeding (DUB).¹⁷

Anatomical	Biochemical	Endocrine	Haematological	latrogenic	Associated factors
Fibroids	Prostaglandins	Hypothalamic– pituitary–gonadal– adrenal axis dysfunction	Von Willebrand's disease	IUDs	Obesity
Polyps		Oestrogen-producing tumours		Anticoagulants	Heavy smoking
Adenomyosis		Thyroid dysfunction	Leukaemia	Exogenous hormones	Excessive alcohol
Infection			Increased endometrial fibrinolytic activity		Depression
Malignancies					Endometriosis

TABLE 1 Causes of HMB (from Garside et al.¹⁶)

IUD, intrauterine device.

Estimating the severity of heavy menstrual bleeding

Subjective estimates of menstrual blood loss do not correlate well with objective measures,^{13,18} and over half of women who have surgery for HMB do not experience a blood loss of 80 ml or more in each cycle.⁸ Women's expectations of normal menstrual loss can shape their perception of the gravity of their condition, inform their demand for treatment and influence their judgement about treatment success.

The presence of other menstrual symptoms may also have an impact on perceptions of bleeding and account for some of the differences between objective and subjective estimates of menorrhagia. Thus, many women presenting with HMB describe other additional symptoms such as painful periods while associated symptoms are more likely to encourage a diagnosis of HMB by clinicians. The impact of HMB is conventionally measured by means of a number of QoL measures. A systematic review of QoL measures in HMB described 15 generic and two condition-specific scales¹⁹ and suggested that there was scope for better ways of assessing the severity of the condition and its impact on women's lives.

Generic scales allow comparison between different clinical conditions in terms of their impact on QoL and may provide a single score or scores across dimensions of QoL, but are relatively insensitive to specifics of a particular condition. Generic measures of QoL used in HMB include the Short Form questionnaire-36 items (SF-36), Nottingham Health Profile, health-status structured history and single global item.¹⁶ SF-36 is generally a well-validated measure used to assess health-related QoL¹⁹ and includes items on global health perception, physical function, social function, role (physical and mental), pain, mental health and energy/vitality.²⁰ The SF-36 has been considered to be a feasible way of assessing QoL in women with HMB, but it has some limitations in this setting²¹ as some questions can be inappropriate for these women. In addition, internal reliability, as assessed by Cronbach's statistic, has been shown to be lower in women with HMB, especially for general health perception and mental health scales.

Clark *et al.*¹⁹ have also reported on the use of generic measures that address particular aspects of QoL such as physical (Modified Townsend Score), mental (General Health Questionnaire) and sexual health (Revised Sabbatsberg Sexual Rating Scale) and social function (Lifestyle Index) in studies of women with HMB bleeding.

Condition-specific scales have the advantage of incorporating attributes of QoL that are specifically affected by the condition of interest. They may therefore be more sensitive to small but important

changes and may be considered to have greater face validity (that is, they include items that are of importance to sufferers and reflect their experience and concerns). Two condition-specific outcome measures have been developed for women with HMB. These include the Menorrhagia Outcomes Questionnaire²² and the Multi-attribute Questionnaire.²³ The Menorrhagia Outcomes Questionnaire includes items on symptoms and satisfaction with care, physical function, psychological and social well-being, global judgement of health and QoL, and personal constructs. The Multi-attribute Questionnaire includes items on practical difficulties, social function, psychological function, physical health, interruption to work and family life.

Preference-based measures elicit preferences for a given health state and, if appropriately scaled, provide weights that can be used in cost–utility analyses.

The EQ-5D[™] (European Quality of Life-5 Dimensions; Euro Qol Group, Rotterdam, the Netherlands), which has been used in studies as a measure of QoL in HMB, includes a multi-attribute scale, with dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a global rating scale for QoL (visual analogue scale).

Measuring patient satisfaction

Patient satisfaction is widely used as a primary outcome measure in studies of treatments for HMB.²⁴ Satisfaction is a subjective and relative concept and represents the extent to which a service meets users' expectations. It is not clear whether satisfaction can be measured on a continuum, from dissatisfied through to satisfied, or whether factors resulting in satisfaction are different from those leading to dissatisfaction.¹⁶ Satisfaction is influenced by patient characteristics²⁴ such as age and health status.

The extent to which these potential biases are addressed in the patient satisfaction measures used in studies of HMB is difficult to assess in the absence of detailed accounts of the development and validation of the measures used. While the use of a similar tool to measure subjective satisfaction for women in both arms of an RCT may provide a comparative measure between these groups, it may remain unclear exactly what is being measured for the reasons outlined above.¹⁶ In addition, the range of techniques and scales used to elicit a measure of satisfaction across studies can limit any attempts to aggregate data by means of meta-analysis.

Current service provision

Treatment for HMB aims to improve women's quality of life through reducing menstrual loss. The current National Institute for Health and Clinical Excellence (NICE) guideline advocates full gynaecological examination followed by appropriate tests such as a full blood count and recognises the need for endometrial biopsy, ultrasound scan and hysteroscopy in specific cases.¹⁵

Medical therapy

According to the recent NICE guideline on HMB,¹⁵ medical treatment should be considered where structural and histological abnormalities of the uterus have been excluded or for fibroids < 3 cm in diameter which do not appear to distort the cavity of the uterus. In addition, the contraceptive needs of the woman should be taken into consideration. In addition to being licensed as a contraceptive device, the levonorgestrel-releasing intrauterine system (LNG IUS or Mirena®, Bayer Healthcare Pharmaceuticals, Pittsburg, PA, USA) is an effective non-surgical

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treatment for HMB which is reversible and fertility sparing. The device, which has to be fitted by a qualified practitioner, has a T-shaped plastic frame and a rate-limiting membrane on the vertical stem which releases a daily dose of 20 µg of LNG. The effects of the LNG IUS are local and hormonal, including prevention of endometrial proliferation, thickening of cervical mucous and suppression of ovulation in a minority of women. It reduces estimated menstrual blood loss by up to 96% by 12 months, with up to 44% of users reporting amenorrhoea,^{25,26} at a cost which is a third of that for hysterectomy.²⁷ It has been recommended that LNG IUS should be considered before oral medication such as tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives.¹⁵ Mirena can lead to troublesome spotting in some women, causing early discontinuation of the device. There are relatively few randomised trials comparing the relative effectiveness of LNG IUS with that of hysterectomy, as well as endometrial ablation (EA), or long-term follow-up data on Mirena use.

Surgical treatment

Despite the availability of a number of medical options, long-term medical treatment is unsuccessful or unacceptable in many cases and surgical alternatives such as EA techniques and hysterectomy may be required.²⁸ In a randomised controlled trial (RCT) of medical management versus transcervical resection of the endometrium (TCRE) in secondary care, total satisfaction with treatment was higher in women who were treated surgically (39% vs 61%; p = 0.01).²⁸ The current NICE guideline on HMB suggests that EA may be offered to women who do not desire future fertility and in whom bleeding is considered to have a major impact on QoL. The guideline development group felt that ablative surgery could be offered as the initial surgical treatment for HMB after full discussion about the risks and benefits of other options.¹⁵

Incidence of surgical operations for heavy menstrual bleeding

Of 51,858 hysterectomies in the public sector in England in 1999–2000, it is likely that half were for HMB.²⁹ Between 1999–2000 and 2004–5, 6500 fewer hysterectomies were performed.³⁰ In contrast there were 826 hysteroscopic EAs in England in 1989, rising to 7173 in 1992–3, before falling to 3847 in 1997–8. In 2004–5, 9701 EAs were performed, of which over half (5457) used second-generation (non-hysteroscopic directed) methods.³⁰ With just 7179 hysterectomies performed for HMB over this period, the predominant operation for HMB was now ablation. The use of LNG IUS has increased concurrently, although the widespread use of this device for contraception as well as for the control of HMB across a number of clinical settings (primary care, sexual reproductive health as well as gynaecology clinics in secondary care) makes it difficult to gather accurate data on uptake rates.

Hysterectomy

Hysterectomy is defined as the surgical removal of the uterus. It offers a definitive treatment for menorrhagia and guarantees amenorrhoea, but is particularly invasive and carries risk of significant morbidity.³¹ Hysterectomy can be performed through a number of routes. In abdominal hysterectomy the uterus is approached through the anterior abdominal wall, while vaginal hysterectomy involves surgical removal of the uterus through the vagina. In laparoscopic hysterectomy surgery is accomplished without the need for a laparotomy. Laparoscopic hysterectomy; (2) laparoscopic hysterectomy; and (3) total laparoscopic hysterectomy. In addition, laparoscopically assisted supracervical hysterectomy involves removal of the body of the uterus while the cervix is retained.

Hysterectomy can also be categorised on the basis of the extent of the operation and organs removed. Removal of the uterus and cervix constitutes total hysterectomy, while excision of the

body of the uterus while conserving the cervix is defined as subtotal hysterectomy. Removal of the uterus alone is conventionally known as simple hysterectomy, while additional removal of the fallopian tubes and ovaries or ovaries alone is referred to as salpingo-oophorectomy or oophorectomy, respectively. Oophorectomy is usually performed in the presence of ovarian pathology but can also be carried out prophylactically to avoid the risk of cancer. Removal of the ovaries in cases of HMB is incidental.¹⁵ Of 37,000 hysterectomies performed in the UK in 1994–5, two-thirds were abdominal (4% of these were subtotal hysterectomies) and 57% were accompanied by removal of tubes and ovaries.⁵

Hysterectomy is generally performed as an inpatient procedure. The need for general anaesthesia, prolonged hospital stay and delayed recovery makes it a potentially expensive treatment.³² Overall, 1 in 30 women suffers a major adverse event after hysterectomy, and the mortality rate is 0.4–1.1 per 1000 operations. Around 3% of women suffer from perioperative problems such as haemorrhage, trauma to other pelvic organs and anaesthetic problems. Immediate postoperative complications include sepsis, bleeding and venous thromboembolism. Adverse events following hysterectomy are summarised in *Table 2*. Although delayed complications including urinary incontinence, fatigue, pelvic pain, hot flushes and sexual problems have been reported,^{5,33–35} satisfaction rates following hysterectomy are very high.³¹

Endometrial ablation

Endometrial ablative techniques, which aim to destroy functionally active endometrium along with some underlying myometrium,^{36,37} offer a conservative surgical alternative to hysterectomy. The first-generation ablative techniques including endometrial laser ablation (ELA),^{38,39} TCRE⁴⁰ and rollerball endometrial ablation (RBEA) were all endoscopic procedures. Although none guarantees amenorrhoea, their effectiveness (in comparison with hysterectomy) has been demonstrated in a number of RCTs.⁴¹⁻⁴⁶

National audits^{47,48} revealed that, although first-generation ablative techniques were less morbid than hysterectomy, they were associated with a number of complications, including uterine perforation, cervical laceration, false passage creation, haemorrhage, sepsis and bowel injury. In addition, fluid overload associated with the use of 1.5% urological glycine (non-ionic) irrigation fluid in TCRE and RBEA resulted in serious and occasionally fatal consequences due to hyponatraemia.^{49,50} Mortality from these techniques has been estimated at 0.26 per 1000.^{47,48}

Second-generation ablative techniques represent simpler, quicker and potentially more efficient means of treating menorrhagia, which require less skill on the part of the operator. Examples of second-generation ablative techniques are fluid-filled thermal balloon EA (TBEA), radiofrequency (thermoregulated) balloon endometrial ablation, hydrothermal EA, 3D bipolar radiofrequency EA, microwave endometrial ablation (MEA), diode laser hyperthermy, cryoablation and photodynamic therapy. The most common techniques in the UK are TBEA

Very common (>1 in 10)	Common (>1 in 100, <1 in 10)	Uncommon (>1 in 1000, <1 in 100)
Sepsis	Haemorrhage	Death
Pyrexia	Blood transfusion	Fluid overload
Wound haematoma	Anaemia	Visceral damage
Hypergranulation	Vault haematoma	Respiratory/heart complications
Urinary tract infection (UTI)	Anaesthetic	Deep-vein thrombosis
	Diarrhoea	
	lleus	

TABLE 2	Complications	followina	hvsterectomv	(from Garside et al.	16)

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(ThermaChoice[®], Ethicon, Livingston, UK and Cavaterm[™], Pnn Medical SA, Morges, Switzerland)⁵¹⁻⁵³ and MEA,^{54,55} while the NovaSure[®] (Hologic Inc., Bedford, MA, USA) device⁵⁶ is becoming more widely used.

First-generation endometrial ablation techniques

Early methods of EA which require direct hysteroscopic visualisation of the endometrial cavity such as TCRE, RBEA and ELA are known as 'first-generation' ablation techniques.⁵⁷ A national survey demonstrated that 99% of first-generation ablative procedures were performed under general anaesthetic.⁴⁷ Endometrial thinning agents are conventionally used prior to ablation in order to ensure an adequate depth of destruction. Drugs such as danazol and gonadotrophin-releasing hormone (GnRH) analogues have been shown to improve operating conditions for the surgeon and increase postsurgical amenorrhoea rates.⁵⁸ GnRHs were found to produce slightly more consistent endometrial thinning than danazol, although both produced satisfactory results.⁵⁸

Transcervical resection of the endometrium requires a hysteroscope with a fibre optic cable to transmit light from an external power source. The cervix is dilated prior to insertion of the resectoscope, which provides a 12° angle of view. A continuous-flow outer sheath circulates liquid (usually glycine) to provide a clear view of the uterine cavity. A cutting loop is used to remove the endometrial lining. TCRE provides good samples of endometrium for biopsy.¹⁶ TCRE may also be used for the excision of small fibroids, and the operation¹⁷ is usually done as a day case.

Rollerball EA also requires visualisation and irrigation using a resectoscope. EA is achieved by means of a rollerball (RB) electrode rather than a cutting loop. A current is passed through the ball which is moved across the surface of the endometrium.⁵⁹ As the RB fits better within the cornua and decreases the chance of perforating this relatively thin-walled part of the uterus,⁴⁷ some surgeons prefer to use the RB to treat this area. In the UK, it is usual for TCRE to be used to treat the uterine walls while RBEA is used for the fundus and cornua.⁶⁰

Potential perioperative adverse effects associated with TCRE and RBEA include electrosurgical vaginal and vulval burns, uterine perforation, haemorrhage, gas embolism, infection and fluid overload (which may cause congestive cardiac failure, hypertension, haemolysis, coma and death). Strategies for avoiding fluid absorption include maintaining the minimum intrauterine pressure compatible with safe surgery, using an efficient suction system to retrieve irrigation fluid and maintaining a strict fluid balance.³⁹

Possible adverse effects of first-generation ablation techniques are shown in Table 3.

Common (>1 in 100, <1 in 10)	Uncommon (>1 in 1000, <1 in 100)
Haemorrhage	Death
Uterine perforation	Pregnancy
Sepsis	Cardiovascular/respiratory complications
Pyrexia	Visceral burn
Fluid overload	Haematoma
	GI obstruction/ileus
	Laparotomy

TABLE 3 Complications of first-generation EA techniques (from Garside et al.)¹⁶

GI, gastrointestinal.

Second-generation endometrial ablation techniques

Since the 1990s, several new methods of EA have been developed. These are often referred to as second-generation techniques. They do not require direct visualisation of the uterine cavity and employ a variety of means to destroy the endometrium – circulation of heated saline within the uterine cavity, use of a diode laser [endometrial laser intrauterine thermo-therapy (ELITT)], punctual vaporising methods, photodynamic methods, radiofrequency, microwaves, a balloon catheter filled with heated fluid and cryotherapy. The treatments are much less dependent on the skill of the surgeon than first-generation techniques, and much more dependent on the reliability of the machines used to ensure safety and efficacy. Complications associated with second-generation techniques include equipment failure, uterine infection, perforation, visceral burn, bleeding and cyclical pain. A limited number of randomised trials indicate that these procedures appear to be as effective as first-generation ablative techniques.⁶¹ In addition, some have the added benefit of being performed under local anaesthetic.

Microwave endometrial ablation

Microwave EA uses microwave energy (at a frequency of 9.2 GHz) to destroy the endometrium with a tissue penetration depth of >6 mm. An 8-mm applicator inserted through the cervix delivers the microwaves using a dielectrically loaded waveguide.⁶² Power is controlled by the surgeon using a footswitch and the temperature inside the uterus is monitored by thermocouples on the surface of the waveguide. Prior to microwave ablation treatment, oral and vaginal thinning agents may be given. Immediately prior to MEA, hysteroscopy is performed to exclude false passages, wall damage and perforation.

Following measurement of uterine cavity length, the cervix is dilated to Hegar 8 or 9 under general or local anaesthetic and the uterine cavity length is measured again. Next, the microwave probe is inserted until the tip reaches the fundus. Graduated centimetre markings on the applicator shaft confirm the length and if these three measurements of uterine length are the same the device is activated.⁶³ When, after a few seconds, the temperature reaches 80 °C, the probe is moved laterally so that the tip is placed in one of the uterine cornua. The temperature briefly falls and rises again and when 80 °C is reached again the probe is moved to the other cornual region and the procedure is repeated.

Maintaining a temperature of 70–90 °C, the probe is withdrawn with side-to-side movements. The temperature measured by the thermocouple is actually the heat transmitted back from the tissue through the plastic sheath to the applicator shaft. Tissue temperature is higher than these measured levels during active treatment. As a marker on the probe appears at the external os, the applicator is switched off to avoid treating the endocervix. The procedure takes 2–3 minutes.⁶² Postoperative analgesia is provided as required.

Thermal balloon endometrial ablation

Thermal balloon EA aims to destroy the endometrium by means of heated liquid within a balloon inserted into the uterine cavity, which should be of normal size and regular shape. Available devices such as ThermaChoice and Cavaterm have an electronic controller, a single-use latex or silicone balloon catheter with a heating element, thermocouples and an umbilical cable. As the balloon must be in direct contact with the uterine wall, the device is unsuitable for women with large or irregular uterine cavities.

In the case of the ThermaChoice device, following dilatation of the cervix to about 5 mm, the balloon is introduced within the uterus and filled with sterile fluid (5% dextrose in water) which causes it to expand to fit the cavity. Once intrauterine pressure is stabilised to 160–180 mmHg, the temperature of the fluid is raised to 87°C and maintained for 8 minutes. Pressure, temperature and time are continuously monitored and the device is switched off if safety parameters

are breached. The heat produced by the device causes destruction of the endometrium. Postoperatively, oral analgesia is prescribed and the treated endometrium sloughs off over the following week to 10 days.

The Cavaterm device acts in a similar fashion. The cervix is dilated to about 6 mm and a silicone balloon is inserted and filled with sterile 5% glucose solution to a pressure of 230–240 mmHg. The liquid is heated at a target temperature of 78°C for 10 minutes.

Endometrial thinning agents are not recommended although curettage immediately prior to the procedure can be used. NSAIDs are given to reduce perioperative cramping.

Impedance-controlled bipolar radiofrequency (NovaSure)

The NovaSure system consists of a single-use bipolar ablation device which is inserted into the uterine cavity transcervically after dilatation to 8 mm. This is connected to a generator which functions at 500 kHz and has a power cut-off limit set at a tissue impedance of 50 Ω . The cavity and cervical length are measured and the difference in centimetres is determined; this setting is selected on the shaft of the device. The device is inserted and the trigger is deployed which delivers the bipolar triangular array into the cavity. With gentle tapping and slight rotation in both directions the array fully deploys with the tips sited in each cornua. The distance between the cornuae is displayed and then entered into the generator, and this determines the energy required. A cavity integrity test is then automatically performed, which must be passed before the energy is delivered. Active treatment times are under 2 minutes, during which time suction pulls the walls onto the device. After completion the array is retracted into the device sheath and withdrawn. While the device is versatile, it cannot effectively treat larger cavities (>11 cm) or distorted cavities. Pre-treatment endometrial thinning is not required and the procedure can be performed under local anaesthetic. A number of randomised trials has been undertaken, one comparing with RBEA⁵⁶ and the others with thermal balloon devices.^{64,65} One of the trials has published follow-up to 5 years.⁶⁶ A randomised trial comparing NovaSure with microwave ablation has been completed and awaits publication. It has approval from NICE.¹⁵ Results have been consistent through the trials, with amenorrhoea rates varying between 42% and 56%, high satisfaction rates of over 90% and low hysterectomy rates. Active treatment times vary between 90 and 120 seconds.

Adverse effects associated with second-generation EA devices include the following:¹⁶ uterine infection, perforation, visceral burn, bleeding, haematometra, laceration, intra-abdominal injury and cyclical pain.

Use of local anaesthetic

Use of local anaesthetic (LA) is a potential advantage of second-generation EA techniques, although this may not be suitable for all women. In a partially randomised trial of general anaesthetic (GA) and LA,⁶⁷ the procedure was considered acceptable under GA in both preferred (100%) and randomised (97%) groups. However, under LA, 97% of those who chose this method and 85% of those allocated to LA found the procedure acceptable.

Selecting an appropriate treatment for heavy menstrual bleeding

The introduction of new EA techniques over the last two decades has been accompanied by a series of randomised clinical trials aimed at evaluating their clinical effectiveness and cost-effectiveness. Initially, first-generation EA techniques such as TCRE and laser EA were compared with hysterectomy.³¹ Subsequent trials, which compared alternative first-generation techniques such as TCRE, laser EA and RBEA, established TCRE as the gold standard for this group of treatments. As less invasive and more user-friendly second-generation techniques such as MEA became available, these were compared with earlier methods of ablation like TCRE and RBEA.

Although not all techniques have been subjected to head-to-head comparisons in the context of randomised trials, an overview of the literature demonstrates that MEA (second generation) has been shown to be comparable with TCRE (first generation) – which in turn has been shown to be an effective alternative to hysterectomy (gold standard). However, questions about the long-term clinical effectiveness and cost implications of alternative forms of surgical treatment remain unanswered. Published data report no more than 5 years of follow-up.^{46,68} Inevitably, some women treated by EA will eventually require repeat ablation or hysterectomy. Following hysterectomy, a proportion of women will also develop further complications such as postsurgical adhesions and pelvic floor dysfunction, which may lead to further surgery. The necessity for a head-to-head comparison between the two most common second-generation methods – MEA and TBEA – has been identified.¹⁵ Given the widespread use of ablative techniques as first-line surgical treatment for menorrhagia at the present time, it is uncertain whether it is either necessary or feasible to compare second-generation techniques directly with hysterectomy. At the same time, the need to obtain comparative information on long-term outcomes is clearly accepted, as is the need to identify the best technique for individual women.

From a clinical perspective, the most relevant research questions at the present time are:

- 1. How do the currently used ablative techniques compare with hysterectomy in the medium to long term?
- 2. Which among the commonly used second-generation ablation techniques is the most effective and cost-effective?
- 3. Are there subgroups of women who are most likely to benefit from either hysterectomy or specific types of ablation?

In this project we have performed a series of studies in order to address these questions by analysis of data from national data sets and randomised trials. Long-term outcomes following EA and hysterectomy in a national cohort have been explored by means of record linkage, while the effectiveness of Mirena, hysterectomy and EA have been determined by individual patient data (IPD) meta-analysis of existing trials. The output has been used (along with other data from the literature) to create a model for the utilisation and costs of the different treatments.

Project objectives

- 1. To determine, using data from record linkage and follow-up of randomised and nonrandomised cohorts of British women, the long-term effects of various second-generation ablative techniques and hysterectomy in terms of failure rates, complications, QoL and sexual function.
- 2. To determine, using IPD meta-analysis of existing RCTs, the short- to medium-term effects of various second-generation ablative techniques and hysterectomy, including the exploration of outcomes in clinical subgroups.
- 3. To undertake a model-based clinical effectiveness and cost-effectiveness analysis comparing various second-generation ablative techniques with hysterectomy using output from the above analyses and to conduct extensive sensitivity analyses to explore the robustness of the results to the assumptions made.
- 4. To devise an algorithm for clinical decision making regarding the choice of surgery for women with HMB in whom medical treatment has failed.

Chapter 2

Hysterectomy, endometrial ablation and Mirena for heavy menstrual bleeding: a systematic review and individual patient data meta-analysis

Introduction

Many women with HMB are not satisfied with medical treatment and end up undergoing surgery.⁶⁹ Hysterectomy was once the only surgical option for HMB; indeed, almost half of the hysterectomies currently performed worldwide are for the treatment of HMB.⁵ EA techniques, which aim to destroy or remove the endometrial tissue,⁷⁰ have become increasingly popular alternatives, and, as a result, the number of hysterectomies in the UK has declined by 64% between 1995 and 2002.⁷¹ EA techniques were introduced in the 1980s, with RB ablation and transcervical resection emerging as the predominant approaches under direct hysteroscopic vision.³⁰ Subsequently, a second generation of non-hysteroscopic techniques, which are easier to perform, have become available. Here, devices are sited and activated to treat the whole endometrial cavity simultaneously without visual control. Destruction is achieved through a variety of modalities, including high temperature fluids and bipolar electrical or microwave energy. Intrauterine coil devices were initially introduced as contraceptives, but the addition of progestogen resulted in reduced menstrual bleeding. Mirena, an LNG-releasing IUS, provides a non-surgical alternative, which is reversible and fertility sparing.⁷²

Women and clinicians now have greater choice of treatment, although evidence to support decision making is inadequate. In the UK, guidelines from NICE¹⁵ recommend the use of Mirena in the first instance for women with benign HMB, followed by EA if pharmaceutical treatments fail to resolve symptoms. Syntheses of evidence from RCTs comparing these treatments have been limited,^{31,61,73} partly because of the scarcity of head-to-head comparisons and variation in outcome measurements used to evaluate effectiveness. We undertook a meta-analysis of IPD from all relevant trials to address previous deficiencies in evidence synthesis. The aim of the study was to compare the relative efficacy of hysterectomy, first- and second-generation EA techniques, and Mirena in women with HMB using a primary outcome measure of patient dissatisfaction. IPD meta-analysis has a number of advantages over traditional published data reviews,⁷⁴ including the ability to carry out data checks, standardise analytical methods and undertake subgroup analyses.

Methods

We sought IPD from RCTs of hysterectomy, EA techniques and Mirena to examine their relative efficacy as a second-line treatment of HMB. The systematic review was conducted based on a protocol designed using widely recommended methods^{75,76} that complied with meta-analysis reporting guidelines⁷⁷ (see *Appendix 10*) (www.bctu.bham.ac.uk/systematicreview/hmb/ protocol.shtml).

Literature search and study selection

The Cochrane Library, MEDLINE (1966–2010), EMBASE (1980 to May 2010) and CINAHL databases (1982 to May 2010) were searched using relevant terms and word variants for population [e.g. menorrhagia, hypermenorrhea, (excessive) menstrual blood loss, HMB, dysfunctional uterine bleeding] and interventions (e.g. hysterectomy, vaginal hysterectomy, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, LNG IUS, Mirena coil and all types and variants of first- and second-generation ablative techniques). Variant names (e.g. EA, resection) and different makes for EA (e.g. Microsulis Medical Ltd, Denmead, UK; Cryogen – now American Medical Systems, Minnetonka, MN, USA) were also searched (see *Appendix 1*). We also hand-searched the bibliographies of all relevant primary articles and reviews to identify any articles missed by the electronic searches. Experts were contacted to identify further studies. To identify any ongoing RCTs, the Meta-Register of Controlled Trials and the International Standard Randomised Control Trial Number register were searched. No language restriction was applied.

Studies were selected in a two-step process. Firstly, we scrutinised the citations identified by the electronic searches and obtained full manuscripts of all the citations that met, or were thought likely to meet, the pre-determined inclusion criteria based on patient entry criteria (women with HMB or abnormal/excessive/prolonged uterine bleeding that was unresponsive to other medical treatment) and study design, the latter limited to RCTs only. We then considered four categories of intervention with the intention of comparing them against each other: *hysterectomy* (performed abdominally, vaginally or laparoscopically); *first-generation' EA techniques* (using operative hysteroscopy, including endometrial laser ablation, TCRE and RBEA); *'second-generation' EA techniques* [those that use a 'blind' device to simultaneously treat the whole cavity, including thermal balloon (Cavaterm, ThermaChoice and Vesta), microwave (Microsulis), laser (ELITT), bipolar radio frequency (NovaSure), cryoablation and hydrothermal ablation]; and *LNG IUS* (Mirena). Studies making a comparison within these categories could not contribute to the meta-analysis, but these data were also requested to allow further exploration of possible predictors of the primary outcome measure.

Data collection and study quality assessment

Repeated attempts were made to contact corresponding authors via post, email or telephone to access data. Where initial attempts failed, we attempted personal contact via our links through the British and European Societies for Gynaecological Endoscopy. Authors were asked to supply anonymised data for each of the pre-specified outcome measures (both published and unpublished to reduce the chance of selective reporting bias) and were invited to become part of the collaborative group with joint ownership of the final publication. Where the investigators declined to take part in the study or could not be contacted, published data were extracted from manuscripts using pre-designed proformas by two independent reviewers (RC and LJM). Any disagreements were resolved by consensus or arbitration by a third reviewer (JPD). Received data were merged into a master database, specifically constructed for the review. The data were cleaned and results were cross-checked against published reports of the trials. Where discrepancies existed authors were contacted for clarification.

Authors of the protocol reviewed all relevant outcome measures to be used in the meta-analysis from articles identified in the literature search. Level of satisfaction with treatment was the most frequently measured outcome across all identified studies, with 21 out of 30 (70%) using this measure, and was used as the primary outcome measure. Dissatisfaction rates are presented to simplify interpretation of statistical output. Responses of 'very satisfied' or 'satisfied' were taken as a positive response, likewise 'very dissatisfied' or 'dissatisfied' as a negative response. Where a 'not sure' or 'uncertain' response was given these were conservatively taken to be a negative rating of treatment, although sensitivity analysis was undertaken to test the robustness of this assumption.

For a small number of studies,⁷⁸⁻⁸¹ surrogate outcomes for satisfaction were used (major problem resolved/improvement of health state/menstrual symptoms successfully treated/degree of recommendation). This assumption was also tested by sensitivity analysis without these studies (indicated in the results section where important) (see *Appendix 2*). A more disease-specific QoL tool¹⁹ would have been the ideal choice for primary measure, but these data were not available from the studies identified. We have shown from the data in this review, though, that a strong relationship between dissatisfaction and patient QoL is apparent (see *Results*).

Other outcome measures were bleeding scores (ranging from a minimum of zero to no upper limit),¹² amenorrhoea rate (converted from a bleeding score of zero where data existed, otherwise as reported), heavy bleeding rate (converted from bleeding scores of > 100¹² where data existed, otherwise as reported), EQ-5D utility score,⁸² SF-36 scores,²⁰ duration of surgery/hospital stay, general anaesthesia rates, postoperative pain score (standardised from visual analogue and ordinal scale scores onto a 0–10 scale), time to return to work/normal activities/sexual activity, dysmenorrhoea/dyspareunia rate and proportion undergoing subsequent ablation/hysterectomy or discontinuing use of Mirena. Pre-defined subgroups were age at randomisation (\leq 40 vs > 40 years), parity (nulliparous vs parous), uterine cavity length (\leq 8 vs > 8 cm), presence or absence of fibroids/polyps and, where available, severity of bleeding at baseline (bleeding score \leq 350 or > 350).

All selected trials were assessed for their methodological quality, using received data sets where available in addition to the reported information. Quality was scrutinised by checking the adequacy of randomisation, group comparability at baseline (examining baseline characteristics for any substantive differences), blinding (where appropriate), use of intention-to-treat (ITT) analysis, completeness of follow-up, compliance, reliability using a priori sample size estimation and generalisability using description of the sample recruited. Adequacy of randomisation was assessed with subquestions examining information on sequence generation, the process of allocation and allocation concealment.

Statistical analysis

To minimise the possibility of bias IPD and aggregate data (AD) were combined in a two-stage approach.⁸³ IPD were reduced to AD to allow studies with AD only to be combined with those where IPD were obtained. Unless specifically stated in the text of the results section, all estimates shown are from all available data (both IPD and AD). Point estimates and 95% confidence intervals (CIs) were calculated for individual studies at each time point. For the primary outcome measure, differences in effect estimates between trials and the pre-defined subgroups of patients are displayed using odds ratio (OR) plots; results from other outcome measures are summarised in tables in the appendices for ease of reference. Heterogeneity was investigated using Cochran's Q⁸⁴ I² statistics²⁴ and Higgins et al.⁸⁵ Subgroup analyses to explore the causes of heterogeneity were undertaken if the *p*-values of these tests were < 0.1. Differences between studies contributing IPD and those with AD only were examined in the same fashion to check that the latter results were consistent with those we received IPD for. Further details are given in the *Results* section if any inconsistency exists. Likewise, further details are given on any obvious publication bias if noted from the assessment of funnel plots. Only a limited amount of data were available for studies comparing Mirena with ED, so Mirena was compared with first- and second-generation studies combined as well as separately. Assumption-free 'fixed-effect' methods were used to combine dichotomous outcome measures and estimate pooled ORs using the method of Peto et al.,⁸⁶ and, for continuous variables, weighted mean differences (WMD) were calculated⁸⁷ at each time point. Data at less than 12 months were combined and are described as results at 6 months. Results from the limited number of studies with follow-up longer than 2 years are not referred to in the text but are given in the appendices.

The primary outcome measure of dissatisfaction was investigated comprehensively using received data. Results at 12 months, where the majority of studies had collected data, were used as the focus for analysis. Where responses were not available at this time point, data were substituted in the first instance from 2 years and, failing that, from 6 months. If it was not possible to make a direct comparison between treatments (e.g. hysterectomy vs second-generation EA), indirect estimates were made⁸⁸ using a logistic regression model⁸⁹ allowing for trial and treatment.⁹⁰ Estimates using dissatisfaction at any time were also examined, along with an analysis allowing for the correlation of the repeated measurements using generalised estimating equations (IPD only).⁹¹

Access to IPD also allowed the inclusion of patient-level covariates to examine possible predictors of dissatisfaction. First, covariates were considered individually, while allowing for differences between trial estimates. If considered statistically important (p < 0.1), covariate parameters were included together in a multivariate analysis to examine adjusted estimates. In addition to the analysis of the primary outcome measure described above, as a sensitivity analysis IPD were also used to explore the effect observed in compliance rates for comparisons between first- and second-generation EA (unfortunately there were insufficient data to extend this analysis to Mirena comparisons). For example, for those women 'satisfied' with treatment but subsequently undergoing a hysterectomy, positive responses were substituted with negative ones. The relationship between dissatisfaction and responses from the SF-36 QoL questionnaire was examined at the patient level using a regression model, allowing for trial. Given the number of analyses performed, any interpretation of *p*-values greater than the conservative threshold of 0.01 has been cautious owing to the likelihood of increased type 1 error rates. REVMAN v5.0 (Cochrane Collaboration, Denmark) and sAs v9.2 (SAS Institute, Cary, NC, USA) software were used for analysis.

Results

Trials and patients

A total of 556 potentially relevant citations were identified by electronic searches. After detailed evaluation, 30 trials were eligible for inclusion in the review (*Figure 1*). Of these trials, seven compared hysterectomy with ED techniques. Six of these studies involved first-generation techniques.^{41-45,78} The seventh study used a combination of first and second generation in equal proportions⁹² and was included here as a first-generation comparison, with a sensitivity analysis performed without the trial. One study compared hysterectomy⁹³ with Mirena. Fourteen studies compared first-generation EA techniques with those of second generation^{53,54,56,79,94-103} and eight studies compared Mirena with EA, three of which were first generation^{80,104,105} and five second generation.^{81,106-109} Characteristics of these studies are shown in *Appendix 2*. Data from a further five studies,^{64,65,110-112} which involved comparisons within first- and second-generation EA, were also received.

Trials comparing hysterectomy with EA and those comparing first- and second-generation ED involved women of a similar age, with average ages of 40.6 years [standard deviation (SD) 5.1 years] and 41.0 years (SD 4.9 years), respectively. Women involved in trials comparing Mirena with ED were slightly older, with an average age of 43.6 years (SD 3.5 years). Eligibility criteria for women with uterine pathology varied between trials; inclusion of women with fibroids was generally limited by size or number. Where included, they amounted to a maximum of 30% of the women in each individual study.

A high proportion of data was received from trials involving hysterectomy (seven of eight studies; 1278 of 1363 women), with less for trials of EA techniques (7 of 14 studies; 1359 of 2448 women)



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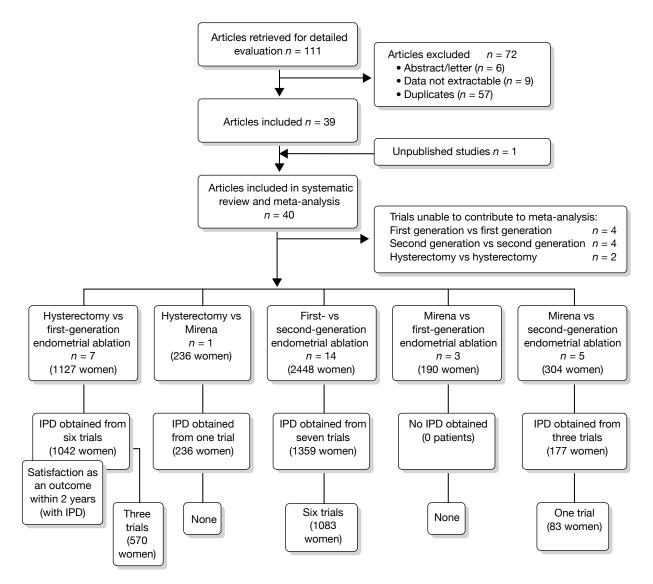


FIGURE 1 Study selection process for systematic review and IPD meta-analysis of randomised trials comparing hysterectomy, EA techniques and Mirena for HMB (details of selected trials in *Appendix 2*).

and those involving Mirena (three of eight studies; 177 of 494 women) (see *Appendix 2*). Overall, we received some IPD from 65% (2814/4305) of women involved in the trials, although only eight studies were able to provide all requested variables.^{41,42,53,94,95,99,102,109} The remaining studies had some missing information, with limited details on patient follow-up covering subsequent operations (e.g. hysterectomy following Mirena). See the section on statistical analysis for details on how data from studies providing IPD were utilised.

Study quality

The methodological quality of the published data from the studies was variable (*Figure 2* and *Appendix 3*).

Over half the studies failed to give adequate information about their randomisation procedure and details on allocation concealment. There was a general lack of true ITT analysis, with some studies stating that an ITT analysis had been performed but only analysing those women who

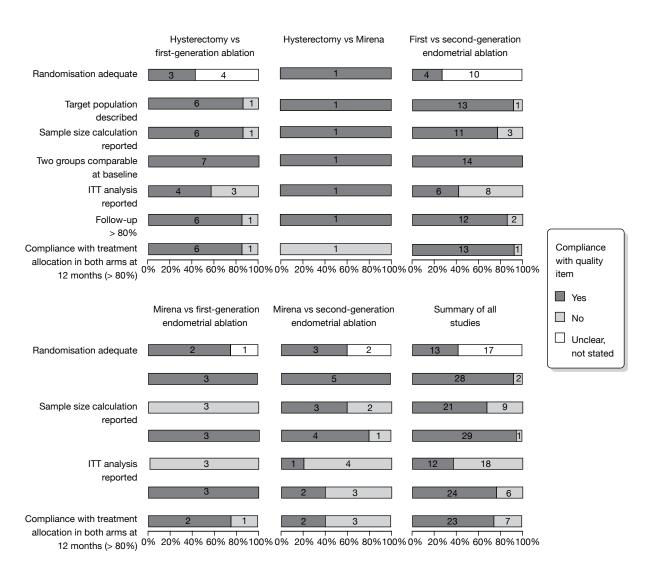


FIGURE 2 Quality of studies included in systematic review and IPD meta-analysis of randomised trials comparing hysterectomy, EA techniques and Mirena for HMB. Numbers inside bars are numbers of studies (details given in *Appendix 3*).

had received treatment. For four studies that reported non-ITT analysis,^{53,95,99,107} ITT analyses were undertaken using the available IPD, although it was not always clear if protocol-deviant patients were followed up correctly in these cases. Small sample sizes often lacked a sensible justification, especially in studies involving Mirena. In the nine trials involving Mirena, only four had greater than 80% of women with Mirena in situ at 12 months post randomisation.

Dissatisfaction as an outcome measure

Data from four studies that provided IPD on both outcomes^{42,54,99,107} showed that satisfied patients had significantly increased scores in seven of eight domains of the SF-36 QoL questionnaire when compared with dissatisfied patients in the analysis of change from baseline scores, including the general health perception (7.4 points, 95% CI 3.1 to 11.8 points; p = 0.0008) and mental health (10.5 points, 95% CI 5.4 to 15.6 points; p < 0.0001) domains (*Table 4*). Differences from absolute differences (not adjusted for baseline score) were highly significant (p < 0.0001) in all eight domains in favour of satisfied patients.

		Change from bas	eline		Absolute		
SF-36 domain		Mean (SD; <i>n</i>)	Difference ^a (95% Cl)	<i>p</i> -value	Mean (SD; <i>n</i>)	Difference ^a (95% Cl)	<i>p</i> -value
General health	Dissatisfied	-4.7 (14.2; 71)	7.4 (3.1 to 11.8)	0.0008	60.3 (20.5; 91)	12.5 (8.5 to 16.6)	< 0.0001
	Satisfied	5.7 (17.0; 507)			77.7 (17.8; 642)		
Physical function	Dissatisfied	0.4 (19.4; 70)	2.8 (-2.6 to 8.3)	0.3	78.1 (27.2; 89)	10.9 (6.7 to 15.1)	< 0.0001
	Satisfied	6.0 (20.7; 497)			91.0 (16.6; 637)		
Role physical	Dissatisfied	5.3 (51.6; 71)	17.4 (5.3 to 29.4)	0.005	60.8 (45.1; 90)	24.0 (17.0 to 31.0)	< 0.0001
	Satisfied	25.2 (44; 504)			88.4 (27.9; 641)		
Role emotional	Dissatisfied	4.2 (54.6; 71)	15.0 (2.9 to 27.0)	0.02	61.1 (44.2; 90)	23.4 (16.3 to 30.4)	< 0.0001
	Satisfied	18.2 (44.4; 505)			87.4 (28.2; 641)		
Mental health	Dissatisfied	-2.1 (22.7; 71)	10.5 (5.4 to 15.6)	< 0.0001	58.5 (21.6; 90)	16.9 (12.8 to 21.0)	< 0.0001
	Satisfied	7.6 (18.7; 504)			76.9 (17.1; 638)		
Social function	Dissatisfied	4.9 (26.2; 70)	6.7 (0.9 to 12.5)	0.02	61.0 (24.2; 90)	17.6 (13.5 to 21.7)	< 0.0001
	Satisfied	11.6 (21.2; 471)			85.5 (18.6; 629)		
Vitality	Dissatisfied	6.5 (23.7; 70)	8.5 (2.4 to 14.6)	0.006	43.6 (23.1; 91)	18.9 (14.1 to 23.8)	< 0.0001
	Satisfied	15.7 (22.9; 503)			65.2 (21.0; 637)		
Pain	Dissatisfied	6.4 (34.3; 71)	9.1 (0.8 to 17.4)	0.03	57.6 (27.2; 91)	20.2 (14.7 to 25.6)	< 0.0001
	Satisfied	20.1 (31.4; 504)			81.0 (23.4; 642)		
	Satisfied	20.1 (31.4; 504)			81.0 (23.4; 642)		

TABLE 4 Results from regression analysis comparing satisfaction response with results from the SF-36 quality of life questionnaire at 12 months

a Adjusted for study.

Effectiveness in reducing dissatisfaction with treatment

Hysterectomy versus first-generation endometrial ablation

More women were dissatisfied at 12 months following first-generation EA than hysterectomy [12.6% vs 5.3%; (57/454 vs 23/432); OR 2.46; 95% CI 1.54 to 3.93; p = 0.0002] (*Figure 3*), with no significant heterogeneity between study estimates (p = 0.9; $I^2 = 0\%$). This estimate of effect size was consistent with, although slightly less than, the estimate from the repeated measures analysis (IPD only) over all time points (OR 3.75; 95% CI 2.18 to 6.46; p < 0.0001) and an analysis using dissatisfaction at any time point (OR 3.37; 95% CI 2.14 to 5.31; p < 0.0001). There was no evidence of any differences between subgroups (see the *Data collection and study quality assessment* section), including between studies providing IPD or AD (test for heterogeneity: p = 0.9).

First- versus second-generation endometrial ablation techniques

Similar dissatisfaction rates were seen with first- and second-generation EA [12.2% vs 10.6% (123/1006 vs 110/1034); OR 1.20; 95% CI 0.88 to 1.62; p = 0.2; test for heterogeneity: p = 0.7)] (*Figure 4*). Comparison estimates were obtained from the repeated measures analysis of IPD (OR 1.21; 95% CI 0.84 to 1.74; p = 0.3), the analysis using dissatisfaction at any time (OR 1.22; 95% CI 0.91 to 1.62; p = 0.2), and also an analysis adjusting for patients who went on to receive a hysterectomy (OR 1.25; 95% CI 0.93 to 1.67; p = 0.1). Results were consistent over all subgroups, including those studies providing IPD or AD only (test for heterogeneity: p = 0.8).

Mirena versus endometrial ablation techniques

Rates of dissatisfaction with Mirena and second-generation EA were similar [18.1% vs 22.5% (17/94 vs 23/102); OR 0.76; 95% CI 0.38 to 1.53; p = 0.4] (*Figure 5*), although the latter rate was

	First generation	neration	Hysterectomy	ctomy				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Petc Peto,	Peto odds ratio Peto, Fixed, 99% Cl
Dickersin 2007 ⁹²	13	107	7	103	26.1%	1.86 (0.55 to 6.21)		
Crosignani 1997 ⁴⁵	5 2	38	2	39	9.3%	2.61 (0.34 to 19.85)		•
O'Connor 1997 ⁴⁴	7	106	0	50	10.7%	1.61 (0.24 to 10.65)		
Pinion 1994 ⁴³	13	104	4	93	22.4%	2.81 (0.76 to 10.39)	1	•
Dwyer 1993 ⁴²	19	66	9	97	31.5%	3.20 (1.06 to 9.61)		
Total (95% CI)		454		382	100.0%	2.46 (1.54 to 3.93)		\diamond
Total events	57		21					
Heterogeneity: $\chi^2 = 1.15$, df = 4 ($p = 0.89$); $l^2 = 0\%$	5, df = 4 (p =	0.89 ; $l^2 = 0^4$	%					
Test for overall effect: $z = 3.75$ ($p = 0.0002$)	= 3.75 (<i>p</i> = (0.0002)						
							0.1 0.2 0.5	5 10
							Higher with hysterectomy	Higher with first generation

FIGURE 3 Dissatisfaction at 12 months – hysterectomy versus first-generation EA.

	First generation	neration	Second generation	eneration			
Study	Events	Total	Events	Total	Weight	Peto odds ratio Fixed, 99% CI	Peto odds ratio Fixed, 99% CI
Brun 2006 ¹⁰³	e	16	5	27	2.5%	2.94 (0.24 to 36.00)	
Cooper 2004 ⁹⁹	-	101	e	201	2.1%	0.68 (0.04 to 10.59)	
Perino 2004 ¹⁰⁰	S	55	ю	56	4.5%	1.74 (0.26 to 11.42)	
Duleba 2003 ⁹⁸	10	72	16	156	12.0%	1.43 (0.45 to 4.53)	
Hawe 2003 ⁹⁴	ო	33	4	37	3.8%	0.83 (0.11 to 6.38)	
van Zon-Rabelink 2004 ⁹⁵	13	58	15	75	13.1%	1.16 (0.38 to 3.47)	
Cooper 2002 ⁵⁶	5	82	1	154	8.1%	0.85 (0.21 to 3.43)	
Pellicano 2002 ¹⁰²	14	38	7	37	9.2%	2.40 (0.64 to 8.96)	
Soysal 2001 [%]	19	48	15	45	13.1%	1.31 (0.43 to 3.94)	
Cooper 1999 ⁵⁴	33	128	29	121	28.0%	1.10 (0.52 to 2.34)	
Meyer 1998 ⁵³	-	120	5	125	3.5%	0.27 (0.03 to 2.24)	
Total (95% CI)		751		1034	100.0%	1.20 (0.88 to 1.62)	
Total events	107		110				>
Heterogeneity: $\chi^2 = 7.47$, df = 10 ($p = 0.68$); $l^2 = 0.68$	= 10 (p = 0.68)	$I_{1}^{2} = 0\%$					
lest for overall effect: $z = 1.17$ ($\rho = 0.24$)	.17 (p = 0.24)						•
							0.1 0.2 0.5 1 2 5 10
						Hi	Higher with second generation Higher with first generation

FIGURE 4 Dissatisfaction at 12 months – first- versus second-generation EA.

twice as high as that seen for second-generation EA when it was compared with first-generation EA (see *Figure 4*). The slightly older age of women in these studies (see *Trials and patients*) could be a possible explanation for this increase, although given the small number of women studied in these trials this difference in rate could easily have arisen by chance. The combined estimate of this and the one study that compared Mirena with first-generation EA⁸⁰ (test for differences between subgroups: p = 0.2) also showed no evidence of a difference (OR 0.94; 95% CI 0.50 to 1.77; p = 0.9). Heterogeneity of estimates overall was of borderline statistical significance (p = 0.09; $I^2 = 54\%$). 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. Sensitivity analysis performed without two studies where surrogates for dissatisfaction were used significantly reduced the data available for analysis but did not change the findings.

Indirect comparisons of hysterectomy with second-generation endometrial ablation techniques and Mirena

Indirect estimates (*Figure 6*) suggest that hysterectomy is also preferable to second-generation EA [5.3% vs 10.6% (23/432 vs 110/1034); 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 per force only include IPD (OR 3.06; 95% CI 1.59 to 5.90; p = 0.0008). The evidence to suggest hysterectomy is preferable to Mirena was weaker [5.3% vs 17.2% (23/432 vs 22/128); 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 and should be cautiously interpreted.

Predictors of dissatisfaction

For second-generation EA, IPD showed that uterine cavity length was the strongest predictor of dissatisfaction (p = 0.02), with shorter uterine cavity length ($\leq 8 \text{ cm vs} > 8 \text{ cm}$) associated with reduced rates (OR 0.59; 95% CI 0.38 to 0.93; p = 0.02) (*Table 5*). Absence of fibroids/polyps also showed a trend towards reduced dissatisfaction (p = 0.07), although no further adjusted estimates including both parameters were attempted as only three studies had data on fibroids/ polyps. There were no convincing associations with any of the variables for hysterectomy or first-generation EA.

Effectiveness in improving other outcomes

Hysterectomy versus endometrial ablation and Mirena

These comparisons focused on recovery times and QoL, as estimates of postoperative menstrual blood loss are redundant after hysterectomy (see *Appendix 4*). EA offered quicker surgery (WMD 32 minutes; 95% CI 30 to 34 minutes; p < 0.0001), shorter hospital stay (WMD 3.0 days; 95% CI 2.9 to 3.1 days; p < 0.00001), faster recovery periods (time to return to normal activities: WMD 5.2 days; 95% CI 4.7 to 5.7 days; p < 0.00001) and less pain postoperatively (WMD 2.5 points; 95% CI 2.2 to 2.9 points; p < 0.0001), although estimates of differences for some of these parameters should be used with caution given the high variability between studies (see *Appendix 4*). One study⁹² suggested no obvious difference in EQ-5D utility scores, while another⁷⁸ suggested differences in favour of hysterectomy in the general health (WMD 9.6 points; 95% CI 5.7 to 13.5 points; p < 0.0001), social function (WMD 24 points; 95% CI 21 to 27 points; p < 0.0001) and vitality (WMD 13 points; 95% CI 9.3 to 16 points; p < 0.0001) domains of the SF-36 questionnaire. Perioperative adverse events associated with hysterectomy were relatively few (0.5%–2.0% each), but UTIs were more common with hysterectomy (43/530; 8.1%) than with EA (9/585; 1.5%). Of the women who were initially treated with EA, 15% had undergone a hysterectomy within 2 years.

Study							
	Total	Events	Total	Weight	Peto odds ratio Fixed, 99% Cl	Peto c Fixed	Peto odds ratio Fixed, 99% Cl
First generation Crosionani 1907 ⁴⁵ 5	νe	0	35	16 8%	264 (034 to 2032)		
	3	J	8 8	16.8%	2.64 (0.56 to 12.48)	Y	
Total events 5 5		0					
Heterogeneity: not applicable	Ĩ						
	(1)						
Second generation							
Shaw 2007 ¹⁰⁸ 5	25	5	28	21.7%	1.15 (0.19 to 6.90)		
Busfield 2006 ¹⁰⁷ 2	37	6	39 39	25.1%	0.24 (0.05 to 1.30)		-
Soysal 2002 ¹⁰⁶ 10	32	6	35	36.3%	1.31 (0.33 to 5.24)		
Subtotal (95% CI)	94		102	83.2%	0.76 (0.38 to 1.53)	$\langle \rangle$	Δ
Total events 17		23					
Heterogeneity: $\chi^2 = 4.43$, df = 2 ($p = 0.11$); $l^2 = 55\%$ Tast for overall effect: $z = 0.76$ ($n = 0.44$)	0.11 ; $l^2 = 55\%$						
	(
Total (95% CI)	128		137	100.0%	0.94 (0.50 to 1.77)	V	
Total events 22		25				1	
Heterogeneity: $\chi^2 = 6.48$, df = 3 ($p = 0.09$); $l^2 = 54\%$ Test for overall effect: $z = 0.19$ ($n = 0.85$)	$(0.09); I^2 = 54\%$						
Test for subgroup differences: $\chi^2 = 2.05$, df = 1 ($p = 0.15$), $\beta =$.05, df = 1 (<i>p</i> =		51.3%				

FIGURE 5 Dissatisfaction at 12 months – first- and second-generation EA versus Mirena.

Hysterectomy vs first generation		2.46 (1.54 to 3.93)
Hysterectomy vs second generation		2.32 (1.27 to 4.24)
Hysterectomy vs Mirena		2.22 (0.94 to 5.29)
Second generation vs first generation		1.20 (0.88 to 1.62)
First generation vs Mirena	p	- 2.64 (0.56 to 12.5)
Second generation vs Mirena		0.76 (0.38 to 1.53)
0.2	0.5 1 2 5	10

FIGURE 6 Dissatisfaction at 12 months summary. Odds ratios (95% CIs) are shown. Estimates >1 indicate increased dissatisfaction for the second treatment listed. Indirect estimates are represented by a dotted line.

TABLE 5 Results from logistic regression analysis with dissatisfaction at 12 months as the outcome

	Hysterectomy			First-generation	on EA		Second-gener	ation EA	
	OR (95% CI)ª	п	<i>p</i> -value	OR (95% CI) ^a	n	<i>p</i> -value	OR (95% CI)ª	п	<i>p</i> -value
Individual estimates ^b									
Uterine cavity length, cm ($\leq 8 \text{ vs} > 8$)	-	-	-	0.97 (0.38 to 2.44)	418	0.9	0.59 (0.38 to 0.93)	817	0.02
Age, years (≤40 vs >40)	2.28 (0.66 to 7.89)	239	0.2	1.21 (0.81 to 1.81)	971	0.4	1.30 (0.87 to 1.93)	942	0.2
Fibroids/polyps (absence vs presence)	0.51 (0.14 to 1.93)	233	0.3	1.15 (0.55 to 2.38)	476	0.7	0.36 (0.12 to 1.07)	302	0.07
Parity (nullparous vs parous)	_	-	_	1.27 (0.36 to 4.43)	778	0.7	0.84 (0.33 to 2.16)	734	0.7
Baseline bleeding score (≤350 vs 350)	-	-	-	0.73 (0.27 to 1.97)	328	0.5	0.96 (0.48 to 1.91)	551	0.9

^aEstimates < 1 favour the first subgroup listed, i.e. have reduced dissatisfaction. ^bAfter allowing for study.

No differences in EQ-5D scores were seen at 6 or 12 months in the single study comparing hysterectomy with Mirena (see Appendix 5), while the only statistically significant effect observed in the SF-36 questionnaire was in the pain domain, which favoured hysterectomy (WMD 9.6 points; 95% CI 2.7 to 16.6 points; p = 0.007). All results were consistent over subgroups.

First-versus second-generation endometrial ablation techniques

The proportion of women with amenorrhoea or still experiencing heavy bleeding was similar in both groups at all time points apart from at 2 years, where there was a borderline significant difference in favour of second-generation techniques (amenorrhoea: OR 0.64, 95% CI 0.41 to 0.99, *p* = 0.04; HMB: OR 1.85, 95% CI 1.04 to 3.32, *p* = 0.04) (see Appendix 6). High heterogeneity for the estimate of amenorrhoea rate at 12 months (OR 1.12, 95% CI 0.93 to 1.35, p = 0.3) appeared to be due to two outlying studies (Duleba⁹⁸ and Perino¹⁰⁰), the results of which could not be verified as IPD were not available. However, analysis without these studies gave very similar results (OR 1.10, 95% CI 0.90 to 1.35, p = 0.4) with lowered heterogeneity (p = 0.1; I^2 = 36%). Change from baseline analysis of bleeding scores showed no evidence of a difference at any of the time points. Inconsistency of estimates for this outcome at 12 months was due to a single study;¹⁰³ sensitivity analysis without this study also showed no change to the overall result (WMD -0.3; 95% CI -27.5 to 27.0; p = 1.0; heterogeneity: p = 0.4; $I^2 = 10\%$). Two studies^{54,99}

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using the SF-36 questionnaire and one small study⁹⁴ using the EQ-5D questionnaire showed no consistent difference between first- and second-generation techniques, in terms of change from baseline results.

Second-generation EA was quicker (WMD 15 minutes; 95% CI 14 to 15 minutes; p<0.0001) and less likely to need general anaesthesia than first generation (OR 0.16; 95% CI 0.12 to 0.20; p < 0.0001), although highly significant heterogeneity makes estimates difficult to interpret. Less frequent use of general anaesthesia with second-generation EA translated to a slightly quicker time to return to work (WMD 1.36 days; 95% CI 0.69 to 2.03 days; p < 0.0001) and time to return to normal activities (WMD 0.48 days; 95% CI 0.20 to 0.75 days; p = 0.0008), although the overall estimate for the latter was somewhat inconsistent (heterogeneity: p = 0.04; $I^2 = 59\%$). Postoperative pain was similar following either method of EA, although estimates from different studies varied widely (heterogeneity: p < 0.0001; $I^2 = 89\%$) without any obvious explanation. Adverse events were relatively low in both groups (each < 2%), but perioperative complications such as uterine perforation (OR 0.20; 95% CI 0.07 to 0.57; *p* = 0.003), excessive bleeding (OR 0.14; 95% CI 0.07 to 0.55; p = 0.005), fluid overload (OR 0.12; 95% CI 0.04 to 0.36; p = 0.0001) and cervical laceration (OR 0.12; 95% CI 0.05 to 0.33; p < 0.0001) were lower with second-generation EA. The number of women requiring a subsequent hysterectomy was lower for second-generation EA, but these differences were not large enough to be statistically significant within the first 2 years (12 months: OR 0.77, 95% CI 0.47 to 1.24, *p* = 0.3; 2 years OR 0.68, 95% CI 0.41 to 1.13, *p* = 0.1). Overall rates were 3.3% (74/2265) and 7.6% (71/939) at these time points. Any differences amongst subgroups were confined to single time points only. Results from studies providing IPD were consistent with those with AD only.

Mirena versus endometrial ablation techniques

Fewer women experienced HMB after Mirena at 6 months (OR 0.23; 95% CI 0.09 to 0.57; p = 0.001) and at 2 years (OR 0.08; 95% CI 0.01 to 0.50; p = 0.007), although total numbers here were small compared with the estimate at 12 months, where there was no evidence of any difference (OR 0.74; 95% CI 0.34 to 1.61; p = 0.5) (see Appendices 7 and 8). Amenorrhoea rates were similar at all time points, although the overall estimate at 12 months, along with the estimate for HMB, was somewhat inconsistent (heterogeneity: p = 0.05 and 0.06, respectively; I^2 = 59% and 55%, respectively). Changes in bleeding scores favoured EA at 12 months only (WMD 38 points; 95% CI 15 to 60 points; p = 0.0009), a result consistent over all studies (heterogeneity: p = 0.5; $I^2 = 0\%$). Other outcome measures could not separate the two treatments. Two studies^{107,109} provided SF-36 changes from baseline scores, and no differences were found in any of the domains. The number of women subsequently undergoing a hysterectomy was slightly higher for Mirena, although total numbers in this comparison were very small; rates at 12 months were 2.3% (2/86) for EA and 6.7% (6/89) for Mirena. A high proportion of women originally prescribed Mirena discontinued use of this treatment - 15.7% (30/191) at 12 months, rising to 27.6% (29/105) by 2 years. Reported adverse events were low with Mirena; around only 3% reported an expelled/migrated coil within the first month. These results were from studies of first- and second-generation studies combined where first-generation data existed, and were consistent over both types of EA.

Discussion

Principal findings

In this review, access to IPD enabled a more rigorous analysis than is possible from published data from trials comparing second-line treatments for HMB. The primary outcome measure of dissatisfaction was shown to be strongly related to increased QoL. Based on direct and indirect

comparisons using all available data, the review found that both first- and second-generation EA techniques were associated with greater dissatisfaction than hysterectomy, although rates were low for all treatments and absolute differences were small. Recovery times and length of hospital stay were longer for hysterectomy. Dissatisfaction levels with second-generation techniques were slightly lower than those associated with first-generation techniques. In addition, second-generation methods of EA were quicker, had faster recovery times, were associated with fewer adverse procedural events and could be offered under local anaesthetic. Fewer women subsequently underwent hysterectomy after second-generation EA than with first-generation EA, but this difference was not statistically significant. Shorter uterine cavity length was associated with lower levels of dissatisfaction for second-generation EA. Comparisons of EA with Mirena suggest comparable efficacy, although studies involving the latter treatment were generally small and consequently imprecise. Substantial discontinuation of Mirena use was noted and makes interpretation of findings for this treatment difficult.

Strengths and limitations of the review

We used optimal methodology, complying with guidelines on reporting of systematic reviews and meta-analyses.¹¹³ An extensive literature search was conducted, with no language restrictions, minimising the risk of missing information. The collection of IPD allowed us to use previously unreported data, improve the assessment of study quality, standardise outcome measures, undertake ITT analysis and use optimal analytical methods. Subgroup, repeated measures and multivariable analyses would not have been possible without the collection of IPD, and, along with the indirect measures analysis, previously have not been reported.

The review was hampered by 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 occasion failed quality checks and so were unusable. The review's inferences are also limited by the inconsistent outcome measure used across trials; studies involving ED and Mirena focused on comparing reduction in bleeding, while hysterectomy trials focused on patient satisfaction, QoL and resource usage.

Interpretation

In this review we found that more women were dissatisfied following EA than following hysterectomy, although this should be placed in context of longer operating time, total hospital stay and recovery period for hysterectomy. Rates of dissatisfaction are relatively low for EA and it is an effective alternative for women with abnormal uterine bleeding who do not seek amenorrhoea. While this review has shown that hysterectomy is a relatively safe operation, other studies with a more comprehensive follow-up of large populations have shown higher levels of morbidity following hysterectomy.⁶ In contrast, EA has low rates of complication.⁴⁷ All these factors need to be taken into consideration when considering any potential benefit of hysterectomy.

We found that second-generation techniques, such as thermal balloon ablation (ThermaChoice and Cavaterm),⁵¹⁻⁵³ the NovaSure device⁵⁶ or microwave (Microsulis),^{54,68} were not significantly different to first-generation techniques in terms of patient dissatisfaction. Moreover, they are simpler and quicker, require less skill on the part of the operator and can be attempted under local anaesthetic. Importantly, fewer operative complications have also been recorded. Thus, they are clearly preferable to first-generation techniques. The association of shorter uterine

cavity length and lower dissatisfaction with second-generation EA could be because endoscopic treatment is technically more difficult, although given the borderline statistical significance it could also have arisen by chance.

The comparisons involving Mirena were encouraging and, given that it is a relatively cheap and minimally invasive procedure, it could be considered first if drug treatment for heavy bleeding fails.¹¹⁴ It may even be an alternative to oral drug treatment as a first-line agent, but we did not address this question in our review. However, the current body of evidence comparing Mirena with more invasive techniques is limited and prohibits us from making any strong conclusions about the current findings of this treatment. Furthermore, research on Mirena presents some specific difficulties in interpretation owing to the high proportion of women discontinuing treatment. This can be seen in the trial by Hurskainen *et al.*,⁹³ which compared Mirena with hysterectomy. While the study was well conducted and reported, the lack of further investigation into the analysis of the primary outcome measure (EQ-5D QoL measure) made the interpretation that there was no evidence of a difference questionable. Of the women allocated Mirena, 20% had received hysterectomy before the main analysis time point at 12 months, with a further 12% no longer using the Mirena. Unfortunately, missing IPD from this trial meant we could not examine further.

Implications for practice

Our review provides evidence that hysterectomy reduces dissatisfaction compared with EA, and this information should be used as part of 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.

Despite the relative paucity of trials evaluating Mirena (particularly in comparison with hysterectomy), it is available in primary care and is less invasive than surgical options. In view of this we can concur with a recent NICE recommendation that women should be offered Mirena before more invasive procedures.¹⁵

Implications for research

This review has shown that further investment in an RCT comparing hysterectomy with second-generation EA would be of limited value given the similar efficacy of first- and second-generation techniques. Questions remain about the long-term clinical effectiveness of all the treatments; evidence from trials with longer term follow-up (≥ 4 years) is limited to a handful of studies involving differing comparisons.^{92,93,115,116} Mirena in particular versus alternative forms of surgical treatment requires further research. While the small studies included in this review have indicated promising results for this treatment, the substantial levels of non-compliance makes interpretation of outcomes difficult and casts some doubt on the equivalent efficacy conclusions.

Individual patient data meta-analysis is an extremely powerful tool if used correctly¹¹⁷ and provides the most definitive synthesis possible of the available evidence. Such collaborative metaanalyses are well established in cancer and have greatly influenced clinical practice, resulting in striking improvements in, for example, breast cancer survival.⁸⁴ Clinicians in speciality groups, such as gynaecology, need to be aware that contributing study results to an IPD is certainly as important as conducting the original research, if not more so. Consensus on optimal outcome measures would also be helpful for meta-analysis.

Chapter 3

Long-term sequelae following hysterectomy or endometrial ablation in Scotland

Introduction

The last two decades have seen the emergence of EA as a conservative surgical alternative to hysterectomy. While the results of hysterectomy are good and amenorrhoea is guaranteed, hysterectomy is invasive and can carry significant short-term morbidity.³¹ Overall, 1 in 30 women suffers a major adverse event, and the mortality rate is 0.4–1.1 per 1000 operations. The need for general anaesthesia, prolonged hospital stay and delayed recovery also makes hysterectomy potentially a more expensive treatment.³² Recent national data from England suggest that EA is now more common than hysterectomy for HMB and second-generation methods are now more commonly performed than hysteroscopic EA.³⁰

Endometrial ablative techniques do not guarantee amenorrhoea, but their effectiveness (in comparison with hysterectomy) has been demonstrated in a number of RCTs⁴¹⁻⁴⁴ (Aberdeen Endometrial Ablation Trials Group, 1999⁴⁶). National audits of first-generation EA (Scottish Hysterectoscopy Audit Group, 1995⁴⁸) have revealed a number of short-term complications including uterine perforation, fluid overload, cervical laceration, false passage creation, haemorrhage, sepsis and bowel injury.^{49,50} Mortality from these techniques has been estimated at 0.26 per 1000.^{47,48} Second-generation ablative techniques represent simpler, quicker and potentially more efficient means of treating menorrhagia, which require less skill on the part of the operator but are associated with complications such as equipment failure, uterine infection, perforation, visceral burn, bleeding and cyclical pain. A number of randomised trials indicate that these procedures appear to be as effective as first-generation ablative techniques.⁶¹

Studies on outcomes after hysterectomy have mainly concentrated on short-term outcomes (in unselected groups of women undergoing the procedure for different underlying reasons¹¹⁸). Similarly, most evaluative studies on first- and second-generation EA have reported short-term complications, although some have included medium- and long-term outcomes (there have been few long-term controlled comparisons of hysterectomy with ablation techniques in women with HMB¹¹⁶).

Objective

To determine, using population-based data from record linkage, long-term effects of ablative techniques and hysterectomy in terms of failure rates and complications.

Research questions

1. What is the risk of further gynaecological surgery following EA compared with that following hysterectomy in women with HMB?

- 2. What is the risk of further gynaecological surgery following different types of hysterectomy in women with HMB?
- 3. What is the risk of gynaecological cancer following EA compared with that following hysterectomy in women with HMB?
- 4. What is the association of age with risk of further gynaecological surgery following EA compared with that following hysterectomy in women with HMB?

Methods

Anonymised 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 Information Services Division (ISD) were used for this study. More information on the ISD is available at www. isdscotland.org. The SMR register is subjected to regular quality assurance checks and has been shown to be more than 99% complete since the late 1970s.¹¹⁹ Approval to perform the study was granted by the Privacy Advisory Committee of the ISD. As researchers had no access to any patient identifiers, the North of Scotland Research Ethics Service were of the opinion that formal ethical approval was not necessary.

The original database supplied by ISD contained a total of 549,223 records. From this, records with an International Classification of Diseases, Tenth Edition (ICD-10) diagnostic code beginning with either N92 (excessive, frequent and irregular menstruation) or N93 (other abnormal uterine and vaginal bleeding excluding neonatal vaginal haemorrhage and pseudo menses) plus any record with ICD, Ninth Edition (ICD-9) codes of -6226, -6270 and -6268 were selected. This identified 61,880 records (29,100 records with relevant ICD-10 codes and 32,780 with relevant ICD-9 codes). A total of 791 subjects who were aged <25 or >55 years were then excluded to avoid clinically implausible diagnoses and those unlikely to have dysfunctional bleeding, leaving 61,089 records. Thirty-seven records were subsequently excluded from women recorded as implausibly having EA following a hysterectomy, leaving 61,052 records. We also excluded 9891 women who had a hysterectomy before 1989 (after making sure that no EA was lost) to ensure a comparable time frame (1989–2006) of initial operation in both the EA and hysterectomy groups. This left 51,198 records (14,078 in the EA group and 37,120 in the hysterectomy group). A total of 2779 women (19.7%) in the EA group went on to have a hysterectomy. We excluded these women since it would be difficult to determine whether subsequent sequelae should be attributed to the initial EA or to the subsequent hysterectomy. The median (interquartile range, IQR) duration between the date of EA and subsequent hysterectomy for these 2779 women was 1.25 (0.66–2.67) years. Similarly, of the original 14,078 women undergoing EA, 379 (2.7%) went on to have a repeat EA procedure within a median (IQR) of 1.17 (0.66–2.83) years. These 379 women have been retained in the EA group.

Following the exclusions detailed above, we were left with a data file containing 48,419 analysable records from women aged 25–55 years who had either an EA (n=11,299) or a hysterectomy (n=37,120) as a primary surgical procedure for dysfunctional uterine bleeding between 1989 and 2006. Note that it was not possible to discriminate between different types of EA owing to inconsistencies with coding in the early years following the introduction of the new technology.

The ISD then linked these 48,419 women to the cancer registry, and ICD-9 and ICD-10 codes corresponding to gynaecological cancers (breast, vaginal, cervical, uterine and ovarian) diagnosed between 1989 and 2006 were made available for analysis. All cancers with a date of diagnosis subsequent to the date of EA or hysterectomy were included in the analysis.

Socioeconomic status was assessed using the Carstairs index,¹²⁰ which was divided into quintiles for analysis. Descriptive statistics (percentage, *n*, mean and SD, median and IQR as appropriate) were used to summarise each of the surgical outcomes and potential predictor variables (age, duration of follow-up and Carstairs quintile) in the EA and hysterectomy groups. Appropriate univariate analyses (chi-squared test for comparing two categorical variables, *t*-test to compare means and the Mann–Whitney *U*-test to compare medians) 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. Hazard ratios and their 95% CI for different outcomes were calculated both before and after adjustment for age, year of primary operation and Carstairs quintile. Kaplan–Meier survival curves for outcomes that were significantly different between groups following adjustment were plotted and the assumption of a constant hazard ratio over time was checked. Similar survival analysis was performed comparing cancer outcomes between the EA and hysterectomy groups and then comparing surgical outcomes between different types of hysterectomy. The association of age with risk of further surgical procedures in the EA and hysterectomy groups was examined by inclusion of an age by group interaction term in the regression model along with the main effects.

International Classification of Diseases codes used in the analysis

Hysterectomy codes used

Hysterectomy	Codes
Any hysterectomy	q07.4, q07.8, q07.9, q07.5, q08.8, q08.9
Any hysterectomy + oophorectomy (bi + removal of only ovary)	(q07.4, q07.8, q07.9, q07.5, q08.8, q08.9) + (q 22.1, q22.3, q23.2, q23.6)
Any total hysterectomy	q 07.4, q07.8, q07.9
Any subtotal hysterectomy	q07.5
Any vaginal hysterectomy	q08.8, q08.9

Operation codes used

Operations	Codes
Oophorectomy	q232, q236, q432
Ovarian surgery	q438, q439, q473, q474, q478, q479, q491, q493, q498, q499
Hysterectomy	q078, q079, q088, q089, q072, q074, q075, q082, q083
Uterine operations	q093, q098, q099, q103, q108, q109, q161, q168, q169
Repeat ablations	q171
Adnexal surgery	q228, q229, q238, q239, q248, q249
Vaginal repair	m531, p228, p229, p238, p239
Tension free vaginal tape (TVT)	m538
Vault repair	p241, p243, p244, p248, p249
Fistula repair	p251, p252, p253, p254
Colporrhaphy (anterior or posterior vaginal repair)	p221, p222, p223, p231, p232, p233

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Cancer codes used

Cancer type	ICD-10	ICD-9
Breast	C50	174
Vagina	C52	184
Cervix	C53	180
Uterine	C54	182
Ovary	C56	183

Results

Between 1989 and 2006, 37,120 Scottish women underwent hysterectomy and 11,299 underwent EA as a primary surgical procedure for dysfunctional uterine bleeding (*Table 6*). Women who underwent EA were significantly older and belonged to a higher socioeconomic group than women who underwent hysterectomy. The median duration of follow-up in women post ablation was shorter, reflecting the increased numbers of ablations performed in more recent years.

Table 7 shows the different types of hysterectomy performed for HMB. Women who underwent bilateral oophorectomy were significantly older than those whose ovaries were conserved (p < 0.001).

Table 8 lists the frequencies and hazard ratios for further surgical outcomes following either EA or hysterectomy. Women were significantly more likely to require further gynaecological surgery after EA (adjusted hazard ratio 3.56; 95% CI 3.26 to 3.89) than after hysterectomy. Most

TABLE 6 Baseline characteristics of women in the two groups

		Endometrial ablation (<i>n</i> =11,299)	Hysterectomy (n=37,120)	<i>p</i> -value
Age at treatment (years), m	iean (SD)	42.5 (5.6)	41.0 (6.0)	< 0.001
Duration of follow-up (year minimum, maximum	s), median (IQR)	6.2 (2.7–10.8), (0.002, 17.91)	11.6 (7.9–14.8), (0.002, 17.91)	< 0.001
Carstairs quintile, n (%)	1	2941 (26)	5617 (15)	< 0.001
	2	2266 (20)	6870 (19)	
	3	1905 (17)	7682 (21)	
	4	1957 (19)	7814 (21)	
	5	2160 (20)	8669 (24)	

TABLE 7 Types of hysterectomy^a

	n (%)	Age in years, mean (SD)
Hysterectomy with conservation of ovaries	20,864 (56)	39.1 (5.5)
Any hysterectomy + oophorectomy (bi + removal of only remaining ovary)	13,036 (35)	44.2 (5.6)
Total hysterectomy	28,961 (78)	41.1 (6.1)
Subtotal hysterectomy	2948 (8)	41.5 (5.8)
Vaginal hysterectomy	5211 (14)	40.4 (5.9)

a The ICD codes for each of these five types of hysterectomy correspond with those listed in the statistical analysis section. Note that these subcategories of hysterectomy are not mutually exclusive, hence the total is > 37,120.

	EA, <i>N</i> =11,299 (<i>n</i> %)	Hysterectomy <i>N</i> =37,120 (<i>n</i> %)	Unadjusted hazard ratio (95% CI)	Adjustedª hazard ratio (95% Cl)
All gynaecological surgery	962 (8.5)	1446 (3.9)	3.60 (3.31 to 3.91)	3.56 (3.26 to 3.89)
Adnexal surgery	37 (0.3)	277 (0.8)	0.64 (0.45 to 0.90)	0.80 (0.56 to 1.15)
Pelvic floor repair	102 (0.9)	817 (2.2)	0.68 (0.55 to 0.84)	0.62 (0.50 to 0.77)
Intrauterine procedures	577 (5.1)	-	-	_
Repeat EA	278 (2.5)	-	-	_
TVT	52 (0.5)	388 (1.1)	0.82 (0.62 to 1.11)	0.55 (0.41 to 0.74)
Genital fistula repair	3 (0.03)	61 (0.2)	0.18 (0.05 to 0.56)	0.18 (0.06 to 0.58)

 TABLE 8
 Surgical outcomes following endometrial ablation and hysterectomy

a Adjusted for age, year of primary operation and Carstairs quintile with hysterectomy as the base group.

of these further procedures were intrauterine procedures (such as dilatation, curettage and hysteroscopy) and repeat EA. Women who underwent EA were less likely to undergo pelvic floor repair (adjusted hazard ratio 0.62; 95% CI 0.50 to 0.77), TVT (adjusted hazard ratio 0.55; 95% CI 0.41 to 0.74) or genital fistula repair (adjusted hazard ratio 0.18; 95% CI 0.06 to 0.58) than the hysterectomy group. *Figures 7–9* show Kaplan–Meier survival curves of all gynaecological surgery, pelvic floor repair and TVT, respectively. The survival curves for genital fistula repair are not shown owing to the small number of women who have this outcome, in the EA group in particular.

Cancer outcomes

Table 9 shows both the incidence of gynaecological cancers in women following hysterectomy or EA and the results of the survival analyses. Overall, the number of women diagnosed with cancer was small. The adjusted hazard ratio of breast cancer was higher and that of ovarian cancer was lower for women in the EA group compared with the hysterectomy group, but neither reached statistical significance. For illustration purposes, we calculated the number of EAs needed to treat to give one extra cancer compared with the hysterectomy group. For breast cancer, the number needed to treat (NNT) was 237 and for ovarian cancer it was 1073.

Outcomes following endometrial ablation versus different types of hysterectomy

Table 10 shows the number and percentage of women having further surgery in the EA group compared with those in the group undergoing different types of hysterectomy. The unadjusted and adjusted hazard ratios are then presented in *Table 11*. The risks of future gynaecological surgery in these subgroups are broadly similar to those seen in the previous comparison between ablation and hysterectomy (all types) combined. Women in the EA group had a significantly lower adjusted risk of having adnexal surgery than women who had undergone hysterectomy with conservation of ovaries (adjusted hazard ratio 0.65; 95% CI 0.45 to 0.95). The adjusted hazard ratios of pelvic floor repair, TVT and genital fistula repair were all significantly lower in the EA group than in women who had undergone vaginal hysterectomy. Similarly, the adjusted hazard ratios of undergoing either a TVT procedure or a genital fistula repair were all lower in women who had undergone EA than in those having either hysterectomy with ovarian conservation, hysterectomy with oophorectomy, total hysterectomy or vaginal hysterectomy.

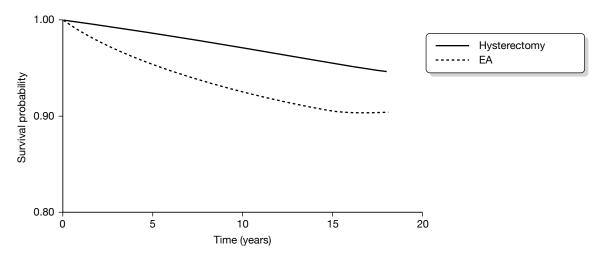


FIGURE 7 Kaplan–Meier survival curve of all gynaecological surgery among the EA and hysterectomy groups.

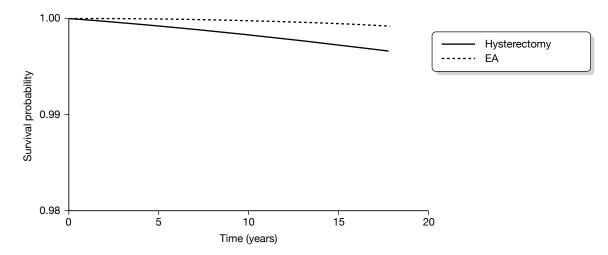


FIGURE 8 Kaplan-Meier survival curve of pelvic floor repair among the EA and hysterectomy groups.

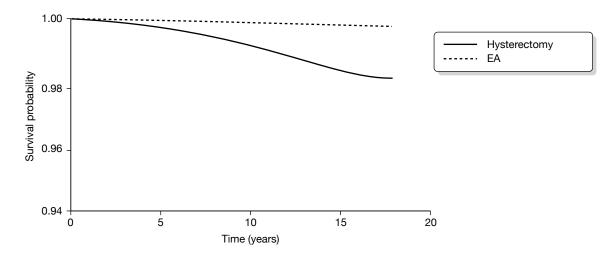


FIGURE 9 Kaplan–Meier survival curve of TVT among the EA and hysterectomy groups.

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TABLE 9 Cancer outcomes following EA and hysterectomy

	EA, <i>N</i> =11,299 (<i>n</i> %)	Hysterectomy, <i>N</i> =37,120 (<i>n</i> %)	Unadjusted hazard ratio (95% CI)	Adjustedª hazard ratio (95% CI)
Breast cancer	130 (1.15)	584 (1.57)	1.22 (1.01 to 1.49)	1.14 (0.93 to 1.39)
Cervical cancer	4 (0.04)	-	_	-
Endometrial cancer	2 (0.02)	-	-	-
Ovarian cancer	5 (0.04)	51 (0.14)	0.70 (0.28 to 1.78)	0.91 (0.35 to 2.39)
Vaginal cancer	-	4 (0.02)	-	-

a Adjusted for age, year of primary operation and Carstairs quintile with hysterectomy as the base group.

TABLE 10 Number of women	(%) having further	surgery following EA or	different types of hysterectomy

	EA, <i>n</i> =11,299	Hysterectomy with conservation of ovaries, n=20,864	Hysterectomy with oophorectomy, n=13,036	Total hysterectomy, <i>n</i> = 28,961	Subtotal hysterectomy, <i>n</i> = 2948	Vaginal hysterectomy, <i>n</i> =5211
All gynaecological surgery	962 (8.5)	901 (4.3)	402 (3.1)	1113 (3.8)	70 (2.4)	263 (5.1)
Adnexal surgery	37 (0.3)	217 (1.0)	_	230 (0.8)	16 (0.5)	31 (0.6)
Pelvic floor repair	102 (0.9)	480 (2.3)	281 (2.2)	618 (2.1)	31 (1.1)	168 (3.2)
TVT	52 (0.5)	228 (1.1)	127 (1.0)	294 (1.0)	25 (0.9)	69 (1.3)
Genital fistula repair	3 (0.03)	39 (0.2)	19 (0.2)	49 (0.2)	-	12 (0.2)

TABLE 11 Risk of further surgery follow	wing EA versus different	types of hysterectomy
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	Adjusted hazard ratio	o (95% CI)ª			
	Ablation vs hysterectomy with conservation of ovaries	Ablation vs hysterectomy with oophorectomy	Ablation vs total hysterectomy	Ablation vs subtotal hysterectomy	Ablation vs vaginal hysterectomy
All gynaecological surgery	3.27 (2.95 to 3.63)	4.49 (3.96 to 5.07)	3.85 (3.49 to 4.24)	4.30 (3.37 to 5.48)	2.53 (2.19 to 2.92)
Adnexal surgery	0.65 (0.45 to 0.95)	-	0.81 (0.57 to 1.17)	0.75 (0.42 to 1.36)	0.85 (0.51 to 1.41)
Pelvic floor repair	0.51 (0.40 to 0.64)	0.74 (0.58 to 0.94)	0.70 (0.56 to 0.88)	0.94 (0.62 to 1.40)	0.36 (0.28 to 0.46)
TVT	0.52 (0.38 to 0.72)	0.59 (0.43 to 0.84)	0.57 (0.42 to 0.78)	0.62 (0.38 to 1.01)	0.41 (0.28 to 0.61)
Genital fistula repair	0.15 (0.04 to 0.50)	0.23 (0.06 to 0.80)	0.16 (0.05 to 0.52)	-	0.16 (0.04 to 0.59)

a Adjusted for age, year of primary operation and Carstairs quintile with type of hysterectomy as base group.

