The National Institute for Health and Care Excellence

Final

Heavy menstrual bleeding (update)

B: Evidence reviews for management of heavy menstrual bleeding

NICE guideline 88

Evidence reviews

March 2018

Final

These evidence reviews were developed by National Guideline Alliance, hosted by the Royal College of Obstetrician and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-2777-7

Contents

Abbreviations

Abbreviation	Definition
AE	Adverse event
AH	Alkaline haematin
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
BNF	British National Formulary
CHCVR	Combined hormonal contraceptive vaginal ring
CI	Confidence interval
CrI	Credible interval
COC	Combined oral contraceptive
D&C	Dilatation and curettage
DIC	Deviation information criterion
EBx	Endometrial biopsy
EE	Ethinyl estradiol
EQ-5D	EuroQol five dimensions questionnaire
FSH	Follicle-stimulating hormone
GnRHa	Gonadotrophin-releasing hormone agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HMB	Heavy menstrual bleeding
HRQoL	Health-related quality of life
HRQoL-4	Health-related Quality of Life – 4 (questionnaire)
HTA	Health Technology Appraisal
LNG-IUS	Levonorgestrel-releasing intrauterine system
MBL	Menstrual blood loss
MD	Mean difference
MEA	Microwave endometrial ablation
MID	Minimally important difference
MPA	Medroxyprogesterone acetate
MR	Mean ratio
MRgFUS	Magnetic resonance-guided focused ultrasound surgery
MRI	Magnetic resonance imaging
N/A	Not applicable
N/C	Not calculable
NGA	National Guideline Alliance
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
OPH	Outpatient hysteroscopy
pD	Effective number of parameters
PICO	Population, intervention, comparison, outcome
PBAC	Pictorial blood loss assessment chart
QoL	Quality of life
QALY	Quality-adjusted life year

Abbreviation	Definition
RAND-36	36-Item Short Form Health Survey
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SD	Standard deviation
SE	Standard error
SF-12	12-Item Short Form Survey
SF-36	36-Item Short Form Survey
TBA	Thermal balloon ablation
TCRE	Transcervical resection of endometrium
TCRF	Transcervical resection of fibroids
TVUS	Transvaginal ultrasound scan
TXA	Tranexamic acid
UAE	Uterine artery embolisation
UFS-QOL	Uterine fibroid symptom and health-related quality of life (questionnaire)
US	Ultrasound
WHO	World Health Organization
WHOQOL-BREF TR	World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Management of heavy menstrual bleeding

Review question

What is the most clinically and cost-effective treatment (pharmacological/surgical) for heavy menstrual bleeding (HMB) in women with suspected or diagnosed fibroids; women with suspected or diagnosed adenomyosis; and women with no identified pathology?

Introduction

There are a number of treatments available to alleviate HMB and improve the health-related quality of life of women with this condition. Treatments can broadly be classified into medical, surgical and radiological options. The variety of therapeutic interventions allows management to be individualised taking into account a woman's preference. This is important because HMB impacts upon women of all reproductive ages and underlying health conditions. Furthermore, other cyclical symptoms such as pain and pre-menstrual syndrome may co-exist. The health professional's role is to allow women to make an informed choice by presenting the range of management options and their particular benefits and harms. Women should be made aware of the safety and effectiveness of therapeutic interventions and their mode of action. The potential side-effects and morbidity from treatment should be discussed. Furthermore, the impact of treatment on current and future fertility should be made explicit. If surgery is considered a woman's preference regarding the retention of her uterus should be taken into account as should the estimated time to return to normal activities.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Inclusions: • Women of reproductive age between menarche and menopause with heavy menstrual bleeding (HMB), including women with adenomyosis • Definition of HMB as described in the study. Studies with more than 66% women with HMB, or where the proportion of women with HMB is not specified will be included. If the analysis has been performed for the women with HMB separately then only this data will be extracted. Exclusions: • Randomised controlled trials (RCTs) with less than 10 participants in each arm will not be included

Intervention	**Pharmacological treatments**
	[of any type and administered at any dose, frequency, treatment duration recommended in the BNF, or by any route of administration]:
	• Nonsteroidal anti-inflammatory drugs (NSAIDs)
	  ○ Ibuprofen
	  ○ Mefenamic acid
	  ○ Other NSAIDs (for example naproxen, diclofenac)
	• Antifibrinolytics
	  ○ Tranexamic acid
	• Progestogens

	○ Oral (groups to be decided a priori dependent on dose, duration, type) - Medroxyprogesterone acetate - Norethisterone - Desogestrel ○ Injectable - Depot medroxyprogesterone acetate ○ Implant • Combined hormonal contraceptives ○ Estradiol valerate/dienogest ○ Noresthisterone acetate/ethinyl estradiol ○ Others (for example EE/levonorgestrel, EE/drospirenone) • Gonadotrophin-releasing hormone agonist (GnRHa) ○ Leuprolide acetate ○ Decapeptyl ○ Goserelin • Ulipristal acetate • Levonorgestrel-releasing intrauterine system (LNG-IUS) **Surgical Treatments** • Hysterectomy (total versus subtotal) ○ Laparoscopic or laparoscopic assisted ○ Robotic ○ Vaginal ○ Open • First Generation (Hysteroscopic-controlled Endometrial Resection) ○ Transcervical Endometrial Resection ○ Endometrial Vaporization ○ Endometrial Ablation- Rollerball • Second Generation Endometrial Resection ○ Radiofrequency Endometrial Ablation (bipolar) ○ Endometrial Cryoablation ○ Thermal Balloon Ablation ○ Hydrothermal (free-fluid) Endometrial Ablation • Uterine artery embolisation • Myomectomy ○ Laparoscopic ○ Hysteroscopic ○ Open • Magnetic resonance imaging (MRI)-guided transcutaneous focussed ultrasound for uterine fibroids Note: interventions not approved in the UK, or not used in clinical practice will not be included in this review. However studies including these interventions may be included in the network meta-analysis (NMA) if they provide data to inform the network. Please see NMA protocol for details.
Comparison	• Pharmacological treatment versus no treatment, usual care or placebo • Pharmacological treatment A versus pharmacological treatment B • Pharmacological treatment versus surgery • Pharmacological treatment versus combinations of pharmacological and surgical treatment • Surgical treatment versus no treatment, usual care (or placebo)

	• Surgical treatment A versus surgical treatment B • Surgical treatment versus combinations of pharmacological and surgical treatment
Outcome	• Reduction in blood loss – Pictorial blood loss assessment chart (PBAC) or alkaline haematin (AH) method • Quality of life (validated scales only) • Patient satisfaction • Adverse events (AEs) ○ For pharmacological treatment - Discontinuation due to AEs - Treatment compliance/discontinuation ○ For LNG-IUS: - Discontinuation due to AEs - Perforation - Expulsion - Infection ○ For surgical treatment: - Length of hospital stay - Severe bleeding requiring a blood transfusion - Infection - Venous thromboembolism - Return to hospital or theatre - Internal organ injury - Long-term complications (for example prolapse, urinary incontinence) - Mortality

AE: adverse event; AH: alkaline haematin; BNF: British National Formulary; EE: ethinyl estradiol; GnRHa: gonadotrophin-releasing hormone analogue; HMB: heavy menstrual bleeding; MRI: magnetic resonance imaging; NMA: network meta-analysis; NSAID: nonsteroidal anti-inflammatory drug; PBAC: pictorial blood loss assessment chart; RCT: randomised controlled trial

For full details see Appendix A – Review protocols.

Clinical evidence

The aim of this review was to identify effective pharmacological and surgical interventions that reduce HMB and improve quality of life for women with HMB. Three populations were defined: women with suspected or diagnosed fibroids, women with suspected or diagnosed adenomyosis, and women with no identified pathology.

A single search was conducted to look for systematic reviews and randomised controlled trials (RCTs). Systematic reviews were assessed for inclusion against the protocol, and if relevant, their quality was assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool. High-quality systematic reviews were included in our review, and where possible, data was taken directly from the review. Individual studies were also retrieved for completeness and accuracy. Low-quality systematic reviews were excluded from our review, but the list of included studies was checked to identify any relevant trials.

The results are presented separately for women with suspected or confirmed fibroids, women with confirmed or suspected adenomyosis and women with no identified pathology. In women with no identified pathology, a network meta-analysis (NMA) was conducted for the following outcomes: health-related quality of life (in studies using EQ-5D; SF-36; SF-12: RAND-36 as validated scales, with up to a 5-year follow-up); patient satisfaction (up to a 5-year follow-up), reduction in blood loss (pictorial blood loss assessment chart [PBAC] or alkaline haematin [AH] method), discontinuation due to adverse events, and treatment

compliance/discontinuation. For other outcomes including disease-specific health-related quality of life, pairwise analyses were conducted.

Included studies

1. Women with suspected or diagnosed fibroids

In women with suspected or diagnosed fibroids, 1 Cochrane Systematic Review (Gupta 2014) and 16 publications from 11 trials were included in this review (de Bruijn 2016 [EMMY trial]; Edwards 2007 [REST trial]; Hehenkamp 2005 [EMMY trial]; Hehenkamp 2008 [EMMY trial]; Jain 2016; Jun 2012; Manyonda 2012 [FUME trial]; Mara 2008; Moss 2011 [REST trial]; Nieman 2011; Pinto 2003; Ruuskanen 2010; Sayed 2011; Tosun 2014; van der Kooij 2010 [EMMY trial]; Volkers 2007 [EMMY trial]).

1 study compared ulipristal acetate to placebo (Nieman 2011). Another study compared levonorgestrel-releasing intrauterine system (LNG-IUS) to combined oral contraceptives (COC) (Sayed 2011). LNG-IUS was compared to norethisterone acetate in 1 study (Tosun 2014). A Cochrane Systematic Review (Gupta 2014) compared uterine artery embolisation (UAE) to different surgical methods, which included 3 studies comparing UAE to hysterectomy (EMMY trial; Pinto 2003; Ruuskanen 2010); 2 studies comparing UAE to myomectomy (Manyonda 2012; Mara 2008); and 2 studies comparing UAE to hysterectomy or myomectomy (Jun 2012; REST trial). 1 study compared thermal balloon ablation to hysterectomy (Jain 2016).

2. Women with suspected or diagnosed adenomyosis

In women with suspected adenomyosis, only 1 study was included in this review (Ozdegirmenci 2011) and compared LNG-IUS to hysterectomy.

3. Women with no identified pathology

In women with no identified pathology, 5 Cochrane Systematic Reviews (Fergusson 2013, Lethaby 2015, Lethaby 2013, Lethaby 2008, and Majoribanks 2016) were included in this review. 58 RCTs were identified (Abbott 2003; Abdel Malak & Shawki 2006; Aberdeen Group 1999; Abu Hashim 2012: Athanatos 2015; Barrington 2003; Bhattacharya 1997; Bongers 2004; Bonnar & Sheppard 1996; Brun 2006: Busfield 2006; Clark 2011; Cooper 1997; Cooper 1999a; Cooper 2002; Cooper 2004; Corson 2000; Corson 2001; Crosignani 1997; Dickersin 2007; Duleba 2003; Dunphy 1998; Dwyer 1993; Endrikat 2009; Ergun 2012; Fraser 2011; Ghazizadeh 2011; Ghazizadeh 2014; Goshtasebi 2013; Gupta 2013; Hawe 2003; Hurskainen 2001; Irvine 1998; Kaunitz 2010; Khajehei 2013; Kiseli 2015; Kittelsen & Istre 1998; Kriplani 2006; Meyer 1998; O'Connor 1997; Pellicano 2002; Penninx 2010; Penninx 2016; Perino 2004; Reid & Virtanen-Kari 2005; Sambrook 2009; Sambrook 2014; Sesti 2011; Sesti 2012; Shaaban 2011; Shaw 2007; Silva-Fihlo 2013; Soysal 2002; Tam 2006; van Zon-Rabelink 2003; Vercillini 1999; Vihko 2003; Zupi 2003). An additional 18 publications of additional outcomes or longer follow-ups of the same RCTs were identifiable (Bongers 2005 and Kleijn 2008 [Bongers 2004]; Cooper 1999b and Cooper 2001 [Cooper 1997]; Cooper 2005 [Cooper 1999a]; Ergun 2011 and Ergun 2012a [Ergun 2012]; Goldrath 2003 [Corson 2001]; Sculpher 1996 [Dwyer 1993]; Gupta 2015 [Gupta 2013]; Hurskainen 2004 [Hurskainen 2001]; Istre & Trolle 2001 and Rauramo 2004 [Kittlesen 1998]; Grainger 2000, Loffer 2001, and Loffer & Grainger 2002 [Meyer 1998]; Penninx 2011 [Penninx 2010]; van Zon-Rabelink 2004 [van Zon-Rabelink 2003]).

Eight studies compared different types of oral medication with each other (Abu Hashim 2012; Bonnar & Sheppard 1996; Fraser 2011; Dunphy 1998; Goshtasebi 2013; Khajehei 2013; Kiseli 2015; Kriplani 2006). 3 publications compared different types of oral medication to first generation endometrial ablation (Cooper 1997; Cooper 1999b; Cooper 2001).

Seven publications compared LNG-IUS to different types of oral medication (Endrikat 2009; Gupta 2013; Gupta 2015; Irvine 1998; Kaunitz 2010; Reid & Virtanen-Kari 2005; Shaaban 2011). 9 publications compared LNG-IUS to first generation endometrial ablation techniques (Abdel Malak & Shawki 2006; Crosignani 1997; Ergun 2012; Ergun 2011; Ergun 2012a; Ghazizadeh 2011; Istre & Trolle 2001; Kittelsen & Istre 1998; Rauramo 2004). 7 studies compared LNG-IUS to second generation endometrial ablation (Barrington 2003; Busfield 2006; Ghazizadeh 2014; Shaw 2007; Silva-Fihlo 2013; Soysal 2002; Tam 2006). 3 publications compared LNG-IUS to hysterectomy (Hurskainen 2001; Hurskainen 2004; Sesti 2012).

One study compared 2 different first generation endometrial ablation techniques (Vercillini 1999). 11 publications compared 2 different second generation endometrial ablation techniques (Abbott 2003; Athanatos 2015; Bongers 2005; Kleijn 2008; Bongers 2004; Clark 2011; Hawe 2003; Penninx 2010; Penninx 2011; Sambrook 2009; Vihko 2003). 19 publications compared first generation endometrial ablation to second generation endometrial ablation (Bhattacharya 1997; Brun 2006; Cooper 1999a; Cooper 2002; Cooper 2004; Cooper 2005; Corson 2000; Corson 2001; Duleba 2003; Goldrath 2003; Grainger 2000, Loffer 2001, Loffer & Grainger 2002; Meyer 1998; Pellicano 2002; Penninx 2016; Perino 2004; van Zon-Rabelink 2004; van Zon-Rabelink 2003). 6 publications compared first generation endometrial ablation to hysterectomy (Aberdeen Group 1999; Sculpher 1996; Dickersin 2007; Dwyer 1993; O'Connor 1997; Zupi 2003). 2 studies compared second generation endometrial ablation to hysterectomy (Dickersin 2007; Sesti 2011).

See Appendix D – Clinical evidence study selection, Appendix G – GRADE tables, Appendix H – Forest plots, Appendix F – Clinical evidence tables. See also Appendices J to N for futher details regarding the NMA.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in Appendix I – Excluded studies.

Summary of clinical studies included in the evidence review

Table 2, Table 3 and Table 4 provide brief summaries of the included studies.

Table 2: Summary of included studies: women with suspected or diagnosed fibroids

Study and setting	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Gupta 2014	UAE versus other medical or surgical interventions	Women with symptomatic uterine fibroids, with either subjective or objective symptoms (expected to be predominantly heavy menstrual bleeding with or without intermenstrual bleeding, but also including pain and bulk-related symptoms), or both.	Health-related quality of life (UFS-QOL, SF-36) at 1 year Patient satisfaction up to 24 months, 5 years Length of hospital stay Adverse events	
RCTs included in the Cochrane Systematic Review				

Study and setting	Intervention/ Comparison	Population	Outcomes	Comments
EMMY trial 2010 (Included in Gupta 2014) Netherlands	UAE versus hysterectomy (open, vaginal, or laparoscopic)	Clinical diagnosis of uterine fibroids confirmed by ultrasonography (size not specified): menorrhagia was their predominant complaint (100%).	Health-related quality of life (SF-36) at 6 weeks, 6, 12, 18, months, 2, 5, 10 years Patient satisfaction at 1, 2, 5, 10 years Length of hospital stay Adverse events	Publications from the EMMY trial with relevant outcomes for this review: De Bruijn 2016 (not in Gupta 2014); Hehenkamp 2005; Hehenkamp 2008; van der Kooij 2010; Volkers 2008
Jun 2012 (Included in Gupta 2014) China	UAE versus hysterectomy or myomectomy (type not specified)	Women aged 28-55 years with fibroids more than 4 cm in diameter causing symptoms of menorrhagia or pelvic pain and pressure which justified surgical treatment.	Health-related quality of life (SF-36) at 12 months Patient satisfaction at 12 months Length of hospital stay	
Manyonda 2012 (Included in Gupta 2014) United Kingdom	UAE versus myomectomy (open) (FUME trial)	Women aged 31-50 years with symptomatic uterine fibroids more than or equal to 4 cm in diameter, who wished to preserve fertility.	Health-related quality of life (UFS-QOL) at 1 year Length of hospital stay Adverse events	
Mara 2008 (Included in Gupta 2014) Czech Republic	UAE versus myomectomy (laparoscopic or open)	Women with reproductive plans with fibroids more than or equal to 4 cm in diameter, age up to 40 years, serum FSH concentration less than 30iu/L, and planned pregnancy. 90.9% were symptomatic fibroids.	Patient satisfaction up to 24 months Length of hospital stay Adverse events	
Pinto 2003 (Included in Gupta 2014) Spain	UAE versus hysterectomy (open)	Women aged 35-57 years with bleeding uterine fibroids less than or equal to 10 cm in diameter who were candidates for hysterectomy.	Patient satisfaction up to 24 years Length of hospital stay Adverse events	

Study and setting	Intervention/ Comparison	Population	Outcomes	Comments
REST trial 2011 (Included in Gupta 2014) United Kingdom	UAE versus hysterectomy or myomectomy (type not specified)	Women over the age of 18 were enrolled, with fibroids (more than 2cm) that could be adequately visualized with the use of magnetic resonance imaging causing symptoms of menorrhagia or pelvic pain and pressure which justified surgical treatment.	Patients satisfaction at 1 and 5 years Health-related quality of life (SF-36) at 1 and 5 years Length of hospital stay Adverse events	Publications from the REST trial with relevant outcomes for this review: Edwards 2007; Moss 2011
Ruuskanen 2010 (Included in Gupta 2014) Finland	UAE versus hysterectomy (open, vaginal, or laparoscopic)	Women aged 39-57 years with fibroids with subjective symptoms (75% with HMB), which had to be severe enough to warrant consideration of hysterectomy, and only women agreeing to hysterectomy, if necessary.	Patient satisfaction up to 24 months Length of hospital stay Adverse events	
RCTs primary studies				
Jain 2016 India	TBA versus hysterectomy (vaginal)	Women older than 40 years who had no desire for future childbearing, heavy menstrual bleeding (PBAC more than 100) with leiomyoma less than or equal to 5 cm in diameter.	Health-related quality of life (UFS-QOL) at 6 months Length of hospital stay Adverse events	
Nieman 2011 United States	Ulipristal acetate (10 mg, 20 mg) versus placebo	Women with symptomatic fibroids more than 2cm in diameter.	Health-related quality of life (SF-36 and UFS-QOL) at 3 months	
Sayed 2011 Egypt	LNG-IUS versus COC (30 micrograms of ethinyl estradiol and 150 micrograms of levenorgestrel)	Women aged 20-50 years with fibroid-related menorrhagia who desired contraception.	Blood loss (AH method and PBAC) at 12 months Health-related quality of life (HRQoL-4) at 12 months	
Tosun 2014 Turkey	LNG-IUS versus oral norethisterone (5mg twice daily)	Women aged 33-45 years with heavy menstrual bleeding with uterine leiomyoma less than or equal to 5 cm in diameter.	Blood loss (PBAC) at 6 months	

AH: alkaline haematin; COC: combined oral contraceptives; FSH: follicle-stimulating hormone; HMB: heavy menstrual bleeding; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; LNG-IUS: levonorgestrel-releasing intrauterine system; PBAC: pictorial blood loss assessment

chart; RCT: randomised controlled trial; SF-36: 36-Item Short Form Survey; TBA: thermal balloon ablation; UAE: uterine artery embolisation; UFS-QOL: Uterine fibroid symptom and health-related quality of life questionnaire

Table 3: Summary of included studies: women with suspected adenomyosis

Study	Intervention/ Comparison	Population	Outcomes	Comments
RCTs primary studies				
Ozdegirmenci 2011 Turkey	LNG-IUS versus hysterectomy (open)	Women with clinical suspicion of adenomyosis complaining of menorrhagia or dysmenorrhea. 100% with HMB.	Health-related quality of life (WHOQOL-BREF TR) at 12 months Adverse events	

HMB: heavy menstrual bleeding; LNG-IUS: levonorgestrel-releasing intrauterine system; RCT: randomised controlled trial; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire Turkish version

Table 4: Summary of included studies: women with no identified pathology

Study	Intervention/ Comparison	Population	Outcomes	Comments
Cochrane systematic reviews				
Fergusson 2013	Endometrial resection/ablation versus hysterectomy	Women of reproductive years with heavy menstrual bleeding (including both heavy regular periods [menorrhagia] and heavy irregular periods [metrorrhagia]), measured objectively or subjectively.	PBAC score Health-related quality of Life Satisfaction with treatment Duration of hospital stay Adverse Events	
Lethaby 2015	LNG-IUS versus no treatment LNG-IUS versus no medical treatment LNG-IUS versus surgical treatment	Women of reproductive years with regular heavy periods measured either objectively (by the alkaline haematin method), semi-objectively (by PBAC score) or subjectively (patient perception)	Menstrual bleeding (AH method and PBAC score) Health-related quality of life (SF-12, SF-36) Satisfaction with treatment Withdrawal Adverse effects	
Lethaby 2013	First generation versus second generation endometrial surgery	Women of reproductive years with regular heavy periods measured either objectively or subjectively.	Blood loss (A-H method, PBAC score) HRQoL	

Study	Intervention/ Comparison	Population	Outcomes	Comments
			Satisfaction Length of hospital stay Adverse events	
Lethaby 2008	Luteal progesterone versus other medical therapy Progestogens day 5-26 versus LNG-IUS	Women of reproductive years with regular heavy periods measured either subjectively by the patient or objectively	Blood loss (A-H method, PBAC score) HRQoL Patient acceptability Adverse events	
Marjoribanks 2016	TCRE versus oral medication Hysterectomy versus oral medication TCRE versus LNG-IUS TBA versus LNG-IUS Bipolar ablation versus LNG-IUS Hysterectomy versus LNG-IUS	Women of reproductive age with regular heavy menstrual periods measured either objectively (e.g. via the alkaline haematin test) or subjectively (e.g. via the pictorial blood loss assessment chart (PBAC), a menstrual blood loss diary or according to a woman's personal judgement).	Blood loss (A-H method, PBAC score) HRQoL Satisfaction Adverse events	
RCTs included in the Cochrane systematic reviews				
Abbott 2003 (Included in Lethaby 2013) UK	Bipolar resection versus TBA	Abnormal uterine bleeding - pictorial blood loss assessment chart score more than 150; no intrauterine pathology demonstrated by in- or outpatient hysteroscopy; normal endometrial biopsy; a uterine length less than 12 cm; premenstrual gonadotrophin levels; normal pap smear; had completed their family	HRQoL at 6 and 12 months Patient Satisfaction at 6 and 12 months	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
Abdel Malak & Shawki 2006 (Included in Lethaby 2015 and Majoribanks 2016) Egypt	LNG-IUS versus TCRE	Women scheduled to undergo hysterectomy for treatment of excessive uterine bleeding	Menstrual Blood loss (PBAC score) at 12 months Satisfaction at 12 months Adverse events	NMA only
Barrington 2003 (Included in Lethaby 2015 and Majoribanks 2016) UK	LNG-IUS versus TBA	Women with menorrhagia refractory to medical treatment referred by GPs to gynaecology clinic in district hospital.	Menstrual Blood loss (PBAC score) at 6 months	NMA only
Bhattacharya 1997 (Included in Lethaby 2013) UK	Laser ablation versus TCRE	Women less than or equal to 50 years of age; less than 100 kg in weight; clinical diagnosis of dysfunctional uterine bleeding (uterus less than size of a pregnancy of 10 weeks and normal endometrial histology)	Satisfaction at 12 months	NMA only
Bongers 2004 (Included in Lethaby 2013) Netherlands	Bipolar resection versus TBA	Menorrhagia (PBAC more than or equal to 150); normal uterus with benign histology and uterine length 6-11 cm; normal PAP smear; negative Chlamydia test, FSH less than 40 iu/L	Satisfaction at 1 year HRQoL (SF-36) at 1 and 5 years	NMA only Publications from the same trial with relevant outcomes for this review: Bongers 2005 Kleijn 2008
Brun 2006 (Included in Lethaby 2013) France	TCRE versus endometrial ablation - cavaterm	Women with menorrhagia unresponsive to medical treatment requesting conservative surgical management; no longer wishing to become pregnant; Higham blood loss score more than 100; internal uterine cavity length 4-12cm; normal endometrial biopsy; normal	Menstrual Blood loss (PBAC score) at 12 months Satisfaction at 12 months	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
		cervical cytology; completed family; using a reliable method of contraception		
Busfield 2006 (Included in Lethaby 2015 and Majoribanks 2016) New Zealand	LNG-IUS versus TBA	Women attended menstrual disorders clinic in Auckland, NZ	PBAC score at 3, 6, 12, 24 months HRQoL (SF-36) at 3, 6, 12, 24 Satisfaction at 3, 6, 12, 24 Adverse events	NMA and pairwise
Clark 2011 (Included in Lethaby 2013) UK	Bipolar ablation versus TBA	Women presenting to gynaecology outpatient clinic with HMB without organic pathology; no response to previous medical therapy; no desire to preserve their fertility; no contraindications to endometrial ablation (uterine cavity length more than 11cm, previous open myomectomy, endometrial resection/ablation and classical CS)	HRQoL (EQ-5D) at 6 months Satisfaction at 12 months	NMA only
Cooper 1997 (Included in Majoribanks 2016) UK	Gonadotrophin-releasing hormone analogue followed 5 weeks later by TCRE versus medical treatment (progestogens, COC, tranexamic acid, tranexamic acid plus mefenamic acid, danazol, or hormone replacement therapy)	Women referred to gynaecologists at Aberdeen Royal Infirmary, Scotland for treatment of clinically diagnosed dysfunctional uterine bleeding (i.e. uterus less than 10 weeks' pregnancy size and normal endometrial pathology	HRQoL (SF-36) at 4 months, 2 years, and 5 years Treatment satisfaction at 4 months, 2 years, and 5 years Treatment acceptability at 4 months, 2 years, and 5 years	Pairwise only Publications from the same trial with relevant outcomes for this review: Cooper 1999b Cooper 2001
Cooper 1999a (Included in Lethaby 2013)	Gonadotrophin-releasing hormone analogue followed 5 weeks later by TCRE versus MEA	Premenopausal, completed their families, dysfunctional uterine bleeding (uterine size	HRQoL (SF-36) at 1 and 5 years Satisfaction at 1 and 5 years	NMA only Publications from the same trial with relevant

Study	Intervention/ Comparison	Population	Outcomes	Comments
UK		equivalent to 10 weeks pregnancy or less), informed consent		outcomes for this review: Cooper 2005
Cooper 2002 (Included in Lethaby 2013) USA	Bipolar endometrial ablation versus loop resection/ rollerball	Menorrhagia verified by validated PBAC equal to 150 for 3 consecutive months; history of failed medical therapy	Menstrual Blood loss (PBAC score) at 3,6, and 12 months	NMA only
Cooper 2004 (Included in Lethaby 2013) Multinational	Gonadotrophin-releasing hormone analogue followed 4 weeks later by MEA versus rollerball	Non pregnant women more than 30 years; no desire for future pregnancy; failed, refused or not tolerated medical treatment; PBACmore than or equal to 185 (previous 1 or 3 months); FSH less than or equal to 30 iu/L; uterine cavity 6-14 cm	Menstrual Blood loss (PBAC score) at 1 year HRQoL (SF-36) at 1 year Satisfaction at 1 year Adverse events	NMA only
Corson 2000 (Included in Lethaby 2013) Multinational	TCRE using rollerball versus vesta device (inflatable balloon with electrode)	Score of more than 150 on PBAC; no plan for more children; either using contraception or 1 of either partner sterilised; failed progestin therapy or refused medical therapy or shown intolerance to these agents	Menstrual Blood loss (PBAC score) at 1 year Adverse events	NMA and pairwise
Corson 2001 (Included in Lethaby 2013) USA	Hydro Thermablator versus rollerball	30-50 years; family planning complete; documentation of excessive bleeding; uterine cavity measuring less than or equal to 10.5 cm; history of ineffective, not tolerated or refused medical therapy	Menstrual Blood loss (PBAC score) at 1 year HRQoL at 1 year Adverse events	NMA and pairwise Publications from the same trial with relevant outcomes for this review: Goldrath 2003
Crosignani 1997 (Included in Lethaby 2015 and Majoribanks 2016) Italy	LNG-IUS versus TCRE	More than 80 mL/cycle loss (as measured by more than 100 points on pictorial charts). Negative smear within 12 months. Endometrial	Menstrual Blood loss (PBAC score) at 6, 12 months HRQoL (SF-36) at 1 year	NMA and pairwise

Study	Intervention/ Comparison	Population	Outcomes	Comments
		pathology excluded by transvaginal ultrasound, diagnostic hysteroscopy and endometrial biopsy. Uterine size less than 8 weeks.	Satisfaction at 1 year Adverse events	
Dickersin 2007 (Included in Fergusson 2013) USA and Canada	Resection/ablation versus hysterectomy (vaginal, laparoscopic, or open)	Women 18 years of age or older; premenopausal; dysfunctional uterine bleeding for at least 6 months (defined as 1 or more of excess duration, amount or unpredictability); refractory to medical treatment for at least 3 months	HRQoL (SF-36) at 1, 2, 3, 4 years Satisfaction at 1, 2, 3, 4 years Adverse events	NMA and pairwise Dysfunctional uterine bleeding - 85% with 'excessive or abnormal bleeding'
Duleba 2003 (Included in Lethaby 2013) USA	Endometrial cryoablation versus TCRE rollerball	Menorrhagia due to benign causes, good general health, documented history of excessive uterine bleeding for at least 3 months, failed traditional therapy, did not desire future fertility, PBAC more than 150	Adverse events	Pairwise only
Dwyer 1993 (Included in Fergusson 2013) UK	Endometrial resection versus open hysterectomy	Women less than 52 years of age, complaint of menorrhagia that could not be con-trolled by conservative means, candidates for open hysterectomy	HRQoL (SF-36) at 2 years Satisfaction at 4 months and 2 years Post-operative complications	NMA and pairwise Publications from the same trial with relevant outcomes for this review: Sculpher 1996
Ergun 2012 (Included in Lethaby 2015 and Majoribanks 2016) Turkey	LNG-IUS versus rollerball	Women with abnormal uterine bleeding which had not responded to medical treatment Inclusion criteria: more than 35 years of age, regular menstrual cycle, score of 100 on PBAC	Menstrual Blood loss (PBAC score) Satisfaction	NMA only Publications from the same trial with relevant outcomes for this review: Ergun 2012a Ergun 2011

Study	Intervention/ Comparison	Population	Outcomes	Comments
Ghazizadeh 2014 (Included in Majoribanks 2016) Iran	Bipolar endometrial ablation versus TCRE versus LNG-IUS	Included: consecutive women with menorrhagia. Patients were candidates for hysterectomy. Mean age: 40 (35 to 45)	Satisfaction at 6 months	NMA only
Gupta 2013 (Included in Lethaby 2015) UK	LNG-IUS versus medical treatment (variety)	Women aged between 25 and 50 years, presenting to primary care physicians with menorrhagia involving at least 3 consecutive menstrual cycles	HRQoL (SF-36) at 6, 12, 24 months and 5 years Withdrawal for any reason Adverse events	NMA and pairwise Publications from the same trial with relevant outcomes for this review: Gupta 2015 * Medical treatment given at the discretion of the physician but included mefenamic acid, tranexamic acid, COC, or medroxyprogesterone.
Hawe 2003 (Included in Lethaby 2013) UK	Laser ablation versus TBA	Normal endometrial biopsy, no intrauterine pathology; normal uterine cavity (uterine length less than 12cm); high on blood loss score (more than 100); normal cervical cytology; completed family and using contraception	HRQoL (EQ-5D and SF-12) at 6 and 12 months Satisfaction at 6 and 12 months	NMA only
Hurskainen 2001 (Included in Lethaby 2015 and Majoribanks 2016) Finland	LNG-IUS versus hysterectomy (open, vaginal, or laparoscopic)	Menorrhagia, still menstruating, family completed, eligible for hysterectomy	Menstrual Blood loss (A-H method) at 1 and 5 years HRQoL (EQ-5D, RAND-36) at 1 and 5 years	NMA and pairwise Publications from the same trial with relevant outcomes for this review:

Study	Intervention/ Comparison	Population	Outcomes	Comments
			Satisfaction at 1 and 5 years Adverse events	Hurskainen 2004
Irvine 1998 (Included in Lethaby 2008 and Lethaby 2015) UK	LNG-IUS versus norethisterone	More than 80mL/cycle loss (as measured by alkaline haematin method), parous (1 or more children), normal pelvic examination, negative cervical cytology, regular menstrual cycle, good general health, uterine cavity sound length less than 10 cm.	Menstrual Blood loss (A-H method) at 1, 3 months Satisfaction Withdrawal due to adverse events Adverse events	NMA and pairwise
Kaunitz 2010 (Included in Lethaby 2015) Multinational	LNG-IUS versus medroxyprogesterone acetate	Parous women aged 18 years or more with idiopathic heavy menstrual bleeding (menstrual blood loss more than or equal to 80 mL per cycle (assessed by alkaline haematin method) desiring intrauterine contraception and willing to use barrier contraception	Menstrual Blood loss (A-H method) at 3, 6 months Discontinuation due to adverse events Adverse events	NMA and pairwise
Kittelsen & Istre 1998 (Included in Lethaby 2015 and Majoribanks 2016) Norway	LNG-IUS versus TCRE	Premenopausal women aged 30 to 49 years with heavy menstrual bleeding recruited from a gynaecology clinic specialising in operative hysteroscopy.	Menstrual Blood loss (PBAC score) at 1,2, 3 years Withdrawal due to adverse events Adverse events	NMA and pairwise Publications from the same trial with relevant outcomes for this review: Istre &Trolle 2001 Rauramo 2004
Meyer 1998 (Included in Lethaby 2013) USA and Canada	Rollerball versus TBA	30 years or more and premenopausal; normal Pap smears; normal endometrial biopsies within last 6 months; history of 3 months of excessive uterine	Menstrual Blood loss (PBAC score) at 1, 2, 3, 5 years Satisfaction at 1, 2, 3, 5 years Adverse events	NMA and pairwise Publications from the same trial with relevant outcomes for this review:

Study	Intervention/ Comparison	Population	Outcomes	Comments
		bleeding (PBAC score more than or equal to 150); ineffective medical therapy; uterine cavity normal (by either hysterosalpingography, hysteroscopy or TVUS) and with a range between 4 and 10 cm; no desire for future fertility; willing to continue current contraception		Grainger 2000 Loffer 2001 Loffer & Grainger 2002
O'Connor 1997 (Included in Fergusson 2013) UK	TCRE versus hysterectomy (open or vaginal)	Women 30 to 50 years of age who had symptomatic menorrhagia that required hysterectomy. Decision to have no more children, regular menstrual cycles of between 21 and 35 days, with each period lasting for less than 50% of the cycle, documented evidence of normal endometrial histology within the previous 12 months and normal cervical smear within the previous 3 years.	Satisfaction at 1 year Discontinuation due to adverse events Adverse events	NMA and pairwise
Pellicano 2002 (Included in Lethaby 2013) Italy	TBA versus TCRE	Women aged less than 50 yrs; weighed less than 100 kg; not desiring pregnancy; history of more than or equal to 3 months failed medical Rx; evidence of normal endometrial histology/Pap smear within previous 12 months	Satisfaction at 2 years	NMA only
Penninx 2010 (Included in Lethaby 2013)	Bipolar endometrial ablation versus hydrothermablation	160 women with menorrhagia, heavy menstrual bleeding, mean age	Satisfaction at 6, 12 months	NMA only Publications from the same trial

Study	Intervention/ Comparison	Population	Outcomes	Comments
Netherlands		45 years, recruited, the Netherlands		with relevant outcomes for this review: Penninx 2011
Perino 2004 (Included in Lethaby 2013) Italy	Intrauterine laser therapy versus TCRE	Women with dysfunctional uterine bleeding not associated with organic pathology and not responding to medical treatment	Satisfaction at 3 years	NMA only
Reid & Virtanen-Kari 2005 (Included in Lethaby 2015) UK	LNG-IUS versus mefenamic acid	Women aged 18 to 47 years; with good general health; regular ovulatory menstrual cycles 21-35 days and HMB measured by alkaline haematin method more than or equal to 80mL.	Menstrual blood loss (A-H method, PBAC score) at 6 months Adverse events	NMA and pairwise
Sambrook 2009 (Included in Lethaby 2013) UK	TBA versus MEA	Women complaining of heavy menstrual loss and requesting endometrial ablation; premenopausal; completed their families; uterine size equivalent to a 12 week pregnancy or less; no histopathological abnormalities; no fibroids obstructing the uterine cavity; lower segment caesarean section if scar thickness more than 10mm on transvaginal US	Menstrual Blood loss (PBAC score) at 1 year HRQoL (EQ-5D) at 1 and 5 years Satisfaction at 1 and 5 years	NMA only
Sesti 2011 (Included in Fergusson 2013) Italy	TBA versus hysterectomy (laparascopic subtotal)	Women 35 to 50 years of age with heavy menstrual bleeding, who had failed appropriate first-line oral medical therapy and required surgical treatment	Menstrual Blood loss (PBAC score) at 3, 6, 12, 24 months HRQoL (SF-36) at 24 months Adverse events	NMA and pairwise

Study	Intervention/ Comparison	Population	Outcomes	Comments
Sesti 2012 (Included in Lethaby 2015 and Majoribanks 2016) Italy	LNG-IUS versus hysterectomy (laparoscopic supracervical)	Presence of HMB, reproductive age 35 to 50 years, completed family, failed appropriate first line oral medical therapy, normal PAP smear, no pelvic pathology at ultrasound, normal endometrial biopsy, PBAC more than or equal to 100 (average of 2 consecutive cycles	Menstrual Blood loss (PBAC score) at 3, 6, 12, 24 months HRQoL (SF-36) at 12, 24 months	NMA only
Shaaban 2011 (Included in Lethaby 2015 and Majoribanks 2016) Egypt	LNG-IUS versus COC	Self-described HMB, requested contraception, 20 to 50 years old at initial assessment, regular cycle, living close to hospital for follow-up	Menstrual blood Loss (A-H method, PBAC score) at 6 and 12 months HRQoL at 6 and 12 months	Pairwise only
Shaw 2007 (Included in Lethaby 2015) UK	LNG-IUS versus TBA	Women aged 25 to 49 years, family complete, failed on appropriate first line oral medical therapy, normal histology on Pipelle endometrial biopsy, no pathology on pelvic ultrasound, normal cervical smear, PBAC score more than 120 (mean of 2 control cycles)	Menstrual Blood loss (PBAC score) at 3, 6, 9, 12 months Satisfaction at 2 years Adverse events	NMA and pairwise

Study	Intervention/ Comparison	Population	Outcomes	Comments
Soysal 2002 (Included in Lethaby 2015 and Majoribanks 2016) Turkey	LNG-IUS versus TBA	Women aged more than 40 years; no further desire for childbearing; complaint of menorrhagia (defined by a PBAC score more than 150 for 2 months prior to the study); refused or non-response to medical treatment	Menstrual Blood loss (PBAC score) score at 12 months HRQoL (SF36) at 12 months Satisfaction at 12 months Adverse events	NMA and pairwise
Tam 2006 (Included in Lethaby 2015 and Majoribanks 2016) Hong Kong	LNG IUS versus TBA (Thermachoice)	Premenopausal womenmore than 40 years with a documented history of heavy menstruation for at least 3 months, completed family or no desire for future fertility, HMB had failed to respond to conventional medical therapy, not currently on hormonal treatment	HRQoL Adverse events	NMA and pairwise
van Zon-Rabelink 2003 (Included in Lethaby 2013) Netherlands	Rollerball versus TBA	Menorrhagia without sufficient relief from medical therapy by GP; menstrual blood loss score equal to 185 points in 2 periods due to dysfunctional uterine bleeding according to ultrasound and diagnostic hysteroscopy	Menstrual Blood loss (PBAC score) at 2 years Satisfaction at 2 years Adverse events	NMA and pairwise Publications from the same trial with relevant outcomes for this review: van Zon-Rabelink 2004
Vercillini 1999 (Included in Lethaby 2013) Italy	Vaporising electrode versus TCRE	Women more than 35 years; referred for hysterectomy; uterine volume less than 12 week pregnancy; normal uterine cavity at hysteroscopy; no evidence of atypical	Menstrual Blood loss (PBAC score) at 1 year Satisfaction at 1 year	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
		hyperplasia; no adnexal tumours on clinical and ultrasonographic examination		
Zupi 2003 (Included in Fergusson 2013) Italy	TCRE versus hysterectomy (laparascopic subtotal)	Women younger than 50 years of age; weight less than 100 kg; not seeking contraception; normal endometrial histology and Pap smear within the previous 6 months; uterus not greater than 12 weeks of pregnancy in size; without submucosal fibroids, adnexal masses or endometriosis	HRQoL (SF-36 at 3 months, SF-12 at 1 and 2 years) Adverse events	NMA and pairwise % HMB not reported
RCTs primary studies				
Abu Hashim 2012 Egypt	Norethisterone versus combined hormonal contraceptive vaginal ring	Women with idiopathic HMB	Menstrual blood loss (PBAC score) at 3 months Satisfaction at 3 months	NMA only
Aberdeen Group 1999 UK	Hysterectomy versus endometrial laser ablation	Women under 50 years of age, weighed under 100 kg. Clinical diagnosis of dysfunctional uterine bleeding and would have otherwise undergone hysterectomy	Satisfaction at 4 years	NMA only
Athanatos 2015 Greece	Bipolar endometrial resection versus MEA	Women with DUB defined by PBAC	Menstrual blood loss (PBAC score) at 12 months Satisfaction at 12 months	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
Bonnar & Sheppard 1996 Ireland	Ethamsylate versus tranexamic acid versus mefenamic acid	Women 35 to 46 years (mean 39) with a mean menstrual blood loss more than 80 mL/ cycle measured over 3 consecutive menstrual periods	Blood loss (A-H method) at 1, 2, 3 months Satisfaction at 3 months Adverse events	NMA only
Dunphy 1998 Canada	Danazol versus medroxyprogesterone acetate	Women 18 years and older with objectively confirmed HMB	Menstrual blood loss (PBAC score) at 3 months	NMA only
Endrikat 2009 Canada	LNG-IUS versus COC (norethindrone acetate 1mg and ethinyl estradiol 20 mcg)	Healthy women with idiopathic menorrhagia over the age of 30.	Menstrual blood loss (PBAC score) at 12 months Discontinuation due to adverse events	NMA only
Fraser 2011 Multinational	Estradiol valerate versus placebo	Healthy women with idiopathic HMB confirmed in 90 day run-in period	Menstrual blood loss (A-H method) at months 1-7 Discontinuation due to adverse events	NMA only
Ghazizadeh 2011 Iran	LNG-IUS versus TCRE	Women age 35-45 with HMB defined by PBAC of more than 100;	Menstrual blood loss (PBAC score) at 6, 12 months Satisfaction at 6, 12 months Adverse events	NMA and pairwise
Goshtasebi 2013 Iran	Medroxyprogesterone acetate versus tranexamic acid	Women with HMB of endometrial origin.	Menstrual blood loss (PBAC score) at 3 months HRQoL (SF-36) at 3 months	NMA only
Khajehei 2013 Iran	Mefenamic acid versus naproxen	Women with HMB aged 20 - 45 years; normal findings on cervical smear test; normal ovulatory cycles	Menstrual blood loss (PBAC score) at 6 months	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
Kiseli 2016 Turkey	Norethisterone versus tranexamic acid versus LNG-IUS	Premenopausal patients (18–45 years) with complaints of regular but heavy periods. Mean PBAC scores of more than or equal to 100 during 2 consecutive periods	Menstrual blood loss (PBAC score) at 1, 3, 6 months HRQoL (WHO short form) at 6 months Satisfaction at 6 months	NMA and pairwise
Kriplani 2006 India	Tranexamic acid versus medroxyprogesterone acetate	Women presenting with HMB confirmed by PBAC;	Menstrual blood loss (PBAC score) at 3 months Satisfaction at 3 months Discontinuation due to adverse events at 3 months	NMA only
Penninx 2016 Netherlands	Bipolar versus balloon ablation	Women with HMB with a minimum of 150 points on PBAC	Patient satisfaction	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
Sambrook 2014 UK	TBA versus MEA	Women complaining of heavy menstrual loss and requesting endometrial ablation; premenopausal; completed their families; uterine size equivalent to a 12 week pregnancy or less; no histopathological abnormalities; no fibroids obstructing the uterine cavity; lower segment caesarean section if scar thickness more than 10mm on transvaginal US	Menstrual blood loss (PBAC score) at 5 years HRQoL at 5 years Satisfaction at 5 years	NMA only
Silva-Filho 2013 Brazil	LNG-IUS versus TBA	Clinical HMB refractory to medical treatment (i.e., oral contraceptive pills, estrogen–progestin preparations, nonsteroidal anti-inflammatory drugs); a 3-month washout period, regular menstrual cycles, age more than or equal to 35 years; menstrual blood loss more than 80 mL as measured by PBAC; a negative pregnancy test, uterine volume less than 200 mL as measured by transvaginal sonogram (the uterine volume was calculated as length×width×height×0.45); a negative Pap smear within the last year	Satisfaction at 5 years	NMA only

Study	Intervention/ Comparison	Population	Outcomes	Comments
Vihko 2003 Finland	Thermal balloon ablation versus cavaterm	Women with HMB	Satisfaction	NMA only

AH: alkaline haematin; COC: combined oral contraceptives; HMB: heavy menstrual bleeding; HRQoL: health-related quality of life; LNG-IUS: levonorgestrel-releasing intrauterine system; MBL: menstrual blood loss; MEA: microwave endometrial ablation; NMA: network meta-analysis; "NMA only": study was only included in network meta-analysis and not pairwise analysis; PBAC: pictorial blood loss assessment chart; SF-36: 36-Item Short Form Survey; TBA: thermal balloon ablation; TCRE: transcervical resection of endometrium; TVUS: *Transvaginal Ultrasound; WHO: World Health Organization*

See Appendix F – Clinical evidence tables for full evidence tables. See Appendix L – Summary of studies and quality appraisal of included in the network meta-analysis for a summary of the study characteristics (Table 56) and risk of bias assessment (Table 57).

Quality assessment of clinical studies included in the evidence review

The Grading of Recommenations, Assessment, Development, and Evaluation (GRADE) methodology was used to evaluate the quality and confidence of each outcome in the evidence.

The quality of each piece of evidence, whether from meta-analysis or from individual studies was then assessed using GRADE methodology. See Appendix G – GRADE tables for full GRADE tables.

The quality of Cochrane systematic reviews were assessed using the AMSTAR tool.

For more details on the quality assessment of clinical studies in the evidence review, please see Methods chapter.

Clinical evidence profile for NMA outcomes

Women with no identified pathology or fibroids less than 3cm in diameter

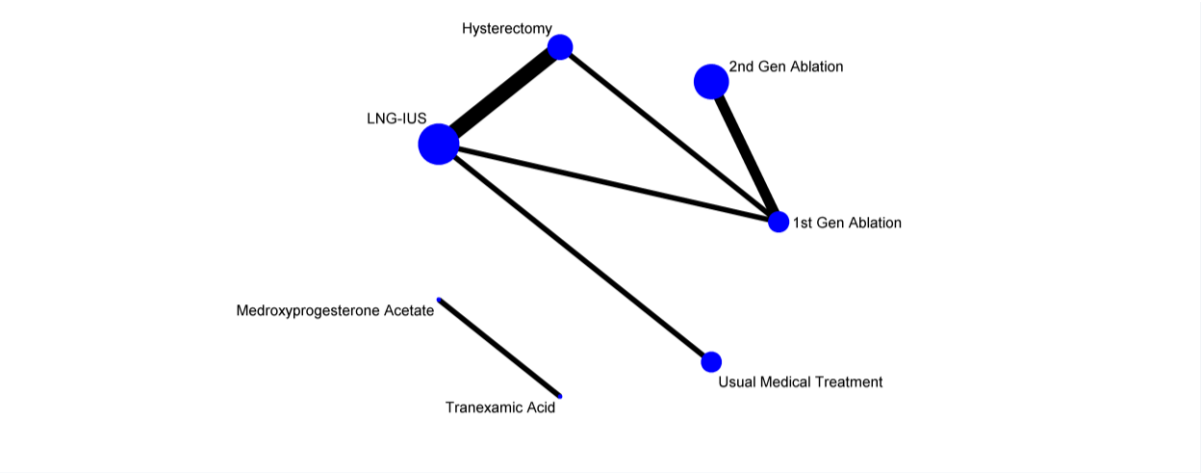
Health-related quality of life – EQ-5D

Treatment efficacy was found to vary depending on study follow-up. Therefore 2 NMAs were conducted separately for short-term (less than or equal to 1 year) follow-up and long-term (more than 1 year) follow-up.

EQ-5D - short-term (less than or equal to 1 year) follow-up

Eleven studies of 5 treatment classes were included in the network for EQ-5D at short-term follow-up, with a total sample size of 2030 women (Figure 1). Five studies were at high risk of bias, 1 had unclear risk of bias, and 3 were at low risk of bias. Data for 5 of the studies were mapped from the SF-36.

Figure 1: Network for HRQoL after short-term follow-up



1st gen ablation: first generation endometrial ablation; 2nd gen ablation: second generation endometrial ablation; HRQoL: health-related quality of life; LNG-IUS: levonorgestrel-releasing intrauterine system; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes. Two treatment classes were not connected and could not be compared in the NMA (medroxyprogesterone acetate and tranexamic acid)

Table 5 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as mean differences (MDs). These results were derived from a fixed effect model.

No meaningful differences in HRQoL after short-term follow-up were found between any treatment classes.

Although usual medical treatment had the highest probability of being the best treatment for short-term HRQoL (30.1%) this was very similar to other treatment classes (Table 6).

Table 5: Matrix of results for the NMA of HRQoL after short-term follow-up

LNG-IUS	**0 (-0.06, 0.06)**		**0.04 (-0.07, 0.16)**	**0 (-0.05, 0.05)**
0.01 (-0.04, 0.06)	**Hysterectomy**		-0.04 (-0.13, 0.06)	
0.02 (-0.07, 0.11)	0.01 (-0.08, 0.1)	**Second generation ablation**	-0.02 (-0.07, 0.03)	
0 (-0.08, 0.08)	-0.01 (-0.09, 0.07)	-0.02 (-0.07, 0.03)	**First generation ablation**	
0 (-0.05, 0.05)	-0.01 (-0.08, 0.06)	-0.02 (-0.13, 0.09)	0 (-0.1, 0.09)	**Usual medical treatment**

HRQoL: health-related quality of life; LNG-IUS: levonorgestrel-releasing intrauterine system; NMA: network meta-analysis; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

Mean differences and 95% credible intervals (CrI) from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Mean

differences greater than 0 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 0.

Table 6: Probabilities of being the best treatment class and the rank and 95% CrI

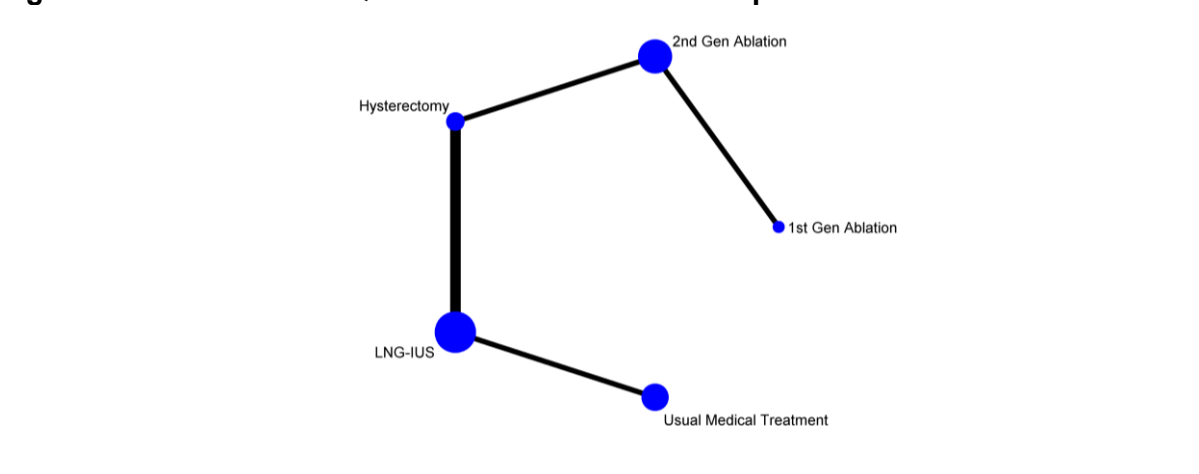
Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
LNG-IUS	471	4	18.18%	3 (1, 5)
Hysterectomy	237	3	12.60%	3 (1, 5)
Second generation ablation	746	6	11.48%	4 (1, 5)
First generation ablation	290	4	27.61%	3 (1, 5)
Usual medical treatment	286	1	30.13%	3 (1, 5)

CrI: Credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

EQ-5D - Long-term (more than 1 year) follow-up

Seven studies of 5 treatment classes were included in the network for EQ-5D at long-term follow-up, with a total sample size of 1591 women (Figure 2). Five studies were at high risk of bias and 2 had unclear risk of bias. Data for 5 of the studies were mapped from the SF-36.

Figure 2: Network for HRQoL after short-term follow-up



1st gen ablation: first generation endometrial ablation; 2nd gen ablation: second generation endometrial ablation; HRQoL: health-related quality of life; LNG-IUS: levonorgestrel-releasing intrauterine system; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 7 presents the results of the conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as MDs. These results were derived from a fixed effects model. Incoherence could not be assessed in this network as there were no closed loops of treatments to assess the difference between direct and indirect evidence for any comparison.

LNG-IUS, hysterectomy and usual medical treatment were all found to be significantly better than either first or second generation endometrial ablation at improving HRQoL in the long-term. No significant differences were found between LNG-IUS, hysterectomy and usual medical treatment, nor between first and second generation endometrial ablation.

Usual medical treatment had the highest probability of being the best treatment for long-term HRQoL (73.4%), followed by LNG-IUS (Table 8).

Table 7: Matrix of results for the NMA of HRQoL after long-term follow-up

LNG-IUS	**-0.03 (-0.08, 0.02)**			**0.02 (-0.03, 0.06)**
-0.03 (-0.08, 0.02)	**Hysterectomy**	**-0.1 (-0.19, -0.01)**		
-0.13 (-0.23, -0.02)	**-0.1 (-0.2, -0.01)**	**Second generation ablation**	-0.01 (-0.07, 0.05)	
-0.14 (-0.26, -0.02)	**-0.11 (-0.23, 0)**	-0.01 (-0.07, 0.05)	**First generation ablation**	
0.02 (-0.03, 0.06)	0.04 (-0.02, 0.11)	**0.15 (0.03, 0.26)**	**0.16 (0.03, 0.29)**	**Usual medical treatment**

HRQoL: health-related quality of life; LNG-IUS: levonorgestrel-releasing intrauterine system; NMA: network meta-analysis; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

Mean differences and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Mean differences greater than 0 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 0.

Table 8: Probabilities of being the best treatment class and the rank and 95% CrI

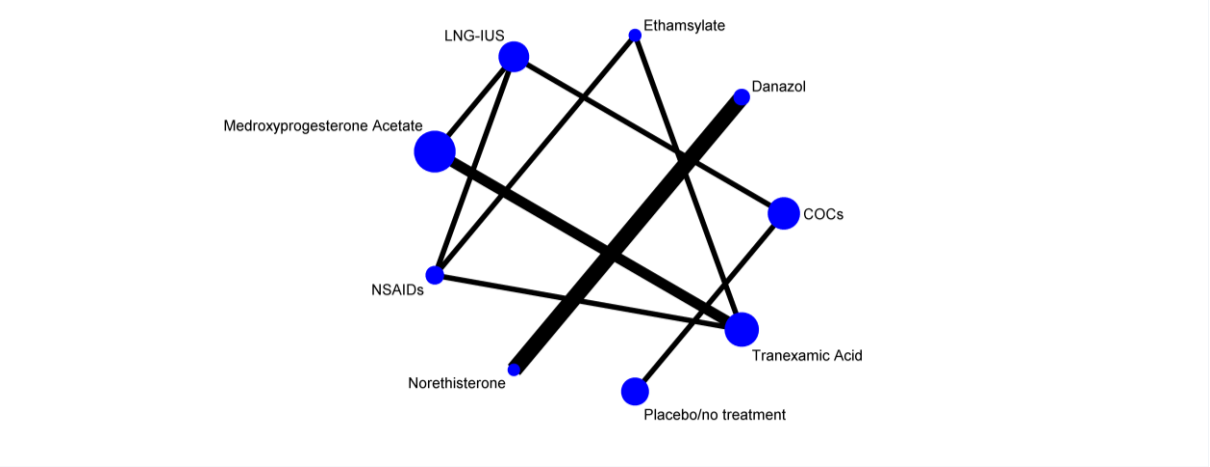
Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
LNG-IUS	438	2	19.79%	2 (1, 3)
Hysterectomy	185	3	6.11%	3 (1, 4)
Second generation ablation	562	4	0.21%	4 (4, 5)
First generation ablation	120	1	0.48%	5 (4, 5)
Usual medical treatment	286	1	73.41%	1 (1, 3)

CrI: Credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

Discontinuation of treatment due to adverse events

Seven trials of 7 treatment classes were included in the network for the outcome of discontinuation of treatment due to adverse events, with a total sample size of 746 women (Figure 3). Five studies were at high risk of bias, 1 had unclear risk of bias, and 1 was at low risk of bias.

Figure 3: Network for discontinuation of treatment due to adverse events



1st Gen Ablation: first generation endometrial ablation; 2nd Gen Ablation: second generation endometrial ablation; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progesterone-only pill

Note: The size of nodes is proportional to the number of women in the network who were given a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes. Two treatment classes were not connected and could not be compared in the NMA (danazol and norethisterone)

Table 9 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as odds ratios (ORs). These results were derived from a fixed effect model. No incoherence was found in any of the closed loops of treatments (Appendix N).

There was considerable uncertainty in the results, primarily as relatively small numbers of women discontinued treatment. Treatment with COCs was found to result in significantly more discontinuations due to adverse events than for all other treatment classes. NSAIDs were also found to lead to less discontinuation due to adverse events than LNG-IUS. The uncertainty in the network meant that there were no other significant differences found between other treatment classes.

Though this outcome was taken where reported in studies as discontinuation ‘due to adverse events’, it is likely that women who are not finding the treatment effective or women who have difficulty with treatment compliance, may be more likely to discontinue treatment due to adverse events. Therefore this outcome is not independent of treatment efficacy. This may explain why NSAIDs had the highest probability of being the best treatment for discontinuation due to adverse events (86.7%), when placebo/no treatment had only a 2.2% probability of being the best treatment (Table 10).

Table 9: Matrix of results for the NMA of discontinuation of treatment due to adverse events

Placebo					**6.24 (2.24, 20.64)**	
0.16 (<0.01, 6.08)	**Etham**	0.2 (0.01, 1.71)	0.72 (0.12, 3.83)			
0.02 (<0.01, 1.07)	0.16 (<0.01, 1.45)	**NSAIDs**	0.91 (<0.01, >999)			**>999 (25.71, >999)**
0.13 (<0.01, 3.25)	0.78 (0.14, 4.05)	4.92 (0.56, 153.8)	**TXA**	1.7 (0.66, 4.53)		
0.23 (<0.01, 5.1)	1.38 (0.2, 9.19)	8.83 (0.86, 295.2)	1.77 (0.69, 4.69)	**MPA**		1.7 (0.66, 4.53)
6.22 (2.24, 20.38)	**38.2 (1.25, >999)**	**266.5 (7.1, >999)**	**48.35 (2.42, >999)**	**27.02 (1.56, >999)**	**COCs**	**0.11 (<0.01, 0.91)**
0.66 (0.02, 7.71)	3.7 (0.31, 57.86)	**24.4 (1.74, >999)**	4.72 (0.71, 46.18)	2.64 (0.49, 22.03)	**0.11 (<0.01, 0.9)**	**LNG-IUS**

COCs: combined oral contraceptives; Etham: Ethamsylate; LNG-IUS: levonorgestrel-releasing intrauterine system; MPA: medroxyprogesterone acetate; NMA: network meta-analysis; NSAIDs: non-steroidal anti-inflammatory drug; TXA: tranexamic acid

Note: Odds ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Odds ratios less than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 10: Probabilities of being the best treatment class and the rank and 95% CrI

Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
Placebo	149	1	2.15%	6 (2, 6)
Ethamsylate	27	1	4.01%	3 (1, 6)
NSAIDs	49	2	86.68%	1 (1, 3)
Tranexamic acid	121	3	6.09%	2 (1, 5)
Medroxyprogesterone acetate	172	3	0.89%	4 (2, 6)
COCs	101	2	0.00%	7 (6, 7)
LNG-IUS	127	3	0.17%	5 (3, 6)

COCs: combined oral contraceptives; CrI: credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs

Blood loss

There was considerable heterogeneity in studies investigating blood loss, particularly in those assessing surgical techniques. Therefore studies were split into 3 NMAs, which helped explain some of the heterogeneity:

- pharmacological studies
- surgical studies including women with no fibroids (or where fibroids were not reported)

- surgical studies including greater than 33% women with non-cavity uterine fibroids less than 3 cm in diameter.

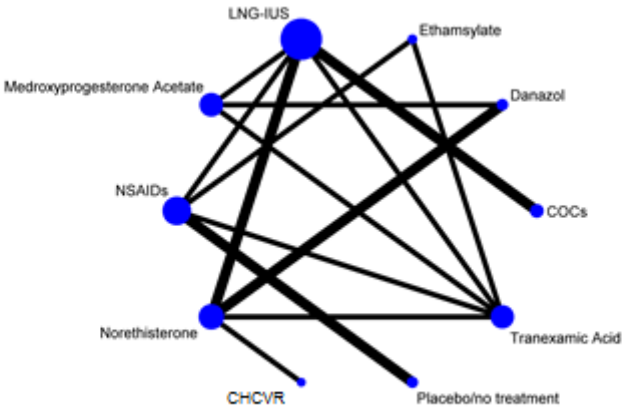
Studies comparing LNG-IUS to a surgical technique were included in the surgical networks, as women in these trials were thought to be similar to other surgical trials.

For the 2 surgical NMAs, there were considerable differences between different surgical techniques within the second generation endometrial ablation class. Therefore the individual treatments in this class were analysed as separate treatments in the networks.

Pharmacological treatments

Twelve trials of 10 pharmacological treatment classes were included in the network for blood loss, with a total sample size of 901 women (Figure 4). Five studies measured blood loss using the Alkaline-Haematin method and 7 studies using the Pictorial Blood Assessment Chart. Ten studies were at high risk of bias, 1 had unclear risk of bias, and 1 was at low risk of bias.

Figure 4: Network of pharmacological treatments for blood loss



CHCVR: combined hormonal contraceptive vaginal ring; COCs: combined oral contraceptives; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs; TXA: tranexamic acid

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 11 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as mean ratios (MRs). These results were derived from a random effects model with low heterogeneity (between-study standard deviation: 0.19 (95% CrI: 0.09, 0.44)).

Incoherence could not be formally assessed in this network, as methods for doing this using MRs are not yet developed. However, visual comparison of direct and NMA estimates show that the 2 results are similar, suggesting that there is no substantial incoherence.

LNG-IUS was found to be considerably better at reducing blood loss than all other treatments (Table 12). No significant differences were found between any of the other treatments, though the results were reasonably imprecise.

LNG-IUS had the highest probability of being the best pharmacological treatment for reducing blood loss (93.3%) (Table 12).

Table 11: Matrix of results for the NMA of pharmacological treatments for blood loss

Placebo			**0.81 (0.55, 1.18)**						
0.86 (0.45, 1.67)	**Danazol**				1.11 (0.64, 1.97)	0.84 (0.49, 1.45)			
0.87 (0.47, 1.59)	1.01 (0.55, 1.84)	**Etham**	0.97 (0.56, 1.66)	0.84 (0.49, 1.44)					
0.81 (0.54, 1.21)	0.94 (0.55, 1.59)	0.94 (0.6, 1.47)	**NSAID**						0.63 (0.36, 1.11)
0.75 (0.44, 1.31)	0.87 (0.56, 1.36)	0.86 (0.56, 1.36)	0.92 (0.64, 1.36)	**TXA**	1.04 (0.61, 1.78)	1.01 (0.59, 1.72)			0.7 (0.4, 1.2)
0.82 (0.45, 1.52)	0.95 (0.66, 1.38)	0.94 (0.55, 1.65)	1.01 (0.64, 1.62)	1.09 (0.76, 1.59)	**NA**			1 (0.58, 1.71)	0.58 (0.29, 1.08)
0.83 (0.46, 1.57)	0.97 (0.67, 1.45)	0.96 (0.57, 1.7)	1.03 (0.66, 1.67)	1.12 (0.8, 1.61)	1.02 (0.7, 1.52)	**MPA**			**0.4 (0.23, 0.71)**
0.67 (0.35, 1.33)	0.78 (0.46, 1.38)	0.77 (0.43, 1.47)	0.83 (0.5, 1.43)	0.89 (0.56, 1.48)	0.82 (0.51, 1.34)	0.8 (0.49, 1.32)	**COCs**		0.72 (0.46, 1.01)
0.81 (0.38, 1.77)	0.95 (0.53, 1.72)	0.94 (0.46, 1.96)	1.01 (0.53, 1.96)	1.09 (0.6, 1.98)	1 (0.63, 1.59)	0.98 (0.53, 1.78)	1.22 (0.62, 2.35)	**CHCVR**	
0.46 (0.27, 0.82)	**0.54 (0.35, 0.83)**	**0.54 (0.32, 0.9)**	**0.57 (0.39, 0.85)**	**0.62 (0.44, 0.87)**	**0.57 (0.41, 0.79)**	**0.56 (0.39, 0.78)**	**0.69 (0.48, 0.97)**	0.57 (0.32, 1.01)	**LNG-IUS**

CHCVR: combined hormonal contraceptive ring; COCs: combined oral contraceptives; Etham: Ethamsylate; LNG-IUS: levonorgestrel-releasing intrauterine system; MPA: medroxyprogesterone acetate; NA: norethisterone; NMA: network meta-analysis; NSAID: non-steroidal anti-inflammatory drug; TXA: tranexamic acid

Note: Mean ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Mean ratios less than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 12: Probabilities of being the best treatment class and the rank and 95% CrI

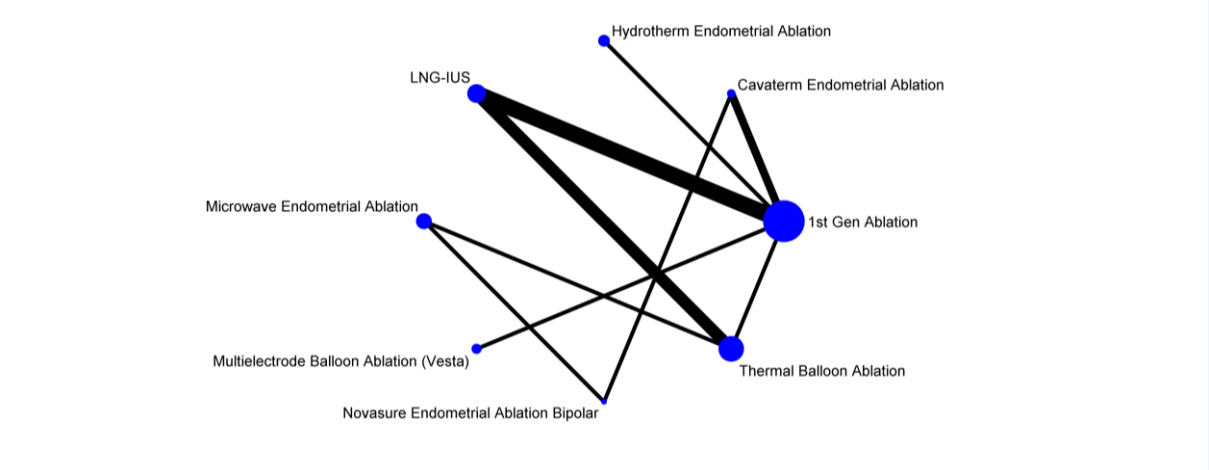
Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
Placebo	32	1	0.60%	2 (9, 10)
Danazol	46	2	0.40%	2 (7, 10)
Ethamsylate	27	1	1.00%	2 (7, 10)
NSAIDs	110	3	0.30%	2 (6, 9)
Tranexamic acid	92	3	0.30%	2 (4, 8)
Norethisterone	109	4	0.10%	2 (6, 10)
Medroxyprogesterone acetate	136	3	0.10%	2 (6, 10)
COCs	76	2	1.60%	2 (3, 9)
Combined hormonal contraceptive vaginal ring	48	1	2.30%	2 (6, 10)
LNG-IUS	225	6	93.30%	1 (1, 2)

COCs: combined oral contraceptives; CrI: credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs

Surgical treatments – women with no identifiable fibroids

Fifteen trials of 8 surgical techniques (including LNG-IUS) were included in the network for blood loss in women with no identifiable fibroids, with a total sample size of 1664 women (Figure 5). All studies measured blood loss using the Pictorial Blood Assessment Chart. 11 studies were at high risk of bias, 1 had unclear risk of bias, and 3 were at low risk of bias.