The hazard ratios of further surgery following different types of hysterectomy are shown in *Table 12*. Women whose ovaries were conserved were significantly more likely to undergo further gynaecological surgery (adjusted hazard ratio 1.39; 95% CI 1.22 to 1.59) as well as pelvic floor repair (adjusted hazard ratio 1.31; 95% CI 1.11 to 1.55) than women who had undergone a hysterectomy and bilateral oophorectomy. In contrast, women having an abdominal total hysterectomy or a subtotal hysterectomy were significantly less likely to undergo either further gynaecological surgery or pelvic floor repair than women undergoing a vaginal hysterectomy. *Figures 10–15* show Kaplan–Meier survival curves for those end points in which there was a significant difference in survival between the different hysterectomy types.

	Adjusted hazard ratio (95%	CI) ^a		
	Hysterectomy with conservation of ovaries vs hysterectomy + bilateral oophorectomy	Total hysterectomy vs subtotal hysterectomy	Abdominal total vs vaginal hysterectomy	Subtotal hysterectomy vs vaginal hysterectomy
All gynaecological surgery	1.39 (1.22 to 1.59)	1.19 (0.93 to 1.53)	0.68 (0.60 to 0.78)	0.54 (0.41 to 0.71)
Adnexal surgery	-	0.99 (0.59 to 1.66)	1.36 (0.93 to 1.99)	1.07 (0.57 to 2.00)
Pelvic floor repair	1.31 (1.11 to 1.55)	1.31 (0.91 to 1.90)	0.54 (0.45 to 0.64)	0.39 (0.26 to 0.58)
TVT	1.09 (0.85 to 1.39)	1.09 (0.71 to 1.66)	0.77 (0.59 to 1.01)	0.69 (0.43 to 1.11)
Genital fistula repair	1.39 (0.76 to 2.55)	_	0.72 (0.38-to 1.36)	-

TABLE 12 Adiu	sted hazard ratio	of further surger	v followina diffe	rent types of h	vsterectomv

a Adjusted for age, year of primary operation and Carstairs quintile with the second listed group as base group. Women who underwent both or neither types of hysterectomy being compared were excluded from the model on a pairwise basis.

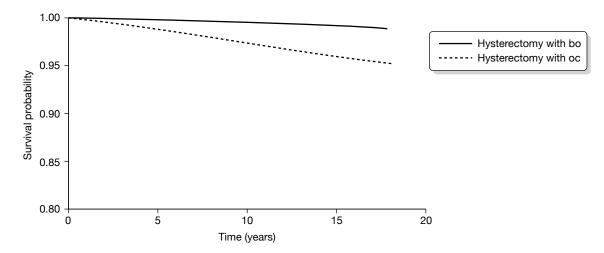


FIGURE 10 Kaplan–Meier survival curve of all gynaecological surgery among the hysterectomy with ovarian conservation (oc) and hysterectomy with bilateral oophorectomy (bo) groups.

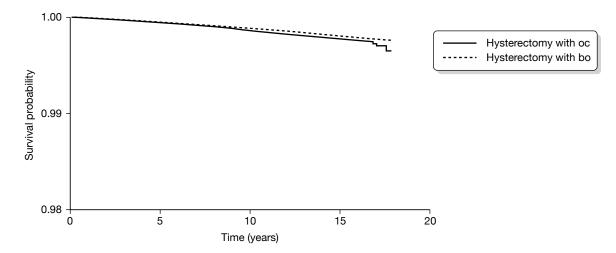


FIGURE 11 Kaplan–Meier survival curve of pelvic floor repair among the hysterectomy with ovarian conservation (oc) and hysterectomy with bilateral oophorectomy (bo) groups.

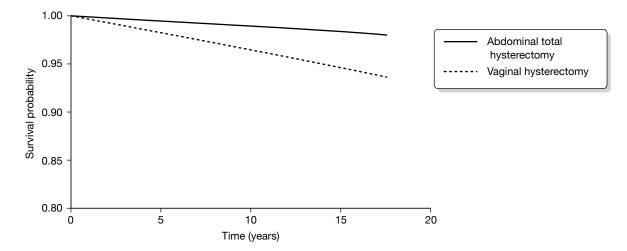


FIGURE 12 Kaplan–Meier survival curve of all gynaecological surgery among the abdominal total and vaginal hysterectomy groups.

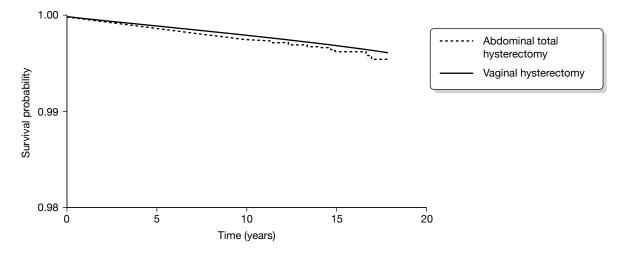


FIGURE 13 Kaplan–Meier survival curve of pelvic floor repair among the abdominal total and vaginal hysterectomy groups.

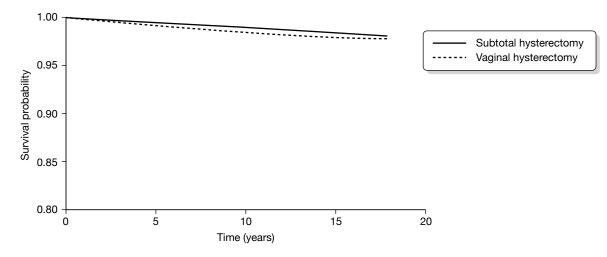


FIGURE 14 Kaplan–Meier survival curve of all gynaecological surgery among the subtotal hysterectomy and vaginal hysterectomy groups.

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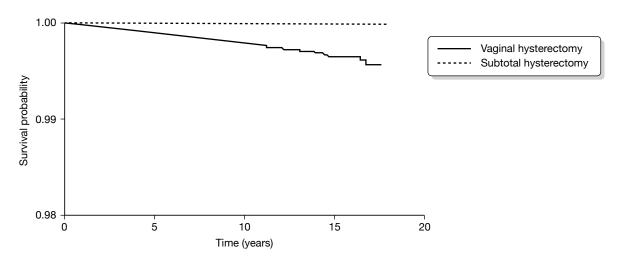


FIGURE 15 Kaplan–Meier survival curve of pelvic floor repair among the subtotal hysterectomy and vaginal hysterectomy groups.

Association of age with risk of further surgical procedures

The association of subsequent surgery with age in the EA and hysterectomy groups was examined by inclusion of an age by group interaction term in the regression model along with the main effects of age and group status. No significant interaction of age with risk of subsequent surgery was found (the *p*-value for the interaction term for all gynaecological surgery was 0.0569; adnexal surgery p = 0.120; pelvic floor repair p = 0.416; TVT p = 0.151 and genital fistula repair p = 0.515).

Discussion

Principal findings

The sociodemographic profile of women who underwent either first- or second-generation EA was different to that of those who received hysterectomy for HMB. Hysterectomy was more likely to lead to surgery for pelvic floor repair and for stress urinary incontinence. Vaginal hysterectomy was associated with a higher chance of further surgery and surgery for pelvic floor prolapse compared with hysterectomy carried out through the abdominal route. The incidence of cancers was generally low in both groups (<1.6%), with endometrial cancer following EA having an incidence of 0.02%.

Strengths and limitations

To our knowledge this is the first large population-based study using national data on long-term outcomes in women who had received alternative surgical treatments for HMB. Use of ICD 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.

This was a retrospective cohort study based on routinely collected national data. Like any observational study, it is not free from the usual problems of bias and confounding. Additionally, 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 among 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.⁴⁷ We were also unable to analyse the long-term outcomes following laparoscopic hysterectomy as numbers were small; these were therefore grouped with abdominal hysterectomy.

Interpretation of findings

Our findings suggest that women from higher socioeconomic groups are more likely to have EA than hysterectomy. This inverse correlation between hysterectomy rates and social class has been noted by some authors¹²¹ but not by others.¹²² None of these studies had a control group of women with HMB who went on to have EA.

Our results confirm previous work⁴⁶ that suggests that women treated initially with EA for HMB are more likely to need subsequent surgery for the same condition than those treated by hysterectomy, which is a more definitive operation. Although they were excluded from the current analysis, we noted that around one in five women had a subsequent hysterectomy following initial EA, while repeat ablations and exploration of the uterus accounted for a substantial minority of cases. As has been noted previously,^{46,112,123} the survival curve indicates that most repeat surgery for persistent HMB occurred within the first 2 years of initial surgery.

Women were more likely to undergo a TVT procedure for stress urinary incontinence after hysterectomy than after EA – corroborating the results of some previous studies that suggested a link between hysterectomy and urinary incontinence.^{34,124} The biological justification of this has been debated in the past and could be due to compromise to the pelvic floor caused by surgical damage to muscular, connective or neurological tissue. The lower risk of genital fistula repair after ablation is explained by the higher probability of pelvic organ damage during hysterectomy.

The risk of gynaecological cancer following EA has been identified as a key clinical and research question in the past. Our results are in agreement with Krogh *et al.*,¹²⁵ who found no significant increase in the incidence of endometrial cancer after ablation in a Danish population. We found no significant difference in the risk of ovarian cancer between women undergoing EA and those who had a hysterectomy. In contrast, Loft *et al.*¹²⁶ reported that the risk of ovarian cancer was lower in women who had hysterectomy (with conservation of at least one ovary) than in those who had not [relative risk (RR) 0.78; 95% CI 0.60 to 0.96]. Owing to an average age of 41 years at initial surgery and the relatively short follow-up (median duration 6.2 and 11.6 years for EA and hysterectomy groups, respectively), many of the women in our study have yet to reach the peak age of incidence for many of the cancers in question and hence the incidence of a common malignancy like breast cancer is low in both groups.

We are able to explore the impact of different types of hysterectomy versus ablation and show that the overall risk of further surgery was significantly higher in the ablation group irrespective of type of hysterectomy. Compared with the ablation group, the odds of TVT were significantly higher in women after a total hysterectomy, but not after subtotal hysterectomy, thus fuelling the ongoing debate on the potential association between total (as opposed to subtotal) hysterectomy and urinary stress incontinence.^{123,127-129} Subtotal hysterectomy has other potential disadvantages, as shown in a small series of women: laparoscopic subtotal hysterectomy led to a 22.9% (16/70) chance of potentially difficult further surgery to remove the cervical stump.¹³⁰ The chances of undergoing surgery for pelvic floor prolapse and urinary stress incontinence were significantly higher in women who had undergone vaginal hysterectomy than in the ablation group. It is impossible to rule out the possibility that the decision to opt for a vaginal route for a hysterectomy may have been informed by prior knowledge of a degree of descent or pelvic laxity. Comparison of different types of hysterectomy revealed that the vaginal route was more likely to be associated with future surgery for prolapse and incontinence. This is supported by data from Blandon et al., 131 who reported that, in comparison with women without prolapse, women who had a hysterectomy for prolapse were at increased risk for subsequent pelvic floor repair.

In the absence of follow-up data from randomised trials, the existing literature on this subject is conflicting as described by Thakar and Sultan.¹²³

There was no significant association between age and risk of further gynaecological operations.

Clinical implications

The results of this study provide clinicians and women with useful data on expected outcomes after EA which can be used to counsel women regarding options of treating HMB. The lower perioperative complications of the less invasive ablation procedures need to be balanced against the 8% chance of repeat surgery for the same symptoms, although the chance of long-term pelvic floor problems may be less. It is also useful to confirm data from other follow-up studies on smaller cohorts that indicate that most repeat procedures occur within 2 years of the initial operation. Our data are broadly reassuring in terms of identifying the risk of endometrial cancer after ablation.

Research implications

This study underlines the limitations of the available literature in this field, which include retrospective studies that have been prone to selection and reporting bias as well as lack of data on key confounders. In the absence of adequately powered large randomised trials with high rates of follow-up, well planned prospective cohort studies with pre-determined end points are needed. It is also important to consider the need for large national audits of EA especially now that new second-generation ablation technologies are being adopted.

Chapter 4

Health economics

Background

The objectives of the economic evaluation were to undertake a cost-effectiveness analysis of hysterectomy versus first- and second-generation ablative techniques and Mirena as additional comparisons were agreed at the request of the National Co-ordinating Centre for Health Technology Assessment prior to funding.

The purpose of the economic evaluations is to inform current treatment policy in this clinical area, while the value of information component will serve to highlight future research needs and agendas, and inform possible future research funding decisions.

The model development process, planned to use as a starting point, was the recently published menorrhagia clinical pathway Markov model.¹⁶ That model, from researchers at the University of Exeter, formed the basis of the national coverage decision by NICE on microwave and TBEA for HMB.¹⁶ As part of model development, the requirements for structural model adjustment were determined through consultation within the research team, drawing on the requisite clinical and modelling expertise.

The model developed by Garside *et al.*¹⁶ was a state transition (Markov) model using Microsoft EXCEL (Microsoft Corporation, Seattle, WA, USA). Their structure was informed by clinical input and the model examined the progress of five hypothetical cohorts of women with HMB who were treated separately with either TBEA, MEA, TCRE, RBEA or hysterectomy. Their evaluation took the perspective of the NHS and the outcomes were presented in quality-adjusted life-years (QALYs). The basic structure and many of the main assumptions from the model-based evaluation of Garside *et al.*¹⁶ formed the basis of our model and assumptions in our model and these will be referred to throughout the report. Refinements that led to the current model structure are described throughout the *Methods* section but are relatively modest and represent a pragmatic adjustment to available data. The key difference in the data used to inform the current model was additional data from the IPD meta-analysis and the addition of the Mirena strategy.

The principal clinical data used in populating the model were drawn from other aspects of our research work on this project, namely the individual patient meta-analyses, data from national registers and existing RCTs.

Methods

The cost-effectiveness component of the work reports the results in terms of incremental cost per QALY gained based on QoL data available from published sources.¹³² The presentation of results in QALYs allows comparison of the results with other available and recently published studies.¹⁶ 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.

The results of the analysis are presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. In addition to probabilistic sensitivity analyses on the base case model, we have included a range of alternative analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used. We also carried out a value of information analysis to explore the extent of uncertainty in the model-based economic evaluation. Such analyses can provide an estimation of whether it is likely that the removal of existing uncertainty (by seeking additional data from additional studies, for example) would impact on the results in a way that would change decisions based on those results.

Cost-effectiveness model

A state transition (Markov) model was developed by the authors using Microsoft EXCEL. The structure was informed by clinical input. The model examines the progress of four hypothetical cohorts of women with HMB who are treated by one of four alternative strategies: Mirena coil; first-generation EA techniques; second-generation EA techniques; or hysterectomy. Given the reliance on secondary data and the nature of available data, the model-based economic evaluation takes the form of a cost–utility analysis and was carried out from the perspective of the NHS in a secondary care setting. An incremental approach was used for the reporting of the results.

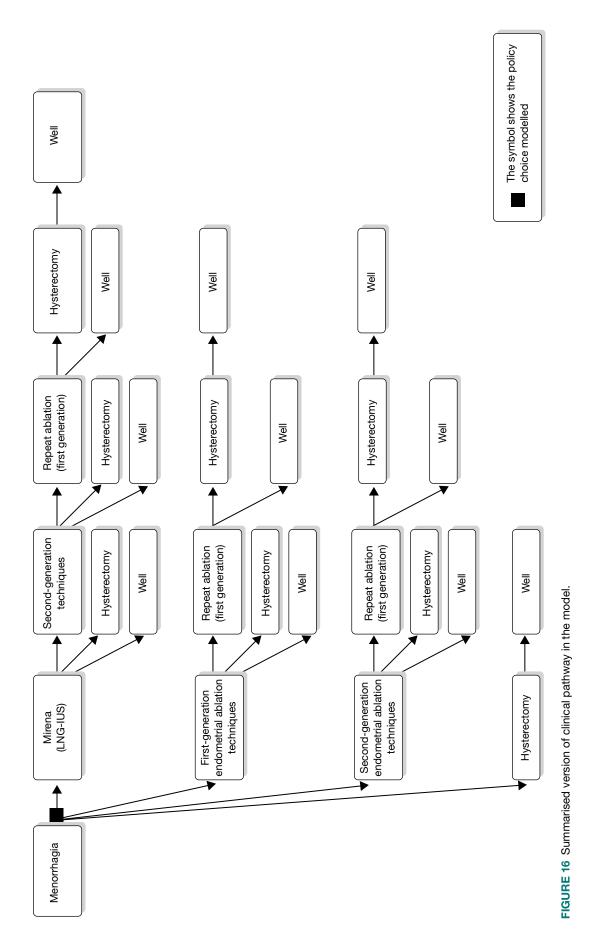
Structure of the economic model

In the model, a cohort of 10,000 eligible women was compared for each strategy (Mirena coil; first-generation EA; second-generation EA; and hysterectomy). The starting age of women in the model is 42 years, and the model runs for a total of 10 years and assumes that all women will become menopausal at the age of 52 years, (the average age of menopause in the UK). These assumptions are those used by Garside *et al.*¹⁶ Each model cycle is 1 month long and represents a typical menstrual cycle. The death rate from causes other than procedures for HMB was based on values for women in the Government Actuary's Department life tables of England and Wales for the years 1998–2008.¹³³

The model is based on the clinical pathways presented in *Figure 16*. The pathway for women undergoing any EA technique (first or second generation) is shown in *Figure 17*. The pathway for women undergoing hysterectomy is shown in *Figure 18*. Health states are shown in boxes and arrows show the transitions that can occur. The health states and pathways are the same for both types of EA technique.

Definition of health states for endometrial ablation pathways

- Menorrhagia all women in the cohort have pre-operative HMB.
- EA techniques women undergo EA by first- or second-generation techniques.
- Complications following EA, some women will experience severe postoperative complications. Perioperative complications are included in the EA state.
- Well following EA, complications or treatment failure, women are satisfied with treatment.
- Symptomatic following EA, complications or well, HMB may recur (treatment failure) at any time. Women may be retreated (repeat ablation), become 'well' or have a hysterectomy after initial or repeat ablation.
- Repeat ablation (RB) if HMB recurs postoperatively, women may choose to have a second EA which occurs 6 months after the initial ablation. Only one repeat EA is permitted and it is always a first-generation technique (RB).
- Hysterectomy if women become symptomatic after the first ablation, they may choose to have a hysterectomy. Hysterectomy is also an option after a failed repeat EA. This operation occurs 6 months after the decision.



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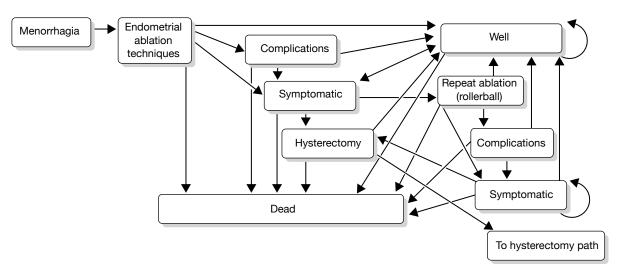


FIGURE 17 Clinical pathway for EA (first- or second-generation techniques).

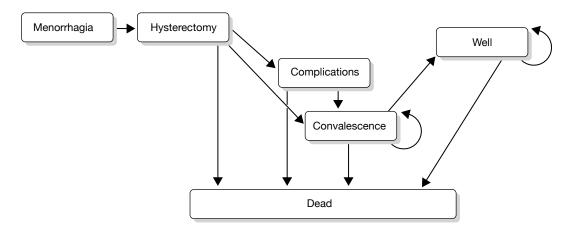


FIGURE 18 Clinical pathway for hysterectomy.

 Death – it is possible to die from natural causes. At hysterectomy and EA, women may also die as a direct result of the surgical procedure.

Definition of health states for hysterectomy pathways

- Menorrhagia all women in the cohort have pre-operative HMB.
- Hysterectomy all women undergo hysterectomy.
- Complications following hysterectomy, some women will experience severe postoperative complications. The effects of these may last for 1 month. Operative complications are included in the hysterectomy state.
- Convalescence following hysterectomy both with and without complications, a period of convalescence is experienced. This may last up to 3 months.
- Well following convalescence women are satisfied with treatment.

Definition of health states in Mirena pathways

- Menorrhagia all women in the cohort have pre-operative HMB.
- Mirena all women have Mirena inserted.
- Well following Mirena, women are satisfied with treatment.

Symptomatic – following Mirena or well, HMB may recur (treatment failure) at any time. Women may be retreated, have a second-generation EA or remain symptomatic.

Clinical assumptions and adverse events

Mirena

The lifespan of Mirena is assumed to be 5 years.¹⁵ If it is successful, treatment is repeated at 5 years. Treatment failure in Mirena is assumed to be more evident in the first year.^{27,93} We also assumed a 2% insertion failure rate where procedure is repeated within a month.²⁷ If Mirena is unsuccessful, women move to the second-generation pathway. No adverse events associated with Mirena were available from the literature.

First- and second-generation endometrial ablation techniques and hysterectomy

Large national audits of hysterectomy and first-generation EA techniques were used as sources for perioperative and severe postoperative adverse events^{5,47} and are presented in *Table 13*. Minor postoperative complications were not modelled. For second-generation EA techniques, complication rates of MEA were used.¹³⁴

TABLE 13 Data used in the model

Description	<i>p</i> -value	Source		
Background mortality rate	0.00015	Life tables ¹³³		
Proportion of symptomatic women (post initial ablation) who have a repeat ablation	0.4	Cooper, 2001 ²⁸		
Proportion of symptomatic women (post initial ablation) who have a hysterectomy	0.6	Cooper, 200128		
	First-generati	on techniquesª	Second-gene	ration techniques
	<i>p-</i> value	Source	<i>p</i> -value	Source
Operative complications	0.0445	Overton, 199747	0.0028	Parkin, 2000134
Severe postoperative complications	0.0292	Overton, 199747	0.0007	Parkin, 2000134
Death after operation	0.0002	Overton, 199747	0	Parkin, 2000134
Severe complications following well	Fit by calibration	n to IPD meta-analysis	Fit by calibration	on to IPD meta-analysis
Symptomatic following well	Fit by calibration	n to IPD meta-analysis	Fit by calibration	on to IPD meta-analysis
Symptomatic following operative	Fit by calibration	n to IPD meta-analysis	Fit by calibration	on to IPD meta-analysis
	LNG IUS		Hysterectomy	b
	<i>p-</i> value	Source	<i>p</i> -value	Source
Operative complications	_	_	0.0358	Maresh, 20025
Severe postoperative complications	_	_	0.0102	Maresh, 20025
Death after operation	_	_	0.0003	Maresh, 2002⁵
Proportion of women with LNG IUS in situ – year 1	0.6806°	Hurskainen, 2001 ⁹³	_	_
Proportion of women with LNG IUS in situ – years 2–5	0.7037°	Hurskainen, 2004 ²⁷	_	_
Insertion failure rate	0.0168	Hurskainen, 2004 ²⁷	-	_

a Complication and mortality rates after repeat ablation (RB) were double those after initial ablation (MacLean-Fraser *et al.*¹³⁵ and professional estimate).

b Complication and mortality rates were adjusted for DUB population only.

c Original values as reported in the papers are presented. Failure per month in year 1 and years 2-5 were calculated.

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Some of the data (specifically proportions in various health states at points in time after initial treatment) related to model outputs rather than model inputs. We applied a method that may be called 'probabilistic calibration' whereby model inputs for the relevant parameters were sampled uniformly across the plausible range, and cost and QALY outcomes were weighted according to the likelihood function comparing the model proportions in the various health states with the data.

Repeat ablation (rollerball)

If EA of any type fails, repeat ablation or hysterectomy is offered. In the model it is assumed that 60% of those with recurrent menorrhagia (symptomatic state) will have a repeat EA and 40% will have a hysterectomy.²⁸ Only one repeat ablation is offered, which is RB (first-generation EA). If the treatment fails a second time, only hysterectomy is available.

Complication rates in the repeat ablation are assumed to be double those incurred for the initial ablation.¹³⁵

Repeat procedure

The transition probability for requiring a repeat procedure (ablation or hysterectomy) is timedependent and is reduced by a constant factor each month. This reflects a decreasing hazard, which is obvious from the IPD data.

Resource use and costs

In order to calculate the costs of each of the procedures, a range of sources was used. All costs in the model are in UK \pounds (2008 value). Appropriate indices were used to inflate some of the costs that were obtained from the literature.¹³⁶ Costs are presented in *Table 14* and are discounted at 3.5% per annum.

Mirena

The cost of insertion of Mirena was estimated at £130.27. This procedure is assumed to be performed in a menstrual clinic as an outpatient procedure. The total cost includes those for the device, the initial consultation (10 minutes with a nurse and 30 minutes with a specialist registrar) and a sterile pack for use during Mirena insertion. Cost of discontinuation (£28.34) includes the cost of the consultation and the consumables (sterile pack) used for removal of the device.

First-generation techniques

The cost of first-generation EA was estimated at £1238. The source was a study which compared the costs of treating women with menorrhagia by hysterectomy or hysteroscopic surgery.³² Costs in this study included pre-surgery treatment for EA, technical equipment (which varied for each method), hospital costs, gynaecological outpatient costs and retreatment. We excluded retreatment from our estimate because this is a separate procedure included in the model.

Second-generation techniques

The cost of second-generation techniques was estimated at £1101. The source for the costs of MEA and TBEA was the HTA report by Garside *et al.*¹⁶ Statistical weights for the weighted cost mean were obtained from a study reporting NHS hospital episode statistics of EA from 1989–90 to 2005.³⁰

TABLE 14 Table of costs

Description	Unit cost (£)ª	Source
First-generation ablation techniques ^b	£1238	Cameron, 1996 ³²
Second-generation ablation techniques ^c	£1101	Garside, 2004 ¹⁶
Repeat ablation (rollerball)	£1238	Cameron, 199632
Hysterectomy	£2162	Cameron, 199632
GP visit for referral to secondary care ^d	£46	PSSRU ¹³⁷
LNG IUS (Mirena)		
Total initial stage cost	£130.27	British National Formulary, 138 National Collaborating Centre
Discontinuation	£28.34	for Women's and Children's Health CG44,15 PSSRU137
Adverse events ^e		
First-generation ablation techniques	£2161	National schedule of reference costs139
Second-generation ablation techniques	£1198	
Hysterectomy	£3008	

a Cost year is 2008.

b Weighted mean for TCRE and RB. Statistical weights assumed to be equal.

c Weighted mean for MEA and TBEA. Statistical weights calculated from Reid.³⁰

d Cost of GP consultations was included as part of the referral to secondary care for a second-generation EA after Mirena failed and for a repeat ablation or a hysterectomy after both ablations failed.

e Values used for both 'immediate operative adverse events' and 'severe postoperative adverse events'.

Hysterectomy

The cost of hysterectomy was estimated at £2162 and the source was a study comparing the costs of treating women with menorrhagia by hysterectomy or hysteroscopic surgery.³² For women who had a hysterectomy after a failed repeat ablation, we included an additional cost of a consultation with a GP for referral from primary to secondary care at £46.¹³⁶

Repeat ablation (rollerball)

The cost of repeat ablation was the same as the cost of the first-generation techniques described above. We also included an additional cost of a GP consultation for referral from primary to secondary care, at £46.¹³⁶

Adverse events

The source for the costs of adverse events was NHS reference costs (2009).¹³⁹ We used the same cost for both perioperative and severe postoperative complications for each of the procedures included in the model. The varying severity of complications of the two different types of EA and hysterectomy is reflected in costs as well. The cost of complications was £2161 for the first-generation techniques, £1198 for the second-generation techniques and £3008 for hysterectomy.

The MISTLETOE study was the source for perioperative and severe postoperative adverse events of the first-generation EA techniques.⁴⁷

For second-generation EA techniques, complication rates of MEA were used as a proxy.¹³⁴ We chose not to use the complications rates from MISTLETOE for the second-generation EA techniques as well for the following reasons:

- The MISTLETOE study included radiofrequency and cryoablation only, and did not include MEA or TBEA, which are the commonest second-generation procedures used at the present time.
- Radiofrequency is no longer performed as it proved to be unsafe.
- The number of cryoablations in MISTLETOE is very low (n = 36) and there were no perioperative complications within that group.
- Severe postoperative complications in the MISTLETOE study are more frequent in the second-generation group than in the first-generation group, which is counterintuitive, as complications in second-generation techniques should be less frequent.

In using the complication rates of MEA from Parkin¹³⁴ (n = 1400), we acknowledge that this study might underestimate the true incidence of complications. All data reported in this study were from a specialist centre and reported complication rates might not be representative of other second-generation techniques. There were no adverse events associated with Mirena.

Utility values

The outcomes of treatment in the analysis are expressed in terms of QALYs gained for each procedure. Published evidence sources were used to identify the QoL weightings associated with each state in the model.^{27,132,140} These values are described in detail in *Table 15*.

Heavy menstrual bleeding is associated with a QoL value of 0.50 – that is, patients who suffer from this illness have reported that they feel a loss in terms of QoL value that is equivalent to half a year at full health.¹³² Treatment with Mirena is associated with a QoL value of 0.84.²⁷ After a successful treatment with Mirena, women move to the 'well' state, which according to the literature is also associated with a QoL value of 0.84.²⁷ EA is associated with a QoL value of 0.76, which captures convalescence as women are assumed to fully recover within 1 month (model cycle). After a successful first-generation ablation, women move to the 'well' state, associated with a QoL value of 0.73.¹³² After a successful second-generation ablation, women move to the 'well' state, associated with a QoL value of 0.84, which is assumed to be the same as the 'well' state after a successful Mirena. This assumption was made in the absence of any available evidence and suggests that women's QoL value is 'better off' after a second-generation ablation compared to the QoL value after a first-generation ablation. We assumed that the 'well post secondgeneration ablation' state is the same as the 'well post LNG IUS' state and *not* same as the 'well post first-generation ablation' state. This was based on the fact that second-generation techniques (generally speaking), if successful, perform better, are less invasive and have fewer adverse events.

Hysterectomy is associated with a QoL value of 0.56 and 'convalescence post hysterectomy' with a QoL value of 0.74.¹³² For the 'hysterectomy' state, we are assessing the mean QoL value for the month in which the hysterectomy is performed. We assumed that the 'hysterectomy' state utility value is 25% lower than the value for the health state 'convalescence post hysterectomy'; that is, zero QoL value for the 25% of that month that is the period of hospitalisation and then convalescence for the rest of the month. This assumption is in line with Garside *et al.*,¹⁶ except we have reduced the hospitalisation to 25% of the month instead of 33% of the month because this is the duration of hospitalisation in our source for the cost of hysterectomy.³² After a successful hysterectomy, women move to the 'well' state, which is associated with a QoL value of 0.88.²⁷

Perioperative and severe postoperative complications of EA and hysterectomy are associated with a QoL value of 0.49.¹⁴⁰ If treatment is unsuccessful, women move to the symptomatic state with a QoL value of 0.50; in the model it is assumed that this state is equivalent to the HMB state in

TABLE 15 Health state utilities

	Utility weight (95% Cl)	Source	Comment
Menorrhagia	0.50 (SE 0.04)	Sculpher, 1998 ¹³²	1
Dead	0	1	By definition
Hysterectomy	0.56	I	Assumed 14 less than 'convalescence post hysterectomy'
Well post hysterectomy	0.88 (0.75 to 0.95) ^a	Hurskainen, 2004 ²⁷	1
Convalescence post hysterectomy	0.74 (SE 0.05)	Sculpher, 1998 ¹³²	1
Severe complications post hysterectomy	0.49	Clegg, 2007 ¹³⁸	1
First-generation EA	0.76 (SE 0.04)	Sculpher, 1998 ¹³²	Includes 'convalescence post first-generation EA'
Well post first-generation EA	0.73 (SE 0.04)	Sculpher, 1998 ¹³²	1
Severe complications post first-generation EA	0.49	1	Same as 'complications post hysterectomy'
Symptomatic post first-generation EA	0.50 (SE 0.04)	Sculpher, 1998 ¹³²	Same as 'menorrhagia'
Second-generation EA	0.76 (SE 0.04)	I	Assumed same as 'first-generation EA'
Well post second-generation EA	0.84 (0.73 to 0.93) ^a	I	Same as 'Mirena'
Severe complications post second-generation EA	0.49	I	Same as 'complications post hysterectomy'
Symptomatic post second-generation EA	0.50 (SE 0.04)	Sculpher, 1998 ¹³²	Same as 'menorrhagia'
Repeat ablation (RB)	0.76 (SE 0.04)	I	Includes 'convalescence post first-generation EA'
Well post repeat ablation	0.73 (SE 0.04)	Sculpher, 1998 ¹³²	1
Severe complications post repeat ablation	0.49	I	Same as 'complications post hysterectomy'
Symptomatic post repeat ablation	0.50 (SE 0.04)	Sculpher, 1998 ¹³²	Same as 'menorrhagia'
Mirena	0.84 (0.73 to 0.93) ^a	Hurskainen, 2004 ²⁷	Same as 'well post Mirena'
Well post Mirena	0.84 (0.73 to 0.93) ^a	Hurskainen, 2004 ²⁷	1
Symptomatic post Mirena	0.50 (SE 0.04)	Sculpher, 1998 ¹³²	Same as 'menorrhagia'
SE, standard error a Mean and width of Cl were fitted.			

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terms of QoL value loss. The QoL value weightings associated with the repeat ablation (RB) are the same as the ones used for the first-generation techniques described above.

For costs, we aggregated according to the distributions at the start of each cycle. This is necessary to account for the full costs of initial treatment. When assessing total QALYs, we aggregated using Simpson's rule, which is an improvement on the half-cycle correction most commonly used (see, for example, Fröberg, 1969).¹⁴¹

Sensitivity analysis and reporting of results

All analyses are carried out from the perspective of the UK National Health Service and are reported in terms of incremental cost-effectiveness ratios (ICERs). Dominance in the results will exist if one strategy is found to be both cheaper and more effective (in terms of producing more QALYs). Two main analyses, Analysis 1 and Analysis 2, are carried out, and probabilistic sensitivity analysis (PSA) is carried out for both analyses. For reasons that will be explained in the discussion, Analysis 2 is assumed to be the base case. Additional alternative analyses carried out in addition to the PSA, including deterministic sensitivity analyses and subgroup analyses, are carried out on Analysis 2 only.

Uncertainty in the model parameters was assessed through PSA. In its most common form, PSA assigns to each input parameter a specific distribution and, by drawing randomly from those distributions, generates a large number of mean cost and effectiveness estimates. These estimates are then used to form an empirical joint distribution of the differences in cost and effectiveness between interventions.^{142,143}

Value of information analysis

Where a decision is not robust to plausible variation in the input parameters, it is possible to estimate a statistic known as the expected value of perfect information (EVPI). This is determined as a function of the threshold ICER, which allows a conversion from QALYs to monetary value. The preferred decision under uncertainty is determined by maximising the mean net benefit across the distribution of input parameter values. For any specific parameter set which leads to the same decision, there is no value of information attached to those parameters. If, however, a parameter set leads to a change in the decision, then the value attached to that parameter set is the difference in net monetary benefit between the decision made under uncertainty and the decision made knowing those parameter values. The EVPI is obtained by calculating the value attached to each parameter set used in the PSA and averaging across all parameter sets, taking into account the weightings determined by the probabilistic calibration described in the previous section.

Subgroup analysis and deterministic sensitivity analysis

All subgroup and sensitivity analyses were carried out for Analysis 2 only, which was assumed to be the base case. Two subgroup analyses were considered appropriate a priori:

1. *A subgroup analysis on the basis of age*: This was planned specifically to analyse the data for women below the age of 40 years in our population in order to ascertain whether the results of the analysis, in terms of costs and satisfaction, were different for this subgroup compared with the women overall.

2. A subgroup analysis on the basis of uterine cavity length: The rationale for this subgroup analysis is that women with shorter uterine cavity length are more amenable to successful ablation (as opposed to hysterectomy). There was some evidence in the raw collated data which suggested the presence of a trend in support of this hypothesis and so a subgroup analysis was deemed appropriate to investigate this.

Three alternative one-way deterministic sensitivity analyses were considered appropriate a priori:

- 1. Utilities are changed from the base case in which the mean utility values are used to an analysis based on reported median values: We carried out the analyses using the median value for the utility scores from Sculpher.¹³² In the base case we have used the mean scores for the utility values reported by Sculpher.¹³² Use of the mean scores is most appropriate in economic evaluation. However, we noted that other published studies which used the same source for the utility values used the reported median values from the same study¹³² and not the reported means, but without explanation or justification. We explored this to see if using the medians made any difference to the base-case results.
- 2. Assumption that all women undergo hysterectomy after a failed repeat ablation: In the base case it is assumed that all (100%) women who have a failed repeat ablation finally resort to a hysterectomy. In the sensitivity analysis this assumption is changed to assume that 10% of women remain symptomatic for the rest of the time period but do not seek further treatment. Thus, in this sensitivity analysis it was assumed that 90% of women chose hysterectomy after a second failed ablation and the remaining 10% chose to remain symptomatic.
- 3. Costs associated with anaesthetic: We considered varying the cost associated with anaesthetic. Seymour et al.¹⁴⁴ have presented the cost of MEA under local versus general anaesthesia. The cost was £440 for general and £428 for local anaesthesia. It had been intended to use the £440 GA estimate in the base case and the £428 LA estimate in the sensitivity analysis to explore any impact. However, on closer examination it became apparent that Seymour et al. excluded the cost of hormonal endometrial preparation (administered 5 weeks prior to MEA) and any pre-admission consultations because they were comparing different types of MEA, and these costs occurred in both types. Thus, we realise that the results from Seymour et al.¹⁴⁴ are not comparable to other reports of EA and hysterectomy used in the current model. Furthermore, by using the cost data from Garside et al.,¹⁶ we have incorporated the balance between procedures undertaken under local versus general anaesthesia in the base-case analysis.

Results

Analysis 1

For Analysis 1, for the first-generation EA, second-generation EA and Mirena strategies, we assumed that repeat procedures (ablation or hysterectomy) are allowed at any age, but with a decreasing hazard.

The deterministic results are presented in *Table 16*.

Total costs (£)	Total QALYs	ICER (vs hysterectomy)
30,040,000	64,485	Dominated
25,950,000	68,965	Dominated
15,630,000	68,758	1600
23,000,000	73,332	-
	30,040,000 25,950,000 15,630,000	30,040,000 64,485 25,950,000 68,965 15,630,000 68,758

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The strategy of hysterectomy

The deterministic results show that hysterectomy dominates both first- and second-generation EA because the hysterectomy strategy is both less costly and produces more QALYs than either of the other two. The strategy of hysterectomy is more costly than the strategy of Mirena but also produces more QALYs. The incremental cost per additional QALY of hysterectomy compared with Mirena is £1600 per QALY.

The second-generation endometrial ablation strategy

Second-generation EA is both cheaper and produces more QALYs than the first-generation EA strategy and so is said to dominate it.

The Mirena strategy

The results show that Mirena is both less costly and produces more QALYs than first-generation EA and thus dominates it. However, although the Mirena strategy costs only half as much as the second-generation EA strategy, the second-generation EA is more effective at producing QALYs. Thus, the ICER for second-generation EA compared with Mirena is £50,000 per QALY. This means that for every woman who is treated with second-generation EA instead of Mirena there is an additional cost of £50,000 to achieve an additional QALY.

Consider for example a threshold ICER of £5000 per QALY; according to our model (not shown), the expected net monetary benefit per woman for hysterectomy is £34,386 at this valuation. This is higher than the expected net benefit for any of the other three options and so hysterectomy is the preferred option given parameter uncertainty. However, replications of the model accounting for approximately 26% of the probability favour different options. So the model probability that hysterectomy is the preferred option is 74%. This is the probability shown on the cost-effectiveness acceptability frontier (CEAF) (*Figure 19*). The limitation of the CEAF as a decision aid is that it does not tell us, in the remaining 26% of cases, whether changing to another option would make a large or a small difference to the expected net benefit.

Figure 20 shows the difference between the expected net benefit of the optimal strategy allowing for perfect information and the expected net benefit of the optimal strategy given current information for any given threshold ICER. If the preferred option could be chosen after completely resolving parameter uncertainty, then the estimated net benefit per woman would be

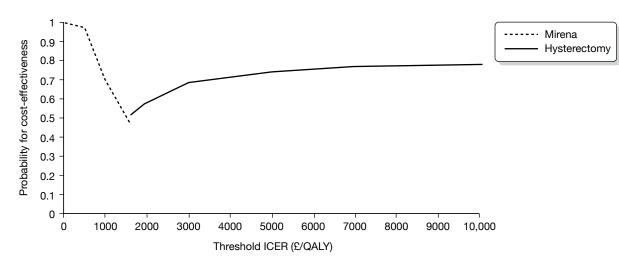


FIGURE 19 Cost-effectiveness acceptability frontier for Analysis 1.

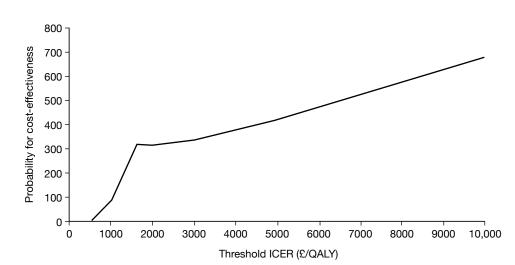


FIGURE 20 Probability that the preferred option is cost-effective for any given threshold ICER.

£34,812 (from the model, not shown). The additional £426 is known as the 'per woman' EVPI. Similar remarks apply at other threshold ICERs. At thresholds below 1600 per QALY (i.e. the kink in *Figure 19*), the preferred option is Mirena, and so the CEAF shows the probability that Mirena is the preferred option. As the threshold approaches zero the decision is effectively to choose the least costly option – this is Mirena in all replications of the model. So the probability shown on the CEAF goes to one, and the EVPI becomes zero. As the threshold ICER becomes very large, the decision is effectively the option with the highest QALY output. There is some residual uncertainty in the model and so the probability on the CEAF does not actually approach one. Had the EVPI been measured in health units, the height of the EVPI curve would tend to a fixed non-zero limit. However, because it is measured in monetary terms, the curve has an increasing slope.

In summary, for every replication in this model, Mirena was the least costly option. For very low-threshold ICERs, Mirena is preferred with certainty (so EVPI tends to zero and CEAF tends to one). In some replications of the model (accounting for 18% of the probability), hysterectomy was not the most effective option (in terms of total number of QALYs). Therefore, the CEAF never goes above 82% and the EVPI does not go to zero.

At an ICER of £1600, the preferred option changes from coil to hysterectomy, so there is a discontinuity in the CEAF and a discontinuity in the gradient of the EVPI curve.

Analysis 2

For Analysis 2, we assumed that if symptoms do not recur within 2 years of the initial ablation, then they are unlikely to do so later, and therefore no repeat procedure takes place thereafter. Thus, we have to limit the time as to when a repeat procedure (ablation or hysterectomy) may occur to 2 years. Similarly, as regards to repeat ablations, if women are not symptomatic within 4.5 years of the initial ablation (2 + 2 years + 6 months from decision to repeat procedure), it is assumed they will never become symptomatic (*Table 17*).

First-generation EA is dominated by all the other strategies.

	Total costs (£)	Total QALYs	ICER (vs hysterectomy)
First-generation EA	23,590,000	63,745	Dominated
Second-generation EA	19,470,000	69,678	970
Mirena	16,150,000	68,566	1440
Hysterectomy	23,000,000	73,332	-

TABLE 17 Deterministic results for Analysis 2

Second-generation endometrial ablation strategy

Second-generation EA is cheaper than all the other strategies except for Mirena; however, it does produce more QALYs than the Mirena strategy. The ICER for second-generation EA versus Mirena is £2980 per additional QALY.

The Mirena strategy

Mirena dominates the first-generation EA strategy but does not dominate second-generation EA.

The hysterectomy strategy

Hysterectomy is the strategy which produces the most QALYS. As this strategy is both cheaper and produces more QALYs than the first-generation EA strategy, it is considered to dominate the latter. Hysterectomy is more expensive but produces more QALYs than the Mirena strategy and the ICER representing the value of the additional benefit of this strategy compared with Mirena is £1440 per additional QALY. Despite being more costly, the hysterectomy strategy produces more QALYs than the second-generation EA strategy and the cost per unit of benefit for this comparison is £970 per additional QALY.

The detailed explanation of the interpretation of *Figures 21 and 22* is similar to the explanation given for the comparable figures for Analysis 1.

In summary, *Figure 21* presents the probability that the preferred option is cost-effective for any given threshold ICER.

In this model, hysterectomy dominates the graph. For all but a few replications, and the few account for a negligible probability, Mirena was the least costly option and for very low-threshold ICERs Mirena is preferred with certainty (so EVPI tends to zero and CEAF tends to one); however, as the threshold ICER increases hysterectomy becomes the preferred option.

However, it is clear that in some replications of the model (accounting for 20% of the probability), hysterectomy was not the most effective option (in terms of total number of QALYs). Therefore, the CEAF never goes above 80% and the EVPI does not go to zero, which would suggest that there is value in finding out whether if the uncertainty was removed hysterectomy would remain the most cost-effective option.

At an ICER of £1440, the preferred option changes from the Mirena coil to hysterectomy, so there is a discontinuity both in the CEAF as well as in the gradient of the EVPI curve presented in *Figure 21*.

Figure 22 presents the difference between the expected net benefit of the optimal strategy allowing for perfect information and the expected net benefit of the optimal strategy given current information for any given threshold ICER.

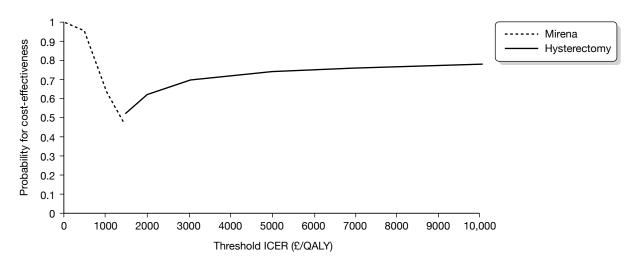
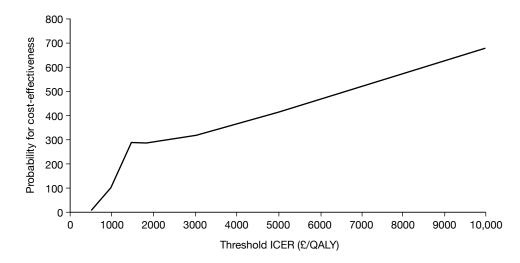
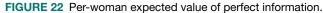


FIGURE 21 Cost-effectiveness acceptability frontier for Analysis 2.





Results of the subgroup analysis and one-way deterministic sensitivity analysis for Analysis 2

Subgroup analysis

On the basis of uterine cavity length

We carried out deterministic analysis assuming (1) that all women had the shortest uterine cavity length and (2) that all women had the longest uterine cavity length. A corresponding PSA was also carried out.

The results of the deterministic analysis are presented in *Table 18*.

The results are broadly similar to those presented in the base case analysis. First-generation ablation is no longer 'dominated' by hysterectomy and the incremental cost per additional QALY of hysterectomy compared with other strategies is now slightly higher than in the base case. However, there is unlikely to be a change in decision based on these results and hysterectomy

	Total costs (£)	Total QALYs	ICER (vs hysterectomy)
Short uterine cavity length			
First-generation EA	21,356,000	63,143	161
Second-generation EA	19,264,000	69,582	996
Mirena	15,667,000	68,201	1429
Hysterectomy	23,000,000	73,332	-
Long uterine cavity length			
First-generation EA	20,104,000	62,809	275
Second-generation EA	17,986,000	69,655	1364
Mirena	15,158,000	68,558	1642
Hysterectomy	23,000,000	73,332	_

TABLE 18 Summary of deterministic sensitivity analysis for uterine cavity length (Analysis 2)

continues to be likely the most cost-effective strategy. The results of the PSA serve to reinforce the results of the deterministic analysis presented above, and so are not presented.

Sensitivity analysis

Utilities are changed from the base case which used mean utility values to median utility values

In the base case analysis the mean value for the health state of 'well' post ablation was lower (0.73) than the mean value for the health state of first-generation ablation (0.76). Furthermore, the health state of 'well' post Mirena coil is not available in the report by Sculpher¹³² and so a value was taken from a different study by Hurskainen *et al.*²⁷ As a result the health state for 'well' post Mirena coil is lower than the health state of 'well' post repeat ablation. Thus, although mean values are most appropriate, the use of mean values for utilities that are available in alternative published sources in our base case presents some slightly counterintuitive results.

Other studies have tackled this issue by using median values from different studies rather than the mean, which leads to a more intuitive set of values being used. But there is no other sensible justification for using median rather than mean values.

We carried out two sensitivity analyses to explore the impact of using the median reported values as opposed to the means.

A. QALY1

In this analysis we used the 'median' QoL values from Sculpher¹³² and the value of 'well' post second EA and set this equal to 'well' post first-generation EA (i.e. 'well' post second-generation EA = 'well' post first-generation EA). It should be noted that 'well' in this instance is not the same as 'well' post Mirena coil that we used in the base case

The deterministic results of this sensitivity analysis are presented in Table 19.

The key change in results compared with the base case (Analysis 2) is that there is a clear shift away from the hysterectomy strategy in favour of the second-generation EA strategy as this

	Total costs (£)	Total QALYs	ICER (vs hysterectomy)
First-generation EA	23,588,000	74,218	2225
Second-generation EA	19,466,000	74,402	Dominates
Mirena	16,151,000	71,089	2391
Hysterectomy	23,000,000	73,954	-

TABLE 19 Deterministic sensitivity analysis where mean values are substituted by median values (QALY1)

now dominates both first-generation EA and hysterectomy. In the base case (Analysis 2), firstgeneration EA was dominated by second-generation EA, but the latter strategy did not dominate the hysterectomy strategy as it now does. The ICER for second-generation EA versus the Mirena strategy is £1000 per additional QALY in this sensitivity analysis.

B. QALY2

In this analysis we used the 'median' QoL values from Sculpher¹³² and we set the value of well post second-generation EA = well post first-generation EA = well post Mirena coil.

The deterministic results from this sensitivity analysis are presented in Table 20.

These results are very similar to those presented in sensitivity analysis A. Once again the strategy of second-generation EA dominates first-generation EA and hysterectomy in contrast to the base case. The ICER for second-generation EA versus Mirena is £3624 per additional QALY.

Assumption that all (100%) women undergo hysterectomy after a failed repeat ablation

In the sensitivity analysis we change this assumption and assume that 10% of women remain symptomatic and only 90% follow the hysterectomy strategy after a failed repeat ablation

The deterministic results for this sensitivity analysis are presented in Table 21.

In this analysis, although the total cost and QALYs for each strategy are different to those in the base case, the overall result is unchanged from the base case.

Two sensitivity analyses deemed worthy of investigation before the main analysis was undertaken were not carried out for the following reasons:

- 1. Subgroup analysis on women below 40 years of age. On scrutinising the data it was clear that women below the age of 40 years had a 100% satisfaction rate with the Mirena coil strategy and therefore it was very clear that any subgroup analysis on the basis of age would be dominated by the strategy of coil. The base case uses 'all ages of women' and so to specifically analyse the subgroup of women older than 40 years would prove fruitless because that result was captured by the main analysis.
- 2. Sensitivity analysis varying the cost of anaesthetic. In the base case analyses, the cost of second-generation techniques (MEA and TBEA) was based on the estimates used by Garside *et al.*¹⁶ The cost estimate from Garside *et al.*¹⁶ already takes into account local versus general anaesthesia. It was thus considered that any recalculations/re-estimations to explore the minor difference in costs of LA versus GA observed in Seymour *et al.*¹⁴² would add more uncertainty.

	Total costs (£)	Total QALYs	ICER (vs hysterectomy)
First-generation EA	23,588,000	74,218	2225
Second-generation EA	19,466,000	74,402	Dominates
Mirena	16,151,000	73,488	14,683
Hysterectomy	23,000,000	73,954	_

TABLE 20 Deterministic sensitivity analysis where mean values are substituted by median values (QALY2)

TABLE 21 Deterministic sensitivity analysis in which 90% of women are assumed to follow the hysterectomy strategy

	Total costs (£)	Total QALYs	ICER (vs hysterectomy)
First-generation EA	23,424,000	63,589	Dominated
Second-generation EA	19,323,000	69,542	970
Mirena	16,059,000	68,508	1440
Hysterectomy	23,000,000	73,332	-

Discussion

Statement of principal findings

The results of base case Analysis 2 show that the strategy of hysterectomy is most cost-effective. Hysterectomy dominates first-generation EA and, although more expensive, produces more QALYs than the other strategies. The ICER for hysterectomy compared with Mirena is £1440 per additional QALY. Compared with the second-generation EA strategy, the ICER for hysterectomy is £970 per additional QALY. These results suggest that hysterectomy would be considered the most cost-effective strategy in the light of the acceptable thresholds used by NICE, which tends to accept new technologies if the ICER is within £20,000 per additional QALY.

The results of this study were robust to all the sensitivity and subgroup analysis that were carried out with the exception of the sensitivity analysis carried out on the QALY data. The results of the main analysis reported in this study are based on an analysis that used the reported values of QALYs that are available in the published literature, specifically the 'mean' reported QALY values. When we carried out the same analysis using the median QALY values, the results changed and second-generation EA became the most cost-effective strategy, dominating both the first-generation ablation strategy and the hysterectomy strategy. In the sensitivity analysis the second-generation EA strategy was more expensive than the Mirena strategy but also produced more QALYs. The ICERs that resulted suggested that second-generation EA would be considered the most cost-effective strategy.

Strengths and limitations

The major strength of the economic component of this study is that it is based on a state-ofthe-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 based on the available evidence as far as possible. Assumptions were agreed with the team before the analysis was carried out and without knowledge of how these assumptions would affect the results.

In terms of limitations, not all aspects of outcome have been included because of the limited time scale in our model and the lack of long-term data. For strategies such as hysterectomy, for

instance, there is a finality associated with the procedure which may have an effect on women and, in the long term, have implications on QoL that have not been captured in our model. These include the possibility of long-term complications such as urinary incontinence for which surgery is required. Furthermore, the utilities used reflect the satisfaction of the outcomes only. It is clear that once women have had a hysterectomy their satisfaction is high since in contrast to the other interventions they experience no bleeding at all. But the utility measure does not capture the anxiety prior to hysterectomy associated with major surgery and GA. It is conceivable that such anxiety may lead to decisions that avoid the strategy and to try other options for as long as possible.

In addition, the fact that the complexity of the model contributed to a long running time has some effect on the extent of sensitivity analyses that were undertaken. Both the main analysis and sensitivity/subgroup analysis had a long model running time and required laborious recalibration, which meant that additional sensitivity and subgroup analyses were not undertaken without serious consideration.

Strengths and weaknesses and assumptions in relation to other studies

With regard to the utility values that have been used in the current study the following points are worth noting.

First, the paper by Sculpher¹³² has been extensively referenced in the literature. Other studies (including Garside *et al.*¹⁶) have used the median values from that paper and not the means. However, for economic evaluation it is the mean values that are most appropriate to use.^{145,146}

There are minor inconsistencies in the results presented by Sculpher¹³² when looking at the QALY values for 'well post TCRE' and 'convalescence post TCRE' compared with the 'well post hysterectomy' and 'convalescence post hysterectomy' states: the mean QALY value for the 'well post TCRE' state is 0.73 while the mean QALY value for the 'convalescence post TCRE' state is 0.76. One would expect that 'well post TCRE' state would have a higher value than the 'convalescence post TCRE' state, which is the case for the median QALY values. This is also true for the mean and median QALY values of the 'well post hysterectomy' and 'convalescence post hysterectomy' states. Despite these apparent inconsistencies, we used the mean values as they were presented in the literature and considered it possible that this might be explained by the greater initial relief that a woman might experience after a hysterectomy than after a TCRE, although no explanation was put forward in the original literature.

Comparison with other studies

Our results are consistent with those reported by Garside *et al.*,¹⁶ who compared MEA and TBEA with TCRE, RB and hysterectomy. A state-transition (Markov) model was used and assumed a hypothetical cohort of 1000 patients for a period of 10 years. Our model used the same assumptions as Garside *et al.*¹⁶ regarding the age of women entering the model, who were assumed to be 42 years; the model ran for 10 years and women became menopausal at age 52 years.

Garside *et al.* concluded that hysterectomy is cost-effective compared with MEA and TBEA. They found that TBEA dominated all other ablation techniques.

In addition, when compared with hysterectomy, MEA and TBEA were found to be less costly but provided fewer QALYs. Garside *et al*.'s ICER for hysterectomy compared with TBEA was £2410 per QALY, and for hysterectomy compared with MEA their ICER was £2108 per QALY. The authors found that, when comparing MEA and TBEA with TCRE, RB and hysterectomy, the model was highly sensitive to the utility values associated with being well following ablation. Garside *et al.*¹⁶ recommended that results are interpreted with caution owing to the sensitivity of the model to the utility values used.

The results of our study do not concur with the result of the trial by Hurskainen *et al.*²⁷ from Finland, which compared Mirena with hysterectomy. Mirena was found to be cost-effective at 5 years when compared with hysterectomy. There was no statistically significant difference in QoL scores at 5 years, as measured by the EQ-5D instrument, between the two treatment groups. Mean direct costs in the Mirena arm remained significantly lower (\$1892) than in the hysterectomy arm (\$2787) despite 40% of women in the Mirena arm going on to have a hysterectomy.

Economic modelling undertaken to inform NICE guidelines on HMB (NICE CG44, 2007)¹⁵ shows that Mirena is cost-effective when compared with both hormonal and non-hormonal treatment. It generates more QALYs at a lower cost than any other medical or surgical treatment strategy considered. This analysis also considered surgery as a comparator treatment. The surgical strategy produced fewer QALYs at a higher cost than Mirena. The NICE model assumed that, within the 5-year lifespan of Mirena, some women who experienced failure would move straight to hysterectomy (based on data from Hurskainen *et al.*²⁷). In contrast, in our study the assumption (based on advice from clinical colleagues) was that all women who experienced failure with the Mirena strategy would follow the second-generation EA pathway in the first instance.

However, while hysterectomy clearly comes out on top, the available long-term follow-up data on Mirena use are so inconsistent that we have to be cautious in our interpretation.

Meaning of the study

The results of this study suggest that hysterectomy is more cost-effective than either ablation or Mirena. These results are based on 'mean' reported values of utilities in published studies and are highly sensitive to the utility values that are used. When 'median' values for utility estimates are used, the strategy of second-generation ablation becomes the most cost-effective strategy. To the current authors there is no clear justification for using median values but they have been used in similar prominent studies without such justification. We assume that this is because some of the 'mean' values reported in the literature appear inconsistent. Replacing 'mean' values that appear inconsistent with 'median' values without clear justification will bias any results. The clear sensitivity of the results to the utility values serves to highlight the importance of using appropriate and robust data for utilities.

The study shows that first-generation ablation techniques are less cost-effective than secondgeneration techniques whatever utility values are used. Based on available data, Mirena does not come through as a cost-effective strategy compared with second-generation ablation or hysterectomy.

Unanswered questions for future research

The current study has used a state-of-the-art model, data from an IPD meta-analysis and all available data on QoL associated with available interventions and the outcomes for alternative treatments for HMB. One of the main causes of uncertainty regards the utility values associated with alternative interventions and their success. There would be little value in future studies comparing the outcomes and costs of any alternative interventions to treat women for menorrhagia without undertaking a comprehensive study to investigate the QoL associated with

the outcomes of the alternative interventions. Future studies should also explore the preferences and a priori anxieties associated with hysterectomy and the alternatives. Our study suggests that current available data are not robust enough.

Finally, both the preferences of women and clinicians perhaps need to be considered, as do the economic consequences of hysterectomy in terms of long-term morbidity such as pelvic floor dysfunction. Many clinicians believe (rightly or wrongly) that there is no one-size-fits-all approach to HMB and individual choices can determine perceived success; thus, evidence on preferences is also required.

Chapter 5

Interpretation of available evidence and consensus regarding treatment

D ata from the IPD meta-analysis suggest that more women are dissatisfied following firstgeneration EA than hysterectomy. However, it is important to note that dissatisfaction rates are low after all treatments and hysterectomy is associated with an increased hospital stay and recovery period. In the absence of head-to-head trials, indirect estimates suggest hysterectomy is also preferable to second-generation EA in terms of patient satisfaction. In terms of cost-effectiveness, hysterectomy is considered the best strategy, but it carries a higher risk of complications and is perceived as a final option by gynaecological experts and consumers. Dissatisfaction rates were comparable between first- and second-generation techniques, although second-generation techniques were cheaper, quicker and associated with a faster recovery and fewer complications. There are few comparisons of Mirena versus more invasive procedures. The few data available suggest that Mirena is potentially cheaper and more effective than firstgeneration ablation techniques, with rates of satisfaction similar to those of second-generation techniques. Owing to small, imprecise trials with relatively high levels of non-compliance, the evidence to suggest that hysterectomy is preferable to Mirena is currently so limited that definitive conclusions cannot yet be made.

Observational data indicate that at 7 years a quarter of women face further gynaecological surgery after EA while an initial hysterectomy for HMB is more likely to lead to further surgery for stress urinary incontinence. The incidence of endometrial cancer following EA is reassuringly low at 0.02%. The type of hysterectomy has an influence on future risk of surgery, with vaginal hysterectomy associated with a higher chance of further surgery for urinary incontinence and pelvic floor prolapse than hysterectomy carried out through the abdominal route.

A summary of the results on effectiveness and cost-effectiveness was sent electronically to 15 national experts (minimal-access gynaecological surgeons) along with a short questionnaire (see *Appendix 9*) to encourage a rapid response. After two mailings, responses were received from 10 clinicians. Their responses are summarised in *Table 22*. Mirena was offered as first-line treatment and second-generation EA as second-line treatment by 9 out of 10 responders, while hysterectomy was considered the final port of call for women with HMB in the absence of demonstrable organic pathology. It is also clear from the responses that such a simplistic approach was not considered appropriate by some of the clinicians, who felt that often the choice of treatment depended on which intervention had been used before. As *Table 22* suggests, some of the clinicians were also keen to incorporate the patients' own preferences. One in particular (Clinician G) indicated that patients should choose any one of the three options in the context of first-line treatment for HMB.

The letter to the clinicians along with a summary of their views was sent electronically to three consumers. All three agreed with the order in which the three treatments were prioritised by the clinicians. Two of them made further comments highlighting potential problems associated with a rigid clinical algorithm and pointed out other factors such as age and fertility status which could have a bearing on the choice of treatments. Both argued for a degree of flexibility in order to accommodate the needs and preferences of individual women (*Table 23*).

	First-line treatment	Second-line treatment	Third-line treatment
Clinician A	Mirena or second-generation EA	Hysterectomy/second-generation EA	Hysterectomy
Clinician B	Mirena	Second-generation EA	Hysterectomy
Clinician C	Mirena	Second-generation EA	Hysterectomy
Clinician D	Mirena	Second-generation EA	Hysterectomy
Clinician E	Mirena	Second-generation EA but will consider hysterectomy	Will depend on previous treatment
Clinician F	Mirena	Second-generation EA	Hysterectomy but may consider repeat ablation
Clinician G	Would offer patient choice of Mirena, ablation and hysterectomy	Hysterectomy	Hysterectomy – (relevant if patient chose Mirena as first option)
Clinician H	Mirena	Second-generation EA	Hysterectomy
Clinician I	Mirena	Second-generation EA (hysterectomy if the patient wishes)	Hysterectomy
Clinician J	Mirena	Second-generation EA	Hysterectomy

TABLE 22 Clinicians' responses to queries regarding the treatment of women with HMB with failed oral medical treatment and no obvious clinical abnormalities

TABLE 23 Consumer responses to clinician comments

	Agree with clinicians' choice of treatment as Mirena, second- generation EA and hysterectomy	Comments
Consumer 1	Yes	'I agree with the findings'
Consumer 2	Yes	'I would definitely go for the least invasive initially but would be looking for some assurance as to effectiveness. However, if I were older, and fertility were not an issue, then I might want to go straight to second-generation ablation. For me, hysterectomy would always be a last resort because it is major surgery. I think I would be happy if the professional presented the choices in the terms outlined'
Consumer 3	Yes	'I do not think that any one of the above (treatments) could be suggested as an outright "winner" in consumer terms. Leaving aside the women with obvious health problems which might dictate the treatment for HMB, the ultimate choice should be made by the woman in full knowledge of the facts. The age of the woman could well influence their choice – younger women might favour Mirena because it is reversible. There are also issues for some women are not happy with surgery'

Conclusion

An IPD meta-analysis of randomised trials as well as the results of a cost-effectiveness analysis favour hysterectomy in women with HMB. Interpretation of these results needs to take into account a number of issues. The limited evidence on the effectiveness of Mirena, concerns about the long-term consequences of hysterectomy and individual preferences of women and gynaecologists are factors that influence the choice of treatment. While hysterectomy results in significantly fewer women being dissatisfied than those undergoing EA, it is worth noting that rates of satisfaction were very high for all treatment modalities. Although economic models used suggest that hysterectomy is the most cost-effective treatment option for HMB, any decision to promote this procedure must balance the morbidity associated with it against the ease of Mirena insertions in the community, and the ability to perform second-generation ablative procedures outwith the traditional theatre setting. The latter could potentially free up theatre time in secondary care which could be used for other procedures. A key reason for the higher success rates associated with hysterectomy is the definitive nature of the procedure. Failure rates

for Mirena remain to be formally established, but those associated with EA are well known. Around a quarter of all women who undergo EA will require subsequent gynaecological surgery, with just under a fifth requiring a hysterectomy. Endometrial cancer rates following EA are very low, although longer term follow-up will be necessary to confirm this. Mirena protects against endometrial hyperplasia and hence endometrial cancer rates should be low. It is clear that clinical experts and consumers considered ease of access to treatment, degree of invasiveness, long-term consequences and patient autonomy to be important determinants. Expert clinical opinion favours offering the least invasive treatment, that is, Mirena first, followed by ablation, with hysterectomy reserved for women in whom the first two options have failed. This approach is endorsed by lay consumers, although they are anxious that women have the opportunity to choose the option that is best for them.

Chapter 6

Conclusion

This study has produced data on the clinical effectiveness and cost-effectiveness of different modalities of treatment of HMB and highlighted the risk of further surgery following EA and hysterectomy. It has also exposed gaps in the literature – especially with regards to the clinical effectiveness of Mirena in comparison with EA and hysterectomy and long-term follow-up data in women using it for HMB.

Despite a longer hospital stay and time to resumption of normal activities, 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 versus 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 first- and second-generation techniques. Owing to a paucity of trials, evidence to suggest that hysterectomy is preferable to Mirena is currently so limited that definitive conclusions cannot yet be made.

A quarter of women undergoing EA as an initial treatment are likely to face further gynaecological surgery (mainly repeat ablation or hysterectomy) for persistent menstrual problems. However, hysterectomy is more likely to lead to future surgery for stress urinary incontinence. Thus, in comparison with hysterectomy, the lower morbidity associated with EA needs to be balanced against the chance of repeat surgery for the same symptoms, although the risk of long-term pelvic floor problems may be less.

The cost-effectiveness analysis identified the strategy of opting for hysterectomy as the most costeffective one. Hysterectomy is both cheaper as well as more effective than first-generation EA. In comparison with second-generation EA and Mirena, hysterectomy costs more but produces more QALYs. The ICER for hysterectomy is £1440 per additional QALY compared with Mirena and £970 per additional QALY compared with second-generation EA. These results suggest that hysterectomy would be considered the most cost-effective strategy in light of the acceptable thresholds used by NICE, which tends to accept new technologies if the ICER is within £20,000 per additional QALY.

Our review provides evidence that hysterectomy reduces dissatisfaction compared with EA and this information should be used as part of 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. Relatively few trials have evaluated the evidence of effectiveness of Mirena. These are small, imprecise and have relatively high levels of compliance. Thus, we concur with a recent NICE recommendation that women should be offered Mirena before more invasive procedures. We have 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. Hysterectomy may be 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 who are swayed by other considerations such as ease of access to treatment, degree of invasiveness, long-term consequences and patient autonomy.

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Individual patient data meta-analysis

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Chapter 3

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Interpretation of evidence and consensus panel

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S Bhattacharya (corresponding author), Professor of Reproductive Medicine, University of Aberdeen, conceived the idea for the project, co-ordinated the project, contributed to the design of the different components, interpreted results, edited *Chapters 2* and 4 and wrote the first draft of the final report.

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1. Middleton LJ, Champaneria R, Daniels JP, Bhattacharya S, Cooper KG, Hilken NH, *et al.* Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. *BMJ* 2010;**341**:c3929.

wrote the initial draft of *Chapter 3* and edited the final report.

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Appendix 1

Full electronic search strategy used in the systematic review

Search strategy for population

#1 menorrhagia/all subheadings
#2 hypermenorrhea/all subheadings
#3 excessive NEAR ("menstrual bleeding" OR "menstrual blood loss")
#4 dysfunctional NEAR ("uterine bleeding" OR "menstrual bleeding")
#5 heavy NEAR ("menstrual bleeding" OR "menstrual blood loss")
#6 "iron deficient anaemia"
#7 (#3 OR #4 OR #5 OR #6) in TI, AB
#8 #1 OR #2 OR #7

Search strategy for interventions

Hysterectomy

- #1 EXPLODE "hysterectomy"/all sub-headings
- #2 "vaginal hysterectomy"/all sub-headings
- #3 "total abdominal hysterectomy"
- #4 "subtotal abdominal hysterectomy"
- #5 "laparoscopic hysterectomy"
- #6 #1 OR #2 OR #3 OR #4 OR #5

Ablation

- #1 EXPLODE "hysteroscopy"/all sub-headings
- #2 ("transcervical resection") NEAR "endometrium"

#3 "TCRE"

- #4 "endometrial ablation"
- #5 "laser ablation"
- #6 "electrosurgery"
- #7 "rollerball"
- #8 "thermal balloon"
- #9 "hypertherm\$"
- #10 "thermotherapy"
- #11 "photodynamic therapy"
- #12 "phototherapy"
- #13 "cryoablation"
- #14 "microwave ablation"
- #15 "radiofrequency"
- #16 "saline irrigation"
- #17 "laser interstitial"
- #18 "Thermachoice"
- #19 "Cavaterm"

- #20 "ELITT" #21 "Vesta" #22 "Novasure" #23 "Microsulis"
- #24 "Cryogen"

Mirena

#1 EXPLODE "contraceptive"/all sub-headings

#2 "Mirena® coil"/all sub-headings

#3 "levonorgestrel"

#4 "intra uterine device"

#5 #1 OR #2 OR #3 OR #4

Search strategy for randomised controlled trials

#1 Randomized Controlled Trial IN PT. #2 Controlled Clinical Trial IN PT. #3 Randomized Controlled Trials IN SH #4 Random Allocation IN SH. #5 Double Blind Method IN SH #6 Single Blind Method IN SH #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6) #8 Animal in SH NOT Human in SH. #9 #7 not # 8 #10 Clinical Trial IN PT. #11 EXPLODE Clinical Trials/all sub-headings #12 (clin\$NEAR trial\$) IN TI, AB #13 ((singl\$OR doubl\$OR trebl\$OR tripl\$) NEAR (blind\$OR mask\$)) IN TI, AB #14 Placebos IN SH #15 placebo\$IN TI, AB #16 random\$IN TI, AB #17 Research Design IN SH #18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 #19 #18 NOT #8 #20 #19 NOT #9 #21 Comparative Study IN SH #22 EXPLORE Evaluation Studies/all-sub-headings #23 Follow Up Studies IN SH #24 Prospective Studies IN SH #25 (control\$OR prospectiv\$OR volunteer\$) IN TI, AB #26 #21 OR #22 OR #23 OR #24 OR #25 #27 #26 NOTt #8 #28 #27 NOT (#9 OR #20) #29 #9 OR #20 OR #28

Appendix 2

Characteristics of studies included in the systematic review of randomised trials comparing hysterectomy, endometrial ablation and Mirena for heavy menstrual bleeding

Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?
Hysterectomy vs	first-generation EA				
Dickersin <i>et al.</i> , 2007 ⁹² (design and methods paper also published ¹⁴⁷) Raw data available n=237	Women with DUB. Up to 3 fibroids allowed, must each be smaller than 3 cm	EA vs hysterectomy	Major problem solved (primary outcome) Resolution of problem Bleeding Pain Fatigue QoL Adverse events Reoperation rate Follow-up reported at 12 months, 2 and 5 years; IPD at 6 months, 3 and 4 years also received	Women were asked if their major problem was solved from baseline Answers were given using the following scale: Yes No	Yes
Zupi <i>et al.</i> , 2003 ⁷⁸ Raw data available n=203	Women with HMB. Fibroids excluded	TCRE vs laparoscopic supracervical hysterectomy	Primary outcome unclear Duration of hospitalisation Period of convalescence Perioperative complications Resumption of usual activities QoL Follow-up reported at 3 months, 1 and 2 years	No comparable measure	Yes
Crosignani <i>et al.</i> ,1997 ⁴⁵ <i>n</i> =92	Women with HMB < 50 years old with a mobile uterus smaller than a 12-week pregnancy. Fibroids excluded if > 3 cm	TCRE vs vaginal hysterectomy	Satisfaction (primary outcome) Improvement in menstrual blood loss Operating time Complications Postoperative hospital stay Resumption of usual activities Resumption of work activities QoL Follow-up reported at 2 years	Women were asked how satisfied they were with their operation Answers were given using the following scale: Very satisfied Satisfied Uncertain Dissatisfied Very dissatisfied	No

continued

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Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?	
O'Connor <i>et al.,</i> 1997 ⁴⁴ Raw data	Women with symptomatic HMB. Fibroids excluded if	TCRE vs abdominal + vaginal hysterectomy	Satisfaction (primary outcome) Need for further surgery QoL	Women were asked how satisfied they were with their treatment	Yes	
available $n=202$	larger than 5 cm		Duration of surgery	Answers were given using the following		
			Duration of hospital stay	scale:		
			Operative and postoperative complications	Very satisfied Satisfied		
			Resumption of work activities	Not sure		
			Resumption of usual activities	Dissatisfied		
			Resumption of sexual activities Follow-up reported at 3 months, then 1, 2 and 3 years	Very dissatisfied		
Pinion <i>et</i>	Women who would	TCRE + laser	Satisfaction (primary outcome)	Women were asked how	Yes	
<i>al.</i> ,1994 ⁴³	have otherwise had a hysterectomy for	vs abdominal hysterectomy	Operative complications	satisfied they were with their treatment		
Raw data available	HMB. IPD showed	nystorootomy	Postoperative recovery	Answers were given		
n=204	that fibroids were included; exact		Relief of menstrual symptoms Relief of other symptoms	using the following scale:		
	eligibility details regarding this		Follow-up reported at 6 and 12	Very satisfied		
	parameter not		months	Moderately satisfied		
	given in paper			Dissatisfied		
				Very dissatisfied		
Dwyer <i>et al.,</i> 1993 ⁴² (health economics papers also	Women needing surgical treatment for HMB. IPD showed that	TCRE vs abdominal hysterectomy	Satisfaction (primary outcome) Postoperative complications Duration of operation	Women were asked how satisfied they were with their operation	Yes	
published ^{132,148}) Raw data	fibroids were included; exact		Length of hospital stay Resumption of work activities	Answers were given using the following scale:		
available	eligibility details		Resumption of usual activities	Very satisfied		
n=200	regarding this parameter not		Resumption of sexual activities	Quite satisfied		
	given in paper		Changes in pre-menstrual	Not very satisfied		
			symptoms QoL	Dissatisfied		
			Need for further surgery			
			Total health service resource cost			
			Follow-up reported at 4 months and 2 years			
Gannon <i>et al.,</i> 199141	Women with HMB. Fibroids excluded	TCRE vs abdominal	Primary outcome unclear	No comparable measure	Yes	
Raw data		hysterectomy	Length of operating time			
available			Hospitalisation			
n=54			Recovery			
			Cost of surgery			
			Change in menstrual blood loss			
			Postoperative complications Need for further surgery			
			Resource cost of surgery			
			noounde door on Surgery			

Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?	
Hysterectomy v	s Mirena					
Hurskainen et al., 2001 ⁹³ (5-year follow- up study also published ²⁷) Raw data available n=236	Women with HMB. Mirena vs Fibroids excluded hysterectomy (abdominally, vaginally or laparoscopically)		QoL (EQ-5D) (primary outcome) QoL (SF-36) Cost-effectiveness Adverse events General health (visual analogue scale, VAS) Anxiety/depression Sexual functioning Follow-up reported at 12 months and 5 years; IPD at 6 months also received	No comparable measure	Yes	
First- vs secona	l-generation EA					
Brun <i>et al.</i> , 2006 ¹⁰³ Raw data available n=62	Women with HMB unresponsive to medical treatment. Submucous fibroids excluded, other fibroids included (further details not given)	TCRE vs thermal balloon (Cavaterm)	Amenorrhoea rate (primary outcome) Satisfaction PBAC (Higham blood loss) score Operative time Discharge time Complication rate Resumption of normal activities Follow-up reported at 6 and 12 months; IPD at 3 months also received	Refers to 'satisfaction rate' Answers were given using the following scale: Excellent Good Moderate Bad	Yes	
Cooper <i>et al.</i> , 2004 ⁹⁹ Raw data available n=322			Women were asked how satisfied they were with their treatment Answers were given using the following scale: Very satisfied Satisfied Dissatisfied	Yes		
Perino <i>et al.</i> , 2004 ¹⁰⁰ <i>n</i> =116	Women with abnormal uterine bleeding. Not stated if fibroids were excluded	TCRE vs ELITT	Amenorrhoea rate (primary outcome) Satisfaction Bleeding status Intraoperative complication rate Duration of procedure Pain Further treatment with hysterectomy Follow-up reported at 12 months and 3 years	Refers to 'patient satisfaction' Answers were given using the following scale: Very satisfied Satisfied Dissatisfied	No	

continued

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Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?	
Duleba <i>et al</i> ., 2003 ⁹⁸ <i>n</i> =279	Women with HMB due to benign causes. Fibroids excluded if > 2 cm	RB vs endometrial cryoablation	PBAC (Higham blood loss) score (primary outcome) Satisfaction	Women were asked how satisfied they were with the outcome of the procedure	No	
			Bleeding Pain Adverse events	Answers were given using the following scale:		
			Anaesthesia	Very		
			Pre-menstrual symptoms	Slightly		
			Follow-up reported at 12 months	Not at all		
Hawe <i>et al.,</i> 2003 ⁹⁴	Women with DUB requesting conservative	Nd:Yag laser vs thermal balloon (Cavaterm)	Amenorrhoea rate (primary outcome)	Women were asked how satisfied they were with their treatment	Yes	
Raw data available n=72	surgical management of their condition.		Satisfaction Effect on blood loss QoL	Answers were given using the following scale:		
	Fibroids excluded		Sexual activity	Very satisfied		
			Acceptability of procedure	Moderately satisfied		
			Follow-up reported at 6 and 12	Dissatisfied		
			months	Very dissatisfied		
Rabelink et al.,II200495 (technicalfisafety report alsoiii	Women with DUB. IPD showed that fibroids were included; exact eligibility details	IPD showed that balloon	PBAC (Higham blood loss) score (primary outcome)	Refers to 'patient satisfaction'	Yes	
		uded; exact ibility details	Satisfaction QoL	Answers were given using the following scale:		
Raw data available <i>n</i> =139	regarding this parameter not given in paper		Menstrual status Follow-up reported at 6 and 12 months and 2 years	Satisfied Not satisfied		
Cooper <i>et al.,</i> 2002 ⁵⁶ <i>n</i> =265	Women with symptomatic HMB. Fibroids excluded	Wire loop resection + RB vs bipolar radiofrequency (NovaSure)	PBAC (Higham blood loss) score (primary outcome) Satisfaction Procedure time	Women were asked how satisfied they were with the outcome of the procedure	No	
			Sedation Intraoperative complications Postoperative complications Follow-up reported at 6 and 12 months	No precise information was given on the scale used to answer this question and IPD were not received. Percentage of women very satisfied or satisfied was quoted		
Pellicano <i>et al.,</i> 2002 ¹⁰² <i>n</i> =82	Women with HMB unresponsive to medical treatment. Fibroids excluded	TCRE vs thermal destruction (Cavaterm)	Satisfaction (primary outcome) Operative time Discharge time	Women were asked about the improvement of their health state after the procedure	No	
			Complication rate Reintervention rate Resumption of normal activities	Answers were given using the following scale:		
			Follow-up reported at 3 and 12	Excellent		
			months and 2 years	Good		
				Moderate		
				No improvement		

Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?	
Corson, 2001 ⁷⁹ n = 276	Women with HMB due to benign	RB vs HA	PBAC (Higham blood loss) score (primary outcome)	No comparable measure	Yes	
	causes. Fibroids		Amenorrhoea rate			
	excluded if $> 4 \text{cm}$		Adverse events			
			Need for further surgery			
			Operative complications			
			Follow-up reported at 6 and 12 months			
Soysal <i>et al.,</i> 2001 ⁹⁶	Menorrhagic women over 40	RB vs thermal balloon	PBAC (Higham blood loss) score (primary outcome)	Women were asked how satisfied they were with	No	
n=96	with a mobile		Satisfaction	their operation		
	myomatous uterus smaller than 12-		Duration of procedure	Answers were given		
	week pregnancy.		Complication rates	using the following scale:		
	Fibroids excluded if		Postoperative pain scores	Very satisfied		
	>3cm		Amenorrhoea rates	Satisfied		
			Follow-up reported at 12 months	Dissatisfied		
Corson <i>et al.</i> , 2000 ¹⁰¹	Women with HMB, without organic	TCRE + RB vs thermal balloon	PBAC (Higham blood loss) score (primary outcome)	No comparable measure.	No	
n=276	uterine disease,	(Vesta)	Amenorrhoea			
	who failed or poorly tolerated		Adverse events			
	medical therapy.		QoL			
	Fibroids excluded if > 2 cm		Follow-up reported at 12 months and 2 years			
Cooper <i>et al</i> ., 1999 ⁵⁴ (2-year ⁵⁵ and 5-year ¹¹⁵	Women referred for EA surgery. Fibroids included;	TCRE + RB vs microwave	Satisfaction (primary outcome) Acceptability of treatment	Women were asked how satisfied they were with their treatment	Yes	
follow-up study also published)	exact eligibility details regarding		Menstrual status QoL	Answers were given using the following		
Raw data	this parameter not		Morbidity	scale:		
available	given in paper		Duration of procedure	Totally satisfied		
n=263			Intraoperative complications	Generally satisfied		
			Postoperative pain relief	Fairly satisfied		
			Postoperative stay.	Fairly dissatisfied		
			Absence from work	Generally dissatisfied		
			Follow-up reported at 12 months, 2 years, 5 years and 10 years	Totally dissatisfied		
Meyer <i>et al.,</i> 1998 ⁵³	Women with HMB. Fibroids excluded	RB vs thermal balloon	PBAC (Higham blood loss) score (primary outcome)	Women were asked how satisfied they were with	Yes	
Raw data		(ThermaChoice)	Satisfaction	their treatment		
available n=275			Improvement in dysmenorrhoea symptoms	Answers were given using the following scale:		
			Inability to work	Very satisfied		
			Complication rate	Satisfied		
			Duration of procedure	Not satisfied		
			Requirement for additional surgery			
			Follow-up reported at 3, 6 and 12 months			

continued

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Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?	
Romer, 1998 ⁹⁷ n=20	Women with recurrent therapy for refractory HMB. Fibroids excluded (intrauterine abnormalities excluded, so assumed this included fibroids)	RB vs thermal balloon (Cavaterm)	Amenorrhoea rate (primary outcome) Hypomenorrhoea rate Follow-up reported at 12 months	No comparable measure	No	
Mirena vs first-g	eneration EA					
Malak, 2006 ¹⁰⁴ n=60	Women with excessive uterine bleeding. Up to 3 fibroids allowed, must each be < 3 cm	TCRE vs Mirena	Primary outcome unclear PBAC (Higham blood loss) score LNG IUS discontinuation rate Effect of menstrual bleeding on general well-being, work performance, physical activity and sexual activity assessed using VAS	No comparable measure	No	
			Follow-up reported at 12 months			
Kittelsen and lstre, 1998^{105} (long-term follow-up paper also published ¹⁵⁰) $n=60$	Women with HMB. Fibroids excluded	TCRE vs Mirena	Primary outcome unclear QoL Additional treatments received Adverse events Follow-up reported at 12 months, 2 years and 3 years	No comparable measure	No	
Crosignani <i>et al.</i> , 1997 ⁸⁰ <i>n</i> =70	Women with DUB. Fibroids excluded	TCRE vs Mirena	Primary outcome unclear Satisfaction Reduction in menstrual bleeding Health-related QoL Amenorrhoea rates Additional treatments Adverse events Follow-up reported at 6 and 12 months	Women were asked how satisfied they were with their treatment Answers were given using the following scale: Very satisfied Satisfied Uncertain Dissatisfied	No	
Mirena vs secon	d-generation EA					
Shaw <i>et al.</i> , 2007 ¹⁰⁸ <i>n</i> =66	Women with HMB. Fibroids excluded	Thermal balloon vs Mirena	PBAC (Higham blood loss) score (primary outcome) Satisfaction Continuation with treatment Hysterectomy rates Follow-up reported at 3, 6, 9 and 12 months, and 2 years	Women were asked for their perception of their treatment effect Answers were given using the following scale: Very good Good Poor	No	