Figure 5: Network of surgical treatments for blood loss in women with no identifiable fibroids



1st Gen Ablation: first generation endometrial ablation; 2nd Gen Ablation: second generation endometrial ablation; LNG-IUS: levonorgestrel-releasing intrauterine system

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 13 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as MRs. These results were derived from a random effects model with high heterogeneity (between-study standard deviation: 0.56 (95% CrI: 0.30, 1.26)).

Incoherence could not be formally assessed in this network, as methods for doing this using MRs are not yet developed. However, visual comparison of direct and NMA estimates show that incoherence may be present – for thermal balloon ablation versus first generation endometrial ablation the direction of effect is reversed, although neither result is significant. The results from this NMA should therefore be interpreted with some caution.

Novasure was found to lead to significantly lower blood loss than most other treatments (LNG-IUS, thermal balloon ablation, microwave endometrial ablation, cavaterm ablation and first generation endometrial ablation). No significant differences were found between any of the other surgical techniques, though the results were generally very imprecise.

Novasure had the highest probability of being the best surgical treatment for reducing blood loss in women with no identifiable fibroids (90.7%) (Table 14).

Table 13: Matrix of results for the NMA of surgical treatments for blood loss in women with no identifiable fibroids

LNG-IUS	**1.01 (0.52, 1.98)**						**0.58 (0.3, 1.03)**
0.92 (0.48, 1.88)	**TBA**	0.77 (0.22, 2.71)					1.22 (0.38, 3.92)
1.09 (0.28, 5.38)	1.18 (0.34, 4.97)	**MEA**					
0.57 (0.16, 1.55)	0.62 (0.16, 1.79)	0.52 (0.08, 2.35)	**Cava**	0.35 (0.1, 1.18)			0.91 (0.4, 2.1)
0.13 (0.02, 0.56)	**0.14 (0.02, 0.62)**	**0.12 (0.01, 0.68)**	**0.23 (0.05, 0.78)**	**Nova**			
0.66 (0.14, 2.79)	0.72 (0.14, 3.2)	0.61 (0.07, 3.87)	1.16 (0.24, 6.48)	5.08 (0.77, 47.51)	**HEA**		0.94 (0.29, 3)
0.55 (0.12, 2.32)	0.59 (0.11, 2.64)	0.5 (0.05, 3.22)	0.95 (0.2, 5.38)	4.2 (0.64, 39.81)	0.83 (0.12, 5.57)	**MBA**	1.13 (0.35, 3.64)
0.62 (0.31, 1.11)	0.67 (0.27, 1.4)	0.57 (0.11, 2.22)	1.09 (0.46, 2.99)	**4.79 (1.17, 26.71)**	0.94 (0.24, 3.63)	1.14 (0.29, 4.38)	**First generation ablation**

Cava: cavaterm endometrial ablation; HEA: hydrotherm endometrial ablation; LNG-IUS: levonorgestrel-releasing intrauterine system; MBA: multielectrode balloon ablation; MEA: microwave endometrial ablation; NMA: network meta-analysis; Nova: novasure radiofrequency endometrial ablation; TBA: thermal balloon ablation

Note: Mean ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Mean ratios less than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 14: Probabilities of being the best treatment class and the rank and 95% CrI

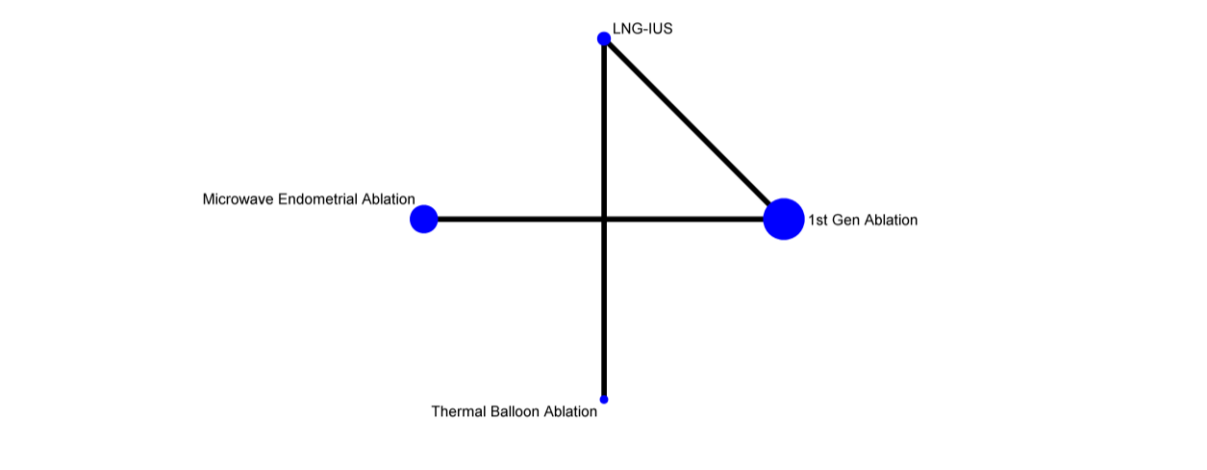
Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
LNG-IUS	225	7	0.00%	4 (7, 8)
Thermal balloon ablation	324	5	0.10%	3 (6, 8)
Microwave endometrial ablation	190	2	0.80%	2 (7, 8)
Cavaterm endometrial ablation	88	3	0.40%	2 (3, 8)
Novasure endometrial ablation bipolar	70	2	90.70%	1 (1, 3)
Hydrotherm endometrial ablation	184	1	2.90%	1 (4, 8)
Multielectrode balloon ablation	112	1	4.80%	1 (3, 8)
First generation ablation	471	9	0.20%	2 (4, 6)

CrI: credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system

Surgical treatments – including women with non-cavity uterine fibroids less than 3 cm in diameter

Four trials of 4 surgical techniques (including LNG-IUS) were included in the network for blood loss in women with non-cavity uterine fibroids less than 3 cm, with a total sample size of 519 women (Figure 6). All studies measured blood loss using the Pictorial Blood Assessment Chart. All 4 studies were at high risk of bias.

Figure 6: Network of surgical treatments for blood loss in women with non-cavity uterine fibroids of 3 cm or more in diameter



1st Gen Ablation: first generation endometrial ablation; LNG-IUS: levonorgestrel-releasing intrauterine system

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 15 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as MRs. These results were derived from a fixed effect model. Incoherence could not be assessed in this network as there were no closed loops of treatments to assess the difference between direct and indirect evidence for any comparison.

Thermal balloon ablation and microwave endometrial ablation were both found to lead to significantly lower blood loss than LNG-IUS and first generation endometrial ablation. No other significant differences were found. Table 15 graphically presents the results computed by the NMA for each treatment versus LNG-IUS.

Microwave endometrial ablation had the highest probability of being the best surgical treatment for reducing blood loss in women with non-cavity uterine fibroids less than 3 cm in diameter (71.1%), followed by thermal balloon ablation (28.9%) (Table 16).

Table 15: Matrix of results for the NMA of surgical treatments for blood loss in women with non-cavity uterine fibroids less than 3 cm

LNG-IUS	**0.64 (0.54, 0.74)**		1.02 (0.87, 1.2)
0.64 (0.54, 0.74)	**TBA**		
0.58 (0.41, 0.8)	**0.9 (0.62, 1.3)**	**MEA**	**1.77 (1.34, 2.38)**
1.02 (0.87, 1.2)	**1.6 (1.29, 2.01)**	**1.77 (1.34, 2.39)**	**First generation ablation**

LNG-IUS: levonorgestrel-releasing intrauterine system; MEA: microwave endometrial ablation; TBA: thermal balloon ablation

Note: Mean ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Mean ratios less than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 16: Probabilities of being the best treatment class and the rank and 95% CrI

Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
LNG-IUS	65	2	0.00%	3 (3, 4)
Thermal balloon ablation	40	1	28.90%	1 (2, 2)
Microwave endometrial ablation	97	1	71.10%	1 (1, 2)
First generation ablation	121	3	0.00%	3 (4, 4)

CrI: credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system

Patient satisfaction

There was considerable heterogeneity in studies investigating patient satisfaction, particularly in those assessing surgical techniques. Therefore studies were split into 3 NMAs, which helped explain some of the heterogeneity:

- pharmacological studies
- surgical studies including women with no fibroids (or where fibroids were not reported)
- surgical studies including greater than 33% women with non-cavity uterine fibroids less than 3 cm in diameter.

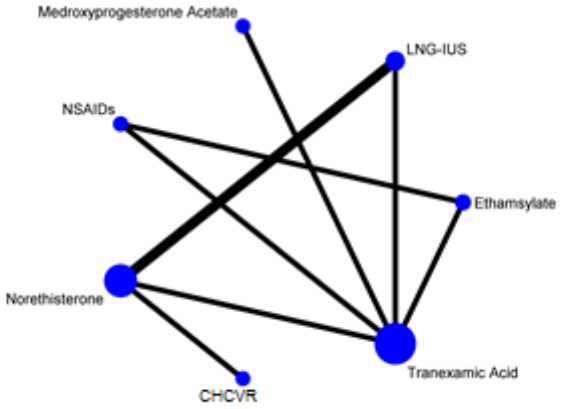
Studies comparing LNG-IUS to a surgical technique were included in the surgical networks, as women in these trials were thought to be similar to other surgical trials.

For the 2 surgical NMAs, there were considerable differences between different surgical techniques within the second generation endometrial ablation class. Therefore the individual treatments in this class were analysed as separate treatments in the networks.

Pharmacological treatments

Five trials of 7 pharmacological treatment classes were included in the network for patient satisfaction, with a total sample size of 371 women (Figure 7). Three studies were at high risk of bias, 1 had unclear risk of bias, and 1 was at low risk of bias.

Figure 7: Network of pharmacological treatments for patient sastisfication



CHCVR: combined hormonal contraceptive vaginal ring; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 17 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as ORs. These results were derived from a fixed effect model. Incoherence could not be assessed in this network as there were no closed loops of treatments that were not from multi-arm trials (which cannot be incoherent).

LNG-IUS and combined hormonal contraceptive vaginal ring were found to have significantly higher patient satisfaction than ethamsylate, norethisterone and medroxyprogesterone acetate (Table 17). Tranexamic acid and norethisterone also had higher numbers of satisfied patients than ethamsylate and medroxyprogesterone acetate.

Combined hormonal contraceptive vaginal ring had the highest probability of being the best pharmacological treatment for improving patient satisfaction (56.6%), followed closely by LNG-IUS (40.0%) (Table 18).

Table 17: Matrix of results for the NMA of pharmacological treatments for patient satisfaction

Etham	**7.27 (2.14, 28.05)**	**8.61 (2.57, 32.69)**				
7.26 (2.13, 27.91)	**NSAID**					
8.56 (2.57, 32.76)	1.18 (0.3, 4.59)	**TXA**	1.36 (0.36, 5.26)	**0.1 (0.01, 0.42)**		3.54 (0.81, 19.89)
11.03 (1.92, 67.83)	1.51 (0.24, 9.45)	1.28 (0.37, 4.42)	**NA**		**3.36 (1.45, 8.11)**	3.19 (0.93, 11.86)
0.84 (0.08, 6.23)	**0.11 (0.01, 0.87)**	**0.1 (0.01, 0.42)**	**0.08 (0.01, 0.53)**	**MPA**		
37.18 (5.3, 277.4)	5.09 (0.67, 38.83)	4.3 (0.96, 19.61)	**3.35 (1.45, 8.09)**	**44.37 (5.25, 532.7)**	**CHCVR**	
32.18 (5.28, 217.7)	4.42 (0.66, 30.44)	3.73 (0.99, 14.85)	**2.92 (1.11, 8.09)**	**38.35 (5.16, 429.3)**	0.87 (0.24, 3.27)	**LNG-IUS**

CHCVR: combined hormonal contraceptive vaginal ring; Etham: ethamsylate; LNG-IUS: levonorgestrel-releasing intrauterine system; MPA: medroxyprogesterone acetate; NA: norethisterone; NMA: network meta-analysis; TXA: tranexamic acid

Note: Odds ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Odds ratios greater than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 18: Probabilities of being the best treatment class and the rank and 95% CrI

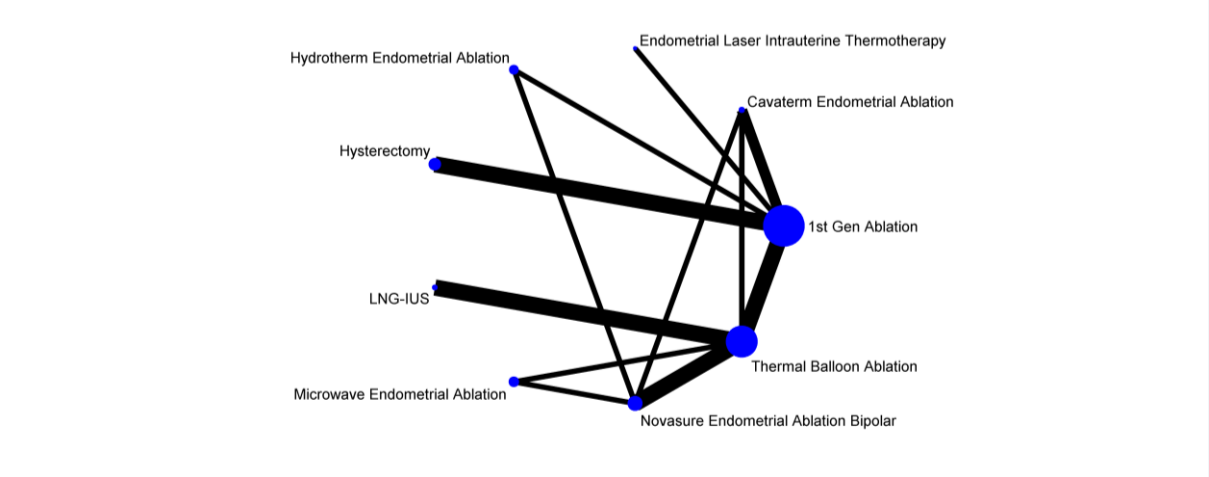
Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
Ethamsylate	27	1	0.0%	6 (6, 7)
NSAIDs	23	1	2.9%	5 (1, 5)
Tranexamic Acid	97	3	0.4%	4 (2, 5)
Norethisterone	89	3	0.0%	3 (3, 5)
Medroxyprogesterone Acetate	45	1	0.0%	7 (6, 7)
Combined contraceptive vaginal ring	48	1	56.6%	1 (1, 3)
LNG-IUS	42	2	40.0%	2 (1, 3)

CrI: credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs

Surgical treatments – women with no identifiable fibroids

Twenty-two trials of 9 surgical techniques (including LNG-IUS) were included in the network for patient satisfaction, with a total sample size of 2719 women (Figure 8). Fourteen studies were at high risk of bias, 4 had unclear risk of bias, and 4 were at low risk of bias.

Figure 8: Network of surgical treatments for patient satisfaction in women with no identifiable fibroids



1st Gen Ablation: first generation endometrial ablation; LNG-IUS: levonorgestrel-releasing intrauterine system

Note: The size of nodes is proportional to the number of women in the network who were given a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 19 presents the results of conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as ORs. These results were derived from a random effects model with moderate heterogeneity (between-study standard deviation: 0.39 [95% CrI 0.02, 1.26]).

Serious incoherence between direct and indirect evidence was found in several closed loops, with the results sometimes changing in direction of effect (Appendix N). Results from this network should therefore be interpreted with caution.

Novasure had significantly higher patient satisfaction than thermal balloon ablation, microwave endometrial ablation, hydrotherm endometrial ablation, and first generation endometrial ablation (Table 20). Hysterectomy also led to higher numbers of satisfied patients than first generation endometrial ablation.

Novasure had the highest probability of being the best surgical treatment for improving patient satisfaction in women with no identifiable fibroids (48.7%), followed by endometrial laser intrauterine thermotherapy (24.8%) and hysterectomy (16.6%) (Table 20).

Table 19: Matrix of results for the NMA of surgical treatments for patient satisfaction in women with no identifiable fibroids

LNG-IUS		**0.88 (0.29, 2.1)**						
1.98 (0.34, 8.28)	**Hyst**							**0.39 (0.16, 0.92)**
0.88 (0.28, 2.13)	0.45 (0.13, 1.53)	**TBA**	1.23 (0.36, 4.19)		0.16 (<0.01, 6.23)	**2.5 (1.05, 5.88)**		1.05 (0.45, 2.59)
0.86 (0.11, 2.87)	0.43 (0.06, 1.83)	0.99 (0.22, 2.38)	**MEA**			**26.39 (1.42, >999)**		
1.69 (0.15, 16.18)	0.86 (0.11, 7.73)	1.92 (0.26, 16.36)	2.03 (0.24, 26.94)	**ELIT**				0.45 (0.06, 2.67)
1.47 (0.25, 6.4)	0.75 (0.17, 3.05)	1.67 (0.46, 5.61)	1.75 (0.39, 10.94)	0.87 (0.09, 7.27)	**Cava**	2.3 (0.27, 19.77)		0.39 (0.1, 1.38)
2.87 (0.76, 9.42)	1.46 (0.39, 6.26)	**3.27 (1.57, 7.66)**	**3.33 (1.19, 18.71)**	1.7 (0.19, 14.92)	1.96 (0.57, 7.93)	**Nova**	0.08 (<0.01, 0.67)	
0.49 (0.05, 3.03)	0.25 (0.03, 1.61)	0.57 (0.09, 2.87)	0.59 (0.08, 5.2)	0.29 (0.02, 3.44)	0.34 (0.04, 2.29)	**0.17 (0.03, 0.81)**	**HEA**	0.8 (0.09, 9.06)
0.76 (0.17, 2.41)	**0.39 (0.15, 0.93)**	0.86 (0.37, 1.9)	0.89 (0.27, 4.67)	0.45 (0.06, 2.79)	0.52 (0.17, 1.59)	**0.26 (0.08, 0.69)**	1.53 (0.3, 9.56)	**First Generation Ablation**

Cava: cavaterm endometrial ablation; ELIT: endometrial laser intrauterine thermotherapy; HEA: hydrotherm endometrial ablation; Hyst: hysterectomy; LNG-IUS: levonorgestrel-releasing intrauterine system; MEA: microwave endometrial ablation; Nova: novasure radiofrequency endometrial ablation; TBA: thermal balloon ablation

Note: Odds ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Odds ratios greater than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 20: Probabilities of being the best treatment class and the rank and 95% CrI

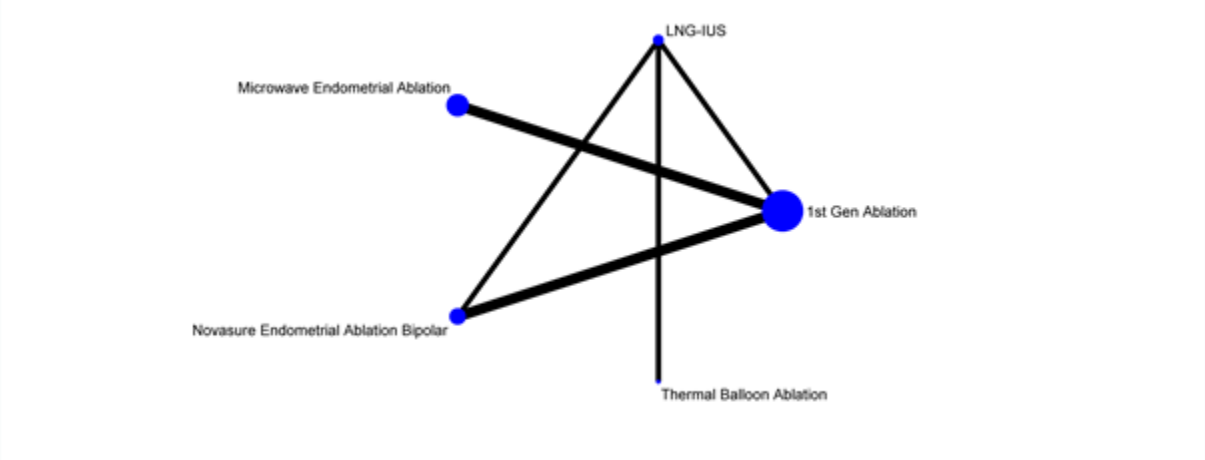
Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
LNG-IUS	92	3	2.3%	5 (2, 9)
Hysterectomy	192	3	16.6%	3 (1, 7)
Thermal balloon ablation	611	11	0.0%	6 (3, 9)
Microwave endometrial ablation	190	2	0.5%	6 (2, 9)
ELIT	55	1	24.8%	3 (1, 9)
Cavaterm endometrial ablation	98	4	6.5%	4 (1, 8)
Novasure endometrial ablation bipolar	311	6	48.7%	2 (1, 4)
Hydrotherm endometrial ablation	206	2	0.6%	9 (3, 9)
First generation ablation	964	11	0.0%	7 (4, 9)

CrI: credible interval; ELIT: endometrial laser intrauterine thermotherapy; LNG-IUS: levonorgestrel-releasing intrauterine system

Surgical treatments – including women with non-cavity uterine fibroids less than 3 cm in diameter

Six trials of 5 surgical techniques (including LNG-IUS) were included in the network for patient satisfaction, with a total sample size of 1045 women (Figure 9). All 6 studies were at high risk of bias.

Figure 9: Network of surgical treatments for patient satisfaction in women with non-cavity uterine fibroids less than 3 cm



LNG-IUS: levonorgestrel-releasing intrauterine system

Note: The size of nodes is proportional to the number of women in the network who were randomised to a particular treatment class. The thickness of connecting lines is proportional to the number of studies directly comparing 2 treatment classes.

Table 21 presents the results of the conventional pair-wise meta-analyses (direct comparisons; upper right section of table) together with the results from the NMA for every possible class comparison (lower left section of table), presented as ORs. These results were derived from a fixed effects model. Incoherence could not be assessed in this network as there were no closed loops of treatments that were not from multi-arm trials (which cannot be incoherent).

Microwave endometrial ablation, novasure, and first generation endometrial ablation all greatly improved the numbers of satisfied patients when compared to LNG-IUS or thermal balloon ablation (Table 22). Microwave endometrial ablation also led to higher numbers of satisfied patients than first generation endometrial ablation.

Microwave endometrial ablation had the highest probability of being the best surgical treatment for improving patient satisfaction in women with non-cavity uterine fibroids less than 3 cm in diameter (94.0%) (Table 22).

Table 21: Matrix of results for the NMA of surgical treatments for patient satisfaction in women with no identifiable fibroids

LNG-IUS	**1.2 (0.48, 3.02)**		**8.2 (1.95, 62.3)**	**8.79 (2.12, 67.97)**
1.2 (0.48, 3.02)	**TBA**			
18.83 (4.72, 91.33)	**15.84 (2.95, 97.56)**	**MEA**		**0.47 (0.25, 0.87)**
7.35 (2.18, 30.69)	**6.2 (1.32, 33.1)**	0.39 (0.12, 1.23)	**Nova**	1.23 (0.42, 4.1)
8.77 (2.57, 37.73)	**7.4 (1.56, 40.72)**	**0.47 (0.25, 0.87)**	1.18 (0.46, 3.32)	**First generation ablation**

LNG-IUS: levonorgestrel-releasing intrauterine system; MEA: microwave endometrial ablation; NMA: network meta-analysis; Nova: novasure radiofrequency endometrial ablation; TBA: thermal balloon ablation

Note: Odds ratios and 95% credible intervals from the NMA (bottom left diagonal) and conventional meta-analyses (top right diagonal) treatment effects between the column-defined and row-defined treatments. Odds ratios greater than 1 favour the row-defined treatment. Numbers in bold, dark grey-shaded cells denote results where the 95% CrI credible intervals do not include 1.

Table 22: Probabilities of being the best treatment class and the rank and 95% CrI

Treatment Class	Number of women	Number of studies	Probability of being best (%)	Median (95% CrI) treatment rank
LNG-IUS	88	2	0.0%	5 (4, 5)
Thermal balloon ablation	39	1	0.0%	4 (4, 5)
Microwave endometrial ablation	312	2	94.0%	1 (1, 2)
Novasure endometrial ablation bipolar	184	2	5.4%	3 (1, 3)
First generation ablation	422	5	0.5%	2 (2, 3)

CrI: credible interval; LNG-IUS: levonorgestrel-releasing intrauterine system

Economic evidence

Included studies

Fourteen economic evaluations on the management of HMB were included in this review, see Table 23. A narrative review of these studies is provided in the Health economics chapter.

One study compared UAE to hysterectomy for the treatment of uterine fibroids (Beinfield 2004).

Three studies compared hysterectomy, LNG-IUS and endometrial ablation in women with HMB (Bhattacharya 2011; Blake 2016; Clegg 2007).

Four studies compared LNG-IUS against other treatment alternatives as first-line treatment for HMB (Ganz 2013; Lete 2011; Calaf 2015; Gupta 2015).

One study compared LNG-IUS with hysterectomy for the treatment of menorrhagia (Heliovaara-Peippo 2013).

One study compared endometrial ablation to hysterectomy for abnormal uterine bleeding (Miller 2015).

One study compared ulipristal acetate with leuprolide acetate in the treatment of moderate-to-severe symptoms of uterine fibroids in women eligible for surgery (Tsoi 2015).

One study compared LNG-IUS, hysterectomy, endometrial ablation and oral medical treatment for the management of menorrhagia (You 2006).

One study compared UAE, hysterectomy and myomectomy for the symptomatic control of uterine fibroids (You 2009).

One study compared magnetic resonance-guided focused ultrasound surgery (MRgFUS) with current practice comprising uterine artery embolisation, myomectomy, and hysterectomy for symptomatic uterine fibroids (Zowall 2008).

Excluded studies

Studies not included in this review with reasons for their exclusion are provided in Appendix I – Excluded studies.

Summary of studies included in the economic evidence review

Table 23: Summary of studies included in the economic evidence review for the management of heavy menstrual bleeding

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Calaf 2015 (Spain) Population: Women diagnosed with HMB who wished to retain their fertility Interventions: LNG-IUS; E2V/DNG; COC; Progestins	Minor [a]	Directly [b]	Markov model. Treatment effects identified from systematic review of the literature. Model structure, treatment switching (after HMB and birth control failure) and inputs verified by a panel of clinical experts. The long-term efficacy of E2V/DNG, COC and PROG was obtained by extrapolating the short-term efficacy data observed from the pattern of change in efficacy of LNG-IUS.	Total costs per patient at 5 years: LNG-IUS €1531 E2V/DNG €2114 COC €2518 PROG €3421 First-line LNG-IUS treatment resulted in savings of €583, €988, and €1891 versus E2V/DNG, COC and PROG, respectively.	QALMs per patient at 5 years: LNG-IUS 49.57 E2V/DNG 47.83 COC 46.24 PROG 44.18 LNG-IUS contributed more QALM than the other treatment alternatives (+1.74 versus E2V/DNG, +3.33 versus COC +3.53 versus PROG). LNG-IUS was associated with a gain of 0.67, 2.22, and 3.53 symptoms free months compared with E2V/DNG, COC and PROG, respectively.	LNG-IUS is the dominant option	OWSA showed similar results to the base case and confirmed that changing the analysis perspective from NHS to the social and increasing the time horizon to 10 years resulted in LNG-IUS continuing to be the dominant option. PSA also confirmed the dominance of LNG-IUS.
Ganz 2013 (USA) Population:	Potentially serious [a, c]	Partially [d]	Markov model. Data for treatment response came from recent clinical trial publications and	Total costs per paitent at 5 years: LNG-IUS $1137 Branded COCs $1804	Total QALYs per patient at 5 years: LNG-IUS 3.78 Branded COCs 3.71	Initiating treatment with LNG-IUS dominated all	Multiple OWSA found that initiating treatment with LNG-IUS resulted in lower costs and more QALYs

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Women with idiopathic HMB wishing to preserve their fertility Interventions: LNG-IUS; Branded COC; Generic COC; Oral progestin; TXA; Ablation; Hysterectomy			systematic literature reviews that assessed the ability of the target treatments to reduce menstrual blood loss to less than 80ml per menstrual cycle.	Generic COCs $1196 Oral progestin $1583 TXA $3065 Ablation $2612 Hysterectomy $6250	Generic COCs 3.71 Oral progestin 3.67 TXA 3.72 Ablation 3.79 Hysterectomy 3.88 Total hysterectomies avoided (per 1000 patients) at 5 years: Branded COCs 994 Generic COCs 963 Oral progestin 963 TXA 887 Ablation 991 Hysterectomy 0	nonsurgical comparators. Ablation resulted in higher QALYs and higher costs than did LNG-IUS (ICER $122,278) but is extendedly dominated by the combination of LNG-IUS and hysterectomy (ICER for hysterectomy versus LNG-IUS $49,614).	gained than with other initial treatment strategies. When outcomes were measured by QALYs, LNG-IUS was the dominant strategy in 49% (versus generic COCs) to 76% (versus branded COCs) of the simulations compared with nonsurgical treatments and dominant against ablation in 40% and against hysterectomy in 33% of the simulations.
Gupta 2015 (UK) Population: Women presenting to their GP wth HMB aged 25-50 years Interventions: LNG-IUS;	Minor [f, g]	Directly	See Sanghera 2014	See Sanghera 2014 for results at 24-months. Total costs per intervention over 5 years: Usual medical treatment £507 LNG-IUS £517 MD £10	See Sanghera 2014 for results at 24-months Total QALYs per intervention (EQ-5D) over 5 years: Usual medical treatment 3.608 LNG-IUS 3.698 MD 0.090	See Sanghera 2014 for results at 24-months 5-year results: Using the EQ-5D, LNG-IUS is the most cost-effective treatment with an ICER of £114 compared to	See Sanghera 2014 for results at 24-months Using the EQ-5D, the CEAC shows that the LNG-IUS has a greater probability of being the more cost-effective intervention from approximately £500

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Usual medical treatment					Total QALYs per intervention (SF-6D) over 5 years: Usual medical treatment 2.797 LNG-IUS 2.795 MD -0.002	medical treatment. Using the SF-6D, usual medical treatment dominates LNG-IUS.	per QALY onwards. Most simulations lie in the east quadrants of the cost-effectiveness plane. Using the SF-6D, for any threshold WTP per QALY, usual medical treatment has the greater probability of being the more cost-effective intervention.
You 2009 (Hong Kong) Population: Women with symptomatic uterine fibroids Interventions: Hyterectomy; UAE; Myomectomy	Potentially serious [h]	Partially [i]	Markov model. Clinical inputs identified from systematic review of the literature.	Total costs (primary intervention, reintervention and indirect) per patient over 5 years: Hysterectomy USD8418 (1USD ¼ 7.8HKD) UAE USD8847 Myomectomy USD9036 Total primary intervention cost (USD) over 5 years: Hysterectomy 7035 UAE 6183	Total QALYs per patient over 5 years: Hysterectomy 4.368 Myomectomy 4.273 UAE 4.245	Hysterectomy became the dominating alternative in year 3. By year 5, hysterectomy dominated both UAE and myomectomy. Myomectomy, compared with UAE, gained higher QALYs with a higher cost. ICER (per additional QALY gained) for myomectomy versus UAE USD6750	Results robust to OWSA. PSA showed that the hysterectomy group was less costly than the UAE and myomectomy groups 84.1% and 79.1% of the time, with mean cost differences of USD1964 (95% CI, 1926– 2002) and USD1198 (95% CI, 1170–1226), respectively. The hysterectomy group also gained a higher number of QALYs than the UAE and myomectomy

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
				Myomectomy 6322 Total reintervention cost (USD) over 5 years: Hysterectomy 0 UAE 1991 Myomectomy 1182			groups 97.8% and 98.3% of the time, with mean QALY differences of 0.1204 (95% CI, 0.1191–0.1217) and 0.0983 (95% CI, 0.0970–0.0996), respectively.
Zowall 2008 (UK) Population: Surgical candidates for uterine fibroids Interventions: MRgFUS; Usual practice	Potentially serious [j, k]	Directly	Markov model. Transition probabilities following MRgFUS were estimated by modelling the relationship between nonperfused volume (NPV) relative to the total fibroids volume and the rate of alternative treatment. Current practice comprises of uterine artery embolization 25%, myomectomy 25% and hysterectomy 50%.	Total direct medical costs of 1,000 women treated at age 39 and followed until menopause or age 56: MRgFUS £3,101,644 Currently available procedures £3,396,913 MRgFUS provides a cost saving of £295,269	MRgFUS treatment compared with current practice increased total QALYs by 10.658.	MRgFUS dominates current practice	MRgFUS dominates current practice in 11 of 13 scenarios. In 86% of PSA simulations, MRgFUS is dominant.
Bhattacharya 2011 (HTA) (UK)	Minor [l]	Directly	Markov model. Structure informed by literature and clinical input. Data	Total costs from a cohort of 1,000 women over 10 years:	Total QALYs from a cohort of 1,000 women over 10 years:	Analysis 1: First generation EA and second generation EA	All subgroup and sensitivity analyses were carried out for Analysis 2 only:

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Population: Women commencing treatment for HMB at 42 years of age Interventions: LNG-IUS; Hysterectomy; First generation EA; Second generation EA			drawn from research work undertaken by the project, namely individual patient meta-analyses, data from national registers and existing RCTs. For Analysis 1, for the first-generation EA, second-generation EA and LNG-IUS strategies, repeat procedures (ablation or hysterectomy) are allowed at any age, but with a decreasing hazard. For Analysis 2, 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.	Analysis 1 First generation EA £30,040,000 Second generation EA £25,950,000 LNG-IUS £15,630,000 Hysterectomy £23,000,000 Analysis 2 First generation EA £23,590,000 Second generation EA £19,470,000LNG-IUS £16,150,000 Hysterectomy £23,000,000	Analysis 1 First generation EA 64,485 Second generation EA 68,965 LNG-IUS 68,758 Hysterectomy 73,332 Analysis 2 First generation EA 63,745 Second generation EA 69,678 Mierna 68,566 Hysterectomy 73,332	dominated by hysterectomy. Hysterectomy more costly and more effective than LNG-IUS with an ICER of £1,600 Analysis 2: Hysterectomy dominates first generation EA. Hysterectomy more costly and more effective than second generation EA with an ICER of £970 per QALY gained. Hysterectomy more costly and more effective than LNG-IUS with an ICER of £1,440 per QALY gained	Hysterectomy most expensive and effective strategy in short and long uterine cavity subgroups with ICERs from £161 to £1,642. Second generation EA dominates hysterectomy when median utility values are used instead of mean values. Results are generally robust to other OWSA undertaken as hysterectomy is the most effective treatment with ICERs <£20,000 per QALY. PSA and EVPI undertaken for certain analysis.
Clegg 2007 (UK)	Minor [m]	Directly	Markov model. The pathways for hysterectomy and L-H were	Total cost per patient over 5 years: L-A £828	Total QALYs per patient over 5 years: L-A 4.14	L-A is the dominant option. Hysterectomy is	Results robust to deterministic SA. At low levels of WTP (< £10 000

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Population: Women with HMB Interventions: LNG-IUS; Hysterectomy; MEA; TBEA			constructed using the main events experienced in a Finish RCT. The pathway for ablation was constructed the inputs for the PenTAG model. To reflect the NICE guidelines, the pathway for L-A was derived from the Finnish study and the PenTAG model, in which patients who fail after LNG-IUS receive ablation in preference to hysterectomy. The pathway for hysterectomy is concordant with that in the PenTAG model. Additional analysis of the Finnish data set was conducted to identify the risk of (a) complications after hysterectomy and (b) hysterectomy following initial	L-H £1355 TBEA £1679 MEA £1812 Hysterectomy £2983	L-H 4.12 TBEA 4.13 Hysterectomy 4.01	also dominated by all options.	per QALY), LNG-IUS is likely to be preferred to surgery. At high levels of WTP, the economic profile of TBEA and MEA were improved. Threshold analysis found that, for the cost per QALY gained with ablation compared to L-A to be £30 000, the rate of failure with LNG-IUS would have to increase from 42.6% to 85.2% (comparison with MEA) or to 90.3% (comparison with TBEA).