Paper/number of women randomised	Patients	Intervention	Stated key outcome measures	Patient satisfaction and how it was measured	IPD received?
Tam et al., 2006109Women with excessiveRaw data availablemenstrual bleeding attending the outpatient gynaecology clinic. IPD showed that fibroids were included; exact eligibility details regarding this parameter not 		Thermal balloon vs MirenaPrimary outcome unclear Health status function SF-36 Follow-up reported at 12 months; IPD at 6 months also received		No comparable measure	Yes
Busfield <i>et al.</i> , 2006 ¹⁰⁷ (cost- effectiveness paper carried out by Brown <i>et al.</i> , 2006 ¹¹⁴) Raw data available n=79	Women with HMB. Fibroids excluded if > 3 cm	Thermal balloon vs Mirena	PBAC (Higham blood loss) score (primary outcome) Satisfaction QoL Menstrual symptoms Adverse events Treatment failures Follow-up reported at 3, 6 and 12 months, and 2 years	Women were asked if the menstrual symptoms had been successfully treated Answers were given using the following scale: Definitely yes Probably yes Not sure Probably no Definitely no	Yes
Barrington <i>et al.</i> , 2003 ⁸¹ Raw data available n=50	Women with HMB. Fibroids excluded	Thermal balloon vs Mirena	Primary outcome unclear PBAC (Higham blood loss) score Amenorrhoea Follow-up reported at 6 months	No comparable measure	Yes
Soysal <i>et al.</i> , 2002 ¹⁰⁶ <i>n</i> =72	Women with dysfunctional HMB. Fibroids excluded if > 2 cm	Thermal balloon vs Mirena	PBAC (Higham blood loss) score (primary outcome) Satisfaction Health-related QoL Additional treatments Adverse events Follow-up reported at 12 months	Women were asked about their degree of satisfaction/ recommendation Answers were given using the following scale: Highly recommends Recommends Did not know Did not recommend	No

Appendix 3

Quality of studies included in the systematic review of randomised trials comparing hysterectomy, endometrial destruction and Mirena for heavy menstrual bleeding

Paper	Was randomisation adequate?	Was the target population described adequately?	Was the sample size calculation reported?	Were the two populations comparable at baseline?	Was an ITT analysis reported?	Was the follow-up >80%?	Was compliance with allocated treatment > 80% in both arms at 12 months?
Hysterectomy vs first-g	generation EA						
Dickersin et al., 200792	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zupi <i>et al.</i> , 2003 ⁷⁸	Unclear, not stated	Yes	Yes	Yes	No	No	Yes
Crosignani <i>et al</i> ., 1997 ⁴⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes
O'Connor et al., 199744	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pinion <i>et al.</i> , 199443	Unclear, not stated	No	Yes	Yes	Yes	Yes	No
Dwyer <i>et al</i> ., 199342	Unclear, not stated	Yes	Yes	Yes	No	Yes	Yes
Gannon <i>et al</i> ., 1991 ⁴¹	Unclear, not stated	Yes	No	Yes	No	Yes	Yes
Hysterectomy vs Miren	a						
Hurskainen <i>et al.,</i> 200193	Yes	Yes	Yes	Yes	Yes	Yes	No
First- vs second-gener	ation EA						
Brun <i>et al</i> ., 2006 ¹⁰³	Yes	Yes	Yes	Yes	No	No	Yes
Cooper <i>et al.</i> , 200499	Unclear, not stated	Yes	Yes	Yes	Yes	Yes	Yes
Perino <i>et al.</i> , 2004100	Unclear, not stated	Yes	Yes	Yes	Yes	Yes	Yes
Duleba <i>et al.</i> , 200398	Unclear, not stated	Yes	Yes	Yes	No	Yes	Yes
Hawe <i>et al.</i> , 200394	Yes	Yes	Yes	Yes	Yes	Yes	Yes
van Zon-Rabelink <i>et al.</i> , 2004 ⁹⁵	Unclear, not stated	Yes	Yes	Yes	Yes	No	Yes
Cooper <i>et al.</i> , 200256	Unclear, not stated	Yes	Yes	Yes	Yes	Yes	Yes

continued

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Paper	Was randomisation adequate?	Was the target population described adequately?	Was the sample size calculation reported?	Were the two populations comparable at baseline?	Was an ITT analysis reported?	Was the follow-up >80%?	Was compliance with allocated treatment > 80% in both arms at 12 months?
Pellicano et al., 2002 ¹⁰²	Unclear, not stated	Yes	No	Yes	No	Yes	Yes
Corson, 200179	Unclear, not stated	Yes	Yes	Yes	No	Yes	Yes
Soysal <i>et al</i> ., 2001 ⁹⁶	Yes	Yes	No	Yes	No	Yes	Yes
Corson <i>et al.</i> , 2000 ¹⁰¹	Unclear, not stated	Yes	Yes	Yes	No	Yes	Yes
Cooper <i>et al</i> ., 1999 ⁵⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Meyer <i>et al.</i> , 1998 ⁵³	Unclear, not stated	Yes	Yes	Yes	No	Yes	Yes
Romer, 199897	Unclear, not stated	No	No	Yes	No	Yes	No
Mirena vs first -genera	tion EA						
Malak <i>et al.</i> , 2006 ¹⁰⁴	Yes	Yes	No	Yes	No	Yes	Yes
Kittelsen, 1998 ¹⁰⁵	Unclear, not stated	Yes	No	Yes	No	Yes	No
Crosignani <i>et al.,</i> 1997 ⁸⁰	Yes	Yes	No	Yes	No	Yes	Yes
Mirena vs second-gene	eration EA						
Shaw <i>et al.</i> , 2007 ¹⁰⁸	Yes	Yes	Yes	Yes	No	No	No
Tam <i>et al.</i> , 2006 ¹⁰⁹	Unclear, not stated	Yes	No	Yes	No	No	No
Busfield et al., 2006107	Yes	Yes	Yes	Yes	No	No	No
Barrington <i>et al.</i> , 2003 ⁸¹	Unclear, not stated	Yes	No	No	No	Yes	Yes
Soysal <i>et al.</i> , 2002 ¹⁰⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Time point	Trials (no.)	WMD (95% CI)	OR (95% CI)	<i>p</i> -value	Hetero (<i>p</i>)/ /² (%)
Duration surgery (minutes)	_	6 (850)	32 (30 to 34)	_	< 0.0001	< 0.0001/99
Duration hospital stay (days)	-	7 (1066)	3.0 (2.9 to 3.1)	_	< 0.0001	< 0.0001/99
Surgery pain score (0–10)	_	2 (367)	2.5 (2.2 to 2.9)	_	< 0.0001	0.8/0
Return to work (days)	_	6 (725)	14 (13 to 16)	_	< 0.0001	< 0.0001/98
Return normal activities (days)	_	5 (770)	5.2 (4.7 to 5.7)	_	< 0.0001	< 0.0001/98
Return sexual activity (days)	_	2 (302)	36 (31 to 41)	_	< 0.0001	< 0.0001/99
Proportion dyspareunia	6 months	1 (166)	_	0.71 (0.39 to 1.31)	0.3	_
	12 months	2 (322)	_	0.87 (0.51 to 1.48)	0.6	0.2/47
SF-36 general health (absolute)	12 months	1 (181)	-9.8 (-13.9 to -5.7)	_	< 0.0001	_
SF-36 physical function (absolute)		1 (181)	-1.2 (-5.3 to 2.9)	_	0.6	_
SF-36 role physical (absolute)		1 (181)	-0.8 (-5.0 to 3.4)	_	0.7	_
SF-36 role emotional (absolute)		1 (181)	-3.9 (-8.2 to 0.4)	_	0.08	-
SF-36 mental health (absolute)		1 (181)	-2.7 (-6.8 to 1.4)	_	0.2	-
SF-36 social function (absolute)		1 (181)	-21.2 (-24.7 to -17.8)	_	< 0.0001	_
SF-36 vitality (absolute)		1 (181)	-11.3 (-14.8 to -7.8)	_	< 0.0001	-
SF-36 pain (absolute)		1 (181)	-1.5 (-6.1 to 3.1)	_	0.5	-
SF-36 general health (absolute)	2 years	2 (225)	-6.5 (-12.1 to -0.9)	_	0.02	0.4/0
SF-36 physical function (absolute)		2 (221)	-2.8 (-7.4 to 1.8)	_	0.2	0.8/0
SF-36 role physical (absolute)		2 (223)	-1.3 (-10.4 to 7.9)	_	0.8	0.4/0
SF-36 role emotional (absolute)		2 (224)	-7.6 (-16.2 to 1.1)	_	0.09	0.7/0
SF-36 mental health (absolute)		2 (221)	-2.8 (-7.4 to 1.8)	_	0.2	0.6/0
SF-36 social function (absolute)		2 (221)	-7.1 (-12.5 to -1.8)	_	0.009	0.5/0
SF-36 vitality (absolute)		2 (222)	-5.0 (-10.5 to 0.5)	_	0.07	0.08/67
SF-36 pain (absolute)		2 (225)	-8.4 (-14.9 to -2.0)	_	0.01	0.6/0
SF-36 general health (change)	12 months	1 (181)	-9.6 (-13.5 to -5.7)	_	< 0.0001	_
SF-36 physical function (change)		1 (181)	-1.0 (-5.0 to 3.0)	_	0.6	-
SF-36 role physical (change)		1 (181)	0.1 (-4.1 to 4.3)	_	1.0	-
SF-36 role emotional (change)		1 (181)	-4.4 (-8.4 to -0.4)	_	0.03	-
SF-36 mental health (change)		1 (181)	-1.0 (-4.9 to 2.9)	_	0.6	_
SF-36 social function (change)		1 (181)	-24 (-27 to -21)	_	< 0.0001	-
SF-36 vitality (change)		1 (181)	-13 (-16 to -9)	_	< 0.0001	-
SF-36 pain (change)		1 (181)	-2.2 (-7.3 to 2.9)	_	0.4	-
EQ-5D (absolute)	6 months	1 (220)	-0.09 (-0.16 to -0.02)	_	0.02	_
	12 months	1 (210)	0.00 (-0.08 to 0.08)	_	1.0	-
	2 years	1 (213)	-0.02 (-0.09 to 0.05)	_	0.6	-
	3 years	1 (157)	0.04 (-0.05 to 0.13)	_	0.4	_
	4 years	1 (98)	-0.01 (-0.12 to 0.10)	_	0.9	-
EQ-5D (change)	6 months	1 (220)	-0.09 (-0.18 to -0.00)	_	0.05	-
	12 months	1 (210)	-0.03 (-0.13 to 0.07)	_	0.5	-
	2 years	1 (213)	-0.03 (-0.12 to 0.06)	_	0.5	-
	3 years	1 (157)	0.06 (-0.05 to 0.17)	_	0.3	_
	4 years	1 (96)	-0.01 (-0.16 to 0.14)	_	0.9	_

continued

	Time point	Trials (no.)	WMD (95% CI)	OR (95% CI)	<i>p</i> -value	Hetero (<i>p</i>)/ /² (%)
		Trials	Frequency			
Repeat EA	6 months	3	11/318 (3%)			
	12 months	3	17/248 (7%)			
	2 years	2	13/222 (6%)			
	3 years	2	15/189 (8%)			
	4 years	1	1/48 (2%)			
	5 years	1	2/123 (2%)			
Hysterectomy after EA	6 months	3	11/305 (4%)			
	12 months	4	27/271 (10%)			
	2 years	3	38/246 (15%)			
	3 years	2	33/194 (17%)			
	4 years	1	23/59 (39%)			
	5 years	1	42/123 (34%)			

Appendix 4

Pooled results for hysterectomy versus first-generation endometrial ablation

Appendix 4.1 Hysterectomy versus first-generation endometrial ablation – complications

	Trials	Frequency (hysterectomy: max. 530; first-generation EA: max. 585)	OR (95% CI)ª	<i>p</i> -value	Hetero (<i>p</i>)/ /² (%)
Periprocedure complications					
Anaesthesia problems (hysterectomy, first- generation EA)	7	3; 0	10.9 (1.08 to 111)	0.04	0.7/0
Excessive bleeding (hysterectomy, first-generation EA)	7	10; 10	1.03 (0.42 to 2.53)	1.0	0.7/0
Injury surrounding organs (hysterectomy)	7	3	-	-	-
Uterine perforation (first-generation EA)	7	11	-	-	-
Fluid overload (first-generation EA)	7	21	-	-	-
Visceral damage (first-generation EA)	7	1	-	-	-
Cervical laceration (first-generation EA)	7	4	-	-	-
Procedure abandoned (first-generation EA)	7	2	-	_	-
Converted to hysterectomy (first-generation EA)	7	14	-	-	-
Further complications (<1 month)					
Urinary tract infection (hysterectomy, first-generation EA)	7	43; 9	4.38 (2.48 to 7.75)	< 0.0001	0.6/0
Deep-vein thrombosis (hysterectomy, first-generation EA)	7	2; 0	6.96 (0.43 to 112)	0.2	_
Excessive bleeding (hysterectomy)	7	9	-	-	-
Embolism (hysterectomy)	7	2	-	_	_
Further bleeding (first-generation EA)	7	0	-	-	-
Sepsis (first-generation EA)	7	9	-	-	-
Pyrexia (first-generation EA)	7	5	-	_	-
Endometriosis (first-generation EA)	7	1	-	_	-
Abdominal pain (first-generation EA)	7	0	-	-	-
Foul discharge (first-generation EA)	7	0	-	_	-
Visceral damage (first-generation EA)	7	0	_	-	-

a <0 favours hysterectomy, >0 favours first-generation EA.

Appendix 4.2 Hysterectomy versus first-generation endometrial ablation

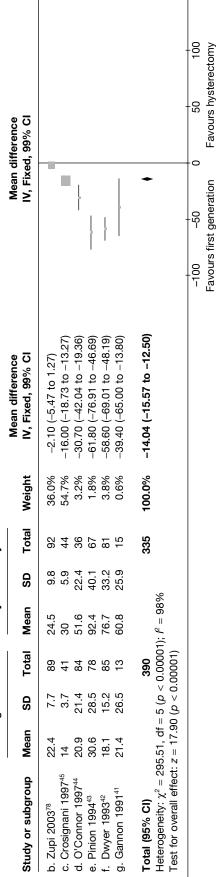
Duration of surgery (minutes)

	First	First generation	ation	Hys	Hysterectomy	шy				
Study or subgroup Mean SD Total Mean	Mean	SD	Total	Mean	SD	SD Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI	fference 99% CI
b. Zupi 2003 ⁷⁸	41.7	19.2	89	71.5	28.1	92	6.3%	-29.80 (-38.99 to -20.61)	-	
c. Crosignani 1997 ⁴⁵	13	3.7	41	71	8.9	44	37.6%	-58.00 (-61.76 to -54.24)		
d. 0'Connor 1997 ⁴⁴	34.3	30.1	100	65.9	42	52	1.9%	-31.60 (-48.49 to -14.71)		
e. Pinion 1994 ⁴³	44.8	13.7	102	61.4	21.9	83	10.5%	-16.60 (-23.71 to -9.49)	ł	
f. Dwyer 1993 ⁴²	36.2	9.9	98	47.9	11.2	97	35.0%	-11.70 (-15.60 to -7.80)		
g. Gannon 1991 ⁴¹	29.4	80	27	49.5	13	25	8.8%	–20.10 (–27.88 to –12.32)	ł	
Total (95% CI)			457			393	100.0%	-31.86 (-33.61 to -30.10)	•	
Heterogeneity: $\chi^2 = 543.45$, df = 5 ($p < 0.00001$); $\beta^2 = 99\%$ Test for overall effect: $z = 35.58$ ($p < 0.00001$)	43.45, df : z = 35.58	= 5 (<i>p</i> < 0)	0.00001	l); <i>f</i> ² = 99 ⁶	8					
									-100 -50 0	50 100
									Favours first generation	Favours hysterectomy

Duration of hospital stay (days)

	LII SL SC	FIRST generation	_	Hyst	Hysterectomy	۲ ۲				
Study or subgroup Me	Mean S	SD To	Total Mean		SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	CI Ce
a. Dickersin 2007 ⁹² 0.1		0.3 11	0	1.9	-	118	36.0%	-1.80 (-2.05 to -1.55)	-	
b. Zupi 2003 ⁷⁸ 1.3	-	.1	39 1	1.6	1.5	92	8.8%	-0.30 (-0.80 to 0.20)	ł	
c. Crosignani 1997 ⁴⁵ 1	0	.1	11 5	10	0.74	44	26.4%	-4.00 (-4.29 to -3.71)	•	
d. O'Connor 1997 ⁴⁴ 1.1	0	0.5 8	80 5		2.4	47	2.7%	-4.30 (-5.21 to -3.39)		
e. Pinion 1994 ⁴³ 2.5		2.9 10	105 7	7.3	2.3	97	2.5%	-4.80 (-5.75 to -3.85)		
f. Dwyer 1993 ⁴² 2.1	0	.7 9	98 6	3.4	-	94	21.4%	-4.30 (-4.62 to -3.98)	¢	
g. Gannon 1991 ⁴¹ 1.6	1	4.	22 7	7.1	1.4	26	2.2%	-5.50 (-6.51 to -4.49)		
Total (95% CI)		548	œ			518	100.0%	-3.01 (-3.12 to -2.89)	-	
Heterogeneity: $\chi^2 = 611.56$, df = 6 ($p < 0.00001$); $l^2 = 99\%$ Test for overall effect: $z = 51.94$ ($p < 0.00001$)	i, df = 6 51.94 (<i>μ</i>	(<i>p</i> < 0.0 < 0.0 < < 0.00 < < 0.000	0001); / 101)	P = 99%						

	First	First generation	ation	Hys	Hysterectomy	my				
Study or subgroup	Mean	S	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	
b. Zupi 2003 ⁷⁸ e. Pinion 1994 ⁴³	3.8 2.6	0.6 2.1	888	6.3 5.2	3.	92 97	76.7% 23.3%	-2.50 (-3.04 to -1.96) -2.60 (-3.57 to -1.63)	= <u> </u>	
Total (95% CI) Heterogeneity: $\chi^2 = 0.05$, df = 1 ($p = 0.82$); $l^2 = 0\%$ Test for overall effect: $z = 13.85$ ($p < 0.00001$)	.05, df = 1 : <i>z</i> = 13.8{	$\begin{array}{l} 1 \ (\rho = 0) \\ 0 \ < 0 \end{array}$	178 .82); <i>I</i> ² = (.00001)	%0		189	100.0%	100.0% –2.52 (–2.88 to –2.17)	•	
									-10 -5 0 Favours first generation Favours	5 10 Favours hysterectomy
Time to return to work (days)	work (days)								
	First	First generation	ition	Hys	Hysterectomy	'n				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	e Ci
- Z	, CC	r 7	0		c	6	\00 00			



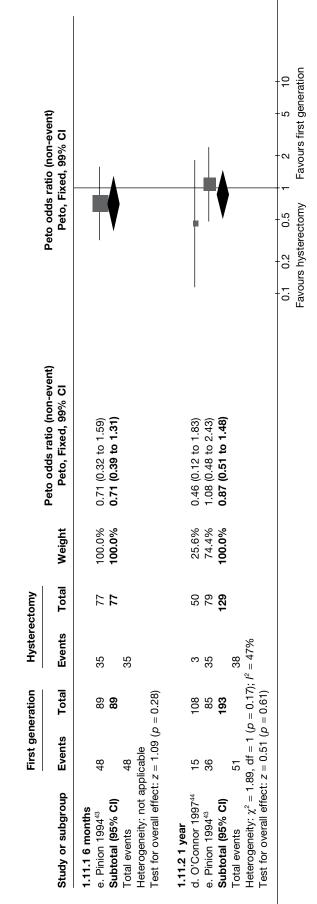
Surgery pain score

Time to return to normal activities (days)

		,	First generation	нуs		ĥ				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	rence 9% CI
b. Zupi 2003 ⁷⁸	8.8	4.3	89	10.3	6.5	92	10.6%	-1.50 (-3.60 to 0.60)	ÚI.	
c. Crosignani 1997 ⁴⁵	8	1.5	41	13	1.1	44	86.2%	-5.00 (-5.74 to -4.26)		
d. O'Connor 199744	13.3	19.5	104	31.6	17.5	44	0.7%	-18.30 (-26.69 to -9.91)	}	
e. Pinion 1994 ⁴³	32.9	34.1	88	85	46.8	74	0.2%	-52.10 (-68.95 to -35.25)		
f. Dwyer 1993 ⁴²	8.3	8.3	98	30.2	15	96	2.3%	–21.90 (–26.40 to –17.40)	ł	
Total (95% CI)			420			350	100.0%	-5.19 (-5.71 to -4.67)	-	
Heterogeneity: $\chi^2 = 180.09$, df = 4 ($\rho < 0.00001$); $\beta = 98\%$ Test for overall effect: $z = 19.47$ ($\rho < 0.00001$)	.09, df = = 19.47	4 (<i>p</i> < 0.(0.00001) 30001)	i; <i>P</i> = 989	\ 0				-	

Time to return to sexual activity (days)

	First	First generation	tion	Hys	Hysterectomy	my					
Study or subgroup Mean SD Total	Mean	SD	Total	Mean	SD	Total	Total Weight	Mean difference IV, Fixed, 99% CI	Mear IV, Fi	Mean difference IV, Fixed, 99% CI	
d. O'Connor 1997 ⁴⁴	28	23.4	23.4 90	40.9	17.1	41	51.7%	51.7% -12.90 (-22.26 to -3.54)	•		
f. Dwyer 1993 ⁴²	17.1	10.9	06	77.8	32.2	81	48.3%	-60.70 (-70.38 to -51.02)	Ļ		
Total (95% CI)			180			122	100.0%	100.0% -36.01 (-41.13 to -30.89)	•		
Heterogeneity: χ^2 = 83.58, df = 1 ($p < 0.00001$); l^2 = 99% Test for overall effect: z = 13.78 ($p < 0.00001$)	3.58, df = z = 13.75	1 (p < 0. 3 (p < 0.	1.00001); 00001)	β = 99%							
									-100 -50	0 50	100
									Favours first generation	Favours hysterectomy	ctomy



Proportion with dyspareunia

SF-36 scores (absolute values)

	First	gener	ation	Hys	terect	omy			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.12.13 SF-36 at 1 y	ear – ger	neral h	ealth						
b. Zupi 2003 ⁷⁸	59.6	13.7	89	69.4	14.2	92	100.0%	-9.80 (-15.14 to -4.46)	
Subtotal (95% CI)			89			92	100.0%	–9.80 (–13.86 to –5.74)	◆
Heterogeneity: not ap Test for overall effect	•	3 (p < 0	0.00001)						
1.12.14 SF-36 at 1 y	ear – nhi	veical f	function						
b. Zupi 2003 ⁷⁸	66.4	15.1	89	67.6	13.2	92	100.0%	-1.20 (-6.64 to 4.24)	
Subtotal (95% CI)			89			92	100.0%	–1.20 (–5.34 to 2.94)	-
Heterogeneity: not ap Test for overall effect		7 (p = 0).57)						
			,						
1.12.15 SF-36 at 1 y b. Zupi 2003 ⁷⁸	ear - role 61.3	e ιιπιτα 14.8	ation (pr 89	1ysical) 62.1	13.9	92	100.0%	-0.80 (-6.30 to 4.70)	
Subtotal (95% CI)			89			92	100.0%	-0.80 (-4.99 to 3.39)	-
Heterogeneity: not ap	•								
Test for overall effect	:: <i>z</i> = 0.37	7 (p = 0	0.71)						
1.12.16 SF-36 at 1 y			-	-		~~	400 554		_
b. Zupi 2003 ⁷⁸	64.2	14.4	89 80	68.1	15.2	92	100.0%	-3.90 (-9.57 to 1.77)	
Subtotal (95% CI) Heterogeneity: not ap	oplicable		89			92	100.0%	–3.90 (–8.21 to 0.41)	
Test for overall effect		7 (p = 0	0.08)						
1.12.17 SF-36 at 1 y	ear – me	ntal he	ealth						
b. Zupi 2003 ⁷⁸	60.5	14.8	89	63.2	13.6	92	100.0%	-2.70 (-8.15 to 2.75)	
Subtotal (95% CI)	policable		89			92	100.0%	–2.70 (–6.84 to 1.44)	-
Heterogeneity: not ap Test for overall effect		3 (p = 0	0.20)						
1.12.18 SF-36 at 1 ye b. Zupi 2003 ⁷⁸	ear – soo 67.3	12.7	etion 89	88.5	11.5	92	100.0%	-21.20 (-25.84 to -16.56)	
Subtotal (95% CI)			89			92	100.0%	–21.20 (–24.73 to –17.67)	\bullet
Heterogeneity: not ap		70 (0.0000	、 、					
Test for overall effect	z = 11.7	ro (p <	0.00001)					
1.12.19 SF-36 at 1 ye	ear – vita 61	ality 12.8	80	72.3	11 0	02	100 00/	11 30 (15 02 + - 6 67)	
b. Zupi 2003 ⁷⁸ Subtotal (95% Cl)	01	12.0	89 89	12.0	11.3	92 92	100.0% 100.0%	-11.30 (-15.93 to -6.67) -11.30 (-14.82 to -7.78)	→
Heterogeneity: not ap	oplicable								-
Test for overall effect	: <i>z</i> = 6.29	9 (p < 0	0.00001)						
1.12.20 SF-36 at 1 y	-								
b. Zupi 2003 ⁷⁸	58.6	17	89	60.1	14	92	100.0%	-1.50 (-7.47 to 4.47)	
Subtotal (95% CI) Heterogeneity: not ap	onlicable		89			92	100.0%	–1.50 (–6.05 to 3.05)	-
Test for overall effect	•	5 (p = 0	0.52)						
1.12.21 SF-36 at 2 y	ears – pł	nysical	functio	n					
c. Crosignani 199745		21	38	88	20.1	39	24.8%	-3.60 (-15.67 to 8.47)	
f. Dwyer 1993 ⁴²	89.4	17.9	77	91.9	14.4	67	75.2%	-2.50 (-9.44 to 4.44)	
Subtotal (95% CI) Heterogeneity: $\chi^2 = 0$	04 df =	1 (n =	115 0 84)· l ²	= 0%		106	100.0%	–2.77 (–7.35 to 1.80)	-
Test for overall effect				270					
1.12.22 SF-36 at 2 y	ears – ro	le limi	tation (p	ohysical)					
c. Crosignani 199745		36.3	38	74.1	37.9	39	30.1%	-6.70 (-28.48 to 15.08)	
f. Dwyer 1993 ⁴²	82.9	33.2	76	81.8	33.8	70	69.9%	1.10 (-13.20 to 15.40)	
Subtotal (95% CI) Heterogeneity: $\chi^2 = 0$	59 df -	1 (n -	114 0 44)· l ²	= 0%		109	100.0%	–1.25 (–10.35 to 7.85)	
Test for overall effect	,		,,	- 070					
1.12.23 SF-36 at 2 y	ears – pa	ain							
c. Crosignani 199745	69.6	27	38	75.9	21.9	39	34.4%	-6.30 (-20.75 to 8.15)	
f. Dwyer 1993 ⁴²	73.5	26.3	80	83	23.1	68	65.6%	-9.50 (-19.96 to 0.96)	
Subtotal (95% CI) Heterogeneity: $\chi^2 = 0$	21 df.	1 (n -	118	- 0%		107	100.0%	–8.40 (–14.85 to –1.95)	
Test for overall effect				- 070					
									–20 –10 0 10 20 Favours Favours
									ravours ravours

Favours hysterectomy Favours first generation

	First	genera	ation	Hys	terecto	omy			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
1.12.24 SF-36 at 2 ye	ears - ge	eneral l	nealth						
c. Crosignani 199745	61.3	22.8	38	71.2	21.9	39	31.4%	-9.90 (-23.03 to 3.23)	
f. Dwyer 199342	74.7	21.6	78	79.6	20.3	70	68.6%	-4.90 (-13.77 to 3.97)	
Subtotal (95% CI)			116			109	100.0%	-6.47 (-12.06 to -0.87)	•
Heterogeneity: $\chi^2 = 0$.66, df =	1 (p =	0.42); <i>I</i> ²	= 0%					
Test for overall effect	: z = 2.27	7 (p = 0	.02)						
1.12.25 SF-36 at 2 ye	ears – vi	tality							
c. Crosignani 199745	52.3	19.3	38	63.6	20.6	39	37.9%	-11.30 (-23.01 to 0.41)	
f. Dwyer 199342	61	20.6	78	62.2	21.9	67	62.1%	-1.20 (-10.34 to 7.94)	
Subtotal (95% CI)			116			106	100.0%	-5.02 (-10.51 to 0.46)	-
Heterogeneity: $\chi^2 = 3$. Test for overall effect				= 67%					
1.12.26 SF-36 at 2 ye	ears – so	ocial fu	nction						
c. Crosignani 199745	70.1	23	38	80.4	21.4	39	29.2%	-10.30 (-23.35 to 2.75)	
f. Dwyer 199342	84.4	22.7	77	90.2	16.1	67	70.8%	-5.80 (-14.17 to 2.57)	
Subtotal (95% CI)			115			106	100.0%	–7.11 (–12.47 to –1.75)	•
Heterogeneity: $\chi^2 = 0$				= 0%					
Test for overall effect	: <i>z</i> = 2.60	(p = 0)	.009)						
1.12.27 SF-36 at 2 ye	ears – ro		•	motiona	ıl)				
c. Crosignani 199745	61.1	37.8	38	71.9	40.7	39	24.5%	-10.80 (-33.85 to 12.25)	<
f. Dwyer 199342	79.5	31.9	78	86	29.9	69	75.5%	-6.50 (-19.63 to 6.63)	
Subtotal (95% CI)			116			108	100.0%	–7.55 (–16.24 to 1.13)	
Heterogeneity: $\chi^2 = 0$				= 0%					
Test for overall effect	: <i>z</i> = 1.71	1 (p = 0	.09)						
1.12.28 SF-36 at 2 ye	ears – m	ental h	ealth						
c. Crosignani 199745	60	17.4	38	64.7	21.2	39	28.1%	-4.70 (-16.07 to 6.67)	
f. Dwyer 199342	74.3	15.7	77	76.4	17.2	67	71.9%	-2.10 (-9.21 to 5.01)	
Subtotal (95% CI)			115			106	100.0%	-2.83 (-7.42 to 1.76)	-
Heterogeneity: $\chi^2 = 0$.25, df =	1 (p =	0.62); <i>I</i> ²	= 0%					
Test for overall effect	: <i>z</i> = 1.21	1 (p = 0	.23)						
									-20 -10 0 10 20
									Favours Favours

Moon difference	wear unrerence IV, Fixed, 99% CI		_	∳		_		•	+	-20 -10 0 10 20 Favours hysterectomy Favours first generation
Maan difforence	IV, Fixed, 99% CI	-9.60 (-14.67 to -4.53) -9.60 (-13.46 to -5.74)	-1.00 (-6.20 to 4.20) -1.00 (-4.96 to 2.96)	0.10 (-5.40 to 5.60) 0.10 (-4.08 to 4.28)	-4.40 (-9.61 to 0.81) -4.40 (-8.36 to -0.44)	-1.00 (-6.17 to 4.17) -1.00 (-4.94 to 2.94)	-24.00 (-28.34 to -19.66) - 24.00 (-27.30 to -20.70)	-12.60 (-16.98 to -8.22) -1 2.60 (-15.93 to -9.27)	-2.20 (-8.89 to 4.49) - 2.20 (-7.29 to 2.89)	
	Weight	100.0% 100.0 %	100.0% 100.0 %	100.0% 100.0%	100.0% 100.0%	100.0% 100.0%	100.0% 100.0%	100.0% 100.0%	100.0% 100.0%	
٨٣	Total	92 92	92 92	92 93	92 92	92 92	92 93	92 92	92 92	
Hysterectomy	SD	13.3	12.2	14.7	13.8	13.3	10.7	10.8	16.7	
Í	Mean	17.3	4.8	2.9	7.8	3.4	34.9	16.9	3.7	
tion	Total	80 80	80 80 80	sical) 89 89	otional) 89 89	80 80 80	80 80	80 80 80	68 68	
First generation	Study or subgroup Mean SD	1.13.13 SF-36 at 1 year – general health b. Zupi 2003^{18} 7.7 13.2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 4.87$ ($p < 0.00001$)	1.13.14 SF-36 at 1 year – physical function b. Zupi 2003^{78} 3.8 14.8 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.50$ ($p = 0.62$)	1.13.15 SF-36 at 1 year - role limitation (physical) b. Zupi2003 18 3 14 89 Subtotal (95% CI) 89 Heterogeneity: not applicable Test for overall effect: $z = 0.05$ ($p = 0.96$)	1.13.16 SF-36 at 1 year – role limitation (emotional) b. Zupi 2003^{78} 3.4 13.4 89 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 2.18$ ($p = 0.03$)	1.13.17 SF-36 at 1 year - mental health b. Zupi 2003 ⁷⁸ 2.4 13.7 Subtotal (95% CI) 2.4 13.7 Heterogeneity: not applicable 13.7 13.7 Test for overall effect: z = 0.50 (p = 0.62) 13.7 13.7	1.13.18 SF-36 at 1 year - social functionb. Zupi 2003^{78} 10.9b. Zupi 2003^{78} 10.9Subtotal (95% CI)Heterogeneity: not applicableTest for overall effect: $z = 14.25$ ($p < 0.00001$)	1.13.19 SF-36 at 1 year – vitality b. Zupi 2003^{18} 4.3 12 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 7.42$ ($p < 0.00001$)	1.13.20 SF-36 at 1 year - pain b. Zupi 2003 ⁷⁸ 1.5 18.2 Subtoral (95% CI) 1.5 18.2 Heterogeneity: not applicable 1.55 (<i>p</i> = 0.40) 1.55 (<i>p</i> = 0.40)	

	First	First generation	ation	Hys	Hysterectomy	м			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.14.2 6 months a. Dickersin 2007 ⁹² 0.69 0.31 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 2.41$ ($p = 0.02$)	0.69 pplicable :: <i>z</i> = 2.41	0.31 I (<i>p</i> = 0.	111 111 02)	0.78	0.24	109 109	100.0% 100.0 %	-0.09 (-0.19 to 0.01) - 0.09 (-0.16 to -0.02)	
1.14.3 12 months a. Dickersin 2007 ⁹² 0.74 0.29 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: <i>z</i> = 0.00 (<i>p</i> = 1.00)	0.74 oplicable :: <i>z</i> = 0.00	0.29 (<i>p</i> = 1.	107 107 00)	0.74	0.27	103 103	100.0% 100.0 %	0.00 (-0.10 to 0.10) 0.00 (-0.08 to 0.08)	
1.14.4 2 years a. Dickersin 2007 ⁹² 0.74 0.27 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.53$ ($p = 0.60$)	0.74 oplicable :: z = 0.53	0.27 3 (<i>p</i> = 0.	106 106 60)	0.76	0.28	107 107	100.0% 100.0 %	-0.02 (-0.12 to 0.08) - 0.02 (-0.09 to 0.05)	
1.14.5 3 years a. Dickersin 2007 ⁹² 0.76 0.25 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.89$ ($p = 0.37$)	0.76 oplicable :: <i>z</i> = 0.85	0.25) (<i>p</i> = 0.	75 75 37)	0.72	0.31	82 82	100.0% 100.0 %	0.04 (-0.08 to 0.16) 0.04 (-0.05 to 0.13)	
1.14.6 4 years a. Dickersin 2007 ⁹² 0.74 0.29 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.18$ ($p = 0.86$)	0.74 oplicable :: <i>z</i> = 0.18	0.29 3 (<i>p</i> = 0.	47 47 86)	0.75	0.27	51 51	100.0% 100.0%	-0.01 (-0.16 to 0.14) - 0.01 (-0.12 to 0.10)	
									-0.5 -0.25 0 0.25 0.5

EQ-5D scores (absolute values)

Favours first generation

Favours hysterectomy

	First	First generation	tion	Hys	Hysterectomy	Ş			:
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.15.1 6 months a. Dickersin 2007 ⁹² 0.14 0.34 1 Subtotal (95% CI) 1 1 Heterogeneity: not applicable Test for overall effect: z = 1.96 (p = 0.05)	0.14 pplicable : <i>z</i> = 1.96	0.34 i (<i>p</i> = 0.0	111 111 05)	0.23	0.34	109 109	100.0% 100.0%	-0.09 (-0.21 to 0.03) -0.09 (-0.18 to -0.00)	
1.15.2 12 months 0.16 0.35 1 a. Dickersin 2007^{92} 0.16 0.35 1 Subtotal (95% Cl) 1 1 Heterogeneity: not applicable 1 Test for overall effect: $z = 0.61$ ($p = 0.54$)	0.16 pplicable : <i>z</i> = 0.61	0.35 (<i>p</i> = 0.5	107 107 54)	0.19	0.36	103 103	100.0% 100.0 %	-0.03 (-0.16 to 0.10) - 0.03 (-0.13 to 0.07)	
1.15.3 2 years 0.18 0.33 1 a. Dickersin 2007 ⁹² 0.18 0.33 1 Subtotal (95% Cl) 1 1 1 Heterogeneity: not applicable Test for overall effect: z = 0.62 (p = 0.53) 1	0.18 pplicable : <i>z</i> = 0.62	0.33 ! (<i>p</i> = 0.5	106 106 53)	0.21	0.37	107 107	100.0% 100.0%	-0.03 (-0.15 to 0.09) -0.03 (-0.12 to 0.06)	
1.15.4 3 years a. Dickersin 2007^{42} 0.22 0.36 Subtotal (95% Cl) Heterogeneity: not applicable Test for overall effect: $z = 1.09$ ($p = 0.28$)	0.22 pplicable : <i>z</i> = 1.09	0.36 (<i>p</i> = 0.2	75 75 28)	0.16	0.33	82 82	100.0% 100.0 %	0.06 (-0.08 to 0.20) 0.06 (-0.05 to 0.17)	
1.15.5 4 years a. Dickersin 2007^{s_2} 0.18 0.38 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.14$ ($p = 0.89$)	0.18 pplicable : <i>z</i> = 0.14	0.38 . (<i>p</i> = 0.8	47 47 39)	0.19	0.35	51 51	100.0% 100.0 %	-0.01 (-0.20 to 0.18) - 0.01 (-0.16 to 0.14)	
									-0.5 -0.25 0 0.25 0.5 Favours hysterectomy Favours first generation

Study or subgroup Fonts Total Fonts Total 16.16 a Dickensin 2007*5 0 114 0 0 114 a Dickensin 2007*5 0 123 0 114 0 0 97 f. Dwyer 1993*5 7 996 0 0 97 0 97 0 97 0 97 0 97 0 97 0 97 0 97 0 97 0 97 96 96 96 96 96 96 96 96 96 96 96 97 90 97 90 97 90 97 90 97 </th <th>Total Weight</th> <th>Deto Fived 00% CI</th> <th></th>	Total Weight	Deto Fived 00% CI	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			Peto, Fixed, 99% CI
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	114 07 36 78/	Not estimable 7 74 /0 57 to 102 30)	
$\begin{array}{c} 1.000, df = 1 \ (p = 0.99); \ l^{2} = 0\% \\ 2.t. \ z = 3.32 \ (p = 0.0009) \\ 2.t. \ z = 3.32 \ (p = 0.0009) \\ 1.t. \ z = 3.32 \ (p = 0.0009) \\ 3 \\ 3 \\ 3 \\ 2.t. \ z = 4.23 \ (p = 0.91); \ l^{2} = 0\% \\ 3 \\ 3 \\ 2.t. \ z = 4.23 \ (p < 0.0001) \\ 1.t. \ z = 4.23 \ (p < 0.0001) \\ 1.t. \ z = 4.23 \ (p < 0.0001) \\ 1.t. \ z = 4.23 \ (p = 0.93); \ l^{2} = 0\% \\ 0 \\ 0.01, df = 1 \ (p = 0.93); \ l^{2} = 0\% \\ 0 \\ 0.01, df = 1 \ (p = 0.93); \ l^{2} = 0\% \\ 0 \\ 0.01, df = 1 \ (p = 0.93); \ l^{2} = 0\% \\ 0 \\ 0.020, df = 1 \ (p = 0.65); \ l^{2} = 0\% \\ 0 \\ 0.20, df = 1 \ (p = 0.65); \ l^{2} = 0\% \\ 0 \\ 0.20, df = 1 \ (p = 0.65); \ l^{2} = 0\% \\ 0 \\ 0.20, df = 1 \ (p = 0.65); \ l^{2} = 0\% \\ 0 \\ 0.20, df = 1 \ (p = 0.65); \ l^{2} = 0\% \\ 0 \\ 0.20, df = 1 \ (p = 0.65); \ l^{2} = 0\% \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 $		7 56 (1 04 to 54 65)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Ŧ	7 61 (9 30 to 95 91)	•
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			•
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		Not estimable	1
248 248 0 0.01, df = 1 (p = 0.91); f' = 0% 248 0 0.01, df = 1 (p = 0.91); f' = 0% 0 0.01, df = 1 (p = 0.93); f' = 0% 0.01, df = 1 (p = 0.93); f'' = 0% 0.01, df = 1 (p = 0.93); f'' = 0% 0 0.01, df = 1 (p = 0.93); f'' = 0% 0 0 0 0.01, df = 1 (p = 0.93); f'' = 0% 0 0 0.01, df = 1 (p = 0.96); f'' = 0% 0 0 0.003) 0 0 0 0.003) 0 0 0 0 0 0 0 0 0	97 81.9%	8.54 (2.05 to 35.52)	
$\begin{array}{c} 17 \\ 0.01, df = 1 \ (p = 0.91); \ \ell = 0\% \\ \text{ct: } z = 4.23 \ (p < 0.0001) \\ 12 \\ 0.12 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 \\$		1.42 (0.36 to 134.22) 8.32 (3.12 to 22.22)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	114 8.1%	6.87 (0.04 to 1190.59)	
222 13 13 13 13 13 13 13		8.15 (1.76 to 37.68)	
$c:t: z = 3.66 \ (p = 0.0003)$ $c:t: z = 3.66 \ (p = 0.0003)$ $1 \qquad 73 \qquad 0$ $14 \qquad 116 \qquad 0$ $14 \qquad 116 \qquad 0$ $16 \qquad 129 \qquad 0$ $0.20, \ df = 1 \ (p = 0.65); \ f = 0\%$	211 100.0%	8.04 (2.63 to 24.56)	♦
1 73 0 14 116 0 15 189 0 0.20, df = 1 ($p = 0.65$); $f = 0\%$ 0 r = -2.65, $f = 0%$			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			
14 116 0 189 189 0 0.20, df = 1 ($p = 0.65$); $l^{2} = 0\%$		12.96 (0.07 to 2544.72)	
189 15 15 0.20, df = 1 (<i>p</i> = 0.65); <i>f</i> = 0% 204 - 2 - 36 (<i>n</i> - 0.003)		4.98 (1.08 to 22.95)	
15 y: $\chi^2 = 0.20$, df = 1 ($p = 0.65$); $\beta = 0\%$ all affect: $\tau - 2$ of f $r = 0.003$	170 100.0%	5.36 (1.75 to 16.38)	♦
1 48 0		29.22 (0.10 to 8234.09)	
% Cl) 48	114 100.0%	29.22 (0.40 to 2137.30)	
l otal events U Heterogeneity: not applicable			
Test for overall effect: $z = 1.54$ ($p = 0.12$)			
1.16.6.5 years	100 001		•
- 123 C		6.92 (0.43 to 111.58)	
2 0)
Heterogeneity: not applicable			
lest for overall effect: $z = 1.30 (p = 0.17)$			-
		(Fa	0.001 0.1 1 10 1000 Favours first generation Favours hysterectomy

First generation Events Tot	ation Total	Hysterectomy Events Tc	tomy Total	Weight	Peto odds ratio Peto. Fixed. 99% Cl	Peto odds ratio Peto. Fixed. 99% Cl
1.17.2.6 months 1.17.2.6 months a. Pictor 1903 ⁴² b. Pintor 1993 ⁴² 5. Dwyer 1993 ⁴² 5. Dwyer 1993 ⁴² 5. Dwyer 1993 ⁴² 5. Dwyer 1993 ⁴² 1. Total events Total events 1. Total events 1.	400 96 305 80	000 0	114 97 308	36.4% 27.4% 36.3% 100.0%	7.88 (0.59 to 105.41) 7.63 (0.38 to 151.65) 7.47 (0.56 to 100.16) 7.66 (2.33 to 25.17)	
1.17.3 1 year a. Dickersin 2007 ⁴² b. Crosignani 1997 ⁴⁵ b. Pinion 1997 ⁴⁵ b. Pinion 1991 ⁴¹ c. Crosignani 1997 ⁴¹ c. Crosignani 1997 ⁴⁵ c. Crosignani 1997 ⁴⁵ c. Crosignani 1997 ⁴⁵ c. Crosignani 1997 ⁴⁵ c. Crosignani 1997 ⁴⁶ c. Crosignani 290 ⁴⁶ c. Crosignani 1997 ⁴⁶ c. Crosignani 290 ⁴⁶ c. Crosignani 1997 ⁴⁶ c. Crosig	105 97 28 271 8	0000 0	114 44 97 283	51.3% 3.9% 7.7% 100.0%	9.19 (2.22 to 38.05) 7.95 (0.05 to 1377.52) 8.15 (1.54 to 43.22) 7.67 (0.19 to 302.89) 8.62 (3.97 to 18.69)	
1.17.4 2 years 18 a. Dickersin 2007 ²² 18 c. Crosignani 1997 ⁴⁶ 4 f. Dwyer 1993 ⁴² 16 Subtotal (95% Cl) 38 Total events 38 Heterogeneity: $\chi^2 = 0.02$, df = 2 ($p = 0.99$); $\beta = 0\%$ Test for overall effect: $z = 6.51$ ($p < 0.00001$)	106 99 246	000 0	114 44 97 255	47.1% 10.9% 42.0% 100.0%	9.49 (2.68 to 33.63) 8.58 (0.62 to 118.47) 8.54 (2.23 to 32.63) 8.98 (4.64 to 17.39)	↓ ↓ ↓
1.17.5 3 years 21 a. Dickersin 2007 ²⁶ 21 d. O'Connor 1997 ⁴⁴ 12 Subtodal (95% CI) 33 Total events 33 Heterogeneity: $\chi^2 = 2.17$, df = 1 ($\rho = 0.14$); $\rho = 54\%$ Test for overall effect: $z = 6.19$ ($\rho < 0.00001$)	78 116 94 %	00 0	114 56 170	64.8% 35.2% 100.0%	15.63 (4.66 to 52.40) 4.88 (0.95 to 25.16) 10.37 (4.95 to 21.76)	[↓] ↓ ↓
1.17.6 4 years a. Dickersin 2007 ²² 23 Subrotal (95% CJ) Total events Heterogeneity: not applicable Test for overall effect: <i>z</i> = 7.14 (<i>p</i> < 0.00001)	20 20	0 0	114 1 4	100.0% 100.0 %	28.85 (8.58 to 97.07) 28.85 (11.46 to 72.63)	+
1.17.7 5 years a. Dickersin 2007 ²² Subtotal (95% CJ) Total events Heterogeneity: not applicable Test for overall effect. $z = 6.86$ ($p < 0.00001$)	123 1 23	0 0	114 11 4	100.0% 100.0 %	10.30 (4.29 to 24.71) 10.30 (5.29 to 20.04)	+

Number of patients with adverse events - periprocedure

	First gen	eration	Hystere	ctomy			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
1.18.1 Anaesthesia p	roblome /k	noth)					
a. Dickersin 200792		110	0	118		Not estimable	
b. Zupi 200378	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	0	92 44		Not estimable	
d. O'Connor 1997	0	116	1	44 56	30.7%	21.57 (0.09 to 5262.64)	
e. Pinion 1994 ⁴³	0	105	2	97	69.3%	8.11 (0.21 to 313.44)	
f. Dwyer 1993 ⁴²	0	99	0	97	03.370	Not estimable	
g. Gannon 1991 ⁴¹	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530	100.0%	10.94 (1.08 to 110.90)	
Total events	0		3				
Heterogeneity: $\chi^2 = 0$. Test for overall effect:							
1.18.2 Excessive ble	eding (both	n)					
a. Dickersin 200792	0	110	0	118		Not estimable	
b. Zupi 2003 ⁷⁸	4	89	5	92	45.2%	1.22 (0.21 to 7.06)	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 199443	6	105	5	97	54.8%	0.90 (0.18 to 4.42)	
f. Dwyer 199342	0	99	0	97		Not estimable	
g. Gannon 199141	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530	100.0%	1.03 (0.42 to 2.53)	-
Total events	10		10				
Heterogeneity: $\chi^2 = 0$.	11, df = 1 (p = 0.74); $I^2 = 0\%$				
Test for overall effect:	z = 0.07 (µ	o = 0.95)					
1.18.3 Injury to surro							
a. Dickersin 200792	0	110	2	118	66.5%	6.96 (0.18 to 268.76)	
b. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 199443	0	105	0	97		Not estimable	
f. Dwyer 199342	0	99	1	97	33.5%	7.54 (0.04 to 1303.16)	
g. Gannon 199141	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530	100.0%	7.15 (0.74 to 69.06)	
Total events	0		3				
Heterogeneity: $\chi^2 = 0$. Test for overall effect:							
1.18.4 Uterine perfor	ation (abla	tion)					
a. Dickersin 2007 ⁹²	3	110	0	118	28.3%	0.12 (0.01 to 2.46)	←
b. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	3	116	0	56	24.8%	0.22 (0.01 to 5.43)	←
e. Pinion 199443	1	105	0	97	9.5%	0.15 (0.00 to 25.33)	←
f. Dwyer 199342	4	99	0	97	37.5%	0.13 (0.01 to 1.80)	←
g. Gannon 199141	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530	100.0%	0.15 (0.04 to 0.50)	
Total events	11		0				
Heterogeneity: $\chi^2 = 0$. Test for overall effect:							
1.18.5 Fluid overload	. ,						
a. Dickersin 200792	1	110	0	118	5.0%	0.13 (0.00 to 21.80)	←
b. Zupi 2003 ⁷⁸	5	89	0	92	24.7%	0.12 (0.01 to 1.28)	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	3	116	0	56	13.1%	0.22 (0.01 to 5.43)	←──────────
e. Pinion 199443	12	105	0	97	57.2%	0.13 (0.03 to 0.60)	
f. Dwyer 199342	0	99	0	97		Not estimable	
g. Gannon 199141	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530	100.0%	0.14 (0.06 to 0.33)	
Total events	21		0				
Heterogeneity: $\chi^2 = 0$. Test for overall effect:							
							0.01 0.1 1 10 100
							Favours hysterectomy Favours first generation

	First ger	neration	Hystere	ectomy			_	
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-eve Peto, Fixed, 99% Cl	nt)
1.18.6 Extra visceral		ablation)						
a. Dickersin 200792	0	110	0	118		Not estimable		
b. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable		
c. Crosignani 199745	0	41	0	44		Not estimable		
d. O'Connor 199744	0	116	0	56		Not estimable		
e. Pinion 199443	1	105	0	97	100.0%	0.15 (0.00 to 25.33)	← ●	
f. Dwyer 199342	0	99	0	97		Not estimable		
g. Gannon 199141	0	25	0	26		Not estimable		
Subtotal (95% CI)		585		530	100.0%	0.15 (0.00 to 7.38)		
Total events	1		0					
Heterogeneity: not ap	plicable							
Test for overall effect		p = 0.34)						
1.18.7 Cervical lacer	ation (abla	ation)						
a. Dickersin 2007 ⁹²	1	110	0	118	26.7%	0.13 (0.00 to 21.80)	←	_
b. Zupi 2003 ⁷⁸	1	89	0	92	26.7%	0.13 (0.00 to 22.62)	←	_
c. Crosignani 199745	0	41	0	44	20.170	Not estimable	_	
d. O'Connor 199744	2	116	0	56	46.6%	0.23 (0.00 to 11.10)		
e. Pinion 199443	0	105	0	97	40.070	Not estimable		
f. Dwyer 1993 ⁴²	0	99	0	97		Not estimable		
g. Gannon 1991 ⁴¹	0	99 25	0	26		Not estimable		
	0	585	0	530	100.0%			
Subtotal (95% CI)	4	200	0	530	100.0%	0.17 (0.02 to 1.26)		
Total events Heterogeneity: $\chi^2 = 0$	-	(- 0.00						
Test for overall effect								
1.18.8 Procedure ab								
a. Dickersin 200792	0	110	0	118		Not estimable		
b. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable		
c. Crosignani 199745	0	41	0	44		Not estimable		
d. O'Connor 199744	1	116	0	56	46.8%	0.23 (0.00 to 55.38)	← ■	
e. Pinion 199443	0	105	0	97		Not estimable		
f. Dwyer 199342	1	99	0	97	53.2%	0.14 (0.00 to 23.86)	<hr/>	
g. Gannon 199141	0	25	0	26		Not estimable		
Subtotal (95% CI)		585		530	100.0%	0.17 (0.01 to 3.04)		
Total events	2		0					
Heterogeneity: $\chi^2 = 0$								
Test for overall effect	: <i>z</i> = 1.20 (p = 0.23)						
1.18.9 Procedure co		-		-	74 50/		_	
a. Dickersin 2007 ⁹²	10	123	0	118	71.5%	0.13 (0.02 to 0.69)		
b. Zupi 2003 ⁷⁸	3	89	0	92	22.0%	0.13 (0.01 to 2.55)	• • •	
c. Crosignani 199745	0	41	0	44	0	Not estimable		
d. O'Connor 199744	1	116	0	56	6.5%	0.23 (0.00 to 55.38)	←	
e. Pinion 1994 ⁴³	0	105	0	97		Not estimable		
. Dwyer 199342	0	99	0	97		Not estimable		
g. Gannon 1991 ⁴¹	0	25	0	26		Not estimable		
Subtotal (95% CI)		598		530	100.0%	0.13 (0.05 to 0.39)		
Total events	14		0					
Heterogeneity: $\chi^2 = 0$.06, df = 2	(p = 0.97	'); <i>I</i> ² = 0%					
Test for overall effect	: <i>z</i> = 3.68 (p = 0.000	02)					
							0.01 0.1 1 10	10

Number of patients with adverse events - postoperatively (within 1 month)

	First gen	eration	Hystere	ctomy			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
1.19.1 Urinary tract i	nfection (b	oth)					
a. Dickersin 200792	2	110	6	118	16.4%	2.61 (0.41 to 16.64)	
. Zupi 2003 ⁷⁸	1	89	1	92	4.2%	0.97 (0.03 to 37.34)	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 199443	6	105	22	97	51.3%	4.11 (1.44 to 11.72)	
. Dwyer 1993 ⁴²	0	99	12	97	24.0%	8.51 (1.84 to 39.35)	
J. Gannon 199141	0	25	2	26	4.1%		
	0		2			7.40 (0.19 to 293.55)	
Subtotal (95% CI)		585	10	530	100.0%	4.38 (2.48 to 7.75)	-
otal events	9		43				
Heterogeneity: $\chi^2 = 3$. Test for overall effect:							
.19.2 Deep vein thro	ombosis (b	oth)					
a. Dickersin 2007 ⁹²	0.	110	2	118	100.0%	6.96 (0.18 to 268.76)	
o. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
Crosignani 199745	0	41	0	44		Not estimable	
1. O'Connor 199744	0	116	0	56		Not estimable	
Pinion 1994 ⁴³	0	105	0	97		Not estimable	
Dwyer 1993 ⁴²	0	99	0	97		Not estimable	
J. Gannon 1991 ⁴¹	0	25	0	26	100 00/	Not estimable	
Subtotal (95% CI)	0	585	0	530	100.0%	6.96 (0.43 to 112.21)	
otal events	0		2				
leterogeneity: not ap est for overall effect:		o = 0.17)					
.19.3 Haematometra	• •	110	0	110			
. Dickersin 2007 ⁹²	0	110	0	118		Not estimable	
 Zupi 2003⁷⁸ 	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	1	44	4.2%	6.90 (0.04 to 1195.94)	
1. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 199443	0	105	11	97	43.8%	8.95 (1.82 to 44.09)	
. Dwyer 199342	1	99	8	97	36.2%	5.17 (0.90 to 29.88)	
g. Gannon 199141	0	25	4	26	15.8%	8.06 (0.57 to 114.90)	
Subtotal (95% CI)		585		530	100.0%	7.14 (3.20 to 15.94)	-
Total events	1		24				
Heterogeneity: $\chi^2 = 0$. Test for overall effect:							
.19.4 Excessive blee				110		Not optimoble	
a. Dickersin 2007 ⁹²	0	110	0	118		Not estimable	
D. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
. Crosignani 1997 ⁴⁵	0	41	0	44	00.00/	Not estimable	
. O'Connor 199744	0	116	3	56	30.8%	22.37 (0.92 to 544.67)	
. Pinion 1994 ⁴³	0	105	0	97		Not estimable	
Dwyer 199342	0	99	6	97	69.2%	7.95 (0.94 to 66.99)	
J. Gannon 1991 ⁴¹	0	25	0	26		Not estimable	
ubtotal (95% CI)		585		530	100.0%	10.94 (2.84 to 42.14)	
otal events	0		9				
Heterogeneity: $\chi^2 = 0$. Test for overall effect:							
.19.5 Embolism (hys	sterectomy	n					
. Dickersin 200792	0	110	2	118	100.0%	6.96 (0.18 to 268.76)	
. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
. Crosignani 199745	0	41	0	44		Not estimable	
. O'Connor 199744	0	116	0	56		Not estimable	
. Pinion 1994 ⁴³	0	105	0	97		Not estimable	
Dwyer 1993 ⁴²	0	99	0	97		Not estimable	
. Gannon 199141	0	99 25	0	26		Not estimable	
	U		U		100 00/		
Subtotal (95% CI)	0	585	0	530	100.0%	6.96 (0.43 to 112.21)	
otal events	0		2				
leterogeneity: not ap est for overall effect:		o = 0.17)					
						+	
						0.0	1 0.1 1 10 100
						Fair	ours hysterectomy Favours first generatio

	First gen	ieration	Hystere	ctomy		Peto odds ratio (non-event)	Peto odds ratio (non-event)
Study or subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 99% Cl	Peto, Fixed, 99% Cl
1.19.6 Further bleed	ing (ablatic	on)					
a. Dickersin 2007 ⁹²	0	110	0	118		Not estimable	
o. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 199443	0	105	0	97		Not estimable	
. Dwyer 199342	0	99	0	97		Not estimable	
g. Gannon 199141	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530		Not estimable	
Total events	0		0				
Heterogeneity: not ap	plicable						
est for overall effect		able					
I.19.7 Sepsis (ablati	on)						
a. Dickersin 2007 ⁹²	0	110	0	118		Not estimable	
b. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	9	116	0	56	100.0%	0.21 (0.03 to 1.38)	
e. Pinion 199443	0	105	0	97		Not estimable	
. Dwyer 199342	0	99	0	97		Not estimable	
g. Gannon 199141	0	25	0	26		Not estimable	
Subtotal (95% CI)		585		530	100.0%	0.21 (0.05 to 0.88)	
Total events	9		0				
Heterogeneity: not ap			v				
Test for overall effect	•	o = 0.03)					
.19.8 Pyrexia (ablat	ion)						
a. Dickersin 2007 ⁹²	1	110	0	118	20.1%	0.13 (0.00 to 21.80)	•
 Zupi 2003⁷⁸ 	2	89	0	92	40.0%	0.13 (0.00 to 4.99)	•
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 1994 ⁴³	0	105	0	97		Not estimable	
. Dwyer 1993 ⁴²	2	99	0	97	40.0%	0.14 (0.00 to 5.27)	
g. Gannon 1991 ⁴¹	0	25	0	26	40.070	Not estimable	
Subtotal (95% CI)	0	585	0	530	100.0%	0.13 (0.02 to 0.76)	
	5	565	0	550	100.0 %	0.13 (0.02 10 0.70)	
Fotal events		(- 100					
Heterogeneity: $\chi^2 = 0$. Fest for overall effect), 7 = 0%				
1.19.9 Endometriosis	s (ablation)						
a. Dickersin 2007 ⁹²	1	110	0	118	100.0%	0.13 (0.00 to 21.80)	←──
5. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable	—
c. Crosignani 199745	0	41	0	44		Not estimable	
d. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 1994 ⁴³	0	105	0	97		Not estimable	
. Dwyer 1993 ⁴²	0	99	0	97 97			
. Dwyer 1993 - g. Gannon 1991 ⁴¹	0	99 25	0	97 26		Not estimable Not estimable	
	U		U		100 00/		
Subtotal (95% CI)		585	0	530	100.0%	0.13 (0.00 to 6.36)	
Fotal events Heterogeneity: not ap	1 plicable		0				
Test for overall effect	: z = 1.04 (j	v = 0.30)					
1.19.10 Abdominal p	ain (ablatio	on)					
a. Dickersin 200792	0	, 110	0	118		Not estimable	
 Zupi 2003⁷⁸ 	0	89	0	92		Not estimable	
c. Crosignani 199745	0	41	0	44		Not estimable	
I. O'Connor 199744	0	116	0	56		Not estimable	
e. Pinion 1994 ⁴³	0	105	0	97		Not estimable	
. Dwyer 1993 ⁴²	0	99	0	97		Not estimable	
	0	99 25			100 00/		
	U		4	26	100.0%	8.06 (0.57 to 114.90)	
g. Gannon 199141		585		530	100.0%	8.06 (1.07 to 60.87)	
g. Gannon 1991 ⁴¹ Subtotal (95% Cl)			4				
g. Gannon 1991 ⁴¹ Subtotal (95% CI) Fotal events	0						
g. Gannon 1991 ⁴¹ Subtotal (95% CI) Fotal events Heterogeneity: not ap	plicable						
. Gannon 1991 ⁴¹ Gubtotal (95% CI) Total events leterogeneity: not ap	plicable	o = 0.04)					
. Gannon 1991 ⁴¹ Subtotal (95% CI) Total events	plicable	o = 0.04)					0.01 0.1 1 10 100

	First ger	neration	Hystere	ctomy						
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event Peto, Fixed, 99% Cl)		s ratio (non-even Fixed, 99% Cl	t)
1.19.11 Foul dischar	ge (ablatio	on)								
a. Dickersin 200792	0	110	0	118		Not estimable				
b. Zupi 2003 ⁷⁸	0	89	0	92		Not estimable				
c. Crosignani 199745	0	41	0	44		Not estimable				
d. O'Connor 199744	0	116	0	56		Not estimable				
e. Pinion 199443	0	105	0	97		Not estimable				
f. Dwyer 199342	0	99	0	97		Not estimable				
g. Gannon 199141	0	25	1	26	100.0%	7.11 (0.04 to 1229.28)				→
Subtotal (95% CI)		585		530	100.0%	7.11 (0.14 to 358.60)				
Total events	0		1							
Heterogeneity: not ap	plicable									
Test for overall effect	: <i>z</i> = 0.98 (p = 0.33)								
1.19.13 Visceral dam	nage (ablat	tion)								
a. Dickersin 200792	0	110	0	118		Not estimable				
b. Zupi 200378	0	89	0	92		Not estimable				
c. Crosignani 199745	0	41	0	44		Not estimable				
d. O'Connor 199744	0	116	0	56		Not estimable				
e. Pinion 199443	0	105	0	97		Not estimable				
f. Dwyer 199342	0	99	0	97		Not estimable				
g. Gannon 199141	0	25	0	26		Not estimable				
Subtotal (95% CI)		585		530		Not estimable				
Total events	0		0							
Heterogeneity: not ap	plicable									
Test for overall effect	•	able								
							0.01	0.1	1 10	100
							Favours	hysterectomy	Favours first	generatio

Appendix 5

Pooled results for hysterectomy versus Mirena

Appendix 5.1 Quality of life – clinical outcome

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95% CI)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
SF-36 general health (absolute)	6 months	1 (211)	-3.2 (-8.8 to 2.4)	_	0.3	_
SF-36 physical function (absolute)		1 (211)	-2.7 (-7.2 to 1.8)	_	0.2	-
SF-36 role physical (absolute)		1 (209)	-10.7 (-19.6 to -1.8)	_	0.02	_
SF-36 role emotional (absolute)		1 (208)	-8.3 (-17.5 to 0.9)	_	0.08	_
SF-36 mental health (absolute)		1 (211)	-5.3 (-10.1 to -0.5)	_	0.03	_
SF-36 social function (absolute)		1 (212)	-6.1 (-11.2 to -1.0)	_	0.02	_
SF-36 vitality (absolute)		1 (211)	-7.8 (-13.8 to -1.8)	_	0.01	_
SF-36 pain (absolute)		1 (212)	-5.7 (-11.8 to 0.4)	_	0.07	-
SF-36 general health (absolute)	12 months	1 (214)	-2.4 (-8.1 to 3.3)	_	0.4	-
SF-36 physical function (absolute)		1 (213)	-3.2 (-7.8 to 1.4)	_	0.2	-
SF-36 role physical (absolute)		1 (210)	-4.4 (-12.4 to 3.6)	_	0.3	_
SF-36 role emotional (absolute)		1 (208)	-9.4 (-18.3 to -0.50)	_	0.04	_
SF-36 mental health (absolute)		1 (214)	-3.9 (-8.6 to 0.8)	_	0.1	_
SF-36 social function (absolute)		1 (213)	-4.0 (-8.7 to 0.7)	_	0.09	_
SF-36 vitality (absolute)		1 (214)	-4.7 (-10.4 to 1.0)	_	0.1	_
SF-36 pain (absolute)		1 (213)	-6.5 (-12.4 to -0.6)	_	0.03	-
SF-36 general health (absolute)	5 years	1 (224)	-2.4 (-7.9 to 3.1)	_	0.4	-
SF-36 physical function (absolute)		1 (221)	-0.6 (-5.8 to 4.6)	_	0.8	-
SF-36 role physical (absolute)		1 (222)	-0.6 (-10.3 to 9.1)	_	0.9	_
SF-36 role emotional (absolute)		1 (225)	-1.0 (-10.2 to 8.2)	_	0.8	_
SF-36 mental health (absolute)		1 (225)	-2.9 (-7.2 to 1.4)	_	0.2	_
SF-36 social function (absolute)		1 (226)	-3.1 (-8.8 to 2.6)	_	0.3	_
SF-36 vitality (absolute)		1 (224)	-1.5 (-7.0 to 4.0)	_	0.6	_
SF-36 pain (absolute)		1 (226)	0.5 (-6.5 to 7.5)	_	0.9	_
SF-36 general health (change)	6 months	1 (209)	-3.8 (-8.2 to 0.6)	_	0.09	_
SF-36 physical function (change)		1 (207)	-2.7 (-6.6 to 1.2)	_	0.2	_
SF-36 role physical (change)		1 (206)	-8.3 (-19.3 to 2.7)	_	0.1	_
SF-36 role emotional (change)		1 (202)	-2.9 (-14.6 to 8.8)	_	0.6	_
SF-36 mental health (change)		1 (207)	-2.9 (-8.0 to -2.2)	_	0.3	_
SF-36 social function (change)		1 (210)	-2.2 (-7.5 to 3.1)	-	0.4	_
SF-36 vitality (change)		1 (208)	-5.9 (-12.0 to 0.2)	_	0.06	_
SF-36 pain (change)		1 (208)	-6.8 (-13.6 to 0.01)	_	0.05	_
SF-36 general health (change)	12 months	1 (212)	-0.6 (-4.9 to 3.7)	_	0.8	_
SF-36 physical function (change)		1 (209)	-2.3 (-6.6 to 2.0)	-	0.3	_
SF-36 role physical (change)		1 (208)	-0.5 (-11.6 to 10.6)	-	0.9	_
SF-36 role emotional (change)		1 (206)	-4.1 (-15.7 to 7.5)	-	0.5	_
SF-36 mental health (change)		1 (210)	-0.3 (-5.2 to 4.6)	_	0.9	-

continued

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95% CI)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
SF-36 social function (change)		1 (212)	-0.5 (-5.7 to 4.7)	_	0.9	_
SF-36 vitality (change)		1 (211)	-2.3 (-7.9 to 3.3)	_	0.4	_
SF-36 pain (change)		1 (210)	-9.6 (-16.6 to -2.7)	_	0.007	_
SF-36 general health (change)	5 years	1 (222)	-1.3 (-6.2 to 3.6)	-	0.6	_
SF-36 physical function (change)		1 (216)	-0.5 (-5.5 to 4.5)	-	0.9	_
SF-36 role physical (change)		1 (219)	-1.1 (-12.3 to 10.1)	_	0.9	_
SF-36 role emotional (change)		1 (221)	4.1 (-7.7 to 15.9)	_	0.5	_
SF-36 mental health (change)		1 (220)	0.5 (-4.4 to 5.4)	_	0.8	_
SF-36 social function (change)		1 (224)	-0.1 (-5.8 to 5.6)	_	1.0	_
SF-36 vitality (change)		1 (221)	-0.4 (-6.2 to 5.4)	_	0.9	_
SF-36 pain (change)		1 (222)	-0.6 (-8.0 to 6.8)	_	0.9	_
EQ-5D (absolute)	6 months	1 (214)	-0.04 (-0.09 to 0.01)	_	0.1	_
	12 months	1 (213)	-0.02 (-0.06 to 0.02)	_	0.4	_
	5 years	1 (224)	-0.03 (-0.08 to 0.02)	_	0.3	_
EQ-5D (change)	6 months	1 (210)	-0.01 (-0.06 to 0.04)	_	0.7	_
	12 months	1 (209)	-0.00 (-0.05 to 0.05)	_	1.0	_
	5 years	1 (220)	-0.01 (-0.07 to 0.05)	-	0.7	-
		Trials	Frequency			
Discontinued Mirena	6 months	1	22/119 (18%)			
	12 months	1	37/119 (31%)			
	5 years	1	60/119 (50%)			
Hysterectomy after Mirena	6 months	1	9/119 (8%)			
	12 months	1	24/119 (20%)			

	Trials	Frequency (hysterectomy: max. 117; Mirena: max. 119)	OR (95% CI) ^a	<i>p</i> -value	Hetero (<i>p</i>)/ <i>l</i> ² (%)
Periprocedure complications (hysterectomy)					
Anaesthesia problems	1	0	_	_	_
Excessive bleeding	1	0	-		_
Injury surrounding organs	1	5	-	-	-
Further complications (hysterectomy, <1 month)					
Urinary tract infection	1	0	-	-	_
Deep-vein thrombosis	1	0	-	_	_
Excessive bleeding	1	0	-	_	_
Embolism	1	0	-	-	-
Complication post-insertion (Mirena)					
Uterine perforation	1	0	-	_	_
Infection	1	5	-	_	_
Expelled/migrated	1	0	-	_	_
Cervical laceration	1	0	-	-	_
Failed to insert	1	2	-	-	_
Removed (before 3 months)	1	10	_	_	_

 $\begin{array}{ll} a & <0 \text{ favours hysterectomy, } >0 \text{ favours Mirena.} \\ b & <1 \text{ favours hysterectomy, } >1 \text{ favours Mirena.} \end{array}$

Appendix 5.2 Hysterectomy versus Mirena

SF-36 scores (absolute values)

		Mirena		Hys	terecto	omy			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% Cl
.3.1 SF-36 6 months	– gener	al hea	th						
. Hurskainen 200193	70.3	20.3	107	73.5	21	104	100.0%	-3.20 (-10.53 to 4.13)	
Subtotal (95% CI)	liandala		107			104	100.0%	–3.20 (–8.78 to 2.38)	
leterogeneity: not app est for overall effect:		(p = 0.	26)						
.3.2 SF-36 6 months	– physic	cal fun	ction						
. Hurskainen 200193	88.9	18.3	107	91.6	14.7	104	100.0%	-2.70 (-8.58 to 3.18)	
Subtotal (95% CI)			107			104	100.0%	–2.70 (–7.17 to 1.77)	-
leterogeneity: not app est for overall effect:		(p = 0.	24)						
.3.3 SF-36 6 months	– role li	mitatio	, n (nhve	ical)					
. Hurskainen 200193		36.7	106	87.4	28.2	103	100.0%	-10.70 (-22.34 to 0.94)	• • • • • • • • • • • • • • • • • • •
Subtotal (95% CI)			106			103	100.0%	–10.70 (–19.56 to –1.84)	
leterogeneity: not app	licable								
est for overall effect:	z = 2.37	(p = 0.	02)						
3.4 SF-36 6 months			-	-	00 4	100	100.004	0.00 (00.44 += 0.04)	_
. Hurskainen 2001 ⁹³	11.5	37.4	105 105	85.8	30.1	103 103	100.0%	–8.30 (–20.41 to 3.81) –8.30 (–17.52 to 0.92)	
Subtotal (95% CI) leterogeneity: not app	licable		100			103	100.0%	-0.00 (-17.02 10 0.92)	
est for overall effect:		(<i>p</i> = 0.	08)						
.3.5 SF-36 6 months		al healt							
. Hurskainen 200193	72.4	19.5	107	77.7	16.2	104	100.0%	-5.30 (-11.65 to 1.05)	
Subtotal (95% CI)	P		107			104	100.0%	-5.30 (-10.13 to -0.47)	
leterogeneity: not app est for overall effect:		(p = 0.	03)						
.3.6 SF-36 6 months . Hurskainen 200193		I functi 21.3	on 108	77.6	16.5	104	100.0%	-6.10 (-12.83 to 0.63)	
Subtotal (95% CI)	71.0	21.0	108	11.0	10.0	104	100.0%	-6.10 (-11.22 to -0.98)	
leterogeneity: not app		<i>,</i>							-
est for overall effect:	z = 2.34	(p = 0.	02)						
'.3.7 SF-36 6 months . Hurskainen 2001 ⁹³		y 24.1	108	69.7	20.5	103	100.0%	-7.80 (-15.72 to 0.12)	
Subtotal (95% CI)	01.5	27.1	108	05.7	20.0	103	100.0%	-7.80 (-13.83 to -1.77)	
leterogeneity: not app	licable								
est for overall effect:	z = 2.54	(p = 0.	01)						
.3.8 SF-36 6 months	-								
. Hurskainen 200193	74.3	22.4	108	80	23	104	100.0%	-5.70 (-13.74 to 2.34)	
Subtotal (95% CI) leterogeneity: not app	licable		108			104	100.0%	–5.70 (–11.81 to 0.41)	
est for overall effect:		(p = 0.	07)						
.3.9 SF-36 1 year - ç		nealth							
. Hurskainen 2001 ⁹³	70.7	19.8	105	73.1	22.6	109	100.0%	-2.40 (-9.87 to 5.07)	
Subtotal (95% CI)	liooble		105			109	100.0%	-2.40 (-8.09 to 3.29)	
leterogeneity: not app est for overall effect:		(p = 0.	41)						
.3.10 SF-36 1 year -	physica	l funct	ion						
. Hurskainen 200193		19.4	104	91.8	14.2	109	100.0%	-3.20 (-9.22 to 2.82)	
Subtotal (95% CI)	P		104			109	100.0%	–3.20 (–7.78 to 1.38)	-
leterogeneity: not app est for overall effect:		(p = 0.	17)						
.3.11 SF-36 1 year -	role lim	itation	(physic)	al)					
. Hurskainen 2001 ⁹³		30.8	103	87.4	27.8	107	100.0%	-4.40 (-14.84 to 6.04)	
Subtotal (95% CI)		- 510	103			107	100.0%	-4.40 (-12.35 to 3.55)	
leterogeneity: not app est for overall effect:		(n = 0							
		u .	,						
.3.12 SF-36 1 year - . Hurskainen 200193		itation 35.7	(emotio 100	nal) 86.4	29.2	108	100.0%	-9.40 (-21.10 to 2.30)	• • • • • • • • • • • • • • • • • • •
Subtotal (95% CI)	••	20.1	100	00r	-0.2	108	100.0%	-9.40 (-18.30 to -0.50)	
leterogeneity: not app	licable		-			-		· · · · · ·	
			04)						

Favours hysterectomy

		Mirena		Hys	terecto	omy			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
3.13 SF-36 1 year -	mental	health							
Hurskainen 200193	74.3	19.7	105	78.2	14.5	109	100.0%	-3.90 (-10.01 to 2.21)	
ibtotal (95% CI)	l'a a la la		105			109	100.0%	–3.90 (–8.55 to 0.75)	
eterogeneity: not app est for overall effect: 2		(p = 0.	10)						
3.14 SF-36 1 year -	social f	unction	n						
Hurskainen 200193		19.2	105	78.5	15.1	108	100.0%	-4.00 (-10.11 to 2.11)	
ubtotal (95% CI)			105			108	100.0%	–4.00 (–8.65 to 0.65)	-
eterogeneity: not app est for overall effect: 2		(p = 0.	09)						
.3.15 SF-36 1 year -	vitalitv								
Hurskainen 200193		23	105	69.9	19.3	109	100.0%	-4.70 (-12.19 to 2.79)	
ubtotal (95% CI)			105			109	100.0%	-4.70 (-10.40 to 1.00)	
eterogeneity: not app est for overall effect:		$(\rho = 0.$	11)						
		ŭ	,						
.3.16 SF-36 1 year – . Hurskainen 2001 ⁹³	-	23.6	105	82.1	20	108	100.0%	-6.50 (-14.23 to 1.23)	
ubtotal (95% CI)			105		-	108	100.0%	-6.50 (-12.38 to -0.62)	
leterogeneity: not app est for overall effect:		(n = 0)	03)						
.3.17 SF-36 5 years - . Hurskainen 2001 ⁹³	- genera 68.5	al healt 20.8	h 111	70.9	21.1	113	100.0%	-2.40 (-9.61 to 4.81)	
ubtotal (95% CI)	55.5	20.0	111	, 0.0		113	100.0%	-2.40 (-7.89 to 3.09)	
leterogeneity: not app	licable					-		, ,	
est for overall effect:	z = 0.86	(p = 0.	39)						
.3.18 SF-36 5 years -				96.0	17.0		100.00/	0.60(7.00 + 0.10)	1
. Hurskainen 2001 ⁹³ ubtotal (95% CI)	86.2	21.6	110 110	86.8	17.3	111 111	100.0% 100.0%	–0.60 (–7.38 to 6.18) –0.60 (–5.76 to 4.56)	
leterogeneity: not app	licable						100.0 /0		
est for overall effect:	z = 0.23	(p = 0.	82)						
.3.19 SF-36 5 years -									
. Hurskainen 2001 ⁹³	76.4	37.4	110 110	77	36.3	112 112	100.0%	-0.60 (-13.34 to 12.14)	
Subtotal (95% CI) leterogeneity: not app	licable		110			112	100.0%	–0.60 (–10.30 to 9.10)	
est for overall effect:		(p = 0.	90)						
.3.20 SF-36 5 years -	- role lir	nitatior	n (emoti	onal)					
. Hurskainen 200193	77.9	35	113	78.9	35.2	112	100.0%	-1.00 (-13.06 to 11.06)	
ubtotal (95% CI)	lioch!-		113			112	100.0%	–1.00 (–10.17 to 8.17)	
eterogeneity: not app est for overall effect: 2		(p = 0.	83)						
3.21 SF-36 5 years -	- menta	l health	n						
. Hurskainen 200193	74.9	18.7	114	77.8	14.3	111	100.0%	-2.90 (-8.61 to 2.81)	
ubtotal (95% CI)			114			111	100.0%	-2.90 (-7.24 to 1.44)	
eterogeneity: not app est for overall effect: 2		(p = 0.	19)						
3.22 SF-36 5 years -		u .	,						
. Hurskainen 200193		23.8	114	75.5	19.6	112	100.0%	-3.10 (-10.56 to 4.36)	
ubtotal (95% CI)			114			112	100.0%	–3.10 (–8.78 to 2.58)	
eterogeneity: not app est for overall effect: 2		(p = 0.	28)						
3.23 SF-36 5 years -			.,						
Hurskainen 200193	65	22.5	111	66.5	19.7	113	100.0%	-1.50 (-8.78 to 5.78)	
ubtotal (95% CI)	lioch!-		111			113	100.0%	–1.50 (–7.04 to 4.04)	
eterogeneity: not app est for overall effect: 2		(p = 0.	60)						
3.24 SF-36 5 years -	- pain								
Hurskainen 200193		25.7	114	75	27.7	112	100.0%	0.50 (-8.66 to 9.66)	
ubtotal (95% CI)	P. 11		114			112	100.0%	0.50 (-6.47 to 7.47)	
eterogeneity: not app est for overall effect:		(n - n)	80)						
	∠ = 0.14	$\mu = 0.$	ບອງ						

SF-36 scores (change from baseline)