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
			treatment with LNG-IUS.				
Lete 2011 (Spain) Population: Women having first line treatment for dyfunctional uterine bleeding Interventions: LNG-IUS; COC; Progestogens	Minor [a]	Directly [b]	Markov model. Structure and inputs informed by the literature and agreed with a panel of experts. Results at 6 months and 1 year also reported.	Total costs per patient at 5 years: LNG-IUS €3099 COC €3409 PROG €36777 LNG-IUS produces savings of €174.2–309.95 and €230.54–577.61 versus COC and PROG, respectively, after 5 years.	QALMs per patient at 5 years: LNG-IUS 50.89 COC 49.82 PROG 48.91 SFMs per patient at 5 years: LNG-IUS 50.53 COC 47.86 PRO 45.59	LNG-IUS is the dominant option.	In all scenarios explored, the therapeutic line initiated with LNG-IUS proved to be dominant or cost-effective (ceiling ratio € 2500/ QALM equivalent to €30,000/QALY). In PSA starting treatment with LNG-IUS remains dominant versus the other alternatives (99.8% and 99.9%, respect COC and PROG). This indicates that even if a WTP for the increment in QALMs is almost € 0, the treatment of choice should still be LNG-IUS.
Miller 2015 (USA) Population: Women with abnormal uterine bleeding Interventions:	Minor	Partially [n]	Markov model. Most clinical and economic data (including treatment patterns, health state transition probabilities, health care resource	Total (direct) cost per patient over 5 years: NovaSure $6,383 Other GEA $10.755 Hysterectomy $15,642	Total QALYs per patient over 5 years: NovaSure 3.876 Other GEA 3.874 Hysterectomy 3.991	NovaSure dominates other GEA. NovaSure is less effective and less costly than hysterectomy with an ICER of $80,902 saved per QALY lost.	State results were not highly sensitive to univariate and probabilistic variation in the parameter values. 10-year scenario found that incremental cost differences

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Novasure; Other GEA; Hysterectomy			utilization, direct costs, and productivity costs) were primarily derived from de novo analyses of three large medical claims database. Results at 1 and 3 years also reported. Other GEA modalities include second-generation GEA techniques (eg, cryotherapy, microwave endometrial ablation, thermal balloon endometrial ablation, hydrothermal ablation) other than bipolar radiofrequency ablation with the NovaSure system.				remained highly favourable for the NovaSure procedure in both the commercial payer and Medicaid perspectives. Cost-effectiveness results seen at Year 5 continued a trend into Year 10, with the NovaSure procedure mostly showing economic dominance over other GEA and hysterectomy in both the commercial and Medicare perspectives.
Tsoi 2015 (Canada) Population: Women with moderate-to-	Potentially serious [o], [p]	Directly [q]	Decision tree. Indirect health care costs also reported and included in a SA. Model inputs based on the PEARL II RCT.	Total (direct health care) costs per patient over 3 months: Leuprolide $1,365 Ulipristal $1,271	Total QALYs per patient over 3 months: Leuprolide 0.165 Ulipristal 0.177	Ulipristal dominates leuprolide	All PSA simulations lay in the south-east quadrant of the cost-effectiveness plane. Across all WTP thresholds, ulipristal had a 100% probability of

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
severe symptoms of uterine fibroids Interventions: ulipristal (5 mg orally daily); leuprolide (3.75 mg intramuscular monthly)							being the most cost-effective strategy. Model robust to all parameters tested in OWSA.
You 2006 (Hong Kong) Population: Population: Women with menorrhagia Interventions: LNG-IUS; Oral medical treatment; Endometrial resection/ablation; Hysterectomy	Minor	Partially [r]	Markov model. Oral medical therapy includes non-steroid anti-inflammatory agents, tranexamic acid, oral contraceptive pills, progestogens and danazol. The clinical inputs of the model were derived from clinical trials included in two meta-analyses on endometrial esection/ablation versus hysterectomy (Lethaby et al., 2005) and surgery versus medical therapy for menorrhagia	Total cost per patient over 5 years: LNG-IUS USD4528 Oral medical USD5508 Endometrial resection/ablation USD6185 Hysterectomy USD6878	Total QALYs per patient over 5 years: LNG-IUS 4.625 Oral medical 4.575 Endometrial resection/ablation 4.624 Hysterectomy 4.725	Oral medical treatment and endometrial resection/ablation dominated by LNG-IUS. Hysterectomy more expensive and more effective than LNG-IUS with an ICER of USD23500 per QALY gained	PSA showed that the hysterectomy group was more costly than the LNG-IUS, oral medical treatment and endometrial resection/ ablation groups 100, 100 and 85% of the time, with MDs of USD2528 (95% CI 2518–2539), USD1470 (95% CI 1464–1476) and USD1038 (95% CI 1018–1058), respectively. The hysterectomy group gained higher number of QALYs than the LNG-IUS, oral medical treatment and endometrial resection/ ablation groups, 99, 99 and 98% of the time,

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
			(Marjoribanks et al., 2005).				with MDs of 0.0587 (95% CI 0.0581–0.0593), 0.0877 (95% CI 0.0869–0.0885) and 0.0546 (95% CI 0.0540–0.0552), respectively. In SA the endometrial resection/ablation group would dominate, LNG-IUS and oral medical treatment when the probability of extra surgery declined to ≤0.055. Whilst hysterectomy remained the most effective alternative treatment option, the ICER of hysterectomy in comparison with the least costly option (endometrial resection/ablation) would become USD53024 and further increase to USD209000 when the probability of extra surgery declined to 0.024.

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
Beinfield 2004 (USA) Population: Women with symptomatic uterine fibroids Interventions: Hysterectomy; UAE	Potentially serious [t]	Not applicable [u, v]	Markov model. Parameter estimates obtained from the literature and confirmed with a gynaecologist.	Total costs per patient over 10 years: No treatment $4,949 UAE $6,916 Hysterectomy $7,847	Total QALYs per patient over 10 years: No treatment 7.31 UAE 8.29 Hysterectomy 8.18	ICER for UAE versus no treatment $20007 per QALY. UAE dominates hysterectomy.	In OWSA UAE had ICERs <$16000 compared to no treatment. In the majority of scenarios UAE dominated hysterectomy. UAE did not dominate hysterectomy when the procedural cost of UAE increased, recovery time for UAE increased and recovery time for hysterectomy decreased.
Blake 2016 (Canada) Population: Women with idiopathic HMB Interventions: LNG-IUS; Hysterectomy; Endometrial ablation	Minor	Directly [w]	Markov model. Clinical data taken from studies identified in clinical evidence review.	Total costs per patient over 9 years: LNG-IUS $3,142 Hysterectomy $6,280 EA $3,514	Total QALYs per patient over 9 years: LNG-IUS 6.32 Hysterectomy 6.28 EA 6.27	LNG-IUS is the dominant option	In PSA, for the comparison of the LNG-IUS and hysterectomy, incremental costs ranged from −$14,008 to $1,609, while incremental QALYs ranged from 0.05 to 0.15. When LNG-IUS was compared with endometrial ablation, incremental cost ranged from −$2,630 to $1,524 and incremental QALYs ranged from

Study	Limitations	Applicability	Other comments	Costs	Effects	Inc. cost-effectiveness	Uncertainty
							0.03 to 0.07. Almost all simulations in the PSA found LNG-IUS to dominate. In OWSA LNG-IUS was the dominant option in all but one scenario[x].
Heliovaara-Peippo 2013 (Finland) Population: Women with menorrhagia Interventions: LNG-IUS; Hysterectomy	Potentially serious [y, z]	Partially, [aa, bb]	Clinical effectiveness and costs taken from a RCT. Indirect costs also reported. DAM not developed.	Total (direct health care) costs per patient over 10 years: LNG-IUS US$ 2,291 Hysterectomy US$ 3,036 Incremental: 3,036 – 2,291 = 745	Total QALYs gained per patient by treatment at 10 years: LNG-IUS 0.45 Hysterectomy 0.51 Incremental: 0.51 - 0.45 = 0.06	Hysterectomy more expensive and more effective than LNG-IUS with an ICER of US$12,417 (calculated by the TT using direct costs)	SA varying the discount rate, cost of complications and cost of complications explored on total costs (including direct and indirect costs). PSA not undertaken.

COC: combined oral contraceptives; DAM: decision analytic model; E2V/DNG: estradiol valerate/dienogest; EA, endometrial ablation; GEA: global endometrial ablation; ICER: incremental cost-effectiveness ratio; L-A: LNG-IUS followed by ablation; L-H: LNG-IUS followed by hysterectomy; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; MEA, microwave endometrial ablation; MRgFUS: Magnetic Resonance-guided Focused Ultrasound Surgery; OPT: outpatient polypectomy treatment; OWSA: one-way sensitivity analysis; PROG: progestins; PSA: probabilistic sensitivity analysis; QALM: quality-adjusted life months; QALY: quality-adjusted life years; RCT: randomised controlled trial; SFM: symptom free months; TBEA: thermal balloon endometrial ablation; TT: technical team; TXA: tranexamic acid; usual medical treatment: mefenamic acid, tranexamic acid, norethisterone, combined oestrogen-progestogen or progestogen-only oral contraceptive pill, or medroxyprogesterone acetate injection; UAE: uterine artery embolisation; WTP: willingness-to-pay

(a) potential conflict of interest (funded by Bayer)
(b) Spanish NHS perspective and a 3% discount rate considered to be negligible deviations from UK practice and NICE's reference case
(c) Resource use in addition to the interventions to treat HMB is unclear
(d) US payer perspective and 3% discount rate
(e) 1-year time horizon may not be sufficiently long to reflect all important differences in costs and outcomes
(f) 2-year time horizon may not be sufficiently long to reflect all important differences in costs and outcomes.
(g) Total costs and QALYs are reported as the mean per intervention rather than the mean per patient which is potentially misleading
(h) Resource use is not described, only unit costs are provided
(i) Hong Kong societal perspective includes indirect costs using a human capital approach
(j) Supported by an unrestricted grant from InSightec whose trials were used to inform clinical effectiveness associated with NPV and MRgFUS

(k) A fully incremental analysis against uterine artery embolization, myomectomy and hysterectomy would be more reliable than the comparison which is a subjective view of current practice
(l) Fully incremental analysis not presented, present pairwise comparisons with hysterectomy
(m) Potential conflict of interest (funded by Schering Health Care)
(n) US Medicaid perspective, US commercial payer perspective also reported but Medicaid perspective is extracted here
(o) 3-month time horizon may not be sufficiently long to reflect all important differences in costs and outcomes
(p) Model inputs not always justified
(q) Canadian (Ontario) public payer perspective (base case) and a 3% discount rate considered to be negligible deviations from UK practice and NICE's reference case
(r) Benefits are not discounted and costs are discounted at 3% as opposed to 3.5% for cost and benefits
(s) Hong Kong public payer perspective noteworthy, but not considered to differ substantially from a UK NHS perspective and setting
(t) PSA not performed and unclear if a systematic review of the literature was undertaken, today the literature would be outdated
(u) US societal perspective not reflective of UK NHS
(v) Paper may reflect outdated practices
(w) Canadian (Ontario) public payer perspective (base case) and a 5% discount rate (3% in SA) considered to be negligible deviations from UK practice and NICE's reference case
(x) When the initial hysterectomy waiting time was excluded, LNG-IUS had lower QALYs than hysterectomy, but remained dominant in the remaining 14 scenarios
(y) The QALYs gained by each treatment at 10 years are reported, rather than the total (cumulative)QALYs
(z) SA is based on the total cost that includes indirect costs and the ICERs from those analysis are not reported, PSA not undertaken
(aa) US setting that measures indirect and direct costs, only direct costs extracted here
(bb) Costs discounted at 3% in base case, benefits not discounted

Economic model

A cost utility analysis was developed to compare the cost-effectiveness of a range of diagnostic and management strategies. A Markov (state transition) model was developed to evaluate the costs and health related quality of life (HRQoL), measured in Quality Adjusted Life Years (QALYs), over a 5-year time frame.

The entry point for the model was women aged 42 years, presenting with HMB in an NHS primary care setting. The model could be run for up to 5 diagnostic strategies, including strategies involving treatment without any prior investigation:

- LNG-IUS alone
- hysterectomy alone
- outpatient hysteroscopy
- TVUS (transvaginal ultrasound)
- endometrial biopsy.

The outcome of the diagnostic tests was used to direct treatment according to the woman's underlying pathology. In the model, diagnostic test accuracy was used to estimate the proportion of women whose condition would be correctly identified and receive the appropriate first line treatment. False positive rates were estimated to determine the proportion of women who would receive 'incorrect' treatment based on a diagnosis that differed from their true underlying pathology. The model comprised 5 underlying pathologies (polyps, submucosal fibroids (SMFS), fibroids less than 3 cm in diameter, fibroids 3 cm or more in diameter, and no identified pathology) and a simplifying assumption was made that the woman could only have a single underlying pathology.

The following surgical and pharmacological interventions were included as possible treatment alternatives in the model:

- LNG-IUS
- tranexamic acid
- COCs
- hysterectomy
- first generation endometrial ablation techniques
- second generation endometrial ablation techniques
- transcervical resection of fibroids (TCRF)
- NSAIDs
- medroxyprogesterone acetate (MPA)
- polypectomy.

The model structure for surgical and medical management is shown in Figure 10 and Figure 11, respectively.

Figure 10: Markov structure for first-line surgical treatment

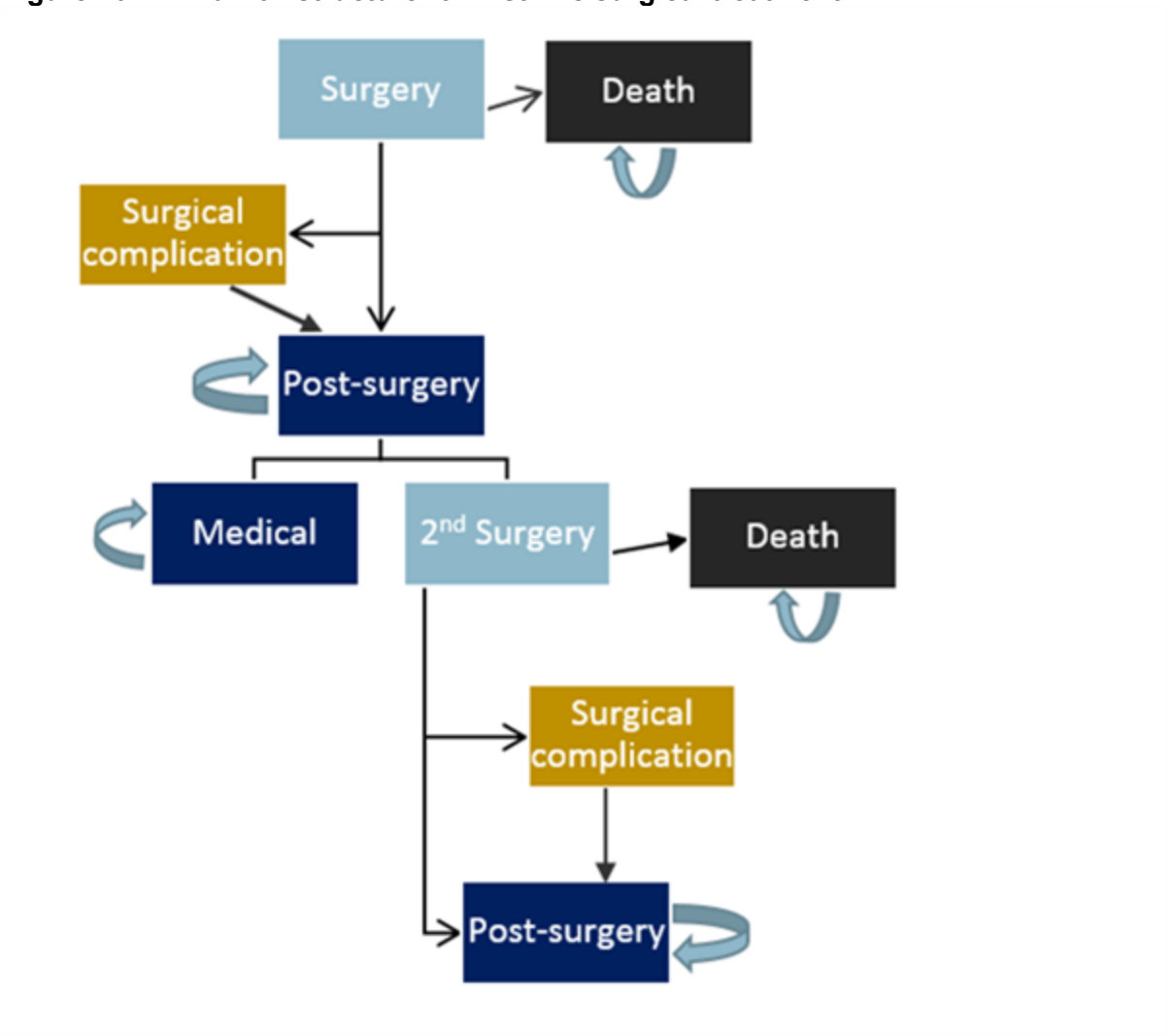
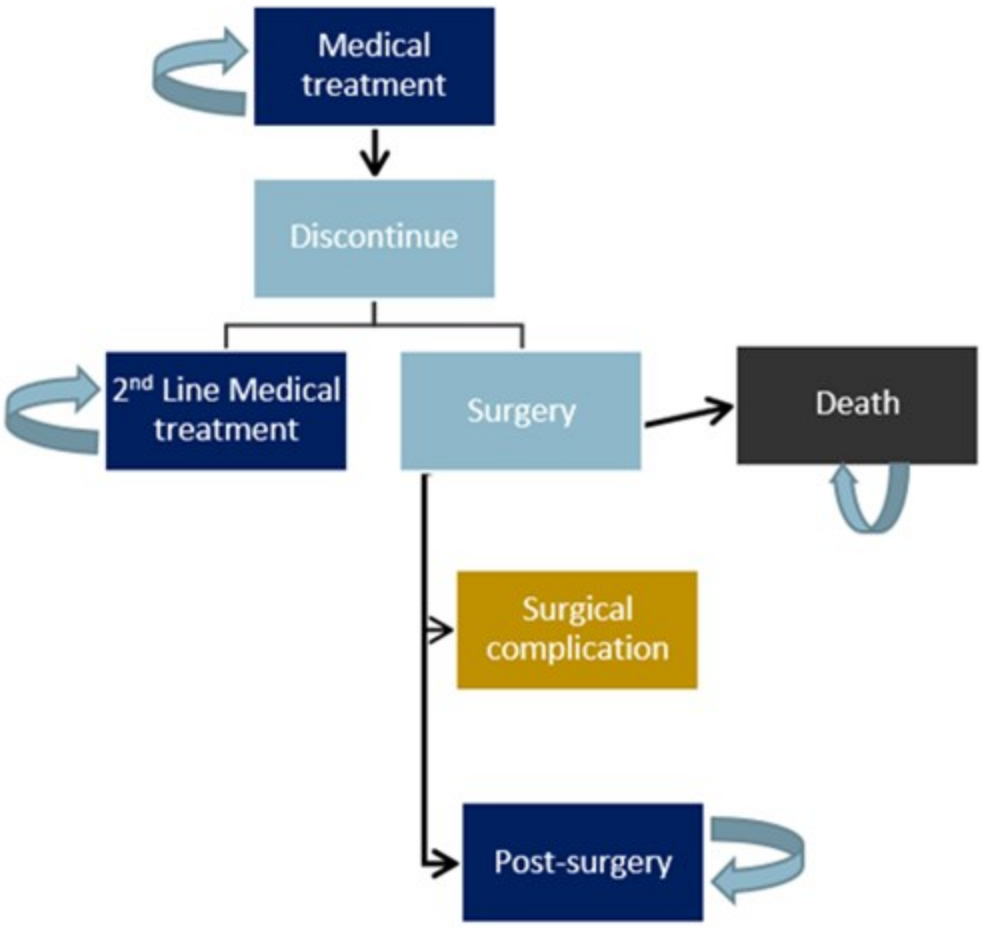


Figure 11: Markov structure for first-line medical treatment



One important limitation of the model was how treatment gain was ascertained. Diagnosis of the underlying pathology is considered important to direct the woman to the most appropriate treatment. However, there are treatments that can be considered appropriate across a range of pathologies, which is why empiric treatment with LNG-IUS, for example, can be considered a plausible clinical option and is commonly used in the UK as current practice. This means that a incorrect diagnosis of a woman's condition can potentially still receive appropriate treatment. Furthermore, in the NMA, the EuroQol five dimensions questionnaire (EQ-5D) data allows a QALY gain to be estimated according to the treatment received but not according to the appropriateness of that treatment for the underlying pathology. So the committee was asked to dichotomise treatments according to whether they thought they were effective or not for a given pathology. Again this was a simplifying assumption as the committee acknowleged that a treatment may still provide some benefit for a given pathology even if it was considered sub-optimal. To reflect the uncertainty about the effectiveness of treatments the committee classified the treatments by pathology as always effective, partially effective and never effective. In the base case scenario it was assumed that both effective and partially effective treatments for a particular pathology would give the QALY gain derived from the NMA when used for a woman with that pathology. However, as a sensitivity

analysis, a more conservative assumption was made where QALY gain was limited to only those treatments deemed effective for a given pathology. No QALY gain would result if the woman received a treatment assessed as only partially effective for her underlying uterine pathology in this sensitivity anaysis.

The analysis used probabilistic sensitivity analysis (PSA) to generate results. This involves Monte Carlo simulation where, instead of using a deterministic model input value, those values subject to uncertainty around their point estimate are sampled from a probability distribution over multiple iterations. The mean costs and QALYs are then calculated over these simulations and used to generate a mean net monetary benefit (NMB) which is calculated as follows:

NMB = QALY x cost-effectiveness threshold – cost

In line with NICE social value judgements (https://www.nice.org.uk/media/default/about/what-we-do/research-and-development/social-value-judgements-principles-for-the-development-of-nice-guidance.pdf) described in the methods chapter, a cost-effectiveness threshold of £20,000 per QALY was used. The strategy with the highest mean NMB was the most cost-effective strategy although to help assess any uncertainty an estimate was also made of the probability that a particular strategy was the most cost-effective. This was based on the proportion of simulations that the strategy is assessed as the most cost-effective.

The model results suggested that empiric LNG-IUS was a cost-effective strategy under the base case assumptions about treatment gain with a NMB of £30,131 and a 96.8% probability of being cost-effective. Under a conservative assumption where LNG-IUS was deemed to be an appropriate treatment for a smaller subset of underlying pathology then that was no longer the case with the NMB falling to £19,039.

When treatment alternatives were held constant, the model did not find large differences in the mean NMB of the 3 diagnostic tests compared. However, endometrial biopsy was dominated (the most expensive test strategy and the strategy generating the least QALY gain) by both TVUS and outpatient hysteroscopy. The comparison of the relative cost-effectiveness of outpatient hysteroscopy and TVUS is more complicated. The analyses suggested that TVUS was a more costly strategy than outpatient hysteroscopy despite being the cheaper diagnostic test. This is because outpatient hysteroscopy facilitates a “see and treat” approach, lowering the combined cost of diagnosis and treatment. In the context of initial presentation of the woman with HMB in primary care, TVUS was generally more cost-effective than outpatient hysteroscopy. This is because the overall diagnostic accuracy of outpatient hysteroscopy may be limited where the prevalence of intramural or subserosal fibroids is sufficiently high as these would not be detected. However, empiric pharmacological treatment is considered to be effective for intramural and subserosal fibroids less than 3cm in diameter whereas women with a different underlying pathology, where outpatient hysteroscopy has superior diagnostic accuracy, are more likely to be refractory to such pharmacological treatment. Therefore, the prevalence of intramural and subserosal fibroids less than 3cm in diameter is likely to be much reduced when considering investigation in a population of women refractory to pharmacological treatment and referred to secondary care. Consequently, as indicated by sensitivity analysis, outpatient hysteroscopy becomes more cost-effective relative to TVUS as the prevalence of intramural and subserosal fibroids of less than 3 cm in diameter as the underlying pathology in women presenting with HMB falls. As reflected in the recommendations, it is likely that outpatient hysteroscopy would be the most cost-effective diagnostic test strategy for women with a history suggesting polyps or SMFs, and that TVUS would be the most cost-effective test where intramural and subserosal fibroids were suspected.

Pharmacological treatments generated relatively high mean NMB values when using base case assumptions about treatment gain across the underlying uterine pathologies.This may support their use in primary care, especially in women who are not refractory to treatment.

Whilst hysterectomy is the most expensive intervention, analyses showed scenarios where it would be more cost-effective than other surgical interventions, such as second generation endometrial ablation.

This model is described in more detail in the Health economics chapter.

Resource impact

The committee did not consider that the recommendations would have a marked impact on current practice for the management of HMB and therefore a significant resource impact is not anticipated from the implementation of these recommendations.

Women with no identified pathology, fibroids less than 3 cm in diameter, suspected or diagnosed adenomyosis

The recommendation to consider LNG-IUS as a first line treatment for women with no identified pathology, fibroids less than 3 cm in diameter, suspected or diagnosed adenomyosis is reflective of current practice and previous NICE guidance. Pharmacological options are a cheap alternative if the woman declines LNG-IUS or if it is not suitable. Whilst the recommendations enable women to have surgery first line if that reflects their preferences, this is likely to be a small subset of women with more significant symptoms or pathology.

Women with fibroids of 3 cm or more in diameter

This classification includes fibroids where the clinical scenario is similar to that of women with fibroids less than 3 cm in diameter but also large fibroids which represent more significant pathology and present with more severe symptoms. Such fibroids are more likely to be refractory to pharmacological treatment.

In women with relatively small fibroids but still 3 cm or more in diameter the management would expected to be the same as for fibroids less than 3 cm in diameter and the recommendations to support this again largely reflect current practice.

The committee believe that for women with more significant pathology that the guideline recommendations could expedite surgical management but these women are unlikely to get long term resolution of symptoms from pharmacological alternatives and will often ultimately receive surgical intervention. Therefore it is not anticipated that the guideline would lead to a long term increase in surgical intervention but could potentially produce a small saving by limiting less efficacious pharmacological treatment.

Evidence statements

1. Women with suspected or diagnosed fibroids

Pharmacological treatment versus no treatment, usual care or placebo

Comparison 1. Ulipristal acetate versus placebo

Outcome: Reduction in blood loss

No studies reported on this important outcome.

Outcome: Health-related quality of life

High quality evidence from 1 RCT (n=38) among women with fibroids more than 2 cm in diameter showed a clinically significant improvement in health-related quality of life (measured in SF-36 quality of life change scores for both physical and mental domains) from

baseline after 3 cycles of treatment in women who received ulipristal acetate (10 or 20 mg) compared to women who received placebo.

High quality evidence from 1 RCT (n=38) among women with fibroids more than 2 cm in diameter showed a clinically significant decrease in UFS-QOL symptom severity score from baseline after 3 cycles of treatment in women who received ulipristal acetate (10 or 20 mg) compared to women who received placebo.

High quality evidence from 1 RCT (n=38) among women with fibroids more than 2 cm in diameter showed a clinically significant improvement in overall health-related quality of life (measured in UFS-QOL change scores from baseline) after 3 cycles of treatment in women who received ulipristal acetate (10 or 20 mg) compared to women who received placebo.

High quality evidence from 1 RCT (n=38) among women with fibroids more than 2 cm in diameter showed a clinically significant improvement in health-related quality of life (measured in UFS-QOL subscale change score from baseline in concern, energy/mood, control, and activities) after 3 cycles of treatment in women who received ulipristal acetate (10 or 20 mg) compared to women who received placebo. Moderate quality evidence from the same RCT showed a clinically significant improvement in the sexual function subscale (measured in change score from baseline) after 3 cycles of treatment in women who received ulipristal acetate (10 or 20 mg) compared to women who received placebo. Moderate quality evidence from the same RCT showed no clinically significant difference in the self-conscious subscale change score from baseline after 3 cycles of treatment between women who received ulipristal acetate (10 or 20 mg) and women who received placebo.

Outcome: Patient satisfaction

No studies reported on this critical outcome.

Outcome: Discontinuation due to adverse events

No studies reported on this critical outcome.

Outcome: Treatment compliance or discontinuation

No studies reported on this important outcome.

Pharmacological treatment A versus pharmacological treatment B

Comparison 2.1 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus norethisterone

Outcome: Reduction in blood loss

Very low quality evidence from 1 RCT (n=60) among women with fibroids less than or equal to 5 cm in diameter showed a clinically significant greater reduction in blood loss (measured in PBAC change score from baseline) after 6 months of treatment in women who received LNG-IUS compared to women who received norethisterone (5 mg twice daily, days 5-25 of cycle).

Outcome: Health-related quality of life

No studies reported on this critical outcome.

Outcome: Patient satisfaction

No studies reported on this critical outcome.

Outcome: Discontinuation due to adverse events

No studies reported on this critical outcome.

Outcome: Treatment compliance or discontinuation

No studies reported on this important outcome.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Infection

No studies reported on this important outcome.

Comparison 2.2 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus combined oral contraceptives (COC)

Outcome: Reduction in blood loss

Very low quality evidence from 1 RCT (n=58) among women with intramural or subserous fibroids less than or equal to 5 cm in diameter showed a clinically significant greater reduction in blood loss (measured in PBAC change score from baseline) at 12 months in women who received LNG-IUS compared to women who received COC (30 µg of ethinyl estradiol and 150 µg of levonorgestrel).

Moderate quality evidence from 1 RCT (n=58) among women with fibroids less than or equal to 5 cm in diameter showed a clinically significant greater reduction in blood loss (measured in change from baseline in menstrual blood loss in ml with alkaline haematin method) at 12 months in women who received LNG-IUS compared to women who received COC (30 µg of ethinyl estradiol and 150 µg of levonorgestrel).

Outcome: Health-related quality of life

Very low quality evidence from 1 RCT (n=58) among women with fibroids less than or equal to 5 cm in diameter showed no clinically significant difference in self-rated health being good or excellent (question 1 in HRQoL-4) at 12 months between women who received LNG-IUS and women who received low-dose COC (30 µg of ethinyl estradiol and 150 µg levonorgestrel).

Very low quality evidence from the same RCT (n=58) showed a clinically significant improvement in health-related quality of life (measured in number of days feeling physically unwell, mentally unwell, or in number of days 'lost' [defined as days when work or other daily activities are not possible] in the previous 30 days, question 2, 3, and 4 in HRQoL-4) at 12 months in women who received LNG-IUS compared to women who received COC (30 µg of ethinyl estradiol and 150 µg of levonorgestrel).

Outcome: Patient satisfaction

No studies reported on this critical outcome.