7.4.1 SF-36 6 months – general 1. Hurskainen 2001 ⁹³ 3.4 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.69$ (p 7.4.2 SF-36 6 months – physica 1. Hurskainen 2001 ⁹³ 5.3 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.35$ (p 7.4.3 SF-36 6 months – role limi 1. Hurskainen 2001 ⁹³ 12 4 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.48$ (p 7.4.4 SF-36 6 months – role limi 1. Hurskainen 2001 ⁹³ 15.4 4 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.49$ (p 7.4.5 SF-36 6 months – mental I 1. Hurskainen 2001 ⁹³ 4.7 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.49$ (p 7.4.6 SF-36 6 months – mental I 1. Hurskainen 2001 ⁹³ 4.7 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.49$ (p 7.4.6 SF-36 6 months – social fu 1. Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.81$ (p 7.4.7 SF-36 6 months – social fu 1. Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – pain 1. Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general hee 1. Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita	16.1 p = 0.1 al fun 15.4 p = 0.1	106 106 09) ction 105 105	Mean 7.2	SD 16.4	Total 103 103	Weight 100.0% 100.0%	Mean difference IV, Fixed, 99% CI -3.80 (-9.59 to 1.99)	Mean difference IV, Fixed, 99% Cl
Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.69$ (p 7.4.2 SF-36 6 months – physical 1. Hurskainen 2001 ⁹³ 5.3 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.35$ (p 7.4.3 SF-36 6 months – role limit 1. Hurskainen 2001 ⁹³ 12 4 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.48$ (p 7.4.4 SF-36 6 months – role limit 1. Hurskainen 2001 ⁹³ 15.4 4 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.49$ (p 7.4.5 SF-36 6 months – mental I 1. Hurskainen 2001 ⁹³ 4.7 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.49$ (p 7.4.5 SF-36 6 months – mental I 1. Hurskainen 2001 ⁹³ 4.7 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.12$ (p 7.4.6 SF-36 6 months – social fu 1. Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.81$ (p 7.4.7 SF-36 6 months – social fu 1. Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – pain 1. Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general hea 1. Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fu 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – nel limital Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.11 SF-36 1 year – role limital Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limital Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limital Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limital	16.1 p = 0.1 al fund 15.4 p = 0. nitatio	106 106 09) ction 105 105		16.4			-3 80 (-9 50 to 1 00)	
. Hurskainen 2001 ⁹³ 3.4 1 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.69$ (p 3.4 2 SF-36 6 months – physical . Hurskainen 2001 ⁹³ 5.3 1 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.35$ (p 3.4 3 SF-36 6 months – role limi . Hurskainen 2001 ⁹³ 12 4 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.48$ (p 3.4 SF-36 6 months – role limi . Hurskainen 2001 ⁹³ 15.4 4 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.49$ (p 3.4 SF-36 6 months – mental I . Hurskainen 2001 ⁹³ 15.4 4 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.49$ (p 3.5 SF-36 6 months – mental I . Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.12$ (p 3.6 SF-36 6 months – social ft . Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.81$ (p 3.7 SF-36 6 months – social ft . Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.12$ (p 3.8 SF-36 6 months – social ft . Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.81$ (p 4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 5.5 1 5.9 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.27$ (p 3.9 SF-36 1 year – general hea . Hurskainen 2001 ⁹³ 5.5 1 5.9 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.27$ (p 3.10 SF-36 1 year – physical ft . Hurskainen 2001 ⁹³ 4.8 1 5.10 5.5 1 	16.1 p = 0.1 al fund 15.4 p = 0. nitatio	106 106 09) ction 105 105		16.4			-3 80 (-9 59 to 1 00)	
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Heterogeneity: not applicable Test for overall effect: $z = 0.49$ (p 7.4.5 SF-36 6 months – mental I L Hurskainen 2001 ⁹³ 4.7 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.12$ (p 7.4.6 SF-36 6 months – social fu L Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.81$ (p 7.4.7 SF-36 6 months – vitality L Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – vitality L Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.86$ (p 7.4.8 SF-36 6 months – pain L Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general her L Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi L Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi L Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita		102			102	100.0%	-2.90 (-14.57 to 8.77)	
2.4.5 SF-36 6 months – mental I . Hurskainen 2001 ⁹³ 4.7 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.12$ (p 2.4.6 SF-36 6 months – social ft . Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 0.81$ (p 2.4.7 SF-36 6 months – vitality . Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.88$ (p 2.4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.88$ (p 2.4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.96$ (p 2.4.9 SF-36 1 year – general hea . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical ft . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.05$ (p 2.4.10 SF-36 1 year – role limita							, , , ,	
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Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.12$ (p 2.4.6 SF-36 6 months – social fu . Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.81$ (p 2.4.7 SF-36 6 months – vitality . Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 2.4.8 SF-36 6 months – pain 1. Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 2.4.9 SF-36 1 year – general here 1. Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical fi 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita			7.0	10.0	100	100.00/		_
Heterogeneity: not applicable Test for overall effect: $z = 1.12$ (p 7.4.6 SF-36 6 months – social fu L Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.81$ (p 7.4.7 SF-36 6 months – vitality L Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – pain L Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general her L Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi L Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi L Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita	20.6	104 104	7.6	16.3	103 103	100.0% 100.0%	–2.90 (–9.55 to 3.75) –2.90 (–7.96 to 2.16)	
Test for overall effect: $z = 1.12$ (p 7.4.6 SF-36 6 months – social fi 1. Hurskainen 2001 ⁹³ 8.1 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.81$ (p 7.4.7 SF-36 6 months – vitality 1. Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – pain 1. Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general here 1. Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita		104			103	100.0 %	-2.90 (-7.90 to 2.10)	
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. Hurskainen 2001^{93} 8.1 2 subtotal (95% CI) leterogeneity: not applicable east for overall effect: $z = 0.81$ (p .4.7 SF-36 6 months – vitality . Hurskainen 2001^{93} 6.3 2 subtotal (95% CI) leterogeneity: not applicable east for overall effect: $z = 1.88$ (p .4.8 SF-36 6 months – pain . Hurskainen 2001^{93} 11.9 2 subtotal (95% CI) leterogeneity: not applicable east for overall effect: $z = 1.96$ (p .4.9 SF-36 1 year – general here . Hurskainen 2001^{93} 5.5 1 subtotal (95% CI) leterogeneity: not applicable east for overall effect: $z = 0.27$ (p .4.10 SF-36 1 year – physical f . Hurskainen 2001^{93} 4.8 1 subtotal (95% CI) leterogeneity: not applicable east for overall effect: $z = 1.05$ (p .4.11 SF-36 1 year – role limita								
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deterogeneity: not applicable est for overall effect: $z = 0.81$ (p 2.4.7 SF-36 6 months – vitality Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) deterogeneity: not applicable est for overall effect: $z = 1.88$ (p 2.4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) deterogeneity: not applicable fest for overall effect: $z = 1.96$ (p 2.4.9 SF-36 1 year – general her . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) deterogeneity: not applicable fest for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical f . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) deterogeneity: not applicable fest for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical f . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) deterogeneity: not applicable fest for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita	20.2	106	10.3	19.1	104	100.0%	-2.20 (-9.19 to 4.79)	
Test for overall effect: $z = 0.81$ (p 2.4.7 SF-36 6 months – vitality . Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) leterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 2.4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) leterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 2.4.9 SF-36 1 year – general hea . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) leterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical fi . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita		106			104	100.0%	–2.20 (–7.52 to 3.12)	
4.7 SF-36 6 months – vitality . Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.88$ (p 4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.96$ (p 4.9 SF-36 1 year – general hea . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 0.27$ (p 4.10 SF-36 1 year – physical fr . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.05$ (p 4.11 SF-36 1 year – role limita	p = 0.	.42)						
. Hurskainen 2001 ⁹³ 6.3 2 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.88$ (p :.4.8 SF-36 6 months – pain . Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.96$ (p :.4.9 SF-36 1 year – general her . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 0.27$ (p :.4.10 SF-36 1 year – physical f . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable cest for overall effect: $z = 1.05$ (p :.4.11 SF-36 1 year – role limita		,						
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Heterogeneity: not applicable Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – pain 1. Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general her 1. Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical f 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita	23	105	12.2	22.2	103	100.0%	-5.90 (-13.97 to 2.17)	
Test for overall effect: $z = 1.88$ (p 7.4.8 SF-36 6 months – pain 1. Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general hea 1. Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical fi 1. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita		105			103	100.0%	-5.90 (-12.04 to 0.24)	
7.4.8 SF-36 6 months – pain Hurskainen 2001 ⁹³ 11.9 2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general her Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical f Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita	o = 0.	.06)						
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Test for overall effect: $z = 1.96$ (p 7.4.9 SF-36 1 year – general her . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical f . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita		105			103	100.0%	-6.80 (-13.61 to 0.01)	
2.4.9 SF-36 1 year – general her . Hurskainen 2001 ⁹³ 5.5 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical fr . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita	p = 0	05)						
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Subtotal (95% CI) leterogeneity: not applicable rest for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical fr . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable rest for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita								
Heterogeneity: not applicable Test for overall effect: $z = 0.27$ (p 2.4.10 SF-36 1 year – physical fr . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita	15.8	104	6.1	16.2	108	100.0%	-0.60 (-6.26 to 5.06)	
Test for overall effect: $z = 0.27$ (p 7.4.10 SF-36 1 year – physical f . Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.05$ (p 7.4.11 SF-36 1 year – role limita		104			108	100.0%	–0.60 (–4.91 to 3.71)	\bullet
2.4.10 SF-36 1 year – physical fr Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) Heterogeneity: not applicable est for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita	n = 0	78)						
. Hurskainen 2001 ⁹³ 4.8 1 Subtotal (95% CI) leterogeneity: not applicable est for overall effect: $z = 1.05$ (p	<u> </u>	,						
Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: <i>z</i> = 1.05 (<i>p</i> 2.4.11 SF-36 1 year – role limita								
leterogeneity: not applicable est for overall effect: <i>z</i> = 1.05 (<i>p</i> :.4.11 SF-36 1 year – role limita	15	102	7.1	16.8	107	100.0%	-2.30 (-7.97 to 3.37)	
est for overall effect: $z = 1.05$ (p 2.4.11 SF-36 1 year – role limita		102			107	100.0%	–2.30 (–6.61 to 2.01)	
.4.11 SF-36 1 year – role limita	n = 0	30)						
-	<u> </u>	55)						
. Hurskainen 200193 18.1 3			-					
	37.8	102	18.6	43.4	106	100.0%	-0.50 (-15.02 to 14.02)	
Subtotal (95% CI)		102			106	100.0%	–0.50 (–11.55 to 10.55)	
leterogeneity: not applicable est for overall effect: z = 0.09 (p	n – 0	93)						
est for overall effect. $z = 0.09$ (p	v = 0.	90)						
.4.12 SF-36 1 year – role limita	ation	(emotio	nal)					
	44	99	19.9	40.4	107	100.0%	-4.10 (-19.30 to 11.10)	
Subtotal (95% CI)		99			107	100.0%	-4.10 (-15.66 to 7.46)	
leterogeneity: not applicable		(0)						
test for overall effect: $z = 0.69$ (p	- ^	49)						
	p = 0							-20 -10 0 10 20

		Mirena		Hys	terecto	omy			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% Cl
.4.13 SF-36 1 year – . Hurskainen 2001 ⁹³ Subtotal (95% CI)	mental 8.1	health 18.5	102 102	8.4	17.3	108 108	100.0% 100.0%	–0.30 (–6.68 to 6.08) –0.30 (–5.15 to 4.55)	
eterogeneity: not app est for overall effect:		(p = 0.				100	10010 /0		
.4.14 SF-36 1 year – . Hurskainen 2001 ⁹³		unction 19.3	104	11	19.5	108	100.0%	–0.50 (–7.36 to 6.36)	
Subtotal (95% CI) leterogeneity: not app fest for overall effect:		(p = 0.	104 85)			108	100.0%	–0.50 (–5.72 to 4.72)	-
. 4.15 SF-36 1 year – . Hurskainen 2001 ⁹³		20.8	102	12.5	20.7	109	100.0%	–2.30 (–9.66 to 5.06)	
Subtotal (95% CI) leterogeneity: not app		20.0	102 102	12.5	20.7	109 109	100.0%	-2.30 (-7.90 to 3.30)	-
est for overall effect:		(p = 0.	42)						
7.4.16 SF-36 1 year – 1. Hurskainen 2001 ⁹³		25.1	103	21.4	26.3	107	100.0%	–9.60 (–18.74 to –0.46)	
Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:		(p = 0.	103 007)			107	100.0%	–9.60 (–16.55 to –2.65)	
.4.17 SF-36 5 years	– genera	al healt	ĥ						
1. Hurskainen 2001 ⁹³ Subtotal (95% CI) Heterogeneity: not app	3.3	19.1	110 110	4.6	18.2	112 112	100.0% 100.0%	–1.30 (–7.75 to 5.15) –1.30 (–6.21 to 3.61)	
Test for overall effect:		(<i>p</i> = 0.	60)						
7.4.18 SF-36 5 years	– physic 1.4	al func 18.8	tion 107	1.9	18.9	109	100.0%	–0.50 (–7.11 to 6.11)	
Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:		(p = 0.	107 85)			109	100.0%	–0.50 (–5.53 to 4.53)	Ŧ
7.4.19 SF-36 5 years	- role lii	nitatior	n (physi	cal)					
I. Hurskainen 2001 ⁹³ Subtotal (95% CI)	9.7	40	108 108	10.8	44.8	111 111	100.0% 100.0%	–1.10 (–15.87 to 13.67) –1.10 (–12.34 to 10.14)	
Heterogeneity: not app Test for overall effect:		(<i>p</i> = 0.	85)						
7.4.20 SF-36 5 years			•						
1. Hurskainen 2001 ⁹³ Subtotal (95% CI)	17	41.6	110 110	12.9	47.4	111 111	100.0% 100.0%	4.10 (–11.35 to 19.55) 4.10 (–7.66 to 15.86)	
Heterogeneity: not app Fest for overall effect:		(p = 0.	49)						
4.21 SF-36 5 years							100.00/		1
1. Hurskainen 2001 ⁹³ Subtotal (95% CI)	8.6	19.8	111 111	8.1	17	109 109	100.0% 100.0%	0.50 (–5.91 to 6.91) 0.50 (–4.37 to 5.37)	
Heterogeneity: not app Test for overall effect:		(<i>p</i> = 0.	84)						
7.4.22 SF-36 5 years				0	04.0		100.007		
1. Hurskainen 2001 ⁹³ Subtotal (95% CI)	7.9	21.8	112 112	8	21.6	112 112	100.0% 100.0%	–0.10 (–7.57 to 7.37) –0.10 (–5.78 to 5.58)	
Heterogeneity: not app Test for overall effect:		(p = 0.	97)						
7.4.23 SF-36 5 years	-			16	a		10		
. Hurskainen 2001 ⁹³ Subtotal (95% CI)	9.6	21.9	109 109	10	22.2	112 112	100.0% 100.0%	–0.40 (–8.04 to 7.24) –0.40 (–6.21 to 5.41)	
leterogeneity: not app est for overall effect:		(<i>p</i> = 0.	89)						
7.4.24 SF-36 5 years	-	05 -		40 -	oo -		100 551		
1. Hurskainen 2001 ⁹³ Subtotal (95% CI)		25.9	111 111	13.7	30.5	111 111	100.0% 100.0%	–0.60 (–10.38 to 9.18) –0.60 (–8.04 to 6.84)	
Heterogeneity: not app Fest for overall effect:		(p = 0.	87)						

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EQ-5D scores (absolute values)

		Mirena		Hys	Hysterectomy	'n			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
7.5.2 6 months 1. Hurskainen 2001 ⁹³ 0.85 0.21 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.65$ ($p = 0.10$)	0.85 licable z = 1.65	0.21 (<i>p</i> = 0.10	111 111 0)	0.89	0.14	103 103	100.0% 100.0 %	-0.04 (-0.10 to 0.02) - 0.04 (-0.09 to 0.01)	
7.5.3 1 year 1. Hurskainen 2001 ⁹³ 0.88 0.16 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.88$ ($p = 0.38$)	0.88 licable z = 0.88	0.16 (<i>p</i> = 0.38	104 104 8)	0.0	0.17	109 109	100.0% 100.0%	-0.02 (-0.08 to 0.04) - 0.02 (-0.06 to 0.02)	
7.5.4 5 years 1. Hurskainen 2001^{93} 0.84 0.23 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.09$ ($p = 0.28$)	0.84 licable z = 1.09	0.23 (<i>p</i> = 0.28	112 112 8)	0.87	0.18	112 112	100.0% 100.0%	-0.03 (-0.10 to 0.04) - 0.03 (-0.08 to 0.02)	
									–0.2 –0.1 0 0.1 0.2 Favours hysterectomy Favours Mirena

108 102 100 102 100.0% $z = 0.38$ ($p = 0.70$) $z = 0.38$ ($p = 0.70$) 0.07 0.16 101 0.07 0.08 100.0% 0.07 0.16 101 0.07 0.23 108 100.0% 0.07 0.16 101 0.07 0.23 108 100.0% $2 = 0.00$ ($p = 1.00$) $2 = 0.00$ $p = 1.00$ 0.05 0.23 111 100.0%	Study or subgroup 7.6.1 6 months	Mean	SD	Total	Mean 0.08	an SD T	Total	Weight 100.0%	Mean difference IV, Fixed, 99% CI -0.01 (-0.08 to 0.06)	Mean difference IV, Fixed, 99% CI	ference 99% CI
	ity: not appl. trall effect: <i>z</i> s en 2001 ⁹³	icable : = 0.00 (0.04	(<i>p</i> = 1.00 0.19	0) 109 109	0.05	0.23	2 = E	100.0%	-0.01 (-0.08 to 0.06) -0.01 (-0.07 to 0.05)		

EQ-5D scores (change from baseline)

Proportion discontinuing Mirena

Study or subgroup								
	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Fe Fe	Peto odds ratio Peto, Fixed, 99% CI
7.10.1 6 months								
I. Hurskainen 2001 ⁹³	0	119	22	117	100.0%	0.02 (0.00 to 0.75)	•	
Subtotal (95% CI)		119		117	100.0%	0.02 (0.00 to 0.31)		
Total events	0		22					
Heterogeneity: not applicable Test for overall affect: 7 - 2 78 (n - 0 005)	le 78 (n – 0 (105)						
		(000						
7.10.2 1 year								
1. Hurskainen 200193	0	119	37	117	100.0%	0.01 (0.00 to 0.37)	•	
Subtotal (95% CI)		119		117	100.0%	0.01 (0.00 to 0.15)		
Total events	0		37					
Heterogeneity: not applicable	le							
Test for overall effect: $z = 3.26$ ($p = 0.001$)	.26 (<i>p</i> = 0.0	(100						
7.10.3 5 years								
2001 ⁹³	0	119	60	117	100.0%	0.00 (0.00 to 0.17)	+	
Subtotal (95% CI)		119		117	100.0%	0.00 (0.00 to 0.07)		
Total events	0		60					
Heterogeneity: not applicable	le							
Test for overall effect: $z = 3.83$ ($p = 0.0001$)	.83 (<i>p</i> = 0.0	(1000						

Favours Mirena

Favours hysterectomy

	Mirena	ene	Hysterectomy	ctomy					
Study or subgroup	Events	Total	Events	Total	Weight	Odds ratio M–H, Fixed, 99% CI	M	Odds ratio M–H, Fixed, 99% CI	
7.13.1 6 months									
1. Hurskainen 2001 ⁹³	0	119	0	117	100.0%	20.20 (0.47 to 861.63)			
Subtotal (95% CI)		119		117	100.0%	20.20 (1.16 to 351.25)			1
Total events	ი		0						
Heterogeneity: not applicable	icable								
Test for overall effect: $z = 2.06$ ($p = 0.04$)	$r = 2.06 \ (p = 0.00)$.04)							
7.13.3 1 year									
1. Hurskainen 200193	24	119	0	117	100.0%	60.29 (1.50 to 2430.77)			Ť
Subtotal (95% CI)		119		117	100.0%	60.29 (3.62 to 1004.33)		T	Å
Total events	24		0						
Heterogeneity: not applicable	icable								
Test for overall effect: $z = 2.86$ ($\rho = 0.004$)	$c = 2.86 \ (p = 0)$.004)							
							0.001 0.1	-1-	1000
							Favours Mirena	ena Favours hysterectomy	sterectomy

Proportion requiring hysterectomy after Mirena

Number of patients with adverse events – periprocedure

Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto o Peto, Fix	Peto odds ratio Peto, Fixed, 99% Cl
7.14.1 Anaesthesia problems (hysterectomy) 1. Hurskainen 2001 ³³ 0 119 Subtotal (95% CI)	blems (hyster 0	ectomy) 119 119	0	117 117		Not estimable Not estimable		
Total events 0 Heterogeneity: not applicable Test for overall effect: not applicable	0 cable ot applicable	2	0	÷				
7.14.2 Excessive bleeding (hysterectomy) 1. Hurskainen 2001 ⁸³ 0 11 1. Letter 1. Andre 2001	ing (hysterect 0	tomy) 119	0	117		Not estimable		
Subucial (95% CJ) Total events 0 Heterogeneity: not applicable Test for overall effect: not applicable	0 cable or applicable	2	o	Ì				
7.14.3 Injury to surrounding organs (hysterectomy)	nding organs ((hysterecto	my)					
Subtotal (95% CI)	D	119	D	117	100.0%	0.13 (0.02 to 0.75)		
Total events 0 Heterogeneity: not applicable	0 cable		S					
Test for overall effect: $z = 2.27$ ($p = 0.02$)	= 2.27 (p = 0.1)	J2)						

Number of patients with adverse events – postoperatively (within 1 month)

	Mire	ena	Hystere	ctomy			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% Cl
.20.1 Urinary tract in	nfection (both)					
. Hurskainen 200193	0	119	0	117		Not estimable	
Subtotal (95% CI)		119		117		Not estimable	
Fotal events	0		0				
Heterogeneity: not ap			0				
Fest for overall effect:		cable					
7.20.2 Deep vein thro							
1. Hurskainen 200193	0	119	0	117		Not estimable	
Subtotal (95% CI)		119		117		Not estimable	
Total events	0		0				
Heterogeneity: not ap	olicable						
Test for overall effect:	not applie	cable					
00 0 E ussesius bla							
7.20.3 Excessive blee 1. Hurskainen 2001 ⁹³	o nys	119	my) 0	117		Not estimable	
	0		0				
Subtotal (95% CI)		119		117		Not estimable	
Total events	0		0				
Heterogeneity: not ap							
Test for overall effect:	not applie	cable					
7.20.4 Further bleedi	ng (hvste	rectomv)				
1. Hurskainen 200193	0	119	2	117	100.0%	0.13 (0.00 to 5.08)	
Subtotal (95% CI)	-	119	-	117	100.0%	0.13 (0.01 to 2.12)	
Total events	0	113	2		100.0 /0	0.10 (0.01 10 2.12)	
			2				
Heterogeneity: not ap							
Test for overall effect:	z = 1.43 (p = 0.15)				
7.20.5 Embolism (hys	terectom	v)					
1. Hurskainen 200193	0	119	0	117		Not estimable	
Subtotal (95% CI)		119		117		Not estimable	
Total events	0		0				
Heterogeneity: not ap			0				
Test for overall effect:		cable					
7.20.6 Abdominal pai							_
1. Hurskainen 200193	0	119	3	117	100.0%	0.13 (0.01 to 2.59)	
Subtotal (95% CI)		119		117	100.0%	0.13 (0.01 to 1.27)	
Total events	0		3				
Heterogeneity: not ap	olicable						
Test for overall effect:	z = 1.75 (p = 0.08	5)				
7.20.7 Uterine perfor	•	•	0	117		Not optimable	
1. Hurskainen 200193	0	119	0	117		Not estimable	
		119		117		Not estimable	
	-		0				
Subtotal (95% CI) Total events	0						
Total events Heterogeneity: not ap	olicable						I
Total events	olicable	cable					
Fotal events Heterogeneity: not ap Fest for overall effect:	olicable not applie	cable					
Total events Heterogeneity: not ap Test for overall effect: 7.20.8 Infection (Mire	olicable not applic na)		0	117	100.0%	7 52 (0 74 to 76 81)	
Fotal events Heterogeneity: not ap Test for overall effect: 7.20.8 Infection (Mire 1. Hurskainen 2001 ⁹³	olicable not applie	119	0	117 117	100.0%	7.52 (0.74 to 76.81)	
Total events Heterogeneity: not ap Test for overall effect: 7.20.8 Infection (Mire 1. Hurskainen 2001 ⁹³ Subtotal (95% CI)	olicable not applie na) 5			117 117	100.0% 100.0%	7.52 (0.74 to 76.81) 7.52 (1.28 to 44.07)	
Total events Heterogeneity: not ap Test for overall effect: 7.20.8 Infection (Mire 1. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events	olicable not applie na) 5	119	0 0				
Fotal events Heterogeneity: not app Fest for overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not app	not applio not applio na) 5 5 plicable	119 119	0				
Fotal events Heterogeneity: not applest For overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not applest	not applio not applio na) 5 5 plicable	119 119	0				
Fotal events Heterogeneity: not ap Fest for overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not ap Fest for overall effect:	blicable not applie na) 5 5 blicable z = 2.24 (119 119	0				
Fotal events Heterogeneity: not app Fest for overall effect: 7.20.8 Infection (Mire 1. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not app Fest for overall effect: 7.20.9 Migrated coil	blicable not applie na) 5 5 blicable z = 2.24 (119 119	0				
Fotal events Heterogeneity: not app Fest for overall effect: 7.20.8 Infection (Mire 1. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not app Fest for overall effect: 7.20.9 Migrated coil 1. Hurskainen 2001 ⁹³	not applio not applio na) 5 5 blicable z = 2.24 (Mirena)	119 119 (<i>p</i> = 0.03	0	117 117		7.52 (1.28 to 44.07)	
Fotal events Heterogeneity: not app Fest for overall effect: 7.20.8 Infection (Mire 1. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not app Fest for overall effect: 7.20.9 Migrated coil 1. Hurskainen 2001 ⁹³ Subtotal (95% CI)	Dicable not applic na) 5 5 Dicable z = 2.24 (Mirena) 0	119 119 <i>(p</i> = 0.03) 119	0 ;) 0	117		7.52 (1.28 to 44.07) Not estimable	
Fotal events Heterogeneity: not app Test for overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events Heterogeneity: not app Test for overall effect: 7.20.9 Migrated coil I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Fotal events	blicable not applie rational point (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	119 119 <i>(p</i> = 0.03) 119	0	117 117		7.52 (1.28 to 44.07) Not estimable	
Total events Heterogeneity: not applest Fest for overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events Heterogeneity: not applest for overall effect: 7.20.9 Migrated coil I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events Heterogeneity: not applest for applest for applest for a point of the subtotal (95% CI)	blicable not applie rational point (applie) $5blicablez = 2.24$ (Mirena) 0 blicable	119 119 (<i>p</i> = 0.03 119 119	0 ;) 0	117 117		7.52 (1.28 to 44.07) Not estimable	
Total events Heterogeneity: not applest Fest for overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events Heterogeneity: not applest for overall effect: 7.20.9 Migrated coil I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events Heterogeneity: not applest for applest for applest for a point of the subtotal (95% CI)	blicable not applie rational point (applie) $5blicablez = 2.24$ (Mirena) 0 blicable	119 119 (<i>p</i> = 0.03 119 119	0 ;) 0	117 117		7.52 (1.28 to 44.07) Not estimable	
Total events Heterogeneity: not applest for overall effect: 7.20.8 Infection (Mire I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events Heterogeneity: not applest for overall effect: 7.20.9 Migrated coil I. Hurskainen 2001 ⁹³ Subtotal (95% CI) Total events	blicable not applie rational point (applie) $5blicablez = 2.24$ (Mirena) 0 blicable	119 119 (<i>p</i> = 0.03 119 119	0 ;) 0	117 117		7.52 (1.28 to 44.07) Not estimable	

	Mire	ena	Hystere	ctomy							
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl			o odds ra Fixed, 99		
7.20.10 Pyrexia (hyst	erectomy)									
1. Hurskainen 200193	0	119	2	117	100.0%	0.13 (0.00 to 5.08)					
Subtotal (95% CI)		119		117	100.0%	0.13 (0.01 to 2.12)					
Total events	0		2								
Heterogeneity: not ap	plicable										
Test for overall effect:	•	(p = 0.15	5)								
7.20.11 Failed to inse	ert										
1. Hurskainen 200193	2	119	0	117	100.0%	7.33 (0.19 to 282.12)					→
Subtotal (95% CI)		119		117	100.0%	7.33 (0.46 to 117.86)					
Total events	2		0			. ,					
Heterogeneity: not ap	plicable										
Test for overall effect:	•	(p = 0.16	6)								
7.20.12 Removed (be	fore 3 m	onths)									
1. Hurskainen 2001 ⁹³	10	119	0	117	100.0%	7.86 (1.49 to 41.41)			_		_
Subtotal (95% CI)		119		117	100.0%	7.86 (2.22 to 27.83)					
Total events	10		0			. ,					
Heterogeneity: not ap	plicable										
Test for overall effect:	•	(p = 0.00)	01)								
			-								
							0.01	0.1	1	10	100
							Fa	avours Miren	а	Favours hys	sterectomy

Appendix 6

Pooled results for first-versus secondgeneration endometrial ablation

Appendix 6.1 Baseline characteristics, quality of life and clinical outcome

	Time point	Trials (no.)	WMD (95% CI)ª	OR (95% CI)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
Proportion amenorrhoea	6 months	5 (736)	_	1.16 (0.81 to 1.66)	0.4	0.09/50
	12 months	13 (2180)	_	1.12 (0.93 to 1.35)	0.3	< 0.0001/74
	2 years	2 (370)	_	0.64 (0.41 to 0.99)	0.04	0.2/36
	3 years	1 (111)	_	0.24 (0.11 to 0.50)	0.0002	_
	5 years	1 (236)	-	1.19 (0.70 to 2.05)	0.5	_
	10 years	1 (189)	-	1.56 (0.69 to 3.51)	0.3	_
Proportion with heavy bleeding	6 months	5 (736)	-	1.33 (0.92 to 1.93)	0.1	0.5/0
	12 months	13 (2180)	_	0.97 (0.74 to 1.28)	0.9	0.8/0
	2 years	2 (370)	_	0.54 (0.30 to 0.97)	0.04	0.8/0
	3 years	1 (111)	-	0.58 (0.14 to 2.41)	0.5	_
	5 years	1 (266)	-	1.05 (0.30 to 3.70)	0.9	_
Bleeding score (change)	6 months	6 (1001)	-2 (-49 to 45)	-	0.9	0.2/33
	12 months	9 (1778)	-10 (-37 to 17)	_	0.5	0.009/61
	2 years	1 121)	6 (-122 to 134)	_	0.9	_
Proportion dysmenorrhoea	6 months	4 (562)	_	0.95 (0.64 to 1.41)	0.8	0.4/0
	12 months	8 (1548)	_	0.84 (0.67 to 1.07)	0.2	0.5/0
	2 years	2 (475)	_	0.95 (0.62 to 1.46)	0.8	0.3/0
	3 years	1 (212)	_	0.91 (0.47 to 1.76)	0.8	_
	5 years	1 (266)	_	1.05 (0.48 to 2.30)	0.9	_
Duration surgery (minutes)		11 (1911)	-15 (-15 to -14)	_	< 0.0001	< 0.0001/96
General anaesthesia		8 (1597)	_	0.16 (0.12 to 0.20)	< 0.0001	< 0.0001/86
Surgery pain score (0–10)		5 (342)	0.05 (-0.17 to 0.27)	_	0.7	< 0.0001/89
Return to work (days)		2 (116)	-1.4 (-2.0 to -0.7)	_	< 0.0001	0.3/10
Return normal activities (days)		5 (901)	–0.48 (–0.75 to –0.20)	-	0.0008	0.04/59
Proportion dyspareunia	6 months	2 (106)	_	1.09 (0.27 to 4.41)	0.9	_
	12 months	3 (330)	_	0.89 (0.46 to 1.73)	0.7	0.2/32
	2 years	1 (247)	_	0.95 (0.46 to 1.96)	0.9	_
	5 years	1 (218)	_	0.40 (0.18 to 0.93)	0.03	_
SF-36 general health (absolute)	6 months	1 (265)	0.6 (-3.5 to 4.7)	_	0.8	_
SF-36 physical function (absolute)		1 (267)	3.0 (-0.6 to 6.6)	_	0.1	_
SF-36 role physical (absolute)		1 (273)	3.3 (-3.1 to 9.7)	_	0.3	_
SF-36 role emotional (absolute)		1 (271)	3.3 (-4.0 to 10.6)	_	0.4	_
SF-36 mental health (absolute)		1 (269)	0.8 (-3.5 to 5.1)	_	0.7	_
SF-36 social function (absolute)		1 (257)	0.6 (-2.8 to 4.0)	_	0.7	_
SF-36 vitality (absolute)		1 (269)	0.6 (-4.6 to 5.8)	_	0.8	_
SF-36 pain (absolute)		1 (269)	0.7 (-4.6 to 6.0)	_	0.8	_

continued

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95% CI)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%
SF-36 general health (absolute)	12 months	2 (522)	-1.5 (-4.5 to 1.4)	_	0.3	0.7/0
SF-36 physical function (absolute)		2 (519)	-0.4 (-3.6 to 2.7)	_	0.8	0.9/0
SF-36 role physical (absolute)		2 (512)	-5.8 (-11.0 to -0.6)	-	0.03	0.7/0
SF-36 role emotional (absolute)		2 (521)	-2.2 (-7.5 to 3.2)	_	0.4	0.7/0
SF-36 mental health (absolute)		2 (521)	-1.5 (-4.8 to 1.9)	_	0.4	0.8/0
SF-36 social function (absolute)		2 (512)	-1.0 (-3.9 to 1.9)	_	0.5	0.3/25
SF-36 vitality (absolute)		2 (521)	-3.1 (-7.0 to 0.9)	_	0.1	0.7/0
SF-36 pain (absolute)		2 (522)	0.7 (-3.6 to 4.9)	-	0.8	0.9/0
SF-36 general health (absolute)	2 years	1 (249)	0.3 (–5.9 to 6.5)	_	0.9	_
SF-36 physical function (absolute)		1 (249)	-2.4 (-8.1 to 3.3)	_	0.4	_
SF-36 role physical (absolute)		1 (249)	-3.9 (-13.9 to 6.1)	_	0.5	_
SF-36 role emotional (absolute)		1 (249)	-5.6 (-15.4 to 4.2)	_	0.3	_
SF-36 mental health (absolute)		1 (249)	-1.3 (-6.5 to 3.9)	_	0.6	_
SF-36 social function (absolute)		1 (249)	-3.2 (-9.2 to 2.8)	_	0.3	_
SF-36 vitality (absolute)		1 (249)	0.4 (-5.5 to 6.3)	_	0.9	_
SF-36 pain (absolute)		1 (249)	-2.0 (-9.1 to 5.1)	_	0.6	_
SF-36 general health (absolute)	5 years	1 (235)	2.8 (-3.6 to 9.2)	_	0.4	_
SF-36 physical function (absolute)	,	1 (232)	-2.2 (-8.7 to 4.3)	_	0.5	_
SF-36 role physical (absolute)		1 (232)	1.3 (-8.8 to 11.4)	_	0.8	_
SF-36 role emotional (absolute)		1 (234)	2.7 (-6.4 to 11.8)	_	0.6	_
SF-36 mental health (absolute)		1 (235)	0.3 (-4.9 to 5.5)	_	0.9	_
SF-36 social function (absolute)		1 (235)	1.6 (-4.7 to 7.9)	_	0.6	_
SF-36 vitality (absolute)		1 (234)	0.0 (-6.3 to 6.3)	_	1.0	_
SF-36 pain (absolute)		1 (235)	2.6 (-4.6 to 9.8)	_	0.5	_
SF-36 general health (change)	6 months	1 (259)	-1.3 (-5.5 to 2.9)	_	0.5	_
SF-36 physical function (change)	0 11011113	1 (259)	3.0 (-2.6 to 8.6)	_	0.3	_
SF-36 role physical (change)		1 (264)	7.6 (-4.2 to 19.4)	_	0.2	_
SF-36 role emotional (change)		1 (264)	3.9 (-6.5 to 14.3)		0.2	_
SF-36 mental health (change)		1 (261)	-1.2 (-6.0 to 3.6)	_	0.6	_
SF-36 social function (change)		1 (230)	1.4 (-4.1 to 6.9)	_	0.6	_
		1 (230)	2.8 (-3.1 to 8.7)	_	0.0	_
SF-36 vitality (change)				_	0.4	_
SF-36 pain (change)	10 months	1 (261)	4.5 (-3.3 to 12.3)	_		-
SF-36 general health (change)	12 months	2 (515)	-3.4 (-6.3 to -0.6)	-	0.02	0.6/0
SF-36 physical function (change)		2 (504)	1.0 (-2.6 to 4.6)	-	0.6	0.6/0
SF-36 role physical (change)		2 (512)	-7.0 (-15.2 to 1.2)	-	0.09	0.04/75
SF-36 role emotional (change)		2 (513)	-0.8 (-9.0 to 7.6)	_	0.9	0.3/0
SF-36 mental health (change)		2 (512)	-2.0 (-5.6 to 1.6)	_	0.3	0.6/0
SF-36 social function (change)		2 (478)	-2.1 (-6.1 to 1.9)	_	0.3	0.2/31
SF-36 vitality (change)		2 (511)	-1.2 (-5.3 to 2.9)	_	0.6	0.9/0
SF-36 pain (change)		2 (512)	-2.1 (-7.7 to 3.6)	_	0.5	0.03/78
SF-36 general health (change)	2 years	1 (249)	-1.9 (-7.4 to 3.6)	_	0.5	_
SF-36 physical function (change)		1 (244)	-1.3 (-6.5 to 3.9)	-	0.6	-
SF-36 role physical (change)		1 (249)	–12.3 (–24.5 to –0.1)	-	0.05	_
SF-36 role emotional (change)		1 (249)	-8.2 (-17.1 to 0.7)	_	0.07	-
SF-36 mental health (change)		1 (248)	-1.8 (-6.9 to 3.3)	_	0.5	-
SF-36 social function (change)		1 (248)	-4.2 (-10.6 to 2.2)	_	0.2	_
SF-36 vitality (change)		1 (248)	0.5 (-5.4 to 6.4)	_	0.9	-
SF-36 pain (change)		1 (249)	-10.8 (-18.6 to -3.0)	-	0.007	_

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95% CI) ^b	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
SF-36 general health (change)	5 years	1 (235)	1.3 (-4.4 to 7.0)	_	0.7	_
SF-36 physical function (change)		1 (228)	-0.7 (-6.5 to 5.1)	_	0.8	_
SF-36 role physical (change)		1 (232)	-6.5 (-19.0 to 6.0)	_	0.3	_
SF-36 role emotional (change)		1 (234)	1.7 (-9.7 to 13.1)	_	0.8	_
SF-36 mental health (change)		1 (234)	0.4 (-5.5 to 6.3)	_	0.9	_
SF-36 social function (change)		1 (234)	0.8 (-6.0 to 7.6)	_	0.8	_
SF-36 vitality (change)		1 (233)	1.9 (-5.0 to 8.8)	_	0.6	_
SF-36 pain (change)		1 (235)	-4.1 (-12.7 to 4.5)	_	0.4	_
SF-36 general health (change)	10 years	1 (189)	1.9 (-4.5 to 8.3)	_	0.6	_
SF-36 physical function (change)		1 (189)	1.4 (-6.0 to 8.8)	_	0.7	_
SF-36 role physical (change)		1 (189)	-4.1 (-18.4 to 10.2)	_	0.6	_
SF-36 role emotional (change)		1 (189)	-7.6 (-21.4 to 6.2)	_	0.3	_
SF-36 mental health (change)		1 (189)	0.7 (-5.9 to 7.3)	_	0.8	_
SF-36 social function (change)		1 (189)	-0.2 (-8.2 to 7.8)	_	1.0	_
SF-36 vitality (change)		1 (189)	2.4 (-5.6 to 10.4)	_	0.6	_
SF-36 pain (change)		1 (189)	0.7 (-9.6 to 11.0)	_	0.9	_
EQ-5D (absolute)	6 months	1 (68)	0.00 (-0.12 to 0.12)	_	1.0	_
. ,	12 months	1 (61)	–0.03 (–0.15 to 0.09)	_	0.6	-
EQ-5D (change)	6 months	1 (66)	0.13 (-0.01 to 0.27)	_	0.08	_
	12 months	1 (60)	0.08 (-0.06 to 0.22)	_	0.3	_
Repeat EA	12 months	6 (1469)	-	0.71 (0.17 to 2.94)	0.6	0.4/0
	2 years	3 (677)	-	0.76 (0.16 to 3.63)	0.7	0.3/0
	3 years	1 (275)	-	5.11 (0.24 to 107)	0.3	_
	5 years	1 (263)	-	0.20 (0.01 to 4.30)	0.3	_
	10 years	1 (263)	-	0.34 (0.04 to 3.32)	0.4	
Hysterectomy after EA	6 months	1 (63)	-	0.56 (0.11 to 2.75)	0.5	_
	12 months	11 (2265)	-	0.77 (0.47 to 1.24)	0.3	1.0/0
	2 years	4 (939)	-	0.68 (0.41 to 1.13)	0.1	0.4/0
	3 years	1 (275)	-	0.48 (0.19 to 1.22)	0.1	_
	5 years	1 (266)	-	0.58 (0.31 to 1.06)	0.08	_
	10 years	1 (263)	-	0.52 (0.29 to 0.94)	0.03	-
		Trials	Frequency			
Repeat EA (overall)	12 months	6	8/1469 (<1%)			
	2 years	3	7/677 (1%)			
	3 years	1	2/275 (1%)			
	5 years	1	2/263 (1%)			
	10 years	1	4/263 (2%)			
Hysterectomy after EA (overall)	6 months	1	7/63 (11%)			
	12 months	11	74/2265 (3%)			
	2 years	4	71/939 (8%)			
	3 years	1	21/275 (8%)			
	5 years	1	55/266 (21%)			
	10 years	1	60/263 (23%)			

	- ···	Frequency (first- generation: max. 1017; second-generation:	00 (050) 000		
	Trials	max. 1467)	OR (95% CI) ^a	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
Periprocedure complications					
Anaesthesia problems	14	0; 2	4.40 (0.23 to 85.1)	0.3	1.0/0
Excessive bleeding	14	8; 0	0.14 (0.03 to 0.55)	0.005	1.0/0
Uterine perforation	14	12; 3	0.20 (0.07 to 0.57)	0.003	0.3/12
Fluid overload	14	14; 0	0.12 (0.04 to 0.36)	0.0001	1.0/0
Visceral damage	14	0; 2	4.40 (0.23 to 85.8)	0.3	_
Cervical laceration	14	15; 2	0.12 (0.05 to 0.33)	< 0.0001	0.9/0
Procedure abandoned	14	7; 16	1.58 (0.67 to 3.72)	0.3	0.3/14
Converted to hysterectomy	14	3; 1	0.38 (0.05 to 2.73)	0.3	0.3/1
Further complications (<1 month)					
Urinary tract infection	14	12; 19	0.90 (0.42 to 1.90)	0.8	0.6/0
Deep-vein thrombosis	14	0; 0	-	_	_
Further bleeding	14	3; 5	1.17 (0.28 to 4.92)	0.8	0.07/57
Sepsis	14	0; 0	-	_	_
Pyrexia	14	1; 3	1.88 (0.25 to 14.2)	0.5	0.4/0
Endometriosis	14	9; 19	1.47 (0.68 to 3.18)	0.3	0.4/10
Haematomata	14	11; 5	0.26 (0.09 to 0.72)	0.01	0.8/0
Abdominal pain	14	34; 31	0.43 (0.26 to 0.74)	0.002	0.009/67
Foul discharge	14	1; 1	0.56 (0.03 to 9.94)	0.7	0.2/47
Visceral damage	14	0; 0	-	_	_

 $\begin{array}{ll} a & <0 \mbox{ favours second-generation EA}, >0 \mbox{ favours first-generation EA}. \\ b & <1 \mbox{ favours second-generation EA}, >1 \mbox{ favours first-generation EA}. \end{array}$

Appendix 6.2 First- versus second-generation endometrial ablation

		FIRST generation	eration			-		
1 1 1 2 2 1 4 2 2 2 3	Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% CI
Term Action 1 2 <th2< th=""> 2 <th2< th=""> 2 <th2< th=""> <th2<< td=""><td>1.1.1 <12 months</td><td>c</td><td>Ļ</td><td></td><td>ç</td><td></td><td></td><td></td></th2<<></th2<></th2<></th2<>	1.1.1 <12 months	c	Ļ		ç			
Norwar Topola 0 5 5 7 4.0% 0.00 Corrent 2001 ¹⁸ 31 120 11 422 40.06 114 Corrent 2001 ¹⁸ 31 120 114 422 100.06 114 Reverts anomina 5 17 19 125 33.4% 110 Reverts anomina 5 17 19 125 33.4% 110 Reverts anomina 5 17 19 125 33.4% 100 33.4% 113 33.4% 113.4% 100 </td <td></td> <td>12 ~</td> <td>27</td> <td>15 4</td> <td>31 20</td> <td>4.2% 12.2%</td> <td>0.86 (0.22 to 3.29)</td> <td></td>		12 ~	27	15 4	31 20	4.2% 12.2%	0.86 (0.22 to 3.29)	
Move 100 ¹⁰ 35 24 71 180 74 180 74.2% 110 Mover 100 ¹⁰ 31 304 114 422 345.9% 113 Mover 100 ¹⁰ 5 7 114 422 345.9% 113 Mover 100 ¹⁰ 5 17 114 422 345.9% 113 Mover 200 ¹⁰ 5 114 23 345.9% 114 23 345.9% 113 Bur 200 ¹⁰ 5 5 11 11 30 2.3% 0.33 Bur 200 ¹⁰ 4 11 25 34 113 2.3% 0.33 Bur 200 ¹⁰ 4 4 2 4 113 2.3% 0.33 Corpore 200 ¹⁰ 4 4 114 4 112 113% 0.3% Systal 200 ¹⁰ 4 12 12 12 12 12 12 12 12 12 12 12 12 1		0	58	5	76	4.0%	0.16 (0.02 to 1.72)	
Answer Constrained (e) Constrained (e) <thconstrained (e)<="" th=""> Constrained (e)<td>i. Corson 2001</td><td>35</td><td>120 120</td><td>71</td><td>180</td><td>46.2%</td><td>1.10 (0.55 to 2.19)</td><td></td></thconstrained>	i. Corson 2001	35	120 120	71	180	46.2%	1.10 (0.55 to 2.19)	
114 114 acogenerity: $\frac{1}{2}$, $\frac{7}{3}$, $\frac{1}{3}$, $\frac{1}{$	Subtotal (95% CI)	5	304	2	432	100.0%	1.16 (0.81 to 1.66)	•
Total constraint Total constraint <thtotal constraint<="" th=""> <thtotal <="" constraint<="" td=""><td>Total events Heterogeneity: $\chi^2 = 7.97$, df = 4 (ρ Tast for overall effect: $z = 0.82$ (ρ</td><td>8 🔍</td><td></td><td>114</td><td></td><td></td><td></td><td>,</td></thtotal></thtotal>	Total events Heterogeneity: $\chi^2 = 7.97$, df = 4 (ρ Tast for overall effect: $z = 0.82$ (ρ	8 🔍		114				,
Durn 2006 ¹⁰ 5 17 11 30 2.3% 0.73 Cooper 2004 ¹⁰ 14 5 14 55 35 55 35 65 63% 0.33 Vertue 2003 ¹⁰ 14 55 55 13 96 112 111.6% 113.0% 0.33 Vertue 2003 ¹⁰ 23 83 55 112 111.6% 113.0% 0.32% 111.7% 0.32% 111.7% 0.32% 111.7% 0.32% 111.7% 0.32%	1.1.2 12 months							
$ \begin{array}{ccccc} \mbox Coold & 49 & 96 & 120 & 194 & 14.2\% & 0.04 \\ \mbox Cooper 2003 & 40 & 72 & 3.33 & 0.124 \\ \mbox Cooper 2003 & 40 & 72 & 3.33 & 0.33 & 0.33 \\ \mbox Cooper 2003 & 40 & 72 & 3.33 & 0.33 & 0.33 \\ \mbox Cooper 2003 & 40 & 122 & 11.8\% & 1.126 & 1.126\% & 1.127 \\ \mbox Cooper 2003 & 200 & 32 & 74 & 5.5 & 6.5 & 1.72 & 0.36 \\ \mbox Cooper 2003 & 22 & 98 & 6.5 & 1.72 & 0.33 & 0$		5	17	11	30	2.3%	(0.14	
$ \begin{array}{c cccc} Control con$		49	96 11	120	194	14.2%	0.33	1
Have 2000 Total action T		41	22 22	35 2	56 156	6.3%	(0.08 14 E6	
win Zin-Rebealthy 2001*6 $\frac{1}{2}$ 55 116 2130% 2132% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2130% 2132		13 0	28	10	30	3.2%	0.43	
Cooper 2002 ⁶⁶ 29 82 65 175 116.66		5 4	55	9	74	2.1%	0.16	
Corsen 2001% 43 65 172 125% 113 Corsen 2001% 38 112 44 112 1125% 118% 113 Corsen 2000% 38 112 48 112 45 1125 113% 113 Corsen 2000% 33 112 4 112 113% 118% 118% 118% 118% 118% 118% 118% 113% 006 066 232.26% 036 006 066 232.26% 038 016 016% 016 006 016 016 006 016 016 006 016 016 006 016 016 006 016<		29	82	63	154	11.6%	0.39	+
Solution a b b correct 1995* 1.18 1.18 1.13		43	83	65 r	172	12.5%	(0.88	
Constribution 33 112 33 112 113 <t< td=""><td></td><td>80 00</td><td>48</td><td>0 0 0</td><td>45 50</td><td>2.6%</td><td>0.34</td><td></td></t<>		80 00	48	0 0 0	45 50	2.6%	0.34	
Model function 32 117 13 120 121 100 111 100 111 100 111 100 111 100 111 100 111 100 111 100 111 100 111 100 00% 213 2100 213 2100 213 2100 213 2100 211 100 00% 213 2100 211 100 00% 213 2100 211 2100 211 2100 211 2100 211 2100 213 2100 211 211 2100 213 214 2100 213 </td <td></td> <td>90</td> <td>194</td> <td>90</td> <td>116</td> <td>13.0%</td> <td></td> <td></td>		90	194	90	116	13.0%		
Romer 1998 ⁴ 3 10 1.1% 0.06 all events 327 899 464 1281 100.0% 1.1% 0.06 all events 327 327 899 464 1281 100.0% 0.13 all events 327 327 899 464 121 0.00001; $F = 74\%$ 0.01 all events 32 years 55 17 66 23.2% 0.38 3 2 years 52 128 58 127 66 20.0% 0.74 an Zon-Habelink 2001* 6 55 128 58 0.74 0.03 an Zon-Habelink 2001* 5 5 128 58 0.75 0.38 an Zon-Habelink 2001* 5 5 138 75 187 100.0% 0.24 an Zon-Habelink 2001* 5 5 138 75 138 0.24 al events al events 5 138 75 138 0.24 <tr< td=""><td></td><td>32</td><td>117</td><td>18</td><td>122</td><td>%0°6</td><td>6.0</td><td>-</td></tr<>		32	117	18	122	%0°6	6.0	-
46.99, df = 12 ($p < 0.00001$); $f = 74\%$ 464 1.281 100.0% 1.13 ct: $z = 1.16$ ($p = 0.25$) 55 17 66 23.2% 0.38 $z = 2.01$ 52 128 55 17 66 23.2% 0.38 $z = 2.01$ ($p = 0.21$); $f = 36\%$ 55 183 75 187 100.0% 0.24 $z = 2.01$ ($p = 0.21$); $f = 36\%$ 13 55 33 56 100.0% 0.24 $z = 2.01$ ($p = 0.21$); $f = 36\%$ 13 55 33 56 100.0% 0.24 $z = 2.01$ ($p = 0.04$) 13 55 33 56 100.0% 0.24 $z = 2.3.76$ ($p = 0.0002$) 13 55 33 56 100.0% 0.24 $z = 2.3.76$ ($p = 0.0002$) 13 55 33 56 100.0% 0.24 $z = 3.76$ ($p = 0.0002$) 82 119 76 117 100.0% 1.19 $z = 2.054$ ($p = 0.52$) 82 76 117 100.0% 1.19 1.16 $z = 0.64$ ($p = 0.52$) 82 76 94 10	n. Romer 1998 ⁹⁷	з	10	4	10	1.1%	0.06	
46.99, df = 12 ($p < 0.337$ / ct $z = 1.16$ ($p = 0.25$) $z 201^{45}$ = $5 = 55$ = 17 = 66 = 23.2% = 0.38 = 128 = 58 = 128 = 58 = 128 = 58 = 121 = 76.8\% = 0.14 = 1.56 = 0.04) ct $z = 2.01$ ($p = 0.04$) = 13 = 55 = 33 = 55 = 13 = 55 = $100.0\% = 0.24 = 13$ = 13 = 55 = 33 = 55 = $100.0\% = 0.24 = 0.24$ = 13 = 55 = 33 = 55 = 117 = $100.0\% = 0.24 = 0.24$ = $100.0\% = 0.24 = 0.24$ = 119 = 76 = 117 = $100.0\% = 0.24 = 0.26$ = $100.0\% = 0.24 = 0.26$ = $100.0\% = 0.24 = 0.26$ = $100.0\% = 0.24 = 0.26$ = 119 = 76 = 117 = $100.0\% = 1.19$ = 1.16 = 0.24 = 0.26 = 110 = 0.26 = 110 = 0.26 = 110 = 0.00 = 110 = 0.00 = 0.24 = 0.000 = 0.24 = 0.24 = 0.26 = 0.000 = 0.24 = 0.000 = 0.24 = 0.000 = 0.24 = 0.24 = 0.000 = 0.24 = 0.000 = 0.24 = 0.000 = 0.24 = 0.000 = 0.24 = 0.000 = 0.24 = 0.000 = 0.24 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.000 = 0.0000 = 0.000 = 0.000 = 0.000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.00000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.0000 = 0.00000 = 0.0000 = 0.00000 = 0.00000 = 0.00000 = 0.00000 = 0.000000 = 0.00000 = 0.00000000 = 0.000000000 = 0.0000000000000000000	Subtotal (95% CI)	100	899		1281	100.0%	(0.93	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	I otal events Heterogeneity: $\chi^2 = 46.99$, df = 12 Test for overall effect: $z = 1.16$ (p :	327 (<i>p</i> < 0.00001); <i>f</i> ² = 74 ⁹ = 0.25)	%	464				
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.1.3 2 years	c	L	1	ŝ			
1.56. df = 1 ($p = 0.21$); $f^{\pm} = 38\%$ 183 75 187 100.0% 0.64 ct: $z = 2.01$ ($p = 0.04$); $f^{\pm} = 38\%$ 13 55 33 56 100.0% 0.24 applicable 13 55 33 56 100.0% 0.24 applicable 13 55 33 56 100.0% 0.24 ct: $z = 3.76$ ($p = 0.0002$) 119 76 117 100.0% 1.19 applicable 82 119 76 117 100.0% 1.19 applicable 82 119 76 117 100.0% 1.19 applicable 82 76 117 100.0% 1.19 ct: $z = 0.64$ ($p = 0.52$) 84 95 78 94 100.0% 1.56 applicable 84 95 78 94 100.0% 1.56	I. Cooper 199954	52 52	128	58	121	76.8%	0.30 (0.12 (0 1.27) 0.74 (0.39 to 1.44)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Subtotal (95% CI)	c L	183	ł	187	100.0%	0.64 (0.41 to 0.99)	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Lotal events Heterogeneity: $\chi^2 = 1.56$, df = 1 (<i>p</i> Test for overall effect: $z = 2.01$ (<i>p</i>			<u>ور</u>				
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1.1.4 3 years	6	22	33	95			
13 33 applicable 13 ct: $z = 3.76$ ($p = 0.0002$) 82 119 76 117 119 76 applicable 76 applicable 76 applicable 76 applicable 95 ct: $z = 0.64$ ($p = 0.52$) 84 95 78 94 applicable 64 100.0% 156 78 94 100.0% 156 78 94 100.0% 156 78 94 100.0% 156	Subtotal (95% CI)	2	22	20	20 20	100.0%	0.24 (0.11 to 0.50)	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Total events Heterogeneity: not applicable Test for overall effect: $z = 3.76$ (p	13 = 0.0002)		33				
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1.1.5 5 years	C	0	01	1	700 001		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Subtotal (95% CI)	70	119	07	117	100.0 %	1.19 (0.39 (0.2.43) 1.19 (0.70 to 2.05)	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Total events Heteroreneity: not annlicable	82		76				
84 95 78 94 100.0% 95 78 94 100.0% 84 78 94 100.0%	Test for overall effect: $z = 0.64$ (p	= 0.52)						
84 95 94 100.0% 7 (<i>p</i> = 0.29)	1.1.6 10 years I. Cooper 1999 ⁵⁴	84	95	78	94	100.0%	1.56 (0.53 to 4.53)	
7 (p = 0.29)	Subtotal (95% CI)	84	95	78	94	100.0%	1.56 (0.69 to 3.51)	•
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Peto, Fixed, 39% CI Peto, Fixed, 39% CI	up Fronts Total Fronts Total Meight Proto, Fract, 196% C1 n 2 <td< th=""><th>up s r_{10}^{10} 2001⁸⁵ r_{10}^{10} 1) r_{10}^{10} = 3.37, df = 4 (p = 0.1 fect: z = 1.50 (p = 0.1</th><th>ents 6 111 11</th><th>Total</th><th>Events</th><th>Total</th><th>Weight</th><th>Peto. Fixed, 99% CI</th><th>Peto, Fixed, 99% CI</th></td<>	up s r_{10}^{10} 2001 ⁸⁵ r_{10}^{10} 1) r_{10}^{10} = 3.37, df = 4 (p = 0.1 fect: z = 1.50 (p = 0.1	ents 6 111 11	Total	Events	Total	Weight	Peto. Fixed, 99% CI	Peto, Fixed, 99% CI
attemp	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	2.2 <12 months Brun 2006 ¹⁰³ Hawe 2003 ⁴⁴ van Zon-Rabelink 2001 ³⁶ Corson 2001 ³⁶ Meyer 1998 ³⁵ Meyer 1998 ³⁵ Lotal (95% CJ) at events at events at events at for overall effect: $z = 1.50$ ($p = 0.13$) saf for overall effect: $z = 1.50$ ($p = 0.13$)	24 11 11 12 1				,		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Brun 2006 ¹⁰³ Hawe 2003 ⁹⁴⁵ van Zon-Rabelink 2001 ⁹⁵⁵ Corson 2001 ¹³⁸ Meyer 1998 ⁵⁵³ Meyer 1998 ⁵⁵³ Latevents tal events tal events tal events tal reproverall effect: $z = 1.50$ ($p = 0.13$) st for overall effect: $z = 1.50$ ($p = 0.13$)	2 5 2 5 6 11 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5						
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Have 2003^{44} van $20n-Babelink 2001^{95}$ Corson 2001^{70} Meyer 1998 ⁵³ bibtotal (95% CI) bibtotal (95% CI) bibtotal (95% CI) bibtotal (95% CI) bibtotal (98% CI) bibtotal (18% CI) bibt	24 11	15	4	20	6.5%	0.39 (0.06 to 2.63)	•
$ \begin{array}{c ccccc} & 24 & 51 & 52 & 52 & 53 & 75 & 23050 & 146 & 106 & 0.345 \\ \hline 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	van Zon-Rabelink 2001 ⁹⁵ Corson 2001 ⁷⁸ Meyer 1998 ⁵³ Meyer 1998 ⁵³ Let events tal events tal events tareogeneity: $\chi^2 = 3.37$, df = 4 ($p = 0.56$ st for overall effect: $z = 1.50$ ($p = 0.13$) 2.3 12 months	24 11	27	2	31	3.4%	0.86 (0.06 to 12.26)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Corson 2001 ⁷⁸ Meyer 1998 ⁵³ Ibtotal (95% CI) tal events teregeneity: $\chi^2 = 3.37$, df = 4 ($p = 0.56$ teregeneity: $\chi^2 = 3.37$, df = 0.13 teregeneity: $\chi^2 = 3.37$, df = 0.13 teregeneity: $\chi^2 = 2.37$, df = 0.13	11	58	38	76	29.9%	1.41 (0.58 to 3.46)	I I I I I I I I I I I I I I I I I I I
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Meyer 1998 ³³ bitotal (95% CI) tal events terogeneity: $\chi^2 = 3.37$, df = 4 ($p = 0.50$ terogeneity: $\chi^2 = 3.37$, df = 0.13 terogeneity: $\chi^2 = 2.31$, df = 0.13 2.3 12 months	•	84	37	180	31.0%	1.65 (0.68 to 3.98)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	biccial (95% CI) tal events terogeneity: $\chi^2 = 3.37$, df = 4 ($\rho = 0.56$ terogeneiti: $\chi^2 = 3.37$, df = 4 ($\rho = 0.13$ st for overall effect: $z = 1.50$ ($\rho = 0.13$ 2.3 12 months	16	120	22	125	29.2%	1.38 (0.56 to 3.43)	ł
$= 377 \text{ dif} = (16 - 0.3)^{4} - 0.6 \qquad 103$ $= 377 \text{ dif} = (16 - 0.3)^{4} - 0.6 \qquad 103$ feat: $z = 150 (10 - 0.13)$ feat: $z = 150 (10 - 0.13)$ feat: $z = 17 \qquad 2 \qquad 21 \qquad 178 \qquad 0.58 (0.0.0.6.43)$ feat: $z = 120 (10 - 0.13)$ feat: $z = 12 \qquad 22 \qquad 23 \qquad 0.41 \qquad 178 \qquad 0.53 (0.0.0.6.43)$ feat: $z = 223 \qquad 0.48 (0.0.0.6.43)$ feat: $z = 203 (0.0.0.6.43)$ feat:	$= 377, d1 = (10 = 0.03)^{F} = 0.6$ $= 377, d1 = (10 = 0.03)^{F} = 0.6$ free: $= 1150(10 = 0.13)$ free: $= 1170(10 = 0.24)$ free: $= 110(10 = 0.24)$ free: $= 100(10 $	tal events terogeneity: $\chi^2 = 3.37$, df = 4 ($p = 0.56$ st for overall effect: $z = 1.50$ ($p = 0.13$ 2.3 12 months		304		432	100.0%	1.33 (0.92 to 1.93)	•
= 37, d1 + 4(p = 0.30), f = 06 $ = 37, d1 + 4(p = 0.30), f = 06 $ $ = 5 $ $ = 150(p = 0.13) $ $ = 4 $ $ = 5 $ $ = 5 $ $ = 5 $ $ = 100(p = 0.13) $ $ = 6 $ $ = 5 $ $ = 5 $ $ = 100(p = 0.14) $ $ = 6 $ $ = 5 $ $ = 110(p = 0.12) $ $ = 110(p = 0.10) $ $ = 110(p = 0.1$	$ = 37. \ dr = 4 \ (p = 0.30), \ k = 0.6 \ (k = 10) \ (p = 0.13) \ (p$	terogeneity: $\chi^2 = 3.37$, df = 4 ($p = 0.56$ st for overall effect: $z = 1.50$ ($p = 0.13$:3 12 months	59		103				-
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	st for overall effect. z = 1.30 (p = 0.13) .3 12 months	0); $P = 0\%$						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2.3 12 months	_						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$								
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Brun 2006 ¹⁰³	2	17	2	30	1.7%	(0.03 to	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Cooper 2004	5	96	5	194	4.1%	0.45 (0.08 to 2.64)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Perino 2004 ¹⁰⁰	4	55	2	56	2.7%	0.49 (0.06 to 4.20)	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Duleba 2003 ⁹⁸	5	72	19	156	8.9%	1.74 (0.53 to 5.74)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		-	28	-	30	0.9%	0.93 (0.02 to 36.86)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		19	55	23	74	13.4%	0.86 (0.32 to 2.27)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		10	82	14	154	9.4%	0.71 (0.22 to 2.28)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		12	83	31	172	15.1%	1.29 (0.51 to 3.23)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		10	48	ŧ	45	7.8%	1.23 (0.34 to 4.37)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		19	112	16	122	14.3%	0.74 (0.29 to 1.90)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$: =	124	σ	116	8 8%	0 87 (0 26 to 2 88)	
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		0	899	0	1281	100.0%	0.97 (0.74 to 1.28)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	al events	11		151	1			•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$a_{1} = 0.5$	$30 \cdot P = 0.0\%$						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	t for overall effect: $z = 0.19$ ($p = 0.85$)							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4 2 vears							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	an Zon-Rabelink 2001 ⁹⁵	19	55	16	76	55.6%	0.50 (0.18 to 1.41)	-+
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		14	128	ġα	101	44.4%	0 50 (0 10 to 1 85)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		<u>t</u>	183	þ	107	100.0%	0.54 (0.30 to 0.07)	• 4
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	al events	33		24			;	•
fect: $z = 2.08$ ($p = 0.04$) b 5 55 3 56 100.0% 0.58 (0.09 to 3.78) c applicable fect: $z = 0.76$ ($p = 0.45$) c 136 5 130 100.0% 1.05 (0.20 to 5.50) c applicable fect: $z = 0.07$ ($p = 0.94$) c 136 (0.20 to 5.50) c 130 100.0% 1.05 (0.20 to 5.50) c 130 100.0% 1.05 (0.20 to 3.70) c 130 100 100 100 100 100 100 100 100 100	fect: $z = 2.08$ ($p = 0.04$) b 5 55 3 56 100.0% 0.58 (0.14 to 2.31) c 4 applicable fect: $z = 0.76$ ($p = 0.45$) c 5 136 5 130 100.0% 1.05 (0.20 to 5.50) c 4 applicable fect: $z = 0.07$ ($p = 0.94$) c 5 130 100.0% 1.05 (0.30 to 3.70) c 4 applicable fect: $z = 0.07$ ($p = 0.94$) c 6 130 to 3.70) c 100.0% 1.05 (0.30 to 3.70) c 100.000 (0.100 (0	erogeneity: $\chi^2 = 0.06$, df = 1 ($p = 0.80$); $P = 0\%$						
1 5 55 55 3 56 100.0% 0.58 $(0.09 \text{ to } 3.78)$ 5 55 3 56 100.0% 0.58 $(0.14 \text{ to } 2.41)$ 6 100.0% 0.38 $(0.14 \text{ to } 2.41)$ 7 100.0% 1.05 $(0.20 \text{ to } 5.6)$ 7 136 5 136 1.05 $(0.20 \text{ to } 5.6)$ 7 136 1.05 $(0.20 \text{ to } 5.6)$ 7 1 100.0% 1.05 $(0.20 \text{ to } 5.6)$ 7 1 100.0% 1.05 $(0.30 \text{ to } 3.70)$ 7 100.0% 1.05 $(0.30 \text{ to } 3.70)$) 5 55 3 56 100.0% 0.58 $(0.09 \text{ to } 3.78)$ 5 55 3 56 100.0% 0.58 $(0.14 \text{ to } 2.41)$ 5 1 applicable fect: $z = 0.76$ ($p = 0.45$) 1 336 5 130 100.0% 1.05 $(0.20 \text{ to } 5.50)$ 1 100.0% 1.05 $(0.20 \text{ to } 3.70)$ 1 10 0.1 10 10	t for overall effect: $z = 2.08$ ($p = 0.04$)	_						
1 5 55 3 56 100.0% 0.58 $(0.04 to 2.78)$ 5 55 3 56 100.0% 0.58 $(0.14 to 2.41)$ 5 5 136 6 100.0% 0.38 $(0.14 to 2.41)$ 6 fect: $z = 0.76$ $(p = 0.45)$ 10 10 10 10 10 10 10 10	b 5 5 5 3 56 100.0% 0.58 (0.14 to 2.41) 5 5 53 3 56 100.0% 0.58 (0.14 to 2.41) fect: $z = 0.76$ ($p = 0.45$) b 5 130 100.0% 1.05 (0.20 to 5.50) c 1 applicable fect: $z = 0.07$ ($p = 0.94$) c 1 $\frac{100.0\%}{5}$ 1.05 (0.20 to 5.50) c 1 $\frac{100.0\%}{5}$ 1.05 (0.20 to 3.70) c 1 $\frac{100.0\%}{5}$ 1.05 (0.20 to 3.70)	5 3 years							
$ \begin{bmatrix} 5 & 55 & 3 & 56 & 100.0\% & 0.58 (0.14 to 2.41) \\ = 0.45) & = 0.45) \\ 5 & 136 & 5 & 130 & 100.0\% & 1.05 (0.20 to 5.50) \\ 5 & 136 & 5 & 130 & 100.0\% & 1.05 (0.30 to 3.70) \\ = 0.94) \end{bmatrix} $	$\begin{bmatrix} 5 & 55 & 3 & 56 & 100.0\% & 0.58 (0.14 to 2.41) \\ = 0.45) & = 0.45) \\ 5 & 136 & 5 & 130 & 100.0\% & 1.05 (0.20 to 5.50) \\ 5 & 136 & 5 & 130 & 100.0\% & 1.05 (0.30 to 3.70) \\ = 0.94) & & & & & & & & & & & & & & & & & & &$	erino 2004 ¹⁰⁰	5	55	ი	56	100.0%	0.58 (0.09 to 3.78)	
5 = 0.45) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94)	5 =0.45) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94) 0.01 0.1 - 10	ototal (95% CI)		55		56	100.0%	0.58 (0.14 to 2.41)	♦
= 0.45) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 130 100.0% 1.05 (0.20 to 3.70) = 0.94)	=0.45) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) = 0.94)	al events	5		e				
= 0.45) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94)	= 0.45) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94)	erogeneity: not applicable							
5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94)	5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.20 to 5.50) = 0.34) - 10 0.1 0.1 - 10	t for overall effect: $z = 0.76$ ($p = 0.45$)	_						
5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94)	5 136 5 130 100.0% 1.05 (0.20 to 5.50) 5 136 5 130 100.0% 1.05 (0.30 to 3.70) = 0.94) 0.1 - 10	.6 5 years							
5 136 5 130 100.0% 1.05 (0.30 to 3.70)	5 136 130 100.0% 1.05 (0.30 to 3.70)	ooper 1999 ⁵⁴	5	136	5	130	100.0%	1.05 (0.20 to 5.50)	
5 5 = 0.94)	5 = 0.94) 5 0.01 0.1 1 10	btotal (95% CI)		136		130	100.0%	1.05 (0.30 to 3.70)	•
= 0.94)	= 0.94)	tal events	5		5				
= 0.94)	= 0.94)	terogeneity: not applicable							
-	0.1	st for overall effect: $z = 0.07$ ($p = 0.94$							
	0.1 1 10								-

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	First	First generation	ation	Secor	Second generation	ration			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.8.2 <12 months									
a. Brun 2006 ¹⁰³	-201	146	15	-351	231	20	14.0%	150.00 (-14.71 to 314.71)	
e. Hawe 2003 ⁹⁴	-361	211	27	-331	133	31	25.9%	-30.00 (-151.35 to 91.35)	
f. van Zon-Rabelink 2001 ⁹⁵	-379	331	58	-336	326	76	17.5%	-43.00 (-190.69 to 104.69)	
	-520	356	06	-534	356	175	26.9%	14.00 (-104.95 to 132.95)	
	-544	641	84	-464	687	180	7.6%	-80.00 (-303.27 to 143.27)	
m. Meyer 1998 ⁵³	-519	592	120	-498	728	125	8.0%		
Subtotal (95% CI)			394			607	100.0%		•
Heterogeneity: $\chi^2 = 7.47$, df = 5 ($p = 0.19$); $l^2 = 33\%$ Test for overall effect: $z = 0.07$ ($p = 0.94$)	= 5 (p = 0.3) 77 ($p = 0.3$	1.19); /² = 94)	= 33%						
1.8.3 12 months									
a. Brun 2006 ¹⁰³	-221	164	17	-471	305	29	3.9%	250.00 (71.73 to 428.27)	
b. Cooper 2004 ⁹⁹	-498	433	106	-444	359	209	7.8%	-54.00 (-179.81 to 71.81)	
d. Duleba 2003 ⁹⁸	-441	348	72	-526	423	156	6.6%	85.00 (-52.00 to 222.00)	
f. van Zon-Rabelink 2001 ⁹⁵	-406	367	55	-344	349	74	4.5%	-62.00 (-226.83 to 102.83)	
g. Cooper 2002 ⁵⁶	-526	353	82	-535	356	154	7.9%		
i. Corson 2001 ⁷⁹	-511	458	83	-494	689	172	3.5%	-17.00 (-204.30 to 170.30)	
j. Soysal 2001 [%]	-347	88	54	-342	86	42	58.1%	-5.00 (-51.04 to 41.04)	-
k. Corson 2000 ¹⁰¹	-417	285	112	-517	594	122	5.1%	100.00 (-54.92 to 254.92)	
m. Meyer 1998 ⁵³	-536	585	117	-510	730	122	2.5%	-26.00 (-245.97 to 193.97)	
Subtotal (95% CI)			698			1080	100.0%	9.94 (-16.77 to 36.65)	*
Heterogeneity: $\chi^2 = 20.26$, df = 8 ($p = 0.009$); $\beta = 61\%$ Test for overall effect: $z = 0.73$ ($p = 0.47$)	¹ = 8 (<i>p</i> =	0.009); <i>i</i> 47)	<i>β</i> = 61%						
1.8.4 2 years									
f. van Zon-Rabelink 2001 ⁹⁵	-404	392	55 7	-398	310	66 20	100.0%	-6.00 (-173.92 to 161.92)	
Subtotal (95% CJ) Heterogeneity: not applicable Test for overall effect: $z = 0.09 \ (\rho = 0.93)$	و 9 (<i>p</i> = 0:	93)	ß			0	%0.00T	-0.00 (-133.77 to 121.77)	
									-200 -100 0 100 200 Favours first generation

Study or subgroup						Dato odde ratio (non-avent)	Dato odde ratio (non-event)
1 0 0 / 10 months	Events	Total	Events	Total	Weight	Peto, Fixed, 99% CI	Peto, Fixed, 99% CI
		1					
a. Brun 2006 ⁷³ e Hawa 2003 ⁹⁴	0 5	30 30	2 06	24 37	1.9%	5.31 (0.12 to 235.80) 1 04 (0 30 to 3 58)	
	22	52 64	38	145	36.9%	0.67 (0.29 to 1.58)	
m. Meyer 1998 ⁵³	26	120	30	125	43.8%	1.14 (0.52 to 2.49)	
Subtotal (95% CI)		231		331	100.0%	0.95 (0.64 to 1.41)	♦
Total events 65 Heterogeneity: $\chi^2 = 2.85$, df = 3 ($p = 0.41$); $\beta = 0\%$ Test for overall effect: $z = 0.26$ ($p = 0.80$)	65 ($p = 0.41$); $l^2 = 0\%$ ($p = 0.80$)		06				
1.9.4 12 months							
a. Brun 2006 ¹⁰³	-	13	0	22	0.3%	0.07 (0.00 to 13.99)	
	33	97	66	196	20.7%	0.98 (0.50 to 1.93)	
d. Duleba 2003 ⁴⁸	37	72	69	156	17.5%	0.75 (0.36 to 1.56)	
	15	28	17	29	5.1%	1.22 (0.31 to 4.78)	9
g. Cooper 2002	28	82	32	153	14.5%	0.50 (0.22 to 1.12)	
Corson 2001	20	67	40	154	13.2%	0.82 (0.35 to 1.92)	
	22	124	24	116	13.3%	1.21 (0.52 to 2.81)	
m. Meyer 1998	29	117	28	122	15.5%	0.90 (0.41 to 1.97)	
Subtotal (95% CI)		600		948	100.0%	0.84 (0.67 to 1.07)	٠
Lotal events 185 Heterogeneity: $\chi^2 = 6.54$, df = 7 ($p = 0.48$); $\beta = 0\%$ Test for overall effect: $z = 1.41$ ($p = 0.16$)	185 ($p = 0.48$); $l^2 = 0\%$ ($p = 0.16$)		276				
1.9.5 2 years							
. Cooper 1999 ⁵⁴	29	128	22	121	48.5%	0.76 (0.34 to 1.71)	
m. Meyer 1998 ³³ Subtotol (06 92 CI)	26	108 226	32	118 000	51.5%	1.17 (0.54 to 2.57) OBE (0.62 to 1.45)	
Jubiciai (33 / 01) Total events	55	200	54	607	× • • • •		•
Heterogeneity: $\chi^2 = 0.98$, df = 1 ($p = 0.32$); $\beta = 0\%$ Test for overall effect: $z = 0.23$ ($p = 0.82$)	(p = 0.32); P = 0.90 p = 0.82)						
1.9.6 3 years							-1
m. Meyer 1998 ⁵³	22	102	22	110	100.0%	0.91 (0.38 to 2.17)	
Subtotal (95% CI)	00	201	00	011	% 0.001	0.31 (0.47 to 1.76)	•
Heterogeneity: not applicable	22		22				
Test for overall effect: $z = 0.28 \ (p = 0.78)$	p = 0.78						
1.9.7 5 years							
l. Cooper 1999 ⁵⁴	14	136	14	130	100.0%	1.05 (0.38 to 2.94)	
Subtotal (95% CI) Total events	14	130	14	130	% 0.001	1.05 (0.48 to 2.30)	-
Heterogeneity: not applicable	:		:				
Test for overall effect: $z = 0.13$ ($p = 0.90$)	p = 0.90						

Favours first generation

Favours second generation

								Mean difference	Mean difference	erence
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 99% CI	IV, Fixed, 99% CI	99% CI
a. Brun 2006 ¹⁰³	52.8	27.4	16	56	31.2	24	0.2%	-3.20 (-27.29 to 20.89)		
b. Cooper 2004 ⁹⁹	20.3	15.6	106	3.4	-	209	7.3%	16.90 (12.99 to 20.81)		ł
c. Perino 2004 ¹⁰⁰	16.4	7.8	55	7.1	0.1	56	15.2%	9.30 (6.59 to 12.01)		ŧ
e. Hawe 2003 ⁹⁴	30.5	9.2	g	15	0.1	37	6.6%	15.50 (11.37 to 19.63)		ł
f. van Zon-Rabelink 2001 ⁹⁵	34.7	12.7	62	18	4.9	77	5.8%	16.70 (12.30 to 21.10)		L
g. Cooper 2002 ⁵⁶	24.2	11.4	6	4.2	3.5	175	11.1%	20.00 (16.83 to 23.17)		ł
h. Pellicano 2002 ¹⁰²	37	9	42	24	4	40	13.4%	13.00 (10.11 to 15.89)		Ļ
j. Soysal 2001 ⁹⁶	37.3	7.5	48	11.5	0.8	45	14.2%	25.80 (22.99 to 28.61)		ŧ
k. Corson 2000 ¹⁰¹	39.3	16.6	126	23.1	9.5	150	6.0%	16.20 (11.90 to 20.50)		ŀ
I. Cooper 1999 ⁵⁴	15	7.2	134	11.4	10.5	129	13.6%	3.60 (0.73 to 6.47)	Ţ	L
m. Meyer 1998 ⁵³	39.2	14.8	129	27.1	10.4	128	6.6%	12.10 (7.99 to 16.21)		ŀ
Total (95% CI) Heterogeneity: $\chi^2 = 261.00$, df = 10 ($p < 0.00001$); $l^2 = 96\%$ Test for overall effect: $z = 35.39$ ($p < 0.00001$)	f = 10 (<i>p</i> 39 (<i>p</i> < 0	< 0.000 .00001)	841 01); <i>f</i> ² = 9	96%		1070	100.0%	14.52 (13.72 to 15.33)		-

25 50 Favours second generation

0

-52

-20

Favours first generation

Duration of surgery (minutes)

Second generation

First generation

134

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Use

	First generation	eration	Second generation	neration			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
a. Brun 2006 ¹⁰³	12	20	20	29	4.9%	1.48 (0.31 to 7.09)	
b. Cooper 2004 ⁹⁹	83	106	93	209	24.2%	0.22 (0.11 to 0.45)	<u></u>
d. Duleba 2003 ⁹⁸	62	86	89	193	10.3%	0.08 (0.03 to 0.22)	
f. van Zon-Rabelink 2001 ⁹⁵	62	62	76	77	0.7%	0.41 (0.01 to 28.01)	
g. Cooper 2002 ⁵⁶	74	06	47	175	17.2%	0.08 (0.03 to 0.18)	
k. Corson 2000 ¹⁰¹	98	123	22	132	17.3%	0.05 (0.02 to 0.12)	-
m. Meyer 1998 ⁵³	107	138	71	137	25.5%	0.31 (0.16 to 0.62)	-
n. Romer 1998 ⁹⁷	10	10	10	10		Not estimable	
Total (95% CI)		635		962	100.0%	0.16 (0.12 to 0.20)	•
Total events	525		428				
Heterogeneity: $\chi^2 = 41.70$, df = 6 ($p < 0.00001$); $l^2 = 86\%$ Test for overall effect: $z = 13.85$ ($p < 0.00001$)	(p < 0.00001) (p < 0.00001)	; $l^2 = 86\%$					
						0.01	01 0.1 1 10
						Favolirs sec	Eavours second generation Eavours first generation

Surgery pain score

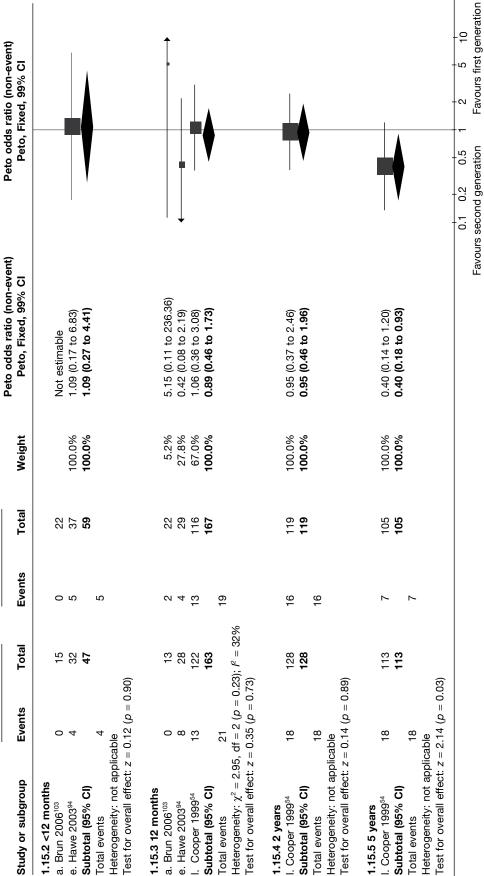
Study or subgroup Mean SD Total Mean a. Brun 2006 ¹⁰³ 2.3 2.9 15 4.7 c. Perino 2004 ¹⁰⁰ 3.7 1.4 55 4.4 e. Hawe 2003 ⁹⁴ 2.4 1.2 6 6.5 h. Pellicano 2002 ¹⁰² 3.8 0.6 42 3.2								
	Total	Mean	S	Total	Weight	Standard mean difference IV, Fixed, 99% CI	Standard mean difference IV, Fixed, 99% CI	lifference % Cl
⁰ 3.7 2 ¹⁰² 3.8	15	4.7	2.8	26	11.0%	-0.83 (-1.70 to 0.04)		
2 ¹⁰² 3.8	55	4.4	2.2	56	34.2%	-0.38 (-0.87 to 0.12)	1	
3.8	9	6.5	2	6	2.5%	-2.22 (-4.05 to -0.40)		
	42	3.2	0.7	40	23.2%	0.91 (0.31 to 1.51)	Ī	L
j. Soysal 2001 ⁹⁶ 3.2 2.1	48	3.1	1.7	45	29.1%	0.05 (-0.48 to 0.59)	-	
Total (95% CI) Heterogeneity: $\chi^2 = 35.01$, df = 4 ($\rho < 0.00001$); $l^2 = 89\%$ Test for overall effect: $z = 0.43$ ($\rho = 0.66$)	166 .00001); . 6)	<i> </i> ² = 89%		176	100.0%	-0.05 (-0.27 to 0.17)	•	
							-42	-2
							Favours first generation Fav	Favours second generation

Time to return to work (days)

First	First generation	ion	Secon	Second generation	ation				
Study or subgroup Mean SD Total Mean SD	sD	Total	Mean	sD	Total	Total Weight	Mean difference IV, Fixed, 99% CI	Mean d IV, Fixe	Mean difference IV, Fixed, 99% Cl
a. Brun 2006 ¹⁰³ 6.4 h. Pellicano 2002 ¹⁰² 6.3	8.2 13 2.1 42	13 42	8.2 4.9	9.1 0.7	21 40	1.3% 98.7%	1.3% -1.80 (-9.58 to 5.98) 8.7% 1.40 (0.52 to 2.28)	•	
Total (95% CI) Heterogeneity: $\chi^2 = 1.11$, df = 1 ($\rho = 0.29$); $\beta = 10\%$ Test for overall effect: $z = 4.00$ ($\rho < 0.0001$)	20 = <i>d</i>) 20 < 0.00	55 29); <i>I</i> ² = 1 001)	10%		61	100.0%	1.36 (0.69 to 2.03)		•

Time to return to normal activities (days)

up Mean SD Total Mean SD Total Weight 5.6 8.1 16 6 5.6 23 0.4% 2^{102} 6.2 3.3 42 4.1 2.6 40 4.7% 2^{102} 6.2 3.3 42 4.1 2.6 40 4.7% 2^{102} 6.2 3.3 42 4.1 2.6 40 4.7% 2^{112} 6.2 3.3 126 2.4 1.8 150 21.6% 1.8 1.5 109 1.4 0.9 114 72.5% 1.8 1.5 109 1.4 0.9 114 72.5% 1.8 1.5 109 1.4 0.9 10.00% 7.5 335 $p = 0.04$ $p = 0.04$ $p = 0.04$ $p = 0.04$ 7.5 516 0.09 1.14 72.5% 7.6	First ge	First generation	Secon	Second generation	ation				
8:1 16 6 5.6 23 0.4% 8:5 92 13.3 17.1 189 0.9% 3:3 42 4.1 2.6 40 4.7% 3 126 2.4 1.8 150 21.6% 1.5 109 1.4 0.9 114 72.5% $= 4$ ($p = 0.04$); $l^2 = 59\%$ 516 100.0% 35 ($p = 0.003$) 5 516 100.0%	ubgroup Mean	SD Total	Mean		Total	Weight	Mean difference IV, Fixed, 99% CI	Mean (IV, Fixe	Mean difference IV, Fixed, 99% CI
^a 11 8.5 92 13.3 17.1 189 0.9% 2^{102} 6.2 3.3 4.2 4.1 2.6 4.0 4.7% 0.1 2.9 3 126 2.4 1.8 150 21.6% 1.8 1.5 109 1.4 0.9 114 72.5% 385 516 100.0% fect: z = 3.35 (p = 0.0008) ffect: z = 3.35 (p = 0.0008)	5.6	8.1 16	9	5.6	23	0.4%	-0.40 (-6.42 to 5.62)		•
^{a2} 6.2 3.3 42 4.1 2.6 40 4.7% 2.9 3 126 2.4 1.8 150 21.6% 1.8 1.5 109 1.4 0.9 114 72.5% 385 516 100.0% 385 516 100.0% e.9.82, df = 4 ($p = 0.04$); $l^2 = 59\%$ set: $z = 3.35$ ($p = 0.0008$)	9 11		13.3	17.1	189	0.9%	-2.30 (-6.23 to 1.63)	+	
2.9 3 126 2.4 1.8 150 21.6% 1.8 1.5 109 1.4 0.9 114 72.5% 385 516 100.0% = 9.82, df = 4 ($p = 0.04$); $l^2 = 59\%$ ect: $z = 3.35$ ($p = 0.0008$)	02	3.3 42	4.1	2.6	40	4.7%	2.10 (0.41 to 3.79)		
1.8 1.5 109 1.4 0.9 114 72.5% 1 385 385 516 100.0% 6 = 9.82, df = 4 (p = 0.043); l^2 = 59% 516 100.0% 6 fect: z = 3.35 (p = 0.0008) 6 6 1		3 126	2.4	1.8	150	21.6%	0.50 (-0.29 to 1.29)	1 -	
516 100.0%		1.5 109	1.4	0.9	114	72.5%	0.40 (-0.03 to 0.83)		
eterogeneity: $\chi^2 = 9.82$, df = 4 ($p = 0.04$); $l^2 = 59\%$ ist for overall effect: $z = 3.35$ ($p = 0.0008$)	ci)	385			516	100.0%	0.48 (0.20 to 0.75)		•
	eity: $\chi^2 = 9.82$, df = 4 (, erall effect: $z = 3.35$ (p	$p = 0.04$); $l^2 = 0.008$) h = 0.0008	= 59%						
								+-+	-2-+4
								Favours first generation	Favours second generation



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Second generation

First generation

Proportion with dyspareunia

SF-36 scores (absolute values)

	First	genera	ation	Secon	d gene	ration		N	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% Cl
.16.1 SF-36 general	health (6 mont	:hs)						
. Cooper 2004 ⁹⁹	82.1	15.3	87	81.5	17.3	178	100.0%	0.60 (-4.79 to 5.99)	
Subtotal (95% CI)			87			178	100.0%	0.60 (-3.50 to 4.70)	+
leterogeneity: not app est for overall effect:		(p = 0)	.77)						
.16.2 SF-36 physical . Cooper 2004 ⁹⁹	93.7	n (om) 11.7	87	90.7	18.3	180	100.0%	3.00 (-1.77 to 7.77)	+
Subtotal (95% CI)			87			180	100.0%	3.00 (-0.63 to 6.63)	-
leterogeneity: not app	olicable								
est for overall effect:	<i>z</i> = 1.62	(p = 0	.11)						
.16.3 SF-36 role limi									
. Cooper 2004 ⁹⁹ Subtotal (95% Cl)	91.8	23.6	91 91	88.5	28.9	182 182	100.0% 100.0%	3.30 (–5.13 to 11.73) 3.30 (–3.11 to 9.71)	
leterogeneity: not ap	olicable		91			102	100.0 %	3.30 (-3.11 10 9.71)	
Test for overall effect:		(p = 0	.31)						
.16.4 SF-36 role limi	tation e	motion	al (6 mc	onths)					
b. Cooper 2004 ⁹⁹	89.4	27.6	91	86.1	31.1	180	100.0%	3.30 (-6.25 to 12.85)	
Subtotal (95% CI)			91			180	100.0%	3.30 (-3.97 to 10.57)	
leterogeneity: not app est for overall effect:		(n – 0	37)						
1.16.5 SF-36 mental I b. Cooper 2004 ⁹⁹	health (6 77.9	6 montl 16.6	1s) 90	77.1	17.7	179	100.0%	0.80 (-4.85 to 6.45)	
Subtotal (95% CI)			90			179	100.0%	0.80 (-3.50 to 5.10)	
Heterogeneity: not app	olicable								
est for overall effect:	<i>z</i> = 0.36	(<i>p</i> = 0	.72)						
.16.6 SF-36 social fu	unction ((6 mon	ths)						
o. Cooper 200499	92.5	12.1	89	91.9	15.3	168	100.0%	0.60 (-3.89 to 5.09)	
Subtotal (95% CI)			89			168	100.0%	0.60 (-2.82 to 4.02)	+
Heterogeneity: not app Test for overall effect:		(p = 0)	.73)						
		u .	,						
1 .16.7 SF-36 vitality (b. Cooper 2004 ⁹⁹	66.5	19.7	92	65.9	22.5	177	100.0%	0.60 (-6.25 to 7.45)	
Subtotal (95% CI)			92			177	100.0%	0.60 (-4.61 to 5.81)	-
Heterogeneity: not app		(- 0	00)						
est for overall effect:	2 = 0.23	(p = 0)	.02)						
1.16.8 SF-36 pain (6 i D. Cooper 2004 ⁹⁹	nonths) 83.8	19.7	92	83.1	23.1	177	100.0%	0.70 (6.22 to 7.62)	
Subtotal (95% CI)	03.0	19.7	92 92	03.1	23.1	177	100.0%	0.70 (–6.23 to 7.63) 0.70 (–4.57 to 5.97)	
Heterogeneity: not app	olicable		52				100.070	0.10 (-4.01 to 0.01)	T
Test for overall effect:		(p = 0	.79)						
.16.9 SF-36 general	health (12 mor	nths)						
. Cooper 2004 ⁹⁹	81.5	16.3	95	82.5	16.7	187	51.9%	-1.00 (-6.33 to 4.33)	
.Cooper 1999 ⁵⁴	65.2	16.4	124	67.3	16.9	116	48.1%	-2.10 (-7.64 to 3.44)	
Subtotal (95% CI)			219	.		303	100.0%	–1.53 (–4.45 to 1.40)	•
Heterogeneity: $\chi^2 = 0$. Test for overall effect:		u u		= 0%					
1.16.10 SF-36 physic	al functi	on (12	months						
o. Cooper 2004 ⁹⁹	92.3	15.3	94	92.9	14.4	185	71.2%	-0.60 (-5.49 to 4.29)	
. Cooper 1999 ⁵⁴	84.9	22.5	124	84.9	23.7	116	28.8%	0.00 (-7.70 to 7.70)	
Subtotal (95% CI)	20 -11		218	00/		301	100.0%	-0.43 (-3.57 to 2.72)	•
Heterogeneity: $\chi^2 = 0.0$ Fest for overall effect:				= 0%					
I.16.11 SF-36 role lin	nitation	nhveic	al (10 m	onthe)					
 Cooper 2004⁹⁹ 	88.9	27.2	ai (12 m 95	94	20.9	187	70.0%	-5.10 (-13.30 to 3.10)	
. Cooper 1999 ⁵⁴	73.8	40.3	124	81.3	34.9	116	30.0%	-7.50 (-20.01 to 5.01)	←
Subtotal (95% CI)			219			303	100.0%	-5.82 (-11.04 to -0.60)	-
Heterogeneity: $\chi^2 = 0$.		u u		= 0%					
est for overall effect:	z = 2.19	(p = 0	.03)						
									-10 -5 0 5 1
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									Favours Favours Favours second generation first generation

	First	genera	ation	Second	d gene	ration			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
1.16.12 SF-36 role lir	nitation	emotio	nal (12	months)					
b. Cooper 200499	89.8	27.1	95	91.2	24	186	68.8%	-1.40 (-9.88 to 7.08)	
 Cooper 1999⁵⁴ 	75.8	39.5	124	79.6	36.2	116	31.2%	-3.80 (-16.39 to 8.79)	·
Subtotal (95% CI)			219			302	100.0%	-2.15 (-7.50 to 3.20)	-
Heterogeneity: $\chi^2 = 0$.	17, df =	1(p = 0)	0.68); <i>I</i> ²	= 0%					
Test for overall effect:	z = 0.79) (p = 0	.43)						
1.16.13 SF-36 menta	l health	(12 mo	nths)						
b. Cooper 2004 ⁹⁹	76.6	17.3	94	78.4	16.7	187	61.2%	-1.80 (-7.37 to 3.77)	
. Cooper 1999 ⁵⁴	69.4	22	124	70.3	20.1	116	38.8%	-0.90 (-7.90 to 6.10)	
Subtotal (95% CI)			218			303	100.0%	-1.45 (-4.77 to 1.87)	+
Heterogeneity: $\chi^2 = 0$.	07, df =	1(p = 0)	0.80); <i>I</i> ²	= 0%					
Test for overall effect:	z = 0.86	6 (p = 0	.39)						
1.16.14 SF-36 social	function	1 (12 m	onths)						
b. Cooper 2004 ⁹⁹	92.3	12.8	92	92.3	14	180	74.7%	0.00 (-4.36 to 4.36)	_ _↓ _
l. Cooper 1999 ⁵⁴	67.8	24	124	71.7	21.1	116	25.3%	–3.90 (–11.40 to 3.60)	
Subtotal (95% CI)			216			296	100.0%	-0.99 (-3.86 to 1.88)	
Heterogeneity: $\chi^2 = 1$.	,	u u	0.25); <i>I</i> ²	= 25%				· · · · · · · · · ·	
Test for overall effect:	z = 0.67	(p = 0	.50)						
1.16.15 SF-36 vitality	-	-	05	00	00.0	100	F7 40/		
b. Cooper 2004 ⁹⁹	65.2	21.3	95	69	20.9	186	57.1%	-3.80 (-10.68 to 3.08)	
 Cooper 1999⁵⁴ 	55.3	25.2	124	57.4	22.5	116	42.9%	–2.10 (–10.03 to 5.83)	
Subtotal (95% CI)			219			302	100.0%	–3.07 (–7.02 to 0.88)	-
Heterogeneity: $\chi^2 = 0$.				= 0%					
Test for overall effect:	z = 1.52	? (p = 0	.13)						
1.16.16 SF-36 pain (1									
b. Cooper 200499	84.3	21.5	95	83.8	23.4	187	60.3%	0.50 (-6.69 to 7.69)	
 Cooper 1999⁵⁴ 	71.2	27.6	124	70.3	25.7	116	39.7%	0.90 (–7.96 to 9.76)	
Subtotal (95% CI)			219			303	100.0%	0.66 (-3.59 to 4.91)	+
Heterogeneity: $\chi^2 = 0$. Test for overall effect:				= 0%					
Test for overall effect.	2 - 0.50	(μ = 0	.70)						
1.16.17 SF-36 genera I. Cooper 1999 ⁵⁴	al health 70.4	(2 year 24.6	r s) 128	70.1	25.3	121	100.0%	0.30 (-7.85 to 8.45)	
	70.4	24.0	120 128	70.1	20.0				
Subtotal (95% CI)			128			121	100.0%	0.30 (–5.90 to 6.50)	
Heterogeneity: not ap Test for overall effect:	•	n(n = 0)	92)						
		u.	,						
1.16.18 SF-36 physic I. Cooper 1999 ⁵⁴	al functi 83.6	i on (2 y 22.8	ears) 128	86	23	121	100.0%	-2.40 (-9.88 to 5.08)	
Subtotal (95% CI)	00.0	22.0	128	00	20	121	100.0%	-2.40 (-8.09 to 3.29)	
Heterogeneity: not ap	nlicable		.20						
Test for overall effect:	•	8 (p = 0	.41)						
1.16.19 SF-36 role lir	nitation	nhveic	al (2 ver	urs)					
I. Cooper 1999 ⁵⁴	70.5	41.1	128	74.4	39.5	121	100.0%	-3.90 (-17.06 to 9.26)	
Subtotal (95% CI)	10.0		128	, .	00.0	121	100.0%	-3.90 (-13.91 to 6.11)	
Heterogeneity: not ap	nlicable		120			121	100.070	0.00 (-10.01 10 0.11)	
Test for overall effect:	•	6 (p = 0	.45)						
1.16.20 SF-36 role lir	nitation	emotio	nal (?)	eare)					
I. Cooper 1999 ⁵⁴	73.2	40.6	128	78.8	38	121	100.0%	-5.60 (-18.43 to 7.23)	←
Subtotal (95% CI)		.0.0	128			121	100.0%	-5.60 (-15.36 to 4.16)	
Heterogeneity: not ap	nlicable		0						
Test for overall effect:	•	2 (p = 0	.26)						
1.16.21 SF-36 menta	l health	(2 vear	s)						
I. Cooper 1999 ⁵⁴	67.9	21.5	3) 128	69.2	20.3	121	100.0%	-1.30 (-8.12 to 5.52)	
Subtotal (95% CI)			128			121	100.0%	-1.30 (-6.49 to 3.89)	$\overline{}$
Heterogeneity: not ap	nlicable		.20						٦
Test for overall effect:	•	n (n - n)	62)						
	z = 0.49	ν ω = U	.021						

Favours second generation Favours first generation

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	First	genera	ation	Secon	d gene	ration			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
.16.22 SF-36 social Cooper 1999 ⁵⁴ ubtotal (95% CI) leterogeneity: not appest for overall effect:	66.8 plicable	25.1	128 128	70	23	121 121	100.0% 100.0%	-3.20 (-11.05 to 4.65) -3.20 (-9.18 to 2.78)	
.16.23 SF-36 vitality Cooper 1999 ⁵⁴ Subtotal (95% CI) leterogeneity: not app est for overall effect:	55.5 plicable	24	128 128 .89)	55.1	23.1	121 121	100.0% 100.0%	0.40 (-7.29 to 8.09) 0.40 (-5.45 to 6.25)	+
.16.24 SF-36 pain (2 Cooper 1999 ⁵⁴ Subtotal (95% CI) leterogeneity: not app rest for overall effect:	67.1 plicable	28.6 (p = 0.	128 128 .58)	69.1	28.6	121 121	100.0% 100.0%	-2.00 (-11.34 to 7.34) -2.00 (-9.11 to 5.11)	-
I.16.25 SF-36 genera . Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app rest for overall effect:	70.3 plicable	22.6	118 118	67.5	27.5	117 117	100.0% 100.0%	2.80 (-5.66 to 11.26) 2.80 (-3.64 to 9.24)	
.16.26 SF-36 physic: Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect:	81.3 plicable	24.9	118 118	83.5	25.7	114 114	100.0% 100.0%	-2.20 (-10.76 to 6.36) -2.20 (-8.71 to 4.31)	-
I.16.27 SF-36 role lin Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:	75.2 plicable	38.5	118 118	r s) 73.9	40.2	114 114	100.0% 100.0%	1.30 (–12.02 to 14.62) 1.30 (–8.83 to 11.43)	
I.16.28 SF-36 role lin Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:	81.1 plicable	34.4	118 118	ears) 78.4	36.6	116 116	100.0% 100.0%	2.70 (–9.26 to 14.66) 2.70 (–6.40 to 11.80)	
I.16.29 SF-36 mental Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:	71.3 plicable	20.8	118 118	71	20	117 117	100.0% 100.0%	0.30 (–6.56 to 7.16) 0.30 (–4.92 to 5.52)	+
1.16.30 SF-36 social . Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:	69.9 plicable	23.5	119 119	68.3	25.4	116 116	100.0% 100.0%	1.60 (–6.63 to 9.83) 1.60 (–4.66 to 7.86)	+
1.16.31 SF-36 vitality . Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:	56.5 plicable	24.8	118 118 .00)	56.5	24.5	116 116	100.0% 100.0%	0.00 (-8.30 to 8.30) 0.00 (-6.32 to 6.32)	+
I.16.32 SF-36 pain (5 . Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Fest for overall effect:	72.2 plicable	27.4 (p = 0.	119 119 .48)	69.6	28.6	116 116	100.0% 100.0%	2.60 (-6.82 to 12.02) 2.60 (-4.56 to 9.76)	

SF-36 scores (change from baseline)

	First	genera	ation	Secon	d gene	ration			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% Cl
I.17.1 SF-36 general	health (6	6 mont	hs)						
o. Cooper 2004 ⁹⁹	6.3	15.7	84	7.6	17.1	175	100.0%	-1.30 (-6.83 to 4.23)	
Subtotal (95% CI)			84			175	100.0%	–1.30 (–5.51 to 2.91)	-
Heterogeneity: not app									
Test for overall effect:	z = 0.61	(p = 0.	54)						
.17.2 SF-36 physical	functio	n (6 mc	onths)						
b. Cooper 200499	8.9	19.8	84	5.9	24.6	175	100.0%	3.00 (-4.34 to 10.34)	
Subtotal (95% CI)			84			175	100.0%	3.00 (-2.59 to 8.59)	-
Heterogeneity: not app Fest for overall effect:		(n - 0)	29)						
		0	,						
1 .17.3 SF-36 role limi b. Cooper 2004 ⁹⁹	tation pl 28.5	hysical 45.4	(6 mont 86	t hs) 20.9	46.9	178	100.0%	7.60 (-7.92 to 23.12)	
Subtotal (95% CI)	2010		86	2010	1010	178	100.0%	7.60 (-4.21 to 19.41)	
leterogeneity: not app	olicable								
est for overall effect:	z = 1.26	(p = 0.	21)						
1.17.4 SF-36 role limi	tation er	motion	al (6 mo	nths)					
o. Cooper 200499	16.1	38.7	87	12.2	44	177	100.0%	3.90 (-9.77 to 17.57)	
Subtotal (95% CI)			87			177	100.0%	3.90 (-6.50 to 14.30)	
Heterogeneity: not app									
Fest for overall effect:	<i>z</i> = 0.74	(p = 0.	46)						
1.17.5 SF-36 mental I	•		is)						
b. Cooper 2004 ⁹⁹	5.3	18.5	86	6.5	18.6	175	100.0%	-1.20 (-7.49 to 5.09)	
Subtotal (95% CI)			86			175	100.0%	–1.20 (–5.98 to 3.58)	-
Heterogeneity: not app Fest for overall effect:		(n = 0)	62)						
.17.6 SF-36 social fu b. Cooper 2004 ⁹⁹	Inction (11.8	6 mont 20.7	:hs) 81	10.4	19.7	149	100.0%	1.40 (-5.84 to 8.64)	
Subtotal (95% CI)	11.0	20.7	81	10.4	13.7	149	100.0%	1.40 (-4.11 to 6.91)	—
Heterogeneity: not app	olicable		01			140	10010 /0		
Test for overall effect:		(p = 0.	62)						
I.17.7 SF-36 vitality (6 month	s)							
. Cooper 200499	15.5	22.4	88	12.7	24.6	173	100.0%	2.80 (-5.01 to 10.61)	
Subtotal (95% CI)			88			173	100.0%	2.80 (-3.14 to 8.74)	-
leterogeneity: not app			\						
Test for overall effect:	z = 0.92	(p = 0.	36)						
1.17.8 SF-36 pain (6 r									
b. Cooper 200499	25.6	31.3	88	21.1	28.7	173	100.0%	4.50 (-5.77 to 14.77)	
Subtotal (95% CI)	liaabla		88			173	100.0%	4.50 (-3.31 to 12.31)	-
leterogeneity: not app est for overall effect:		(p = 0.	26)						
.17.9 SF-36 general		0							
5. Cooper 2004 ⁹⁹	6.4	12 mon 17.2	tns) 92	8.5	17.6	183	43.3%	-2.10 (-7.81 to 3.61)	
Cooper 1999 ⁵⁴	-2.2	14.3	124	2.2	15.6	116	56.7%	-4.40 (-9.39 to 0.59)	
Subtotal (95% CI)			216			299	100.0%	–3.40 (–6.26 to –0.55)	◆
Heterogeneity: $\chi^2 = 0.6$ Fest for overall effect:	,			0%					
		0	,						
1.17.10 SF-36 physica b. Cooper 2004 ⁹⁹		-	-		21	180	38 60/	0 10 (7 68 + 7 7 49)	
. Cooper 2004 ⁵⁵ . Cooper 1999 ⁵⁴	7.9 2.4	23.5 16.7	89 122	8 0.7	21 18.9	180 113	38.6% 61.4%	-0.10 (-7.68 to 7.48) 1.70 (-4.31 to 7.71)	
Subtotal (95% CI)	2.4	10.7	211	0.7	10.9	293	100.0%	1.00 (-2.58 to 4.59)	↓
Heterogeneity: $\chi^2 = 0.2$	23, df = 1	1 (p = 0		0%					
Test for overall effect:		u u							
.17.11 SF-36 role lim	nitation i	ohysica	ıl (12 ma	onths)					
b. Cooper 2004 ⁹⁹	27.8	47.7	89	26.2	43.5	183	49.0%	1.60 (-13.83 to 17.03)	
. Cooper 1999 ⁵⁴	9.9	41.9	124	25.2	48.5	116	51.0%	–15.30 (–30.42 to –0.18)	+=
Subtotal (95% CI)			213			299	100.0%	-7.03 (-15.24 to 1.19)	-
Heterogeneity: $\chi^2 = 4.0$				75%					
Test for overall effect:	z = 1.68	(<i>p</i> = 0.	09)						
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	First	t gener	ation	Secon	nd gene	eration			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
1.17.12 SF-36 role li			•						
b. Cooper 2004 ⁹⁹	18.7	45.6	91	15.6	43.3	182	53.6%	3.10 (–11.73 to 17.93)	
I. Cooper 1999 ⁵⁴	12.6	48.6	124	17.8	47.2	116	46.4%	-5.20 (-21.13 to 10.73)	
Subtotal (95% CI)			215			298	100.0%	–0.75 (–9.01 to 7.51)	-
Heterogeneity: χ ² = 0 Test for overall effect				= 0%					
1.17.13 SF-36 menta	al health	(12 mo	nths)						
b. Cooper 200499	4.8	19.1	89	7.8	18.8	183	54.6%	-3.00 (-9.33 to 3.33)	
I. Cooper 199954	5.7	22.4	124	6.5	19.3	116	45.4%	-0.80 (-7.74 to 6.14)	
Subtotal (95% CI)			213			299	100.0%	-2.00 (-5.56 to 1.56)	•
Heterogeneity: $\chi^2 = 0$	36 df =	1(n = 0)		= 0%		200	10010 /0	2.00 (0.00 to 1.00)	
Test for overall effect				- 070					
1.17.14 SF-36 social	function	ı (12 m	onths)						
b. Cooper 200499	11.2	19.9	82	11.1	20.1	157	55.4%	0.10 (-6.91 to 7.11)	_ _
I. Cooper 1999 ⁵⁴	7.3	22.4	123	12.1	24.4	116	44.6%	-4.80 (-12.62 to 3.02)	
Subtotal (95% CI)	-		205	-		273	100.0%	-2.08 (-6.05 to 1.89)	-
Heterogeneity: $\chi^2 = 1$.45. df =	1(p = 0)		= 31%					
Test for overall effect				0170					
1.17.15 SF-36 vitality	/ (12 mor	nths)							
b. Cooper 200499	15.3	23.1	91	16.3	24.4	181	47.5%	-1.00 (-8.79 to 6.79)	
I. Cooper 1999 ⁵⁴	11.8	23.5	123	13.1	21	116	52.5%	-1.30 (-8.72 to 6.12)	
Subtotal (95% CI)			214			297	100.0%	-1.16 (-5.25 to 2.93)	-
Heterogeneity: $\chi^2 = 0$	01 df -	1(p = 0)		= 0%					
Test for overall effect				070					
1.17.16 SF-36 pain (12 month	ns)							
b. Cooper 2004 ⁹⁹	26.3	32.1	91	22.1	32.4	181	48.6%	4.20 (-6.46 to 14.86)	
I. Cooper 1999 ⁵⁴	7.6	31.3	124	15.6	31	116	51.4%	-8.00 (-18.36 to 2.36)	
Subtotal (95% CI)			215			297	100.0%	-2.07 (-7.73 to 3.58)	-
Heterogeneity: $\chi^2 = 4$.47. df =	1(p = 0)		= 78%		-		· · · · · · · · · · · · · · · · · · ·	
Test for overall effect									
1.17.17 SF-36 generation	al health	(2 year	rs)						
I. Cooper 1999 ⁵⁴	2.8	20.4	128	4.7	23.5	121	100.0%	-1.90 (-9.10 to 5.30)	
Subtotal (95% CI)			128			121	100.0%	-1.90 (-7.38 to 3.58)	-
Heterogeneity: not ap	plicable		-						
Test for overall effect	•	s (p = 0	.50)						
1.17.18 SF-36 physic	al functi	on (2 y	ears)						
I. Cooper 1999 ⁵⁴	1	20.3	126	2.3	21.2	118	100.0%	-1.30 (-8.15 to 5.55)	
Subtotal (95% CI)			126			118	100.0%	-1.30 (-6.51 to 3.91)	+
Heterogeneity: not ap	plicable								
Test for overall effect) (p = 0	.63)						
1.17.19 SF-36 role li	mitation	physica	al (2 yea	ırs)					
l. Cooper 1999 ⁵⁴	6.1	43.7	128	18.4	53.5	121	100.0%	-12.30 (-28.30 to 3.70)	
Subtotal (95% CI)			128			121	100.0%	-12.30 (-24.47 to -0.13)	-
Heterogeneity: not ap	plicable							- ·	
Test for overall effect		s (p = 0	.05)						
1.17.20 SF-36 role li	mitation	emotio	nal (2 ye	ears)					
. Cooper 1999 ⁵⁴	9.4	47.9	128	17.6	17.4	121	100.0%	-8.20 (-19.84 to 3.44)	←=+
Subtotal (95% CI)			128			121	100.0%	-8.20 (-17.06 to 0.66)	-
Heterogeneity: not ap Test for overall effect		(n = 0							
		u .	,						
1.17.21 SF-36 menta			-	~	01 -	101	100.001		
. Cooper 1999 ⁵⁴	4.2	19.7	127	6	21.5	121	100.0%	-1.80 (-8.55 to 4.95)	
Subtotal (95% CI)			127			121	100.0%	–1.80 (–6.94 to 3.34)	-
Heterogeneity: not ap Test for overall effect	•	(n - 0)	10)						
	. 2 – 0.09	$\mu = 0$							
									-10-50510

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	First	genera	ation	Secon	d gene	ration			
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.17.22 SF-36 social f . Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: 2	6.2 licable	23.7	127 127 127	10.4	27.6	121 121	100.0% 100.0%	-4.20 (-12.63 to 4.23) - 4.20 (-10.62 to 2.22)	-=-
1.17.23 SF-36 vitality I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	11.9 licable	22.6	127 127 87)	11.4	25	121 121	100.0% 100.0%	0.50 (-7.31 to 8.31) 0.50 (-5.44 to 6.44)	+
1.17.24 SF-36 pain (2 I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: 2	3.4	30.1 (p = 0.	128 128 007)	14.2	32.5	121 121	100.0% 100.0%	-10.80 (-21.04 to -0.56) -10.80 (-18.59 to -3.01)	
1.17.25 SF-36 general I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: 2	3.3 licable	18.5	118 118	2	25.6	117 117	100.0% 100.0%	1.30 (-6.21 to 8.81) 1.30 (-4.41 to 7.01)	
1.17.26 SF-36 physica I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	-0.8 licable	20.6	116 116	-0.1	23.9	112 112	100.0% 100.0%	-0.70 (-8.32 to 6.92) -0.70 (-6.50 to 5.10)	+
1.17.27 SF-36 role lim I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	10.6 licable	42.7	118 118	rs) 17.1	53.4	114 114	100.0% 100.0%	-6.50 (-22.89 to 9.89) -6.50 (-18.97 to 5.97)	
1.17.28 SF-36 role lim I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	20.1 licable	41.1	118 118	ears) 18.4	47.6	116 116	100.0% 100.0%	1.70 (–13.29 to 16.69) 1.70 (–9.70 to 13.10)	
1.17.29 SF-36 mental . Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	8.3 licable	21.9	117 117	7.9	24.2	117 117	100.0% 100.0%	0.40 (–7.37 to 8.17) 0.40 (–5.51 to 6.31)	
1.17.30 SF-36 social fi I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	9.7 Ilicable	24.6	118 118	8.9	28.6	116 116	100.0% 100.0%	0.80 (–8.19 to 9.79) 0.80 (–6.04 to 7.64)	
1.17.31 SF-36 vitality I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Heterogeneity: not app Test for overall effect: <i>2</i>	13.4 licable	24.4	117 117 59)	11.5	29.4	116 116	100.0% 100.0%	1.90 (–7.22 to 11.02) 1.90 (–5.04 to 8.84)	
1.17.32 SF-36 pain (5 I. Cooper 1999 ⁵⁴ Subtotal (95% Cl) Heterogeneity: not app Test for overall effect: <i>2</i>	9.2	30.9	119 119 35)	13.3	36.4	116 116	100.0% 100.0%	-4.10 (-15.46 to 7.26) -4.10 (-12.74 to 4.54)	

Favours Favours second generation

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1.7.33 S7-36 general health (10 years) 1. Cooper 1999 ⁴⁴ 2.8 22 95 94 100.0% 1.90 (-6.53 to 10.33) Subtotal (95% C) 95 94 100.0% 1.90 (-6.53 to 10.33) 1.17.34 S7-36 polysical function (10 years) 0.00% 1.40 (-8.25 to 11.15) 1.17.34 S7-36 role limitation physical (10 years) 1.40 (-6.02 to 8.82) 1.17.35 S7-36 role limitation physical (10 years) 0.00% -4.10 (-22.88 to 14.68) 1.17.35 S7-36 role limitation physical (10 years) 0.00% -4.10 (-23.88 to 14.68) 1.17.36 S7-36 role limitation physical (10 years) 0.00% -4.10 (-22.88 to 14.68) 1.17.36 S7-36 role limitation emotional (10 years) 0.00% -7.60 (-25.79 to 10.59) 1.17.36 S7-36 metal health (10 years) 0.00% -7.60 (-27.44 to 6.24) 1.17.37 S7-36 metal health (10 years) 0.00% 0.70 (-7.95 to 9.35) 1.00.09% 0.70 9.5 94 100.0% -7.60 (-27.44 to 6.24) 1.17.36 S7-36 social function (10 years) 0.00% 0.70 (-7.95 to 9.35) 94 1.00.09% 0.70 (-7.95 to 9.3		First	gener	ation	Secon	d gene	eration			
L Cooper 1996 ¹³ 2.8 22 95 0.9 23 94 100.0% 1.90 (-6.53 to 10.33) Heterogeneity: not applicable Test for overall effect: $z = 0.56 (p = 0.56)$ 1.17.34 SF-36 physical function (10 years) L Cooper 1999 ¹⁶ -3 25 95 -4.4 27 94 100.0% 1.40 (-6.35 to 11.15) Subtotal (65% CI) 95 94 100.0% 1.40 (-6.02 to 8.82) Heterogeneity: not applicable Test for overall effect: $z = 0.37 (p = 0.71)$ 1.17.35 SF-36 role limitation physical (10 years) L Cooper 1999 ¹⁶ 10.9 47 95 15 39 94 100.0% -4.10 (-22.88 to 14.68) Subtotal (65% CI) 95 94 100.0% -4.10 (-22.88 to 14.68) Subtotal (65% CI) 95 94 100.0% -7.60 (-25.79 to 10.59) Subtotal effect: $z = 0.56 (p = 0.57)$ 1.17.35 SF-36 role limitation emotional (10 years) L Cooper 1999 ¹⁶ 13.5 47 95 21.1 50 94 100.0% -7.60 (-25.79 to 10.59) Subtotal (65% CI) 95 94 100.0% -7.60 (-25.79 to 10.59) Subtotal (65% CI) 95 94 100.0% 0.70 (-7.95 to 9.35) Subtotal (65% CI) 95 95 94 100.0% 0.70 (-5.88 to 7.28) Heterogeneity: not applicable Test for overall effect: $z = 0.21 (p = 0.83)$ 1.17.37 SF-36 mental health (10 years) L Cooper 1999 ¹⁶ 7.9 29 95 7.2 21 94 100.0% 0.70 (-5.88 to 7.28) Heterogeneity: not applicable Test for overall effect: $z = 0.21 (p = 0.83)$ 1.17.38 SF-36 social function (10 years) L Cooper 1999 ¹⁶ 7.9 29 95 94 100.0% 0.70 (-5.88 to 7.28) Heterogeneity: not applicable Test for overall effect: $z = 0.05 (p = 0.56)$ 1.17.39 SF-36 vitality (10 years) L Cooper 1999 ¹⁶ 15.3 27 95 12.9 29 94 100.0% 2.40 (-8.10 to 12.90) Subtotal (65% CI) 95 94 100.0% 0.70 (-12.80 to 14.20) Heterogeneity: not applicable Test for overall effect: $z = 0.59 (p = 0.56)$ 1.17.40 SF-36 pin (10 years) L Cooper 1999 ¹⁶ 12.3 35 95 11.6 37 94 100.0% 0.70 (-12.80 to 14.20) Subtotal (65% CI) 95 94 100.0% 0.70 (-12.80 to 14.20) Subtotal (65% CI) 95 94 100.0% 0.70 (-2.57 to 10.37) Heterogeneity: not applicable Test for overall effect: $z = 0.13 (p = 0.89)$	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight		
Subtoral (95% C) 95 94 100.0% 1.90 (-4.52 to 8.32) Test for overall effect: $z = 0.58$ ($p = 0.56$) 1.17.34 SF-36 physical function (10 years) 1. Cooper 1999 ⁴⁷ -3 25 95 -4.4 27 94 100.0% 1.40 (-8.35 to 11.15) Subtoral (86% C) 95 94 100.0% 1.40 (-8.35 to 11.15) Subtoral (86% C) 95 94 100.0% -4.10 (-22.88 to 14.68) Subtoral (86% C) 95 94 100.0% -4.10 (-22.88 to 14.68) Subtoral (86% C) 95 94 100.0% -4.10 (-22.88 to 14.68) Subtoral (86% C) 95 94 100.0% -4.10 (-22.88 to 14.68) Subtoral (86% C) 95 94 100.0% -4.10 (-22.88 to 14.68) Subtoral (86% C) 95 95 94 100.0% -7.60 (-25.79 to 10.59) Subtoral (86% C) 95 95 94 100.0% -7.60 (-25.79 to 10.59) Subtoral (86% C) 95 95 94 100.0% 0.70 (-7.95 to 9.35) Subtoral (86% C) 95 95 94 100.0% 0.70 (-5.88 to 7.28) Heterogeneity: not applicable Test for overall effect: $z = 0.21$ ($p = 0.83$) 1.17.39 SF-36 social function (10 years) 1. Cooper 1999 ⁴⁷ 1.3 25 95 7.2 21 94 100.0% 0.70 (-7.95 to 9.35) Subtoral (86% C) 95 94 100.0% 0.70 (-5.88 to 7.28) Heterogeneity: not applicable Test for overall effect: $z = 0.21$ ($p = 0.83$) 1.17.39 SF-36 social function (10 years) 1. Cooper 1999 ⁴⁷ 1.5 3 27 95 12.9 29 94 100.0% 0.70 (-5.88 to 7.28) Heterogeneity: not applicable Test for overall effect: $z = 0.5(p = 0.56)$ 1.17.40 SF-36 social function (10 years) 1. Cooper 1999 ⁴⁷ 15.3 27 95 12.9 29 94 100.0% 2.40 (-8.10 to 12.80) Subtoral (86% C) 95 94 100.0% 0.70 (-12.80 to 10.39) Heterogeneity: not applicable Test for overall effect: $z = 0.5(p = 0.56)$ 1.17.40 SF-36 pin (10 years) 1. Cooper 1999 ⁴⁷ 12.3 35 95 11.6 37 94 100.0% 0.70 (-12.80 to 14.20) Subtoral (86% C) 95 94 100.0% 0.70 (-12.80 to 14.20) Subtoral (86% C) 95 94 100.0% 0.70 (-2.57 to 10.37) Heterogeneity: not applicable Test for overall effect: $z = 0.51 (p = 0.56)$ 1.17.40 SF-36 pin (10 years) 1. Cooper 1999 ⁴⁷ 12.3 35 95 11.6 37 94 100.0% 0.70 (-9.57 to 10.57) Heterogeneity: not applicable Test for overall effect: $z = 0.13 (p = 0.89)$	1.17.33 SF-36 genera	al health	(10 yea	ars)						
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Cooper 1999 ⁵⁴ 9.9 26 95 10.1 30 94 100.0% -0.20 (-10.72 to 10.32) Subtotal (95% CI) 95 94 100.0% -0.20 (-8.21 to 7.81) Heterogeneity: not applicable 94 100.0% -0.20 (-8.21 to 7.81) Intervention 95 94 100.0% -0.20 (-8.21 to 7.81) Intervention 95 94 100.0% -0.20 (-8.21 to 7.81) Intervention 95 94 100.0% -0.20 (-8.21 to 7.81) Intervention 999 100.0% 2.40 (-8.10 to 12.90) 2.40 (-8.10 to 12.90) Subtotal (95% CI) 95 94 100.0% 2.40 (-5.59 to 10.39) Heterogeneity: not applicable 7.59 ($p = 0.56$) 7.40 (-5.59 to 10.39) Intractice 7.95 ($p = 0.56$) 7.40 (-5.59 to 10.39) Intractice 7.40 (-9.57 to 10.97) 7.40 (-9.57 to 10.97) Heterogeneity: not applicable 7.50 ($p = 0.89$) 7.70 (-9.57 to 10.97) Heterogeneity: not applicable 7.50 ($p = 0.89$) 7.70 (-9.57 to 10.97)	.17.38 SF-36 social	function	(10 ye	ars)						
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I.17.40 SF-36 pain (10 years) . Cooper 1999 ⁵⁴ 12.3 35 95 11.6 37 94 100.0% 0.70 (-12.80 to 14.20) Subtotal (95% Cl) 95 94 100.0% 0.70 (-9.57 to 10.97) Heterogeneity: not applicable Fest for overall effect: $z = 0.13$ ($p = 0.89$) 100.0% 0.70 (-9.57 to 10.97)	• •	plicable		90			34	100.0%	2.40 (-0.09 10 10.09)	
.17.40 SF-36 pain (10 years) Cooper 1999 ⁵⁴ 12.3 35 95 11.6 37 94 100.0% 0.70 (-12.80 to 14.20) Subtotal (95% CI) 95 94 100.0% 0.70 (-9.57 to 10.97) leterogeneity: not applicable	• •		(n ^	56)						
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Subtotal (95% Cl) 95 94 100.0% 0.70 (-9.57 to 10.97) Heterogeneity: not applicable Test for overall effect: z = 0.13 (p = 0.89) 100.0% 0.70 (-9.57 to 10.97)	• •									
Heterogeneity: not applicable Test for overall effect: <i>z</i> = 0.13 (<i>p</i> = 0.89)		12.3	35		11.6	37				
Test for overall effect: z = 0.13 (p = 0.89)	• •			95			94	100.0%	0.70 (–9.57 to 10.97)	
	• • •									
	est for overall effect:	<i>z</i> = 0.13	(p = 0	.89)						

-10-5 0 5 10 Favours Favours second generation first generation

144



	First	First generation	ation	Second		generation				
Study or subgroup Mean SD Total Mean	Mean	ß	Total	Mean	SD	SD Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	
1.18.2 6 months e. Hawe 2003⁰₄ Subtotal (95% CI)	0.8	0.24	31 31	0.8	0.27	37 37	100.0% 100.0%	0.00 (-0.16 to 0.16) 0.00 (-0.12 to 0.12)		
Heterogeneity: not applicable Test for overall effect: $z = 0.00 \ (p = 1.00)$	plicable $z = 0.00$	1. (<i>p</i> = 1.	(00						ļ	
1.18.3 12 months e. Hawe 2003 ⁹⁴ Subtotal (95% CI)	0.82	0.25	28 28	0.85	0.23	33 33	100.0%	-0.03 (-0.19 to 0.13) -0.03 (-0.15 to 0.09)		
Heterogeneity: not applicable Test for overall effect: $z = 0.48$ ($p = 0.63$)	plicable : z = 0.48) (<i>p</i> = 0.1	63)			}				
									-0.5 -0.25 0 0.25 0.5 Favours second generation Favours first generation	tion



	First	First generation	ation	Second (d genei	generation				
Study or subgroup Mean SD Total Mean	Mean	ß	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI	rence 9% CI
1.19.1 6 months e. Hawe 2003 ⁹⁴ 0.15 0.29 2 Subtotal (95% CI) Heterogeneity: not applicable Taet for overall effect: 7 − 1 78 (n − 0.08)	0.15 plicable	0.29 29 29	29 29	0.02	0.3	37 37	100.0% 100.0 %	0.13 (-0.06 to 0.32) 0.13 (-0.01 to 0.27)		
1.19.2 12 months e. Hawe 2003^{94} 0.13 0.22 2 Subtotal (95% Cl) Heterogeneity: not applicable Test for overall effect: $z = 1.14$ ($p = 0.25$)	0.13 0.13 plicable : z = 1.14	0.22 0.22 · (<i>p</i> = 0.2	27 27 25)	0.05	0.32	33 33	100.0% 100.0%	0.08 (-0.10 to 0.26) 0.08 (-0.06 to 0.22)		
									-0.5 -0.25 0 Favours second generation 1	0.25 0.5 Favours first generation

Proportion requiring repeat endometrial ablation

Option Events Total Events Total Meight aproup Events 106 0 209 19.7% 19.7% 10.4% 200 33 19.7% 19.7% 10.4% 200 209 33 19.7% 19.4% 2 21.9% 2 21.9% 2 21.9% 2 21.9% 2 21.9% 2 21.9% 2 21.9% 2 21.9% 2	Neight 19.7% 19.4% 39.1% 21.9% 20.0% 100.0% 100.0% 100.0% 100.0% 100.0%	Intervents Total V 0 0 209 1 33 175 3 1755 37 3 1755 37 3 129 137 2 343 1 2 343 1 2 137 1 2 137 1 2 137 1 2 137 1 2 137 1
Cooper 2004*** 0 106 0 203 Cooper 2002*** 1 0 106 0 203 Dulchas 2003*** 0 37 19,4% Cooper 2002*** 1 37 19,4% Cooper 1999*** 2 137 19,4% Cooper 1998*** 2 138 0 137 Cooper 1998*** 2 138 0 137 Cooper 1998*** 2 138 0 137 Lal events 4 4 4 4 An Zon-Rabelink 201** 2 0.43); $\beta = 0.43$; $\beta = 0.43$ 2 33.7% Lal events 2 134 0 129 2 39.1% Cooper 1998** 0 133 0 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137 100.0% 137	19.7% 19.4% 39.1% 21.9% 100.0% 100.0% 100.0% 100.0%	0 209 1 37 2 33 1 75 2 3 3 175 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
Cooper 2004 ¹⁶ 0 106 0 209 Dulcha 2003 ¹⁶ 1 96 9 37 19,4% Cooper 1999 ¹⁴ 2 133 175 39,1% Cooper 1999 ¹⁴ 2 133 0 137 19,4% Cooper 1999 ¹⁴ 2 133 0 137 19,4% Cooper 1999 ¹⁴ 2 133 0 137 19,4% Cooper 1999 ¹⁴ 2 133 0 137 100,0% Meyer 1998 ¹⁵ 4 4 4 133 0 137 0.2 2 years 0 138 0 133 0 137 0.2 2 years 0 138 0 133 0 137 0.2 2 years 0 138 0 133 0 0 0.2 1 years 0 138 0 133 100.0% 137 100.0% Meyer 1998 ¹⁶ 0 138 2 137	19.7% 19.4% 39.1% 21.9% 26.3% 26.3% 100.0% 100.0% 100.0%	0 209 1 37 3 175 0 137 1 175 3 175 3 175 3 175 3 175 3 137 1 137 1 137 1 137 1 137 1 137 1 137
Duleba 2003** 1 86 0 193 19.7% Have 2003** 0 35 1 37 19.4% Cooper 2003** 0 35 1 37 19.4% Cooper 1999** 2 134 0 137 19.4% Cooper 1999** 0 138 0 137 100.0% Mayer 1998** 0 138 0 100.0% 137 100.0% Laterporentik: $x^2 = 2.75$, df = 3 ($p = 0.43$); $\beta = 0.43$; $\beta = 0.43$; $\beta = 0.43$; $\beta = 0.53$ % 334 343 100.0% Laterporentik: $x^2 = 2.75$, df = 3 ($p = 0.43$); $\beta = 0.64$ 334 343 100.0% Mayer 1998** 0 138 0 137 23.7% Cooper 1999** 0 138 0 137 100.0% Mayer 1998** 0 138 0 137 100.0% Mayer 1998** 0 138 0 137 100.0% Kateropeneity: $x^2 = 0.97$, df = 1 ($p = 0.32$); $\beta = 0.3$ 343 100.0%	19.7% 19.4% 39.1% 21.9% 100.0% 100.0% 100.0% 100.0% 100.0%	1 1 3 1 3 3 3
Hawe 2003 ⁴⁴ 0 35 1 37 19.4% Cooper 2002 ⁴⁶ 1 90 3 175 33.1% Cooper 1999 ⁴⁴ 2 134 0 129 21.9% Meyer 1998 ⁴⁵ 2 134 0 129 21.9% Meyer 1998 ⁴⁵ 2.75, df = 3 ($p = 0.43$); $l^2 = 0.75$, df = 3 ($p = 0.43$); $l^2 = 0.75$ 880 100.0% terogeneity: $\chi^2 = 2.75$, df = 3 ($p = 0.43$); $l^2 = 0.96$ 33.23 33.23 33.23 terogeneity: $\chi^2 = 2.75$, df = 1 ($p = 0.64$) 33.3 0 137 100.0% Meyer 1998 ⁴³ 0 138 0 137 100.0% Cooper 1998 ⁴³ 0 138 0 137 100.0% Meyer 1998 ⁴³ 0 138 0 137 100.0% terogeneity: $\chi^2 = 0.97$, df = 1 ($p = 0.29$); $l^2 = 0.97$, df = 0.73) 138 0 137 100.0% Meyer 1998 ⁴⁵ 0 138 2 137 100.0% 137 100.0% Leroverall effect: $z = 0$	19.4% 39.1% 21.9% 100.0% 100.0% 100.0% 100.0% 100.0%	1 37 37 3 175 175 3 175 137 3 1 129 1 1 129 2 3 333 3 3 333 3 3 333 1 1 129 1 137 1 1 137 1 1 137 1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	39.1% 21.9% 73.7% 26.3% 100.0% 100.0% 100.0%	3 175 0 1 1 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 3
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	21.9% 100.0% 26.3% 100.0% 100.0% 100.0%	0 129 2 33 7 7 2 33 880 3 33 3 33 1 37 1 29 1 37 1 29 1 37 1 29 1 37 1 29 1 37 1 29 1 37 1 3
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	100.0% 73.7% 26.3% 100.0% 100.0% 100.0%	137 137 3 4 3 3 3 137 1 137 1 137 1 129 1 137 1 137 1 129 1 137 1 137 1 137
1)589589100.0% $= 2.75, df = 3 (p = 0.43); l^2 = 0\%$ $= 2.75, df = 3 (p = 0.43); l^2 = 0\%$ $= 2.75, df = 3 (p = 0.43); l^2 = 0\%$ ffect: $z = 0.47$ ($p = 0.64$) 2 $3 (p = 0.43); l^2 = 0\%$ $3 (p = 0.43); l^2 = 0\%$ fink 2001^{16} 2 134 0 138 2 134 0 138 0 10 334 334 343 100.0% 10 334 334 343 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 0 138 2 137 100.0% 10 2 134 0 129 100.0% 10 2 134 1 129 100.0% 10 3 134 1 129 100.0% 10 124 1 129 100.0% 10 124 1 129 100.0% 10 134 1 129 100.0% 134 1 129 100.0%	100.0% 73.7% 26.3% 100.0% 100.0% 100.0% 100.0%	880 4 6 880 1 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
$ = 2.75, df = 3 (p = 0.43); l^{2} = 0\% $ ffect: $z = 0.47 (p = 0.64)$ ffect: $z = 0.47 (p = 0.64)$ ffect: $z = 0.47 (p = 0.64)$ ffect: $z = 0.37 (p = 0.32); l^{2} = 0\% $ ffect: $z = 0.34 (p = 0.32); l^{2} = 0\% $ ffect: $z = 0.34 (p = 0.73)$ ffect: $z = 0.34 (p = 0.73)$ ffect: $z = 1.05 (p = 0.32); l^{2} = 0\% $ ffect: $z = 1.05 (p = 0.29)$ ffect: $z = 1.05 (p = 0.29)$ ffect: $z = 1.02 (p = 0.31)$	73.7% 26.3% 100.0% 100.0% 100.0%	4 6 0 0 0 1 37 1 1 29 1 37 1 1 29 1 20 1
$ = 2.75, \text{ df} = 3 (p = 0.43); l^{p} = 0\% $ ffect: $z = 0.47 (p = 0.64)$ ffect: $z = 0.37 (p = 0.73)$ ffect: $z = 0.34 (p = 0.32); l^{2} = 0\% $ ffect: $z = 0.34 (p = 0.32); l^{2} = 0\% $ ffect: $z = 0.34 (p = 0.32); l^{2} = 0\% $ ffect: $z = 0.34 (p = 0.73)$ ffect: $z = 0.34 (p = 0.73)$ ffect: $z = 0.34 (p = 0.73)$ ffect: $z = 1.05 (p = 0.32); l^{2} = 0\% $ ffect: $z = 1.05 (p = 0.29)$ ffect: $z = 1.02 (p = 0.21)$ ffect: $z = 1.02 (p = 0.31)$	73.7% 26.3% 100.0% 100.0% 100.0%	3 77 0 129 0 137 3 343 1 37 1 1 2 137 1 1 2 129
link 2001 ⁶⁵ 2 62 3 77 73.7% 1 2 2 134 0 137 26.3% 1 3 234 3 0 137 100.0% 1 3 334 3 0 137 100.0% 1 5 $(-10^{-1})^{-1} = 0^{-1}$ 1 $(-10^{-1})^{-1} = $	73.7% 26.3% 100.0% 100.0% 100.0%	3 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
link 2001 ⁴⁵ 2 62 3 77 73.7% 2 134 0 138 0 137 26.3% 1) 334 3 334 3 343 100.0% fect: $z = 0.37$, $df = 1$ ($p = 0.32$); $l^2 = 0\%$ fect: $z = 0.34$ ($p = 0.73$) 10 0 138 2 137 100.0% fect: $z = 0.34$ ($p = 0.73$) 138 2 137 100.0% 137 10	73.7% 26.3% 100.0% 100.0% 100.0%	2 129 2 137 2 137 137 137 1 129 1 129 1 129 1 129 1 1 1 1 1 1 1 1 1 1 1 1 1
4 2 134 0 129 26.3% 1) 334 3 343 100.0% 1) 334 3 343 100.0% 1) 334 3 343 100.0% 1) 334 3 343 100.0% 10 138 3 343 100.0% 10 138 2 137 100.0% 1) 0 138 2 137 100.0% 1) 0 138 2 137 100.0% 1) 0 138 2 137 100.0% 10 138 2 137 100.0% 10 138 2 137 100.0% 1) 2 134 0 129 100.0% 1) 2 134 1 129 100.0% 10 2 134 1 129 100.0% 10 3 134 1 129 100.0%	26.3% 100.0% 100.0% 100.0% 100.0%	0 129 2 3 343 2 137 1 137 1 29 1 29 1 29
1) 0 138 0 137 100.0% $= 0.97$, df = 1 ($p = 0.32$); $l^2 = 0\%$ 343 100.0% 343 100.0% $= 0.97$, df = 1 ($p = 0.32$); $l^2 = 0\%$ 138 2 137 100.0% $= 0.97$, df = 1 ($p = 0.73$) 0 138 2 137 100.0% 1) 0 138 2 137 100.0% 1) 0 138 2 137 100.0% 1) 0 138 2 137 100.0% 1) 0 138 2 137 100.0% 1) 2 134 0 129 100.0% 1) 2 134 0 129 100.0% 1) 2 134 1 129 100.0% 1) 3 134 1 129 100.0%	100.0% 100.0% 100.0% 100.0%	0 137 3 343 2 137 2 137 0 129
1)334333100.0% $= 0.97$, df = 1 ($p = 0.32$); $l^2 = 0\%$ $= 0.97$, df = 1 ($p = 0.22$); $l^2 = 0\%$ $= 0.97$, df = 1 ($p = 0.22$); $l^2 = 0\%$ $= 0.97$, df = 1 ($p = 0.32$); $l^2 = 0.32$); $l^2 = 0.32$ $= 0.32$); $l^2 = 0.36$ $= 0.138$ $= 1.177$ 1)01382137100.0%1)01382137100.0%1)21340129100.0%1)21340129100.0%1)21341129100.0%1)31341129100.0%	100.0% 100.0% 100.0% 100.0%	3 343 2 137 137 129
$= 0.97, df = 1 (p = 0.32); l^2 = 0\%$ act: $z = 0.34 (p = 0.73)$ = 0.34 (p = 0.73) = 0 138 2 137 100.0% = 0 138 2 137 100.0% = 0 2 = 1.05 (p = 0.29) applicable = 0 129 100.0% = 1.02 (p = 0.31) = 0 129 100.0% = 0 134 1 129 100.0%	100.0% 100.0% 100.0%	3 2 137 137 137 137 137
$\begin{array}{c} 0.94, \ dr = 1 \ (p = 0.32); \ r = 0.96 \\ \texttt{oct} \ z = 0.34 \ (p = 0.73) \\ \texttt{oct} \ z = 0.34 \ (p = 0.73) \\ \texttt{oct} \ oct$	100.0% 100.0% 100.0%	2 137 137 137 137
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	100.0% 100.0% 100.0%	138 2 137 138 2 137 2 137 134 0 129
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	100.0% 100.0% 100.0%	138 2 137 138 2 137 2 137 134 0 129
136 136 137 100.0% applicable $2 = 1.05$ ($p = 0.29$) $2 = 1.00.0\%$ 129 100.0% $2 = 1.02$ ($p = 0.31$) $2 = 1.02$ ($p = 0.31$) 129 100.0% $3 = 134$ $1 = 129$ 100.0% $3 = 134$ $1 = 129$ 100.0%	100.0%	134 0 129
applicable cet: $z = 1.05$ ($p = 0.29$) cet: $z = 1.05$ ($p = 0.29$) 2 134 0 129 100.0% applicable 2 0 applicable cet: $z = 1.02$ ($p = 0.31$) 3 134 1 129 100.0% 134 1 129 100.0%	100.0% 100.0%	134 0 129
$\begin{bmatrix} 2 & 134 & 0 & 129 & 100.0\% \\ 134 & 0 & 129 & 100.0\% \\ applicable \\ act: z = 1.02 (p = 0.31) \\ 3 & 134 & 1 & 129 & 100.0\% \\ 134 & 1 & 129 & 100.0\% \\ \end{bmatrix}$	100.0% 100.0%	0 129
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	100.0% 100.0%	0 129
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2 (<i>p</i> = 0.31) 3 134 1 129 100.0% 134 1 129 100.0%		0
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3 134 1 129 100.0% 134 1 129 100.0%		
134 129 100.0%	100.0%	1 129
	100.0%	129
l otal events 3 1		-
Test for overall effect: $z = 0.93$ ($p = 0.35$)		

Favours first generation

Favours second generation

	First generation	ation	Second generation	eration		Peto odds ratio (non-event)	Peth odds ratio (non-event)
Study or subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 99% Cl	Peto, Fixed, 99% Cl
1.21.1 <12 months e. Hawe 2003^{44} Subtortal (95% CI) Total events Heterogeneity: not applicable Test for overall effect: $z = 0.71$ ($p = 0.48$)	4 4	38 8	<i>т</i> т	છ સુ	100.0% 100.0%	0.56 (0.07 to 4.53) 0.56 (0.11 to 2.75)	
1.2.1.2.12 months a. Brun 2006 ¹⁰³ b. Cooper 2004 ⁹⁹ c. Perino 2004 ¹⁰⁰ d. Duleba 2003 ⁹⁴ e. Hawe 2003 ⁹⁴ e. Corson 2000 ¹⁰⁴ j. Soysal 2001 ⁸⁶ j. Soysal 2001 ⁸⁶ j. Soysal 2001 ⁸⁶ f. Corson 2000 ¹⁰¹ j. Soysal 2001 ⁸⁶ j. Soysal 2001 ⁸⁷ j. Soysal 2001 ⁸⁶ j. Soysal 2001 ⁸⁶ j. Soysal 200 ⁸⁶ j	2000 300 2000 2000 2000 2000 2000 2000	20 20 20 20 20 20 20 20 20 20 20 20 20 2	000-10004400 0 0	31 209 209 31 31 175 175 175 150 150 129 129 2 33 2 3	2.4% 2.5% 1.2.5% 2.25% 7.1% 7.1% 2.2.5% 7.1% 2.2.9% 7.19%	0.12 (0.00 to 6.82) 2.57 (0.05 to 140.43) 0.57 (0.08 to 3.97) 1.35 (0.02 to 3.97) 1.35 (0.02 to 91.67) 0.77 (0.14 to 4.30) 0.77 (0.07 to 8.25) 0.77 (0.04 to 8.25) 0.77 (0.16 to 7.21) 0.66 (0.11 to 3.84) 0.76 (0.23 to 2.49) 0.76 (0.23 to 2.49) 0.77 (0.47 to 1.24) 0.77 (0.47 to 1.24)	
1.21.3 2 years 6 f. van Zon-Rabelink 2001 ⁵⁶ 6 k. Corson 2000 ¹⁰¹ 9 h. Cooper 1999 ⁵⁴ 17 m. Mayer 1998 ⁵⁴ 17 m. Mayer 1998 ⁵⁴ 7 f. Houser 1998 ⁵⁴ 9 Subtrat (95% CI) 41 Heterogeneity: $\chi^2 = 2.77$, df = 3 ($p = 0.43$); $\beta^2 = 0.43$; $\beta^2 = 0.74$) Test for overall effect: $z = 1.48$ ($p = 0.14$)	6 17 9 81 81 81 81 81 81 81 81 81 81 81 81 81	62 126 138 454	89.47° 8	77 150 121 137	20.5% 20.3% 44.7% 14.5% 100.0 %	1.08 (0.25 to 4.69) 0.45 (0.10 to 1.95) 0.85 (0.32 to 2.31) 0.32 (0.06 to 1.84) 0.68 (0.41 to 1.13)	
1.21.4 3 years m. Meyer 1998 [™] subtotal (95% CI) Total events Heterogeneity: not applicable Test for overall effect: z = 1.54 (p = 0.12)	4 4 1	138 138	7 7	137 137	100.0% 100.0 %	0.48 (0.14 to 1.64) 0.48 (0.19 to 1.22)	
1.21.5 5 years 1. Cooper 1999 ⁵⁴ Subtotal (95% CI) Total events Heterogeneity: not applicable Test for overall effect: $z = 1.77$ ($p = 0.08$)	34 34	136	21	130 1 30	100.0% 100.0 %	0.58 (0.26 to 1.28) 0.58 (0.31 to 1.06)	
1.21.6 10 years I. Cooper 1999 ⁵⁴ Subtotal (95% CI) Total events Heterogeneity: not applicable Test for overall effect: <i>z</i> = 2.17 (<i>p</i> = 0.03)	38 38 38	134 134	22 22	129	100.0% 100.0%	0.52 (0.29 to 0.94) 0.52 (0.29 to 0.94)	•
							0.1 0.2 0.5 1 2 5 10 Favours second generation

Number of patients with adverse events – periprocedure

	First gen	eration	Second ge	eneration			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
.22.1 Anaesthesia problem	IS						
. Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
. Cooper 2004 ⁹⁹	0	107	0	215		Not estimable	
. Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
. Duleba 200398	0	86	1	193	48.7%	4.24 (0.02 to 1123.03)	_
. Hawe 2003 ⁹⁴	0	34	0	37		Not estimable	
van Zon-Rabelink 200195	0	62	0	77		Not estimable	
. Cooper 2002 ⁵⁶	0	90	1	175	51.3%	4.55 (0.02 to 1046.63)	_ →
. Pellicano 2002 ¹⁰²	0	42	0	40		Not estimable	
Corson 200179	0	89	0	187		Not estimable	
Soysal 2001 ⁹⁶	0	48	0	45		Not estimable	
Corson 2000 ¹⁰¹	0	123	0	144		Not estimable	
Cooper 199954	0	134	0	129		Not estimable	
n. Meyer 1998 ⁵³	0	117	0	128		Not estimable	
. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	
ubtotal (95% CI)	-	1017	-	1467	100.0%	4.40 (0.23 to 85.11)	
otal events	0		2				_
eterogeneity: $\chi^2 = 0.00$, df = est for overall effect: $z = 0.9$	1 (<i>p</i> = 0.98); <i>I</i> ² = 0%	_				
22.2 Excessive bleeding							
Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
. Cooper 2004 ⁹⁹	0	107	0	215		Not estimable	
Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
Duleba 200398	0	86	0	193		Not estimable	
Hawe 2003 ⁹⁴	1	34	0	37	12.6%	0.12 (0.00 to 21.50)	·
van Zon-Rabelink 200195	0	62	0	77		Not estimable	
Cooper 2002 ⁵⁶	0	90	0	175		Not estimable	
Pellicano 2002 ¹⁰²	0	42	0	40		Not estimable	
Corson 200179	0	89	0	187		Not estimable	
Soysal 2001 ⁹⁶	2	48	0	45	25.0%	0.14 (0.00 to 5.51)	· · · · · · · · · · · · · · · · · · ·
Corson 2000 ¹⁰¹	0	123	0	144	20.070	Not estimable	
Cooper 1999 ⁵⁴	5	134	0	129	62.3%	0.14 (0.01 to 1.39)	
	0		0		02.370		
n. Meyer 1998 ⁵³		117		128		Not estimable	
. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	-
ubtotal (95% CI)	-	1017		1467	100.0%	0.14 (0.03 to 0.55)	
otal events	8		0				
eterogeneity: $\chi^2 = 0.00$, df = est for overall effect: $z = 2.8$							
22.3 Uterine perforation							
.22.3 Uterine perforation Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
22.3 Uterine perforation	0 0	20 107	0 2	31 215	12.5%	Not estimable 4.49 (0.09 to 215.97)	_
.22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹					12.5%		
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰	0	107	2	215	12.5% 6.0%	4.49 (0.09 to 215.97)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸	0 0	107 55	2 0	215 56		4.49 (0.09 to 215.97) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ³⁸ Hawe 2003 ⁹⁴	0 0 1	107 55 86	2 0 0	215 56 193		4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32)	·
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵	0 0 1 0 3	107 55 86 34 62	2 0 0 0	215 56 193 37 77	6.0% 20.6%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶	0 0 1 0 3 3	107 55 86 34 62 90	2 0 0 0 0 0	215 56 193 37 77 175	6.0% 20.6% 18.8%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰²	0 0 1 0 3	107 55 86 34 62 90 42	2 0 0 0 0 0 0	215 56 193 37 77 175 40	6.0% 20.6%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹	0 0 1 3 3 2 0	107 55 86 34 62 90 42 89	2 0 0 0 0 0 0 0 0	215 56 193 37 77 175 40 187	6.0% 20.6% 18.8%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶	0 0 1 3 3 2 0 0	107 55 86 34 62 90 42 89 48	2 0 0 0 0 0 0 0 0	215 56 193 37 77 175 40 187 45	6.0% 20.6% 18.8% 13.9%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹	0 0 1 3 3 2 0 0	107 55 86 34 62 90 42 89 48 123	2 0 0 0 0 0 0 0 0 0	215 56 193 37 77 175 40 187 45 144	6.0% 20.6% 18.8% 13.9% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable Not estimable 0.11 (0.00 to 20.02)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴	0 0 1 0 3 3 2 0 0 0 1	107 55 86 34 62 90 42 89 48 123 134	2 0 0 0 0 0 0 0 0 0 0 1	215 56 193 37 77 175 40 187 45 144 129	6.0% 20.6% 18.8% 13.9% 7.0% 14.1%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³	0 0 1 0 3 3 2 0 0 1 1 1	107 55 86 34 62 90 42 89 48 123 134 117	2 0 0 0 0 0 0 0 0 0 0 1	215 56 193 37 77 175 40 187 45 144 129 128	6.0% 20.6% 18.8% 13.9% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁹⁶ Corson 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ . Meyer 1998 ⁵³ Romer 1998 ⁹⁷	0 0 1 0 3 3 2 0 0 0 1	107 55 86 34 62 90 42 89 48 123 134 117 10	2 0 0 0 0 0 0 0 0 0 0 1	215 56 193 37 175 40 187 45 144 129 128 10	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁹⁶ Corson 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI)	0 0 1 0 3 3 2 0 0 1 1 1 0	107 55 86 34 62 90 42 89 48 123 134 117	2 0 0 0 0 0 0 0 0 0 0 1 0 0	215 56 193 37 77 175 40 187 45 144 129 128	6.0% 20.6% 18.8% 13.9% 7.0% 14.1%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1998 ⁵³ Romer 1998 ⁹⁷ Jubtotal (95% CI) otal events	0 0 1 0 3 3 2 0 0 1 1 1 0	107 55 86 34 62 90 42 89 48 123 134 114 110 1017	2 0 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 175 40 187 45 144 129 128 10	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ . Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) tal events eterogeneity: $\chi^2 = 7.96$, df =	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ 7 \left(\rho = 0.34 \right) \end{array}$	107 55 86 34 62 90 42 89 48 123 134 117 10 1017 ; <i>J²</i> = 12%	2 0 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 175 40 187 45 144 129 128 10	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) otal events eterogeneity: χ^2 = 7.96, df = est for overall effect: <i>z</i> = 3.0	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ 7 \left(\rho = 0.34 \right) \end{array}$	107 55 86 34 62 90 42 89 48 123 134 117 10 1017 ; <i>J²</i> = 12%	2 0 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 175 40 187 45 144 129 128 10	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) Dtal events eterogeneity: $\chi^2 = 7.96$, df = est for overall effect: $z = 3.0$	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ 7 \left(\rho = 0.34 \right) \end{array}$	107 55 86 34 62 90 42 89 48 123 134 117 10 1017 ; <i>J²</i> = 12%	2 0 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 175 40 187 45 144 129 128 10	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) otal events eterogeneity: χ^2 = 7.96, df = est for overall effect: <i>z</i> = 3.0 22.4 Fluid overload Brun 2006 ¹⁰³	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ 7 \ (p = 0.34 \\ 2 \ (p = 0.003 \\ 0 \\ 1 \\ 1 \\ 0 \\ 12 \\ (p = 0.003 \\ 0 \\ 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 1 \\ 1 \\ 1 \\ 1$	$107 55 86 34 62 90 42 89 48 123 134 117 10 1017 (); l^2 = 12\%$	2 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 77 175 40 187 45 144 129 128 10 1467	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable 0.20 (0.07 to 0.57)	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1998 ⁵³ Romer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) Dtal events eterogeneity: $\chi^2 = 7.96$, df = est for overall effect: $z = 3.0$ 22.4 Fluid overload Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ (p = 0.34 \\ 2 \\ (p = 0.003 \\ 0 \\ 0 \\ 0 \\ \end{array}$	107 55 86 34 62 90 42 89 48 123 134 134 101 1017 1017 1017 20 107	2 0 0 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 77 175 40 187 45 144 129 128 10 1467 31 215	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable 0.20 (0.07 to 0.57) Not estimable Not estimable	
22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ³³ Romer 1998 ⁹⁷ ubtotal (95% CI) total events eterogeneity: χ^2 = 7.96, df = est for overall effect: <i>z</i> = 3.0 22.4 Fluid overload Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ 7 \\ (p = 0.34 \\ 2 \\ (p = 0.003 \\ 0 \\ 0 \\ 0 \\ 0 \end{array}$	$107 \\ 55 \\ 86 \\ 34 \\ 62 \\ 90 \\ 42 \\ 89 \\ 48 \\ 123 \\ 134 \\ 117 \\ 10 \\ 1017 \\ 1017 \\ 10 \\ 1017 \\ 55 \\ 20 \\ 107 \\ 55 \\ 107 \\ 107 \\ 55 \\ 107 \\$	2 0 0 0 0 0 0 0 0 0 0 0 1 0 0 3	215 56 193 37 775 40 187 45 144 129 128 10 1467 31 215 56	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable 0.20 (0.07 to 0.57) Not estimable Not estimable Not estimable	
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22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) otal events eterogeneity: χ^2 = 7.96, df = est for overall effect: <i>z</i> = 3.0 22.4 Fluid overload Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 7 \\ (p = 0.34 \\ 2 \\ (p = 0.003 \\ 0 \\ 0 \\ 0 \\ 3 \\ \end{array}$	$107 55 86 34 62 90 42 89 48 123 134 117 10 1017); l^{2} = 12\%)20107558634343435894812313410710755863412313410710$	2 0 0 0 0 0 0 0 0 0 1 0 0 3 3	215 56 193 37 77 75 40 187 45 144 129 128 10 1467 31 215 56 193 37	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0% 100.0% 21.4%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable 0.20 (0.07 to 0.57) Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable	
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22.3 Uterine perforation Brun 2006 ¹⁰³ Cooper 2004 ⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵ Cooper 2002 ⁵⁶ Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ Meyer 1998 ⁵³ Romer 1998 ⁹⁷ ubtotal (95% CI) otal events eterogeneity: $\chi^2 = 7.96$, df = est for overall effect: $z = 3.0$ 22.4 Fluid overload Brun 2006 ¹⁰³ Cooper 2004 ¹⁹⁹ Perino 2004 ¹⁰⁰ Duleba 2003 ⁹⁸ Hawe 2003 ⁹⁴ van Zon-Rabelink 2001 ⁹⁵	$\begin{array}{c} 0 \\ 0 \\ 1 \\ 0 \\ 3 \\ 3 \\ 2 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 12 \\ 7 \\ (p = 0.34 \\ 2 \\ (p = 0.003 \\ 0 \\ 0 \\ 0 \\ 3 \\ 1 \end{array}$	107 55 86 34 62 90 42 89 48 123 134 117 10 1017 1017 107 55 86 34 62 90 90 42 89 48 123 134 107 10	2 0 0 0 0 0 0 0 0 0 0 0 3 3	215 56 193 37 77 175 40 187 45 144 129 128 10 1467 31 215 566 193 37 77	6.0% 20.6% 18.8% 13.9% 7.0% 14.1% 7.0% 100.0% 21.4%	4.49 (0.09 to 215.97) Not estimable 0.04 (0.00 to 10.32) Not estimable 0.10 (0.01 to 2.09) 0.05 (0.00 to 1.20) 0.14 (0.00 to 5.42) Not estimable 0.11 (0.00 to 20.02) 1.04 (0.03 to 39.99) 0.12 (0.00 to 21.39) Not estimable 0.20 (0.07 to 0.57) Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable 0.12 (0.01 to 2.39) 0.11 (0.00 to 18.92)	