Outcome: Discontinuation due to adverse events

No studies reported on this critical outcome.

Outcome: Treatment compliance or discontinuation

No studies reported on this important outcome.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Infection

No studies reported on this important outcome.

Pharmacological treatment versus surgery

No studies identified for any comparison.

Pharmacological treatment versus combinations of pharmacological and surgical treatment

No studies identified for any comparison.

Surgical treatment versus no treatment, usual care [or placebo]

No studies identified for any comparison.

Surgical technique A versus surgical technique B

Comparison 3.1 Uterine artery embolisation (UAE) versus hysterectomy

Outcome: Reduction in blood loss

No studies reported on this important outcome.

Outcome: Health-related quality of life

Very low to low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed no difference in health-related quality of life (measured in SF-36 mental component summary score change from baseline) at 6 weeks, at 6 months, at 12 months, at 18 months, at 2 years, at 5 years, or at 10 years between women who underwent UAE compared to women who underwent hysterectomy. Because the uncertainty around the scores were not reported, the imprecision and clinical significance of these estimates could not be assessed.

Low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed better quality of life (measured in SF-36 physical component summary score change from baseline) at 6 weeks in women who underwent UAE compared to women who underwent hysterectomy. However, the same RCT showed no difference in the same measurement of health-related quality of life (SF-36 physical component summary score change from baseline) at 6 months, 12 months, 18 months, 2 years, 5 years, or 10 years in women who underwent UAE compared to women who underwent hysterectomy. The quality of the evidence ranged from low to very low. Because the uncertainty around the scores were not reported the imprecision and clinical significance of these estimates could not be assessed.

Outcome: Patient satisfaction

Low quality evidence from 3 RCTs (n=266) among women with fibroids (size not specified or less than or equal to 10 cm in diameter) showed no clinically significant difference in satisfaction with treatment (measured by asking women whether they would undergo the same treatment again) up to 24 months between women who underwent UAE compared to women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed no clinically significant difference in satisfaction with treatment (measured by asking women whether they would undergo the same treatment again) at 5 years and at 10 years between women who underwent UAE compared to women who underwent hysterectomy.

Outcome: Length of hospital stay

Evidence from 3 RCTs was available on the length of hospital stay. Evidence from all 3 RCTs showed a shorter length of hospital stay among women who underwent UAE compared to women who underwent hysterectomy. However, due to high heterogeneity of the estimates, it was not possible to pool these results and therefore the results are presented individually. Heterogeneity could be explained by differing settings since practice of hospital stay may vary according to setting.

Dutch setting

Moderate quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed a clinically significant shorter length of hospital stay (measured in days) in women who underwent UAE compared to women who underwent hysterectomy.

Finnish setting

Low quality evidence from 1 RCT (n=53) among women with fibroids unsuitable for hysteroscopic myomectomy showed a clinically significant shorter length of hospital stay (measured in days) in women who underwent UAE compared to women who underwent hysterectomy.

Spanish setting

Moderate quality evidence from 1 RCT (n=57) among women with fibroids less than or equal to 10 cm in diameter showed a clinically significant shorter length of hospital stay (measured in days) in women who underwent UAE compared to women who underwent hysterectomy.

Outcome: Blood transfusion

Moderate quality evidence from 2 RCTs (n=216) among women with fibroids (less than or equal to 10 cm in diameter or not specified) showed a clinically significant lower risk of blood transfusions in women who underwent UAE compared to women who underwent hysterectomy.

Outcome: Infection

Very low quality evidence from 1 RCT (n=60) among women with fibroids less than or equal to 10 cm in diameter showed no clinically significant difference in incidence of urinary tract infection within 30 days post-procedure between women who underwent UAE and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed no clinically significant difference in incidence of urinary tract infection during hospital stay or up to 6 weeks post-discharge between women who underwent UAE and women who underwent hysterectomy.

Very low quality evidence from 1 RCT (n=60) among women with fibroids less than or equal to 10 cm in diameter showed no clinically significant difference in incidence of vulvovaginitis within 30 days post-procedure between women who underwent UAE and women who underwent hysterectomy.

High quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed that none of the women who underwent UAE (n=81) had endometritis during hospital stay and 2 had endometritis within 6 weeks post-discharge. Endometritis was not applicable

as an outcome for women who underwent hysterectomy (n=75), therefore, the 2 intervention groups could not be compared.

High quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed that none of the women in either intervention group had pneumonia during hospital stay. Within 6 weeks post-discharge, 1 out of 81 women who underwent UAE had pneumonia compared to none in the group of women who underwent hysterectomy, showing no clinically significant difference in the incidence of pneumonia between the groups. The evidence was of low quality.

Very low quality evidence from 1 RCT (n=60) among women with fibroids less than or equal to 10 cm in diameter showed that there may be a clinically significant lower incidence of surgical wound abscess within 30 days post-procedure in women who underwent UAE compared to women who underwent hysterectomy but there is uncertainty around the estimate.

Low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed no clinically significant difference in the incidence of wound abscess during hospital stay or within 6 weeks post-discharge between women who underwent UAE and women who underwent hysterectomy.

Very low quality evidence from 1 RCT (n=60) among women with fibroids less than or equal to 10 cm in diameter showed no clinically significant difference in the incidence of intra-abdominal abscess within 30 days post-procedure between women who underwent UAE and women who underwent hysterectomy.

High quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed that none of the women in either intervention group had intra-abdominal infection during hospital stay or within 6 weeks post-discharge.

High quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed that none of the women in either intervention group had sepsis during hospital stay. Low quality evidence from the same RCT showed that 1 out of 81 women who underwent UAE had sepsis within 6 weeks post-discharge compared with none in the group of women who underwent hysterectomy, showing no clinically significant difference in the incidence of sepsis between the groups.

Outcome: Venous thromboembolism

Very low quality evidence from 1 RCT (n=60) among women with fibroids less than or equal to 10 cm in diameter showed no clinically significant difference in the incidence of deep venous thrombosis within 30 days post-procedure between women who underwent UAE and women who underwent hysterectomy.

High quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed that none of the women in either intervention group had thrombosis during hospital stay or up to 6 weeks post-discharge.

Low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed no clinically significant difference in the incidence of pulmonary embolism during hospital stay between women who underwent UAE and women who underwent hysterectomy. High quality evidence from the same RCT showed that none the women in either intervention group had pulmonary embolism within 6 weeks post-discharge.

Outcome: Return to hospital or theatre

Low quality evidence from 2 RCTs (n=217) among women with fibroids (less than or equal to 10 cm in diameter or not specified) showed a clinically significant increase in unscheduled

readmission rate within 4 to 6 weeks in women who underwent UAE compared to women who underwent hysterectomy.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

Very low quality evidence from 1 RCT (n=57) among women with fibroids unsuitable for hysteroscopic myomectomy showed no clinically significant difference in incidence of urinary stress incontinence at 2 years follow-up between women who underwent UAE and women who underwent hysterectomy.

Outcome: Mortality

Low quality evidence from 1 RCT (n=156) among women with fibroids (size not specified) showed that none of the women in either intervention group died during hospital stay or within 6 weeks post-discharge.

Comparison 3.2 Uterine artery embolisation (UAE) versus myomectomy

Outcome: Reduction in blood loss

No studies reported on this important outcome.

Outcome: Patient satisfaction

Moderate quality evidence from 1 RCT (n=110) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in patient satisfaction (measured by asking the women if they obtained symptom relief) up to 24 months between women who underwent UAE and women who underwent myomectomy.

Outcome: Health-related quality of life

Very low quality evidence from 1 RCT (n=122) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in symptom severity (measured in UFS-QOL symptom severity change score from baseline) at 1 year between women who underwent UAE and women who underwent myomectomy.

Very low quality evidence from 1 RCT (n=122) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in health-related quality of life (measured in UFS-QOL total health-related quality of life change score from baseline and the following subscales: concern, activities, mood, control, self-control, sex function) at 1 year between women who underwent UAE and women who underwent myomectomy.

Outcome: Length of hospital stay

Evidence from 2 RCTs was available on length of hospital stay. Due to high heterogeneity of the estimates, it was not possible to pool these results and therefore the results are presented individually. Heterogeneity could be explained by differing settings since practice of hospital stay may vary according to setting.

UK setting

Moderate quality evidence from 1 RCT (n=122) among women with fibroids more than or equal to 4 cm in diameter showed a clinically significant shorter length of hospital stay (measured in days) in women who underwent UAE compared to women who underwent myomectomy.

Czech setting

Low quality evidence from 1 RCT (n=121) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in length of hospital stay (measured in days) between women who underwent UAE and women who underwent myomectomy.

Outcome: Blood transfusion

Low quality evidence from 1 RCT (n=121) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in need for blood transfusion between women who underwent UAE and women who underwent myomectomy.

Outcome: Infection

Very low quality evidence from 1 RCT (n=122) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in incidence of pneumonia or sepsis (within 1 year post-procedure) between women who underwent UAE and women who underwent myomectomy.

Low quality evidence from 1 RCT (n=122) among women with fibroids more than or equal to 4 cm in diameter showed that there was a clinically significant lower incidence of urinary tract infection (within 1 year post-procedure) in women who underwent UAE compared to women who underwent myomectomy.

Low quality evidence from 1 RCT (n=121) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in need for antibiotics within 30 days post-procedure between women who underwent UAE and women who underwent myomectomy.

Outcome: Venous thromboembolism

Very low quality evidence from 1 RCT (n=122) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in the incidence of pulmonary embolus within 1 year post-procedure between women who underwent UAE and women who underwent myomectomy.

Outcome: Return to hospital or theatre

Low quality evidence from 1 RCT (n=121) among women with fibroids more than or equal to 4 cm in diameter showed no clinically significant difference in unscheduled readmission rate within 4 to 6 weeks post-procedure between women who underwent UAE and women who underwent myomectomy.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Comparison 3.3 Uterine artery embolisation (UAE) versus myomectomy or hysterectomy

Outcome: Reduction in blood loss

No studies reported on this important outcome.

Outcome: Patient satisfaction

Very low quality evidence from 2 RCTs (n=264) among women with fibroids more than 2 cm in diameter showed no clinically significant difference in satisfaction with treatment (measurement method not specified) at 12 months between women who underwent UAE and women who underwent hysterectomy or myomectomy.

Very low quality evidence from 1 RCT (n=139) among women with fibroids more than 2 cm in diameter showed no clinically significant difference in satisfaction with treatment (measurement method not specified) at 5 years between women who underwent UAE and women who underwent hysterectomy or myomectomy.

Outcome: Health-related quality of life

Moderate quality evidence from 1 RCT (n=124) among women with fibroids more than 4 cm in diameter showed a clinically significant better health-related quality of life (measured in SF-36 score in physical function, social function, mental health, emotional role and vitality) at 6 months in women who underwent UAE compared to women who underwent hysterectomy or myomectomy.

Very low to low quality evidence from 1 RCT (n=157) among women with fibroids more than 2 cm in diameter showed no clinically significant difference in health-related quality of life (measured in SF-36 score in physical function, mental health, emotional role and vitality) at 1 year and 5 years in women who underwent UAE compared to women who underwent hysterectomy or myomectomy.

Outcome: Length of hospital stay

Low quality evidence from 2 RCTs (n=273) among women with fibroids more than 2 cm in diameter showed a clinically significant shorter length of hospital stay (measured in days) in women who underwent UAE compared to women who underwent hysterectomy or myomectomy.

Outcome: Blood transfusion

No studies reported on this important outcome.

Outcome: Infection

Low quality evidence from 1 RCT (n=157) among women with fibroids more than 2 cm in diameter no showed that 2 out of 51 (3.9%) women in the hysterectomy or myomectomy group had a wound infection. This outcome is not applicable for UAE, therefore the 2 intervention groups cannot be compared.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Comparison 3.4 Thermal balloon ablation (TBA) versus hysterectomy

Outcome: Reduction in blood loss

No studies reported on this important outcome.

Outcome: Health-related quality of life

Low quality evidence from 1 RCT (n=40) among women with fibroids less than or equal to 5 cm in diameter showed worse symptom severity and health-related quality of life (measured in UFS-QOL symptom severity score and health-related quality of life score change from baseline) at 6 months in women who underwent TBA compared to women who underwent hysterectomy. Because the uncertainty around the estimates were not reported, the imprecision and clinical significance of these estimates could not be assessed.

Outcome: Patient satisfaction

No studies reported on this critical outcome.

Outcome: Length of hospital stay

Low quality evidence from 1 RCT (n=40) among women with fibroids less than or equal to 5 cm in diameter showed shorter length of hospital stay (measured in hours) in women who underwent TBA compared to women who underwent hysterectomy. Because the uncertainty around the estimates were not reported, the imprecision and clinical significance of these estimates could not be assessed.

Outcome: Blood transfusion

High quality evidence from 1 RCT (n=40) among women with fibroids less than or equal to 5 cm in diameter showed a clinically significant beneficial effect on the need of blood transfusion in women who underwent TBA compared to women who underwent hysterectomy.

Outcome: Infection

No studies reported on this critical outcome.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Surgery versus combinations of pharmacological and surgical treatment

No studies identified for any comparison.

2. Women with suspected or diagnosed adenomyosis

Pharmacological treatment versus no treatment, usual care or placebo

No studies identified for any comparison.

Pharmacological treatment A versus pharmacological treatment B

No studies identified for any comparison.

Pharmacological treatment versus surgery

Comparison 1. Levonorgestrel-releasing intrauterine system (LNG-IUS) versus hysterectomy

Outcome: Reduction in blood loss

No studies reported this on important outcome.

Outcome: Health-related quality of life

Very low to low quality evidence from 1 RCT (n=75) among women with suspected adenomyosis showed no difference in health-related quality of life (measured in median score of WHOQOL-BREF TR score in the physical domain, psychological domain, and social domain, whereas the environmental domain was measured in a mean score) at 1 year follow-up between women who received LNG-IUS or women who underwent hysterectomy. However, the uncertainty around these estimates were not reported, therefore, the imprecision and clinical significance of these estimates could not be assessed.

Outcome: Patient satisfaction

No studies reported on this critical outcome.

Outcome: Discontinuation due to adverse events

No studies reported on this critical outcome.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Infection

Low quality evidence from 1 RCT (n=75) among women with suspected adenomyosis showed that 1 out of 32 (3.1%) women in the hysterectomy group had a post-operative wound infection. This outcome is not applicable for the LNG-IUS group, therefore, the 2 intervention groups cannot be compared.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Pharmacological treatment versus combinations of pharmacological and surgical treatment

No studies identified for any comparison.

Surgical treatment versus no treatment, usual care [or placebo]

No studies identified for any comparison.

Surgical technique A versus surgical technique B

No studies identified for any comparison.

Surgery versus combinations of pharmacological and surgical treatment

No studies identified for any comparison.

3. Women with no identified pathology

Pharmacological treatment versus no treatment, usual care or placebo

Comparison 1. Combined oral contraceptives (COC) versus placebo

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Pharmacological treatment A versus pharmacological treatment B

Comparison 2.1 Mefenamic acid versus naproxen

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Comparison 2.2 Tranexamic acid versus nonsteroidal anti-inflammatory drugs (NSAIDs)

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Comparison 2.3 Tranexamic acid versus progestogen

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Low quality evidence from 1 RCT (n=90) among women with no identified pathology showed no clinically significant difference in health-related quality of life (measured in Menorrhagia Questionnaire change score from baseline) after 3 cycles of treatment between women who received medroxyprogesterone acetate (5mg every 12 hours for 21 days from day 5 of menses) and women who received tranexamic acid (500mg every 6 hours for 5 days from day 1 of menses).

Very low to low quality evidence from 1 RCT (n=84) among women with no identified pathology showed no difference in health-related quality of life (measured in WHOQOL-BREF TR change score from baseline in the following domains: physical, psychosocial, social, environmental [general], and environmental [Turkey-specific]) after 6 cycles of treatment between women who received norethisterone acetate (5 mg 3 times daily for 10 days between the 14th and 23rd day of menstrual cycle) and women who received tranexamic acid (1 g 4 times daily for the first 4 days of the cycle).

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Comparison 2.4 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus nonsteroidal anti-inflammatory drugs (NSAIDs)

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

High quality evidence from 1 RCT (n=51) among women with no identified pathology showed that 1 out of 25 (4%) women who received LNG-IUS developed chlamydial endometritis and despite successful treatment the LNG-IUS was expelled after 29 days. The outcome was not relevant for the women who received mefenamic acid (500 mg 3 times daily for the first 4 days of the menstrual cycle), therefore, the 2 interventions could not be compared, and imprecision could not be assessed.

Outcome: Infection

See above (Outcome: Expulsion).

Comparison 2.5 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus tranexamic acid

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Very low to low quality evidence from 1 RCT (n=84) among women with no identified pathology showed no difference in health-related quality of life (measured in WHOQOL-BREF TR change score from baseline in the following domains: physical, psychosocial, social, environmental [general], and environmental [Turkey-specific]) after 6 cycles of treatment between women who received LNG-IUS and women who received tranexamic acid (1 g 4 times daily for the first 4 days of the cycle).

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Infection

No studies reported on this important outcome.

Comparison 2.6 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus progestogens

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Very low to low quality evidence from 1 RCT (n=84) among women with no identified pathology showed no difference in health-related quality of life (measured in WHOQOL-BREF TR change score from baseline in the following domains: physical, psychosocial, social, environmental [general], and environmental [Turkey-specific]) after 6 cycles of treatment between women who received LNG-IUS and the women who received norethisterone acetate (5 mg 3 times daily for 10 days between the 14th and 23rd day of menstrual cycle).

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

High quality evidence from 2 RCTs (n=206) among women with no identified pathology showed that the LNG-IUS was expelled in 5 out of 102 (4.9%) women within up to 6 months/cycles of treatment. This outcome was not relevant for the women who received medroxyprogesterone acetate, therefore, the 2 interventions could not be compared and inconsistency, imprecision and clinical significance could not be assessed.

Outcome: Infection

Moderate quality evidence from 1 RCT (n=162) among women with no identified pathology showed that they may be a clinically significant lower incidence of vaginitis within 6 months/cycles of treatment in women who received medroxyprogesterone acetate (10 mg once daily for 10 consecutive days of the cycle starting day) compared to women who received LNG-IUS but there is uncertaintly around the estimate.

Low quality evidence from the same RCT (n=162) among women with no identified pathology showed no clinically significant difference in the incidence of urinary tract infection within 6 months/cycles of treatment between women who received medroxyprogesterone acetate and women who received LNG-IUS.

Comparison 2.7 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus combined oral contraceptives (COCs)

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Very low quality evidence from 1 RCT (n=112) among women with no identified pathology showed no clinically significant difference in self-rated health being very good or excellent (question 1 in HRQoL-4) at 12 months between women who received LNG-IUS and women who received low-dose COC (30 µg of ethinyl estradiol and 150 µg levonorgestrel).

Very low quality evidence from 1 RCT (n=112) among women with no identified pathology showed no clinically significant difference in health-related quality of life (measured in number of days feeling physically unwell in the previous 30 days, question 2 in HRQoL-4, change from baseline) at 12 months between women who received LNG-IUS and women who received low-dose COC.

Low quality evidence from 1 RCT (n=112) among women with no identified pathology showed a clinically significant harmful effect on health-related quality of life (measured in number of days feeling mentally unwell in the previous 30 days, question 3 in HRQoL-4, change from baseline) at 12 months in women who received LNG-IUS compared to women who received low-dose COC.

Low quality evidence from 1 RCT (n=112) among women with no identified pathology showed a clinically significant beneficial effect on health-related quality of life (measure in number of ‘lost’ days [defined as days when work or other daily activities are not possible] in the previous 30 days, question 4 in HRQoL-4, change from baseline) at 12 months in women who received LNG-IUS compared to comen who received low-lose COC.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Infection

No studies reported on this important outcome.

Comparison 2.8 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus variety of pharmacological treatments

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Moderate quality evidence from 1 RCT (n=549) among women with no identified pathology showed a clinically significant improvement in health-related quality of life (measured in Menorrhagia Multi-Attribute Scale [MMAS] summary score change from baseline) at 6 months, at 12 months, and at 2 years follow-up in women who received LNG-IUS compared to women who received usual medical treatment (mefenamic acid, tranexamic acid, norethisterone, combined oestrogen-progestogen or progestogen-only oral contraceptive pill, or medroxyprogesterone acetate injection, chosen by the physician and patient according to contraceptive needs and desire to avoid hormone therapy). However, there was no clinically significant difference in quality of life (measured in Menorrhagia Multi-Attribute Scale [MMAS] summary score change from baseline) at 5 years.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Infection

No studies reported on this important outcome.

Pharmacological treatment versus surgery

Comparison 3.1 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus first generation endometrial resection/ablation

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Expulsion

Moderate quality evidence from 3 RCTs (n=109) among women with no identified pathology showed that the LNG-IUS was expelled in 12 out of 109 (11%) women within 1 year post-procedure (for 1 case, timing not clear). This outcome was not relevant for the women who underwent first generation endometrial ablation, therefore, the 2 interventions could not be compared and inconsistency, imprecision and clinical significance could not be assessed.

Outcome: Length of hospital stay

No studies reported on this important outcome.

Outcome: Blood transfusion

No studies reported on this important outcome.

Outcome: Infection

Low quality evidence from 1 RCT (n=59) among women with no identified pathology showed no clinically significant difference in the incidence of pelvic inflammatory disease or endometritis (timing not specified) between women who received LNG-IUS and women who underwent first generation endometrial resection/ablation.

Very low quality evidence from 1 RCT (n=60) among women with no identified pathology showed no clinically significant difference in the incidence of post-procedure vaginitis between women who received LNG-IUS and women who underwent first generation endometrial resection/ablation.

Low quality evidence from 1 RCT (n=41) among women with no identified pathology showed no clinically significant difference in the incidence of post-procedure endometritis between women who received LNG-IUS and women who underwent first generation endometrial resection/ablation.

Low quality evidence from 1 RCT (n=41) among women with no identified pathology showed no clinically significant difference in the incidence of post-procedure myometritis between

women who received LNG-IUS and women who underwent first generation endometrial resection/ablation.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

Low quality evidence from 1 RCT (n=104) among women with no identified pathology showed no clinically significant difference in the incidence of uterine perforation between women who received LNG-IUS and women who underwent first generation endometrial resection/ablation.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Comparison 3.2 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus second generation endometrial ablation

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Perforation

No studies reported on this important outcome.

Outcome: Expulsion

Moderate quality evidence from 4 RCTs (n=127) among women with no identified pathology showed that the LNG-IUS was expelled in 9 out of 127 women (3.9%) (the follow-up times varied between the studies from 3 months to 2 years). This outcome is not relevant for the women who underwent second generation endometrial ablation, therefore, the 2 interventions could not be compared and inconsistency, imprecision and clinical significance could not be assessed.

Outcome: Length of hospital stay

No studies reported on this important outcome.

Outcome: Blood transfusion

No studies reported on this important outcome.

Outcome: Infection

High quality evidence from 1 RCT (n=39) among women with no identified pathology showed that 5 out of 39 (12.8%) women who underwent second generation endometrial resection/ablation received post-operative antibiotics due to possible endometritis. This outcome was not applicable for the women who received LNG-IUS, therefore, the 2 intervention groups could not be compared and inconsistency, imprecision and clinical significance could not be assessed.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Comparison 3.3 Levonorgestrel-releasing intrauterine system (LNG-IUS) versus hysterectomy

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Discontinuation due to adverse events

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Treatment compliance or discontinuation

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Expulsion

No studies reported on this important outcome.

Outcome: Length of hospital stay

No studies reported on this important outcome.

Outcome: Blood transfusion

No studies reported on this important outcome.

Outcome: Infection

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed a clinically significant higher incidence of post-procedure wound infection in women who underwent hysterectomy compared to women who received LNG-IUS.

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of post-procedure infected pelvic haematoma between women who received LNG-IUS and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of post-procedure peritonitis between women who received LNG-IUS and women who received hysterectomy.

Outcome: Venous thromboembolism

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of thromboembolic event (timeframe not clear) between women who received LNG-IUS and women who underwent hysterectomy.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of vesicovaginal fistula between women who received LNG-IUS and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of ureter lesion between women who received LNG-IUS and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of bladder perforation between women who received LNG-IUS and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=232) among women with no identified pathology showed no clinically significant difference in the incidence of bowel perforation between women who received LNG-IUS and women who underwent hysterectomy.

Outcome: Long-term complications

Moderate quality evidence from 1 RCT (n=221) among women with no identified pathology showed that there may be a clinically significant higher incidence of stress urinary incontinence (time of follow-up not clear) in women who received hysterectomy compared to women who received LNG-IUS but there is uncertainty around the estimate.

Moderate quality evidence from 1 RCT (n=221) among women with no identified pathology showed no clinically significant difference in the incidence of urge urinary incontinence (time of follow-up not clear) between women who received LNG-IUS and women who received hysterectomy.

Outcome: Mortality

No studies reported on this important outcome.

Pharmacological treatment versus combinations of pharmacological and surgical treatment

Comparison 4. Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone analogue (GnRHa) injection

Outcome: Reduction in blood loss

No studies reported on this important outcome.

Outcome: Health-related quality of life

Low quality evidence from 1 RCT (n=187) among women with no identified pathology showed a clinically significant improvement in health-related quality of life (measured in SF-36 mean score change from baseline) at 4 months in the following domains: energy/fatigue, social function, mental health, and general health among women who underwent transcervical endometrial resection (with a one-off injection of GnRHa 5 weeks prior to the resection) compared to women who received medical management (either progestogen, tranexamic acid, COC, danazol, or hormone-replacement therapy). There was no clinically significant difference in the following domains of health-related quality of life at 4 months between the groups: physical function, physical role, emotional role, and pain. The evidence was of low quality.

At 2 years follow-up, low to moderate quality evidence from the same RCT showed no difference in health-related quality of life (measured in SF-36 mean change score from baseline) in any of the aforementioned domains between the groups.

At 5 years follow-up, very low quality evidence from the same RCT showed a clinically significant beneficial effect on the health-related quality of life in the mental health and emotional role domains among women who underwent transcervical endometrial resection (with a one-off injection of GnRHa 5 weeks prior to the resection) compared to women who received medical management. However, there was no difference in health-related quality of life in the other domains of SF-36 (physical functioning, energy/fatigue, physical role, social functioning, pain or general health) between the groups. The evidence was of very low to low quality.

Outcome: Patient satisfaction

Low to moderate quality evidence from 1 RCT (n=187) among women with no identified pathology showed a clinically significant beneficial effect on satisfaction with treatment (totally or generally satisfied with treatment) at 4 months and at 2 years among women who underwent transcervical endometrial resection (with a one-off injection of GnRHa 5 weeks prior to the resection) compared to women who received medical management (either progestogen, tranexamic acid, COC, danazol, or hormone-replacement therapy). However, at 5 years, there was no longer a clinically significant difference in patient satisfaction between the groups. The evidence was of very low quality.

Low to moderate quality evidence from the same RCT showed a clinically significant increased likelihood of recommending the treatment to a friend at 4 months, at 2 years and at 5 years among women who underwent transcervical endometrial resection compared with women who received medical management.

Outcome: Length of hospital stay

No studies reported on this important outcome.

Outcome: Blood transfusion

No studies reported on this important outcome.

Outcome: Infection

No studies reported on this critical outcome.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

No studies reported on this critical outcome.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Surgical treatment versus no treatment, usual care [or placebo]

No studies identified for any comparison.

Surgical technique A versus surgical technique B

Comparison 5.1 First generation endometrial ablation versus hysterectomy

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Length of hospital stay

Evidence from 4 RCTs was available on length of hospital stay. Due to a high level of heterogeneity, it was not possible to pool these results and therefore the results are presented individually. A possible explanation for the high level of heterogeneity in the length of hospital stay could be variation in clinical practice secondary to the differences in settings.

UK Setting

Moderate quality evidence from 1 RCT (n=176) among women with no identified pathology showed a clinically significant shorter length of hospital stay (measured in days) in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Moderate quality evidence from 1 RCT (n=196) among women with no identified pathology showed a beneficial effect in length of hospital stay (measured in days) in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy, however the uncertainty around the estimates were not reported and the imprecision and clinical significance could not be assessed.

US Setting

Low quality evidence from 1 RCT (n=171) among women with no identified pathology showed a clinically significant beneficial effect in length of hospital stay (measured in days) in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Italian Setting

Moderate quality evidence from 1 RCT (n=181) among women with no identified pathology showed no clinically significant difference in length of hospital stay (measured in days) in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Outcome: Blood transfusion

Moderate quality evidence from 3 RCTs (n=549) among women with no identified pathology showed a clinically significant lower incidence of blood transfusions in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Outcome: Infection

Very low quality evidence from 3 RCTs (n=548) among women with no identified pathology showed a clinically significant lower incidence of post-operative urinary tract infections in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Low quality evidence from 2 RCTs (n=367) among women with no identified pathology showed that 16 out of 215 (7.4%) women in the hysterectomy group had a post-operative abdominal wound infection. This outcome is not applicable for the first generation endometrial ablation group, therefore the 2 intervention groups cannot be compared and inconsistency and imprecision could not be calculated.

Low quality evidence from 1 RCT (n=171) among women with no identified pathology showed that 1 out of 53 (1.9%) women in the first generation endometrial ablation group had endometritis up to 42 days after the procedure. This outcome is not applicable for the hysterectomy group, therefore the 2 intervention groups cannot be compared.

Low quality evidence from 1 RCT (n=196) among women with no identified pathology showed no clinically significant difference in the incidence of post-operative pelvic infection between women who underwent first generation endometrial ablation and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=172) among women with no identified pathology showed no clinically significant difference in the incidence of sepsis (before discharge) between women who underwent first generation endometrial ablation and women who underwent hysterectomy.

High quality evidence from 1 RCT (n=172) among women with no identified pathology showed a clinically significant lower incidence of sepsis (after discharge) in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Outcome: Venous thromboembolism

Very low quality evidence from 1 RCT (n=171) among women with no identified pathology showed no clinically significant difference in the incidence of thromboembolic events during the perioperative period between women who underwent first generation endometrial ablation and women who underwent hysterectomy.

Outcome: Return to hospital or theatre

Very low quality evidence from 3 RCTs (n=539) among women with no identified pathology showed a clinically significant lower incidence of readmission or return to theatre (within up to 6 weeks post-procedure) in women who underwent first generation endometrial ablation compared to women who underwent hysterectomy.

Outcome: Internal organ injury

High quality evidence from 1 RCT (n=172) among women with no identified pathology showed that 2 out of 116 (1.7%) women in the first generation endometrial ablation group had a cervical tear. This outcome is not applicable for the hysterectomy group, therefore the 2 intervention groups cannot be compared.

Low quality evidence from 3 RCTs (n=539) among women with no identified pathology showed that 8 out of 268 (3%) women in the first generation endometrial ablation group had a uterine perforation. This outcome is not applicable for the hysterectomy group, therefore the 2 intervention groups cannot be compared and the inconsistency and imprecision could not be calculated.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Comparison 5.2 Second generation endometrial ablation versus hysterectomy

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Length of hospital stay

Low quality evidence from 1 RCT (n=175) among women with no identified pathology showed a clinically significant shorter length of hospital stay in women who underwent second generation endometrial ablation compared to women who underwent hysterectomy.

Outcome: Blood transfusion

High quality evidence from 1 RCT (n=68) among women with no identified pathology showed that none of the women in either intervention group received a blood transfusion during their hospital stay.

Outcome: Infection

Very low quality evidence from 1 RCT (n=175) among women with no identified pathology showed no clinically significant difference in the incidence of urinary tract infections within 42 days post-procedure between women who underwent second generation endometrial ablation and women who underwent hysterectomy.

Low quality evidence from 1 RCT (n=175) among women with no identified pathology showed that none of the women in the second generation endometrial ablation group had endometritis within 42 days post-procedure. This outcome was not applicable to the group of women who underwent hysterectomy, therefore, the 2 groups cannot be compared.

Low quality evidence from 1 RCT (n=175) among women with no identified pathology showed that 5 out of 118 (4.2%) women in the hysterectomy group had a post-operative abdominal wound infection. This outcome was not applicable to the group of women who underwent second generation endometrial ablation, therefore, the 2 groups cannot be compared.

Outcome: Venous thromboembolism

Very low quality evidence from 1 RCT (n=175) among women with no identified pathology showed no clinically significant difference in the incidence of thromboembolic events during the perioperative period in women who underwent second generation endometrial ablation and women who underwent hysterectomy.

Outcome: Return to hospital or theatre

Very low quality evidence from 2 RCTs (n=243) among women with no identified pathology showed no clinically significant difference in the incidence of readmission or return to operating theatre (within up to 42 days post-procedure) in women who underwent second generation resection or ablation and women who underwent hysterectomy.

Outcome: Internal organ injury

Low quality evidence from 1 RCT (n=175) among women with no identified pathology showed that 2 out of 57 (3.5%) women in the second generation resection/ablation group had a uterine perforation. This outcome is not applicable for the hysterectomy group, therefore the 2 intervention groups cannot be compared.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Comparison 5.3 First generation versus second generation endometrial ablation

Outcome: Reduction in blood loss

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Health-related quality of life

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Patient satisfaction

NMA outcome, see Clinical evidence profile for NMA outcomes.

Outcome: Length of hospital stay

No studies reported on this important outcome.

Outcome: Blood transfusion

No studies reported on this important outcome.

Outcome: Infection

Very low quality evidence from 2 RCTs (n=418) among women with no identified pathology showed no clinically significant difference in the incidence of post-operative infection in women who underwent first generation endometrial ablation and women who underwent second generation endometrial ablation.

Very low quality evidence from 4 RCTs (n=1,044) among women with no identified pathology showed no clinically significant difference in the incidence of post-operative endometritis or urinary tract infection in women who underwent first generation endometrial ablation and women who underwent second generation endometrial ablation.

Outcome: Venous thromboembolism

No studies reported on this critical outcome.

Outcome: Return to hospital or theatre

No studies reported on this important outcome.

Outcome: Internal organ injury

Low quality evidence from 3 RCTs (n=765) among women with no identified pathology showed that there may be a clinically significant increased risk in the incidence of cervical laceration in women who underwent first generation endometrial ablation compared to women who underwent second generation endometrial ablation, but there is uncertainty around this estimate.

Low quality evidence from 4 RCTs (n=907) among women with no identified pathology showed a clinically significant increased risk of uterine perforation in women who underwent first generation endometrial ablation compared to women who underwent second generation endometrial ablation.