Favours Favours second generation first generation

Deck of all states Deck of all states Pete odds ratio (non-event) Pete odds ratio (non-event) Peter		First ger	neration	Second ge	eneration			
 develation develation	Study or subgroup	Events	Total	Events	Total	Weight	· · · ·	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
L coren 2000 ¹¹ 1 1 122 0 144 7.34 0.11 (0.0 b ≥ 0.02) h Meyer 1988 ²¹ 2 117 0 128 14.65 0.12 (0.0 b - 4.72) h Meyer 1988 ²¹ 2 117 0 120 100 0 4.72 h Meyer 1988 ²¹ 1 0.01 101 0 101 0 1467 100.04 0.12 (0.0 b - 4.72) h Meyer 1988 ²¹ 1 0.01 101 0 101 0 0 0 0 12 (0.0 b - 0.53) 225 Excessive visceral dimensione Estim 2000 ¹¹ 0 107 0 215 Not estimable b mole estimable 1 0000 ¹¹ 0 107 0 215 Not estimable 1 0000 ¹² 0 107 0 215 Not estimable 1 0000 ¹² 0 107 0 215 Not estimable 1 0000 ¹² 0 122 0 44 0 Not estimable 1 0000 ¹² 0 123 0 144 Not estimable 1 0000 ¹² 0 100 10 0 10 0 Not estimable 1 0 000 ¹² 0 0 218 120 Not estimable 1 0 000 ¹² 0 0 218 120 Not estimable 1 0 000 ¹² 0 0 0 175 Not estimable 1 0 000 ¹² 0 0 0 175 10.998 0 00 176 10.998 0 00 176 10.998 0 00 100 12.09 1 0 Not estimable 1 0 000 ¹² 0 0 13 0 Not estimable 1 0 No	Corson 200179	0	89	0	187		Not estimable	
Cooper 1998 ¹⁴ 0 134 0 129 1A0 Not estimable Former 1998 ¹⁵ 0 10 0 10 Not estimable Former 1998 ¹⁵ 0 10 0 0 0 0 Table events 14 0 146 0.12 (0.00 to 0.472) Not estimable 225 Encosity formal effect z = 3.5 (p = 0.0001) 1467 100.0% 0.12 (0.04 to 0.39) 225 Encosity formal effect z = 3.5 (p = 0.0001) 147 100.0% 0.12 (0.04 to 0.39) 225 Encosity formal effect z = 3.6 (p = 0.001) 147 100.0% 0.12 (0.04 to 0.39) 1 Have 2002 ¹⁶ 0 2.5 Not estimable Not estimable 1 Have 2002 ¹⁶ 0 2.4 10 Not estimable 1 Have 2002 ¹⁶ 0 2.4 10 Not estimable 1 Have 2002 ¹⁶ 0 2.4 10 Not estimable 1 Have 2002 ¹⁶ 0 13 Not estimable Not estimable 1 Have 2002 ¹⁶ 0	Soysal 200196	2	48	0	45	14.5%	0.14 (0.00 to 5.51)	←
l.egist 1384(6) 2 1 17 0 128 14.6(6) 1.2 (20.01 6.4.72) Not call and be write the overall field events 14 0 100 117 0 116 0 100.9(6) 0.12 (0.04 to 0.39) Not call make be added by 2(6) 0.02, df = 5 (p = 1.00; P = 0% 0 116 0 0.05% 0.12 (0.04 to 0.39) 116 0 100.9(6) 0.12 (0.04 to 0.39) 117 0 128 Not catimable	Corson 2000 ¹⁰¹	1	123	0	144	7.3%	0.11 (0.00 to 20.02)	·
$ \begin{array}{c} \mbod leng 0.5 \\ \mbod leng 0.5 $	Cooper 1999 ⁵⁴	0	134	0	129		Not estimable	
ububble (95) C0) 1017 1467 100.0% 0.12 (0.04 to 0.38) deterogeneity: $\chi^{a} = 0.02$, $d = 5 (p = 1.00; F = 0.96)$ estimate interval int	1. Meyer 1998 ⁵³	2	117	0	128	14.6%	0.12 (0.00 to 4.72)	←_ <u>-</u>
$ \begin{array}{c} \text{tell eventis} & 14 & 0 \\ \text{eter orgenity} & 2 & 02, df = 5 (p = 100); F = 0% \\ \text{et for overall effect; } x = 3.85 (p = 0.001)! \\ \hline 22.5 & \text{Excessive visceral damage} \\ \text{Event2007} & 0 & 20 & 0 & 31 \\ \text{Cooper 2007} & 0 & 107 & 0 & 215 \\ \text{Not estimable} \\ Not esti$. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	ubtotal (95% CI)		1017		1467	100.0%	0.12 (0.04 to 0.36)	◆
set for overall effect: z = 3.85 (p = 0.0001) 22.5 Excessive viaceral damage Bun 2000 ¹⁰ 0 21 Not estimable 0.00per 2004 ¹⁰ 0 107 0 215 Not estimable 0 38 Not estimable 0.00per 2002 ¹⁰ 0 31 Not estimable 0.00per 2002 ¹⁰ 0 32 Not estimable 0.00per 2002 ¹⁰ 0 42 40 Not estimable 0.00per 1009 ¹⁰ 0 133 0 144 Not estimable 0.00per 1099 ¹⁰ 0 134 129 Not estimable 0.00per 1099 ¹⁰ 0 134 129 Not estimable 0.00per 1099 ¹⁰ 0 10 10 Not estimable Not estimable Not estimable Not estimable Not estimable 1.80per 1098 ¹⁰ 0 107 1467 100.0% 4.40 (0.23 to 58.78) 2.00per 2004 ¹⁰ 2 107 2 22.5 Not estimable 1.00per 2002 ¹⁰ 34 0 37 Not estimable 1.00per 2002 ¹⁰ <td></td> <td></td> <td></td> <td>0</td> <td></td> <td></td> <td></td> <td></td>				0				
Bun 2006 ¹⁰⁰ 0 20 0 31 Not estimable Perino 2004 ¹⁰⁰ 0 55 Not estimable Not estimable Hawe 2005 ¹⁰ 0 34 0 37 Not estimable Van Zon-Rabelnk 2001 ¹⁰⁰ 0 20 177 Not estimable Not estimable Cooper 2002 ¹⁰ 0 90 0 175 Not estimable Cooper 2002 ¹⁰⁰ 0 127 Not estimable Not estimable Cooper 2002 ¹⁰⁰ 0 134 129 Not estimable Coroper 1999 ¹¹ 0 134 129 Not estimable Coroper 1999 ¹¹ 0 10 Not estimable Not estimable Coroper 2004 ¹¹ 2 107 2 15 2.2.9 Not estimable Cooper 2004 ¹¹ 2 107 2 15 2.2.9 Not estimable Duleba 2003 ¹¹ 0 0 0 10 Not estimable Not estimable Cooper 2004 ¹¹ 2	• • •							
$ \begin{array}{c} \text{Cooper 2004}^{\text{m}} & 0 & 107' & 0 & 215 & \text{Not estimable} \\ \text{Deleba 2003}^{\text{m}} & 0 & 86 & 0 & 133 & \text{Not estimable} \\ \text{Deleba 2003}^{\text{m}} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Not estimable} & \text{Not estimable} \\ \text{Van Zon-Rabelnik 2001^{\text{m}}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Not estimable} & \text{Not estimable} \\ \text{Cooper 2002}^{\text{m}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Soyal 2001}^{\text{m}} & 0 & 43 & 0 & 45 & \text{Not estimable} \\ \text{Soyal 2001}^{\text{m}} & 0 & 43 & 0 & 45 & \text{Not estimable} \\ \text{Cooper 1989}^{\text{m}} & 0 & 114 & 0 & 128 & \text{Not estimable} \\ \text{Cooper 1989}^{\text{m}} & 0 & 116 & 0 & 128 & \text{Not estimable} \\ \text{Cooper 1989}^{\text{m}} & 0 & 116 & 0 & 128 & \text{Not estimable} \\ \text{Locaper 1989}^{\text{m}} & 0 & 1017 & 1467 & 100.0^{\text{h}} & 4.0 (0.23 to 55.78) \\ \text{Have 2003}^{\text{m}} & 0 & 20 & 0 & 21 & \text{Not estimable} \\ \text{stor overlife effects } 0 & 0 & 0 & 2 & \text{eterogeneity}; not applicable \\ \text{est for overlife effects } 0 & 20 & 0 & 21 & \text{Not estimable} \\ \text{Have 2003}^{\text{m}} & 0 & 20 & 0 & 21 & \text{Not estimable} \\ \text{Have 2003}^{\text{m}} & 0 & 20 & 0 & 21 & \text{Not estimable} \\ \text{Have 2003}^{\text{m}} & 0 & 20 & 0 & 21 & \text{Not estimable} \\ \text{Have 2003}^{\text{m}} & 0 & 20 & 0 & 21 & \text{Not estimable} \\ \text{Have 2003}^{\text{m}} & 0 & 36 & 0 & 197 & \text{Not estimable} \\ \text{Have 2003}^{\text{m}} & 0 & 36 & 0 & 175 & 15.9^{\text{h}} & 010 (0.01 to 2.09) \\ \text{Have 2003}^{\text{m}} & 1 & 42 & 0 & 45 & 0.51 & (0.00 to 2.48) \\ \text{Cooper 2004}^{\text{m}} & 0 & 134 & 0 & 175 & 15.9^{\text{h}} & 010 (0.01 to 2.48) \\ \text{Have 2003}^{\text{m}} & 1 & 177 & 0 & 218 & \text{Not estimable} \\ \text{Cooper 1999}^{\text{m}} & 0 & 104 & 0 & 177 & \text{Not estimable} \\ \text{Cooper 2004}^{\text{m}} & 0 & 55 & 0 & 56 & \text{Not estimable} \\ \text{Cooper 1999}^{\text{m}} & 0 & 104 & 0 & 177 & \text{Not estimable} \\ \text{Cooper 2004}^{\text{m}} & 0 & 57 & 0 & 56 & \text{Not estimable} \\ \text{Cooper 1999}^{\text{m}} & 0 & 177 & 0 & 218 & \text{Not estimable} \\ \text{Cooper 1999}^{\text{m}} & 0 & 177 & 0 & 218 & \text{Not estimable} \\ \text{Cooper 1999}^{\text{m}} & 0 & 177 & 0 & 28 & \text{Not estimable} \\ \text{Cooper 1999}^{\text{m}} & 0 & 177 & 0 & 28 $	22.5 Excessive visceral da	amage						
Perinc 2004 ¹⁶¹ 0 55 0 56 Not estimable Have 2003 ¹⁶¹ 0 34 0 37 Not estimable Cooper 2002 ¹⁶² 0 90 0 175 Not estimable Corson 2001 ¹⁶¹ 0 88 2 177 Not estimable Corson 2001 ¹⁶² 0 88 2 187 100.0% 4.40 (0.09 to 218.13) Cooper 1099 ¹⁶¹ 0 123 0 144 Not estimable Corson 2001 ¹⁶² 0 123 0 144 Not estimable Corson 2001 ¹⁶³ 0 117 0 128 Not estimable Env 2008 ¹⁶⁴ 0 107 0 10 0 10 Not estimable Env 2008 ¹⁶⁴ 0 107 2 215 Not estimable Env 2008 ¹⁶⁴ 0 107 2 215 22.2% 0.47 (0.03 to 27.9) Life of the standard of the	Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
$ \begin{array}{c} \text{Dubba} 2003^{\text{ell}} & 0 & 86 & 0 & 193 \\ \text{Not estimable} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{van} Zan-Rabelink 2001^{\text{ell}} & 0 & 62 & 0 & 77 & \text{Not estimable} \\ \text{Ocoper 2002^{\text{ell}}} & 0 & 90 & 0 & 175 & \text{Not estimable} \\ \text{Not estimable} & \text{Not estimable} & \text{Not estimable} \\ \text{Soyal 2001^{\text{ell}}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Soyal 2001^{\text{ell}}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001^{\text{ell}}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001^{\text{ell}}} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2001^{\text{ell}}} & 0 & 134 & 0 & 128 & \text{Not estimable} \\ \text{Corson 2001^{\text{ell}}} & 0 & 101 & 0 & 10 & \text{Not estimable} \\ \text{Romer 1998^{\text{ell}}} & 0 & 117 & 0 & 128 & \text{Not estimable} \\ \text{Romer 1998^{\text{ell}}} & 0 & 107 & 2 & 215 & 22.2\% & 0.47 (0.33 \text{ to } 7.7) \\ \text{Datel events} & 0 & 2 & 215 & 22.2\% & 0.47 (0.33 \text{ to } 7.7) \\ \text{Datel events} & 0 & 2 & 31 & \text{Not estimable} \\ \text{Bun 2006^{\text{ell}}} & 2 & 107 & 2 & 215 & 22.2\% & 0.47 (0.03 \text{ to } 7.7) \\ \text{Datel events} & 0 & 2 & 35 & 56 & \text{Not estimable} \\ \text{Datel a 2003^{\text{ell}}} & 0 & 36 & 0 & 133 & \text{Not estimable} \\ \text{Datel a 2003^{\text{ell}}} & 0 & 36 & 0 & 175 & 15.9\% & 0.10 (0.01 \text{ to } 2.9) \\ \text{Perice 2004^{\text{ell}}} & 2 & 107 & 2 & 215 & 22.2\% & 0.47 (0.03 \text{ to } 7.7) \\ \text{Datel a 2003^{\text{ell}}} & 1 & 17 & 0 & 128 & \text{Not estimable} \\ \text{Not estimable} & \text{Not estimable} & \text{Not estimable} \\ \text{Not estimable} & \text{Not estimable} & \text{Not estimable} \\ \text{Datela 2003^{\text{ell}}} & 1 & 17 & 0 & 128 & \text{Old (0.01 to } 2.2) \\ \text{Perice 2004^{\text{ell}}} & 2 & 107 & 2 & 15.5\% & 0.10 (0.01 \text{ to } 2.1) \\ \text{Perice 2004^{\text{ell}}} & 0 & 100 & 0 & 104 & 0.3\% & 0.12 (0.00 \text{ to } 2.13) \\ \text{Perice 2004^{\text{ell}}} & 0 & 107 & 0 & 1125 & \text{Not estimable} \\ \text{Not estimable} & \text{Not estimable} \\ Not estimab$. Cooper 2004 ⁹⁹	0	107	0	215		Not estimable	
Have 2003 ⁴⁴ 0 37 Not estimable 0.000P 2002 ⁵⁶ 0 97 Not estimable 0.000P 2002 ⁵⁶ 0 90 0 175 Not estimable 0.000P 2002 ⁵⁶ 0 90 0 175 Not estimable 0.000P 2002 ⁵⁶ 0 92 40 Not estimable 0.000P 2009 ⁵⁶ 0 123 0 144 Not estimable 0.000P 1998 ⁵⁶ 0 117 0 128 Not estimable New 1998 ⁵⁶ 0 117 0 100 Not estimable ubtotal (65% CI) 1017 1467 100.0% 4.40 (0.23 to 85.78) 22.66 Cervical loceration 1 Not estimable Not estimable 1.4000 ⁴⁷⁹ 0 20 0 37 Not estimable 1.400 200 ⁴⁷⁹ 0 103 0 37 Not estimable 1.400 200 ⁴⁷⁹ 0 137 1.5% Not estimable 1.0% 1.400 200 ⁴⁷⁹ 0	. Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
vn ZorRabelink 2001 ¹⁶ 0 62 0 77 Not estimable Not est		0	86	0	193		Not estimable	
$\begin{array}{c} \text{cooper 2002\%} & 0 & 90 & 0 \\ \text{Pelicano 2001\%} & 0 & 48 & 0 \\ \text{Corson 2001\%} & 0 & 48 & 0 \\ \text{Corson 2001\%} & 0 & 48 & 0 \\ \text{Corson 2000\%} & 0 & 133 & 0 \\ \text{Corson 2000\%} & 0 & 133 & 0 \\ \text{Corson 2000\%} & 0 & 133 & 0 \\ \text{Corson 2000\%} & 0 & 134 & 0 \\ \text{Corson 1998\%} & 0 & 117 & 0 \\ \text{Corson 1998\%} & 0 & 117 & 0 \\ \text{Nore estimable} \\ \text{Sonor 1998\%} & 0 & 10 & 0 \\ \text{Lectual events} & 0 & 2 \\ \text{eterogeneity: not applicable} \\ \text{sst for overall effect: 2 = 0.98 (p = 0.33): \\ \hline \textbf{22.6 Cervical locartion} \\ \text{Bun 2003\%} & 0 & 20 & 0 \\ \text{Cooper 2002\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 1 & 42 & 0 & 40 & 6.3\% & 0.51 (0.01 to 2.09) \\ \text{Have 2003\%} & 0 & 34 & 0 \\ \text{Cooper 2002\%} & 1 & 42 & 0 & 40 & 6.3\% & 0.51 (0.00 to 2.21) \\ \text{Cooper 2002\%} & 1 & 48 & 0 & 45 & 6.3\% & 0.51 (0.00 to 2.45 & 5) \\ \text{Corson 2001\%} & 1 & 48 & 0 & 45 & 6.3\% & 0.51 (0.00 to 2.45 & 5) \\ \text{Corson 2000\%} & 0 & 13 & 144 & 125\% & 0.11 (0.00 to 2.49 & 5) \\ \text{Corson 2000\%} & 1 & 40 & 0 & 10 & 0 \\ \text{Cooper 2002\%} & 1 & 177 & 0 & 128 & 0.12 (0.00 to 2.45 & 5) \\ \text{Corson 2000\%} & 0 & 134 & 0 & 177 & 125\% & 0.11 (0.00 to 4.40) \\ \text{Never 1998\%} & 1 & 117 & 0 & 128 & 0.12 (0.00 to 2.13) \\ \text{Never 1998\%} & 0 & 10 & 0 & 10 & \text{Not estimable} \\ \text{Have 2003\%} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Have 2003\%} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Ator a Con-Rabelink 2001\%} & 0 & 20 & 0 & 31 & \text{Not estimable} \\ \text{Have 2003\%} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001\%} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001\%} & 0 & 20 & 0 & 31 & \text{Not estimable} \\ \text{Corson 2001\%} & 0 & 31 & 31 & 32 & 20 & 44 & \text{Not estimable} \\ \text{Corson 2001\%} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ Corson 2$	Hawe 2003 ⁹⁴	0	34	0	37		Not estimable	
$\begin{array}{c} \text{Pelicano 2002}^{\text{IVE}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Soyal 2011}^{\text{IVE}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Soyal 2011}^{\text{IVE}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Occore 1999}^{\text{IVE}} & 0 & 134 & 0 & 128 & \text{Not estimable} \\ \text{Cocore 1999}^{\text{IVE}} & 0 & 134 & 0 & 128 & \text{Not estimable} \\ \text{Cocore 1999}^{\text{IVE}} & 0 & 10 & 0 & 10 & \text{Not estimable} \\ \text{Never 1998}^{\text{IVE}} & 0 & 10 & 0 & 10 & \text{Not estimable} \\ \text{Not estimable} & 0 & 2 & 0 & 0 & 215 & 22.256 & 25.781 \\ \text{referegarely: rotapilcable} & \text{estimable} & \text{Not estimable} \\ \text{ether or overall effect: } z = 0.98 (p = 0.33) \\ \hline 22.6 \ \text{Cervical lacertion} & 0 & 20 & 0 & 231 & \text{Not estimable} \\ \text{ether or overall effect: } & 2 & 0.98 (p = 0.33) \\ \hline 22.6 \ \text{Cervical lacertion} & 0 & 55 & 0 & 56 & \text{Not estimable} \\ \text{ether or overall effect: } & 0 & 0 & 0 & 175 & 16.99 & 0.000 \ 10 & 10 & 2.09 & 0 & 0.000 \ 10 & 10 & 0.000 \ 10 & 2.05 & 0.06 \ (0.00 \ 10 & 2.05) & 0.000 \ 10 & 10 & 0.000 \ 10 & 2.05 & 0.06 \ (0.00 \ 10 & 2.09) & 0 & 0.000 \ 10 & 2.000 \ 11 & 0.000 \ 10 & 2.05 \ 11 & 0.000 \ 10 & 2.05 \ 10 & 0.001 \ 10 & 2.09 & 0 & 0.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 \ 10 & 2.000 \ 10 & 0.000 $	van Zon-Rabelink 200195	0	62	0	77		Not estimable	
. Pelicano 2002 ¹⁰⁰ 0 42 0 40 Not estimable Corone 2001 ¹⁰ 0 48 0 45 Not estimable Cooper 1999 ¹⁴ 0 134 0 45 Not estimable Cooper 1999 ¹⁴ 0 134 0 129 Not estimable N	. Cooper 2002 ⁵⁶	0	90	0	175		Not estimable	
Soyal 2001 th 0 48 0 45 Not estimable Cooper 1989 ⁴⁴ 0 128 Not estimable Not estimable Cooper 1989 ⁴⁷ 0 10 0 Not estimable Romer 1989 ⁴⁷ 0 10 0 Not estimable Workal (SC) 101 0 Not estimable Burd 206 ⁴⁷ 0 107 2 Perrogencity: not applicable 2 107 2 215 22.25% 0.47 (0.03 to 7.27) Perino 2001 ⁴⁷⁰ 0 55 5 5 5 100 (0.05 to 7.27) Perino 2001 ⁴⁷⁰ 0 55 0 56 Not estimable Cooper 2002 ⁴⁸ 2 0 77 115.5% 0.10 (0.01 to 2.09) Cooper 2003 ⁴⁸ 0 37 Not estimable 10 10 Cooper 2003 ⁴⁸ 142 0 140 0.29% 10 0.11 to 2.09 10 Cooper 2004 ⁴⁸ 0 145 5.3% 0.14 (0.00 to	Pellicano 2002 ¹⁰²	0	42	0	40		Not estimable	
Soyal 2001** 0 48 0 45 Not estimable Cooper 1999** 0 134 0 128 Not estimable Cooper 1999** 0 10 0 10 Not estimable Romer 1998** 0 10 0 10 Not estimable World (SFC) 1017 1467 100.0% 4.40 (0.23 to 85.78) Z26 Cervical lacention Env 2006** 2 215 22.25% 0.47 (0.03 to 7.27) Perino 2004** 2 107 2 215 22.26% 0.47 (0.03 to 7.27) Dueba 2003*** 0 66 193 Not estimable 10 Cooper 2004** 2 0 44 6.33% 0.10 (0.01 to 2.09) Cooper 2005*** 3 60 175 18.5% 0.10 (0.01 to 2.45.5) Cooper 2005*** 3 0 175 18.6% 0.14 (0.00 to 2.45.5) Cooper 1998** 0 107 1467 0.02 (0.0 to 2.45.5) Corean 2001*** <t< td=""><td>Corson 200179</td><td>0</td><td>89</td><td>2</td><td>187</td><td>100.0%</td><td>4.40 (0.09 to 218.13)</td><td>↓_∎→</td></t<>	Corson 200179	0	89	2	187	100.0%	4.40 (0.09 to 218.13)	↓_ ∎→
$ \begin{array}{c} \text{Cooper 1999}^{\text{constrained}} & 0 & 134 & 0 & 129 & \text{Not estimable} \\ \text{Romer 1998}^{\text{constrained}} & 0 & 10 & 0 & 10 & \text{Not estimable} \\ \text{Romer 1998}^{\text{constrained}} & 0 & 2 & 2 & 2 & 2 & 2 & 2 & 2 & 2 & 2$	Soysal 200196	0	48	0	45		Not estimable	
h. Meyer 1988 ¹⁰ 0 117 0 128 Not estimable Not estimable ubtoal (65% CI) 1017 1467 100.0% 4.40 (0.23 to 85.76) 11467 100.0% 14.00 10 7.27) 11467 100.0% 14.00 10 7.27) 11467 100.0% 14.00 10 7.27) 11467 100.0% 14.00 10 7.27) 11467 100.0% 14.00 10 7.27) 11467 100.0% 14.00 10 7.27) 11467 100.0% 14.00 10 7.20 1140 100 10 10 10 10 10 10 10 10 10 10 10 1	Corson 2000 ¹⁰¹	0	123	0	144		Not estimable	
Pamer 1998 ¹⁷ 0 10 Not estimable bibliol (65% CI) 1017 1467 100.0% 4.40 (0.23 to 85.76) stal events 0 2 2 eterogeneity: not applicable	Cooper 1999 ⁵⁴	0	134	0	129		Not estimable	
ububble (65% CI) 1017 1467 100.0% 4.40 (0.23 to 85.76) 4.40 (0.23 to 85.76) 22.5 Cervical faceration Eun 200 ⁶⁷⁰ 0 20 0 31 Not estimable Cooper 2004 ⁴⁹ 0 55 0 56 Not estimable 1.0 (0.01 to 2.09) 4.40 (0.03 to 7.27) Perinc 2004 ⁴⁰⁰ 0 55 0 56 Not estimable 4.40 (0.23 to 7.27) Perinc 2004 ⁴⁰⁰ 0 55 0 56 Not estimable 4.40 (0.03 to 7.27) Cooper 2002 ⁴¹⁰ 0 34 0 37 Not estimable 4.40 (0.03 to 7.27) Perinc 2004 ⁴⁰⁰ 0 36 C 0 77 18.5% 0.10 (0.01 to 2.09) 4.40 (0.00 to 12.0) Perinc 2002 ⁴¹⁰ 1 42 0 40 6.3% 0.14 (0.00 to 12.0) Perinc 2002 ⁴¹⁰ 1 48 0 45 6.3% 0.14 (0.00 to 2.21) Corson 2001 ⁴¹⁰ 2 89 0 117 11.0% 0.04 (0.00 to 2.21) Corson 2001 ⁴¹⁰ 1 48 0 45 6.3% 0.11 (0.00 to 4.49) Corson 2001 ⁴¹⁰ 2 123 0 144 12.5% 0.11 (0.00 to 4.49) Corson 2001 ⁴¹⁰ 1 117 1467 0.12 (0.05 to 0.33) 4.40 (2 0.05 to 0.33) 4.41 (2.00 to 14.40) And estimable And estim		0	117	0	128		Not estimable	
total events 0 0 2 events 0 0 2 est for overall effect: $z = 0.88$ ($\rho = 0.33$) 22.6 Cervical laceration Brun 2004 ¹⁰⁰ 0 20 0 31 Not estimable Cooper 2004 ¹⁰⁰ 0 55 0 56 Not estimable 1.2006 ¹⁰⁰ 0 34 0 37 Not estimable Have 2003 ¹⁴⁰ 0 34 0 37 Not estimable Have 2003 ¹⁴⁰ 0 34 0 37 Not estimable 1.2007 ¹⁰⁰ 1 42 0 40 6.3% 0.110 (0.01 to 2.09) Pelicano 2002 ¹⁰⁰ 1 42 0 40 6.3% 0.14 (0.00 to 2.45) Cooper 2002 ¹⁰⁰ 1 42 0 40 6.3% 0.14 (0.00 to 2.45) Corson 2001 ¹¹⁰ 2 123 0 1144 12.5% 0.110 (0.01 to 2.49) Pelicano 2002 ¹⁰⁰ 1 1 48 0 45 0.3% 0.114 (0.00 to 2.49) Corson 2001 ¹¹⁰ 1 1 48 0 45 0.3% 0.114 (0.00 to 2.49) Corson 2001 ¹¹⁰ 1 1 48 0 45 0.3% 0.112 (0.00 to 1.40) Cooper 1996 ²⁰ 1 117 0 128 0.12 (0.00 to 1.2.39) Romer 1998 ²⁰ 1 117 0 10 Not estimable Evencyonely: 2 2.56, df - 7 (0.00 to 2.13) Pelicano 2004 ¹⁰⁰ 0 10 Not estimable Pelicano 2004 ¹⁰⁰ 0 10 Not estimable Not estimable Pelicano 2004 ¹⁰⁰ 0 2.15 Not estimable Pelicano 2004 ¹⁰⁰ 0 2.15 Not estimable Pelicano 2004 ¹⁰⁰ 0 107 0 2.15 Not estimable Pelicano 2004 ¹⁰⁰ 0 34 0 37 Not estimable Pelicano 2004 ¹⁰⁰ 0 42 0 40 Not estimable Pelicano 2004 ¹⁰⁰ 0 42 0 40 Not estimable Pelicano 2004 ¹⁰⁰ 0 34 0 37 Not estimable Pelicano 2004 ¹⁰⁰ 0 42 0 40 Not estimable Pelicano 2004 ¹⁰⁰ 0 10 Not estimable Pelicano 2004 ¹⁰⁰ 0 123 0 114 Not estimable Pelicano 2004 ¹⁰⁰ 0 10 No	Romer 199897	0	10	0	10		Not estimable	
eterogeneity: not applicable est for overall effect: $z = 0.98$ ($p = 0.33$) 22.6 Cervical laceration Even 2006 ¹⁰⁰ 0 20 0 215 22.2% 0.47 (0.03 to 7.27) Perino 2004 ¹⁰⁰ 0 55 0 66 Not estimable Dubba 2003 ¹⁰ 0 34 0 37 Not estimable Not estimable Van Zon-Rabelink 2001 ¹⁰⁰ 3 62 0 77 18.5% 0.10 (0.01 to 2.09) Pellicane 2002 ¹⁰⁰ 1 42 0 40 6.3% 0.14 (0.00 to 24.55) Corson 2001 ¹⁰⁰ 1 48 0 45 6.3% 0.14 (0.00 to 24.55) Corson 2001 ¹⁰⁰ 1 48 0 45 6.3% 0.14 (0.00 to 24.95) Corson 2001 ¹⁰⁰ 1 48 0 142 0 Not estimable Not estimable Not estimable Not estimable Not estimable 2.7 Procedure abadomed Everogeneity: $z^2 = 2.56$, df = 7 ($p = 0.92$); $P = 0\%$ est for overall effect: $z = 4.14$ ($p < 0.0001$) 2.7 Procedure abadomed Not estimable Not estimable Not estimable Not estimable Corson 2001 ¹⁰⁰ 0 20 0 31 Not estimable Corson 2004 ¹⁰⁰ 0 55 0 56 Not estimable Corson 2004 ¹⁰⁰ 0 107 0 215 Not estimable Corson 2004 ¹⁰⁰ 0 34 0 37 Not estimable Corson 2004 ¹⁰⁰ 0 107 0 215 Not estimable Corson 2004 ¹⁰⁰ 0 86 0 133 Not estimable Corson 2004 ¹⁰⁰ 0 86 0 133 Not estimable Corson 2004 ¹⁰⁰ 0 107 0 215 Not estimable Corson 2004 ¹⁰⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁰⁰ 0 44 00 Not estimable Corson 2001 ¹⁰⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁰⁰ 0 10 Not estimable Corson 2001 ¹⁰⁰ 0 10 Not estimable Corson 2001 ¹⁰⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁰⁰ 0 10 Not estimable Corson 2001 ¹⁰⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁰⁰ 0 10 Not estimable Corson 2001 ¹⁰⁰ 0 10 Not estimable Corson 2001 ¹⁰⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁰⁰ 0 10 Not estimable Corson 2001 ¹⁰⁰ 0 123 0 144 Not estimable Corson 2000	ubtotal (95% Cl)		1017		1467	100.0%	4.40 (0.23 to 85.78)	
est for overall effect: $z = 0.98 (p = 0.33)$ 22.6 Carvical Iscention Brun 2006 ¹⁰⁵ 0 20 0 31 Not estimable Cocoper 2004 ¹⁰⁶ 0 55 0 56 Not estimable Dubtels 2003 ¹⁰⁶ 0 86 0 193 Not estimable Have 2003 ¹⁰⁷ 0 34 0 37 Not estimable Van Zon-Rabelink 2001 ¹⁰⁷ 3 62 0 77 18.5% 0.10 (0.00 to 2.09) Have 2002 ¹⁰⁶ 1 42 0 40 6 6.3% 0.14 (0.00 to 2.4.55) Corson 2001 ¹⁰⁷ 2 89 0 187 11.0% 0.04 (0.00 to 2.4.95) Corson 2001 ¹⁰⁷ 1 48 0 45 6.3% 0.14 (0.00 to 2.4.95) Corson 2001 ¹⁰⁷ 1 48 0 45 6.3% 0.14 (0.00 to 2.4.95) Corson 2001 ¹⁰⁷ 1 1 48 0 45 6.3% 0.14 (0.00 to 2.4.95) Sysal 2001 ²⁰⁷ 1 1 17 0 128 0.12 (0.00 to 21.39) Not estimable Ubtotal (95% C) 1017 1 1467 Out estimable Ubtotal (95% C) 1017 1 1467 Cocoper 2002 ⁴⁰⁶ 0 20 0 31 Not estimable Dubtes 2003 ⁴⁰ 0 35 0 56 Not estimable Dubtes 2003 ⁴⁰ 0 37 Not estimable Cocoper 2004 ⁴⁰ 0 155 0 56 Not estimable Dubtotal (95% C) 1017 1 1467 Carson 2004 ⁴⁰ 0 45 0 64 (0.00 to 2.1.9) Perinca 2004 ⁴⁰ 0 177 0 215 Not estimable Dubtes 2003 ⁴⁰ 0 45 0 66 Not estimable Dubtes 2003 ⁴⁰ 0 45 0 66 Not estimable Dubtes 2003 ⁴⁰ 0 45 0 66 Not estimable Dubtes 2003 ⁴⁰ 0 44 0 37 Not estimable Cocoper 2002 ⁴⁰⁹ 0 17 0 215 Not estimable Cocoper 2002 ⁴⁰⁹ 0 44 175 25.2% 1.03 (0.11 to 9.68) Not estimable Cocoper 2002 ⁴⁰⁹ 0 10 0 10 Not estimable Cocoper 2002 ⁴⁰⁹ 0 44 175 25.2% 1.03 (0.11 to 9.68) Not estimable Cocoper 2002 ⁴⁰⁹ 0 10 0 10 Not estimable Perinca 2001 ⁴⁰ 0 10 Not estimable Cocoper 2002 ⁴⁰⁹ 0 10 0 10 Not estimable Cocoper 1999 ⁴⁴ 5 134 5 129 46.1% 1.04 (0.20 to 5.46) Not estimable Romer 1998 ⁴⁰ 0 10 0 10 Not estimable Romer 1998 ⁴⁰ 0 10 0 10 Not estimable Romer 1998 ⁴⁰ 0 10 0 10 Not estimable Bernore 1998 ⁴⁰ 0 10 0 10 Not estimable Bernore 1998 ⁴⁰ 0 10 0 10 Not estimable	otal events	0		2				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	• • • • •							
$\begin{array}{c} \text{Cooper 2004}^{\text{MS}} & 2 & 107 & 2 & 215 & 22.2\% & 0.47 \ (0.03 \text{ fr} 2.7), \\ \text{Perino 2004}^{\text{MS}} & 0 & 55 & 0 & 56 \\ \text{Not estimable} \\ \text{Have 2003}^{\text{MS}} & 0 & 34 & 0 & 37 \\ \text{Van Zon-Rabelink 2001}^{\text{MS}} & 0 & 34 & 0 & 37 \\ \text{Van Zon-Rabelink 201}^{\text{MS}} & 3 & 90 & 0 & 175 & 16.3\% & 0.16 \ (0.01 \text{ to } 2.09) \\ \text{Cooper 2002}^{\text{MS}} & 3 & 90 & 0 & 175 & 16.3\% & 0.16 \ (0.00 \text{ to } 24.59) \\ \text{Corson 2001}^{\text{MS}} & 1 & 48 & 0 & 45 & 6.3\% & 0.14 \ (0.00 \text{ to } 24.98) \\ \text{Corson 2001}^{\text{MS}} & 1 & 48 & 0 & 45 & 6.3\% & 0.14 \ (0.00 \text{ to } 24.98) \\ \text{Corson 2001}^{\text{MS}} & 1 & 48 & 0 & 45 & 6.3\% & 0.14 \ (0.00 \text{ to } 24.98) \\ \text{Corson 2001}^{\text{MS}} & 1 & 117 & 0 & 128 & 0.12 \ (0.00 \text{ to } 21.39) \\ \text{Never 1998}^{\text{MS}} & 1 & 117 & 0 & 128 & 0.12 \ (0.00 \text{ to } 21.39) \\ \text{Never 1998}^{\text{MS}} & 0 & 10 & 0 & 10 \\ \text{Not estimable} & 0 & 106 & 0 & 106 \\ \text{Subtal (95% CI)} & 1017 & 1467 & 0.12 \ (0.00 \text{ to } 21.39) \\ \text{Subtal (95\% CI)} & 0 & 107 & 0 & 215 & \text{Not estimable} \\ \text{Have 2003}^{\text{MS}} & 0 & 66 & 0 & 193 & \text{Not estimable} \\ \text{Brun 2006}^{\text{MS}} & 0 & 62 & 0 & 77 & \text{Not estimable} \\ \text{Duleba 2003}^{\text{MS}} & 0 & 42 & 0 & 40 & 37 & \text{Not estimable} \\ \text{Duleba 2003}^{\text{MS}} & 0 & 42 & 0 & 175 & 25.2\% & 1.03 \ (0.11 \text{ to } 9.68) \\ \text{Van Zon-Rabelink 201}^{\text{MS}} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 107 & 0 & 128 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 177 & 187 & 28.6\% & 4.52 \ (0.55 \text{ to } 5.74) \\ \text{Cooper 1998}^{\text{MS}} & 0 & 117 & 0 & 128 & \text{Not estimable} \\ \text{Corson 2001}^{\text{MS}} & 0 & 107 & 0 & 10 & \text{Not estimable} \\ \text{Rome 1198}^{\text{MS}} & 0 & 107 & 0 & 128 & \text{Not estimable} \\ \text{Rome 1198}^{\text{MS}} & 0 & 107 & 0 & 128 & \text{Not estimable} \\ \text{Rome 1198}^{\text{MS}} & 0 & 107 & 0 & 128 & Not est$	22.6 Cervical laceration							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $. Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Cooper 2004 ⁹⁹	2	107	2	215	22.2%	0.47 (0.03 to 7.27)	
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
van Zon-Rabelink 2001 ⁹⁶ 3 62 0 77 18.5% 0.10 (0.01 to 2.09) Cooper 2002 ⁹⁶ 3 90 0 175 16.9% 0.05 (0.00 to 1.20) Pellicano 2002 ¹⁰⁷ 2 89 0 46.3% 0.14 (0.00 to 24.55) Corson 2001 ⁹⁷ 2 89 0 187 11.0% 0.04 (0.00 to 24.95) Corson 2001 ⁹⁰ 1 48 0 45 6.3% 0.14 (0.00 to 24.95) Corson 2001 ⁹⁰ 2 123 0 144 12.5% 0.11 (0.00 to 4.40) Cooper 1999 ⁵⁴ 0 134 0 129 Not estimable Meyer 1998 ³³ 1 117 0 128 0.12 (0.00 to 21.39) Romer 1989 ⁸⁷⁷ 0 100 0 10 Not estimable 22.7 Procedure abandoned Brun 2006 ¹⁰⁹ 0 20 0 31 Not estimable Dueba 2003 ⁴⁶ 0 107 0 215 Not estimable Perino 2004 ⁴⁰⁰ 0 55 0 56 Not estimable Dueba 2003 ⁴⁰ 0 34 0 37 Not estimable Hawe 2003 ⁴⁶ 0 34 0 37 Not estimable Cooper 2004 ⁴⁰⁰ 0 45 0 56 Not estimable Cooper 2004 ⁴⁰⁰ 0 44 0 37 Not estimable Cooper 2004 ⁴⁰⁰ 0 44 0 37 Not estimable Cooper 2002 ⁴⁶⁰ 0 34 0 37 Not estimable Cooper 2002 ⁴⁶⁰ 0 34 0 37 Not estimable Cooper 2002 ⁴⁶⁰ 0 44 175 25.2% 1.03 (0.11 to 9.68) Pelicano 2001 ¹⁰⁶ 0 42 0 40 Not estimable Cooper 2002 ⁸⁶ 2 90 4 175 25.2% 1.03 (0.11 to 9.68) Pelicano 2001 ¹⁰⁶ 0 42 0 40 Not estimable Cooper 2002 ⁸⁶ 2 90 4 175 25.2% 1.03 (0.11 to 9.68) Pelicano 2001 ¹⁰⁶ 0 42 0 40 Not estimable Cooper 2002 ⁸⁶ 2 90 4 175 25.2% 1.03 (0.11 to 9.68) Pelicano 2001 ¹⁰⁶ 0 48 0 45 Not estimable Cooper 1999 ⁵⁴ 5 134 5 129 46.1% 1.04 (0.20 to 5.46) Meyer 1998 ³⁷ 0 10 0 10 Not estimable Cooper 1999 ⁵⁴ 5 134 5 129 46.1% 1.04 (0.20 to 5.46) Meyer 1998 ⁹⁷⁷ 0 10 0 10 Not estimable Libtotal (95% CI) 1017 1467 100.0% 1.58 (0.67 to 3.72) tal events 7 7 16 tetro genetity: $z^2 = 2.32$, $df = 2 (p = 0.31)$; $P = 14\%$ est for overall effect: $z = 1.05 (p = 0.30)$	Duleba 200398	0	86	0	193		Not estimable	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Hawe 200394	0	34	0	37		Not estimable	
Pelicano 2002 ¹⁰² 1 42 0 40 6.3% 0.14 (0.00 to 24.55) Corson 2001 ¹⁰⁷ 2 89 0 187 11.0% 0.04 (0.00 to 2.21) Soysal 2001 ¹⁶⁶ 1 48 0 45 6.3% 0.14 (0.00 to 24.95) Corson 2000 ¹⁰¹ 2 123 0 144 12.5% 0.11 (0.00 to 4.40) Cooper 1998 ⁴³ 0 134 0 129 Not estimable Meyer 1998 ¹³⁰ 1 117 0 128 0.12 (0.00 to 2.39) Romer 1988 ¹⁷ 0 10 0 10 Not estimable ubtotal (95% CI) 1017 1467 0.12 (0.05 to 0.33) tal events 15 2 eterogeneity: $2^2 = 2.56$, df = 7 ($p = 0.92$); $P = 0\%$ st for overall effect: $z = 4.14$ ($p < 0.0001$) 22.7 Procedure abandoned Brun 2006 ¹⁰⁰ 0 25 0 51 Not estimable Duleba 2003 ⁸⁴ 0 86 0 193 Not estimable Duleba 2003 ⁸⁴ 0 34 0 37 Not estimable Duleba 2003 ⁸⁴ 0 34 0 37 Not estimable Corson 2001 ¹⁷⁹ 0 42 0 40 Not estimable Cooper 2002 ⁶⁴ 2 90 4 175 25.2% 1.03 (0.11 to 9.68) Pellicano 2002 ¹⁰² 0 42 0 40 Not estimable Cooper 2002 ⁸⁴ 5 134 5 129 46.1% 1.04 (0.20 to 5.46) Not estimable Cooper 1998 ⁴⁷ 0 10 0 10 Not estimable Cooper 1998 ⁴⁷ 0 10 0 10 Not estimable Cooper 1998 ⁴⁷ 0 10 0 10 Not estimable Cooper 1998 ⁴⁸ 5 134 5 129 46.1% 1.04 (0.20 to 5.46) Meyer 1998 ⁴⁷ 0 10 0 10 Not estimable Cooper 1998 ⁴⁷ 0 10 0 10 Not estima	van Zon-Rabelink 200195	3	62	0	77	18.5%	0.10 (0.01 to 2.09)	←
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Cooper 2002 ⁵⁶	3	90	0	175	16.9%	0.05 (0.00 to 1.20)	←==── <u></u>
Soysal 2001 ⁹⁸ 1 48 0 45 6.3% 0.14 (0.00 to 24.95) Corson 2000 ¹⁰¹ 2 123 0 144 12.5% 0.11 (0.00 to 4.40) Cooper 1999 ⁵⁴ 0 134 0 129 Not estimable 1. Meyer 1998 ⁵³ 1 117 0 128 0.12 (0.00 to 21.39) Romer 1998 ⁵⁷ 0 10 0 10 Not estimable ubtotal (95% CI) 1017 1467 0.12 (0.05 to 0.33) cal events 15 2 eterogeneity: $\chi^2 = 2.56$, df = 7 ($p = 0.92$); $P = 0\%$ est for overall effect: $z = 4.14$ ($p < 0.0001$) 22.7 Procedure abandoned Envn 2006 ¹⁰⁰ 0 20 0 31 Not estimable Duleba 2003 ⁸⁰ 0 86 0 193 Not estimable Hawe 2003 ⁸⁴ 0 34 0 37 Not estimable Locoper 2004 ⁹⁹ 0 107 0 215 Not estimable Cooper 2004 ⁹⁹ 0 34 0 37 Not estimable Cooper 2003 ⁸⁴ 0 34 0 37 Not estimable Cooper 2002 ⁹⁴ 0 34 0 37 Not estimable Corson 2001 ¹⁷⁰ 0 42 0 40 Not estimable Corson 2001 ¹⁷⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁰ 0 123 0 144 Not estimable Corson 2001 ¹⁹¹ 0 123 0 144 Not estimable Corson 2001 ¹⁹² 0 10 117 128 Not estimable Corson 2001 ¹⁹³ 0 10 0 10 Not estimable Corson 2001 ¹⁹⁴ 0 143 0 144 Not estimable Corson 2001 ¹⁹⁵ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁵ 0 10 0 10 Not estimable Corson 2001 ¹⁹⁵ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁶ 0 148 0 45 Not estimable Corson 2001 ¹⁹⁷ 0 128 Not estimable Corson 2001 ¹⁹⁶ 0 148 0 45 Not estimable Corson 2001 ¹⁹⁷ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁶ 0 123 0 144 Not estimable Corson 2001 ¹⁹⁷ 0 128 Not estimable Corson 2001 ¹⁹⁶ 0 10 0 10 Not estimable Romer 1998 ⁹⁷⁷ 0 10 0 10 Not estimable Romer 1998 ⁹⁷⁷ 0 10 0 10 Not estimable Able (Corson 2000 ¹⁹⁷⁵ 0 10 0 10 Not estimable New effect: $z = 1.05$ ($p = 0.30$) ubtotal (effect: $z = 1.05$ ($p = 0.30$) ubtotal (effect: $z = 1.05$ ($p = 0.30$)	Pellicano 2002 ¹⁰²	1	42	0	40	6.3%	0.14 (0.00 to 24.55)	←
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Corson 200179	2	89	0	187	11.0%	0.04 (0.00 to 2.21)	<u>←</u>
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Soysal 2001 ⁹⁶	1	48	0	45	6.3%	0.14 (0.00 to 24.95)	·
h. Mayer 1998 ⁵³ 1 117 0 128 0.12 (0.00 to 21.39) Romer 1998 ¹⁷⁷ 0 10 0 10 Not estimable ubtotal (95% Cl) 1017 1467 0.12 (0.05 to 0.33) cale events 15 2 eterogeneity: $\chi^2 = 2.56$, df = 7 ($p = 0.92$); $P = 0.06$ est for overall effect: $z = 4.14$ ($p < 0.0001$) 22.7 Procedure abandoned - - . Brun 2006 ¹⁰³ 0 20 31 Van Zon-Rabelink 2001 ⁴⁰⁰ 0 55 56 Duleba 2003 ⁴⁶ 0 86 193 Van Zon-Rabelink 2001 ⁴⁵⁰ 62 0 77 Van Zon-Rabelink 2001 ⁴⁵⁰ 62 0 77 Van Zon-Rabelink 2001 ⁴⁵⁰ 62 0 100 Coroper 2002 ⁵⁶ 2 90 4 175 25.2% Pellicano 2002 ¹¹⁰² 0 42 40 Not estimable Coroper 2002 ¹⁵⁰ 0 48 0 45 Not estimable Coroper 2002 ¹⁵⁰ 0 144 Not estimable 100 Coroper 1999	. Corson 2000 ¹⁰¹	2	123	0	144	12.5%	0.11 (0.00 to 4.40)	←
Romer 1998 ⁹⁷ 0 10 0 10 Not estimable ubtotal (95% CI) 1017 1467 0.12 (0.05 to 0.33) colal events 15 2 leterogeneity: $\chi^2 = 2.56$, df = 7 ($p = 0.92$); $P = 0\%$ 90% est for overall effect: $z = 4.14$ ($p < 0.0001$) 215 Not estimable Perino 2004 ¹⁰⁰ 0 55 56 Not estimable Derino 2004 ¹⁰⁰ 0 55 56 Not estimable Perino 2004 ¹⁰⁰ 0 31 Not estimable van Zon-Rabelink 2001 ⁹⁶ 62 0 77 Not estimable Cooper 2002 ⁹⁶ 2 90 4 175 25.2% 1.03 (0.11 to 9.68) Van Zon-Rabelink 2001 ⁹⁶ 642 0 77 Not estimable Coroson 2001 ¹⁷⁰ 89 7 187 28.6% 4.52 (0.55 to 37.14) Soyal 2001 ⁹⁶ 0 48 0 45 Not estimable Coroson 2000 ¹⁹⁷ 10 128 Not estimable 0.01 0.4 0.45 (0.20 to 5.46) Meyer 1998 ³³ 0 117 128 <t< td=""><td>Cooper 1999⁵⁴</td><td>0</td><td>134</td><td>0</td><td>129</td><td></td><td>Not estimable</td><td></td></t<>	Cooper 1999 ⁵⁴	0	134	0	129		Not estimable	
ubtatal (95% Cl) 1017 1467 0.12 (0.05 to 0.33) otal events 15 2 eterogeneity: $\chi^2 = 2.56$, df = 7 ($p = 0.92$); $l^2 = 0\%$ est for overall effect: $z = 4.14$ ($p < 0.0001$) 22.7 Procedure abandoned . . . Brun 2006 ¹⁰³ 0 20 0 31 Not estimable . Cooper 2004 ⁹⁰ 0 107 0 215 Not estimable . Duleba 2003 ⁸⁸ 0 86 193 Not estimable . Hawe 2003 ⁸⁴ 0 34 0 37 Not estimable van Zon-Rabelink 2001 ⁸⁵ 0 62 0 77 Not estimable . Cooper 2002 ⁵⁶ 2 90 4 175 25.2% 1.03 (0.11 to 9.68) . Pellicano 2002 ¹⁰² 0 42 0 Not estimable - . Corson 2001 ¹⁷⁹ 0 89 7 187 28.6% 4.52 (0.55 to 37.14) Soyaal 2001 ⁸⁶ 0 48 0 45 Not estimable - . Corson 2000 ¹⁷⁹ 0 123 144 Not estimable -	n. Meyer 1998 ⁵³	1	117	0	128		0.12 (0.00 to 21.39)	·
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			1017		1467			◆
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	eterogeneity: $\chi^2 = 2.56$, df =	= 7 (p = 0.92						
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$								
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bala events 7 16 eterogeneity: $\chi^2 = 2.32$, df = 2 ($p = 0.31$); $l^2 = 14\%$ 6 est for overall effect: $z = 1.05$ ($p = 0.30$) 0.01 0.01 0.1 1 10 100	Romer 199897	0	10	0	10		Not estimable	
bal events 7 16 eterogeneity: $\chi^2 = 2.32$, df = 2 ($p = 0.31$); $l^2 = 14\%$ est for overall effect: $z = 1.05$ ($p = 0.30$) 0.01 0.1 1 10	ubtotal (95% CI)		1017		1467	100.0%	1.58 (0.67 to 3.72)	+
leterogeneity: $\chi^2 = 2.32$, df = 2 ($p = 0.31$); $l^2 = 14\%$ est for overall effect: $z = 1.05$ ($p = 0.30$) 0.01 0.1 1 10	otal events	7		16			-	
0.01 0.1 1 10 100		= 2 (p = 0.31); <i>I</i> ² = 14%					
	est for overall effect: $z = 1.0$	05 (p = 0.30)						
Favours Favours								0.01 0.1 1 10 100
								Favours Favours

	First gen	eration	Second ge	eneration			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
1.22.8 Procedure converted	I to hystered	ctomy					
a. Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
b. Cooper 2004 ⁹⁹	0	107	0	215		Not estimable	
c. Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
d. Duleba 200398	0	86	0	193		Not estimable	
e. Hawe 2003 ⁹⁴	0	34	0	37		Not estimable	
. van Zon-Rabelink 2001 ⁹⁵	0	62	0	77		Not estimable	
g. Cooper 2002 ⁵⁶	0	90	0	175		Not estimable	
n. Pellicano 2002 ¹⁰²	2	42	0	40	49.8%	0.14 (0.00 to 5.42)	·
. Corson 2001 ⁷⁹	0	89	0	187		Not estimable	
. Soysal 2001 ⁹⁶	0	48	0	45		Not estimable	
 Corson 2000¹⁰¹ 	0	123	0	144		Not estimable	
. Cooper 1999 ⁵⁴	1	134	1	129	50.2%	1.04 (0.03 to 39.99)	+
n. Meyer 1998 ⁵³	0	117	0	128		Not estimable	
n. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	
Subtotal (95% CI)		1017		1467	100.0%	0.38 (0.05 to 2.73)	
Total events	3		1				
Heterogeneity: $\chi^2 = 1.01$, df =	= 1 (p = 0.32); <i>I</i> ² = 1%					
Test for overall effect: $z = 0.9$							
							0.01 0.1 1 10 100

Favours Favours second generation first generation

Number of patients with adverse events - postoperatively (within 1 month)

		First ger	neration	Second g	eneration			
a. Brun 2006 ¹¹⁰ 0 200 1 31 3.5.% 5.18 (0.03 to 1013.23) c. Perino 2004 ¹¹ 1 106 1 200 1 10.2.79 b. Coloper 2004 ¹¹ 1 260 1 10.7% 0.50 (0.02 to 10.02) e. Haw 2003 ¹¹ 1 260 1 77 8.5% 0.48 (0.00 to 10.2.7) b. Coloper 2005 ¹¹ 0 34 0 37 Not estimable b. Corear 2007 ¹¹ 0 2 86 0 107 4 45.5% 0.48 (0.00 to 10.8.2) c. Corear 2007 ¹¹ 0 48 0 445 Not estimable b. Corear 2007 ¹¹ 0 48 0 445 Not estimable b. Corear 1998 ¹² 0 117 1 128 Not estimable b. Corear 1998 ¹² 0 113 0 117 1 128 Not estimable b. Corear 2007 ¹¹ 0 48 0 445 Not estimable b. Corear 1998 ¹² 0 110 0 10 0 10 Not estimable b. Corear 2007 ¹¹ 0 100 1 10 Not estimable b. Corear 2007 ¹¹ 0 1 100 1 0 10 Not estimable 1. Corear 2007 ¹¹ 0 100 1 10 Not estimable 1. Corear 2007 ¹¹ 0 200 0 31 Not estimable 1. Corear 2007 ¹¹ 0 200 0 200 Not estimable 1. Corear 2007 ¹¹ 0 200 0 200 Not estimable 1. Corear 2007 ¹¹ 0 100 10 0 10 Not estimable 1. Corear 2007 ¹¹ 0 28 0 77 Not estimable 1. Corear 2004 ¹¹ 0 200 0 200 Not estimable 1. Corear 2004 ¹¹ 0 200 0 31 Not estimable 1. Paleian 2004 ¹¹ 0 34 0 37 Not estimable 1. Paleian 2004 ¹¹ 0 34 0 37 Not estimable 1. Paleian 2004 ¹¹ 0 34 0 37 Not estimable 1. Paleian 2004 ¹¹ 0 34 0 37 Not estimable 1. Paleian 2004 ¹¹ 0 34 0 37 Not estimable 1. Corear 2004 ¹¹ 0 34 0 37 Not estimable 1. Corear 2004 ¹¹ 0 34 0 129 Not estimable 1. Corear 2004 ¹¹ 0 34 0 129 Not estimable 1. Corear 2004 ¹¹ 0 34 0 129 Not estimable 1. Corear 2004 ¹¹ 0 34 0 129 Not estimable 1. Corear 2004 ¹¹ 0 34 0 129 Not estimable 1. Corear 2004 ¹¹ 0 34 0 177 Not estimable 1. Corear 1998 ¹² 0 117 1 128 Not estimable 1. Corear 1998 ¹² 0 117 1 128 Not estimable 1. Corear 1998 ¹² 0 117 1 128 Not estimable 1. Corear 1998 ¹² 0 117 1 128 Not estimable 1. Corear 2004 ¹¹ 0 34 0 177 Not estimable 1. Corear 2004 ¹¹ 0 34 0 177 Not estimable 1. Corear 2004 ¹¹ 0 140 Not estimable 1. Corear 2	Study or subgroup	Events	Total	Events	Total	Weight	· · ·	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
b. $Cooper 2004^{11}$ 1 106 1 209 6.5% 0.48 (20.11 to 22.79) c. Perino 2004 ¹² 1 26 5 1 56 17.74 0.56 (20.2 to 10.29) t. Unit 2001 ¹² 1 26 0 77 3.8% 0.41 (0.00 to 18.29) t. van 2.0-rRabelink 2001 ¹² 1 26 0 77 3.8% 0.11 (0.00 to 18.29) t. van 2.0-rRabelink 2001 ¹² 0 42 0 40 Not estimable t. Conson 2001 ¹² 2 48 5 187 21.8% 119 (0.14 to 1.70) t. Conson 2001 ¹² 0 42 0 40 Not estimable t. Conson 2001 ¹² 0 42 0 40 Not estimable t. Conson 2001 ¹² 0 123 0 123 0 120 Not estimable t. Conson 2001 ¹² 0 123 0 120 Not estimable t. Conson 2001 ¹² 0 123 0 120 Not estimable t. Conson 2001 ¹² 0 117 1 128 3.8% 6.78 (0.04 to 1.70) Not estimable t. Conson 2001 ¹² 0 10 0 10 Not estimable t. Conson 2001 ¹² 0 120 0 134 0 120 Not estimable t. Conson 2001 ¹² 0 100 100 100 Not estimable t. Conson 2001 ¹² 0 120 0 130 Not estimable t. Conson 2001 ¹² 0 120 0 130 Not estimable t. Conson 2001 ¹² 0 120 0 175 Not estimable t. Conson 2001 ¹² 0 120 0 175 Not estimable t. Conson 2001 ¹² 0 120 0 175 Not estimable t. Conson 2001 ¹² 0 124 0 140 Not estimable t. Conson 2001 ¹² 0 124 0 140 Not estimable t. Conson 2001 ¹² 0 124 0 140 Not estimable t. Conson 2001 ¹² 0 124 0 140 Not estimable t. Conson 2001 ¹² 0 124 0 140 Not estimable t. Conson 2001 ¹² 0 124 0 144 Not estimable t. Conson 2001 ¹² 0 128 0 144 Not estimable t. Conson 2001 ¹² 0 128 0 144 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 134 0 129 Not estimable t. Conson 2001 ¹² 0 120 170 128 Not estimable t. Conson 2001 ¹² 0 120 171 0 128 Not estimable t. Conson 2001 ¹² 0 120 171 0 128 Not estimable t. Conson 2001 ¹² 0 120 171 0 128 Not estimable t. Conson 2001 ¹² 0 120 171 0 128 Not estimable t. Conson 2001 ¹² 0 120 171 0 128 Not estimable t. Conson 2001 ¹² 0 120 1	1.23.1 Urinary tract infectior	ı						
c. Parine 2004 ¹¹⁰ 2 55 1 56 10.746 0.50 (0.02 to 10.02) a. Have 2003 ¹¹ 0 34 0 37 Not estimable a. Have 2002 ¹¹⁰ 0 34 0 37 Not estimable b. Copper 2002 ¹¹⁰ 5 90 9 175 43.5% 0.11 (0.00 to 19.3.2) b. Copper 2002 ¹¹⁰ 0 42 0 40.5% 0.22 (0.21 to 4.09) b. Corear 2007 ¹¹⁰ 0 48 5 187 21.8% 194 (0.00 to 19.3.2) b. Corear 2000 ¹¹¹ 0 48 0 10 Not estimable b. Corear 1098 ¹¹¹ 0 144 128 8.09 (0.04 to 112.0.4) 10 b. Corear 1098 ¹¹¹ 0 11 10 3.6% 0.14 (0.01 to 1.0.2) 10 theoregonetic y= 0.6.8, df = 8 (n - 0.5%); P = 0.5% 10 10 0.36 Not estimable theoregonetic y= 0.78 1 10 0.37 Not estimable theaco 2004 ¹¹¹ 0 10	a. Brun 2006 ¹⁰³	0	20	1	31	3.5%	5.18 (0.03 to 1013.33)	
1. Dubeb 2003 th 1 86 0 919 3.1% 0.04 (0.00 to 13.2) - um Zon-Rabelink 2001 th 1 62 0 77 3.6% 0.11 (0.00 to 18.2) - beliance 2002 th 0 42 0 40 Not estimable - Corsen 2001 th 2 88 5 177 3.6% 0.11 (0.00 to 18.2) - Felicinance 2002 th 0 42 0 40 Not estimable - Soyial 2001 th 0 48 0 45 Not estimable - Corsen 2000 th 0 123 144 3.6% 6.78 (0.04 to 117.23) - Roman 1986 th 0 17 128 6.6% 7.6 (0.04 to 117.23) - Roman 1986 th 0 10 0 31 Not estimable - Corsen 2001 th 0 20 31 Not estimable - Corsen 2004 th 0 20 0 Not estimable - Corsen 2004 th 0 20 0 Not estimable -	 Cooper 2004⁹⁹ 	1	106	1	209	6.5%	0.48 (0.01 to 22.79)	
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un 20rhabelink 2001 [™] 1 ét de 2 0 77 8.6% 0.11 (0.00 to 18.92) Net estimable Net estimable Net estimable Corano 2001 [™] 0 42.0 0 L Pallicano 2002 [™] 0 42.0 44 0 table Not estimable Cooper 2002 [™] Not estimable						3.1%	0.04 (0.00 to 10.32)	← <u></u>
$ \begin{array}{c} 1 \text{ Corper 2002**} & 5 & 90 & 9 & 175 & 43.5\% & 0.92 (0.21 to 4.09) \\ \hline \text{Pelicano 2002**} & 0 & 42 & 0 & 40 \\ \hline \text{Not estimable} & 190 (14 to 9.76) \\ \hline \text{Scyall 201**} & 0 & 48 & 0 & 45 \\ \hline \text{Corear 2000***} & 0 & 123 & 1 & 144 & 3.6\% & 6.38 (0.44 to 1120.84) \\ \hline \text{Corear 2000***} & 0 & 134 & 122 & 80 \\ \hline \text{Corear 1998***} & 0 & 117 & 1 & 128 & 3.6\% & 6.78 (0.44 to 1177.23) \\ \hline \text{Not estimable} & 12 & 19 \\ \hline \text{tetrogeneity} \ x^2 = 6.48 , df = 8 (p = 0.59); F = 0.5\% \\ \hline \text{tetrogeneity} \ x^2 = 6.48 , df = 8 (p = 0.59); F = 0.5\% \\ \hline \text{tetrogeneity} \ x^2 = 6.48 , df = 8 (p = 0.59); F = 0.5\% \\ \hline \text{tetrogeneity} \ x^2 = 6.48 , df = 0.59); F = 0.5\% \\ \hline \text{tetrogeneity} \ x^2 = 0.40 & 100 & 0 & 209 \\ \hline \text{Not estimable} & 12 \\ \hline \text{tetrogeneity} \ x^2 = 0.40 & 100 & 0 & 209 \\ \hline \text{Not estimable} & 12 \\ \hline \text{corper 2004**} & 0 & 55 & 0 & 55 \\ \hline \text{Rem 2004**} & 0 & 30 & 377 \\ \hline \text{Not estimable} & 12 \\ \hline \text{Ladea 2003**} & 0 & 42 & 0 & 177 \\ \hline \text{Not estimable} & 160 & 120 \\ \hline \text{Ladea 2003**} & 0 & 48 & 0 & 45 \\ \hline \text{Not estimable} & 160 & 120 \\ \hline \text{Ladea 2003**} & 0 & 48 & 0 & 477 \\ \hline \text{Not estimable} & 160 & 120 \\ \hline \text{Corper 2004**} & 0 & 43 & 0 & 177 \\ \hline \text{Not estimable} & 160 & 120 \\ \hline \text{Corper 2004**} & 0 & 48 & 0 & 45 \\ \hline \text{Corper 2004**} & 0 & 134 & 0 & 129 \\ \hline \text{Not estimable} & 160 & 100 \\ \hline \text{Corper 2004**} & 0 & 117 & 0 & 128 \\ \hline \text{Not estimable} & 1461 \\ \hline \text{Not estimable} & 160 & 100 \\ \hline \text{Corper 2004**} & 0 & 117 & 0 & 128 \\ \hline \text{Corper 2004**} & 0 & 160 & 0 \\ \hline \text{Corper 2004**} & 0 & 160 & 0 \\ \hline \text{Corper 2004**} & 0 & 160 & 0 \\ \hline \text{Corper 2004**} & 0 & 160 & 0 \\ \hline \text{Corper 2004**} & 0 & 160 & 0 \\ \hline \text{Corper 2004**} & 0 & 177 & 128 \\ \hline \text{Not estimable} & 1461 \\ \hline \text{Not estimable} & 160 \\ \hline \text{Not estimable} & 160 \\ \hline \text{Corper 2004**} & 0 & 160 & 0 \\ \hline \text{Corper 2004**} & 0 & 177 & 128 \\ \hline \text{Corper 2004**} & 0 & 100 & 0 \\ \hline \text{Not estimable} & 1461 \\ \hline \text{Not estimable} & 177 \\ \hline \text{Not estimable} & $								
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$ \begin{array}{c} Core 12000^{11} & 0 & 123 & 1 & 144 & 3.8\% & 6.38 (0.04 to 112.0.84) \\ \hline \mbox{matrix} & 0 & 117 & 1 & 128 & 3.8\% & 6.78 (0.04 to 1177.23) \\ \hline \mbox{matrix} & 0 & 1016 & 0 & 100 & Not estimable \\ \hline \mbox{mable} & 0 & 100 & 0 & 100 & Not estimable \\ \hline \mbox{mable} & 0 & 20 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 20 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 31 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 77 & Not estimable \\ \hline \mbox{mable} & 0 & 200 & 0 & 175 & Not estimable \\ \hline \mbox{mable} & 0 & 420 & 0 & 175 & Not estimable \\ \hline \mbox{mable} & 0 & 420 & 0 & 175 & Not estimable \\ \hline \mbox{mable} & 0 & 420 & 0 & 175 & Not estimable \\ \hline \mbox{mable} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 420 & 0 & 175 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 123 & 0 & 144 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 10 & 0 & 10 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 106 & 0 & 200 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 106 & 0 & 200 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 106 & 0 & 200 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 106 & 0 & 200 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 37 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 123 & 0 & 144 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 123 & 0 & 144 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 & 45 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 123 & 0 & 144 & Not estimable \\ \hline \mbox{coreson2001}^{10} & 0 & 48 & 0 &$						21.8%	· · · · · ·	
$ \begin{array}{c} \operatorname{Cooper 1999^{bit}}{} 0 & 134 & 0 & 129 & \operatorname{Not estimable} \\ \operatorname{Not estimable} & \operatorname{Not estimable} \\ $	-					0.00/		
$\begin{split} & \text{Meyer 1989}^{\text{B}} & 0 & 117 & 1 & 128 & 3.6\% & 6.78 (0.04 to 1177.23) \\ & \text{abtoal (95% CI)} & 0 & 1016 \\ & oth extins the introduces in the introduce introduce introduces in the introduce introduces in the introduces introduces in the introduces intr$						3.6%	,	
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total events 12 12 19 letterogeneity: $\chi_{1}^{2} = 64.3$ (f = 0.659); $P = 0.56$ est for overall effect: $z = 0.28$ ($p = 0.73$) 2.82 Deg-vein thrombosis B nn 200 ⁶ ¹⁰¹ 0 220 0 31 Not estimable Cooper 2004 ¹⁰⁰ 0 86 0 193 Not estimable Dubba 2003 ¹⁰¹ 0 34 0 37 Not estimable Have 2003 ¹¹ 0 34 0 37 Not estimable Cooper 2002 ¹⁰² 0 42 0 40 Not estimable Cooper 2002 ¹⁰³ 0 48 0 45 Not estimable Cooper 2002 ¹⁰⁴ 0 148 0 45 Not estimable Cooper 2002 ¹⁰⁴ 0 148 0 45 Not estimable Cooper 2002 ¹⁰⁴ 0 148 0 45 Not estimable Cooper 1999 ¹⁰⁴ 0 170 128 Not estimable Cooper 1999 ¹⁰⁴ 0 1016 10 Not estimable Ander 1998 ¹⁰⁷ 0 100 0 10 Not estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Cooper 1999 ¹⁰⁵ 0 34 0 37 Not estimable Market 2003 ¹¹ Not estimable More 1998 ¹⁰⁷ 0 106 0 209 Not estimable More 1998 ¹⁰⁷ 0 1076 0 117 Not estimable More 1998 ¹⁰⁷ 0 106 0 209 Not estimable More 1998 ¹⁰⁷ 0 1076 0 100 10 Not estimable More 1998 ¹⁰⁷ 0 106 0 209 Not estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 2.3 Further bleeding Estimable 3. Occoper 2004 ¹⁰⁷ 0 42 0 40 Not estimable 3. Occoper 2004 ¹⁰⁷ 0 42 0 40 Not estimable 3. Occoper 2004 ¹⁰⁷ 0 42 0 40 Not estimable 3. Occoper 2004 ¹⁰⁷ 0 134 3 129 39.8% 7.80 (0.39 to 154.58) 4. Perinc 2001 ¹⁰⁷ 0 128 Not estimable 3. Occoper 1999 ¹⁴ 0 117 0 128 Not estimable 3. Occoper 1999 ¹⁴ 0 117 0 128 Not estimable 3. Occoper 1999 ¹⁴ 0 116 1000 Not estimable 3. Occoper 1999 ¹⁴ 0 116 1000 Not estimable 3. Port 1998 ¹⁴ 0 117 0 128 Not estimable 3. Port 1998 ¹⁴ 0 117 0 128 Not estimable 3. Port 1998 ¹⁴ 0 117 Not estimable 3. Port 1998 ¹⁴ 0 116 1000 Not estimable 3. Port 1998 ¹⁴ 0 117 Not estimable 3. Port 1998 ¹⁴ 0 107 Not estimable 3. Port 1998 ¹⁴ 0 100 0 1		U		0		100 00/		
$\begin{aligned} \text{dercognerity: } y^2 &= 6.48, dr = 8 (p = 0.58); F = 0.96 \\ \text{est for overall effect: } z = 0.28 (p = 0.78) \\ \end{aligned} \\ \begin{aligned} \textbf{22.2 Decy-vein thrombosis} \\ \textbf{Enn 2000^{116}} & 0 & 20 & 0 & 31 & \text{Not estimable} \\ \textbf{Cooper 2004^{40}} & 0 & 65 & 0 & 56 & \text{Not estimable} \\ \textbf{Duleba 2003^{41}} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \textbf{Duleba 2003^{41}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \textbf{Cooper 2004^{40}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \textbf{Cooper 2004^{40}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \textbf{Cooper 2002^{410}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \textbf{Cooper 1909^{410}} & 0 & 134 & 0 & 129 & \text{Not estimable} \\ \textbf{Corson 2001^{41}} & 0 & 134 & 0 & 129 & \text{Not estimable} \\ \textbf{Corson 2001^{41}} & 0 & 134 & 0 & 129 & \text{Not estimable} \\ \textbf{Corson 2001^{41}} & 0 & 134 & 0 & 129 & \text{Not estimable} \\ \textbf{Corson 1999^{410}} & 0 & 177 & 0 & 128 & \text{Not estimable} \\ \textbf{Corson 1999^{410}} & 0 & 177 & 0 & 128 & \text{Not estimable} \\ \textbf{Corson 2001^{41}} & 0 & 0 & 0 & 0 & 10 & \text{Not estimable} \\ \textbf{Corson 2001^{41}} & 0 & 0 & 0 & 0 & 0 & 0 \\ \textbf{eterogeneity: not applicable} & \textbf{stendarde} & \textbf{Not estimable} \\ \textbf{Not estimable} & \textbf{Not estimable} & \textbf{Not estimable} \\ \textbf{Not estimable} & \textbf{Not estimable} & \textbf{Not estimable} \\ \textbf{Perino 2004^{42}} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \textbf{Parino 2004^{42}} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \textbf{Parino 2004^{42}} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & 0 & 62 & 0 & 77 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & 0 & 62 & 0 & 77 & \text{Not estimable} \\ \textbf{Parino 2004^{41}} & 0 & 10 & 175 & 23.96 & 0.49 (0.01 to 23.00) \\ \textbf{Parina 20n-Babelink 201^{42}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \textbf{Parino 2004^{41}} & 0 & 134 & 3 & 129 & 39.86 & 7.00 (0.39 to 154.58) \\ \textbf{Parina 2000^{511}} & 0 & 20 & 0 & 31 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & 0 & 10 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & 0 & 10 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & 0 & 106 & 0 & 299 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & 0 & 106 & 0 & 299 & \text{Not estimable} \\ \textbf{Parino 2004^{410}} & $		10	1010	10	1401	100.0%	0.90 (0.42 18 1.90)	T
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$\begin{array}{c} \text{Cooper 2004}^{\text{M}} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \text{Perino 2004}^{\text{M}} & 0 & 65 & 0 & 56 & \text{Not estimable} \\ \text{Juleba 2003}^{\text{M}} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Var Zon-Rabelink 2001}^{\text{M}} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Cooper 2002}^{\text{M}} & 0 & 43 & 0 & 177 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2000}^{\text{M}} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2000}^{\text{M}} & 0 & 103 & 0 & 10 & \text{Not estimable} \\ \text{Corson 2000}^{\text{M}} & 0 & 104 & 0 & 108 & \text{Not estimable} \\ \text{Corson 2000}^{\text{M}} & 0 & 100 & 0 & 10 & \text{Not estimable} \\ \text{Mayer 1998}^{\text{M}} & 0 & 100 & 0 & 10 & \text{Not estimable} \\ \text{Moter 1998}^{\text{M}} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \text{Ustotal (655 CI)} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \text{Uetrogenetity: not applicable} \\ \text{est for overall effect: not applicable} \\ \text{est for overall effect: not applicable} \\ \text{Perino 2004}^{\text{M}} & 0 & 55 & 0 & 56 & \text{Not estimable} \\ \text{Luea 2003}^{\text{M}} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Luea 2003}^{\text{M}} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 48 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 123 & 0 & 137 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 100 & 0 & 0 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 108 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 100 & 0 & 0 & \text{Not estimable} \\ \text{Corson 2001}^{\text{M}} & 0 & 100 & 0 & 0 & \text{Not estimable} \\ \text{Corson 2000}^{\text{M}} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \text{Corson 2000}^{\text{M}} & 0 & 106 & 0 & 209 & \text{Not estimable} $	-							
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$\begin{array}{c} \text{Corson 2000}^{191} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Cooper 1999}^{24} & 0 & 134 & 0 & 129 & \text{Not estimable} \\ \text{Meyer 1998}^{173} & 0 & 117 & 0 & 128 & \text{Not estimable} \\ \text{ubtatal (95% CI)} & 1016 & 1461 & \text{Not estimable} \\ \text{ubtatal (95% CI)} & 0 & 0 \\ \text{eterogeneity: not applicable} \\ \text{est for overall effect: not applicable} \\ \hline 23.3 Further bleeding \\ \text{Envn 2006}^{103} & 2 & 20 & 0 & 31 & 25.0\% & 0.07 (0.00 to 3.21) \\ \text{Cooper 2004}^{49} & 0 & 106 & 0 & 209 & \text{Not estimable} \\ \hline Duleba 2003^{48} & 0 & 36 & 1 & 133 & 11.4\% & 4.24 (0.02 to 1123.03) \\ \text{Hawe 2003}^{44} & 0 & 34 & 0 & 37 & \text{Not estimable} \\ \text{Corson 2001}^{170} & 0 & 62 & 0 & 77 & \text{Not estimable} \\ \text{Cooper 2002}^{46} & 1 & 90 & 1 & 175 & 23.9\% & 0.49 (0.01 to 23.00) \\ \text{Pellicano 2002}^{102} & 0 & 42 & 0 & 40 & \text{Not estimable} \\ \text{Corson 2001}^{170} & 0 & 89 & 0 & 187 & \text{Not estimable} \\ \text{Soysal 2001}^{49} & 0 & 148 & 0 & 45 & \text{Not estimable} \\ \text{Corson 2000}^{111} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2000}^{111} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2000}^{111} & 0 & 123 & 0 & 144 & \text{Not estimable} \\ \text{Corson 2000}^{111} & 0 & 128 & \text{Not estimable} \\ \text{Motat (B5% CI) & 1016 & 1146 & 100.0\% & 11.77 (0.28 to 4.92) \\ \text{ubtatal (95% CI) & 1016 & 1461 & 100.0\% & 1.17 (0.28 to 4.92) \\ \text{val can finable} & 3 & 5 \\ \text{Ieterogeneity: } x^2 = 6.39, df = 3 (\rho = 0.07); P = 57\% \\ \text{est for overall effect: } z = 0.22 (\rho = 0.83) \\ \hline 224 \text{ Sepsis} & & \\ \text{Bun 2006}^{113} & 0 & 20 & 0 & 31 & \text{Not estimable} \\ \text{Dubba 2003}^{49} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 366 & 0 & 133 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 344 & 0 & 377 & \text{Not estimable} \\ \text{Lowe 2003}^{44} & 0 & 346 &$								
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D. Cooper 2004 ⁹⁹ 0 106 0 209 Not estimable D. Perino 2004 ¹⁰⁰ 0 55 0 56 Not estimable D. Duleba 2003 ⁹⁸ 0 86 0 193 Not estimable Hawe 2003 ⁹⁴ 0 34 0 37 Not estimable van Zon-Rabelink 2001 ⁹⁵ 0 62 0 77 Not estimable		0	20	0	31		Not estimable	
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0.01 0.1 1 10 100

Favours Favours second generation

Study or subgroup Eve n. Pellicano 2002^{102} 0 Corson 2001^{79} 0 Soysal 2001^{96} 0 Corson 2000^{101} 0 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 n. Meyer 1998 ⁵³ 0 n. Romer 1998 ⁹⁷ 0 Subtotal (95% CI) Fotal events Fotal events 0 A. Brun 2006^{103} 0 D. Cooper 2004^{99} 0 C. Corper 2004^{100} 0 D. Cooper 2004^{100} 0 D. Duleba 2003^{84} 0 Corper 2002^{56} 0 Perino 2001^{102} 0 Cooper 2002^{56} 0 Corson 2001^{101} 1 Cooper 1999^{54} 0 Soysal 2001^{56} 0 Newer 1998^{87} 0 Newer 1998^{97} 0 Subtotal (95% CI) 1 Total events 1 Heterogeneity: $\chi^2 = 0.65$, df = 1 (p Test fo	42 89 48 123 134 117 10 1016	Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 40 187 45 144 129 128 10 1461	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
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Brun 2006 ¹⁰³ 0 Cooper 2004 ⁹⁹ 0 Perino 2004 ¹⁰⁰ 0 Duleba 2003 ⁹⁸ 0 Hawe 2003 ⁹⁴ 0 van Zon-Rabelink 2001 ⁹⁵ 0 Cooper 2002 ⁵⁶ 0 Pellicano 2002 ¹⁰² 0 Corson 2001 ⁷⁹ 0 Soysal 2001 ⁹⁶ 0 Corson 2001 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 Neyer 1998 ⁵³ 0 Romer 1998 ⁹⁷ 0 Subtotal (95% CI) 1 feterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p Rrun 2006 ¹⁰³ 0 Cooper 2004 ⁹⁹ 0 Perino 2004 ¹⁰⁰ 0	106 55 86 34 62 90 42 89	2				
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1. Duleba 2003 ⁹⁸ 0 4. Duleba 2003 ⁹⁴ 0 9. Hawe 2003 ⁹⁴ 0 1. van Zon-Rabelink 2001 ⁹⁵ 0 0. Cooper 2002 ⁵⁶ 0 1. Pellicano 2002 ¹⁰² 0 Corson 20001 ⁷⁹ 0 Soysal 2001 ⁹⁶ 0 c. Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 b. Romer 1998 ⁹⁷ 0 Subtotal (95% CI) 5 otal events 1 teterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p . Brun 2006 ¹⁰³ 0 . Cooper 2004 ⁹⁹ 0 . Perino 2004 ¹⁰⁰ 0 4. Bue 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	86 34 62 90 42 89	0	209	47.3%	4.54 (0.10 to 215.47)	
Hawe 2003 ⁹⁴ 0 van Zon-Rabelink 2001 ⁹⁵ 0 I. Cooper 2002 ⁵⁶ 0 Dellicano 2002 ¹⁰² 0 Corson 20001 ⁷⁹ 0 Soysal 2001 ⁸⁶ 0 Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 Bomer 1998 ⁹⁷ 0 Subtotal (95% CI) 0 Total events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p	34 62 90 42 89		56		Not estimable	
van Zon-Rabelink 2001 ⁹⁵ 0 Cooper 2002 ⁵⁶ 0 Pellicano 2002 ¹⁰² 0 Corson 2001 ⁷⁹ 0 Soysal 2001 ⁹⁶ 0 Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 b. Romer 1998 ⁹⁷ 0 Subtotal (95% CI) 0 fotal events 1 feterogeneity: $\chi^2 = 0.65$, df = 1 (p 	62 90 42 89	0	193		Not estimable	
van Zon-Rabelink 2001 ⁹⁵ 0 Cooper 2002 ⁵⁶ 0 Pellicano 2002 ¹⁰² 0 Corson 2001 ⁷⁹ 0 Soysal 2001 ⁹⁶ 0 Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 b. Romer 1998 ⁹⁷ 0 Subtotal (95% CI) 0 fotal events 1 feterogeneity: $\chi^2 = 0.65$, df = 1 (p 	62 90 42 89	0	37		Not estimable	
. Cooper 2002 ⁵⁶ 0 . Pellicano 2002 ¹⁰² 0 Corson 2001 ¹⁹³ 0 Soysal 2001 ⁹⁶ 0 Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 Romer 1998 ⁵⁷ 0 iubtotal (95% CI) 0 total events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p = . S3.6 Endometritis 0 Perino 2004 ¹⁰³ 0 Perino 2004 ¹⁹⁹ 0 Perino 2004 ¹⁰⁰ 0 Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	90 42 89	0	77		Not estimable	
Pellicano 2002^{102} 0 Corson 2001^{79} 0 Soysal 2001^{96} 0 Corson 2000^{101} 1 Cooper 1999^{54} 0 Meyer 1998^{93} 0 Nemer 1998^{97} 0 ubtotal (95% CI) 0 otal events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p = .23.6 Endometritis . Brun 2006^{103} 0 . Cooper 2004^{99} 0 . Perino 2004^{100} 0 Hawe 2003^{94} 2 van Zon-Rabelink 2001^{95}	42 89	0	175		Not estimable	
Corson 2001 ⁷⁹ 0 Soysal 2001 ⁹⁶ 0 . Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 . Meyer 1998 ⁵³ 0 . Romer 1998 ⁹⁷ 0 bibtotal (95% CI) 0 otal events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p . 23.6 Endometritis . Brun 2006 ¹⁰³ 0 . Cooper 2004 ⁹⁹ 0 . Perino 2004 ¹⁰⁰ 0 Duleba 2003 ⁹⁸ 0 . Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	89	0	40		Not estimable	
Soysal 2001 ⁹⁶ 0 Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 Romer 1998 ⁹⁷ 0 ubtotal (95% CI) otal events otal events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p . Brun 2006 ¹⁰³ 0 . Cooper 2004 ⁹⁹ 0 . Perino 2004 ¹⁰⁰ 0 . Duleba 2003 ⁹⁸ 0 . Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0		0	40 187		Not estimable	
Corson 2000 ¹⁰¹ 1 Cooper 1999 ⁵⁴ 0 N. Meyer 1998 ⁵³ 0 Romer 1998 ⁹⁷ 0 ubtotal (95% CI) 0 otal events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p		0				
Cooper 1999 ⁵⁴ 0 n. Meyer 1998 ⁵³ 0 c. Romer 1998 ⁹⁷ 0 ubtotal (95% CI) 0 otal events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p .23.6 Endometritis . Brun 2006 ¹⁰³ 0 . Cooper 2004 ⁹⁹ 0 . Perino 2004 ¹⁰⁰ 0 . Duleba 2003 ⁹⁸ 0 . Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0			45	E0 70/	Not estimable	1
n. Meyer 1998 ⁵³ 0 . Romer 1998 ⁵⁷ 0 ubtotal (95% CI) total events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p = .23.6 Endometritis . Brun 2006 ¹⁰³ 0 . Cooper 2004 ⁹⁹ 0 . Perino 2004 ⁹⁹ 0 . Perino 2004 ⁹⁰ 0 . Duleba 2003 ⁹⁸ 0 . Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	123	1	144	52.7%	0.85 (0.02 to 33.19)	
. Romer 1998 ⁹⁷ 0 subtotal (95% CI) 0 otal events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p = . 23.6 Endometritis . Brun 2006 ¹⁰³ 0 . Cooper 2004 ⁹⁹⁹ 0 . Perino 2004 ¹⁰⁰ 0 . Duleba 2003 ⁹⁸ 0 . Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	134	0	129		Not estimable	
Subtotal (95% Cl) total events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p	117	0	128		Not estimable	
total events 1 leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p	10	0	10		Not estimable	
leterogeneity: $\chi^2 = 0.65$, df = 1 (p est for overall effect: $z = 0.61$ (p .23.6 Endometritis . Brun 2006 ¹⁰³ 0 Cooper 2004 ⁹⁹ 0 Perino 2004 ¹⁰⁰ 0 Duleba 2003 ⁹⁸ 0 Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵	1016		1461	100.0%	1.88 (0.25 to 14.20)	-
est for overall effect: z = 0.61 (p = .23.6 Endometritis . Brun 2006 ¹⁰³ 0. Cooper 2004 ⁹⁹ 0. Perino 2004 ¹⁰⁰ 0. Duleba 2003 ⁹⁸ 0. Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵		3				
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 Perino 2004¹⁰⁰ Duleba 2003⁹⁸ Hawe 2003⁹⁴ van Zon-Rabelink 2001⁹⁵ O 	20	0	31		Not estimable	
Perino 2004 ¹⁰⁰ 0 I. Duleba 2003 ⁹⁸ 0 J. Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	106	6	209	20.5%	4.63 (0.49 to 43.60)	
Duleba 2003 ⁹⁸ 0 Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	55	0	56		Not estimable	
. Hawe 2003 ⁹⁴ 2 van Zon-Rabelink 2001 ⁹⁵ 0	86	0	193		Not estimable	
van Zon-Rabelink 2001 ⁹⁵ 0	34	4	37	21.6%	1.87 (0.21 to 16.65)	
	62	0	77	21.070	Not estimable	
	90	2	175	17.2%	0.31 (0.03 to 3.57)	
				17.270		
	42	0	40	10 10/	Not estimable	
Corson 2001 ⁷⁹ 1	89	2	187	10.1%	0.95 (0.04 to 23.18)	
Soysal 2001 ⁹⁶ 1	48	2	45	11.4%	2.11 (0.10 to 42.82)	
. Corson 2000 ¹⁰¹ 1	123	0	144	3.9%	0.11 (0.00 to 20.02)	·
Cooper 1999 ⁵⁴ 0	134	0	129		Not estimable	
n. Meyer 1998 ⁵³ 1	117	3	128	15.3%	2.52 (0.19 to 33.71)	
. Romer 1998 ⁹⁷ 0	10	0	10		Not estimable	
Subtotal (95% CI)	1016		1461	100.0%	1.47 (0.68 to 3.18)	+
otal events 9		19			. ,	
Heterogeneity: $\chi^2 = 6.64$, df = 6 (p rest for overall effect: $z = 0.98$ (p						
.23.7 Hematometra	0-	0				
1. Brun 2006 ¹⁰³ 0	20	0	31		Not estimable	
0. Cooper 2004 ⁹⁹ 0	106	0	209		Not estimable	
. Perino 2004 ¹⁰⁰ 0	55	0	56		Not estimable	
. Duleba 2003 ⁹⁸ 0	86	0	193		Not estimable	
. Hawe 2003 ⁹⁴ 0	34	0	37		Not estimable	
van Zon-Rabelink 200195 0	62	0	77		Not estimable	
. Cooper 2002 ⁵⁶ 2	90	2	175	24.5%	0.49 (0.03 to 7.48)	
. Pellicano 2002 ¹⁰² 0	42	0	40		Not estimable	
Corson 2001 ⁷⁹ 5	89	2	187	41.4%	0.16 (0.02 to 1.31)	_ _
Soysal 2001 ⁹⁶ 2	48	1	45	20.3%	0.54 (0.03 to 10.94)	
. Corson 2000 ¹⁰¹ 1	123	0	144	6.9%	0.11 (0.00 to 20.02)	,
				0.9%		
•	134	0	129	6 00/	Not estimable	
n. Meyer 1998 ⁵³ 1	117	0	128	6.9%	0.12 (0.00 to 21.39)	·
. Romer 1998 ⁹⁷ 0	10	0	10		Not estimable	
Subtotal (95% CI)	1016	_	1461	100.0%	0.26 (0.09 to 0.72)	◆
otal events 11		5				
leterogeneity: $\chi^2 = 1.40$, df = 4 (p						

0.01 0.1 1 10 100

Favours Favours second generation

	First ger	neration	Second g	eneration			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-even Peto, Fixed, 99% Cl
1.23.8 Abdominal pain							
a. Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
 Cooper 2004⁹⁹ 	9	106	11	209	30.7%	0.58 (0.17 to 2.05)	
2004 ¹⁰⁰	0	55	0	56		Not estimable	
1. Duleba 200398	0	86	0	193		Not estimable	
e. Hawe 2003 ⁹⁴	0	34	1	37	1.8%	6.81 (0.04 to 1182.26)	,
van Zon-Rabelink 2001 ⁹⁵	0	62	4	77	7.1%	6.33 (0.46 to 86.91)	
 Cooper 2002⁵⁶ 	4	90	6	175	15.9%	0.76 (0.13 to 4.36)	
n. Pellicano 2002 ¹⁰²	0	42	0	40	101070	Not estimable	
. Corson 2001 ⁷⁹	18	89	9	187	39.1%	0.18 (0.06 to 0.54)	
	0	48	0	45	00.170	Not estimable	-
. Soysal 2001 ⁹⁶ . Corson 2000 ¹⁰¹	0		0				
		123		144	F 40/	Not estimable	
. Cooper 1999 ⁵⁴	3	134	0	129	5.4%	0.14 (0.01 to 2.74)	·
n. Meyer 1998 ⁵³	0	117	0	128		Not estimable	
n. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	
Subtotal (95% CI)		1016		1461	100.0%	0.43 (0.26 to 0.74)	◆
Total events	34		31				
Heterogeneity: $\chi^2 = 15.22$, df =			%				
Test for overall effect: $z = 3.08$	3 (p = 0.002)	2)					
1.23.9 Foul discharge							
a. Brun 2006 ¹⁰³	1	20	0	31	51.6%	0.08 (0.00 to 15.27)	→ ■→
 Cooper 2004⁹⁹ 	0	106	1	209	48.4%	4.51 (0.02 to 1052.05)	_
. Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
d. Duleba 200398	0	86	0	193		Not estimable	
e. Hawe 2003 ⁹⁴	0	34	0	37		Not estimable	
van Zon-Rabelink 2001 ⁹⁵	0	62	0	77		Not estimable	
g. Cooper 2002 ⁵⁶	0	90	0	175		Not estimable	
n. Pellicano 2002 ¹⁰²	0	42	0	40		Not estimable	
. Corson 2001 ⁷⁹	0	89	0	187		Not estimable	
. Soysal 2001 ⁹⁶	0	48	0	45		Not estimable	
c. Corson 2000 ¹⁰¹	0	123	0	144		Not estimable	
. Cooper 1999 ⁵⁴	0	134	0	129		Not estimable	
n. Meyer 1998 ⁵³	0	117	0	128		Not estimable	
1. Romer 1998 ⁹⁷	0	10	0	10		Not estimable	
Subtotal (95% CI)	0	1016	U	1461	100.0%	0.56 (0.03 to 9.94)	
Total events	1	1010	1	1401	100.0 /0	0.00 (0.00 10 0.04)	
Heterogeneity: $\chi^2 = 1.90$, df = Test for overall effect: $z = 0.40$	1 (p = 0.17)); <i>I</i> ² = 47%	·				
.23.10 Visceral damage							
a. Brun 2006 ¹⁰³	0	20	0	31		Not estimable	
 Cooper 2004⁹⁹ 	0	106	0	209		Not estimable	
c. Perino 2004 ¹⁰⁰	0	55	0	56		Not estimable	
d. Duleba 200398	0	86	0	193		Not estimable	
e. Hawe 2003 ⁹⁴	0	34	0	37		Not estimable	
. nawe 2000	0	54 62	0	37 77			
van Zon-Rabolink 200195	0					Not estimable	
		90	0	175		Not estimable	
g. Cooper 2002 ⁵⁶			0	40		Not estimable	
n. Pellicano 2002 ¹⁰²	0	42				Not estimable	
g. Cooper 2002 ⁵⁶ n. Pellicano 2002 ¹⁰² . Corson 2001 ⁷⁹	0 0	89	0	187			
 Geoper 2002⁵⁶ Pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ 	0			187 45		Not estimable	
 G. Cooper 2002⁵⁶ Pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ 	0 0	89	0				
 G. Cooper 2002⁵⁶ Pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ Corson 2000¹⁰¹ 	0 0 0	89 48	0 0	45		Not estimable	
 G. Cooper 2002⁵⁶ Pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ Corson 2000¹⁰¹ Cooper 1999⁵⁴ 	0 0 0 0	89 48 123	0 0 0	45 144		Not estimable Not estimable	
 G. Cooper 2002⁵⁶ Pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ Corson 2000¹⁰¹ Cooper 1999⁵⁴ n. Meyer 1998⁵³ 	0 0 0 0 0	89 48 123 134 117	0 0 0 0	45 144 129 128		Not estimable Not estimable Not estimable Not estimable	
 g. Cooper 2002⁵⁶ Pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ Corson 2000¹⁰¹ Cooper 1999⁵⁴ n. Meyer 1998⁵³ Romer 1998⁹⁷ 	0 0 0 0 0	89 48 123 134 117 10	0 0 0 0	45 144 129 128 10		Not estimable Not estimable Not estimable Not estimable Not estimable	
 g. Cooper 2002⁵⁶ pellicano 2002¹⁰² Corson 2001⁷⁹ Soysal 2001⁹⁶ Corson 2000¹⁰¹ Cooper 1999⁵⁴ n. Meyer 1998⁵³ Romer 1998⁹⁷ Subtotal (95% CI) 	0 0 0 0 0 0	89 48 123 134 117	0 0 0 0 0	45 144 129 128		Not estimable Not estimable Not estimable Not estimable	
g. Cooper 2002 ⁵⁶ n. Pellicano 2002 ¹⁰² . Corson 2001 ⁷⁹ . Soysal 2001 ⁹⁶ . Corson 2000 ¹⁰¹ . Cooper 1999 ⁵⁴ n. Meyer 1998 ⁵³ 3. Romer 1998 ⁹⁷ Subtotal (95% CI) Fotal events	0 0 0 0 0	89 48 123 134 117 10	0 0 0 0	45 144 129 128 10		Not estimable Not estimable Not estimable Not estimable Not estimable	
g. Cooper 2002 ⁵⁶ h. Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ h. Meyer 1998 ⁵³ b. Romer 1998 ⁸⁷ Subtotal (95% CI) Fotal events Heterogeneity: not applicable	0 0 0 0 0 0	89 48 123 134 117 10	0 0 0 0 0	45 144 129 128 10		Not estimable Not estimable Not estimable Not estimable Not estimable	
g. Cooper 2002 ⁵⁶ n. Pellicano 2002 ¹⁰² Corson 2001 ⁷⁹ Soysal 2001 ⁹⁶ Corson 2000 ¹⁰¹ Cooper 1999 ⁵⁴ n. Meyer 1998 ⁵³ b. Romer 1998 ⁵³ Subtotal (95% CI) Total events Heterogeneity: not applicable	0 0 0 0 0 0	89 48 123 134 117 10	0 0 0 0 0	45 144 129 128 10		Not estimable Not estimable Not estimable Not estimable Not estimable	
g. Cooper 2002 ⁵⁶ n. Pellicano 2002 ¹⁰² . Corson 2001 ⁷⁹ . Soysal 2001 ⁹⁶ . Corson 2000 ¹⁰¹ . Cooper 1999 ⁵⁴ n. Meyer 1998 ⁵³ 3. Romer 1998 ⁹⁷ Subtotal (95% CI) Fotal events	0 0 0 0 0 0	89 48 123 134 117 10	0 0 0 0 0	45 144 129 128 10		Not estimable Not estimable Not estimable Not estimable Not estimable	0.01 0.1 1 10 100 Favours Favours

Appendix 7

Pooled results for Mirena versus firstgeneration endometrial ablation

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95%CI) ^₅	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
Proportion amenorrhoea	12 months	3 (177)	_	0.84 (0.43 to 1.63)	0.6	0.3/11
	2 years	1 (44)	-	0.68 (0.19 to 2.45)	0.6	_
	3 years	1 (41)	_	0.68 (0.19 to 2.38)	0.5	_
Proportion with heavy bleeding	12 months	2 (125)	-	1.13 (0.33 to 3.86)	0.9	0.3/0
	3 years	1 (41)	-	1.84 (0.29 to 11.7)	0.5	-
Bleeding score (change)	6 months	1 (68)	-28 (-57 to 1.4)	_	0.06	_
	12 months	3 (168)	-39 (-66 to -12)	_	0.004	0.6/0
	2 years	1 (44)	41 (-189 to 271)	_	0.7	_
	3 years	1 (41)	37 (-202 to 276)	_	0.8	-
SF-36 general health (absolute)	12 months	1 (62)	-6.2 (-14.6 to 2.2)	_	0.2	-
SF-36 physical function (absolute)		1 (62)	-1.2 (-12.7 to 10.3)	-	0.8	_
SF-36 role physical (absolute)		1 (62)	-1.7 (-19.0 to 15.6)	-	0.9	_
SF-36 role emotional (absolute)		1 (62)	-11.1 (-29.1 to 6.9)	-	0.2	_
SF-36 mental health (absolute)		1 (62)	0.5 (-9.2 to 10.2)	-	0.9	_
SF-36 social function (absolute)		1 (62)	0.1 (-11.5 to 11.7)	-	1.0	_
SF-36 vitality (absolute)		1 (62)	1.5 (-7.3 to 10.3)	-	0.7	_
SF-36 pain (absolute)		1 (62)	-11.4 (-24.2 to 1.4)	-	0.08	_
Hysterectomy after EA/Mirena	12 months	1 (70)	_	7.39 (0.15 to 372)	0.3	_
		Trials	Frequency			
Discontinued Mirena	12 months	3	12/95 (13%)			
	2 years	1	8/30 (27%)			
	3 years	1	9/30 (30%)			
EA after Mirena	12 months	1	4/30 (13%)			
Hysterectomy after Mirena	12 months	1	0/35 (0%)			