Outcome: Long-term complications

No studies reported on this important outcome.

Outcome: Mortality

No studies reported on this important outcome.

Surgery versus combinations of pharmacological and surgical treatment

No studies identified for any comparison.

4. Health economic evidence statements

One cost-utility analysis (Calaf 2015) undertaken in Spain found LNG-IUS to dominate estradiol valerate/dienogest, COC and PROG using a 5-year time horizon in women with HMB who wish to retain their fertility. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Lete 2011) undertaken in Spain found LNG-IUS to dominate COC and PROG using a 5-year time horizon in women with idiopathic dysfunctional uterine bleeding. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Gupta 2015) undertaken in the UK found that using the EQ-5D, LNG-IUS is cost-effective (more expensive and more effective) compared to usual medical treatment with ICERs (per QALY gained) of £1,600 and £114 at years 2 and 5, respectively for women with menorrhagia in primary care. However, using the SF-6D, usual medical treatment dominated LNG-IUS at 2 and 5 years. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Blake 2016) undertaken in Ontario found LNG-IUS to dominate endometrial ablation and hysterectomy using a 9-year time horizon in women with HMB. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Ganz 2011) undertaken in the US, using a 5-year time horizon, found LNG-IUS to dominate all nonsurgical comparators (COCs, oral progestin, tranexamic acid) for women with HMB and wanting contraception. Ablation is also more expensive and effective than LNG-IUS with an ICER of $122,278 per QALY gained but ablation is extendedly dominated (ICER is higher than that of the next most effective treatment) by LNG-IUS and hysterectomy. Hysterectomy is the most expensive and effective intervention with an ICER of $49,614 per QALY gained vs. LNG-IUS. This analysis is partially applicable with potentially serious limitations.

One cost-utility analysis (You 2006) undertaken in Hong Kong found LNG-IUS to dominate oral medical treatment and endometrial resection/ablation dominated using a 5-year time horizon in women of reproductive age and with regular heavy menstrual periods. Hysterectomy is more expensive and more effective than LNG-IUS with an ICER of US$ 23500 per QALY gained. This analysis is partially applicable with minor limitations.

One cost-utility analysis (Clegg 2007) undertaken in the UK using data from a Finnish RCT over a 5-year time horizon, found LNG-IUS followed by ablation to dominate LNG-IUS followed by hysterectomy, TBEA, MEA and hysterectomy in women with HMB. Hysterectomy is also dominated (hysterectomy more expensive and less effective) by all options. This analysis is directly applicable with minor limitations.

One cost-utility analysis (You 2009) undertaken in Hong Kong found hysterectomy to dominate UAE and myomectomy using a 5-year time horizon in women presenting with symptomatic uterine fibroids. This analysis is partially applicable with potentially serious limitations.

One cost-utility analysis (Zowall 2008) undertaken in the UK, following women from the age of 39 to 56 years, found MRgFUS to dominate current practice (uterine artery embolization 25%, myomectomy 25% and hysterectomy 50%) in women for whom surgical treatment for uterine fibroids is being considered. This analysis is directly applicable with potentially serious limitations.

One cost-utility analysis (Miller 2015) conducted in the US found thermal (radio-frequency) endometrial ablation to dominate other global endometrial ablation techniques using a 5-year time horizon in premenopausal women seeking a permanent final treatment for their abnormal uterine bleeding. Hysterectomy is more expensive and more effective than thermal (radio-frequency) endometrial ablation with an ICER of $80,902 per QALY gained. This analysis is partially applicable with minor limitations.

One cost-utility analysis (Beinfield 2004) conducted in the US found UAE is more expensive and more effective than no treatment with an ICER of $2,007 per QALY gained in women aged 40 years and a diagnosis of uterine fibroids. UAE also dominates hysterectomy. This analysis is not applicable with potentially serious limitations.

One cost-utility analysis (Tsoi 2015) undertaken in Ontario found ulipristal to dominate leuprolide in women with moderate to severe symptoms of uterine fibroids and eligible for surgery. This analysis is directly applicable with potentially serious limitations.

One cost-utility analysis (Bhattacharya 2011) undertaken in the UK conducted 2 analysis with a 10-year time horizon in women aged 42 years with HMB. In analysis 1 (repeat procedures are allowed at any age, but with a decreasing hazard) hysterectomy dominates (hysterectomy less expensive and more effective) first generation EA and second generation EA. Hysterectomy is also more costly and more effective than Mirena with an ICER of £1,600 per QALY gained. In analysis 2 (if symptoms do not recur within 2 years of the initial ablation, then they are unlikely to do so later) hysterectomy dominates (hysterectomy less expensive and more effective) first generation EA. Hysterectomy is also more costly and more effective than second generation EA with an ICER of £970 per QALY gained, and more costly and more effective than Mirena with an ICER of £1,440 per QALY gained. This analysis is directly applicable with minor limitations.

One cost-utility analysis (Heliovaara-Peippo 2010) conducted found hysterectomy to be more expensive and more effective than LNG-IUS, with an ICER of $12,417 per QALY using a 10-year time horizon in women aged 35-49 years referred to hospital with menorrhagia who had completed their childbearing. This analysis is partially applicable with potentially serious limitations.

One US cost-utility analysis (Kong 2014) with a lifetime time horizon found MRgFUS to be more expensive than hysterectomy with an ICER of $33,110 per QALY in the treatment of women with symptomatic uterine fibroids. UAE was reported to be more expensive than UAE or hysterectomy with an ICER of $270,057 per QALY relative to MRgFUS. This analysis is partially applicable with potentially serious limitations.

One cost-utility analysis (O'Sullivan 2009) in the US reported an ICER of $21,800 per QALY for hysterectomy relative to pharmacotherapy in the treatment of symptomatic uterine fibroids in premenopausal women using a lifetime time horizon. It calculated that the ICER for MRgFUS when compared to hysterectomy was $41,400 per QALY and the ICER for UAE when compared to MRgFUS was $54,200 per QALY. Myomectomy was reported to be dominated by other treatment alternatives. This analysis is partially applicable with potentially serious limitations.

One cost-utility analysis (Cain-Nielsen 2014) in the US found that myomectomy was dominated by MRgFUS in premenopausal women with uterine fibroids and wishing to preserve their uteri using a time horizon of 5 years. MRgFUS was estimated to have an ICER of $46,250 per QALY relative to myomectomy. This analysis is partially applicable with potentially serious limitations.

One cost-utility analysis in Canada (Babashov 2015) calculated that myomectomy and MRgFUS were dominated by UAE in the treatment of symptomatic uterine fibroids that are refractory to phamaclogical treatment in premenopausal women using a time horizon of 11 years. It also reported that UAE had an ICER of CAD $46,480 per QALY relative to hysterectomy. This analysis is partially applicable with potentially serious limitations.

An economic model developed for the guideline found that empiric treatment with LNG-IUS was a cost-effective when compared to strategies where diagnosis was used to determine treatment under the assumption that LNG-IUS was effective for all underlying pathology (see Health Economics Chapter, Analyses 1, 3, and 10).

An economic model developed for the guideline found that first line treatment with TXA was cost-effective under the assumption that pharmaceutical treatment was effective for all underlying pathology (see Health Economics Chapter, Analysis 8).

An economic model developed for the guideline found that first line treatment with TXA was cost-effective for women with fibroids less 3 cm in diameter and no identified pathology under conservative assumptions about treatment effectiveness of pharmaceutical interventions (see Health Economics Chapter, Analysis 9).

An economic model developed for the guideline found that hysterectomy was cost-effective for fibroids smaller than 3 cm in diameter when compared to first and second generation endometrial eblation (Analysis 12).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the aim of managing HMB is to improve the woman's health-related quality of life, therefore health-related quality of life was considered a critical outcome for decision making. Patient satisfaction following an intervention was also considered a critical outcome, because it was deemed crucial to assess the success of an intervention from the woman's point of view. Discontinuation of pharmacological treatment owing to adverse events was also considered to be a critical outcome to guide decision making. For surgical interventions, serious adverse events such as internal organ injury, infection, and venous thromboembolism were considered critical outcomes to assess the safety of the interventions and guide the decision making process.

Reduction in blood loss (measured in PBAC score or AH method); treatment compliance or discontinuation (reason not specified) for pharmacological interventions; perforation, expulsion, and infection due to LNG-IUS; length of hospital stay, need for blood transfusion, return to hospital or operating theatre, long-term complications, and mortality for surgical interventions were considered important outcomes. From the woman's point of view, methods to objectively assess reduction in menstrual blood loss are considered to be a poor indicator of treatment effectiveness for HMB. For example, no correlation between PBAC score and actual menstrual blood loss (Reid 2000) or quality of life (de Souza 2010) has been found. However, many studies report this outcome and therefore, it was included as an outcome in this review. Adverse events in relation to LNG-IUS were considered important but not critical for decision making. Length of hospital stay was not considered a critical outcome from the woman's point of view. Mortality was considered so rare that it was not considered critical for decision making.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology, whereas the RCTs included in the NMAs were assessed using the Cochrane Collaboration's tool for assessing risk of bias.

The quality of evidence in these reviews ranged from very low to high with most evidence being of low quality. The committee agreed that the quality of evidence was most often downgraded because of a lack of blinding of participants and/or assessors on subjective outcomes such as health-related quality of life and satisfaction, unclear allocation concealment, and considerable loss to follow-up.

The committee discussed that the populations in the included studies were not always identical to the population of interest in this guideline (premenopausal women with heavy menstrual bleeding). For pragmatic reasons considering the types of studies available, the committee agreed in the review protocol that one third of the women included in the studies could be women without HMB, for example, women with pelvic pain without HMB. Therefore, most studies in this review included a proportion of women that were not the population of interest. This was accounted for in the quality assessment of the evidence.

Evidence on the management of HMB among women with adenomyosis was scarce. The committee recognised that adenomyosis can be difficult to diagnose and assumed that some of the women with no identified pathology might actually have adenomyosis. Thus, the committee decided to combine women with no identified pathology and adenomyosis in the recommendations.

Considerable heterogeneity was observed in the studies investigating patient satisfaction and blood loss, in particular those assessing surgical techniques.Therefore, studies were incorporated into 3 NMAs (pharmacological; surgical including women with no fibroids; and surgical studies including greater than 33% of women with non-cavity uterine fibroids less than 3 cm in diameter), which helped explain some of the heterogeneity. Studies comparing LNG-IUS to a surgical technique were included in the surgical network, as women in these trials were thought to be similar to other surgical trials. For the 2 surgical NMAs, there were considerable differences between different surgical techniques within the second generation endometrial ablation class. Therefore the individual treatments in this class were analysed as separate treatments in the networks. The committee acknowledged the heterogeneity in the NMA due to the varying populations across studies, despite not being able to compare pharmacological versus surgical treatment directly, the committee considered LNG-IUS to be the common link in all 3 networks and drew recommendations based on this assumption.

No evidence was found on MRI-guided transcutaneous focused ultrasound for uterine fibroids nor for the progestogen-only pill, injectable progestogens, or progestogen implants. The committee prioritised research recommendations on the effectiveness of MRI-guided transcutaneous focused ultrasound for uterine fibroids as a novel uterine sparing radiological intervention and the progestogen-only pill, implantable or injectable progestogens for alleviating HMB in view of the the scarcity of evidence.

Benefits and harms

For recommendations on the management of HMB, women with HMB were divided into 2 broad groups:

- women with HMB and no identified pathology, fibroids smaller than 3 cm in diameter, suspected or diagnosed adenomyosis
- women with HMB and fibroids 3 cm or more in diameter.

The committee discussed that the division of women into these 2 broad groups, were aligned to differences in treatment strategies. Large fibroids would be expected to respond differently to treatment compared to small fibroids or adenomyosis.

The committee emphasised the importance of patient choice and preference when agreeing a management strategy. The treatment strategy should consider any co-morbidities, the presence of any known cause for HMB (such as fibroids, including their size, number and location), or other related symptoms such as pain and pressure. Information about all possible treatment options should be discussed with the woman, including their risks and benefits. The discussion should also cover if she wants to conserve her fertility or the uterus or if she is trying to get pregnant. In women who are actively trying to conceive, non-hormonal pharmacological treatments are the appropriate option, whereas in women who desire contraception, hormonal pharmacological treatment should be considered. The committee agreed that for women who no longer want to conserve their fertility, depending on the pathology, UAE or surgery could be offered as a treatment option. Furthermore, in

women who do not want to conserve their uterus, a hysterectomy may be offered as an appropriate treatment option.

Treatment for women with HMB and no identified pathology, fibroids less than 3 cm in diameter, suspected or confirmed adenomyosis

In women with HMB and no identified pathology, fibroids less than 3 cm in diameter, suspected or diagnosed adenomyosis, the committee decided that LNG-IUS should be considered as the first line treatment option. The evidence in this population showed that LNG-IUS is as effective, or more effective, than other treatments for HMB in terms of improving health-related quality of life, treatment satisfaction, discontinuation rates, and blood loss. In addition, it is widely used in clinical practice and is routinely available within primary care. The evidence on general (non-disease-specific) health-related quality of life ranked usual medical treatment treatment (tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, or progestogen-only pill) higher than LNG-IUS in the NMA; however, the committee noted that the evidence for this was based on 1 RCT in which participants were only recruited from primary care, which is not a true reflection of the typical population of women with HMB, and therefore, put less weight on this piece of evidence. Despite there being strong evidence supporting the use of LNG-IUS in this population, the committee agreed that there was a paucity of evidence on the use of investigations prior to LNG-IUS compared to LNG-IUS as a stand alone management strategy. Thus, in view of this uncertainty and questionable benefit to the woman the committee decided to assign a lower strength to the recommendation (see research recommendation).

In women who decline LNG-IUS or are actively trying to conceive, a non-hormonal pharmacological treatment option was deemed appropriate by the committee as first line treatment, however a distinction between which pharmacological agents to prescribe was not made due to the paucity of evidence. The committee also highlighted that the non-hormonal agents are often used in combination in clinical practice, thus a ranking of such agents would be inappropriate.

If LNG-IUS is an unsuitable treatment option, but the woman desires contraception, the committee agreed that a choice of hormonal pharmacological treatments was appropriate based on the preference of the woman. The evidence showed that combined oral contraceptives had higher discontinuation rates in comparison to other oral pharmacological agents, however the committee considered this as weak evidence to not recommend combined oral contraceptives based on its wide clinical use and tolerability in practice. The committee discussed the combined hormonal contraceptive vaginal ring's high satisfaction rates, however as the evidence to support the combined hormonal contraceptive vaginal ring was based on only 1 RCT where the population of the study included women 20-35 years old, the committee decided not to prioritise combined hormonal contraceptive vaginal ring over other hormonal pharmacological options as the evidence was not a true representation of the HMB population.

No evidence was identified on the use of the progestogen-only contraceptives (pill, injectable or implantable progestogens) as treatments for HMB. In their licenced role as contraceptives they are known to suppress menstruation, and the committee agreed that this effect could be beneficial in women with HMB. The committee was also aware that in clinical practice, especially in primary care, they are used for treatment of HMB. However, more research is needed on their effectiveness on HMB (see research recommendation).

The committee discussed that in current clinical practice, women with HMB face difficulty in gaining access to surgery, often having tried and failed various treatment strategies over a prolonged period of time before even being considered for surgery. The committee agreed that for women who do not wish to have pharmacological treatment and who do not want to conserve their fertility, surgical options could be considered as a first-line treatment option. The evidence showed that, in women with HMB and no identified pathology or fibroids less than 3 cm in diameter, hysterectomy and second generation endometrial ablation were more effective than first generation endometrial ablation techniques on patient satisfaction. The committee decided that based on the evidence, hysterectomy or second generation surgical techniques should be used where surgery is deemed an appropriate first-line treatment option. The evidence further showed that hysterectomy was more effective than first and second generation endometrial ablation on health-related quality of life. However, the committee decided that not all women would want their uterus removed nor desire major surgery and thus hierarchy was not to be given to hysterectomy over second generation endometrial ablation.

The evidence from the NMA favoured radiofrequency endometrial ablation as a preferential second generation endometrial ablation technique for the outcomes of blood loss and satisfaction. The committee also recognised radiofrequency endometrial ablation's current position in clinical practice with a majority of the market share. However, division of the specific second generation endometrial ablation techniques was done ad-hoc and the NMA showed incoherence, indicating that the results should be interpreted with caution. The committee were also aware of ongoing research in the development of other second generation surgical techniques, thus decided not to exclude other second generation surgical techniques from the recommendation. However the committee agreed that when selecting a second generation technique, providers should select 1 that is expected to deliver outcomes at least equivalent to those from radiofrequency endometrial ablation.

The committee also discussed that referral to specialist care may be appropriate for women who decline initial pharmacological treatment. These women may benefit from a discussion on the risks and benefits of the different treatment options, including pharmacological and surgical options, with a specialist in order to find the most appropriate treatment strategy for the woman.

Where symptoms are severe, the committee agreed that women may benefit from referral to specialist care for consideration of further investigations and to discuss treatment options further. Early referral of these women to specialists may result in a more appropriate management plan earlier on, avoiding prolonged suffering.

In women who do not respond to pharmacological treatment, the committee agreed that these women may benefit from referral to specialist care for consideration of further investigations and discuss treatment options further. Second line treatment options for women with HMB and no identified pathology, fibroids less than 3 cm in diameter, suspected or confirmed adenomyosis, in whom first-line treatment is unsuccessful were discussed by the committee. The evidence (especially on pharmacological treatments) often did not stipulate whether the treatment options were used as first or second line, thus given the paucity of evidence on second line treatment options the committee decided that there should be a choice of second line treatment options in the form of a different pharmacological therapeutic class or surgery. Management options should be discussed with the women, explaining the benefits and risks, and also taking into account her fertility intentions, desire to preserve her uterus, and individual factors such as co-morbidities.

The committee decided that the recommendations for treatment should be the same for women with no identified pathology, women with small, non-cavity fibroids, and for women with suspected or confirmed adenomyosis, as the treatment options are the same regardless whether these conditions are identified or not. Nonetheless, the committee recognised the importance of diagnosing these conditions, as it may be valuable for the woman to get a diagnosis in order to explain the cause of her symptoms. Alternatively, in the case of no identified pathology, offer reassurance to the woman that there is no significant pathology, while recognising that many women have to endure with symptoms without an identified pathology. The committee agreed that where treatable lesions are identifiable (e.g. submucosal fibroids or polyps), that these may be removed prior to possible further treatment. Hysteroscopic removal of submucosal fibroids could be done at the time of diagnostic hysteroscopy where see-and-treat services are available.

No eligible evidence was found on the use of UAE for the management of adenomyosis. However, the committee were aware of the interventional procedural guidance on UAE for treating adenomyosis (IPG473, NICE 2013) which was based on observational evidence from 7 case series and 2 case reports. This report concluded that UAE is efficacious for symptom relief in the short term and medium term for a substantial proportion of women, with no major safety concerns. However it was also noted that symptoms may return and that further procedures may be needed. In practice UAE is not widely used for treating adenomyosis. Therefore in the absence of trial evidence and any evidence for long term effectiveness and without widespread use in practice, the committee did not deem it appropriate to recommend UAE for the treatment of adenomyosis. Similarly no evidence was found on the treatment of fibroids smaller than 3 cm with UAE thus no recommendation was made.

Treatment for women with HMB and fibroids of 3 cm or more in diameter

Where a fibroid is 3 cm or more in diameter, the uterus is enlarged and considered at least equivalent to a 12-week size gravid uterus. This would usually be detectable by abdominal palpation. The committee noted that the evidence on the clinical effectiveness of pharmacological treatments for women with fibroids were mainly in women with fibroids not substantially greater than 3 cm in diameter, whereas interventional and surgical techniques were generally in women with fibroids that were substantially greater than 3 cm in diameter.

When treating women with HMB and fibroids of 3 cm or more in diameter, the committee agreed that in addition to patient preference, consideration of size, location, number of fibroids, and severity, as well as other symptoms such as pressure and pain, is essential when making decisions with the woman about the most appropriate treatment approach. The committee agreed that women with fibroids that are substantially greater than 3 cm in diameter may not respond to pharmacological treatment (apart from ulipristal acetate) and instead may benefit from a more invasive treatment option such as UAE or surgery, thus referral to specialist care for further investigations and to discuss all treatment options with the woman should be considered. On the other hand women with fibroids that are 3 cm or more in diameter but still relatively small might respond well to pharmacological treatment and surgical treatment is not needed.

In women who are actively trying to conceive or who decline hormonal treatment, a non-hormonal pharmacological treatment option as first-line was deemed appropriate by the committee, however a distinction between which pharmacological agents to prescribe was not made due to the paucity of evidence. The committee also

highlighted that the non-hormonal agents are often used in combination in clinical practice, thus a ranking of such agents would be inappropriate.

In women who desire pharmacological treatment and contraception, the committee decided that a choice of hormonal pharmacological treatment as first-line treatment was appropriate based on the preference of the woman. Poor quality evidence showed that LNG-IUS is more effective than norethisterone and COCs in reducing blood loss. Whereas for health-related quality of life there was mixed evidence from one poor quality RCT comparing LNG-IUS and COCs. In view of this, the committee considered the evidence not robust enough to recommend LNG-IUS over norethisterone and COCs.

In 2016, NICE conducted a rapid update on the use of medical treatment with progesterone receptor modulators for women with HMB and large fibroids. This update resulted in recommendations on the use of ulipristal acetate in the treatment of women with HMB and fibroids greater than 3 cm in diameter. It should be noted that given the recent publication and rigorous methods used by the NICE guideline update group, this evidence and the recommendations covered by this rapid update was not revisited in the 2017 update.

For women who want to conserve their uterus, myomectomy or UAE should be offered as treatment options alongside pharmacological treatment options. The evidence did not show a difference between myomectomy and UAE in long-term disease-specific health-related quality of life, treatment satisfaction, and post-operative complications. However, the committee were aware of an RCT in women with symptomatic fibroids comparing UAE with surgery (myomectomy or hysterectomy) showing a significantly higher re-intervention rate with UAE at both 1 and 5 years (Edwards 2007; Moss 2011). The outcome of re-intervation rate did not meet the inclusion criteria for this review as the committee did not consider it a critical outcome for formulation of the guideline recommendations. In view of this, the committee thought that UAE should be offered as an option alongside myomectomy.

In women who are indifferent regarding conserving their uterus, the committee agreed that hysterectomy, myomectomy, or UAE, should be offered as treatment options alongside pharmacological treatment options. The evidence showed no differences between hysterectomy and UAE on long-term general health-related quality of life, satisfaction, and post-operative complications. As fertility and pregnancy outcomes were not assessed, the committee felt it was not possible to make an evidence-based recommendation about the preferred treatment option for women with fibroids who wish to maintain their fertility.The committee further highlighted that UAE focused on a reduction of bleeding, rather than the problems around bulk related symptoms often experienced with large fibroids causing HMB. Poor quality evidence showed a clinically significant increase in unscheduled readmission rates with UAE compared to hysterectomy, however due to the quality of evidence the committee decided that the evidence was not robust enough to recommend hysterectomy over UAE. In addition, although reintervention rates were not listed as critical or important outcomes and thus not assessed, the committee were aware of higher reintervention rates with UAE and myomectomy over hysterectomy. However, as these outcomes were not assessed no clear hierarchy between hysterectomy, myomectomy, or UAE, was given and patient preference was emphasised. The committee agreed that prior to scheduling a myomectomy or UAE, an ultrasound should be performed to assess the feasibility and suitability of myomectomy or UAE for the woman in question. Sometimes MRI might also be needed for more information on the fibroid position, size, number and vascularity. These were covered by an old recommendation from 2007. If myomectomy or hysterectomy is the preferred treatment option and the fibroids are causing an

enlarged or distorted uterus, the committee agreed that pretreatment should be considered to reduce the size of the fibroids before surgery (recommendation in the 2007 guideline). In addition to GnRHa, ulipristal acetate should be considered as the pre-operative treatment.

The role of second generation endometrial ablation in the treatment of fibroids of 3 cm of more in diameter was discussed by the committee. The size and shape of the uterine cavity are the main determinants of the feasibility and effectiveness of second generation endometrial ablation procedures. Fibroids of 3 cm or more in diameter lead to substantial uterine enlargement and distortion and so may be associated with poorer clinical outcomes or contraindicate the use of ablation procedures. However, the use of second generation endometrial ablation can be considered if such fibroids do not distort, nor enlarge, the uterine cavity, in line with the specific device's manufacturer's restrictions. The committee agreed that there were limitations to the wording of "manufacturers' instructions", nonetheless due to differing cavity dimensions set by the manufacturers to achieve therapeutic effectiveness and the limitations in the different techniques and devices, it was deemed too simplistic to write a recommendation only taking into consideration the size and shape of the endometrial cavity. The committee also recognised that the wording of the recommendation may be perceived as vague, however they believed that the wording of "manufacturers' instructions" was pragmatic and generic enough to the specificities of each separate ablative technique and device.

Second line treatment options for women with HMB and fibroids 3 cm or more in diameter in whom first line treatment is unsuccessful were discussed by the committee. The evidence often did not stipulate whether the treatment options were used as first or second line, thus given the paucity of evidence on second line treatment options the committee decided that there should be a choice of second line treatment options in the form of a different pharmacological therapeutic class or surgery, taking into account the woman's needs and preferences. Further investigations might also be warranted.

No eligible evidence was found on the use of MRgFUS for the management of fibroids. However, the committee were aware of the interventional procedural guidance on Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids (IPG413, NICE 2011) which was based on 1 non-randomised comparative study, 6 case series and 2 case reports. The committee agreed that MRgFUS is not widely used in practice. Therefore, in the absence of robust evidence and without widespread use in practice, the committee did not deem ir appropriate to recommend MRgFUS as a treatment for fibroids.

Cost-effectiveness and resource use

For recommendations on the management of HMB, women with HMB were divided into 2 broad groups:

- women with HMB and no identified pathology, fibroids smaller than 3 cm in diameter, suspected or diagnosed adenomyosis
- women with HMB and fibroids 3 cm or more in diameter

The committee did not think that the recommendations on the management of HMB would have a significant resource impact on the NHS (more than £1 million) as they do not represent a marked change from current practice or previous NICE guidance. The recommendations allow access to surgical intervention to be expedited where this is aligned with the overall clinical picture and the women's preferences. However, the committee noted that these women often present with more significant symptoms

and pathology and will often ultimately proceed to surgical intervention after being shown to be refractory to pharmacological treatment alternatives.

An original economic model developed for the guideline compared combined diagnostic and treatment strategies for HMB. Treatment effectiveness was based on 2 NMAs focused on short and long term quality of life data based on the EQ-5D. However, it is important to be cautious in drawing conclusions from the model. The most cost-effective treatment is likely to vary according to the underlying pathology and limitations with the model make this difficult to assess. This is because treatment effectiveness in the model, and the NMA underpinning the estimates of treatment effectiveness, is based solely on the treatment without taking into account how treatment effectiveness would vary with the underlying pathology. The model does take this into account by dichotomising treatments as effective or ineffective for particular strategies and then undertaking sensitivity analysis on this as an acknowledgemnt of the uncertainty surrounding some of this effectiveness classification.

Furthermore, not all treatment options were included in the NMA, and therefore if those treatments were included in the model some assumptions about equivalence with other treatments had to be made.

In general the published evidence and the model developed for this guideline can be considered as supportive of offering women a range of treatment alternatives to reflect their own preferences and individual clinical circumstances.

Treatment for women with HMB and no identified pathology, fibroids less than 3 cm in diameter, suspected or confirmed adenomyosis

In women with HMB and no identified pathology, fibroids less than 3 cm in diameter, suspected or diagnosed adenomyosis, the committee noted that many published studies (Clegg 2007; Lete 2011; Gupta 2015; Blake 2016) support the use of LNG-IUS as a cost-effective strategy, whether compared to pharmacological or surgical interventions. However, one study (Bhattacharya 2011) which adopted a much longer timeframe than other analyses concluded that hysterectomy was more cost-effective than LNG-IUS. Its longer temporal perspective meant that the replacement costs of LNG-IUS were taken into account when LNG-IUS reached the end of its 5 year lifespan.The committee noted that the model developed for the guideline suggested that empiric LNG-IUS could be a cost-effective strategy. It also suggested that usual medical treatment (mefenamic acid, tranexamic acid, norethisterone, combined oestrogen-progestogen or progestogen-only oral contraceptive pill, or medroxyprogesterone acetate injection), at least for treatment naïve patients in a primary care population, could also be cost-effective.

Treatment for women with HMB and fibroids of 3 cm or more in diameter

For some women with fibroids of 3 cm or more in diameter the clinical picture is similar to that for women with HMB and no identified pathology, fibroids less than 3 cm in diameter, suspected or confirmed adenomyosis and such women will follow a similar management pathway and this is reflected in the recommendations. The committee agreed that cost-effective considerations would not be different in this group. However, for women with fibroids substantially greater than 3 cm in diameter will often present with more severe symptoms and pathology and will often prove refractory to pharmacological interventions.

Whilst hysterectomy was the most expensive surgical treatment the committee noted that model developed for this guideline did provide cost-effectiveness evidence in support of its use. They also noted that a UK study (Bhattacharya 2011) found

hysterectomy to be more cost-effective than other LNG-IUS, first and second endometrial ablation.

The committee recognised a role for surgical alternatives to hysterectomy, but thought that cost-effective use of these technologies might be restricted to a subset of women due to the high rates of reintervention for some of these techniques.

Two studies (Beinfield 2004; You 2009) reported on UAE but reached different conclusion with regard to its cost-effectiveness relative to other surgical interventions. Another published study suggested that thermal (radio-frequency) endometrial ablation could be considered cost-effective relative to other ablation techniques and hysterectomy. A study also suggested an economic case for MRgFUS, however in reaching this result the authors had to make inferred comparisons due to an absence of RCT data. As a result of the lack of clinical evidence the committee did not feel able to make a recommendation for the use of MRgFUS.

Other factors the committee took into account

This partial update of the guideline did not review evidence on the route of hysterectomy and removal of ovaries. However, the committee thought it was important to make editorial amendments the recommendations from 2007 to reflect current practice. Regarding the route of hysterectomy, the committee discussed that laparoscopic route is often the preferred route, however, since the evidence on the best route was not reviewed, the route could not be specified in the recommendation. The committee emphasised the importance of considering the woman's preferences when agreeing on the route of hysterectomy. The committee agreed that ovaries should only be removed if the woman explicitly wishes it and only after she has been provided with information about the associated risks and benefits.

The guideline committee also amended the recommendation from 2007 on dilatation for non-hysteroscopic endometrial ablation to reflect the guidance from the Medicines and Health products Regulatory Agency (MHRA 2011).

The committee discussed the wording around 'conservation of uterus' or 'conservation of fertility' in the recommendation, the conservative wording of 'conservation of uterus' was decided upon given the uncertainty around 'conservation of fertility' when undergoing these surgical techniques.

During the scoping phase the following groups were identifiable as requiring special consideration:

- women who have difficulties communicating in English
- women with learning difficulties
- women from some minority ethnic groups (because women from some minority ethnic groups might find it difficult to talk about HMB with health care professionals)
- women from disadvantaged socio-economic groups.

The committee noted that these groups might need special consideration in terms of information provision and communication, however, the committee agreed that this is not specific to HMB and is covered by the NICE guideline on Patient experience in adult NHS services: improving the experience of care for people using adult NHS services (CG138). The committee also recognised that some women might prefer a female practitioner when discussing HMB and receiving treatment.

The committee discussed whether the effectiveness of the progestogen-only pill, injectable progestogens and progestogen implants in alleviating heavy menstrual

bleeding should be prioritised as a research recommendation. They noted that many women have contraindications to use combined oral contraceptives, and other progestogens used for contraception have far fewer contraindications but their effectiveness as treatment for HMB has not been studied.

The committee highlighted that there is a gap in the evidence on the best treatment for the management of adenomyosis, despite studies reporting a prevalence of 20 to 30%. Based on this, they decided there would be benefit in investigating the long-term clinical outcomes of pharmacological and uterine-sparing surgical treatments for women with HMB associated with adenomyosis.

The committee also agreed there would be benefit in investigating the effectiveness of hysteroscopic removal of submucosal fibroids. This is because there is evidence from non-comparative studies reporting improvement in HMB symptoms, but evidence from RCTs comparing hysteroscopic myomectomy to other long term pharmacological treatments or more invasive surgical interventions is lacking.

Finally, the committee noted that pharmacological treatments appear to be less effective in women with HMB associated to adenomyosis or uterine fibroids, and they agreed that the effectiveness of second generation endometrial ablation in these women should also be prioritised as a research recommendation to inform future guidance.