Appendix 7.1 Clinical outcome and quality of life

	Trials	Frequency (first- generation: max. 95; Mirena: max. 95)	OR (95% Cl)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%
Periprocedure complications					
Uterine perforation (first- generation, Mirena)	5	0; 0	-	-	_
Cervical laceration (first- generation, Mirena)	5	0; 0	-	_	-
Anaesthesia problems (first- generation)	5	0	_	_	_
Excessive bleeding (first- generation)	5	0	_	-	_
Fluid overload (first-generation)	5	0	_	_	_
Visceral damage (first-generation)	5	0	_	_	_
Procedure abandoned (first- generation)	5	0	_	_	_
Converted to hysterectomy (first- generation)	5	0	-	_	-
Failed to insert (Mirena)	5	0	-	-	-
Further complications (< 1 month)					
Urinary tract infection (first- generation)	5	0	-	-	_
Deep-vein thrombosis (first- generation)	5	0	-	_	-
Further bleeding (first-generation)	5	7	_	-	_
Sepsis (first-generation)	5	0	_	-	_
Pyrexia (first-generation)	5	0	_	-	_
Endometriosis (first-generation)	5	2	_	-	_
Haematomata (first-generation)	5	3	_	-	_
Abdominal pain (first-generation)	5	4	_	-	_
Foul discharge (first-generation)	5	0	_	-	-
Visceral damage (first-generation)	5	0	-	-	-
Infection (Mirena)	5	0	_	-	-
Expelled/migrated (Mirena)	5	2	_	-	_
Removed before 3 months (Mirena)	5	4	_	-	_

 $\begin{array}{ll} a & <0 \text{ favours first-generation EA}, >0 \text{ Mirena.} \\ b & <1 \text{ favours first-generation EA}, >1 \text{ Mirena.} \end{array}$

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Appendix 7.2 First- and second-generation endometrial ablation versus Mirena

Proportion with amenorrhoea < 12 months

	Both ger	Both generations	Mirena	na					
Study or subgroup	Events	Total	Total Events	Total Weight	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto od Pet	Peto odds ratio (non-event) Peto, Fixed, 99% CI	int)
1.1.2 Second generation	-								
f. Busfield 2006 ¹⁰⁷	÷	31	ო	32	50.6%	2.77 (0.20 to 38.81)			I
g. Barrington 2003 ⁸¹	2	23	N	21	49.4%	1.10 (0.08 to 15.98)		-	
Subtotal (95% CI)		54		53	100.0%	1.76 (0.42 to 7.34)			
Total events	ო		ъ С						
Heterogeneity: $\chi^2 = 0.40$, df = 1 ($p = 0.53$); $l^2 = 0\%$	df = 1 ($p = 0.$	53); $l^2 = 0\%$							
Test for overall effect: $z = 0.77$ ($p = 0.44$)	= 0.77 (<i>p</i> = 0.4	4)							
							0.01 0.1	10	100

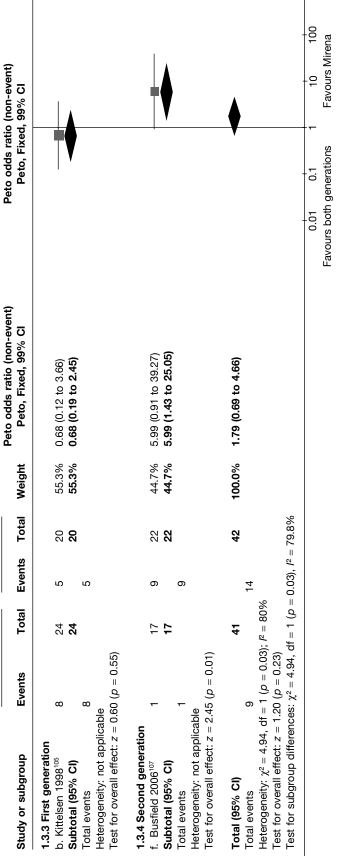
Health Technology Assessment 2011; Vol. 15: No. 19

Favours Mirena

Favours both generations

Proportion with amenorrhoea – 12 months

	Both generations	erations	Miren	na			
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl
1.2.1 First generation							
a. Malak 2006 ¹⁰⁴	13	30	14	26	33.5%	1.51 (0.38 to 5.94)	
b. Kittelsen 1998 ¹⁰⁵	7	28	ę	24	19.4%	0.45 (0.08 to 2.75)	•
c. Crosignani 1997 ⁴⁵	б	35	9	34	28.2%	0.63 (0.14 to 2.79)	
Subtotal (95% CI)		93		84	81.0%	0.84 (0.43 to 1.63)	♦
Total events	29		23				
Heterogeneity: $\chi^2 = 2.25$, df = 2 ($\rho = 0.32$); $l^2 = 11\%$ Test for overall effect: $z = 0.53$ ($\rho = 0.60$)	df = $2 (p = 0.32)$: 0.53 $(p = 0.60)$); <i>I</i> ² = 11%					
1.2.3 Second generation	_						
d. Shaw 2007 ¹⁰⁸	-	27	9	23	14.4%	6.18 (0.77 to 49.76)	
e. Tam 2006 ¹⁰⁹	2	15	0	15	4.6%	0.13 (0.00 to 5.13)	
f. Busfield 2006 ¹⁰⁷	0	25	0	22		Not estimable	
Subtotal (95% CI)		67		60	19.0%	2.43 (0.61 to 9.67)	¢
Total events	ო		9				,
Heterogeneity: $\chi^2 = 5.56$, df = 1 ($p = 0.02$); $l^2 = 82\%$ Test for overall effect: $z = 1.26$ ($p = 0.21$)	df = 1 (p = 0.02) : 1.26 (p = 0.21)); <i>I</i> ² = 82%					
Total (95% CI)		160		144	100.0%	1.02 (0.56 to 1.87)	_◆
Total events	32		29				
Heterogeneity: $\chi^2 = 9.66$, df = 4 ($p = 0.05$); $l^2 = 59\%$	df = 4 ($p = 0.05$)); <i>I</i> ² = 59%					
Test for overall effect: $z = 0.07$ ($p = 0.94$)	$0.07 \ (p = 0.94)$						
Test for subgroup differences: $\chi^2 = 1.85$, df = 1 ($p = 0.17$), $l^2 =$	nces: $\chi^2 = 1.85$, o	df = 1 (p =	: 0.17), <i>I</i> ² =	45.9%			
							0.01 0.1 1 10 100
						Fav	Favours both generations Favours Mirena
							1



Proportion with amenorrhoea – 2 years

Mirena

Both generations

Proportion with amenorrhoea – 3 years

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Total Events Total	Total	Weight	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	Peto odds ratio (non-event) Peto, Fixed, 99% Cl	(non-event) 99% CI
1.4.4 First generation								
b. Kittelsen 1998 ¹⁰⁵	6	22	9	19	100.0%	0.68 (0.13 to 3.53)		
Subtotal (95% CI)		22		19	100.0%	0.68 (0.19 to 2.38)		
Total events	0		9				1	
Heterogeneity: not applicable	licable							
Test for overall effect: $z = 0.61$ ($p = 0.54$)	$z = 0.61 \ (p = 0)$	1.54)						
							0.01	10 100
							Favours both generations Favours Mirena	Favours Mirena

Proportion with heavy bleeding – <12 months

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Total Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	s ratio 99% CI
1.5.2 Second generation								
d. Shaw 2007 ¹⁰⁸	2	29	0	26	10.3%	6.91 (0.17 to 274.46)		Î
f. Busfield 2006 ¹⁰⁷	12	31	Ŋ	32	66.0%	3.17 (0.74 to 13.52)	+	
g. Barrington 2003 ⁸¹	5	23	0	21	23.7%	8.24 (0.73 to 92.84)	+	
Subtotal (95% CI)		ß		79	100.0%	4.30 (1.76 to 10.56)		♦
Total events	19		Ŋ					
Heterogeneity: $\chi^2 = 0.88$, df = 2 ($p = 0.64$); $P = 0.64$	$df = 2 \ (p = 0.6)$	4); <i>P</i> = 0%						
Test for overall effect: $z = 3.19$ ($p = 0.001$)	3.19 (<i>p</i> = 0.00	1)						
							0.01 0.1	10 100
							Favours both generations Favours Mirena	Favours Mirena

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	Both generations	erations	Mire	irena				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% Cl	
1.6.1 First generation								
a. Malak 2006 ¹⁰⁴	ი	30	-	26	15.0%	2.49 (0.17 to 35.41)		
c. Crosignani 1997 ⁴⁵	ი	35	4	34	25.5%	0.71 (0.09 to 5.44)		
Subtotal (95% CI)		65		09	40.5%	1.13 (0.33 to 3.86)	♦	
Total events	9		5)	
Heterogeneity: $\chi^2 = 0.93$, df = 1 ($\rho = 0.33$); $l^2 = 0\%$ Test for overall effect: $z = 0.19$ ($\rho = 0.85$)	df = 1 (<i>p</i> = 0.33 = 0.19 (<i>p</i> = 0.85)	3); <i>P</i> ² = 0%)						
1.6.4 Second generation	c							
d. Shaw 2007 ¹⁰⁸	2	27	0	23	7.8%	6.62 (0.16 to 265.81)		•
e. Tam 2006 ¹⁰⁹	F	15	S	15	19.8%	0.20 (0.02 to 2.02)		
f. Busfield 2006 ¹⁰⁷	80	25	0	22	32.0%	3.81 (0.62 to 23.54)	-	
h. Soysal 2001 ⁹⁶	0	35	0	32		Not estimable		
Subtotal (95% CI)		102		92	59.5%	1.54 (0.56 to 4.24)	♦	
Total events	11		7					
Heterogeneity: $\chi^2 = 7.86$, df = 2 ($p = 0.02$); $p = 75\%$ Test for overall effect: $z = 0.83$ ($p = 0.41$)	df = 2 (p = 0.02 = 0.83 (p = 0.41)	2); <i>P</i> = 75%)	_					
Total (95% CI)		167		152	100.0%	1.36 (0.62 to 2.97)	•	
Total events	17		12				•	
Heterogeneity: $\chi^2 = 8.94$, df = 4 ($p = 0.06$); $P = 55\%$	df = 4 ($p = 0.06$	3); <i>I</i> ² = 55%						
Test for overall effect: $z = 0.76$ ($p = 0.45$)	$= 0.76 \ (p = 0.45)$							
Test for subgroup differences: $\chi^2 = 0.14$, df = 1 ($\rho = 0.70$), β	inces: $\chi^2 = 0.14$,	df = 1 (<i>p</i> =	= 0.70), <i>I</i> ² =	$^{2} = 0\%$				
							0.01 0.1 1 10	100

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Favours both generations Favours Mirena

Proportion with heavy bleeding – 2 years

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto oc Peto, Fixe	Peto odds ratio Peto, Fixed, 99% Cl
1.7.5 Second generation	_							
f. Busfield 2006 ¹⁰⁷	5	17	0	22	100.0%	100.0% 12.99 (1.11 to 151.40)		↑
Subtotal (95% CI)		17		52	100.0%	12.99 (2.00 to 84.16)		
Total events	5		0					
Heterogeneity: not applicable	able							
Test for overall effect: $z = 2.69$ ($p = 0.007$)	$= 2.69 \ (p = 0.00)$	(2)						
							0.01	100
							Favours both generations	Eavours Mirena



Study or subgroupEventsTotalEventsTotal1.8.2 First generation b. Kittelsen 1998 ¹⁰⁵ 3192221D. Kittelsen 1998 ¹⁰⁵ 3192221D. Kittelsen 1998 ¹⁰⁵ 3192221D. Kittelsen 1998 ¹⁰⁵ 3192221D. Kittelsen 1998 ¹⁰⁵ 3192221Total events3192221Total events3192221Test for overall effect: $z = 0.65$ ($p = 0.52$)111		Both generations	erations	Mirena	na				
on $3 19 2 22 23 3 3 3 22 22 22 22 22$	Study or subgroup	Events	Total	Events		Weight	Peto odds ratio Peto, Fixed, 99% Cl		Peto odds ratio Peto, Fixed, 99% Cl
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.8.2 First generation								
19 22 . 3 3 2 2 2 3 applicable ct: <i>z</i> = 0.65 (<i>p</i> = 0.52)	b. Kittelsen 1998 ¹⁰⁵	ო	19	2	22	100.0%	1.84 (0.16 to 21.02)		
	Subtotal (95% CI)		19		22	100.0%	1.84 (0.29 to 11.74)	V	
Heterogeneity: not applicable Test for overall effect: $z = 0.65$ ($p = 0.52$)	Total events	ო		0)
Test for overall effect: $z = 0.65$ ($p = 0.52$)	Heterogeneity: not ap	olicable							
	Test for overall effect:	$z = 0.65 \ (p = 0)$	1.52)						
								0.01 0.1	1 10 100
							Fav	Favours both generations	Favours Mirena

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	Both	generations	tions		Mirena
Study or subgroup	Mean	SD	Total	Mean	-
1.17.1 First generation c. Crosignani 1997 ⁴⁵ Subtotal (95% CI) Heteroneneity, not anolicable	–173 hle	68	34 34	-145	
Test for overall effect: $z = 1.87$ ($p = 0.06$)	1.87 (<i>p</i> = 0	0.06)			
		376	27	-326	230
e. Tam 2006 ¹⁰⁹ f. Busfield 2006 ¹⁰⁷	-431 -364	168 460		-92 -451	265 410
g. Barrington 2003 ⁸¹ Subtotal (95% Cl)	-62	47	23 8	-76	
= 4.25 ect: <i>z</i>	, df = 3 (<i>p</i> = 0.2 ⁴ = 0.41 (<i>p</i> = 0.68)	0.24); <i>l</i> 0.68)	² = 29%		
Total (95% CI) Heterogeneity: $\chi^2 = 6.03$, df = 4 ($p = 0.20$); l^2 Test for overall effect: $z = 1.37$ ($p = 0.17$) Test for subgroup differences: $\chi^2 = 1.78$, df =	, df = 4 (p = 0.20 = 1.37 (p = 0.17) ences: χ^2 = 1.78,	0.20); / 0.17) .78, df	118 = 34% = 1 (<i>p</i> =	0.18), <i>I</i> ² =	= 43.7%

-3.00 (-219.44 to 213.44) -339.00 (-805.62 to 127.62) 87.00 (-196.09 to 370.09) 14.00 (-53.31 to 81.31) **9.86 (-37.41 to 57.12)**

2.3% 0.5% 1.3% 23.8% **27.9%**

29 32 85

-17.44 (-42.40 to 7.52)

100.0%

119

iths

Mean difference IV, Fixed, 99% CI

Mean difference IV, Fixed, 99% CI

Weight

Total

-28.00 (-66.63 to 10.63) -28.00 (-57.40 to 1.40)

72.1% **72.1%**

8 **8**

100

0

-50

-100

Favours Mirena 50

Favours both generations

Bleeding/pictorial blood loss assessment chart scores (change from baseline) – 12 months

	Both	Both generations	ations		Mirena				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.18.2 First generation									
a. Malak 2006 ¹⁰⁴	-340	111	30	-278	103	26	15.8%	-62.00 (-135.70 to 11.70)	
b. Kittelsen 1998 ¹⁰⁵	-371	456	58	-376	311	24	1.1%	5.00 (-270.70 to 280.70)	
c. Crosignani 1997 ⁴⁵	-179	67	80	-146	54	30	52.4%	-33.00 (-73.47 to 7.47)	+
Subtotal (95% CI)			88			80	69.4%	-38.99 (-65.76 to -12.22)	•
Heterogeneity: $\chi^2 = 0.96$, df = 2 ($p = 0.62$); $l^2 = 0\%$ Test for overall effect: $z = 2.85$ ($p = 0.004$)	df = 2 (<i>p</i> = 2.85 (<i>p</i> =	- 0.62); 0.004)	l ² = 0%						•
1.18.4 Second generation	ç								
d. Shaw 2007 ¹⁰⁸	-348	402	20	-424	256	21	1.2%	76.00 (-196.61 to 348.61)	
e. Tam 2006 ¹⁰⁹	-504	572	റ	-216	269	2	0.3%	-288.00 (-868.71 to 292.71)	•
f. Busfield 2006 ¹⁰⁷	-360	433	25	-474	375	22	0.9%	114.00 (-189.59 to 417.59)	•
h. Soysal 2001 ⁹⁶	-395	75	35	-353	96	31	28.3%	-42.00 (-97.13 to 13.13)	
Subtotal (95% CI)			88			79	30.6%	-34.84 (-75.15 to 5.47)	♦
Heterogeneity: $\chi^2 = 4.06$, df = 3 ($p = 0.25$); $l^2 = 26\%$ Test for overall effect: $z = 1.69$ ($p = 0.09$)	df = 3 (<i>p</i> = 1.69 (<i>p</i> = 1.61	= 0.25);	/² = 26%						
Total (95% Cl)			177			159	100.0%	-37.72 (-60.02 to -15.42)	
Heterogeneity: $\chi^2 = 5.05$, df = 6 ($p = 0.54$); $l^2 = 0\%$ Test for overall effect: $z = 3.32$ ($p = 0.0009$) Test for subgroup differences: $\chi^2 = 0.03$, df = 1 ($p = 0.87$), $l^2 = 0.03$	df = 6 (p = 3.32 (p = 1 ces: χ^2 = 0	- 0.54); ₋ 0.0009) 0.03, df	$p^2 = 0\%$ $= 1 (p = 1)$	0.87), <i>P</i> ² =	*0%				•
									-100 -50 0 50 100

	Mean difference IV, Fixed, 99% CI			
	Mean difference IV, Fixed, 99% CI	41.00 (-261.10 to 343.10) 41.00 (-188.87 to 270.87)	117.00 (–184.63 to 418.63) 117.00 (–112.51 to 346.51)	79.06 (-83.36 to 241.47)
	Weight	49.9% 49.9%	50.1% 50.1%	100.0%
	Total	20 20	5 7 55	42
Mirena	SD	334	445	%0
	Mean	-409	-471	
ions	Total	24 24	17 17	41 = 0% = 1 (<i>p</i> = 0
Both generations	SD	443 0.73)	283 0.32)	0.65); /²).34) 21, df =
Both	Mean	-368 able 0.35 (<i>p</i> = 0	n –354 able 1.00 (<i>p</i> = 0	df = 1 (p = 0.95 (p = 0.05: χ^2 = 0
	Study or subgroup	1.19.3 First generation b. Kittelsen 1998 ¹⁰⁵ -368 445 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.35$ ($p = 0.73$)	1.19.5 Second generationf. Busfield 2006^{107} -354285Subtotal (95% Cl)Heterogeneity: not applicableTest for overall effect: $z = 1.00$ ($p = 0.32$)	Total (95% CI) Heterogeneity: $\chi^2 = 0.21$, df = 1 ($\rho = 0.65$); $l^2 = 0\%$ Test for overall effect: $z = 0.95$ ($\rho = 0.34$) Test for subgroup differences: $\chi^2 = 0.21$, df = 1 ($\rho = 0$

Bleeding/pictorial blood loss assessment chart scores (change from baseline) – 2 years

Favours Mirena

Favours both generations

100 200

0

-200

Bleeding/pictorial blood loss assessment chart scores (change from baseline) – 3 years

Study or subgroup Mean SD Total Mean SD Total Weight 1.20.4 First generation		Meen difference
1.20.4 First generation	/eight IV, Fixed, 99% CI	IV, Fixed, 99% CI
b. Kittelsen 1998 ¹⁰⁵ –374 442 22 –411 337 19 11	100.0% 37.00 (–276.97 to 350.97)	
Subtotal (95% CI) 22 19 10	100.0% 37.00 (–201.90 to 275.90)	
Heterogeneity: not applicable		1
Test for overall effect: $z = 0.30 \ (p = 0.76)$		

Proportion with dysmenorrhoea – <12 months

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Total Weight Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% Cl	s ratio 99% CI
1.21.1 Second generation	L L							
f. Busfield 2006 ¹⁰⁷	16	41	19	42	100.0%	0.78 (0.25 to 2.43)		
Subtotal (95% CI)		41		42	100.0%	0.78 (0.33 to 1.85)	•	
Total events	16		19					
Heterogeneity: not applicable	able							
Test for overall effect: $z = 0.57$ ($p = 0.57$)	= 0.57 (<i>p</i> = 0.57	(
							0.01 0.1	10 100
							Favours both generations	Favours Mirena

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto oc Peto, Fixe	Peto odds ratio Peto, Fixed, 99% Cl
1.22.3 Second generation f. Busfield 2006 ¹⁰⁷	ω L	21	5	27	100.0%	0.77 (0.17 to 3.49)		
Subtotal (95% CI) Total events	œ	21	12	27	100.0%	0.77 (0.25 to 2.43)		
Heterogeneity: not applicable Test for overall effect: $z = 0.44$ ($p = 0.66$)	able 0.44 (<i>p</i> = 0.66)	(!					
							0.01 0.1 Favours both generations	1 10 100 Favours Mirena
Proportion with dysmenorrhoea – 2 years	menorrhoe	∋a – 2 year	Ś					
	Both generations	erations	Mirena	па				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto oc Peto, Fixe	Peto odds ratio Peto, Fixed, 99% Cl
1.23.4 Second generation f. Busfield 2006 ¹⁰⁷	n	42	2	41	100.0%	0.97 (0.22 to 4.36)	T	
Subtotal (95% CI)	٢	42	٢	41	100.0%	0.97 (0.31 to 3.05)		
			_					



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100

Favours Mirena 9

Favours both generations

0.1

0.01

Heterogeneity: not applicable Test for overall effect: z = 0.05 (p = 0.96)

SF-36 general health (absolute values) – 12 months

	Both	Both generations	tions		Mirena					
Study or subgroup	Mean	S	Total	Mean	S	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean di IV, Fixed	Mean difference IV, Fixed, 99% CI
1.24.1 First generation c. Crosignani 1997 ⁴⁵ Subtotal (95% CI) Heterogeneity: not applicable	70.3 cable	15.1	31 33	64.1	18.6	31 31	36.5% 36.5 %	6.20 (-4.88 to 17.28) 6.20 (-2.23 to 14.63)		
Test for overall effect: $z = 1.44$ ($p = 0.15$)	= 1.44 (<i>p</i> =	0.15)								
1.24.2 Second generation	uo									
e. Tam 2006 ¹⁰⁹	60.3	26.2	റ	34.1	15.5	10	6.7%	26.20 (0.40 to 52.00)		
f. Busfield 2006 ¹⁰⁷	73.3	22.3	32	82.6	15.2	31	29.4%	-9.30 (-21.65 to 3.05)		
h. Soysal 2002 ¹⁰⁶	47	20	33	52	20	32	27.4%	-5.00 (-17.78 to 7.78)		
Subtotal (95% CI)			74			73	63.5%	-3.68 (-10.07 to 2.71)		•
Heterogeneity: $\chi^2 = 10.35$, df = 2 ($p = 0.006$); $l^2 = 81\%$ Test for overall effect: $z = 1.13$ ($p = 0.26$)	5, df = 2 (<i>p</i> = 1.13 (<i>p</i> =	= 0.006) 0.26)); <i>I</i> ² = 81 ⁻	%						
Total (95% CI)			105			104	100.0%	-0.08 (-5.17 to 5.02)		
Heterogeneity: $\chi^2 = 13.70$, df = 3 ($p = 0.003$); $l^2 = 78\%$ Test for overall effect: $z = 0.03$ ($p = 0.98$) Test for subgroup differences: $\chi^2 = 3.35$, df = 1 ($p = 0.07$), $l^2 =$	0, df = 3 (p = 0.03 (p = β sinces: χ^2 = β	= 0.003) 0.98) 3.35, df :); $l^2 = 78$ = 1 ($p =$	% 0.07), <i>P</i> ² =	: 70.2%					
									-20 -10 0	0 10 20
									Favours Mirena	Favours both generations

	Both	Both generations	tions	-	Mirena					
Study or subgroup	Mean	SD	Total	Mean	S	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean di IV, Fixed	Mean difference IV, Fixed, 99% CI
1.25.1 First generation c. Crosignani 1997 ⁴⁵ Substat (05%, CI)	79.2	23.7	3	78	22.4	9	21.0%	1.20 (-13.89 to 16.29)		
Heterogeneity: not applicable Test for overall effect: $z = 0.20$ ($p = 0.84$)	able 0.20 (<i>p</i> = (0.84)	5			0	9 2 1 2			
1.25.2 Second generation	c									
e. Tam 2006 ¹⁰⁹	76.1	18.8	თ	20	17.5	თ	9.8%	6.10 (-15.95 to 28.15)		
f. Busfield 2006 ¹⁰⁷	88.1	20	32	06	15.3	31	36.0%	-1.90 (-13.43 to 9.63)		
j. Soysal 2002 ¹⁰⁶	75	18.8	33	72.5	18.8	32	33.2%	2.50 (-9.51 to 14.51)		
Subtotal (95% CI)			74			72	79.0%	0.94 (-4.98 to 6.87)	V	
Heterogeneity: $\chi^2 = 0.88$, df = 2 ($p = 0.64$); $l^2 = 0\%$ Test for overall effect: $z = 0.31$ ($p = 0.75$)	df = 2 (p = 0.31 (p = 0	0.75); <i>I</i> ²	s = 0%							
Total (95% Cl)			105			103	100.0%	1.00 (-4.27 to 6.26)		
Heterogeneity: $\chi^2 = 0.88$, df = 3 ($p = 0.83$); $l^2 = 0\%$ Test for overall effect: $z = 0.37$ ($p = 0.71$)	df = 3 (p = 0.37 (p = 0.3	0.83); /2 0.71)	s = 0%							
Test for subgroup differences: $\chi^2 = 0.00$, df = 1 ($p = 0.97$), $P = 0.96$	ices: $\chi^2 = C$).00, df ₌	= 1 (<i>p</i> = 1	0.97), <i>P</i> ² =	%0					
									-20 -10 0	0 10 20
									Favours Mirena	Favours both generations

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SF-36 mental health (absolute values) – 12 months

	Mean difference Weight IV, Fixed, 99% CI	27.2% -0.50 (-13.18 to 12.18) 27.2% -0.50 (-10.15 to 9.15)	11.5% 19.10 (-0.42 to 38.62) 32.7% -4.90 (-16.46 to 6.66) 28.7% 0.00 (-12.33 to 12.33) 72.8% 0.81 (-5.09 to 6.70)	100.0% 0.45 (-4.58 to 5.48)
	Total We	31 27 31 2 7	110 11 31 32 73 72	104 100
Mirena	SD T	18.2	18.8 16. 19.3	•
Σ	Mean	60.1	46.4 79.9 52	82), <i>I</i> ² = (
suo	Total	3 3	8 32 33 73 = 73%	104 = 60% 1 (<i>p</i> = 0
Both generations	SD	20.5 2.92)	13.3 19.5 19.3 0.02); <i>I</i> ² 0.79)	0.06); /² J.86) I.05, df =
Both	Mean	n 59.6 llicable z = 0.10 (<i>p</i> = 0	(tion 65.5 75 52 7, df = 2 ($p = c$ z = 0.27 ($p = 0$	2, df = 3 (p = 2 z = 0.18 (p = 0 rences: χ^2 = 0
	Study or subgroup	1.26.1 First generation c. Crosignani 1997 ⁴⁵ 59.6 20. Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.10$ ($p = 0.92$)	1.26.3 Second generation e. Tam 2006 ¹⁰⁹ 65.5 13.3 8 f. Busfield 2006 ¹⁰⁷ 75 19.5 32 j. Soysal 2002 ¹⁰⁶ 52 19.3 33 Subtotal (95% CI) 52 19.3 73 Heterogeneity: $\chi^2 = 7.47$, df = 2 ($p = 0.02$); $l^2 = 73\%$ Test for overall effect: $z = 0.27$ ($p = 0.79$)	Total (95% CI) Heterogeneity: $\chi^2 = 7.52$, df = 3 ($p = 0.06$); $l^2 = 60\%$ Test for overall effect: $z = 0.18$ ($p = 0.86$) Test for subgroup differences: $\chi^2 = 0.05$, df = 1 ($p = 0.82$), $l^2 = 1$

Favours both generations

Favours Mirena

- 12 months
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	Both	Both generations	tions	-	Mirena					
Study or subgroup	Mean	ß	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI	(, Fixed, 99% CI
1.27.1 First generation c. Crosignani 1997 ⁴⁵ 54.8 20. Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.33$ ($p = 0.74$)	54.8 ble 0.33 (<i>p</i> =	20.7 0.74)	ਲ ਲ	56.3	14.1	3 3	31.6% 31.6%	-1.50 (-13.09 to 10.09) -1.50 (-10.32 to 7.32)		
1.27.4 Second generation e. Tam 2006 ¹⁰⁸ 50 22.2 9 f. Busfield 2006 ¹⁰⁷ 63 20.7 32 j. Soysal 2002 ¹⁰⁸ 45 17.6 33 Subtotal [95% CI] 45 74 74 Heterogeneity: $\chi^2 = 2.15$, df = 2 ($\rho = 0.34$); $l^2 = 7\%$ 74 Test for overall effect: $z = 0.03$ ($\rho = 0.98$) 74	n 50 63 45 1f = 2 (<i>p</i> = 0.03 (<i>p</i> =	22.2 20.7 17.6 = 0.34); <i>f</i> ^g 0.98)	9 32 33 74 7%	39 66.7 45	14.7 18 17.6	72 30	8.4% 26.4% 33.6% 68.4%	11.00 (-11.51 to 33.51) -3.70 (-16.37 to 8.97) 0.00 (-11.25 to 11.25) -0.08 (-6.08 to 5.91)		
Total (95% CI) Heterogeneity: $\chi^2 = 2.22$, df = 3 ($p = 0.53$); $l^2 = 0\%$ Test for overall effect: $z = 0.21$ ($p = 0.83$) Test for subgroup differences: $\chi^2 = 0.07$, df = 1 ($p = 0.79$),	df = 3 (p = 0.21 (p = 0.21 (z = 0.21))	= 0.53); <i>1</i> ² 0.83) 0.07, df =	105 = 0%		<i>P</i> ² = 0%	103	100.0%	-0.53 (-5.49 to 4.43)	•	
									-20 -10 0 Favours Mirena	10 20 Favours both generations

SF-36 physical role limitation (absolute values) – 12 months

Outp Mean SD Total Mean SD Total Mean SD Total Mean difference		Both	Both generations	ations	_	Mirena					
907^{45} 74.2 35.6 31 72.5 33.7 31 28.4% 1.70 (-20.98 to 24.38) Cl)31 31 28.4% 1.70 (-15.56 to 18.96)or applicableeffect: $z = 0.19$ ($p = 0.85$) 31 28.4% 1.70 (-15.56 to 18.96)or applicableeffect: $z = 0.19$ ($p = 0.85$) 31 28.4% 1.70 (-15.56 to 18.96)of applicableeffect: $z = 0.19$ ($p = 0.85$) 31 28.4% 1.70 (-15.56 to 18.96)of applicable 72.2 36.3 9 62.5 42.9 10 6.7% 97 72.2 36.3 9 62.5 42.9 10 6.7% 9.70 (- 37.12 to 56.52) 90 37.5 30.5 28.8 31 39.5% -0.40 (- 19.65 to 18.85) 90 37.5 30.5 37.5 $22.5.5\%$ 25.00 (1.04 to 48.96) 60 37.5 33 25 37.5 $22.5.5\%$ 25.00 (1.04 to 48.96) 61 73 74 73 71.6% 9.57 (-1.30 to 20.45) 61 extr< $z = 1.73$ ($p = 0.10$); $l^{e} = 56\%$ 104 100.0% 7.33 (-1.36 to 16.53) $7^{2} = 5.10$, df = 3 ($p = 0.16$); $l^{e} = 176$ $p = 0.45$), $l^{e} = 0.57$, df = 1 ($p = 0.45$), $l^{e} = 0.56$ 105 106 7.33 (-1.36 to 16.53) $p = 0.45$) 106 100.0% 7.33 (-1.36 to 16.53) $7^{2} = 5.10$, df = 3 ($p = 0.12$) $p = 0.45$), $l^{e} = 0.56$	Study or subgroup	Mean		Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% C	
Cl)3128.4%1.70 (-15.56 to 18.96)not applicableeffect: $z = 0.19$ ($p = 0.83$)effect: $z = 0.19$ ($p = 0.83$)generation $z = 2.2$ 30.5 30.5 32.5 30.5 32.5 30.5 32.5 30.5 32.5 <td>1.28.1 First generation c. Crosignani 1997⁴⁵</td> <td>74.2</td> <td>35.6</td> <td></td> <td>72.5</td> <td>33.7</td> <td>31</td> <td>28.4%</td> <td>1.70 (–20.98 to 24.38)</td> <td></td> <td></td>	1.28.1 First generation c. Crosignani 1997 ⁴⁵	74.2	35.6		72.5	33.7	31	28.4%	1.70 (–20.98 to 24.38)		
9 10 6.7% 9.70 (-37.12 to 56.52) 8 31 39.5% -0.40 (-19.65 to 18.85) 5 32 25.5% 25.00 (1.04 to 48.96) 73 71.6% 9.57 (-1.30 to 20.45) 104 100.0% 7.33 (-1.86 to 16.53)	Subtotal (95% CI)			31			31	28.4%	1.70 (–15.56 to 18.96)	♦	
generation 72.2 36.3 9 62.5 42.9 10 6.7% 9.70 (- 37.12 to 56.52) 8^{107} 87.5 30.5 32 87.9 28.8 31 39.5% -0.40 (- 19.65 to 18.85) 8^{10} 50 37.5 32 28.8 31 39.5% -0.40 (- 19.65 to 18.85) 8^{10} 50 37.5 32 28.8 31 39.5% -0.40 (- 19.65 to 18.85) 8^{10} 74 73 74 73 71.6% 9.57 (- 1.30 to 20.45) $c)$ 74 73 71.6% 9.57 (- 1.30 to 20.45) x^2 = 4.53 , df = 2 ($p = 0.10$); $\beta' = 56\%$ 9.57 (- 1.30 to 20.45) -0.45 $effect: z = 1.73$ ($p = 0.08$) 104 100.0% 7.33 (- 1.86 to 16.53) x^2 = 5.10 , df = 3 ($p = 0.16$); $\beta' = 41\%$ 104 100.0% 7.33 (- 1.86 to 16.53) x^2 = 0.57 , df = 1 ($p = 0.45$), $\beta' = 0\%$ 104 100.0% 7.33 (- 1.86 to 16.53) x^2 = 0.57 , df = 1 ($p = 0.45$), $\beta' = 0\%$	Heterogeneity: not applica Test for overall effect: <i>z</i> =	able 0.19 (<i>p</i> =	0.85)								
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.28.5 Second generation	F									
$s_{10}^{107} = 87.5 = 30.5 = 32 = 87.9 = 28.8 = 31 = 39.5\% = -0.40 (-19.65 to 18.85) = 50 = 37.5 = 33 = 25.5\% = 25.00 (1.04 to 48.96) = CI) = 74 = 73 = 71.6\% = 9.57 (-1.30 to 20.45) = 61 = 1.73 (p = 0.10); p^{2} = 56\% = 6101; p^{2} = 6.10; p^{2} = 0.10; p^{2} = 6.10; p^{2} = 0.10; $	e. Tam 2006 ¹⁰⁹		36.3	6	62.5	42.9	10	6.7%	9.70 (-37.12 to 56.52)		
50 37.5 33 25 37.5 32 25.5% $25.00 (1.04 \text{ to } 48.96)$ 74 73 71.6% $9.57 (-1.30 \text{ to } 20.45)$ $4.53, df = 2 (p = 0.10); l^2 = 56\%$ $25.00 (1.04 \text{ to } 48.96)$ act: $z = 1.73 (p = 0.08)$ 105 71.6% $9.57 (-1.30 \text{ to } 20.45)$ act: $z = 1.73 (p = 0.08)$ 105 104 100.0% $7.33 (-1.86 \text{ to } 16.53)$ $5.10, df = 3 (p = 0.16); l^2 = 41\%$ $ct: z = 1.56 (p = 0.12)$ 104 100.0% $7.33 (-1.86 \text{ to } 16.53)$ $ct: z = 1.56 (p = 0.12)$ 104 100.0% $7.33 (-1.86 \text{ to } 16.53)$: Busfield 2006 ¹⁰⁷	87.5	30.5	32	87.9	28.8	31	39.5%	-0.40 (-19.65 to 18.85)		
74 73 71.6% 9.57 (-1.30 to 20.45) 4.53, df = 2 ($p = 0.10$); $l^{e} = 56\%$ ct: $z = 1.73$ ($p = 0.08$) 105 104 100.0% 7.33 (-1.86 to 16.53) 5.10, df = 3 ($p = 0.16$); $l^{e} = 41\%$ ct: $z = 1.56$ ($p = 0.12$) 104 100.0% 7.33 (-1.86 to 16.53) 6.10, df = 3 ($p = 0.16$); $l^{e} = 41\%$ ct: $z = 1.56$ ($p = 0.12$) 104 100.0% 7.33 (-1.86 to 16.53) 6.11 $z = 0.12$) defences: $\chi^{2} = 0.57$, df = 1 ($p = 0.45$), $l^{e} = 0\%$ 104 100.0% 7.33 (-1.86 to 16.53)	. Soysal 2002 ¹⁰⁶	50	37.5	33	25	37.5	32	25.5%	25.00 (1.04 to 48.96)		1
4.53, df = 2 ($p = 0.10$); $l^{2} = 56\%$ cf: $z = 1.73$ ($p = 0.08$) 105 104 100.0% 7.33 (-1.86 to 16.53) 5.10 , df = 3 ($p = 0.16$); $l^{2} = 41\%$ cf: $z = 1.56$ ($p = 0.12$) differences: $\chi^{2} = 0.57$, df = 1 ($p = 0.45$), $l^{2} = 0\%$	Subtotal (95% CI)			74			73	71.6%	9.57 (-1.30 to 20.45)	¢	
$\chi^2 = 5.10$, df = 3 ($p = 0.16$); $\beta^2 = 41\%$ effect: $z = 1.56$ ($p = 0.12$) up differences: $\chi^2 = 0.57$, df = 1 ($p = 0.45$), $\beta^2 = 0\%$	Heterogeneity: $\chi^2 = 4.53$, (Test for overall effect: $z =$	df = 2 (p = 1.73 (p =	= 0.10);	β = 56%)	
0.45), $l^2 = 0.06$	Total (95% Cl)			105			104	100.0%	7.33 (-1.86 to 16.53)	¢	
$df = 1 \ (p = 0.45), \ l^2 = 0\%$	Heterogeneity: $\chi^2 = 5.10$, c Test for overall effect: $z =$	df = 3 (<i>p</i> = 1.56 (<i>p</i> =	= 0.16); / 0.12)	P = 41%							
	Test for subgroup differen	ces: $\chi^2 =$	0.57, df	= 1 (<i>p</i> =	0.45), <i>I</i> ² =	%0					
											- 2

Favours both generations

Favours Mirena

SF-36 emotional role limitation (absolute values) – 12 months

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by the Secretary of State for Health.	

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bMeanSDTotalMeanSDitionitionif 72.4 36.8 31 323 33.3 41.4 33.3 31.1 , df = 2 (p = 0.02); f^2 = 75%ct: z = 1.01 (p = 0.31)	31 Total	Weight	Mean difference	
tition function z^{5} 72.4 36.8 31 61.3 applicable ct: $z = 1.21$ ($p = 0.23$) eration 77.8 37.3 9 36.7 76 36.2 32 91.4 33.3 41.4 33 33.3 8.11, df = 2 ($p = 0.02$); $f = 75\%$ ct: $z = 1.01$ ($p = 0.31$) ct: $z = 1.01$ ($p = 0.31$)	3 3		IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
31applicablect: $z = 1.21$ ($p = 0.23$)ct: $z = 1.21$ ($p = 0.23$)eration77.877.87633.333.333.3311, df = 2 ($p = 0.02$); $l^2 = 75\%$ ct: $z = 1.01$ ($p = 0.31$)	č	27.5%	11.10 (–12.59 to 34.79)	
36.7 91.4 33.3	5	27.5%	11.10 (–6.92 to 29.12)	•
letation 77.8 37.3 9 36.7 76 36.2 32 91.4 33.3 41.4 33 33.3 8.11, df = 2 ($p = 0.02$); $f = 75\%$ ct: $z = 1.01$ ($p = 0.31$)				
77.8 37.3 9 36.7 76 36.2 32 91.4 33.3 41.4 33 33.3 74 8.11, df = 2 (p = 0.02); F = 75% ct: z = 1.01 (p = 0.31)				
76 36.2 32 91.4 33.3 41.4 33 33.3 74 8.11, df = 2 (p = 0.02); P = 75% ct: z = 1.01 (p = 0.31)	10	6.4%	41.10 (–8.01 to 90.21)	
33.3 41.4 33 33.3 74 74 ct: $z = 1.01$ ($p = 0.31$) ct: $z = 1.01$ ($p = 0.31$)	31	44.0%	-15.40 (-34.12 to 3.32)	
Subtotal (95% CI) 74 Heterogeneity: $\chi^2 = 8.11$, df = 2 ($p = 0.02$); $\beta^2 = 75\%$ Test for overall effect: $z = 1.01$ ($p = 0.31$)	32	22.1%	0.00 (–26.46 to 26.46)	
Heterogeneity: $\chi^2 = 8.11$, df = 2 ($p = 0.02$); $l^2 = 75\%$ Test for overall effect: $z = 1.01$ ($p = 0.31$)	73	72.5%	–5.72 (–16.83 to 5.38)	♦
Total (95% Cl) 105 1	104	100.0%	-1.10 (-10.55 to 8.36)	•
Heterogeneity: $\chi^2 = 10.54$, df = 3 ($p = 0.01$); $l^e = 72\%$ Test for overall effect: $z = 0.23$ ($p = 0.82$)				
Test for subgroup differences: $\chi^2 = 2.43$, df = 1 ($p = 0.12$), $l^2 = 58.8\%$				
				-50 -25 0 25 50

SF-36 social function (absolute values) – 12 months

Studv or subaroup M										
	Mean	SD	Total	Mean	S	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	G
1.30.1 First generation c. Crosignani 1997 ⁴⁵ 66	69.7	24.1	31	69.8	22.3	31	20.6%	-0.10 (-15.29 to 15.09)		
Subtotal (95% CI)			31			31	20.6%	–0.10 (–11.66 to 11.46)	♦	
Heterogeneity: not applicable Test for overall effect: $z = 0.02$ ($p = 0.99$)	o = d	(66								
1.30.7 Second generation										
	75.3	15.5	б	63.3	16.6	10	13.2%	12.00 (-6.97 to 30.97)		
3 ¹⁰⁷	73.6	19.3	32	81.4	12	31	44.0%	-7.80 (-18.19 to 2.59)	+	
	50	22.9	33	50	22.9	32	22.2%	0.00 (–14.63 to 14.63)	-	
Subtotal (95% CI)			74			73	79.4%	–2.33 (–8.21 to 3.56)	•	
Heterogeneity: $\chi^2 = 5.79$, df = 2 ($p = 0.06$); $l^2 = 65\%$ Test for overall effect: $z = 0.77$ ($p = 0.44$)	2 (p = 0)	0.06); <i>I</i> ² .44)	= 65%							
Total (95% CI)			105			104	100.0%	-1.87 (-7.11 to 3.38)	•	
Heterogeneity: $\chi^2 = 5.90$, df = 3 ($\rho = 0.12$); l ² = 49% Test for overall effect: $z = 0.70$ ($\rho = 0.49$)	(p = 0)	0.12); /² .49)	= 49%	2 1	òò					
lest for subgroup differences: $\chi^{2} = 0.11$, at = 1 ($\rho = 0.74$), $f^{2} = 0.14$	χ ² = υ.	11, dt =) = d) L :	J. / 4), / =	%n					

		,							
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.31.1 First generation c. Crosignani 1997 ⁴⁵ 70.3 23. Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 1.74$ ($p = 0.08$)	70.3 e 74 (<i>p</i> = C	23.3 0.08)	31 31	58.9	28	31 31	26.8% 26.8%	11.40 (–5.45 to 28.25) 11.40 (–1.42 to 24.22)	
1.31.8 Second generation e. Tam 2006 ¹⁰⁹ 70.4 24.2 f. Busfield 2006^{107} 79.5 23.3 j. Soysal 2002^{106} 51 27.5 Subtotal (95% CI) 51 27.5 Heterogeneity: $\chi^2 = 0.05$, df = 2 ($p = 0.98$); l^2 Test for overall effect: $z = 0.29$ ($p = 0.78$)	70.4 79.5 51 = 2 (<i>p</i> = 29 (<i>p</i> = C	24.2 23.3 27.5 0.98); <i>I</i> ² 0.98); <i>I</i> ²	9 32 33 74 = 0%	71.1 81.4 51	28.3 18.7 27.5	10 31 73	7.9% 40.6% 24.7% 73.2%	-0.70 (-31.73 to 30.33) -1.90 (-15.59 to 11.79) 0.00 (-17.57 to 17.57) -1.13 (-8.89 to 6.63)	
Total (95% CI) Heterogeneity: $\chi^2 = 2.73$, df = 3 ($p = 0.43$); $l^2 = 0\%$ Test for overall effect: $z = 0.66$ ($p = 0.51$) Test for subgroup differences: $\chi^2 = 2.68$, df = 1 ($p = 0.10$), $l^2 =$	= 3 (p = 0) 36 $(p = 0)$ 3: $\chi^2 = 2$	0.43); <i>I</i> ²).51) .68, df =	105 = 0% = 1 (<i>p</i> = 0	0.10), <i>f</i> ² =	62.8%	104	100.0%	2.23 (-4.41 to 8.87)	•
									-50 -25 0 25 50 Favours Mirena Favours both generations
SF-36 general health (absolute values) – 2 yea	losde	ute va	lues) .	- 2 yea	ILS				
	Both	Both generations	ions	-	Mirena				
Study or subgroup	Mean	S	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.32.2 Second generation f. Busfield 2006^{107} 77.2 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: $z = 0.28$ ($p =$	77.2 3 (p =	23.2 0.78)	5 5	78.9	18.9	27 27	100.0% 100.0%	-1.70 (-17.51 to 14.11) -1.70 (-13.73 to 10.33)	

SF-36 physical function (absolute values) – 2 years

udy or subgroupMeanSDTotalMeanSDTotalMean difference33.2 Second generationS291.115.328100.0%1.20 (-7.74 to 10.14)Busfield 2006 ¹⁰⁷ 92.392291.115.328100.0%btotal (95% CI)2291.115.328100.0%1.20 (-7.74 to 10.14)sterogeneity: not applicablest for overall effect: $z = 0.35$ ($p = 0.73$)		Both	Both generations	itions	E	Airena					
eration 92.3 9 22 91.1 15.3 28 100.0% applicable ct: z = 0.35 (p = 0.73)	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference	IV, Fixed, 99% CI
22 28 100.0% applicable ct: $z = 0.35$ ($p = 0.73$)	33.2 Second generatio. Busfield 2006 ¹⁰⁷		ი	52	91.1	15.3	28	100.0%	1.20 (-7.74 to 10.14)		
sterogeneity: not applicable ist for overall effect: $z = 0.35$ ($p = 0.73$)	ubtotal (95% CI)			22			28	100.0%	1.20 (-5.60 to 8.00)	V	
st for overall effect: $z = 0.35$ ($p = 0.73$)	sterogeneity: not applics	able									
	st for overall effect: z =	0.35 (<i>p</i> =	0.73)								
										Favours Mirena	Favours both generations

SF-36 mental health (absolute values) – 2 years

Study or subgroupMeanSDTotalMean difference1.34.3 Second generationF. Busfield 2006^{107} 79.415.2217914.828100.0%0.40 (-10.78 to 11.58)f. Busfield 2056^{107} 79.415.2217914.828100.0%0.40 (-10.78 to 11.58)feterogeneity: not applicable2128100.0%0.40 (-8.10 to 8.90)0.40 (-8.10 to 8.90)Test for overall effect: $z = 0.09$ ($p = 0.93$)100.0%0.40 (-8.10 to 8.90)14.8		Both	Both generations	ations		Mirena					
eration 79.4 15.2 21 79 14.8 28 applicable ct: <i>z</i> = 0.09 (<i>p</i> = 0.93)	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed,	d, 99% CI
79.4 15.2 21 79 14.8 28 21 29 14.8 28 applicable ct: z = 0.09 (p = 0.93)	1.34.3 Second generatio	Ę									
21 28 100.0% applicable $ t = 0.09 \ (p = 0.93) $	f. Busfield 2006 ¹⁰⁷	79.4	15.2	21	79	14.8	28	100.0%	0.40 (-10.78 to 11.58)		1
Heterogeneity: not applicable Test for overall effect: $z = 0.09$ ($p = 0.93$)	Subtotal (95% CI)			21			28	100.0%			
Test for overall effect: $z = 0.09$ ($p = 0.93$)	Heterogeneity: not applic:	able									
	Test for overall effect: $z =$	= a 0.09	0.93)								
										Favours Mirena Favours	Favours both generations

	Both	Both generations	itions	-	Mirena				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Mean SD Total Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
1.35.4 Second generation						:			
t. Bustield 2006	63.6	19.9	21	65.4	16.3	28	100.0%	-1.80 (-15.51 to 11.91)	
Subtotal (95% CI)			5			28	100.0%	-1.80 (-12.24 to 8.64)	
Heterogeneity: not applicable	cable								
Test for overall effect: $z = 0.34$ ($p = 0.74$)	= 0.34 (<i>p</i> = 1	0.74)							
									-20 -10 0 10 20
									Favours Mirena Favours both generations
SE-36 physical role limitation (absolute	limitatio	del u	coluto	values) – 2 vears		STEEL			
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	Both	Both generations	itions	-	Mirena				
Study or subgroup	Mean	SD	Mean SD Total	Mean	SD	Total	SD Total Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
1.36.5 Second generation									
f. Busfield 2006 ¹⁰⁷	86.4	27.5 22	22	94.6	17.2	28	100.0%	–8.20 (–25.47 to 9.07)	
Subtotal (95% CI)			22			28	100.0%	-8.20 (-21.34 to 4.94)	¢
Heterogeneity: not applicable	ble								•
Test for overall effect: $z = 1.22$ ($p = 0.22$)	1.22 (p =	0.22)							
									-50 -25 0 25 50
									Favours Mirena Favours both generations

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SF-36 emotional role limitation (absolute values) – 2 years

SF-36 social function (absolute values) – 2 years

	Both	Both generations	tions	-	Mirena					
Study or subgroup	Mean	SD	Mean SD Total Mean	Mean	SD	Total	SD Total Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	ed, 99% CI
1.38.7 Second generation				c T		0				
f. Bustield 2006 ¹⁰⁷	76.8 18.1	18.1	22	79	4	28	100.0%	–2.20 (–14.25 to 9.85)		
Subtotal (95% CI)			5			28	100.0%	-2.20 (-11.37 to 6.97)	¢	
Heterogeneity: not applicable	ole									
Test for overall effect: $z = 0.47$ ($p = 0.64$)	(47) (p = 0)	0.64)								
									-20 -10 0 10 20	20
									Favours Mirena Favour	Favours both generations

	Both	Both generations	tions	~	Mirena				
Study or subgroup	Mean		SD Total Mean	Mean	sD	Total	Total Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.39.8 Second generation f. Busfield 2006 ¹⁰⁷	74.2	21.5	22	82.9	17.2	28	100.0%	-8.70 (-23.17 to 5.77)	
Subtotal (95% CI) Heterogeneity: not applicable	ele		22			28	100.0%	–8.70 (–19.71 to 2.31)	¢
Test for overall effect: $z = 1.55$ ($p = 0.12$)	.55 (<i>p</i> =	0.12)							
									-50 -25 0 25 50
									Favours Mirena Favours both generations
SF-36 general health (change from baseline) –	(chan	ge fro	m bas	eline) -		12 months	45		
	Both	Both generations	tions	E	Mirena				

Study or subgroup Mean SD Total Mean difference 1.40.1 Second generation 15.9 28.3 8 2.1 14.2 10 15.4% 13.80 (-14.45 to 42.05) Mean difference Nean	Mean SD Total Mean SD Total Weight W. Fixed, 99% CI eration 15.9 28.3 8 2.1 14.2 10 15.4% 13.80 (-14.45 to 42.05) 4 19.3 32 8.8 17.9 31 84.6% -4.80 (-16.88 to 7.28) 2.43, df = 1 ($p = 0.12$); $l^2 = 59\%$ 41 100.0% -1.93 (-10.38 to 6.52) 2.12; $l^2 = 59\%$ 2.1 14.1 100.0% -1.93 (-10.38 to 6.52)										
eration15.928.382.114.21015.4%13.80 (-14.45 to 42.05)419.3328.817.93184.6%-4.80 (-16.88 to 7.28)404041100.0%-1.93 (-10.38 to 6.52)2.43, df = 1 ($p = 0.12$); $P = 59\%$ 5151512.45 ($p = 0.65$)515151	ration 15.928.382.114.21015.4%13.80 (-14.45 to 42.05)419.3328.817.93184.6%-4.80 (-16.88 to 7.28)419.3328.817.941100.0%-1.93 (-10.38 to 6.52)2.43, df = 1 ($p = 0.12$); $P = 59\%$ 2.45 ($p = 0.65$)-1.93 (-10.38 to 6.52)-1.93 (-10.38 to 6.52)	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
15.9 28.3 8 2.1 14.2 10 15.4% 13.80 (-14.45 to 42.05) 4 19.3 32 8.8 17.9 31 84.6% -4.80 (-16.88 to 7.28) 40 40 41 100.0% -1.93 (-10.38 to 6.52)	15.9 28.3 8 2.1 14.2 10 15.4% 13.80 (-14.45 to 42.05) 4 19.3 32 8.8 17.9 31 84.6% -4.80 (-16.88 to 7.28) 40 40 41 100.0% -1.93 (-10.38 to 6.52) 2.43, df = 1 ($p = 0.12$); $l^{p} = 59\%$ 2:43, df = 1 ($p = 0.12$); $l^{p} = 59\%$ 2.1 100.0% -1.93 (-10.38 to 6.52) 2:45 ($p = 0.65$) -1.65 -1.65 -1.65 -1.65	1.40.1 Second generation	_								
4 19.3 32 8.8 17.9 31 84.6% -4.80 (-16.88 to 7.28) 40 40 41 100.0% -1.93 (-10.38 to 6.52) 2.43, df = 1 ($p = 0.12$); $l^2 = 59\%$ 31 84.6% -1.93 (-10.38 to 6.52) $xt: z = 0.45$ ($p = 0.65$) -1.93 (-10.38 to 6.52) -1.93 (-10.38 to 6.52)	4 19.3 32 8.8 17.9 31 84.6% -4.80 (-16.88 to 7.28) 40 40 41 100.0% -1.93 (-10.38 to 6.52) 2.43, df = 1 ($p = 0.12$); $l^e = 59\%$ 51 100.0% -1.93 (-10.38 to 6.52) 21: $z = 0.45$ ($p = 0.65$) 2.41 100.0% -1.93 (-10.38 to 6.52)	e. Tam 2006 ¹⁰⁹	15.9	28.3	8		14.2	10	15.4%		
40 41 100.0% -1.93 (-10.38 to 6.52) 2.43, df = 1 (p = 0.12); l^{e} = 59% 11: z = 0.45 (p = 0.65)	40 41 100.0% -1.93 (-10.38 to 6.52) 2.43, df = 1 ($p = 0.12$); $l^{e} = 59\%$ 31: $z = 0.45$ ($p = 0.65$)	f. Busfield 2006 ¹⁰⁷	4	19.3	32		17.9	31	84.6%	-4.80 (-16.88 to 7.28)	
2.43, df = 1 ($p = 0.12$); $l^{e} = 59\%$ 21: $z = 0.45$ ($p = 0.65$)	2.43, df = 1 ($p = 0.12$); $l^{e} = 59\%$ xt: z = 0.45 ($p = 0.65$)	Subtotal (95% CI)			4			41	100.0%	-1.93 (-10.38 to 6.52)	
		Heterogeneity: $\chi^2 = 2.43$, c	f = 1 (p = 1)	0.12); /	$P^{2} = 59\%$						
		Fest for overall effect: z =	0.45 (p = 1)	0.65)							

Favours both generations

Favours Mirena

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Favours both generations 20 <u>9</u> 0 Favours Mirena -20 -10 5.60 (-17.51 to 28.71) -1.80 (-17.06 to 13.46) **0.45 (-9.24 to 10.14)** 30.4% 69.6% **100.0%** SF-36 mental health (change from baseline) – 12 months ი წ **ჭ** 20.1 21.4 4.4 8.7 Heterogeneity: $\chi^2 = 0.47$, df = 1 (p = 0.49); $\beta = 0\%$ Test for overall effect: z = 0.09 (p = 0.93) 9 % **4** 25.5 17.9 10 6.9 1.41.2 Second generation e. Tam 2006¹⁰⁸ f. Busfield 2006¹⁰⁷ Subtotal (95% CI)

Study or subgroup Mean SD Total Weight Weight W, Fixed, 99% CI Mean difference N, Fixed, 99% CI 1.42.3 Second generation 5 18.5 8 -14.8 20.2 10 17.5% 19.80 (-3.75 to 43.35) Mean difference N, Fixed, 99% CI 6. Tam 2006^{100} 5.1 16.4 32 6.7 17 31 82.5% -1.60 (-12.45 to 9.25) -1.60 (-12.45		Both	Both generations	ations	-	Mirena				
5 18.5 8 -14.8 20.2 10 17.5% 5.1 16.4 32 6.7 17 31 82.5% = 1 ($p = 0.03$); $l^2 = 78\%$.56 ($p = 0.57$)	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
5 18.5 8 -14.8 20.2 10 17.5% 3^{107} 5.1 16.4 32 6.7 17 31 82.5% CI 40 40 41 100.0% $\chi^2 = 4.52$, df = 1 ($p = 0.03$); $l^2 = 78\%$ effect: $z = 0.56$ ($p = 0.57$)	1.42.3 Second generatic	u								
5.1 16.4 32 6.7 17 31 82.5% 40 41 100.0% : 4.52, df = 1 ($p = 0.03$); $l^2 = 78\%$: ct: $z = 0.56$ ($p = 0.57$)	e. Tam 2006 ¹⁰⁹	S	18.5	8	-14.8	20.2	10	17.5%	19.80 (–3.75 to 43.35)	
40 41 100.0% 4.52, df = 1 ($p = 0.03$); $l^2 = 78\%$ ct: $z = 0.56$ ($p = 0.57$)	f. Busfield 2006 ¹⁰⁷	5.1	16.4	32	6.7	17	31	82.5%	-1.60 (-12.45 to 9.25)	
Heterogeneity: $\chi^2 = 4.52$, df = 1 ($p = 0.03$); $l^2 = 78\%$ Test for overall effect: $z = 0.56$ ($p = 0.57$)	Subtotal (95% CI)			40			41	100.0%	2.14 (–5.35 to 9.64)	
	Heterogeneity: $\chi^2 = 4.52$, Test for overall effect: $z =$	df = 1 (p = = 0.56 (p = 0	0.03); 3.57)	l ² = 78%						,
										Favours Mirena Favours both generations

SF-36 physical function (change from baseline) – 12 months

Mean difference IV, Fixed, 99% CI

Mean difference IV, Fixed, 99% CI

Weight

Total

S

Mean

Total

SD

Mean

Study or subgroup

Mirena

Both generations

	Both	Both generations	ations	_	Mirena				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.43.4 Second generation e. Tam 2006 ¹⁰⁹	n -1.3	28	ω	0.5	20.3	6	19.4%	–1.80 (–32.19 to 28.59)	
f. Busfield 2006 ¹⁰⁷	18.4	19.1	32	15.5	25.7	30	80.6%	2.90 (-11.99 to 17.79)	
Subtotal (95% CI) 40 Heterogeneity: $\chi^2 = 0.13$, df = 1 ($p = 0.72$); $l^2 = 0\%$	df = 1 (<i>p</i> =	= 0.72); <i>I</i>	40 ² = 0%			40	100.0%	1.99 (–8.18 to 12.16)	
lest for overall effect: $z = 0.38$ ($p = 0.70$)	0.38 (<i>p</i> =	0.70)							
SF-36 physical role limitation (change from	limitatic	n (ch	lange fi	rom bé	aselin	e) – 12	baseline) – 12 months	S	
	Both	Both generations	ations	_	Mirena				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.44.5 Second generation e. Tam 2006 ¹⁰⁹	n 19.4	49.7	თ	17.5	47.2	10	25.2%	1.90 (-55.54 to 59.34)	
f. Busfield 2006 ¹⁰⁷	30.5	51.1	0	21.8	51.5	31	74.8%	8.70 (-24.60 to 42.00)	
Subtotal (95% CI)						41	100.0%	6.99 (-14.93 to 28.91)	
Heterogeneity: $\chi^2 = 0.07$, df = 1 ($p = 0.79$); $l^2 = 0.\%$	df = 1 (p =	= 0.79); /	$l^2 = 0\%$)
Test for overall effect: $z = 0.62$ ($\rho = 0.53$)	0.62 (<i>p</i> =	0.53)							

SF-36 vitality (change from baseline) – 12 months

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Favours both generations 50

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0

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Favours Mirena -25

SF-36 bodily pain (change from baseline) – 12 months

Study or subgroup Mean SD Total Mean difference 1.45.8 Second generation 21 26.3 9 7.8 19.6 10 32.1% 13.20 (-14.46 to 40.86) Mean difference IV, Fixed, 99% CI a. Tam 2006 ¹⁰⁰ 21 26.3 9 7.8 19.6 10 32.1% 13.20 (-14.46 to 40.86) f. Busfield 2006 ¹⁰⁷ 26 30.3 32 20.4 28.3 31 6.7.9% 5.60 (-13.42 to 24.62) Subtotal (95% CI) 41 100.0% 8.04 (-3.88 to 19.97) 10.97) 10.13.42 to 24.62) Hetrogeneity: $\chi^2 = 0.34$, df = 1 ($p = 0.56$); $\beta = 0.\%$ 41 100.0% 8.04 (-3.88 to 19.97) 10.97)		Both	Both generations	itions	-	Mirena				
neration 21 26.3 9 7.8 19.6 10 32.1% 26 30.3 32 20.4 28.3 31 67.9% 41 100.0% 50.34, df = 1 ($p = 0.56$); $l^{e} = 0\%$ set: $z = 1.32$ ($p = 0.19$)	Study or subgroup	Mean	S	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
21 26.3 9 7.8 19.6 10 32.1% 26 30.3 32 20.4 28.3 31 67.9% 41 41 41 100.0% 0.34 , df = 1 ($p = 0.56$); $l^2 = 0$ % ct: $z = 1.32$ ($p = 0.19$)	1.45.8 Second generatio	Ę								
26 30.3 32 20.4 28.3 31 67.9% 41 41 100.0% = 0.34, df = 1 (p = 0.56); l^{c} = 0% set: z = 1.32 (p = 0.19)	э. Тат 2006 ¹⁰⁹	21	26.3	6	7.8	19.6		32.1%	13.20 (–14.46 to 40.86)	
41 41 100.0% 0.34, df = 1 (p = 0.56); l^2 = 0% ct: z = 1.32 (p = 0.19)	. Busfield 2006 ¹⁰⁷	26	30.3	32	20.4	28.3	31	67.9%	5.60 (-13.42 to 24.62)	
Heterogeneity: $\chi^2 = 0.34$, df = 1 ($p = 0.56$); $l^e = 0\%$ Test for overall effect: $z = 1.32$ ($p = 0.19$)	Subtotal (95% CI)			41			41	100.0%	8.04 (–3.88 to 19.97)	♦
	Heterogeneity: $\chi^2 = 0.34$, Fest for overall effect: $z =$	df = 1 (p = 1.32 (p = 0	0.56); <i>l</i> 0.19)	² = 0%						
										Favours Mirena Favours both generations

SF-36 social function (change from baseline) – 12 months

	Both	Both generations	ntions	-	Mirena					
Study or subgroup	Mean	SD	Mean SD Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	⁻ ixed, 99% CI
1.46.7 Second generation	_									
e. Tam 2006 ¹⁰⁹	9.9	16.1	6	0	15.7	10	39.4%	9.90 (-8.93 to 28.73)	+	
f. Busfield 2006 ¹⁰⁷	11.8	25.1	32	15.1	21.6	31	60.6%	-3.30 (-18.48 to 11.88)		
Subtotal (95% CI)			41			41	100.0%	1.90 (-7.09 to 10.89)		
Heterogeneity: $\chi^2 = 1.98$, df = 1 ($p = 0.16$); $\beta = 49\%$ Test for overall effect: $z = 0.41$ ($p = 0.68$)	ff = 1 (p = 0.41 (p = 0.	: 0.16); <i>i</i> 0.68)	² = 49%)	
									-20 -10 0 10 20	20
									Favours Mirena Favo	Favours both generations

	Both	Both generations	tions		Mirena				
Study or subgroup	Mean	SD	Total	Mean	S	Total	Weight	Mean difference IV, Fixed, 99% Cl	Mean difference IV, Fixed, 99% CI
1.47.6 Second generation									
e. Tam 2006 ¹⁰⁹	25.9	54.7	ი	-10	35.3	10	23.5%	35.90 (–19.17 to 90.97)	
f. Busfield 2006 ¹⁰⁷	14.6	51.5	32	28	42.2	31	76.5%	-13.40 (-43.91 to 17.11)	
Subtotal (95% CI)			41			4	100.0%	-1.82 (-22.13 to 18.49)	
Heterogeneity: $\chi^2 = 4.07$, df = 1 ($p = 0.04$); l ² = 75% Test for overall effect: $z = 0.18$ ($p = 0.86$)	ff = 1 (p = 0.18 (p = 0.18))	= 0.04);	l ² = 75%)
									-50 -25 0 25 50
									Favours Mirena Favours both generations
SF-36 general health (change from baseline)	i (chan	ge frc	im bas		- 2 years	ars			
	Both	Both generations	tions	_	Mirena				
Study or subgroup	Mean	SD	Total	Mean	S	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.48.1 Second generation f. Busfield 2006¹ ⁰⁷	ი -	15	22	4.9	20.3	27	100.0%	4.10 (-8.90 to 17.10)	
Subtotal (95% CI)			22			27	100.0%	4.10 (-5.80 to 14.00)	
Heterogeneity: not applicable Test for overall effect: $z = 0.81$ ($p = 0.42$)	D.81 (<i>p</i> = 1	0.42)							



Favours both generations

100

20-

0

–100 –50 Favours Mirena

SF-36 physical function (change from baseline) – 2 years

Study or subgroupMeanSDTotalMeanMean difference1.49.2 Second generationMeanSDTotalWeightV, Fixed, 99% CIMean difference1.49.2 Second generation13.218228.819.828100.0%4.40 (-9.41 to 18.21)1.49.2 Second generation22238.8190.0%4.40 (-6.11 to 14.91)Mean difference IV, Fixed, 99% CI1.49.2 Second generation2228100.0%4.40 (-6.11 to 14.91)Mean difference IV, Fixed, 99% CI1.49.2 Second generation2228100.0%4.40 (-6.11 to 14.91)Mean difference IV, Fixed, 99% CI1.40 coverall effect: $z = 0.82$ ($p = 0.41$)2228100.0%4.40 (-6.11 to 14.91)		Both	Both generations	tions	<u> </u>	Mirena				
13.2 18 22 8.8 19.8 28 100.0% 22 28 28 10.0% Ne 182 (p = 0.41)	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99%
13.2 18 22 8.8 19.8 28 100.0% applicable ct: z = 0.82 (<i>p</i> = 0.41)	1.49.2 Second generation				0					
22 28 100.0% applicable ${\rm ct:} \ z = 0.82 \ (p = 0.41)$	t. Bustield 2006	13.2	18	22	8.8	19.8	28	100.0%	4.40 (-9.41 to 18.21)	1
Heterogeneity: not applicable Test for overall effect: $z = 0.82$ ($p = 0.41$)	Subtotal (95% CI)			52			28	100.0%	4.40 (-6.11 to 14.91)	٠
Test for overall effect: $z = 0.82$ ($p = 0.41$)	Heterogeneity: not applicabl	Ð								,
	Test for overall effect: $z = 0.$	82 (<i>p</i> = C	.41)							

SF-36 mental health (change from baseline) – 2 years

				Mean difference	
Study or subgroup Mean SD Total Mean		SD Total Weight	Weight	IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.50.3 Second generation]
f. Busfield 2006 ¹⁰⁷ 10.3 16.2 21 4.6	6 13.4	28	100.0%	5.70 (-5.50 to 16.90)	
Subtotal (95% Cl) 21		28	100.0%	5.70 (-2.82 to 14.22)	♦
Heterogeneity: not applicable					
Test for overall effect: $z = 1.31$ ($p = 0.19$)					

Study or subgroupMeanSDTotalMeanMean difference1.51.4 Second generation1.51.4 Second generation21.4 19.3 2111.8 18.6 28100.0% 9.60 (-4.53 to 23.73)6. Busfield 2000 W21.4 19.3 2111.8 18.6 28100.0% 9.60 (-1.15 to 20.35)7. Explored Force21.4 19.3 2111.8 18.6 28100.0% 9.60 (-1.15 to 20.35)1 Heterogeneity: not applicable21.4 19.3 2121.4 19.3 2121.4 19.3 211 Fet for overall effect: $z = 1.75$ ($p = 0.08$)2.60 (-1.15 to 20.35)-100 -50 0 50 100Factor overall effect: $z = 1.75$ ($p = 0.08$)2.60 (-1.15 to 20.35)-100 -50 0 50 100Factor overall effect: $z = 1.75$ ($p = 0.08$)2.60 (-1.15 to 20.35)-100 -50 0 50 100Factor overall effect: $z = 1.75$ ($p = 0.08$)2.60 (-1.15 to 20.35)-100 -50 0 50 100Factor overall effect: $z = 1.75$ ($p = 0.08$)2.60 (-1.15 to 20.35)-100 -50 0 50 100Factor overall effect: $z = 1.75$ ($p = 0.08$)-100 -50 0 50 0 5050 100Factor overall effect: $z = 1.75$ ($p = 0.08$)-100 -50 0 50 0 5050 100Factor overall effect: $z = 1.75$ ($p = 0.08$)-100 -50 0 5050 100Factor overall effect: $z = 1.75$ ($p = 0.08$)-100 -50 0 5050 100Factor overall effect: $z = 1.75$ ($p = 0.08$)-100 -50 0 5050 100Study or subgroupMean SDTotalMean differenceMean differenceMaen differenceMean differenceMean differenceStudy or subgroupMean ZDTotalMean differenceMean difference <td< th=""><th>tt IV, Fixed, 99% CI Mean difference IV % 9.60 (-4.53 to 23.73) % 9.60 (-1.15 to 20.35) -100 -50 0 Favours Mirena t IV, Fixed, 99% CI Mean difference IV</th><th></th><th>Both</th><th>Both generations</th><th>ations</th><th>_</th><th>Mirena</th><th></th><th></th><th></th><th></th><th></th></td<>	tt IV, Fixed, 99% CI Mean difference IV % 9.60 (-4.53 to 23.73) % 9.60 (-1.15 to 20.35) -100 -50 0 Favours Mirena t IV, Fixed, 99% CI Mean difference IV		Both	Both generations	ations	_	Mirena					
 9.60 (-4.53 to 23.73) 9.60 (-1.15 to 20.35) -100 -50 0 Favours Mirena Mean difference Iv, Mean difference Iv, 	 % 9.60 (-4.53 to 23.73) % 9.60 (-1.15 to 20.35) -100 -50 0 Favours Mirena Mean difference IV, Fixed, 99% CI Mean difference 	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference	IV, Fixed, 99% CI
-100 -50 0 Favours Mirena Mean difference IV, Fixed, 99% Cl Mean difference IV	-100 -50 0 Favours Mirena tt IV, Fixed, 99% CI Mean difference IV	1.51.4 Second generatio f. Busfield 2006 ¹⁰⁷ Subtotal (95% CI)	n 21.4	19.3		11.8	18.6	28	100.0% 100.0%	9.60 (-4.53 to 23.73) 9.60 (-1.15 to 20.35)		
-100 -50 0 Favours Mirena Mean difference tt IV, Fixed, 99% Cl Mean difference IV	-100 -50 0 Favours Mirena Mean difference It IV, Fixed, 99% CI Mean difference IV	Heterogeneity: not applic: Test for overall effect: <i>z</i> =	able : 1.75 (<i>p</i> = (0.08)								
Mean difference It IV, Fixed, 99% CI	Mean difference It IV, Fixed, 99% CI										–50 avours Mirena	50 Favours both ger
Both generations Mirena Mean difference Mean SD Total Mean SD Total Mean SD Total Weight IV, Fixed, 99% Cl	Both generations Mirena Mean difference Mean SD Total Mean SD Total Weight IV, Fixed, 99% Cl	F-36 physical role l	'imitatio	n (ch	ange 1	from bé	selin	e) – 2 J	/ears			
Mean SD Total Mean SD Total Weight IV, Fixed, 99% Cl	Mean SD Total Mean SD Total Weight IV, Fixed, 99% Cl		Both	genera	Itions	-	Mirena					
		Study or subgroup	Mean	SD	Total	Mean	S	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference	IV, Fixed, 99% CI

		,	,								
Study or subgroup	Mean	SD	Mean SD Total Mean	Mean	SD	Total	SD Total Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI	V, Fixed, 99% (5
1.52.5 Second generation											
f. Busfield 2006 ¹⁰⁷	26.1	54.3	22	25	40.8 28	28	100.0%	1.10 (–34.73 to 36.93)			
Subtotal (95% CI)			22			28	100.0%	1.10 (-26.16 to 28.36)	V		
Heterogeneity: not applicable	e										
Test for overall effect: $z = 0.08$ ($p = 0.94$)	08 (<i>p</i> = C	.94)									
									-100 -50 0	20	100
									Favours Mirena	Favours both generations	generations

SF-36 vitality (change from baseline) – 2 years

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SF-36 bodily pain (change from baseline) – 2 years

udy or subgroupMeanSDTotalMean differenceS3.8 Second generationS3.8 Second generationIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII		Both	Both generations	ations	2	Mirena				
32.7 22 21 24.8 28 100.0% 22 28 100.0% : 0.88)	Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
19.7 32.7 22 21 24.8 28 100.0% applicable sct: z = 0.15 (<i>p</i> = 0.88)	53.8 Second generation									
22 28 100.0% applicable ct: <i>z</i> = 0.15 (<i>p</i> = 0.88)	Busfield 2006 ^{10/}	19.7	32.7	22	21	24.8	28	100.0%		1
terogeneity: not applicable st for overall effect: $z = 0.15$ ($p = 0.88$)	btotal (95% CI)			ដ			28	100.0%	-1.30 (-17.76 to 15.16)	•
st for overall effect: $z = 0.15$ ($p = 0.88$)	terogeneity: not applica.	ble								
	st for overall effect: z =	0.15 (<i>p</i> =	0.88)							
										Favours Mirena Favours both generations

SF-36 social function (change from baseline) – 2 years

	Both	Both generations	ntions	-	Mirena				
Study or subgroup	Mean	SD	Mean SD Total Mean	Mean	SD	Total	SD Total Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.54.7 Second generation f. Busfield 2006 ^{to7}	15.2	26	22	10.3	17.9 28	28	100.0%	100.0% 4.90 (–11.83 to 21.63)	
Subtotal (95% CI)			53			28	100.0%	4.90 (-7.83 to 17.63)	٠
Heterogeneity: not applicable	ole								
Test for overall effect: $z = 0.75$ ($\rho = 0.45$)).75 (p = (0.45)							
									-100 -50 0 50 100
									Favours Mirena Favours both generations

	Both	Both generations	ations	E	Mirena				
Study or subgroup	Mean	SD	SD Total	Mean	SD	SD Total Weight	Weight	Mean difference IV, Fixed, 99% CI	Mean difference IV, Fixed, 99% CI
1.55.6 Second generation									
f. Busfield 2006 ¹⁰⁷	18.2	42.1	22	20.2	49.1	28	100.0%	–2.00 (–35.25 to 31.25)	
Subtotal (95% CI)			22			28	100.0%	-2.00 (-27.30 to 23.30)	¢
Heterogeneity: not applicable	le								
Test for overall effect: $z = 0.15$ ($p = 0.88$)	.15 (<i>p</i> = (0.88)							
									-100 -50 0 50 100
									Favours Mirena Favours both generations

Proportion requiring endometrial ablation – 12 months

Study or subgroup Eve 1.56.1 First generation		-					
1.56.1 First generation	Events Total	tal Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio sto, Fixed, 99% Cl
a. Malak 2006 ¹⁰⁴ 1	30	4	30	62.6%	0.28 (0.03 to 3.00)		
Subtotal (95% CI)	30		30	62.6%	0.28 (0.04 to 1.70)		
Total events 1		4					
Heterogeneity: not applicable							
Test for overall effect: $z = 1.39$ ($p = 0.16$)) (<i>p</i> = 0.16)						
1.56.2 Second generation							
e. Tam 2006 ¹⁰⁹ 0	15	က	18	37.4%	0.14 (0.01 to 3.09)	•	1
Subtotal (95% CI)	15		18	37.4%	0.14 (0.01 to 1.48)		
Total events 0		ო					
Heterogeneity: not applicable							
Test for overall effect: $z = 1.63$ ($p = 0.10$)	3 (<i>p</i> = 0.10)						
Total (95% CI)	45		48	100.0%	0.21 (0.05 to 0.90)		
Total events		7					
Heterogeneity: $\chi^2 = 0.19$, df = 1 ($p = 0.66$); $l^2 = 0\%$	$1 \ (p = 0.66);$	P = 0%					
Test for overall effect: $z = 2.10$ ($p = 0.04$)	(p = 0.04)		200				
Lest for subgroup differences: $\chi^2 = 0.19$, at $= 1 \ (\rho = 0.00)$,	χ ⁻ = υ. 19, ατ		$\Gamma = 0\%$			-	-
						0.01 0.1 1	10 100
						Favours both generations	Favours Mirena

Proportion requiring endometrial ablation – 2 years

	Both generations	erations	Mirena	na					
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto od Peto, Fixe	Peto odds ratio Peto, Fixed, 99% CI	
1.57.2 Second generation									
f. Busfield 2006 ¹⁰⁷	0	41	4	42	100.0%	0.13 (0.01 to 1.77)	+		
Subtotal (95% CI)		41		42	100.0%	0.13 (0.02 to 0.95)			
Total events	0		4						
Heterogeneity: not applicable									
Test for overall effect: $z = 2.01$ ($p = 0.04$)	$1 \ (p = 0.04)$								
							0.01 0.1	-9-	100
							Favours both generations	Favours Mirena	ena

Proportion requiring hysterectomy – <12 months

	Both generations	erations	Mire	rena					
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto c Peto, Fiy	Peto odds ratio Peto, Fixed, 99% CI	
1.58.1 Second generation	tion								
g. Barrington 2003 ⁸¹	S	25	ო	25	100.0%	1.79 (0.25 to 12.82)			
Subtotal (95% CI)		25		25	100.0%	1.79 (0.40 to 8.01)	V		
Fotal events	5		ო						
Heterogeneity: not applicable	licable								
Test for overall effect: $z = 0.76$ ($p = 0.45$)	$r = 0.76 \ (p = 0.7)$	45)							
							0.01 0.1	-0-	100
							Favours both generations	Favours Mirena	Mirena

months
1
1
hysterectomy
6
requiring
Proportion

)							
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto c Peto, Fi	Peto odds ratio Peto, Fixed, 99% Cl	
1.59.1 First generation									
c. Crosignani 1997 ⁴⁵	-	35	0	35	13.2%	7.39 (0.04 to 1276.22)			Î
Subtotal (95% CI)		35		35	13.2%	7.39 (0.15 to 372.38)			
Total events	-		0						
Heterogeneity: not applicable	cable								
Test for overall effect: $z = 1.00 \ (\rho = 0.32)$	= 1.00 (<i>p</i> = 0	J.32)							
1.59.2 Second generation	ion								
e. Tam 2006 ¹⁰⁹	0	15	÷	18	13.1%	0.16 (0.00 to 28.21)	•		
h. Soysal 2002 ¹⁰⁶	-	36	5	36	73.7%	0.24 (0.03 to 2.11)			
Subtotal (95% CI)		51		54	86.8%	0.22 (0.05 to 1.04)			
Total events	-		9				ŀ		
Heterogeneity: $\chi^2 = 0.03$, df = 1 ($p = 0.85$); $l^2 = 0\%$	$a_{1}, df = 1 (p = 1)$	0.85 ; $l^2 = 0\%$							
Test for overall effect: $z = 1.92$ ($p = 0.06$)	= 1.92 (<i>p</i> = 0	0.06)							
Total (95% CI)		86		89	100.0%	0.36 (0.09 to 1.48)	¢		
Total events	0		9						
Heterogeneity: $\chi^2 = 2.68$, df = 2 ($p = 0.26$); $l^2 = 25\%$	a, df = 2 (p = 1)	0.26 ; $l^2 = 25^{\circ}$	%						
Test for overall effect: $z = 1.42$ ($p = 0.16$)	= 1.42 (p = 0)	0.16)							
Test for subgroup differences: $\chi^2=2.65,~df=1~(\rho=0.10),~\beta^2=$	ences: $\chi^2 = 2$.65, df = 1 (<i>p</i>	= 0.10), <i>f</i> ² = 6	62.3%					
							+00		-00-

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Favours Mirena

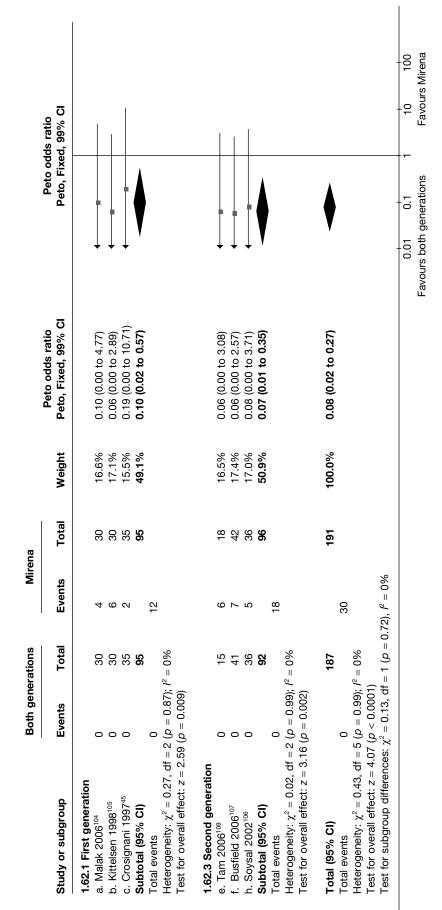
Favours both generations

Proportion requiring hysterectomy – 2 years

Study or subgroupEventsTotalPeto odds ratioPeto odds ratioStudy or subgroupEventsTotalEventsTotalWeightPeto, Fixed, 99% CI1.60.3 Second generation43083357.4%0.50 (0.10 to 2.57)Peto, Fixed, 99% CI1. Shaw 2007 ¹⁰⁸ 43083357.4%0.50 (0.10 to 2.57)Peto, Fixed, 99% CI1. Shaw 2007 ¹⁰⁸ 54134242.6%1.77 (0.26 to 11.91)1. Subtotal (95% CI)97175100.0%0.86 (0.33 to 2.21)1. Total events91175100.0%0.86 (0.33 to 2.21)1. Fetorogeneity: $\chi^2 = 1.69$, df = 1 ($p = 0.19$); $p^2 = 41\%$ 100.0%0.86 (0.33 to 2.21)1. Fetorogeneity: $\chi^2 = 0.32$ ($p = 0.75$)100.0%0.86 (0.33 to 2.21)		Both generations	erations	Mirena	na				
eneration $4 30 8 33 57.4\%$ 5 41 3 42 42.6% 1) $71 75 100.0\%$ $= 1.69, df = 1 (p = 0.19); l^2 = 41\%$ fect: $z = 0.32$ ($p = 0.75$)	Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odd Peto, Fixed	s ratio , 99% CI
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.60.3 Second generation								
7 5 41 3 42 42.6% 1) 71 75 100.0% 1 $= 1.69, df = 1 (p = 0.19); l^2 = 41\%$ fect: $z = 0.32 (p = 0.75)$	d. Shaw 2007 ¹⁰⁸	4	30	80	33	57.4%	0.50 (0.10 to 2.57)		I
71 75 100.0% 9 9 11 $(p = 0.19); l^2 = 41\%$ set: $z = 0.32$ ($p = 0.75$)	f. Busfield 2006 ¹⁰⁷	5 D	41	ო	42	42.6%	1.77 (0.26 to 11.91)		
Ŧ	Subtotal (95% CI)		7		75	100.0%	0.86 (0.33 to 2.21)		
Heterogeneity: $\chi^2 = 1.69$, df = 1 ($p = 0.19$); $l^2 = 41\%$ Test for overall effect: $z = 0.32$ ($p = 0.75$)	Total events	6		11				,	
	Heterogeneity: $\chi^2 = 1.69$, df Test for overall effect: $z = 0$	= 1 (p = 0.19); .32 (p = 0.75)	<i>I</i> ² = 41%						
								Favours both generations	Favours Mirena