See Appendix O – Care pathway for illustration of the management recommendations

References

Aberdeen Endometrial Ablation Trials Group 1999

Aberdeen Endometrial Ablation Trials Group, A randomised trial of endometrial ablation versus hysterectomy for the treatment of dysfunctional uterine bleeding: outcome at four years, BJOG: An International Journal of Obstetrics and Gynaecology, 106, 360-6, 1999

Abbott 2003

Abbott, J., Hawe, J., Hunter, D., Garry, R., A double-blind randomized trial comparing the Cavaterm and the NovaSure endometrial ablation systems for the treatment of dysfunctional uterine bleeding, Fertility and Sterility, 80, 203-8, 2003

Abdel Malak and Shawki 2006

Abdel Malak, K., Shawki, O., Management of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection, Gynecological surgery, 3, 275-80, 2006

Abu Hashim 2012

Abu Hashim, H., Alsherbini, W., Bazeed, M., Contraceptive vaginal ring treatment of heavy menstrual bleeding: a randomized controlled trial with norethisterone, Contraception, 85, 246-52, 2012

Ara and Brazier 2008

Ara, R., Brazier, J., Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available), Value Health, 11, 1131-43, 2008

Athanatos 2015

Athanatos, D., Pados, G., Venetis, C. A., Stamatopoulos, P., Rousso, D., Tsolakidis, D., Stamatopoulos, C. P., Tarlatzis, B. C., Novasure impedance control system versus microwave endometrial ablation for the treatment of dysfunctional uterine bleeding: a double-blind, randomized controlled trial, Clinical and experimental obstetrics & gynecology, 42, 347-51, 2015

Babashov 2015

Babashov, D., Palimaka, S., Blackhouse, G., O'Reilly, D., Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MRgHIFU) for Treatment of Symptomatic Uterine Fibroids: An Economic Analysis (Structured abstract), HTA Database: Health Quality Ontario, 2015

Barrington 2003

Barrington, J. W., Arunkalaivanan, A. S., Abdel-Fattah, M., Comparison between the levonorgestrel intrauterine system (LNG-IUS) and thermal balloon ablation in the treatment of menorrhagia, European Journal Of Obstetrics Gynecology And Reproductive Biology, 108, 72-4, 2003

Beinfield 2004

Beinfeld, M. T., Bosch, J. L., Isaacson, K. B., Gazelle, G. S., Radiology. Cost-effectiveness of uterine artery embolization and hysterectomy for uterine fibroids, 230, 207-13, 2004

Bhattacharya 1997

Bhattacharya, S., Cameron, I. M., Parkin, D. E., Abramovich, D. R., Mollison, J., Pinion, S. B., Alexander, D. A., Grant, A., Kitchener, H. C., A pragmatic randomised comparison of transcervical resection of the endometrium with endometrial laser ablation for the treatment of menorrhagia, BJOG: An International Journal of Obstetrics and Gynaecology, 104, 601-7, 1997

Bhattacharya 2011

Bhattacharya, S., Middleton, L. J., Tsourapas, A., Lee, A. J., Champaneria, R., Daniels, J. P., Roberts, T., Hilken, N. H., Barton, P., Gray, R., Khan, K. S., Chien, P., O'Donovan, P., Cooper, K. G., International Heavy Menstrual Bleeding Individual Patient Data Meta-analysis Collaborative Group, Abbott, J., Barrington, J., Bhattacharya, S., Bongers, M. Y., Brun, J. L., Busfield, R., Clark, T. J., Cooper, J., Cooper, K. G., Corson, S. L., Dickersin, K., Dwyer, N., Gannon, M., Hawe, J., Hurskainen, R., Meyer, W. R., O'Connor, H., Pinion, S., Sambrook, A. M., Tam, W. H., van Zon-Rabelink, I. A., Zupi, E., Hysterectomy, endometrial ablation and Mirena® for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis, Health Technology Assessment, 15, 1-252, 2011

Blake 2016

Blake, J., Costescu, D., Dunn, S., Leyland, N., Rheault, K., Levonorgestrel-Releasing Intrauterine System (52 mg) for Idiopathic Heavy Menstrual Bleeding: A Health Technology Assessment, Ontario Health Technology Assessment Series, 16, 1-119, 2016

Bongers 2004

Bongers, M. Y., Bourdrez, P., Mol, B. W., Heintz, A. P., Brolmann, H. A., Randomised controlled trial of bipolar radio-frequency endometrial ablation and balloon endometrial ablation, BJOG: An International Journal of Obstetrics and Gynaecology, 111, 1095-102, 2004

Bongers 2005

Bongers, M. Y., Bourdrez, P., Heintz, A. P., Brolmann, H. A., Mol, B. W., Bipolar radio frequency endometrial ablation compared with balloon endometrial ablation in dysfunctional uterine bleeding: impact on patients' health-related quality of life, Fertility and Sterility, 83, 724-34, 2005

Bonnar and Sheppard 1996

Bonnar, J., Sheppard, B. L., Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid, BMJ, 313, 579-82, 1996

Brun 2006

Brun, J. L., Raynal, J., Burlet, G., Galand, B., Quereux, C., Bernard, P., Cavaterm thermal balloon endometrial ablation versus hysteroscopic endometrial resection to treat menorrhagia: the French, multicenter, randomized study, Journal of Minimally Invasive Gynecology, 13, 424-30, 2006

Busfield 2006

Busfield, R. A., Farquhar, C. M., Sowter, M. C., Lethaby, A., Sprecher, M., Yu, Y., Sadler, L. C., Brown, P., Johnson, N., A randomised trial comparing the levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 257-63, 2006

Cain-Nielsen 2014

Cain-Nielsen, A. H., Moriarty, J. P., Stewart, E. A., Borah, B. J., Cost-effectiveness of uterine-preserving procedures for the treatment of uterine fibroid symptoms in the USA, J Comp Eff Res, 3, 503-14, 2014

Calaf 2015

Calaf, J., Lete, I., Canals, I., Crespo, C., Espinos, B., Cristobal, I., Cost-effectiveness analysis in the treatment of heavy menstrual bleeding in Spain, European Journal of Obstetrics & Gynecology and Reproductive Biology, 184, 24-31, 2015

Clark 2011

Clark, T. J., Samuel, N., Malick, S., Middleton, L. J., Daniels, J., Gupta, J. K., Bipolar radiofrequency compared with thermal balloon endometrial ablation in the office: a randomized controlled trial, Obstetrics and Gynecology, 117, 109-18, 2011

Clegg 2007

Clegg, J. P., Guest, J. F., Hurskainen, R., Cost–utility of levonorgestrel intrauterine system compared with hysterectomy and second generation endometrial ablative techniques in managing patients with menorrhagia in the UK, Current Medical Research and Opinion, 23, 1637–48, 2007

Cooper 1997

Cooper, K. G., Parkin, D. E., Garratt, A. M., Grant, A. M., A randomised comparison of medical and hysteroscopic management in women consulting a gynaecologist for treatment of heavy menstrual loss, BJOG: An International Journal of Obstetrics and Gynaecology, 104, 1360-6, 1997

Cooper 1999a

Cooper, K. G., Bain, C., Parkin, D. E., Comparison of microwave endometrial ablation and transcervical resection of the endometrium for treatment of heavy menstrual loss: a randomised trial, Lancet, 354, 1859-63, 1999

Cooper 1999b

Cooper, K. G., Parkin, D. E., Garratt, A. M., Grant, A. M., Two-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes, BJOG: An International Journal of Obstetrics and Gynaecology, 106, 258-65, 1999

Cooper 2001

Cooper, K. G., Jack, S. A., Parkin, D. E., Grant, A. M., Five-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes, BJOG: An International Journal of Obstetrics and Gynaecology, 108, 1222-8, 2001

Cooper 2002

Cooper,J., Gimpelson,R., Laberge,P., Galen,D., Garza-Leal,J.G., Scott,J., Leyland,N., Martyn,P., Liu,J., A randomized, multicenter trial of safety and efficacy of the NovaSure system in the treatment of menorrhagia, Journal of the American Association of Gynecologic Laparoscopists, 9, 418-428, 2002

Cooper 2004

Cooper, J. M., Anderson, T. L., Fortin, C. A., Jack, S. A., Plentl, M. B., Microwave endometrial ablation vs. rollerball electroablation for menorrhagia: A multicenter randomized trial, Journal of the American Association of Gynecologic Laparoscopists, 11, 394-403, 2004

Cooper 2005

Cooper, K. G., Bain, C., Lawrie, L., Parkin, D. E., A randomised comparison of microwave endometrial ablation with transcervical resection of the endometrium; follow up at a minimum of five years, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 470-5, 2005

Corson 2000

Corson, S. L., Brill, A. I., Brooks, P. G., Cooper, J. M., Indman, P. D., Liu, J. H., Soderstrom, R. M., Vancaillie, T. G., One-year results of the vesta system for endometrial ablation, Journal of the American Association of Gynecologic Laparoscopists, 7, 489-97, 2000

Corson 2001

Corson, S. L., A multicenter evaluation of endometrial ablation by Hydro ThermAblator and rollerball for treatment of menorrhagia, Journal of the American Association of Gynecologic Laparoscopists, 8, 359-67, 2001

Crosignani 1997

Crosignani, P. G., Vercellini, P., Mosconi, P., Oldani, S., Cortesi, I., De Giorgi, O., Levonorgestrel-releasing intrauterine device versus hysteroscopic endometrial resection in the treatment of dysfunctional uterine bleeding, Obstetrics & Gynecology, 90, 257-63, 1997

de Bruijn 2016

de Bruijn, A. M., Ankum, W. M., Reekers, J. A., Birnie, E., van der Kooij, S. M., Volkers, N. A., Hehenkamp, W. J., Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial, American Journal of Obstetrics & Gynecology, 5, 5, 2016

Dickersin 2007

Dickersin, K., Munro, M. G., Clark, M., Langenberg, P., Scherer, R., Frick, K., Zhu, Q., Hallock, L., Nichols, J., Yalcinkaya, T. M., Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial, Obstetrics and Gynecology, 110, 1279-89, 2007

Duleba 2003

Duleba, A. J., Heppard, M. C., Soderstrom, R. M., Townsend, D. E., A randomized study comparing endometrial cryoablation and rollerball electroablation for treatment

of dysfunctional uterine bleeding, Journal of the American Association of Gynecologic Laparoscopists, 10, 17-26, 2003

Dunphy 1998

Dunphy, B. C., Goerzen, J., Greene, C. A., de la Ronde, S., Seidel, J., Ingelson, B., A double-blind randomised study comparing danazol and medroxyprogesterone acetate in the management of menorrhagia, Journal of Obstetrics & Gynaecology, 18, 553-5, 1998

Dwyer 1993

Dwyer, N., Hutton, J., Stirrat, G. M., Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for the surgical treatment of menorrhagia, BJOG: An International Journal of Obstetrics and Gynaecology, 100, 237-43, 1993

Edwards 2007

Edwards, R. D., Moss, J. G., Lumsden, M. A., Wu, O., Murray, L. S., Twaddle, S., Murray, G. D., Uterine-artery embolization versus surgery for symptomatic uterine fibroids, New England Journal of Medicine, 356, 360-70, 2007

Endrikat 2009

Endrikat, J., Shapiro, H., Lukkari-Lax, E., Kunz, M., Schmidt, W., Fortier, M., A Canadian, multicentre study comparing the efficacy of a levonorgestrel-releasing intrauterine system to an oral contraceptive in women with idiopathic menorrhagia, Journal of Obstetrics & Gynaecology Canada: JOGC, 31, 340-7, 2009

Ergun 2011

Ergun, B., Kuru, O., Sen, S., Kilic, Y., Comparison between roller-ball endometrial ablation and levonorgestrel intrauterine system (LNG-IUS) in the treatment of abnormal uterine bleeding, Turk Jinekoloji ve Obstetrik Dernegi Dergisi, 8, 259-63, 2011

Ergun 2012

Ergun, B., Bastu, E., Kuru, O., Sen, S., Kilic, Y., Dural, O., Comparison of rollerball endometrial ablation and levonorgestrel releasing intrauterine system in the management of abnormal uterine bleeding, International Journal of Gynaecology and Obstetrics, 119, S672, 2012

Ergun 2012a

Ergun, B., Kuru, O., Sen, S., Kilic, Y., Bastu, E., Roller-ball endometrial ablation versus levonorgestrel releasing intrauterine system in the management of abnormal uterine bleeding, Gineco.ro, 8, 199-201, 2012

Fergusson 2013

Fergusson, R. J., Lethaby, A., Shepperd, S., Farquhar, C., Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 29, 2013

Franks 2004

Franks, P., Lubetkin, E. I., Gold, M. R., Tancredi, D. J., Jia, H., Mapping the SF-12 to the EuroQol EQ-5D Index in a national US sample, Medical Decision Making, 24, 247-54, 2004

Fraser 2011

Fraser, I. S., Romer, T., Parke, S., Zeun, S., Mellinger, U., Machlitt, A., Jensen, J. T., Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: A randomized, double-blind Phase III trial, Human Reproduction, 26, 2698-708, 2011

Frempong-Ainguah and Hill 2014

Frempong-Ainguah, F., Hill, A., Reliability, validity and responsiveness of the short form-36 health survey: Findings from the women's health study of Accra, Ghana, Quetelet Journal, 2, 7-29, 2014

Friedrich 2008

Friedrich, J. O., Adhikari, N. K., Beyene, J., The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study, BMC Medical Research Methodology, 8, 32, 2008

Ganz 2013

Ganz, M., Shah, D., Gidwani, R., Filonenko, A., Su, W., Pocoski, J., Law, A., The cost-effectiveness of the levonorgestrel-releasing intrauterine system (LNG-IUS, mirena) for the treatment of heavy menstrual bleeding in the United States, Value in Health, 16, 325-33, 2013

Ghazizadeh 2011

Ghazizadeh, S., Bakhtiari, F., Rahmanpour, H., Davari-Tanha, F., Ramezanzadeh, F., A randomized clinical trial to compare levonorgestrel-releasing intrauterine system (Mirena) vs transcervical endometrial resection for treatment of menorrhagia, International Journal of Women's Health, 3, 207-11, 2011

Ghazizadeh 2014

Ghazizadeh, S., Panahi, Z., Ghanbari, Z., Menshadi, A. T., Farahmandian, T., Javadian, P., Comparative efficacy of novasure, the levonorgestrel-releasing intrauterine system, and hysteroscopic endometrial resection in the treatment of menorrhagia: A randomized clinical trial, Journal of Gynecologic Surgery, 30, 215-8, 2014

Goldrath 2003

Goldrath, M. H., Evaluation of HydroThermAblator and rollerball endometrial ablation for menorrhagia 3 Years after treatment, Journal of the American Association of Gynecologic Laparoscopists, 10, 505-11, 2003

Goshtasebi 2013

Goshtasebi, A., Moukhah, S., Gandevani, S. B., Treatment of heavy menstrual bleeding of endometrial origin: randomized controlled trial of medroxyprogesterone acetate and tranexamic acid, Archives of Gynecology & Obstetrics, 288, 1055-60, 2013

Grainger 2000

Grainger, D. A., Tjaden, B. L., Rowland, C., Meyer, W. R., Thermal balloon and rollerball ablation to treat menorrhagia: two-year results of a multicenter, prospective, randomized, clinical trial, Journal of the American Association of Gynecologic Laparoscopists, 7, 175-9, 2000

Gupta 2014

Gupta, J. K., Sinha, A., Lumsden, M. A., Hickey, M., Uterine artery embolization for symptomatic uterine fibroids, Cochrane Database of Systematic Reviews, 2014

Gupta 2015

Gupta, J. K., Daniels, J. P., Middleton, L. J., Pattison, H. M., Prileszky, G., Roberts, T. E., Sanghera, S., Barton, P., Gray, R., Kai, J., A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: The ECLIPSE trial, Health Technology Assessment, 19, 1-118, 2015

Hawe 2003

Hawe, J., Abbott, J., Hunter, D., Phillips, G., Garry, R., A randomised controlled trial comparing the Cavaterm endometrial ablation system with the Nd:YAG laser for the treatment of dysfunctional uterine bleeding, BJOG: An International Journal of Obstetrics and Gynaecology, 110, 350-7, 2003

Hehenkamp 2005

Hehenkamp, W. J., Volkers, N. A., Donderwinkel, P. F., de Blok, S., Birnie, E., Ankum, W. M., Reekers, J. A., Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial, American Journal of Obstetrics and Gynecology, 193, 1618-29, 2005

Hehenkamp 2008

Hehenkamp, W. J., Volkers, N. A., Birnie, E., Reekers, J. A., Ankum, W. M., Symptomatic uterine fibroids: treatment with uterine artery embolization or hysterectomy--results from the randomized clinical Embolisation versus Hysterectomy (EMMY) Trial, Radiology, 246, 823-32, 2008

Heliovaara-Peippo 2013

Heliovaara-Peippo, S., Hurskainen, R., Teperi, J., Aalto, A. M., Grenman, S., Halmesmaki, K., Jokela, M., Kivela, A., Tomas, E., Tuppurainen, M., Paavonen, J., Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: a 10-year randomized controlled trial, American Journal of Obstetrics and Gynecology, 209, 535.e1-535.e14, 2013

Higham 1990

Higham, J. M., O'Brien, P. M. S., Shaw, R. W., Assessment of menstrual blood loss using a pictorial chart, BJOG: An International Journal of Obstetrics and Gynaecology, 97, 734-9, 1990

Hoaglin 2013

Hoaglin, D. C., Filonenko, A., Glickman, M. E., Wasiak, R., Gidwani, R., Use of mixed-treatment-comparison methods in estimating efficacy of treatments for heavy menstrual bleeding, European Journal of Medical Research, 18, 17, 2013

Hurskainen 2001

Hurskainen, R., Teperi, J., Rissanen, P., Aalto, A. M., Grenman, S., Kivela, A., Kujansuu, E., Vuorma, S., Yliskoski, M., Paavonen, J., Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial, Lancet, 357, 273-7, 2001

Hurskainen 2004

Hurskainen, R., Teperi, J., Rissanen, P., Aalto, A. M., Grenman, S., Kivela, A., Kujansuu, E., Vuorma, S., Yliskoski, M., Paavonen, J., Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up, JAMA, 291, 1456-63, 2004

Irvine 1998

Irvine, G. A., Campbell-Brown, M. B., Lumsden, M. A., Heikkila, A., Walker, J. J., Cameron, I. T., Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia, BJOG: An International Journal of Obstetrics and Gynaecology, 105, 592-8, 1998

Istre and Trolle 2001

Istre, O., Trolle, B., Treatment of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection, Fertility and Sterility, 76, 304-9, 2001

Jain 2016

Jain, P., Rajaram, S., Gupta, B., Goel, N., Srivastava, H., Randomized controlled trial of thermal balloon ablation versus vaginal hysterectomy for leiomyoma-induced heavy menstrual bleeding, International Journal of Gynaecology & Obstetrics, 135, 140-4, 2016

Jun 2012

Jun, F., Yamin, L., Xinli, X., Zhe, L., Min, Z., Bo, Z., Wenli, G., Uterine artery embolization versus surgery for symptomatic uterine fibroids: a randomized controlled trial and a meta-analysis of the literature, Archives of Gynecology and Obstetrics, 285, 1407-13, 2012

Kaunitz 2010

Kaunitz, A. M., Bissonnette, F., Monteiro, I., Lukkari-Lax, E., Muysers, C., Jensen, J. T., Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding: a randomized controlled trial, Obstetrics and Gynecology, 116, 625-32, 2010

Khajehei 2013

Khajehei, M., Abdali, K., Tabatabaee, H., The effect of mefenamic acid and naproxen on heavy menstrual bleeding: A placebo-controlled study, South African Journal of Obstetrics and Gynaecology, 19, 31-4, 2013

Kiseli 2016

Kiseli, M., Kayikcioglu, F., Evliyaoglu, O., Haberal, A., Comparison of therapeutic efficacies of norethisterone, tranexamic acid and levonorgestrel-releasing intrauterine system for the treatment of heavy menstrual bleeding: A randomized controlled study, Gynecologic and Obstetric Investigation, 81, 447-53, 2016

Kittelsen and Istre 1998

Kittelsen, N., Istre, O., A randomized study comparing levonorgestrel intrauterine system (LNG IUS) and transcervical resection of the endometrium (TCRE) in the treatment of menorrhagia: Preliminary results, Gynaecological Endoscopy, 7, 61-5, 1998

Kleijn 2008

Kleijn, J. H., Engels, R., Bourdrez, P., Mol, B. W., Bongers, M. Y., Five-year follow up of a randomised controlled trial comparing NovaSure and ThermaChoice endometrial ablation, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 193-8, 2008

Kong 2014

Kong, C. Y., Meng, L., Omer, Z. B., Swan, J. S., Srouji, S., Gazelle, G. S., Fennessy, F. M., MRI-guided focused ultrasound surgery for uterine fibroid treatment: a cost-effectiveness analysis, AJR Am J Roentgenol, 203, 361-71, 2014

Kriplani 2006

Kriplani, A., Kulshrestha, V., Agarwal, N., Diwakar, S., Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate, Journal of Obstetrics & Gynaecology, 26, 673-8, 2006

Lete 2011

Lete, I., Cristobal, I., Febrer, L., Crespo, C., Arbat, A., Hernandez, F. J., Brosa, M., Economic evaluation of the levonorgestrel-releasing intrauterine system for the treatment of dysfunctional uterine bleeding in Spain, European Journal of Obstetrics & Gynecology and Reproductive Biology, 154, 71-80, 2011

Lethaby 2008

Lethaby, A., Irvine, G. A., Cameron, I. T., Cyclical progestogens for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 2008

Lethaby 2013

Lethaby, A., Penninx, J., Hickey, M., Garry, R., Marjoribanks, J., Endometrial resection and ablation techniques for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 2013

Lethaby 2015

Lethaby, A., Hussain, M., Rishworth, J. R., Rees, M. C., Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 2015

Loffer and Grainger 2002

Loffer, F. D., Grainger, D., Five-year follow-up of patients participating in a randomized trial of uterine balloon therapy versus rollerball ablation for treatment of menorrhagia, Journal of the American Association of Gynecologic Laparoscopists, 9, 429-35, 2002

Loffer 2001

Loffer, F. D., Three-year comparison of thermal balloon and rollerball ablation in treatment of menorrhagia, Journal of the American Association of Gynecologic Laparoscopists, 8, 48-54, 2001

Lu 2014

Lu, G., Kounali, D., Ades, A. E., Simultaneous Multioutcome Synthesis and Mapping of Treatment Effects to a Common Scale, Value in Health, 17, 280-7, 2014

Manyonda 2012

Manyonda, I. T., Bratby, M., Horst, J. S., Banu, N., Gorti, M., Belli, A. M., Uterine artery embolization versus myomectomy: impact on quality of life--results of the FUME (Fibroids of the Uterus: Myomectomy versus Embolization) Trial, Cardiovascular and Interventional Radiology, 35, 530-6, 2012

Mara 2008

Mara, M., Maskova, J., Fucikova, Z., Kuzel, D., Belsan, T., Sosna, O., Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy, Cardiovascular and Interventional Radiology, 31, 73-85, 2008

Marjoribanks 2016

Marjoribanks, J., Lethaby, A., Farquhar, C., Surgery versus medical therapy for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 2016

Meyer 1998

Meyer, W. R., Walsh, B. W., Grainger, D. A., Peacock, L. M., Loffer, F. D., Steege, J. F., Thermal balloon and rollerball ablation to treat menorrhagia: a multicenter comparison, Obstetrics & Gynecology, 92, 98-103, 1998

MHRA 2011

Medicines and Healthcare products Regulatory Agency (MHRA), Guidance on the responsibilities of manufacturers, the regulator and clinicians with respect to endometrial ablation, MHRA, 2011 http://webarchive.nationalarchives.gov.uk/20141206133509/http:/www.mhra.gov.uk/home/groups/clin/documents/publication/con108727.pdf (Accessed 16 October 2017)

Miller 2015

Miller, J. D., Lenhart, G. M., Bonafede, M. M., Basinski, C. M., Lukes, A. S., Troeger, K. A., Cost effectiveness of endometrial ablation with the NovaSure system versus other global ablation modalities and hysterectomy for treatment of abnormal uterine bleeding: US commercial and medicaid payer perspectives, International Journal of Women's Health, 7, 59-73, 2015

Moss 2011

Moss, J. G., Cooper, K. G., Khaund, A., Murray, L. S., Murray, G. D., Wu, O., Craig, L. E., Lumsden, M. A., Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results, BJOG: An International Journal of Obstetrics & Gynaecology, 118, 936-44, 2011

Myles 2001

Myles, P. S., Hunt, J. O., Fletcher, H., Solly, R., Woodward, D., Kelly, S., Relation between quality of recovery in hospital and quality of life at 3 months after cardiac surgery, Anesthesiology, 95, 862-7, 2001

Nieman 2011

Nieman, L. K., Blocker, W., Nansel, T., Mahoney, S., Reynolds, J., Blithe, D., Wesley, R., Armstrong, A., Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study, Fertility and Sterility, 95, 767-72, 2011

O'Connor 1997

O'Connor, H., Broadbent, J. A., Magos, A. L., McPherson, K., Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia, Lancet, 349, 897-901, 1997

O'Sullivan 2009

O'Sullivan, A. K., Thompson, D., Chu, P., Lee, D. W., Stewart, E. A., Weinstein, M. C., Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids, Int J Technol Assess Health Care, 25, 14-25, 2009

Ozdegirmenci 2011

Ozdegirmenci, O., Kayikcioglu, F., Akgul, M. A., Kaplan, M., Karcaaltincaba, M., Haberal, A., Akyol, M., Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis, Fertility & Sterility, 95, 497-502, 2011

Pellicano 2002

Pellicano, M., Guida, M., Acunzo, G., Cirillo, D., Bifulco, G., Nappi, C., Hysteroscopic transcervical endometrial resection versus thermal destruction for menorrhagia: a prospective randomized trial on satisfaction rate, American Journal of Obstetrics & Gynecology, 187, 545-50, 2002

Penninx 2010

Penninx, J. P., Mol, B. W., Engels, R., Rumste, M. M., Kleijn, C., Koks, C. A., Kruitwagen, R. F., Bongers, M. Y., Bipolar radiofrequency endometrial ablation compared with hydrothermablation for dysfunctional uterine bleeding: a randomized controlled trial, Obstetrics and Gynecology, 116, 819-26, 2010

Penninx 2011

Penninx, J. P., Herman, M. C., Mol, B. W., Bongers, M. Y., Five-year follow-up after comparing bipolar endometrial ablation with hydrothermablation for menorrhagia, Obstetrics and Gynecology, 118, 1287-92, 2011

Penninx 2016

Penninx, J. P., Herman, M. C., Kruitwagen, R. F., Ter Haar, A. J., Mol, B. W., Bongers, M. Y., Bipolar versus balloon endometrial ablation in the office: A randomized controlled trial, European Journal of Obstetrics Gynecology and Reproductive Biology, 196, 52-6, 2016

Perino 2004

Perino, A., Castelli, A., Cucinella, G., Biondo, A., Pane, A., Venezia, R., A randomized comparison of endometrial laser intrauterine thermotherapy and hysteroscopic endometrial resection, Fertility and Sterility, 82, 731-4, 2004

Pinto 2003

Pinto, I., Chimeno, P., Romo, A., Paul, L., Haya, J., de la Cal, M. A., Bajo, J., Uterine fibroids: uterine artery embolization versus abdominal hysterectomy for treatment--a prospective, randomized, and controlled clinical trial, Radiology, 226, 425-31, 2003

Rauramo 2004

Rauramo, I., Elo, I., Istre, O., Long-term treatment of menorrhagia with levonorgestrel intrauterine system versus endometrial resection, Obstetrics and Gynecology, 104, 1314-21, 2004

Reid 2000

Reid, P. C., Coker, A., Coltart, R., Assessment of menstrual blood loss using a pictorial chart: a validation study, BJOG: An International Journal of Obstetrics and Gynaecology, 107, 320-2, 2000

Reid and Virtanen-Kari 2005

Reid, P. C., Virtanen-Kari, S., Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: a multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment charts, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1121-5, 2005

Ruuskanen 2010

Ruuskanen, A., Hippelainen, M., Sipola, P., Manninen, H., Uterine artery embolisation versus hysterectomy for leiomyomas: primary and 2-year follow-up results of a randomised prospective clinical trial, European Radiology, 20, 2010

Sambrook 2009

Sambrook, A. M., Cooper, K. G., Campbell, M. K., Cook, J. A., Clinical outcomes from a randomised comparison of Microwave Endometrial Ablation with Thermal Balloon endometrial ablation for the treatment of heavy menstrual bleeding, BJOG: An International Journal of Obstetrics and Gynaecology, 116, 1038-45, 2009

Sambrook 2014

Sambrook, A. M., Elders, A., Cooper, K. G., Microwave endometrial ablation versus thermal balloon endometrial ablation (MEATBall): 5-year follow up of a randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 748-54, 2014

Sayed 2011

Sayed, G. H., Zakherah, M. S., El-Nashar, S. A., Shaaban, M. M., A randomized clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia, International Journal of Gynaecology and Obstetrics, 112, 126-30, 2011

Sculpher 1996

Sculpher, M. J., Dwyer, N., Byford, S., Stirrat, G. M., Randomised trial comparing hysterectomy and transcervical endometrial resection: effect on health related quality of life and costs two years after surgery, BJOG: An International Journal of Obstetrics and Gynaecology, 103, 142-9, 1996

Sesti 2011

Sesti, F., Ruggeri, V., Pietropolli, A., Piancatelli, R., Piccione, E., Thermal balloon ablation versus laparoscopic supracervical hysterectomy for the surgical treatment of heavy menstrual bleeding: a randomized study, Journal of Obstetrics & Gynaecology Research, 37, 1650-7, 2011

Sesti 2012

Sesti, F., Piancatelli, R., Pietropolli, A., Ruggeri, V., Piccione, E., Levonorgestrel-releasing intrauterine system versus laparoscopic supracervical hysterectomy for the treatment of heavy menstrual bleeding: a randomized study, Journal of Women's Health, 21, 851-7, 2012

Shaaban 2011

Shaaban, M. M., Zakherah, M. S., El-Nashar, S. A., Sayed, G. H., Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial, Contraception, 83, 48-54, 2011

Shaw 2007

Shaw, R. W., Symonds, I. M., Tamizian, O., Chaplain, J., Mukhopadhyay, S., Randomised comparative trial of thermal balloon ablation and levonorgestrel intrauterine system in patients with idiopathic menorrhagia, The Australian & New Zealand Journal of Obstetrics & Gynaecology, 47, 335-40, 2007

Silva-Filho 2013

Silva-Filho, A. L., Pereira Fde, A., Souza, S. S., Loures, L. F., Rocha, A. P., Valadares, C. N., Carneiro, M. M., Tavares, R. L., Camargos, A. F., Five-year follow-up of levonorgestrel-releasing intrauterine system versus thermal balloon ablation for the treatment of heavy menstrual bleeding: a randomized controlled trial, Contraception, 87, 409-15, 2013

Soysal 2002

Soysal, M., Soysal, S., Ozer, S., A randomized controlled trial of levonorgestrel releasing IUD and thermal balloon ablation in the treatment of menorrhagia, Zentralblatt fur Gynakologie, 124, 213-9, 2002

Tam 2006

Tam, W. H., Yuen, P. M., Shan Ng, D. P., Leung, P. L., Lok, I. H., Rogers, M. S., Health status function after treatment with thermal balloon endometrial ablation and levonorgestrel intrauterine system for idiopathic menorrhagia: a randomized study, Gynecologic and Obstetric Investigation, 62, 84-8, 2006

Tosun 2014

Tosun, A. K., Tosun, I., Suer, N., Comparison of levonorgestrel-releasing intrauterine device with oral progestins in heavy menstrual bleeding (HMB) cases with uterine leiomyoma (LNG-IUD and oral progestin usage in myoma uteri), Pakistan Journal of Medical Sciences, 30, 2014

Tsoi 2015

Tsoi, B., Blackhouse, G., Ferrazzi, S., Reade, C. J., Chen, I., Goeree, R., Incorporating ulipristal acetate in the care of symptomatic uterine fibroids: a Canadian cost-utility analysis of pharmacotherapy management, ClinicoEconomics and Outcome Research, 7, 213-25, 2015

van der Kooij 2010

van der Kooij, S. M., Hehenkamp, W. J., Volkers, N. A., Birnie, E., Ankum, W. M., Reekers, J. A., Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial, American Journal of Obstetrics & Gynecology, 203, 105.e1-13, 2010

van Zon-Rabelink 2003

van Zon-Rabelink, I. A., Vleugels, M. P., Merkus, H. M., de Graaf, R., Endometrial ablation by rollerball electrocoagulation compared to uterine balloon thermal ablation. Technical and safety aspects, European Journal of Obstetrics Gynecology and Reproductive Biology, 110, 220-3, 2003

van Zon-Rabelink 2004

van Zon-Rabelink, I. A., Vleugels, M. P., Merkus, H. M., De Graaf, R., Efficacy and satisfaction rate comparing endometrial ablation by rollerball electrocoagulation to uterine balloon thermal ablation in a randomised controlled trial, European Journal of Obstetrics Gynecology, & Reproductive Biology, 114, 97-103, 2004

Vercellini 1999

Vercellini, P., Oldani, S., Yaylayan, L., Zaina, B., De Giorgi, O., Crosignani, P. G., Randomized comparison of vaporizing electrode and cutting loop for endometrial ablation, Obstetrics and Gynecology, 94, 521-7, 1999

Vihko 2003

Vihko, K. K., Raitala, R., Taina, E., Endometrial thermoablation for treatment of menorrhagia: comparison of two methods in outpatient setting, Acta Obstetricia et Gynecologica Scandinavica, 82, 269-74, 2003

Volkers 2007

Volkers, N. A., Hehenkamp, W. J., Birnie, E., Ankum, W. M., Reekers, J. A., Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial, American Journal of Obstetrics and Gynecology, 196, 519.e1-11, 2007

You 2006

You, J. H., Sahota, D., S., MoYuen, P., A cost-utility analysis of hysterectomy, endometrial resection and ablation and medical therapy for menorrhagia, Human Reproduction, 21, 1878-83, 2006

You 2009

You, J., H., S., Singh Sahota, D., Yuen, P.M., Uterine artery emolization, hysterectomy, or myomectomy for symptomatic uterine fibroids: a cost-utility analysis, Fertility and Sterility, 91, 580-8, 2009

Zhou 2013

Zhou, K., Zhuang, G., Zhang, H., Liang, P., Yin, J., Kou, L., Hao, M., You, L., Psychometrics of the Short Form 36 Health Survey version 2 (SF-36v2) and the Quality of Life Scale for Drug Addicts (QOL-DAv2.0) in Chinese mainland patients with methadone maintenance treatment, PLoS One, 8, e79828, 2013

Zowall 2008

Zowall, H., Cairns, J. A., Brewer, C., Lamping, D. L., Gedroyc, W. M., Regan, L., Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids, BJOG: An International Journal of Obstetrics & Gynaecology, 115, 653-62, 2008

Zupi 2003

Zupi, E., Zullo, F., Marconi, D., Sbracia, M., Pellicano, M., Solima, E., Sorrenti, G., Hysteroscopic endometrial resection versus laparoscopic supracervical hysterectomy for menorrhagia: a prospective randomized trial, American Journal of Obstetrics and Gynecology, 188, 7-12, 2003