Proportion discontinuing Mirena – <12 months

Study or subgroupEventsTotalWeightOdds ratioOdds ratioStudy or subgroupEventsTotalVertsTotalWeightPeto, Fixed, 99% CIPeto, Fixed, 99% CII.61.2 Second generation041342100.0%0.14 (0.00 to 6.96)Peto, Fixed, 99% CISubtotal (95% CI)41342100.0%0.14 (0.01 to 2.72)Peto, Fixed, 99% CIFotal events0342100.0%0.14 (0.01 to 2.72)Peto, Fixed, 99% CIFet rogeneity: not applicable130.14 (0.01 to 2.72)Petoteci 2.2 = 1.31 ($\rho = 0.19$)Fet row overall effect: $z = 1.31$ ($\rho = 0.19$)1111		Both generations	erations	Mirena	na				
3 42 100.0% 42 100.0 % 3	Study or subgroup	Events	Total	Events	Total	Weight	Odds ratio Peto, Fixed, 99% CI	Odds ra Peto, Fixed,	atio , 99% CI
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.61.2 Second generation								
$\begin{array}{cccc} & \textbf{41} & \textbf{42} & \textbf{100.0\%} \\ 0 & 3 & \textbf{32} \\ applicable \\ \text{ct: } z = 1.31 \ (p = 0.19) \end{array}$	f. Busfield 2006 ¹⁰⁷	0	41	ი	42	100.0%	0.14 (0.00 to 6.96)	•	
0 3 applicable ct: $z = 1.31$ ($p = 0.19$)	Subtotal (95% CI)		41		42	100.0%	0.14 (0.01 to 2.72)		
Heterogeneity: not applicable Test for overall effect: $z = 1.31$ ($p = 0.19$)	Total events	0		ო					
Test for overall effect: $z = 1.31$ ($p = 0.19$)	Heterogeneity: not applicable	۵ ۵							
	Test for overall effect: z = 1.	31 ($p = 0.19$)							
								Favours both generations	Favours Mirena



Proportion discontinuing Mirena –12 months

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Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	ls ratio 1, 99% CI
1.63.2 First generation								
h Kittelsen 1998 ¹⁰⁵	C	30	α	30	33.0%	0 04 (0 00 to 1 97)		I
Subtotal (95% CI)	þ	8 8)	8 8	33.0%	0.04 (0.00 to 0.79)		
Total events	0		80					
Heterogeneity: not applicable								
Test for overall effect: $z = 2.12$ ($\rho = 0.03$)	2 (<i>p</i> = 0.03)							
1.63.4 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	13	33	33.6%	0.02 (0.00 to 0.99)	+	
f. Busfield 2006 ¹⁰⁷	0	41	8	42	33.4%	0.05 (0.00 to 2.18)	•	1
Subtotal (95% CI)		74		75	67.0%	0.03 (0.00 to 0.26)		
Total events	0		21					
Heterogeneity: $\chi^2 = 0.14$, df = 1 ($p = 0.71$); $l^2 = 0.6$	(p = 0.71);	$P^{2} = 0\%$						
Test for overall effect: $z = 3.27$ ($p = 0.001$)	7 (p = 0.001)							
Total (95% CI)		104		105	100.0%	0.04 (0.01 to 0.19)	♦	
Total events	0		29					
Heterogeneity: $\chi^2 = 0.16$, df = 2 ($p = 0.92$); $l^2 = 0\%$	p = 0.92;	P = 0%						
Test for overall effect: $z = 3.90$ ($p < 0.0001$)	0 (p < 0.0001)	_						
Test for subgroup differences: $\chi^2 = 0.02$, df = 1 ($p = 0.88$), $l^2 =$	$\chi^{2} = 0.02, df$	i = 1 (<i>p</i> = 0.8	38), <i>I</i> ² = 0%					
							0.01	10
							Favours both generations	Favours Mirena

Proportion discontinuing Mirena – 3 years

dy or subgroupEventsTotalVeightOdds ratioOdds ratioddy or subgroupEventsTotalEventsTotalWeightPeto, Fixed, 99% CIPeto, Fixed, 99% CI.3 First generation.3 First generation.3 100.0%0.04 (0.00 to 1.67)Peto, Fixed, 99% CIPeto, Fixed, 99% CI.1 events030930100.0%0.04 (0.00 to 1.67)Peto, Fixed, 99% CI.1 events0930100.0%0.04 (0.00 to 0.67)Peto, Fixed, 99% CI.1 events09.100.0%0.04 (0.00 to 0.67)Peto, Fixed, 99% CI.1 events09.100.0%.100.0%.100.0%.1 events09 <th></th> <th>Both generations</th> <th>erations</th> <th>Mirena</th> <th>na</th> <th></th> <th></th> <th></th> <th></th>		Both generations	erations	Mirena	na				
9 30 100.0% 30 100.0% 9	Study or subgroup		Total	Events	Total	Weight	Odds ratio Peto, Fixed, 99% CI	Odds ra Peto, Fixed,	atio 99% CI
0 30 9 30 100.0% 30 30 100.0% 0 9 the policable the zero of the second se	.3 First generatic	u n							
30 30 100.0% 9 (<i>p</i> = 0.03)	ittelsen 1998 ¹⁰⁵	0	30	б	30	100.0%	0.04 (0.00 to 1.67)	•	
(p = 0.03)	total (95% CI)		30		30	100.0%	0.04 (0.00 to 0.67)		
rogeneity: not applicable for overall effect: $z = 2.23$ ($p = 0.03$)	l events	0		ი					
for overall effect: $z = 2.23$ ($p = 0.03$)	rogeneity: not ap	plicable							
	for overall effect:	z = 2.23 (p =	0.03)						
								Eavours both generations	Eavours Mirana

	Both gene	Both generations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto, F	Peto odds ratio Peto, Fixed, 99% Cl
1.65.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect: not applicable	olicable							
1.65.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	0	0	0		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	0	0	0		Not estimable		
g. Barrington 2003 ⁸¹	0	0	0	0		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	0	0	0		Not estimable		
Subtotal (95% CI)		33		33		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Fest for overall effect: not applicable	olicable							
Total (95% CI)		128		128		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect [.] not applicable	olicable							
Test for subgroup differences: not applicable	not applicab	le						
							0.01 0.1	10
							:	:

Patients with adverse events – periprocedure (uterine perforation)

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Feto odds ratio Feto odds ratio 701al Weight Peto odds ratio 30 Not estimable 33 30 Not estimable Not estimable 31 Not estimable Not estimable 32 Not estimable Not estimable 33 Not estimable Not estimable 22 Not estimable Not estimable 23 Not estimable Not estimable 23 Not estimable Not estimable 25 Not estimable Not estimable 253 Not estimable Not estimable 26 Not estimable Not estimable 26 Not estimable Not estimable 36 Not estimable Not estimable 37 Not estimable Not estimable		Both generations	nerations	Mirena	na				
ioni	Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% Cl	tratio 99% CI
	1.66.1 First generation								
	a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
	b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
0 95 Not estimable 1 0 95 Not estimable 1 1 1 1 1 0 33 0 1 1 0 33 0 1 1 0 22 0 1 1 0 22 0 1 0 25 0 25 0 0 1 1 1 1 1 0 1 1 1 0 25 0 25 0 1 0 1 0 1 0 1 1 0 1 0 1 1 0 1 0 1 0 1 1 0 1 0 1 1 0 1 1 1 1 0 1 1 1 1 0 1 1 1 1 0 0 1 1 1 0 0 0 0 1 0 0 0 0 1 0 0 0 0	c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
pplicable $t: tot applicable$ t: tot applicable $t: tot applicable$ t: not applicable 0 33 0 33 Not estimable 0 22 Not estimable 0 22 0 22 Not estimable 0 22 0 22 Not estimable 157 0 25 0 25 Not estimable 157 0 25 0 256 Not estimable 157 0 256 Not estimable 157 0 256 Not estimable 158 Not estimable 15	Subtotal (95% CI)		95		95		Not estimable		
pricable :: not applicable :: not applicable :: not applicable :: not applicable 1 : not applicable 0 33 0 33 Not estimable Not estimable 0 22 0 22 Not estimable 0 25 0 22 Not estimable 157 0 25 0 256 Not estimable 157 158 Not estimable 158 Not	Total events	0		0					
the transform the transform of the transformation of the transf	Heterogeneity: not applica	tble							
ration033033Not estimable022022Not estimable024025Not estimable025025Not estimable025025Not estimable01570158Not estimable01570158Not estimable01570158Not estimable02520253Not estimable02520253Not estimable0158Not estimableNot estimable158158Not estimable02520253025302530158Not estimable0158Not estimable0158Not estimable0158Not estimable02531000100253002530100	Test for overall effect: not	applicable							
	1.66.2 Second generation	E							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	I. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	l. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
157 158 Not estimable 0 0 applicable act: not applicable 252 253 Not estimable 0 0 252 253 Not estimable applicable 0 0 252 253 Not estimable applicable 0 0 0 10 10 applicable 0 0 10 10 10 affferences: not applicable 0 10 10 10	ı. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
0 0 0 licable 252 253 Not estimable 0 252 0 253 Not estimable olicable contraction of the structure of the s	ubtotal (95% CI)		157		158		Not estimable		
licable 0 252 253 Not estimable 0 0 licable i not applicable	otal events	0		0					
licable 252 253 Not estimable 0 0 0 Iicable i not applicable	leterogeneity: not applica	tble							
0 252 253 Not estimable blicable : not applicable	est for overall effect: not	applicable							
0 0 Jicable : not applicable	otal (95% CI)		252		253		Not estimable		
licable : not applicable	otal events	0		0					
	Heterogeneity: not applica Test for overall effect: not	tble applicable							
0.01 0.1 1 Favours both generations	Test for subgroup differen	ces: not applical	ble						
Eavours both generations									100
							Favo	Favours both generations	Favours Mirena

Patients with adverse events – periprocedure (cervical laceration)

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99%	Peto odds ratio Peto, Fixed, 99% Cl
1.67.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	olicable							
1.67.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	olicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable Test for subgroup differences: not applicable	olicable : not applicab	le						
						ľ	0.01 0.1 1	1 10 100
						-	Favours both generations	Favours Mirena

Patients with adverse events – periprocedure (anaesthesia problems)

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	Both generations	erations	Mirena	ы				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto od Peto, Fixe	Peto odds ratio Peto, Fixed, 99% Cl
1.68.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	θ							
Test for overall effect: not applicable	oplicable							
1.68.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	Θ							
Test for overall effect: not applicable	oplicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	Ð							
Test for overall effect: not applicable	oplicable							
Test for subgroup differences: not applicable	s: not applicat	ole						
							0.01 0.1	10 100
							Favours both generations	Favours Mirena

Patients with adverse events – periprocedure (excessive bleeding)

196

	Both gene	Both generations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto c Peto, Fi	Peto odds ratio Peto, Fixed, 99% Cl
1.69.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	licable							
1.69.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	licable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall offect: not applicable	ahaci							
Test for subgroup differences: not applicable	not applicab	le						
							0.01	10

Patients with adverse events – periprocedure (fluid overload)

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Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99%	Peto odds ratio Peto, Fixed, 99% Cl
1.70.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	le							
Test for overall effect: not applicable	tpplicable							
1.70.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	le							
Test for overall effect: not applicable	tpplicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect: not applicable	ole upolicable							
Test for subgroup differences: not applicable	es: not applicat	ole						
							0.01	100
							Favours both generations	Favours Mirena

Patients with adverse events – periprocedure (excessive visceral damage)

	Both generations	erations	Mirena	ena				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% CI	ls ratio 1, 99% CI
1.71.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect: not applicable	licable							
1.71.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	licable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for subgroup differences: not applicable	not applicable	le						
							0.01	10

Patients with adverse events – periprocedure (procedure abandoned)

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Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% CI	ratio 99% CI
1.72.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	e							
Test for overall effect: not applicable	oplicable							
1.72.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	e Solicoblo							
rest for overall effect: not applicable	oplicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall offect: not applicable	e anlicabla							
Test for subgroup differences: not applicable	opilcable ss: not applicat	ole						
							0.01 0.1 1	10 100
							Former heth concertance	

Patients with adverse events – periprocedure (procedure converted to hysterectomy)

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% Cl	ds ratio d, 99% Cl
1.73.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	:							
Test for overall effect: not applicable	plicable							
1.73.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	plicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect: not applicable	nicabla							
Test for subgroup differences: not applicable	s: not applicab	le						
							0.01	100
							aen	urs M

Patients with adverse events – periprocedure (failed insert)

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	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% CI	atio 9% Cl
1.74.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	¢.							
Test for overall effect: not applicable	plicable							
1.74.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	0							
Test for overall effect: not applicable	plicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	0							
Test for overall effect: not applicable	plicable							
Test for subgroup differences: not applicable	s: not applicat	ole						
							0.01 0.1 1	100
							Favours both generations	Favours Mirena

Patients with adverse events – postoperatively (urinary tract infection)

	both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% CI	ds ratio d, 99% CI
1.75.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect: not applicable	e plicable							
1.75.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	plicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable Test for suboroup differences: not applicable	plicable « not annlicab	<u>a</u>						
		2						
							0.01 0.1 1	100 100
							Favours both generations	Favours Mirena

Patients with adverse events – postoperatively (deep-vein thrombosis)

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(further bleeding)
postoperatively (
S I
th adverse events

Study or subaroup	Fvents	Total	Events	Total	Weight	Peto odds ratio	Peto odds ratio Peto, Fixed, 99% CI
decision of comp							
1.76.1 First generation							
a. Malak 2006 ¹⁰⁴	5	30	0	30	70.3%	8.55 (0.79 to 92.91)	
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30	29.7%	7.65 (0.19 to 301.43)	
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable	
Subtotal (95% CI)		95		95	100.0%	8.27 (1.80 to 37.91)	
Total events	7		0				
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($p = 0.95$); $l^2 = 0.\%$	1 (p = 0.95); f	² = 0%					
Test for overall effect: $z = 2.72$ ($p = 0.007$)	(p = 0.007)						
1.76.2 Second generation							
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable	
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable	
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable	
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable	
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable	
Subtotal (95% CI)		157		158		Not estimable	
Total events	0		0				
Heterogeneity: not applicable							
Test for overall effect: not applicable	licable						

Study or subgroup	,)		na				
	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% Cl	Peto o Peto, Fix	Peto odds ratio Peto, Fixed, 99% Cl
1.77.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	cable							
1.77.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	cable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable Test for subgroup differences: not applicable	cable not applicabl	Ø						
							100	10-
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Patients with adverse events – postoperatively (sepsis)

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	Both generations	lerations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	ds ratio d, 99% Cl
1.78.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	ole							
Test for overall effect: not applicable	applicable							
1.78.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	ole							
Test for overall effect: not applicable	applicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	ole							
Test for overall effect: not applicable	applicable							
Test for subgroup differences: not applicable	ses: not applicat	ole						
							0.01 0.1	10
							Favours both generations	Favours Mirena

Patients with adverse events - postoperatively (pyrexia)

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		born generations	Mirena	na				
						Peto odds ratio	Peto c	Peto odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 99% CI	Peto, Fi)	Peto, Fixed, 99% CI
1.79.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30	29.3%	7.65 (0.19 to 301.43)		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95	29.3%	7.65 (0.47 to 125.22)		
Total events	0		0					
Heterogeneity: not applicable Test for overall effect: $z = 1.43$ ($p = 0.15$)	e 13 (<i>p</i> = 0.15)							
1.79.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	S	41	0	42	70.7%	8.40 (0.79 to 89.18)		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		I
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158	70.7%	8.40 (1.39 to 50.69)		
Total events	S		0					•
Heterogeneity: not applicable Test for overall effect: $z = 2.32$ ($p = 0.02$)	e 32 (<i>p</i> = 0.02)							
Total (95% CI)		252		253	100.0%	8.17 (1.80 to 37.07)		
Total events	2		0					
Heterogeneity: $\chi^z = 0.00$, df = 1 ($p = 0.96$); $F = 0\%$ Test for overall effect: $\tau = 2.72$ ($n = 0.006$)	= 1 (p = 0.96); ? (p = 0.006)	F = 0%						
Test for subgroup differences: $\chi^2 = 0.00$, df = 1 ($p = 0.96$); l^2	s: $\chi^2 = 0.00$, d1	= 1 (p = 0.9	36); <i>I</i> ² = 0%					
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Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	ds ratio d, 99% CI
1.80.1 First generation								
a. Malak 2006 ¹⁰⁴	÷	30	0	30	33.7%	7.39 (0.04 to 1276.22)		
b. Kittelsen 1998 ¹⁰⁵	2	30	0	30	66.3%	7.65 (0.19 to 301.43)		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		I
Subtotal (95% CI)		95		95	100.0%	7.56 (0.78 to 73.62)	-	
Total events	ო		0					
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($p = 0.99$); $l^2 = 0\%$	If = 1 ($p = 0.99$);	$P^{2} = 0\%$						
Test for overall effect: $z = 1.74$ ($\rho = 0.08$)	$1.74 \ (p = 0.08)$							
1.80.2 Second generation	-							
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	ble							
Test for overall effect: not applicable	applicable							
Total (95% CI)		252		253	100.0%	7.56 (0.78 to 73.62)		
Total events	ო		0					
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($\rho = 0.99$); $\beta = 0\%$ Test for overall effect: $z = 1.74$ ($\rho = 0.08$)	If = 1 ($p = 0.99$); 1.74 ($p = 0.08$)	<i>P</i> ² = 0%						
Test for subgroup differences: not applicable	ces: not applicab	ole						
							0.01	100

Study or subgroupEventsTotalEventsTotal1.81.1 First generation a. Malak 20061041.81.1 First generation a. Malak 200610443030b. Kittelsen 1998105 c. Crosignani 199745 D. Kittelsen 19981050333030b. Kittelsen 1998105 c. Crosignani 199745 D. Kittelsen 19981050333030b. Kittelsen 1998105 c. Crosignani 199745 D. Kittelsen 19981050333030c. Crosignani 199745 D. Colal events495035Subtotal (95% CI) Total events022022b. Soysal 2002106 f. Busfield 2006107 G. Barrington 200381 f. Busfield 200610702442c. Tam 2006108 G. D. Ob025025h. Soysal 2002106 f. Busfield 2006107025025h. Soysal 2002106 f. Busfield 2006107025025f. Busfield 2006107 f. Busfield 2006107025025f. Soysal 2002108 f. Busfield 2006107025025f. Soysal 2002108 f. CI)025025f. Soysal 2002108 f. Busfield 20061070249025f. Soysal 2002108 f. Subtotal (95% CI)02490253f. Sotal 2002108 f. Subtotal events02490253f. Sotal 2002108 f. Subtotal events02490253f. Sotal 2002108 f. Sotal events02490	Mirena		
ion 4 30 0 0 0 35 0 0 35 0 95 pplicable 4 95 0 $t: z = 2.05 (p = 0.04)$ 33 0 0 station 0 32 0 0 o 22 0 24 0 o 0 249 0 1 o 0 249 0 2 pplicable 0 0 249 2 t: z = 2.05 (p = 0.04) 154 0 1 t: rot applicable 0 249 0 1 f: rot applicable 0 154 0 1 t: r z = 2.05 (p = 0.04) 1 154 0 1		Peto odds ratio Peto, Fixed, 99% Cl	Peto odds ratio Peto, Fixed, 99% CI
0.04) 0 2.05 0 2.0 0 0 2.10 0			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	30 100.0%	8.22 (0.58 to 115.71)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		Not estimable	
95 95 95 $zt z = 2.05 (p = 0.04)$ $zt = 2.05 (p = 0.04)$ $zt = 2.05 (p = 0.04)$ station 0 30 0 station 0 30 0 0 22 0 0 0 22 0 0 0 0 25 0 0 0 25 0 0 0 249 0 0 0 249 0 0 0 0 0 pplicable 0 0 154 1 $z = 2.05 (p = 0.04)$ f: $z = 2.05 (p = 0.04)$ f: $z = 2.05 (p = 0.04)$ 1	35	Not estimable	
pplicable 4 pplicable 4 ct. $z = 2.05$ ($p = 0.04$) ct.	95 100.0%	8.22 (1.10 to 61.49)	
pplicable :t: $z = 2.05$ ($p = 0.04$) eration 0 30 0 0 222 0 0 255 0 154 0 154 0 pplicable :t: not applicable :t: rot applicable t: $z = 2.05$ ($p = 0.04$) f: $z = 2.05$ ($p = 0.04$)			
it $z = 2.05$ ($p = 0.04$) eration 0 30 0 0 22 0 0 25 0 0 25 0 0 154 0 it not applicable it not applicable 0 249 0 pplicable 0 249 0 0 249 0 0 249 0 0 249 0 0 249 0 0 156 ($p = 0.04$)			
station 0 30 0 0 22 0 0 0 22 0 41 0 0 25 0 36 0 0 25 0 36 0 0 25 0 154 0 0 0 154 0 0 154 0 249 0 1 1 249 0 0 1 1 1 2 249 0 1 1 1 1 1 2 249 0 1			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	33	Not estimable	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	22	Not estimable	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	42	Not estimable	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	25	Not estimable	
applicable 0 154 0 applicable 0 0 0 249 0 0 0 0 0 0 0 0 0 0	36	Not estimable	
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	158	Not estimable	
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effect: not applicable 249 0 0 0 0 0 0 0 0 0 effect: $z = 2.05$ ($p = 0.04$)			
$\begin{array}{c} 249 \\ 0 \\ \text{not applicable} \\ \text{effect: } z = 2.05 \\ (p = 0.04) \\ \text{sound fifterences not applicable} \end{array}$			
Total events 0 0 Total events 0 $+$ deterogeneity: not applicable fest for overall effect: $z = 2.05$ ($p = 0.04$)	253 100.0%	8.22 (1.10 to 61.49)	
Heterogeneity: not applicable fest for overall effect: $z = 2.05$ ($p = 0.04$) fest for subsciences: not applicable			
Test for subtround differences not annlicable			
		0.01	0.1 1 10 100
		Favours both generations	Favours Mi

Patients with adverse events – postoperatively (abdominal pain)

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	Both generations	lerations	Mirena	а				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	s ratio , 99% Cl
1.82.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	le							
Test for overall effect: not applicable	tpplicable							
1.82.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	le							
Test for overall effect: not applicable	tpplicable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	le							
Test for overall effect: not applicable	ipplicable							
Test for subgroup differences: not applicable	es: not applicat	ole						
							0.01 0.1 1	10 100
							Favours both generations	Favours Mirena

Patients with adverse events – postoperatively (foul discharge)

210

	Both generations	erations	Mirena	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto o Peto, Fix	Peto odds ratio Peto, Fixed, 99% CI
1.83.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	licable							
1.83.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	licable							
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable Test for suboroup differences: not applicable	licable not applicab	le						
	-							
							0.01 0.1	1 10 100
							Favours both generations	Favours Mirena

Patients with adverse events – postoperatively (visceral damage)

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Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% CI	ratio 9% CI
1.84.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95		Not estimable		
Total events	0		0					
Heterogeneity: not applicable	:							
	hindable							
1.84.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42		Not estimable		
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158		Not estimable		
Total events	0		0					
Heterogeneity: not applicable								
Test for overall effect: not applicable	plicable							
Test for subgroup differences: not applicable	s: not applicat	ole						
Total (95% CI)		252		253		Not estimable		
Total events	0		0					
Heterogeneity: not applicable Test for overall offect: not applicable	elicable							
Test for subgroup differences: not applicable	s: not applicat	ole						
							0.01	10 100

Patients with adverse events - postoperatively (infection)

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migrated
postoperatively (
lverse events -
Patients with ao

			MILENA	na				
Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto, F	Peto odds ratio Peto, Fixed, 99% CI
1.85.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	0	30		Not estimable		
b. Kittelsen 1998 ¹⁰⁵	0	30	-	30	14.4%	0.14 (0.00 to 23.37)	Ļ	
c. Crosignani 1997 ⁴⁵	0	35	-	35	14.4%	0.14 (0.00 to 23.37)	Ļ	
Subtotal (95% CI)		95		95	28.8%	0.14 (0.01 to 2.16)		
Total events	0		0					
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($p = 1.00$); $\beta^2 = 0\%$ Test for overall effect: $z = 1.41$ ($p = 0.16$)	$f = 1 \ (p = 1.00);$ 1.41 $(p = 0.16)$	f ² = 0%						
1.85.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	-	33	14.4%	0.14 (0.00 to 23.37)	+	
e. Tam 2006 ¹⁰⁹	0	22	0	22	28.1%	0.13 (0.00 to 5.15)	+	
f. Busfield 2006 ¹⁰⁷	0	41	÷	42	14.4%	0.14 (0.00 to 23.95)	+	
g. Barrington 2003 ⁸¹	0	25	0	25		Not estimable		
h. Soysal 2002 ¹⁰⁶	0	36	-	36	14.4%	0.14 (0.00 to 23.37)	Ļ	
Subtotal (95% CI)		157		158	71.2%	0.13 (0.02 to 0.78)		
Total events	0		5)	
Heterogeneity: $\chi^2 = 0.00$, df = 3 ($p = 1.00$); $l^2 = 0\%$ Test for overall effect: $z = 2.24$ ($p = 0.03$)	f = 3 (p = 1.00); 2.24 (p = 0.03)	<i>P</i> ² = 0%						
Total (95% CI)		252		253	100.0%	0.13 (0.03 to 0.59)		
Total events	0	ç	7					
Heterogeneity: $\chi^{z} = 0.00$, df = 5 ($p = 1.00$); $l^{z} = 0\%$ Test for overall effect: $z = 2.65$ ($p = 0.008$)	$f = 5 \ (p = 1.00);$ 2.65 $(p = 0.008)$	<i>I</i> ^z = 0%	ç					
Test for subgroup differences: χ^2 = 0.00, df = 1 ($ ho$ = 0.99)	tes: $\chi^2 = 0.00$, d1	= 1 (p = 0.9)	99); <i>I</i> ² = 0%					
							0.01 0.1	10-100
							Equitor both according	

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Study or subgroup	Events	Total	Events	Total	Weight	Peto odds ratio Peto, Fixed, 99% CI	Peto odds ratio Peto, Fixed, 99% Cl	ratio 99% CI
1.86.1 First generation								
a. Malak 2006 ¹⁰⁴	0	30	4	30	49.1%	0.12 (0.01 to 1.71)		
b. Kittelsen 1998 ¹⁰⁵	0	30	0	30		Not estimable		
c. Crosignani 1997 ⁴⁵	0	35	0	35		Not estimable		
Subtotal (95% CI)		95		95	49.1%	0.12 (0.02 to 0.91)		
Total events	0		4					
Heterogeneity: not applicable	Ð							
Test for overall effect: $z = 2.05$ ($\rho = 0.04$)	05 (<i>p</i> = 0.04)							
1.86.2 Second generation								
d. Shaw 2007 ¹⁰⁸	0	33	0	33		Not estimable		
e. Tam 2006 ¹⁰⁹	0	22	0	22		Not estimable		
f. Busfield 2006 ¹⁰⁷	0	41	0	42	25.6%	0.14 (0.00 to 5.28)	•	
g. Barrington 2003 ⁸¹	0	25	2	25	25.3%	0.13 (0.00 to 5.15)	•	1
h. Soysal 2002 ¹⁰⁶	0	36	0	36		Not estimable		
Subtotal (95% CI)		157		158	50.9%	0.13 (0.02 to 0.96)		
Total events	0		4)	
Heterogeneity: $\chi^2 = 0.00$, df = 1 ($p = 0.98$); $\beta = 0\%$	$= 1 \ (p = 0.98);$	$P^{2} = 0\%$						
Test for overall effect: $z = 2.00 \ (\rho = 0.05)$	$00 \ (p = 0.05)$							
Total (95% CI)		252		253	100.0%	0.13 (0.03 to 0.52)	¢	
Total events	0		80					
Heterogeneity: $\chi^2 = 0.00$, df = 2 ($p = 1.00$); $\beta = 0\%$ Test for overall effect: $z = 2$ 87 ($n = 0.004$)	= 2 (p = 1.00);	$l^{2} = 0\%$						
Test for subgroup differences: $\chi^2 = 0.00$, df = 1 ($p = 0.95$); $l^2 =$	s: $\chi^2 = 0.00$, d	f = 1 (p = 0)	95); <i>I</i> ² = 0%					
							0.01 0.1 1	100

Appendix 8

Pooled results for Mirena versus second-generation endometrial destruction

Appendix 8.1 Quality of life and clinical outcomes

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95%Cl)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
Proportion amenorrhoea	6 months	2 (107)	_	1.76 (0.42 to 7.34)	0.4	0.5/0
	12 months	3 (127)	-	2.43 (0.61 to 9.67)	0.2	0.02/82
	2 years	1 (39)	_	5.99 (1.43 to 25.1)	0.01	-
Proportion with heavy bleeding	6 months	3 (162)	_	4.30 (1.76 to 10.6)	0.001	0.6/0
	12 months	4 (200)	-	1.54 (0.56 to 4.24)	0.4	0.02/75
	2 years	1 (39)	_	13.0 (2.00 to 84.2)	0.007	-
Bleeding score (change)	6 months	4 (169)	10 (-37 to 57)	_	0.7	0.2/29
	12 months	4 (168)	-35 (-75 to 5)	_	0.09	0.3/26
	2 years	1 (39)	117 (–113 to 347)	_	0.7	_
Proportion dysmenorrhoea	6 months	1 (83)	-	0.78 (0.33 to 1.85)	0.6	_
	12 months	1 (48)	-	0.77 (0.25 to 2.43)	0.7	_
	2 years	1 (83)	-	0.97 (0.31 to 3.05)	1.0	_
SF-36 general health (absolute)	12 months	3 (147)	3.7 (-2.7 to 10.1)	_	0.3	0.006/81
SF-36 physical function (absolute)		3 (146)	-0.9 (-6.9 to 5.0)	_	0.8	0.6/0
SF-36 role physical (absolute)		3 (147)	-9.6 (-20.5 to 1.3)	_	0.08	0.1/56
SF-36 role emotional (absolute)		3 (147)	5.7 (-5.4 to 16.8)	_	0.3	0.02/75
SF-36 mental health (absolute)		3 (146)	-0.8 (-6.7 to 5.1)	_	0.8	0.02/73
SF-36 social function (absolute)		3 (147)	2.3 (-3.6 to 8.2)	_	0.4	0.06/65
SF-36 vitality (absolute)		3 (146)	0.01 (-5.9 to 6.1)	_	1.0	0.3/7
SF-36 pain (absolute)		3 (147)	1.1 (-6.6 to 8.9)	_	0.8	1.0/0
SF-36 general health (absolute)	2 years	1 (49)	1.7 (–10.3 to 13.7)	_	0.8	-
SF-36 physical function (absolute)		1 (50)	-1.2 (-8.0 to 5.6)	_	0.7	-
SF-36 role physical (absolute)		1 (50)	8.2 (-4.9 to 21.3)	_	0.2	-
SF-36 role emotional (absolute)		1 (50)	-1.0 (-16.4 to 14.4)	_	0.9	-
SF-36 mental health (absolute)		1 (49)	-0.4 (-8.9 to 8.1)	_	0.9	_
SF-36 social function (absolute)		1 (50)	2.2 (-7.0 to 11.4)	_	0.6	_
SF-36 vitality (absolute)		1 (49)	1.8 (-8.6 to 12.2)	_	0.7	_
SF-36 pain (absolute)		1 (50)	8.7 (-2.3 to 19.7)	_	0.1	_

continued

	Time point	Trials (no.)	WMD (95% CI) ^a	OR (95%Cl)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
SF-36 general health (change)	12 months	2 (81)	1.9 (-6.5 to 10.4)	_	0.7	0.1/59
SF-36 physical function (change)		2 (81)	-0.5 (-10.1 to 9.2)	_	0.9	0.5/0
SF-36 role physical (change)		2 (82)	-7.0 (-28.9 to 14.9)	-	0.5	0.8/0
SF-36 role emotional (change)		2 (82)	1.8 (–18.5 to 22.1)	_	0.9	0.04/75
SF-36 mental health (change)		2 (81)	-2.1 (-9.6 to 5.4)	_	0.6	0.03/78
SF-36 social function (change)		2 (82)	-1.9 (-10.9 to 7.1)	_	0.7	0.2/49
SF-36 vitality (change)		2 (80)	-2.0 (-12.2 to 8.2)	_	0.7	0.7/0
SF-36 pain (change)		2 (82)	-8.0 (-20.0 to 3.9)	_	0.2	0.6/0
SF-36 general health (change)	2 years	1 (49)	-4.1 (-14.0 to 5.8)	_	0.4	_
SF-36 physical function (change)		1 (50)	-4.4 (-14.9 to 6.1)	_	0.4	_
SF-36 role physical (change)		1 (50)	-1.1 (-28.4 to 26.2)	_	0.9	_
SF-36 role emotional (change)		1 (50)	2.0 (–23.3 to 27.3)	_	0.9	_
SF-36 mental health (change)		1 (49)	-5.7 (-14.2 to 2.8)	_	0.2	_
SF-36 social function (change)		1 (50)	-4.9 (-17.6 to 7.8)	_	0.5	_
SF-36 vitality (change)		1 (49)	-9.6 (-20.4 to 1.2)	_	0.08	_
SF-36 pain (change)		1 (50)	1.3 (–17.8 to 15.2)	-	0.9	_
Hysterectomy after EA/Mirena	6 months	1 (50)	_	1.79 (0.40 to 8.01)	0.5	_
	12 months	2 (105)	_	0.22 (0.05 to 1.04)	0.06	0.9/0
	2 years	2 (146)	-	0.86 (0.33 to 0.21)	0.8	0.2/41
		Trials	Frequency			
Discontinued Mirena	6 months	1	3/42 (7%)			
	12 months	3	18/96 (19%)			
	2 years	2	21/75 (28%)			
EA after Mirena	12 months	1	3/18 (17%)			
	2 years	1	4/42 (10%)			
	6 months	1	3/25 (12%)			
Hysterectomy after Mirena	12 months	2	6/54 (11%)			
	2 years	2	11/75 (15%)			

	Trials	Frequency (second- generation: max. 157; Mirena: max. 158)	OR (95% CI)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>I</i> ² (%)
Periprocedure complications					
Uterine perforation (second-generation, Mirena)	5	0; 0	_	_	_
Cervical laceration (second-generation, Mirena)	5	0; 0	_	-	_
Anaesthesia problems (second-generation)	5	0	_	-	_
Excessive bleeding (second-generation)	5	0	_	-	_
Fluid overload (second-generation)	5	0	_	-	_
Visceral damage (second-generation)	5	0	_	-	_
Procedure abandoned (second-generation)	5	0	_	-	_
Converted to hysterectomy (second-generation)	5	0	_	-	_
Failed to insert (Mirena)	5	0	_	_	_

	Trials	Frequency (second- generation: max. 157; Mirena: max. 158)	OR (95% CI)⁵	<i>p</i> -value	Hetero (<i>p</i>)/ <i>l</i> ² (%
Further complications (< 1 month)					
Urinary tract infection (second-generation)	5	0	_	_	-
Deep-vein thrombosis (second-generation)	5	0	_	-	_
Further bleeding (second-generation)	5	0	_	-	_
Sepsis (second-generation)	5	0	_	-	_
Pyrexia (second-generation)	5	0	_	-	_
Endometriosis (second-generation)	5	0	_	-	_
Haematomata (second-generation)	5	0	_	-	_
Abdominal pain (second-generation)	5	0	_	-	_
Foul discharge (second-generation)	5	0	_	-	_
Visceral damage (second-generation)	5	0	_	-	_
Infection (Mirena)	5	0	_	-	_
Expelled/migrated (Mirena)	5	5	_	-	_
Removed before 3 months (MIrena)	5	4	_	-	_

 $\begin{array}{ll} a & <0 \mbox{ favours second-generation EA, } >0 \mbox{ favours Mirena.} \\ b & <1 \mbox{ favours second-generation EA, } >1 \mbox{ favours Mirena.} \end{array}$

Appendix 9 (for Chapter 5)

Survey of gynaecologists with expertise in minimal access surgery

Dear Dr _____

We would value your opinion as an expert in gynaecological surgery on the outcome of a recent Department of Health (Health Technology Assessment Panel)-funded systematic review of the evidence for the treatment of heavy menstrual bleeding (HMB). Our aim was to evaluate the comparative effectiveness and cost-effectiveness of hysterectomy, Mirena[®] and second-generation endometrial ablation (microwave, balloon and NovaSure). We aggregated and analysed results of trials comparing endometrial ablations with hysterectomy and each other and also trials comparing Mirena[®] with hysterectomy and with ablation. There were very few trials in the last category.

We would be grateful if you could read the summary of our key findings on the comparative clinical effectiveness of the alternative treatments for HMB and answer the questions below.

Your answers will provide much needed guidance to us in interpreting the results of our review and will inform the recommendation in our final report to the HTA.

Thank you for taking the time to read this letter

On behalf of the HMB IPD Collaborative Group

Kevin Cooper, Patrick Chien, Peter O'Donovan, Khalid Khan, Siladitya Bhattacharya

Our findings (based on individual patient data and aggregated data meta-analysis of randomised trials) suggest:

* At 12 months after treatment, more women (21/382 or 12.6% vs 57/454 or 5.3%) were dissatisfied with first-generation hysteroscopic techniques than hysterectomy (OR 2.46; 95% CI 1.54 to 3.93; p = 0.0002), but hospital stay (WMD 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.

* Indirect estimates (*Figure 6*) suggest hysterectomy is also preferable to second-generation ED (OR 2.32; 95% CI 1.27 to 4.24; p = 0.006) in terms of patient dissatisfaction.

* Hysterectomy is cheaper and more effective than either first- or second-generation endometrial ablation but carries a higher risk of complications.

* Satisfaction rates were comparable between first- and second-generation techniques (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; p < 0.00001) and women recovered sooner (WMD 0.48 days; 95% CI 0.20 to 0.75; p = 0.0008) with fewer procedural complications.

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* Second-generation techniques are cheaper and more effective than first-generation techniques.

* There are few comparisons of Mirena[®] versus 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 which are similar to second-generation ED (18.1% vs 22.5%; OR 0.76; 95% CI 0.38–1.53; p = 0.4).

* Owing to a paucity of trials, the evidence to suggest hysterectomy is preferable to Mirena[®] is weak (OR 2.22; 95% CI 0.94–5.29; p = 0.07). In a single study comparing hysterectomy with Mirena[®], QoL was similar in both groups although residual pelvic pain was less common after hysterectomy.

* Hysterectomy is more expensive than Mirena[®] (ICER = 1600).

Based on these data, could you please answer the questions below by deleting all responses other than the most appropriate one.

Please send in your answers by replying to this email:

1: What would you consider to be first-line treatment in women with HMB and failed oral medical treatment associated with no obvious clinical abnormalities.

N.B. Any uterine fibroids present are < 3 cm and do not impinge on the endometrial cavity.

- i. * Mirena®
- ii. * First-generation endometrial ablation
- iii. * Second-generation endometrial ablation
- iv. * Hysterectomy
- 2: If the first treatment fails, what in your view should be the next treatment:
 - i. * Mirena®
 - ii. * Second-generation ablation
 - iii. * First-generation ablation (e.g. rollerball)
 - iv. * Hysterectomy
- 3: If the second treatment fails what, in your view, should be the next line treatment
 - i. * Mirena®
 - ii. * Repeat second-generation ablation
 - iii. * First-generation ablation (e.g. rollerball)
 - iv. * Hysterectomy

Appendix 10 PRISMA checklist

Section/topic	#	Checklist item	Reported or page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis or both	11
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. URL), and, if available, provide registration information including registration number	
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. P) for each meta-analysis	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta- regression), if done, indicating which were pre-specified	13, 14

continued

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Section/topic	#	Checklist item	Reported on page #
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	13, 14, <i>Figure 1</i>
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see <i>ltem 12</i>)	15,16, Figure 2, Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group; (b) effect estimates and confidence intervals, ideally with a forest plot	17–22, Figures 3–6, Appendices 4–8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	17–22, Figures 3–6, Appendices 4–8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	17–22
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression) (see <i>Item 16</i>)	17–22
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health-care providers, users and policy makers)	22, 23
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias) and at review level (e.g. incomplete retrieval of identified research, reporting bias)	23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	24
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	N/A

For more information, visit: www.prisma-statement.org.

Appendix 11

Protocol

Maly Manuh

Signed: Siladitya Bhattacharya

Dated 5 February 2010

The effectiveness of hysterectomy, ablation and levonorgestrelreleasing intra-uterine device in the management of heavy menstrual bleeding

Background

Heavy menstrual bleeding (menorrhagia) is a common problem. It affects nearly one-third of women (Corrado, 1990; Rees, 1991) and prompts 5% of all women of reproductive age to consult their general practitioners with menstrual problems. Menstrual disorders account for 20% of gynaecology outpatient referrals and are responsible for over 23,000 hysterectomies each year in England. One in five women in the United Kingdom is likely to have had a hysterectomy by the age of 55 years (Vessey *et al.*, 1992). HMB affects many aspects of everyday life – including work as well as social activities – and leads to a measurable reduction in QoL.

A literature search was undertaken using the Cochrane Library, MEDLINE (1966–2006), EMBASE (1980 to July 2006) and CINAHL (1982 to July 2006) using the following terms: menorrhagia, hypermenorrhea, (excessive) menstrual blood loss, heavy menstrual bleeding, dysfunctional uterine bleeding, hysterectomy, vaginal hysterectomy, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, transcervical resection of the endometrium, transcervical resection of the endometrium, endometrial ablation, laser ablation, hysteroscopy, electrosurgery, rollerball, (thermal) balloon, hypertherm(ia), thermotherapy, photodynamic therapy, phototherapy, cryoablation, microwave endometrial ablation, radiofrequency, saline irrigation, laser interstitial, ThermaChoice[®], Cavaterm[™], ELITT, Vesta, NovaSure, Microsulis, Cryogen. The metaregister of controlled trials and the ISRCTN register were searched for any trials with menorrhagia and endometrial ablation as keywords.

Current recommendations in the UK promote medical methods for the initial management of HMB. Mefenamic acid, tranexamic acid and the combined oral pill are considered to be suitable first-line drugs [Royal College of Obstetricians and Gynaecologists (RCOG) guideline, 1998]. The LNG-releasing IUS (Mirena[®]) is an effective non-surgical treatment which is reversible and fertility-sparing. It reduces estimated menstrual blood loss by up to 96% by 12 months, with up to 44% of users reporting amenorrhoea (Milsom *et al.*, 1991; Lahteenmaki *et al.*, 1998), at a cost which is one-third that for hysterectomy (Hurskainen *et al.*, 2001). Despite the availability of these options, long-term medical treatment is unsuccessful or unacceptable in many and surgery is required (Cooper *et al.*, 2001).

Hysterectomy offers a definitive treatment for menorrhagia and guarantees amenorrhoea, but it is particularly invasive and carries significant morbidity (Lethaby *et al.*, 1999). Overall 1 in 30 women suffers a major adverse event, and the mortality rate is 0.4–1.1 per 1000 operations. The need for GA, prolonged hospital stay and delayed recovery also makes hysterectomy an expensive treatment (Cameron *et al.*, 1996).

Endometrial ablative techniques aimed at destruction of the functionally active endometrium along with some of the underlying myometrium (Duffy *et al.*, 1991; Duffy *et al.*, 1992) offer a conservative surgical alternative to hysterectomy. The first-generation ablative techniques including endometrial laser ablation (ELA) (Goldrath and Fuller, 1981; Davis, 1989), TCRE (Magos *et al.*, 1989) and REA were all endoscopic procedures. Although they do not guarantee amenorrhoea, their effectiveness (in comparison with hysterectomy – the existing gold standard) has been demonstrated in a number of RCTs (Gannon *et al.*, 1991; Dwyer *et al.*, 1993; Pinion *et al.*, 1994, O'Connor *et al.*, 1997; Crosignani *et al.*, 1997; Aberdeen Endometrial Ablation Trials Group, 1999).

National audits (Overton *et al.*, 1997; Scottish Hysteroscopy Audit Group, 1995) revealed that although first-generation ablative techniques were less morbid than hysterectomy they were associated with a number of complications including uterine perforation, cervical laceration, false passage creation, haemorrhage, sepsis and bowel injury. In addition they were also related to fluid overload associated with the use of 1.5% urological glycine (non-ionic) irrigation fluid in TCRE and RBA, resulting in serious and occasionally fatal consequences due to hyponatraemia (Arrief and Ayus, 1993; Rosenberg, 1995). Mortality from these techniques has been estimated at 0.26 per 1000 (Overton *et al.*, 1997; Scottish Hysteroscopy Audit Group, 1995).

Second-generation ablative techniques represent simpler, quicker and potentially more efficient means of treating menorrhagia, which require less skill on the part of the operator. Examples of second-generation ablative techniques are fluid-filled TBEA, radiofrequency (thermoregulated) balloon EA, hydrothermal EA, three-dimensional bipolar radiofrequency EA, MEA, diode laser hyperthermy, cryoablation and photodynamic therapy. The most common techniques in the UK are TBEA (ThermaChoice and Cavaterm) (Loffer, 2001; Loffer and Grainger, 2002; Meyer *et al.*, 1998) and MEA (Cooper *et al.*, 1999; Bain *et al.*, 2002), while the NovaSure device (Cooper *et al.*, 2002) is gaining in popularity. TBEA destroys the endometrium by means of heated liquid within a balloon inserted into the uterine cavity. It cannot be used in women with large or irregular uterine cavities. MEA uses microwave energy (at a frequency of 9.2 GHz) to destroy the endometrium. Complications associated with second-generation techniques include equipment failure, uterine infection, perforation, visceral burn, bleeding and cyclical pain. A limited number of randomised trials indicate that these procedures appear to be as effective as first-generation ablative techniques (Lethaby *et al.*, 2005). In addition, some have the added benefit of being performed under LA.

The introduction of new EA techniques over the last two decades has been accompanied by a series of RCTs aimed at evaluating their clinical effectiveness and cost-effectiveness. Initially, first-generation EA techniques such as TCRE and laser ablation were compared with hysterectomy (Lethaby *et al.*, 1999). Subsequent trials, which compared alternative first-generation techniques such as TCRE, laser EA and REA, established TCRE as the gold standard for this group of treatments. As less invasive and more user-friendly second-generation techniques such as MEA became available, these were compared with earlier methods of ablation like TCRE and REA. Although not all techniques have been subjected to head-to-head comparisons in the context of randomised trials, an overview of the literature demonstrates that MEA (second generation) has

been shown to be comparable with TCRE (first generation) – which, in turn, has been shown to be an effective alternative to hysterectomy (gold standard). However, questions about long-term clinical effectiveness and cost implications of alternative forms of surgical treatment remain unanswered. Published data report no more than 5 years of follow-up (Aberdeen Endometrial Ablation Trials Group, 1999; Cooper et al., 2005). Inevitably, some women treated by EA will eventually require repeat ablation or hysterectomy. Following hysterectomy, a proportion of women will also develop further complications such as postsurgical adhesions and pelvic floor dysfunction, which may lead to further surgery. The necessity for a head-to-head comparison between the two most common second-generation methods - MEA and TBEA - has been identified (NICE, 2004). Our group has recently completed recruitment to such a trial involving over 200 women funded by the Chief Scientist Office Scotland (CZH/4/117) (Sambrook, unpublished). Given the widespread use of ablative techniques as first-line surgical treatment for menorrhagia at the present time, it is uncertain whether it is either necessary or feasible to compare second-generation techniques directly with hysterectomy in a new randomised trial, which is unlikely to produce any meaningful results for another 4–5 years. At the same time, the need to obtain comparative information on long-term outcomes is clearly accepted, as is the need to identify the best technique for individual women.

From a clinical perspective, we believe that the most relevant research questions at the present time are:

- i. How do the currently used ablative techniques and the Mirena IUS system compare with hysterectomy in the medium to long term?
- ii. Which among the commonly used second-generation ablation techniques is the most effective and cost-effective?
- iii. Are there subgroups of women who are most likely to benefit from hysterectomy, Mirena or specific types of ablation?

We propose to address these questions by analysis of data from national data sets and randomised trials. We plan to assess long-term outcomes by means of record linkage and follow-up of randomised cohorts, and perform IPD meta-analysis of existing trial data. The output will be used to create a model for the utilisation and costs of the different treatments, which can inform an algorithm for clinical decision making.

Overall aims of the project:

- 1. To determine, using data from record linkage and follow-up of randomised and nonrandomised cohorts of British women, long-term effects of various second-generation ablative techniques and hysterectomy in terms of failure rates, complications and further surgery.
- 2. To determine, using IPD meta-analysis of existing RCTs, short- to medium-term effects of various second-generation ablative techniques, Mirena IUS and hysterectomy, including exploration of outcomes in clinical subgroups.
- 3. To undertake a model-based clinical effectiveness and cost-effectiveness analysis comparing Mirena IUS and various second-generation ablative techniques with hysterectomy using output from the above analyses and to conduct extensive sensitivity analyses to explore robustness of the results to the assumptions made.
- 4. To devise a parsimonious algorithm for clinical decision making regarding the choice of surgery for women with HMB with failed medical treatment.

Record linkage study protocol

Research Group (Aberdeen), Professor S Bhattacharya,¹ Dr K Cooper,² Dr P Chien,³ Professor A Lee¹ and Dr V Timmuraju¹

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Aim

To determine, using data from record linkage and follow-up of randomised and non-randomised cohorts of British women, long-term effects of various second-generation ablative techniques and hysterectomy in terms of failure rates, complications, QoL and sexual function.

This will be addressed by means of:

Analysis of a large population-based anonymised, observational data set generated by the ISD Scotland, in order to identify medium- and long-term effects of hysterectomy and second-generation EA techniques. This will overcome some of the potential limitations of data from trials which are based on relatively small numbers of women. This is thus an area where observational data will be invaluable in assessing outcomes in all categories of women rather than the highly selected group who have been recruited to trials.

This aim has had to be modified as long-term data on QoL and sexual function as well as variables listed in the previous analysis plan (uterine size, presence of fibroids, coexisting gynaecological pathology) are not available in the ISD data set.

Predictor variables which are available in the ISD data set include age, type of procedure, CARSTAIR quintile for social deprivation, year of operation and cancer.

Analytical approach

Data sets

Population-based routinely collected data will be used in the analysis to meet this objective. We have confirmation of availability of access to population-based data in Scotland. An initial search within the ISD data set has identified over 40,000 hysterectomies (1985–2005) and 14,000 ablative techniques (1989–2005) performed in women with DUB. This includes a subset of women randomised to alternative treatments for menorrhagia. The custodians of the ISD registry have given their approval to proceed along these lines and have agreed to generate an anonymised data set for analysis.

Analysis

Descriptive statistics will be used to summarise each of the outcomes and potential predictor variables (age, type of procedure, uterine size, presence of fibroids, coexisting gynaecological pathology). Appropriate univariate analyses (two sample *t*-test, chi-squared test and non-parametric tests) will be used initially to examine the association between these potential predictors and the outcomes of interest (repeat surgery, hysterectomy, other pelvic surgery).

Multiple logistic regression techniques will be used to examine the mutually adjusted effects of potential predictors identified in the univariate analysis. The predictive ability of the models will not be assessed by determination of the area under the ROC curve owing to the unavailability of the predictor variables (uterine size, presence of fibroids, coexisting gynaecological pathology). Comparison of the predictive ability of models incorporating only two variables using area under the ROC curve was therefore deemed inappropriate. The analysis will generally be carried out stratified by the women's age group.

Appropriate univariate analyses (chi-squared test; *t*-test) will examine the association between the ISD-linked Scottish randomised trial women and future retreatment. The women will be analysed by appropriate subgroups. Multiple logistic regression will be used to quantify the risk of treatment failure among subgroups of women after adjustment for confounders such as age, CARSTAIR quintiles, year of operation and cancer.

Sample size

From the ISD data set, we envisage assembling a cohort of at least 13,000 women post ablation and 40,000 post hysterectomy. With a data set of 13,000 ablations, the two-sided 95% CI around an estimated prevalence of retreatment of 25% would be 24.3%–25.7%.

The effectiveness of hysterectomy, ablation and levonorgestrelreleasing intra-uterine device: individual patient data metaanalysis

The International HMB (Heavy Menstrual Bleeding) IPD Meta-analysis Collaborative Group, Management Group Aberdeen, UK, S Bhattacharya,¹ K Cooper,² KS Khan,³ J Daniels,³ L Middleton,⁴ R Champaneria³ and R Gray⁴

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Aim

To determine, using IPD meta-analysis of existing RCTs, short- to medium-term effects of various second-generation ablative techniques, Mirena IUS and hysterectomy, including exploration of outcomes in clinical subgroups.

Objectives

To assess the comparative effectiveness of hysterectomy, ablative techniques and LNG IUS for the treatment of menorrhagia using the following comparisons:

- 1. hysterectomy versus ablation
- 2. ablation versus ablation (comparison of different techniques)
- 3. ablation versus LNG IUS
- 4. hysterectomy versus LNG IUS.

Eligibility

Types of studies

Studies will only be included if they are RCTs with adequate randomisation concealment, excluding quasi-randomisation and non-randomisation.

Types of participants

Inclusion criteria

Participants in the trials will be included in IPD meta-analysis if women have menorrhagia or abnormal/excessive/prolonged uterine bleeding that is unresponsive to medical treatment without obvious clinically detectable underlying pathology.

As many of the trials have been pragmatic, prior hysteroscopy will not have been performed. Thus, they will include women with small fibroids.

Exclusion criteria

Participants in the trial who have uterine bleeding caused by polyps and other uterine pathologies will not be included in the main IPD meta-analysis or, if considered necessary, will be analysed as a subgroup

Types of intervention

Randomised controlled trials comparing hysterectomy, endometrial resection or ablation, and LNG IUS in any of the combinations laid out in the *Objectives* section. *Table 1* shows the range of interventions that will be included.

Types of outcome measures

Primary outcomes

The primary outcome of interest is subjective reduction in MBL. Any studies that do not include a measurement of MBL will be excluded. MBL can be assessed in a number of ways including VAS or PBAC.

Secondary outcomes

Other outcomes will be collected for meta-analysis to investigate the effect of the interventions on other aspects of HMB, adverse effects and resource implications. These will include:

- patient satisfaction
- safety of procedure (morbidity, adverse effects, operative complications)
- length of operating time
- length of hospital stay
- fluid deficit
- pain
- anxiety, depression, sexual functioning
- long-term complications
- QoL
- health-related QoL
- pre-menstrual symptoms
- repeated surgery for HMB.

Intervention	Туре	Trade name
Hysterectomy	Total (both the body of uterus and cervix removed)	
	Subtotal (the body of the uterus is removed, leaving the cervix in place)	
	± Salpingo-oophorectomy	
	± Bilateral salpingo-oophorectomies	
	Wertheim (will be excluded) (body of uterus and cervix, part of the vagina, fallopian tubes, usually the ovaries, parametrium – the broad ligament below the fallopian tubes – and lymph glands and fatty tissue in the pelvis removed. This type of hysterectomy is also called a radical hysterectomy)	
Ablation – endometrial	First generation	
	TCRE	
	RBI	
	Laser (Nd:YAG)	
	Second generation	
	Thermal balloon	ThermaChoice, Cavaterm
	Hydrothermal	
	3D bipolar radiofrequency	
	Microwave	NovaSure
	Diode laser hyperthermy	
	Cryoablation	
	Photodynamic therapy	
LNG IUS	LNG IUS	Mirena coil

TABLE 1 Intervention groups and surgical techniques

Methods

An overview of the process of collecting and synthesising data is shown in Figure 1.

Literature searching

An original literature search was undertaken using the Cochrane Library, MEDLINE (1966–2007), EMBASE (1980 to July 2007) and CINAHL (1982 to July 2007).

To select studies of surgical interventions for menorrhagia the following search terms were used: menorrhagia, hypermenorrhea, (excessive) menstrual blood loss, heavy menstrual bleeding, dysfunctional uterine bleeding, hysterectomy, vaginal hysterectomy, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, transcervical resection of the endometrium, TCRE, endometrial ablation, laser ablation, hysteroscopy, electrosurgery, rollerball, (thermal) balloon, hypertherm(ia), thermotherapy, photodynamic therapy, phototherapy, cryoablation, microwave endometrial ablation, radiofrequency, saline irrigation, laser interstitial, ThermaChoice, Cavaterm, ELITT, Vesta, NovaSure, Microsulis, Cryogen.

To identify any ongoing RCTs the following were searched: the Meta-Register of Controlled Trials and the ISRCTN register with 'menorrhagia' and 'endometrial ablation' as keywords.

All identified trials are shown in *Appendix A*.

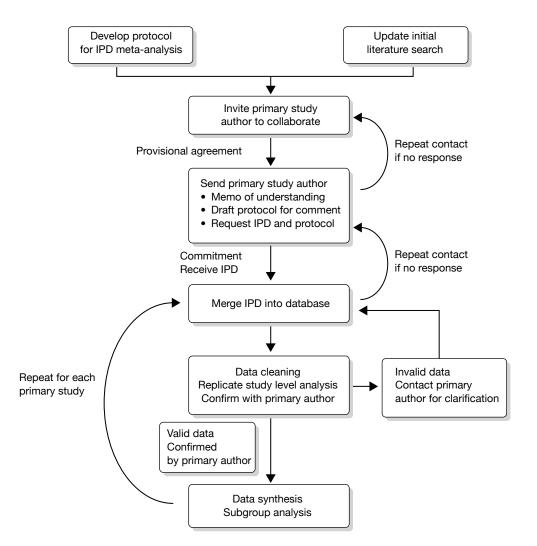


FIGURE 1 Summary of steps in undertaking the HMB IPD meta-analysis.

The search will be repeated every three months throughout the project to ensure any newly published studies are identified. *Appendix B* gives the full search strategy.

Once the collaborative group has been established, investigators from the identified studies will be asked to review the included study list to identify any studies that might have been missed.

Collection of IPD from authors of primary RCTs

Initial contact has already been made with the first named author of the included primary studies. Authors that have not as yet responded to the initial invitation will be sent another letter. If attempts from investigators within the collaboration fail, they may be contacted via the British or International Society for Gynaecological Endoscopy. Confirmation of commitment to the collaboration and ability to supply IPD will then be sought. The responding authors will be sent the overview protocol and a request to send the trial data set, original study protocol and data collection forms. The data can be supplied in either a Microsoft ACCESS database (preferred choice) or a Microsoft EXCEL spreadsheet.

Inclusion in the collaborative group and provision of data will be covered by a Memorandum of Understanding.

Data requested will include primary and secondary outcomes. In addition, the baseline demographic and clinical details listed below will need to be collected:

- age at randomisation
- parity
- uterine cavity length
- presence of fibroids and/or polyps
- number of previous caesarean sections.

All data received will be incorporated into an overview database, taking care to preserve any referential integrity within relational databases. All the data supplied will be subjected to range and consistency checks. Any missing data, obvious errors, inconsistencies between variables or outlying values will be queried and rectified as necessary by correspondence with the investigators. Study level analysis will be repeated to verified published results.

Once the data have been checked and validated, the original authors will be contacted to confirm their acceptance of individual study results before proceeding to the meta-analysis. If the integrity of the data/study is questionable they may be excluded from the analysis.

Data synthesis

Statistical analysis will be carried out on all the patients ever randomised, and will be based on the ITT principle. Results from separate trials will be combined and analysed using suitable methods, including Mantel–Haenszel for dichotomous outcomes at pre-specified time points and multilevel modelling techniques for continuous repeated measurements. The latter method maximises power and allows us to estimate overall treatment effects over time. Trial of origin will be included as a fixed or random effect as deemed appropriate.

Owing to different scales of measurement in individual studies, it is anticipated that the standardised mean difference (SMD) will be used for continuous data. It may also be necessary to convert data on different scales using an appropriate transformation, for example the standard correction factor of $\Pi/3$ to convert from SMD to log odds ratio.

Initially, analyses will be performed using the direct comparisons only (hysterectomy versus ablation, ablation versus ablation and LNG IUS versus ablation). However, it is anticipated that there may be a limited number of direct comparisons available. In this case, a method of adjusted indirect comparison will be used to estimate comparative efficacy. In simple terms, this approach enables a comparison of interventions A and B if both have been compared with C. This will allow us to explore the ranking of treatment effectiveness.

Subgroup analysis

Subgroup analyses, if not carefully planned, can lead to misleading results, for example owing to the play of chance with multiple testing. Extreme caution will be used in interpretation of subgroup results. Any subgroup analysis will be limited to the following parameters:

- 1. intervention
- 2. \pm pathology
- 3. age < 35, 35–45 and > 45 years
- 4. uterine cavity length < 8 cm, 8-10 cm and > 10 cm
- 5. presence or absence of submucous fibroids > 2 cm
- 6. previous ablation/treatment
- 7. nulliparous
- 8. mode of delivery (i.e. caesarean section).

HMB IPD meta-analysis Collaborative Group organisation Management of the Collaborative Group

The Birmingham Clinical Trials Unit will act as the group secretariat for the IPD meta-analysis and will hold the main database. All data will be held securely and treated with the strictest of confidence. The overview will be managed by a small group including grant holders and research staff employed on the project grant listed below:

Lead investigator, overall responsibility for Overview Group		
Clinical lead, BSGE (British Society for Gynaecological Endoscopy) representative, contact with authors		
Clinical lead, methodology		
Methodology and analysis		
Project management		
Overview statistician		
Overview systematic reviewer		

Memorandum of Understanding for the collaborative group

The activities of the IPD meta-analysis will be governed by an initial Memorandum of Understanding, to be agreed by all collaborators within this group including primary triallists and secondary researchers, at the start of the project. The Memorandum of Understanding will set out the aims, scope, responsibilities and tasks required of all investigators.

Relationships with the other components of the guidelines development

group

The IPD meta-analysis is a component of a larger project aiming to generate evidence-based, cost-effective clinical guidelines. The results of the IPD meta-analysis will be incorporated into a decision analytic model, which will then inform the development of guidelines. The International HMB IPD Meta-analysis Collaborative Group will not be directly involved in these processes, other than lead investigators from the Management Group.

Outputs

Outputs from this project will be:

- IPD meta-analysis of direct comparisons of interventions
- indirect comparison of rankings of different types of ablations
- input for the health economics model
- development of methodological methods for IPD meta-analyses
- identification of the need for more primary research (in areas where clinical uncertainties remain).

Publication policy

The results from the IPD meta-analysis will be presented at a collaborators meeting. Any subsequent articles on the results of the meta-analysis will be published under the name of the collaborative group – the International HMB IPD Meta-analysis Collaborative Group. It will also be circulated to the collaborators for comment, amendments and approval before finally being submitted. In the case of any disagreement, the following fundamental principle will be applied: that the report should provide the meta-analysis results, presenting all of the available evidence, but will not include any interpretations of the data, except those that are unanimously decided upon by all collaborators. Any collaborating group is free to withdraw its data at any stage.

Cost-effectiveness analysis

Aim

To undertake a cost-effectiveness analysis of hysterectomy versus second-generation ablative techniques and alternative forms of second-generation ablation using information generated from the above analyses.

This project will involve the development of a decision analytic simulation model as a framework for conducting cost-effectiveness and cost-utility analyses and associated value of information analyses (Felli and Hazen, 1998; Claxton *et al.*, 2001). The economic evaluations will inform current treatment policy in this clinical area, while the value of the information component will serve to highlight future research needs and agendas, and inform possible future research funding decisions. A modelling framework is ideally suited to demonstrate and explore the importance of the inherent uncertainty.

The model development process will use, as a starting point, the recently published menorrhagia clinical pathway Markov model (Garside *et al.*, 2004). This model, generated by researchers at the University of Exeter, formed the basis of the national coverage decision by NICE on microwave and thermal balloon EA for menorrhagia. Any requirements for structural model adjustments will be determined through:

- consideration of other recent HMB models (such as the model developed as part of the NICE HMB guideline prepared by the National Collaborating Centre for Women's and Children's Health – draft out for consultation currently)
- consultation within the research team, drawing on the requisite clinical and modelling expertise; and with appropriate external advisers (such as those involved in the modelling work reported in Garside *et al.*, 2004).

The principal clinical data to be used in populating the model will be drawn from other aspects of our research work, namely the individual patient meta-analyses and data from both national registers and follow-up of existing RCTs (as detailed earlier in this proposal). Assuming that a Markov model is found to be appropriate, it will be constructed using TREEAGE PRO (TreeAge Software Inc., Williamstown, MA, USA) software. This is a widely used and highly user-friendly software package ideally suited to the construction and analysis of decision tree and Markov models.

The economic evaluation will adopt a broad perspective and seek to include consideration of costs incurred by the health sector, by patients and by the economy more broadly in terms of productivity issues. An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from current practice to alternative treatment strategies. The cost-effectiveness component of the work will report results in terms of an ICER of cost per woman successfully treated and cost per hysterectomy avoided. However, QoL data suitable for use in a cost–utility framework are available from published sources (for example, Sculpher, 1998) and so the economic evaluation will additionally present results in terms of incremental cost per QALY gained. Resource use will be estimated from the existing published evidence and additional cost data will be sought from other sources such as the annual review of unit health and social care costs (by the University of Kent) and national schedule for reference costs.

The results of the cost–utility analysis (CUA) will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also include a value of information analysis to quantify the total uncertainty in terms of the value of removing that uncertainty. As appropriate, we shall include partial value of information analysis calculations. In addition to this probabilistic sensitivity analysis on our base-case model, we shall include a range of alternative analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

To develop an algorithm for clinical decision making in women with heavy menstrual bleeding

Aim

To devise a parsimonious algorithm for clinical decision making, regarding the choice of surgery for women with HMB with failed medical treatment.

The call for proposals asks for patient perspectives to be taken into account. For many patients, the choice is likely to be straightforward if there is absolute certainty about comparative outcomes. Where such certainty is lacking, the ultimate decision may be influenced by personal preference. In this proposal we have planned to produce clinical algorithms which will guide practice, without overriding a clear preference a particular patient may have. We accept that, for an algorithm to be useful in a pragmatic context, it should be flexible enough to accommodate consumer preference. We therefore plan to develop algorithms for a typical (default) situation in a way which is highly sensitive to the needs and preferences of individual patients.

We will use consensus development processes to produce an interim or indicative algorithm. A hybrid method (modified Delphi technique) incorporating a postal questionnaire for the first round of ratings followed by a meeting where the second round of ratings occurs is the preferred technique for this project.

Delphi participants will include a panel (of about 15–20 respondents) selected from the following groups of stakeholders: general practitioners, general gynaecologists, gynaecologists with a special interest in minimal-access surgery (members of the British Gynaecological Endoscopy Society) and representatives from the Royal College of Obstetrics and Gynaecology. A questionnaire will be developed for the consensus process, based on the results from clinical effectiveness and cost-effectiveness data. Participants will initially complete the questionnaire by post/email. Potential loss to follow-up will be minimised by postal/email and telephone repeat reminders.

A subset of individuals will subsequently attend a facilitated face-to-face meeting (unless a consensus emerges from responses to postal questionnaires). At this meeting, each participant will receive a new copy of the questionnaire with a reminder of their own initial ratings and the distribution of ratings for the group as a whole. Each item will be discussed in turn and reasons for any differences explored, after which participants will privately re-rate the questions. Participants at the face-to-face group meeting will also include two patient representatives.

Amendment

Following consultation with HTA this part of the protocol (to develop an algorithm for clinical decision making in women with HMB) was amended. The amendment was approved by the NETSCC consultant advisor on 5 February 2010

The last research question, i.e. development of a clinical algorithm, was felt to be important at the time of submission of the application in 2006. Its current relevance is questionable as NICE has already issued a guideline on HMB which incorporates an algorithm for investigation and treatment. This guideline is due to be revised soon and is expected to take into account the results from this HTA project. In view of the presence of the existing NICE guideline as well as the imminent deadline for submission of the final report (14 February), we felt that a modification of the original protocol was appropriate.

A questionnaire survey of 18 stakeholders (15 clinical experts) was undertaken in January 2010. Responses from 15 experts have shown remarkable consensus in terms of decision making in HMB of unknown origin. Nine out of 10 responders indicated that, on the basis of the effectiveness and cost data generated by this project, they would favour Mirena, followed by second-generation ablation techniques, followed by hysterectomy as first-, second- and thirdline approaches to HMB. Under these circumstances the value of a formal consensus process, involving a face-to-face meeting of experts who seem to be in general agreement, seems limited. Instead, based on the responses received, and input from a panel of consumer representatives, we intend to provide a simple clinical algorithm.

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Appendix A

 TABLE 1a
 Characteristics of available trials^a (hysterectomy vs ablation)

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Crosignanani,	Italy	Women < 50 years	Vaginal hysterectomy	Satisfaction		Not as yet,
1997		Failed medical treatment	vs TCRE	MBL		but trying to contact via
n=92		Uterine size < 12 weeks		QoL		Vercellini
		Submucous fibroid < 3 cm		Duration of surgery	Minutes	group
				Hospital stay	Days	
				Return to work	Weeks	
				Retreatment (further surgery)		
Dickersin, 2007	USA	Premenopausal women	Hysterectomy vs	Menstrual status		Yes, willing to
n=242	with DUB aged ≥ 18 years	ablation	QoL	EuroQoL (EQ-5D)	collaborate	

continued

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Dwyer, 1993 n=200	Weston- Super-Mare, UK	Age < 52 years rre, Failed medical treatment	Abdominal hysterectomy vs TCRE	Patient satisfaction (4 months and 2.8 years)		Not as yet
		Uterus < 12 weeks		MBL (subjective)		
				QoL at 2.8 years	Days	
				Hospital stay	Weeks	
				Return to work		
				Retreatment (further surgery)	£	
				Total resource use at 2.8 years		
Gannon, 1991	Ireland, UK	Women median age 40	Abdominal	MBL		Yes, willing to
n=54		years	hysterectomy vs TCRE	Duration of surgery	Minutes	collaborate
		Failed medical treatment		Hospital stay	Days	
	Uterine size <12 weeks		Return to work	Days		
		Submucous fibroid < 3 cm Endometrial prep		Retreatment (further surgery)		
				Resource use for surgery	£	
0'Connor, 1997 n=202	London, UK	Women age 30–50 years Failed medical treatment	Abdominal hysterectomy	Patient satisfaction (2 years)		Yes, NOT willing to
		Uterine size < 12 weeks	(28) + vaginal	MBL		collaborate
		Submucous fibroid < 5 cm	hysterectomy (28) vs TCRE	QoL at 2 years		
				Hospital stay	Days	
				Retreatment (further surgery)		
Pinion, 1994	Dundee, UK	Women age < 50 years	Abdominal	Patient satisfaction		Yes, willing to
n=204		Failed medical treatment	hysterectomy vs TCRE + ELA	(1 and 4 years)		collaborate
		Uterine size < 10 weeks	IUNE + ELA	MBL	VAS	
				QoL		
				Hospital stay	Number of nights in hospital	
				Return to work	Weeks/ months	
				Retreatment (further surgery)	Weeks/ months	
				Health service and patient costs	£	
Zupi, 2003	Italy	Women age < 50 years	TCRE vs hysterectomy	Patient satisfaction		
<i>n</i> =181		Failed medical treatment Weight < 100 kg		MBL		

	TABLE 1a Characteristics of available trials ^a	(hysterectomy	vs ablation)	(continued)
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a In addition to the above trials we have identified a further abstract of a study published in the *Chinese Medical Journal* (Lin, 2006). We have requested the full paper and need to verify whether this was a randomised trial and therefore suitable for inclusion.

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Trials comparing	first-generatio	on ablative techniques				
Bhattacharya, 1997 n=372	Aberdeen, UK	Age < 50 years Mean age 41 years Uterine size < 10 weeks Clinical diagnosis of DUB Normal histology	TCRE + rollerball vs laser	Satisfaction at 1 year Amenorrhoea Duration of surgery Complications Retreatment	Minutes	Yes, willing to collaborate
Boujida, 2002 <i>n</i> =120	Denmark	Age > 35 years	TCRE vs rollerball endometrial coagulation	Hysterectomy rate 5 years later Days with bleeding Recommend treatment	Days	Not as yet, but still trying to make contact
McClure, 1992 <i>n</i> =38	Ireland	Mean age 42 years Menorrhagia unresponsive to medical treatment MBL > 70 ml	TCRE + rollerball vs laser (argon)	MBL reduction Amenorrhoea Duration of surgery Complications	MBL (> 70 ml) Minutes	Yes, willing to collaborate
Trials comparing	first- with sec	ond-generation ablative tech	niques			
Brun, 2006 <i>n</i> =51	France	Higham blood loss score > 100	TCRE vs Cavaterm TBEA	Amenorrhoea Higham bleeding score	Higham bleeding score	Yes, willing to collaborate
Cooper, 1999 <i>n</i> =263	Aberdeen, UK	Mean age 41 years Uterine size < 10 weeks Clinical diagnosis of DUB Normal histology	TCRE + rollerball vs MEA	PBAC Satisfaction at 1 year QoL (SF-36) Amenorrhoea Duration of surgery Postoperative stay Return to work Complications Retreatment	PBAC SF-36 Minutes Hours Days	Yes, willing to collaborate
Cooper, 2002 n=265	USA	Age 25–50 years Menorrhagia (PBAC > 150) Failed medical treatment	NovaSure vs wire loop resection + rollerball	PBAC Duration of surgery Sedation Complications	PBAC Minutes	Deceased, but industry willing to collaborate
Cooper, 2004 n=322	USA	Mean age 41 years Age > 30 years Failed/refused medical treatment PBAC > 185 Uterine cavity 6–14 cm	Microwave vs rollerball	PBAC > 75 Satisfaction QoL (SF-36) Amenorrhoea Duration of surgery Sedation Complications	PBAC SF-36 Minutes	Deceased, but industry willing to collaborate
Corson, 2000 <i>n</i> =276	USA	PBAC > 150 Distorted uterine cavity Cavity length > 9.75 cm	Vesta balloon vs TCRE + rollerball	PBAC: proportion > 76 Amenorrhoea Adverse events	PBAC	Not as yet

TABLE 1b Characteristics of available trials (ablation versus ablation)

continued

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Corson, 2001	USA	Age 30–50 years	Rollerball vs HTA	PBAC	PBAC	Not as yet
n=276		Myomas < 4 cm	(hydrotherm ablator)	Menstrual diary	PBAC	
		-		Amenorrhoea		
				Proportion with PBAC <75	PBAC	
				QoL	SF-36	
				Retreatment		
Duleba, 2003	USA	Age 30–50 years	Rollerball vs	PBAC	PBAC	Not as yet
n=279		PBAC > 150	endometrial cryoablation	Menstrual diary	PBAC	
		Uterine cavity > 10 cm	cryoablation	Bleeding and pain	PBAC	
		Intramural myomas <2 cm		Satisfaction		
Hawe, 2003	UK	Age 29–51 years	Cavaterm TBEA vs	Amenorrhoea		Yes, willing t
n=72		Uterine length <12 cm	Nd:Yag laser	QoL (SF-12)	SF-12	collaborate
				Satisfaction		
				VAS pain	VAS	
				Operative details + complications		
Meyer, 1998 <i>n</i> =272	USA	Age 29–50 years	Rollerball vs TBEA	Satisfaction		Yes, willing t
		PBAC score > 150	(ThermaChoice)	PBAC	PBAC	collaborate
		Ineffective medical		Complications		
		therapy		Duration of surgery	Minutes	
		Uterine cavity size 4–10 cm		Retreatment rate		
Pellicano, 2002		Mean age 43 years	TCRE vs Cavaterm	Satisfaction		Not as yet
n=82		Age < 50 years	TBEA	Complications		
		Weight < 100 kg		Duration of surgery	Minutes	
		Uterine size < 12 weeks		Retreatment rate		
Perino, 2004	Italy	Age 36–48 years	TCRE vs ELITT	Amenorrhoea	VAS	Yes, willing t
<i>n</i> =116		DUB	(endometrial laser intrauterine thermal therapy)	Complications		collaborate
				Duration of surgery	Minutes	
				Retreatment rate		
Romer, 1998	Germany	Age 35–52 years	Rollerball vs	Satisfaction		Not as yet
n=20			Cavaterm TBEA	Amenorrhoea	VAS	
Soysal, 2001	Turkey	Age 40–49 years	Rollerball vs TBEA	Satisfaction		Not as yet
n=96				Amenorrhoea	PBAC	
				Complications		
				Duration of surgery		
van Zon- Rabelonk, 2003	Netherlands	Age unreported	Rollerball vs TBEA	Technical safety Reduction in		Yes, willing t collaborate
n=139				menstrual bleeding		
Vercellini, 1999	Italy	Age > 35 years	TCRE vs vaporising	Satisfaction		Not as yet
n=46	-	Unterine size < 12 weeks	electrode	Amenorrhoea	PBAC	,
		Normal cavity		Complications		
		,		Duration of surgery	Minutes	
				PBAC	PBAC	

TABLE 1b Characteristics of available trials (ablation versus ablation) (continued)

TABLE 1b Characteristics of available trials (ablation versus ablation) (continued)

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Trials comparing	second-genera	tion ablative techniques				
Abbott, 2003 <i>n</i> =57	Australia	Mean ages + 40.5 years (Novasure) and 40.5 years (Cavaterm) DUB Uterine length < 12 cm	Novasure vs Cavaterm TBEA	Amenorrhoea QoL Satisfaction acceptability	EuroQoL (EQ-5D)	Yes, willing to collaborateVAS
Bongers, 2004 n=126 5-year report published, Kleijn <i>et al.</i> , 2008	Netherlands	Mean age 43 years PBAC > 150 Uterine length 6–12 cm	Novasure vs ThermaChoice TBEA	Amenorrhoea Satisfaction Duration of surgery Retreatment	PBAC Minutes	Yes, willing to collaborate
Clark, 2007 Sambrook, 2009 <i>n</i> = 240	Birmingham, UK Aberdeen, UK	Unpublished	NovaSure vs ThermaChoice ThermaChoice TBEA vs MEA	QoL Satisfaction PBAC	PBAC	Yes, willing to collaborate Yes, willing to collaborate

TABLE 1c Characteristics of available trials (Mirena versus ablation)

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Barrington, 2003 <i>n</i> =44	Devon, UK	Menorrhagia refractory to medical treatment Uterine length < 12 cm	LNG IUS Mirena vs TBEA	PBAC score Improvement in bleeding Need for further treatment	PBAC	Yes, NOT willing to collaborate
Busfield, 2006 n=79 Cost- effectiveness study carried out by Brown <i>et al.</i> , 2006	New Zealand	Heavy menstrual bleeding Age 25–50 years Regular cycle	LNG-IUS vs TBEA	Menstrual blood loss Patient satisfaction QoL Menstrual symptoms Treatment side effects	PBAC SF-36	Yes, willing to collaborate
Crosignani, 1997 <i>n</i> =70	Italy	Age 38–53 years MBL > 80 ml/cycle Uterine size < 8 weeks	TCRE	PBAC Patient satisfaction SF-36 Amenorrhoea at 12 months	SF-36	Contact again via Vercellini group
Kittelsen, 1998 <i>n</i> =53	Norway	Age 30–49 years PBAC > 100 Regular uterine cavity	LNG IUS Mirena vs TCRE	PBAC	PBAC	Not as yet
Malak, 2006 <i>n</i> = 56	Egypt	Age 40–50 years Cavity < 10 cm	LNG-IUS vs TCRE	Amenorrhoea PBAC score		Not as yet

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Shaw, 2007 <i>n</i> =66	England	Age 25–49 years Failed medical treatment Normal biopsy PBAC < 120	TBEA vs LNG-IUS	PBAC score at 12 months	PBAC	Not as yet
Soysal, 2002 <i>n</i> =72	Turkey	Mean age 44 years	LNG IUS vs TBEA	Reduction in menstrual bleeding QoL		Not as yet
TALIS 2003		Age 25–50 years	LNG IUS vs TBEA	PBAC Satisfaction	PBAC	Not as yet
Tam, 2006 <i>n</i> =33	China	Premenopausal women >40 years Uterine cavity <10 cm	LNG IUS vs TBEA	SF-36	SF-36	Yes, willing to collaborate

TABLE 1c Characteristics of available trials (Mirena versus ablation) (continued)

TABLE 1d Characteristics of available trials (Mirena versus hysterectomy)

Study reference, number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of outcome	Response
Hurskainen, 2001	Finland	Menorrhagia	LNG IUS Mirena vs	EQ-5D		Not as yet
n=236		Age 35–49 years	hysterectomy	Rand 36		
5-year report published, Halmesmaki <i>et</i> <i>al.</i> , 2007				MBL		

Appendix B Search strategy for population

- #1 Menorrhagia/all subheadings
- #2 Hypermenorrhea/all subheadings
- #3 Excessive NEAR ('menstrual bleeding' OR 'menstrual blood loss')
- #4 Dysfunctional NEAR ('uterine bleeding' OR 'menstrual bleeding')
- #5 Heavy NEAR ('menstrual bleeding' OR 'menstrual blood loss')
- #6 'Iron deficient anaemia'
- #7 (#3 OR #4 OR #5 OR #6) in TI, AB
- #8 #1 OR #2 OR #7

Search strategy for interventions

Hysterectomy

- #1 EXPLODE 'hysterectomy'/all subheadings
- #2 'Vaginal hysterectomy'/all subheadings
- #3 'Total abdominal hysterectomy'
- #4 'Subtotal abdominal hysterectomy'
- #5 'Laparoscopic hysterectomy'

#6 #1 OR #2 OR #3 OR #4 OR #5

Ablation

#1 EXPLODE 'hysteroscopy'/all subheadings

#2 ('Transcervical resection') NEAR 'endometrium' #3 'TCRE' #4 'Endometrial ablation' #5 'Laser ablation' #6 'Electrosurgery' #7 'Rollerball' #8 'Thermal balloon' #9 'Hypertherm\$' #10 'Thermotherapy' #11 'Photodynamic therapy' #12 'Phototherapy' #13 'Cryoablation' #14 'Microwave ablation' #15 'Radiofrequency' #16 'Saline irrigation' #17 'Laser interstitial' #18 'Thermachoice' #19 'Cavaterm' #20 'ELITT' #21 'Vesta' #22 'Novasure' #23 'Microsulis' #24 'Cryogen'

Mirena

#1 EXPLODE 'contraceptive'/all subheadings
#2 'Mirena coil'/all subheadings
#3 'Levonorgestrel'
#4 'Intra uterine device'
#5 #1 OR #2 OR #3 OR #4

Search strategy for randomised controlled trials

#1 Randomized controlled trial IN PT #2 Controlled clinical trial IN PT #3 Randomized controlled trials IN SH #4 Random allocation IN SH. #5 Double blind method IN SH #6 Single blind method IN SH #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6) #8 Animal in SH NOT human in SH #9 #7 not # 8 #10 Clinical trial IN PT. #11 EXPLODE clinical trials/all subheadings #12 (clin NEAR trial) IN TI, AB #13 [(Single OR double OR treble OR triple) NEAR (blind OR mask)] IN TI, AB #14 Placebos IN SH #15 Placebos IN TI, AB #16 Random IN TI, AB #17 Research Design IN SH #18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 #19 #18 NOT #8 #20 #19 NOT #9

#21 Comparative study IN SH
#22 EXPLORE evaluation studies/all subheadings
#23 Follow-up studies IN SH
#24 Prospective studies IN SH
#25 (Control OR prospective OR volunteer) IN TI, AB
#26 #21 OR #22 OR #23 OR #24 OR #25
#27 #26 NOT #8
#28 #27 NOT (#9 OR #20)
#29 #9 OR #20 OR #28

Version 4 5 February 2010

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The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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