Appendices

Appendix A – Review protocols

Review protocol for management of heavy menstrual bleeding

Item	Details
Areas in the scope	Management of heavy menstrual bleeding, including: • pharmacological management [note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients] • surgical management.
Review questions in the scope	Management of heavy menstrual bleeding • What is the most clinically and cost-effective **pharmacological** treatment for heavy menstrual bleeding in women with: ○ suspected or confirmed fibroids ○ suspected or confirmed adenomyosis ○ no identified pathology? • What is the most clinically and cost-effective **surgical** treatment for heavy menstrual bleeding in women with: ○ suspected or confirmed fibroids ○ suspected or confirmed adenomyosis ○ no identified pathology? • What is the most clinically and cost-effective **treatment** for heavy menstrual bleeding among pharmacological and surgical treatments? Note: The surgical options for treating women with heavy menstrual bleeding and adenomyosis will include uterine artery embolisation.
Review question for the guideline	What is the most clinically and cost-effective treatment (pharmacological/surgical) for heavy menstrual bleeding in women with: • suspected or confirmed fibroids • suspected or confirmed adenomyosis • no identified pathology? Note: The surgical options for treating women with heavy menstrual bleeding will include uterine artery embolisation.
Objective	The objective of these reviews is to identify effective pharmacological and surgical treatment classes and interventions to reduce heavy menstrual bleeding and improve quality of life for women with heavy menstrual bleeding.
Population and directness	Inclusions: • women of reproductive age between menarche and menopause with heavy menstrual bleeding, including women with adenomyosis • definition of HMB as described in the study. Studies with more than 66% women with HMB, or where the proportion of women with HMB is not specified will be included. If the analysis has been performed for the women with HMB separately then only this data will be extracted. Exclusions: • RCTs with less than 10 participants in each arm will not be included

Item	Details

Intervention	**Pharmacological treatments**
	[of any type and administered at any dose, frequency, treatment duration recommended in the BNF, or by any route of administration]:
	• NSAIDs
	  ○ Ibuprofen
	  ○ Mefenamic acid
	  ○ Other NSAIDs (e.g naproxen, diclofenac)
	• Antifibrinolytics
	  ○ Tranexamic acid
	• Progestogens
	  ○ Oral (groups to be decided a priori dependent on dose, duration, type)
	  - Medroxyprogesterone acetate
	  - Norethisterone
	  - Desogestrel
	  ○ Injectable
	  - Depot medroxyprogesterone acetate
	  ○ Implant
	• Combined hormonal contraceptives (groups to be decided a priori dependent on dose, duration, type)
	  ○ Estradiol valerate/dienogest
	  ○ Noresthisterone acetate/ethinyl estradiol
	  ○ Others (EE/levonorgestrel EE/drospirenone etc.)
	• GnRHa
	  ○ Leuprolide acetate
	  ○ Decapeptyl
	  ○ Goserelin
	• Ullipristal acetate
	• **Levonorgestrel-releasing intrauterine system** (LNG-IUS) (groups to be decided a priori)
	Surgical treatments
	• Hysterectomy (total versus subtotal)
	  ○ Laparoscopic/laparoscopic assisted
	  ○ Robotic
	  ○ Vaginal
	  ○ Open
	• First generation (hysteroscopic-controlled endometrial resection)
	  ○ Transcervical endometrial resection
	  ○ Endometrial vaporization
	  ○ Endometrial ablation - rollerball
	• Second generation endometrial resection (non-hysteroscopy-controlled endometrial resection)
	  ○ Radiofrequency endometrial ablation (bipolar)
	  ○ Endometrial cryoablation
	  ○ Thermal balloon ablation
	  ○ Hydrothermal (free-fluid) endometrial ablation
	• Uterine artery embolisation
	• Myomectomy
	  ○ Laparoscopic
	  ○ Hysteroscopic (e.g. submucosal fibroids/fibroid polyps)

Item	Details
	○ Open • MRI-guided transcutaneous focussed ultrasound for uterine fibroids NOTE: interventions not approved in the UK (for example dienogest), or not used in clinical practice (for example danazol, flurbiprofen, ethamsylate, microwave ablation, laser ablation, endometrial laser intrauterine thermo therapy and cavaterm endometrial ablation) will not be included in this review. However studies including this interventions may be included in the NMA if they provide data to inform the network. Please see NMA protocol for details.
Comparison	• Pharmacological treatment versus no treatment, usual care or placebo • Pharmacological treatment A versus pharmacological treatment B • Pharmacological treatment versus surgery • Pharmacological treatment versus combinations of pharmacological and surgical treatment • Surgical treatment versus no treatment, usual care [or placebo] • Surgical technique A versus surgical technique B • Surgery versus combinations of pharmacological and surgical treatment Note: only between-class comparisons will be performed in this review
Outcomes	• Reduction in blood loss – Pictoral blood loss assessment chart (PBAC, Higham 1990) or Alkaline-Haematin (AH) method • Quality of life – all scales must be validated • Patient satisfaction • Adverse events (AEs): ○ for pharmacological treatment: - discontinuation due to AEs - treatment compliance/discontinuation ○ for LNG-IUS: - discontinuation due to AEs - perforation - expulsion - infection ○ for surgery: - length of hospital stay - severe bleeding requiring a blood transfusion - infection - venous thromboembolism - return to hospital and/or theatre - internal organ injury - long-term complications (e.g. prolapse, urinary incontinence) - mortality
Importance of outcomes	Critical outcomes for decision making: • patient satisfaction • quality of life - all scales must be validated • adverse events: ○ for pharmacological treatments and LNG-IUS: - discontinuation due to AEs ○ for surgery: - injury to internal organs

Item	Details
	- infection - venous thromboembolism Important outcomes: • reduction in blood loss – PBAC or AH method • adverse events: ○ for pharmacological treatment: - treatment compliance/discontinuation ○ for LNG-IUS: - perforation - expulsion - infection ○ for surgery: - length of hospital stay - severe bleeding requiring a blood transfusion - return to hospital and/ or theatre - long-term complications (e.g. prolapse, urinary incontinence) - mortality
Setting	No particular setting specified.
Stratified, subgroup and adjusted analyses	The following groups of interventions will be reviewed, analysed and presented separately. • First-line treatments (pharmacological treatment will be considered to be first-line where not specified in papers) • Second-line treatments (surgery will be considered to be second-line where not specified in papers) Pre-specified subgroup analyses: • treatment type ○ pharmacolocial treatments ○ surgical treatments • women presenting with pain in addition to HMB • women with suspected or confirmed fibroids: ○ 3 cm or more in diameter ○ less than 3 cm in diameter ○ submucosal fibroid of any size • women who wish to preserve fertility In the presence of hererogeneity, the following sub-groups will be analysed separately: • mixed populations (including women with abnormal uterine bleeding but not necessarily) versus all women with HMB
Language	English
Study design	• Systematic reviews of RCTs • RCTs • In absence of full text published RCTs, conference abstracts will be considered • Cross over RCTs will be considered where it is appropriate
Search strategy	Sources searched: Cochrane, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Embase Date limit: • 2007 onwards (including relevant studies from previous guideline) See Appendix E – Literature search strategies for full strategies.

Item	Details
Review strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using the Cochrane risk of bias tool • The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. • If studies only report p-values, this information will be plotted in GRADE tables without an assessment of imprecision being made. • Studies with 80-99% women with HMB will be downgraded once for indirectness. Studies with 66-80% women with HMB, or where the proportion of women with HMB is not specified, will be downgraded twice for indirectness. Synthesis of data: • Pairwise meta-analysis will be conducted where appropriate for all other outcomes • Network meta-analysis (see separate protocol) • When meta-analysing continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed. Minimal important differences (MIDs): • Mortality – any change (statistical significance) • Internal organ injury – any change (statistical significance) • For all other outcomes default MIDs will be used: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes to assess imprecision.
Equalities	None noted
Notes/additional information	
Key papers	None noted

Appendix B – Health economic quality assessment

Table 24: Health quality assessment for the management of heavy menstrual bleeding

Study identification **Calaf, J., Lete, I., Canals, I., Crespo, C., Espinos, B., Cristobal, I. Cost-effectiveness analysis in the treatment of heavy menstrual bleeding in Spain. European Journal of Obstetrics & Gynecology and Reproductive Biology 184, 24–31, 2015**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Fertile women diagnosed with HMB who initially wished to remain fertile
1.2 Are the interventions appropriate for the review question?	Yes	Levonorgestrel-releasing intrauterine system (LNG-IUS) compared with the estradiol valerate/dienogest multiphase oral contraceptive (E2V/DNG), combined oral contraceptives (COC) and progestins (PROG).
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	Spain
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Spanish NHS in base case
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 5 years. Costs and benefits discounted at 3% (note slight deviation from NICE reference case of 3.5%)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	Quality-adjusted life months (QALM)
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		

Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with 6 month cycles. Women who fail to control HMB or birth control, switch to other alternative as a second-line therapy, according to current clinical practice in Spain.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 5 years
2.3 Are all important and relevant outcomes included?	Yes	Report symptom-free months, surgery-free months and QALM.
2.4 Are the estimates of baseline outcomes from the best available source?	Unclear	Appear to be inferred by the panel of clinical experts
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Identified from systematic review of the literature and agreed with a panel of clinical experts *
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	Agreed with a panel of clinical experts
2.8 Are the unit costs of resources from the best available source?	Yes	Spanish Health Costs Database eSALUD and General Council of Pharmaceutical Associations of Spain Database (CGCOF)
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	OWSA and PSA (1,000 iterations)
2.11 Is there any potential conflict of interest?	Yes	Funded by Bayer Hispania, the manufacturer of LNG-IUS and E2V/DNG, and developed by Oblikue Consulting on its behalf.
2.12 Overall assessment: Minor limitations		
Other comments: * The long-term efficacy of E2V/DNG, COC and PROG was obtained by extrapolating the short-term efficacy data observed from the pattern of change in efficacy of LNG-IUS.		
Study identification **Ganz, M., Shah, D., Gidwani, R., Filonenko, A., Su, W., Pocoski, J., Law, A. The cost-effectiveness of the levonorgestrel-releasing intrauterine system (LNG-IUS, mirena) for the treatment of heavy menstrual bleeding in the United States. VALUE IN HEALTH 16 (2013) 325–333.**		

Guidance topic: HMB		Question no: 3
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	Yes/partly/no/unclear/NA	Comments
1.1 Is the study population appropriate for the review question?	Yes	Hypothetical women with HMB who also desired contraception
1.2 Are the interventions appropriate for the review question?	Yes	LNG-IUS, oral treatments, or surgery. Oral treatments included generic COCs, branded COCs, TXA, and oral progestins; surgery included endometrial ablation and hysterectomy.
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	US payer perspective
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 5 years. Costs and benefits discounted at 3% (note slight deviation from NICE reference case of 3.5%)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	Yes/partly/no/unclear/NA	Comments
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with 3 month cycles. Women can initiate treatment with nonsurgical or surgical therapies. Women who continue treatment remain on the same therapy until treatment failure, unintended pregnancy, or they discontinue for other reasons. Women who fail their first– or second-line

		nonsurgical therapies can switch directly to the surgical therapy option. Women who discontinue their current nonsurgical treatment can either discontinue all treatments or switch to the next line of therapy. Probabilities of treatment switching derived from Thomson Medstats MarketScan Commerical Chains database.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon 5 years
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Data for treatment response came from recent clinical trial publications and systematic literature reviews that assessed the ability of the target treatments to reduce menstrual blood loss to less than 80ml per menstrual cycle.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Partly	Does not account for the costs associated with pregnancy, births, abortions, or miscarriages because they state the focus was on the costs associated with HMB.
2.7 Are the estimates of resource use from the best available source?	Unclear	Insufficient detail regarding assumptions used
2.8 Are the unit costs of resources from the best available source?	Partly	US sources: physician and surgery costs were obtained from the Market Scan database. Drug and LNG-IUS costs were obtained from the Medi-Span Price Rx database
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Extensive OWSA and PSA (number of iterations not reported)
2.11 Is there any potential conflict of interest?	Yes	Financial support from Bayer
2.12 Overall assessment: Potentially serious limitations		
Other comments:		

Study identification **Gupta, J. K., Daniels, J. P., Middleton, L. J., Pattison, H. M., Prileszky, G., Roberts, T. E., Sanghera, S., Barton, P., Gray, R., Kai, J., Eclipse Collaborative Group. A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial. HEALTH TECHNOLOGY ASSESSMENT 2015. Vol 19. Issue 88**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Prospective RCT enrolled 571 women with menorrhagia in primary care from 63 UK centres (ECLIPSE trial)
1.2 Are the interventions appropriate for the review question?	Yes	Levonorgestrel-releasing intrauterine device (LNG-IUS) and usual medical treatment (mefenamic acid, tranexamic acid, norethisterone, a combined estrogen/progestogen or progestogen only oral contraceptive pill (any formulation), or methoxyprogesterone acetate injection)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	3.5% applied to costs and QALYs when a 5 year time horizon was explored
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**

2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model informed by clinical input and the pathways followed by the women in the ECLIPSE trial. Monthly cycles.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Time horizon: 2 and 5 years
2.3 Are all important and relevant outcomes included?	Yes	ECLIPSE trial
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Unclear if data beyond ECLIPSE was considered
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.3
2.6 Are all important and relevant costs included?	Yes	See 2.3
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.3
2.8 Are the unit costs of resources from the best available source?	Yes	BNF, PSSRU
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Seterministic SA and PSA (1,000 iterations)
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Study identification **You, J. H., Sahota, D. S, Yuen, P. M., Uterine artery embolization, hysterectomy, or myomectomy for symptomatic uterine fibroids: a cost-utility analysis, Fertility and Sterility, 91, 580–8, 2009**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Hypothetical cohort of women presenting with symptomatic uterine fibroids with HMB
1.2 Are the interventions appropriate for the review question?	Yes	Hysterectomy, myomectomy, and uterine artery embolization (UAE)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Hong Kong
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	Societal perspective

1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 5 years Costs and benefits discounted at 4% (note slight deviation from NICE reference case of 3.5%)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?		Markov model with annual cycles. The risk of symptomatic relapse with time and recurrence of symptomatic fibroids and interventions may occur more than once.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 5 years
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Systematic review of the literature
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Partly	Both direct medical costs and indirect costs were considered from the perspective of Hong Kong society
2.7 Are the estimates of resource use from the best available source?	Unclear	Assumptions not clarified, only unit costs reported
2.8 Are the unit costs of resources from the best available source?	Yes	Hong Kong Gazette
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	OWSA and PSA (10,000 iterations)

2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Potentially serious limitations		
Study identification **Zowall, H., Cairns, J. A., Brewer, C., Lamping, D. L., Gedroyc, W. M., Regan, L., Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids, BJOG: An International Journal of Obstetrics & Gynaecology, 115, 653–62, 2008**		
Guidance topic: HMB		Question no: 3
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women for whom surgical treatment for uterine fibroids is being considered
1.2 Are the interventions appropriate for the review question?	Yes	Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) as compared with current practice comprising of uterine artery embolization 25%, myomectomy 25% and hysterectomy 50%.
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	England and Wales
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Costs and benefits discounted at 3.5%
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with annual cycles. The nonperfused volume (NPV) ratio is a surrogate measure of treatment success. Higher NPV ratios are associated with lower probabilities of recurrence due

		to fibroid regrowth and a reduced need for additional procedures.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Model starts at age 39 and follows women until age 56
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Taken from the literature and InSighttec clinical studies
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	Hospital costs of MRgFUS are based on estimates of resource use obtained from St Mary's NHS Trust, London including all personnel costs, medical consumables, MR time, equipment and maintenance costs.
2.8 Are the unit costs of resources from the best available source?	Yes	Outpatient medical costs - NHS Reference Costs and PSSRU. Outpatient medication costs - BNF and Scottish Prescription Cost Analysis
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Partly	ICERs presented for MRgFUS against usual care, but usual care is subjective and may misinterpret the cost-effectiveness of MRgFUS compared to each separate intervention included in usual care
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Extensive SA and PSA (20,000 iterations)
2.11 Is there any potential conflict of interest?	Partly	Supported by an unrestricted grant from InSightec (Haifa, Israel). Their clinical trials were also used to inform clinical effectiveness associate with NPV and MRgFUS.
2.12 Overall assessment: Potentially serious limitations		
Study identification **Bhattacharya, S., Middleton, L. J., Tsourapas, A., Lee, A. J., Champaneria, R., Daniels, J. P., Roberts, T., Hilken, N. H., Barton, P., Gray, R., Khan, K. S., Chien, P., O'Donovan, P., Cooper, K. G., International Heavy Menstrual Bleeding Individual Patient Data Meta-analysis Collaborative, Group, Abbott, J., Barrington, J., Bhattacharya, S., Bongers, M. Y., Brun, J. L., Busfield, R., Clark, T. J., Cooper, J., Cooper, K. G., Corson, S. L., Dickersin, K., Dwyer, N., Gannon, M., Hawe, J., Hurskainen, R., Meyer, W. R., O'Connor, H., Pinion, S., Sambrook, A. M., Tam, W. H., van Zon-Rabelink, I. A.,**		

Zupi, E., Hysterectomy, endometrial ablation and Mirena for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis, Health Technology Assessment, 15, 2011		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women with HMB with a starting age of 42
1.2 Are the interventions appropriate for the review question?	Yes	Mirena coil, first generation endometrial ablation, second generation endometrial ablation and hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 10 years Costs and benefits discounted at 3.5%
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with monthly cycles. Structure informed by literature and clinical input
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 10 years
2.3 Are all important and relevant outcomes included?	Yes	Structure informed by literature and clinical input
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Data drawn from research work undertaken by the project, namely individual patient meta-analyses, data from national registers and existing RCTs

2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	Structure informed by literature and clinical input
2.7 Are the estimates of resource use from the best available source?	Yes	Taken from the literature
2.8 Are the unit costs of resources from the best available source?	Yes	Literature, PSSRU, BNF, NHS Reference Costs, NICE CG44
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Partly	ICERs are versus hysterectomy, a fully incremental analysis is not presented.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Subgroup analyses for age and uterine cavity length and OWSA PSA carried out to produce CEAC, but little detail and results of PSA reported
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Study identification **Clegg, J. P., Guest, J. F., Hurskainen, R., Cost-utility of levonorgestrel intrauterine system compared with hysterectomy and second generation endometrial ablative techniques in managing patients with menorrhagia in the UK, Current Medical Research and Opinion, 23, 1637-48, 2007**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women with HMB to reflect women in the Finnish RCT
1.2 Are the interventions appropriate for the review question?	Yes	Levonorgestrel intrauterine system (LNG-IUS; Mirena*) followed by ablation (L-A); LNG-IUS followed by hysterectomy (L-H); immediate ablation (MEA or TBEA) and immediate hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK perspective using a Finnish RCT
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS

1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 5 years Costs and benefits discounted at 3.5%
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with monthly transitions. Clinical pathway followed NICE guidance on treatment sequencing, Finnish RCT and PenTAG model (Garside 2003)
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon 5 years
2.3 Are all important and relevant outcomes included?	Yes	Finnish RCT and PenTAG model
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	See 2.3
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.3
2.6 Are all important and relevant costs included?	Yes	See 2.3
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.3
2.8 Are the unit costs of resources from the best available source?	Yes	PenTAG model, BNF, PSSRU, NHS Reference Costs
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Extensive SA, threshold analysis and PSA (1,000 iterations)
2.11 Is there any potential conflict of interest?	Yes	Financially supported by Schering Health Care
2.12 Overall assessment: Minor limitations		

Study identification **Lete, I. C., Febrer, L. C., Crespo, A., Arbat, F.J., Hernandez, M. B., Economic evaluation of the levonorgestrel-releasing intrauterine system for the treatment of dysfunctional uterine bleeding in Spain, European Journal of Obstetrics & Gynecology and Reproductive Biology, 154, 71–80, 2011**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women with idiopathic dysfunctional uterine bleeding (DUB)
1.2 Are the interventions appropriate for the review question?	Yes	Levonorgestrel-releasing intrauterine system (LNG-IUS) versus combined oral contraception (COC) and progestogens (PROG) in first-line treatment of DUB
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	Spain
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 5 years. Costs and benefits discounted at 3% (note slight deviation from NICE reference case of 3.5%)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	Quality-adjusted life months (QALM)
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model structure agreed with a panel of experts. Six month cycles. Those women who fail controlling DUB or birth control, switch to other

		alternative as a second-line therapy, according to current clinical practice in Spain.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 5 years
2.3 Are all important and relevant outcomes included?	Yes	Model inputs taken from the literature and agreed with a panel of experts. Outcomes to assess incremental cost-effectiveness include QALMs, symptom-free months and surgery-free months
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Model inputs taken from the literature and agreed with a panel of experts
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	See 2.4
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.4
2.8 Are the unit costs of resources from the best available source?	Yes	Medicine database of medicines of the General Council of Official Associations of Pharmacists. e-Salud health costs database.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Extensive SA and PSA (10,000 iterations)
2.11 Is there any potential conflict of interest?	Yes	Funded by Bayer HealthCare Spain, the manufacturer of LNG-IUS, and developed by Oblikue Consulting on its behalf
2.12 Overall assessment: Minor limitations		
Study identification **Miller, J. D., Lenhart, G. M., Bonafede, M. M., Basinski, C. M., Lukes, A. S., Troeger, K. A., Cost effectiveness of endometrial ablation with the NovaSure system versus other global ablation modalities and hysterectomy for treatment of abnormal uterine bleeding: US commercial and medicaid payer perspectives, International Journal of Women's Health, 7, 59–73, 2015**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**

1.1 Is the study population appropriate for the review question?	Yes	Premenopausal women for whom childbearing is complete and who seek a permanent, non-reversible, one-time treatment option for their AUB. Starting age 42 years.
1.2 Are the interventions appropriate for the review question?	Yes	NovaSure, hysterectomy, other global endometrial ablation (GEA). Other GEA modalities include second-generation GEA techniques (eg, cryotherapy, microwave endometrial ablation, thermal balloon endometrial ablation, hydrothermal ablation) other than bipolar radiofrequency ablation with the NovaSure system. 'Hysterectomy' includes laparoscopic/robotic-assisted hysterectomy, vaginal hysterectomy, and abdominal hysterectomy.
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	Two versions of the model were created – one containing clinical and economic data oriented from the US commercial health care payer perspective and the other from a US Medicaid perspective. Underlying clinical and cost data differed in the two versions of the model, but the structure and functional operation were identical, with the exception that the commercial payer perspective version of the model generated outputs associated with work absence and short-term disability and the associated 'indirect costs' from these productivity losses.
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Time horizon: 1, 3, 5 and 10 years. Costs and benefits discounted at 3% (note slight deviation from NICE reference case of 3.5%)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	

1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with monthly cycles. Approach is said to be similar to other published models for AUB treatment.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 1, 3, 5 and 10 years
2.3 Are all important and relevant outcomes included?	Yes	Reference other models this is similar to
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Most clinical and economic data (including treatment patterns, health state transition probabilities, health care resource utilization, direct costs, and productivity costs) were primarily derived from de novo analyses of three large medical claims databases: 1) the Truven Health MarketScan® Commercial Claims and Encounters Database, 2) the Truven Health MarketScan® Medicaid Multi-State Database, and 3) the Truven Health MarketScan® Health Productivity and Management Database
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	See 2.4
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.4
2.8 Are the unit costs of resources from the best available source?	Yes	MarketScan® database analyses (US specific)
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Deterministic SA and PSA (1,000 iterations)
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		

Other comments:		
Study identification **Tsoi, B., Blackhouse, G., Ferrazzi, S., Reade, C. J., Chen, I., Goeree, R., Incorporating ulipristal acetate in the care of symptomatic uterine fibroids: a Canadian cost-utility analysis of pharmacotherapy management, ClinicoEconomics and Outcomes Research, 7, 213–25, 2015**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Moderate-to-severe symptoms of uterine fibroids in women eligible for surgery
1.2 Are the interventions appropriate for the review question?	Yes	Ulipristal acetate (5 mg orally daily) compared to leuprolide acetate (3.75 mg intramuscular monthly)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	Canada
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Ontario public payer in base case, societal considered in SA
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	NA	Time horizon <1 year
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Decision tree reflects short time horizon
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Pre-surgical period of 3 months to reflect the licensed indication for ulipristal
2.3 Are all important and relevant outcomes included?	Yes	RCT (PEARL II)

2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Unclear if data beyond PEARL II was considered
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.3
2.6 Are all important and relevant costs included?	Yes	As this model captures the pre-surgical period, costs were calculated from the initial presentation (ie, surgical consultation) until the completion of the drug regimen before undergoing surgery.
2.7 Are the estimates of resource use from the best available source?	Partly	Assumptions not justified
2.8 Are the unit costs of resources from the best available source?	Yes	Patented Medicine Prices Review Board. Wholesale up-charge policies of Canada's public drug plan. Ontario Ministry of Health and Long-term Care Ontario Drug Benefit Program: Dispensing fees. Ontario Ministry of Health and Long-term Care. Drugs funded by Ontario Drug Benefit Program e-Formulary
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Extensive OWSA, scenario and PSA (1,000 iterations)
2.11 Is there any potential conflict of interest?	Partly	Supported by a grant from the Mitacs Accelerate Internship program. Matched funding was provided by both Mitacs and Actavis Specialty Pharmaceuticals Co. The authors of this publication had full and independent control over the methods, analyses and preparation of the final report and the economic model.
2.12 Overall assessment: Potentially serious limitations		
Study identification **You, J. H., Sahota, D. S., MoYuen, P., A cost-utility analysis of hysterectomy, endometrial resection and ablation and medical therapy for menorrhagia. Human Reproduction, 21, 1878-83, 2006**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**

1.1 Is the study population appropriate for the review question?	Yes	Patient selection criteria of the model were adopted from the Cochrane reviews on surgery, endometrial resection and ablation, and medical therapy for menorrhagia (Lethaby et al., 2005; Marjoribanks et al., 2005). Included women of reproductive years (≤40 years old) with regular heavy menstrual periods
1.2 Are the interventions appropriate for the review question?	Yes	Conventional oral medical therapy (non-steroid anti-inflammatory agents, tranexamic acid, oral contraceptive pills, progestogens and danazol), LNG-IUS, endometrial resection/ablation and hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Hong Kong
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Public healthcare provider in Hong Kong (indirect cost such as loss of productivity because of absence from work not included)
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: 5 years Costs discounted at 3%. Discount rate for benefits not reported
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	Markov model with annual cycles. Structure appears to be based on the literature, but does not appear to be verified.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 5 years

2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	The clinical inputs of the model were derived from clinical trials included in two meta-analyses on endometrial esection/ablation versus hysterectomy (Lethaby et al., 2005) and surgery versus medical therapy for menorrhagia (Marjoribanks et al., 2005).
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.3
2.6 Are all important and relevant costs included?	Yes	Hong Kong Gazette
2.7 Are the estimates of resource use from the best available source?	Yes	Taken from the literature
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Deterministic SA and PSA (10,000 iterations)
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Study identification **Beinfeld, M. T., Bosch, J. L., Isaacson, K. B., Gazelle, G. S., Cost-effectiveness of uterine artery embolization and hysterectomy for uterine fibroids, Radiology, 230, 207-13, 2004**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women aged 40 years with a diagnosis of uterine fibroids and no desire for pregnancy
1.2 Are the interventions appropriate for the review question?	Yes	Uterine artery embolization and hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	US and potentially outdated practice (published 2004)
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	Societal perspective
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	

1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: 10 years Survival and costs discounted at 3%, unclear if benefits are discounted.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Not applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with monthly cycles
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 10 years
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Parameter estimates obtained from the literature and confirmed with a gynaecologist, but unclear if a systematic review was undertaken
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	Medicaid reimbursements (US specific)
2.8 Are the unit costs of resources from the best available source?	Yes	Medicare Provider Analysis and review database. Institution's hospital accounting database. (US specific)
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Extensive OWSA, no PSA
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Potentially serious limitations		

Other comments:		
Study identification **Blake, J., Costescu, D., Dunn, S., Leyland, N., Rheault, K., Levonorgestrel-Releasing Intrauterine System (52 mg) for Idiopathic Heavy Menstrual Bleeding: A Health Technology Assessment, Ontario Health Technology Assessment Series, 16, 1-119, 2016**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women aged 42 years with heavy menstrual bleeding
1.2 Are the interventions appropriate for the review question?	Yes	LNG-IUS compared with endometrial ablation and hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	Ontario, Canada
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Perspective of the Ontario Ministry of Health and Long-Term Care (non-societal)
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: 9 years Costs and benefits discounted at 5% (3% tested in SA)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov model with monthly cycles. Components of the model were based on the health states commonly observed in prior studies

2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon: 9 years
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Taken from a clinical review of the literature
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	Expert opinion and inpatient or outpatient hospital administrative data
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.6
2.8 Are the unit costs of resources from the best available source?	Yes	Ontario Schedule of Benefits for Physician Services, the Ontario Drug Benefit Formulary, Ontario administrative data, inpatient and outpatient hospital care databases
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Extensive OWSA and PSA (1,000 iterations)
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Minor limitations		
Study identification **Heliovaara-Peippo, S., Hurskainen, R., Teperi, J., et al., Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: a 10-year randomized controlled trial, American Journal of Obstetrics and Gynecology, 209, 535.e1-14, 2013**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women, aged 35-49 years who had completed childbearing, referred to hospital for menorrhagia
1.2 Are the interventions appropriate for the review question?	Yes	LNG-IUS and hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Partly	Report direct and indirect cost (productivity losses and out-of-pocket costs) separately

1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: 10 years. Costs discounted at 3% in base case (note deviation from NICE reference case of 3.5% for both costs and benefits).
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	NA	DAM not developed
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon 10 years
2.3 Are all important and relevant outcomes included?	Yes	RCT on 236 women in Finland
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Systematic review not undertaken but based on relevant RCT
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	See 2.4
2.6 Are all important and relevant costs included?	Yes	Medical records and questionnaires used in the RCT
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.4
2.8 Are the unit costs of resources from the best available source?	Yes	A pricing system based on diagnostic related groups used by the Helsinki University Central Hospital was used for pricing hospital procedures
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Partly	Can be calculated from the data. Total QALYs over 10 years not reported.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	SA varying the discount rate, cost of complications and cost of complications explored. PSA not undertaken.

2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Potentially serious limitations		
Study identification **Cain-Nielsen, AH., Moriaty, JP., Stewart, EA., et al., Cost-effectiveness of uterine preserving procedures for the treatment of uterine fibroids in the United States, Journal of Comparative Effectiveness Research, 3(5), 503-514, 2014**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Uterine fibroids in premenopausal wishing to preserve their uteri
1.2 Are the interventions appropriate for the review question?	Yes	Myomectomy, Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) and uterine artery embolization. Myomectomy was included as a second line treatment where symptom relief was insufficient or if there was recurrence of fibroids
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US, a high income setting
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Partly	Report direct and indirect cost (productivity losses and out-of-pocket costs) separately
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Proportion with adaquate relief, probability of recurrence, probability of major complications
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: 5 years. Costs discounted at 3% in base case (note deviation from NICE reference case of 3.5% for both costs and benefits).
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**

2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Simple Markov structure with the following health states; treatment, adequate relief, inadequate relief, recurrence
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Time horizon 5 years
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Not clear	Mixed sources including literature, weighted average from the literature and expert opinion
2.5 Are the estimates of relative intervention effects from the best available source?	Not clear	See 2.4
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.5
2.8 Are the unit costs of resources from the best available source?	Yes	Medical insurance claims database
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Probabilistic sensitivity analysis undertaken with some use of uniform distribution
2.11 Is there any potential conflict of interest?	Yes	InSightec Inc research funding paid to Mayo Clinic, Abbott, Gynesonics, Bayer Health Care, GlaxoSmith Kline
2.12 Overall assessment: Potentially serious limitations		
Study identification **Kong, CY., Omer, BA., Pandharipande, PV., et al., MRI-Guided Focused Ultrasound surgery for uterine fibroid treatment: A cost-effectiveness analysis, American Journal of Roentgenology, 203(2), 361-371, 2014**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Women aged 40 years with symptomatic uterine fibroids
1.2 Are the interventions appropriate for the review question?	Yes	Myomectomy, Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS), uterine artery embolization and abdominal hysterectomy

1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US, a high income setting
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Partly	Report health service costs and productivity losses
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	Symptom relief, recurrence
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: Lifetime Costs discounted at 3% in base case (note deviation from NICE reference case of 3.5% for both costs and benefits).
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Simple Markov structure with the following health states; survival or death following the procedure , symptom relief, no symptom relief, death from natural causes
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Not clear	Mixed sources including literature and expert opinion
2.5 Are the estimates of relative intervention effects from the best available source?	Not clear	See 2.4
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	See 2.5
2.8 Are the unit costs of resources from the best available source?	Yes	Medicare reimbursements

2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	No probabilistic sensitivity analysis undertaken and limited one-way sensitivity analysis
2.11 Is there any potential conflict of interest?	Yes	Funding General Electric AUR Radiology Research Academic Fellowship
2.12 Overall assessment: Potentially serious limitations		
Study identification **Babashov, V., Palimaka, S., Blackhouse, G., et al., Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MRgHIFU) for Treatment of Symptomatic Uterine Fibroids: An Economic Analysis, Ontario Health Technology Assessment Series; Vol. 15: No. 5, pp. 1–61, March 2015**		
Guidance topic: HMB		**Question no: 3**
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Premenopausal women aged 40-51 years with symptomatic uterine fibroids that are refractory to pharmacological treatment
1.2 Are the interventions appropriate for the review question?	Yes	Myomectomy, Magnetic Resonance-guided High-Intensity Focused Ultrasound (MRgHIFU), uterine artery embolization and hysterectomy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Canada, a high income setting
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Perspective of the Ontario Ministry of Health and Long Term Care
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: From age 40 years until the menopause (51 years) Costs discounted at 5% in base case (note deviation from NICE reference case of 3.5% for both costs and benefits).
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	

1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov structure with the following health states; symptomatic, asymptomatic, treatment received and death
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Not clear	Published literature
2.5 Are the estimates of relative intervention effects from the best available source?	Not clear	See 2.4
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	Ontario Schedule of Benefits for Physician Services, Ontario Case Costing Initiative, Ontario Schedule of Benefits for Labatory Services, Clinical experts and manufacturer
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Probabilistic sensitivity analysis undertaken but parameters for distributions not specified, One-way sensitivity analysis also undertaken
2.11 Is there any potential conflict of interest?	No	
2.12 Overall assessment: Potentially serious limitations		
Study identification **O'Sullivan, AK., Thompson, D., Chu, P., et al., Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids, International Journal of Technology Assessment in Health Care, 25:1, 14–25, 2009**		
Guidance topic: HMB		**Question no: 3**

Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	Yes/partly/no/unclear/NA	Comments
1.1 Is the study population appropriate for the review question?	Yes	Premenopausal women with symptomatic uterine fibroids
1.2 Are the interventions appropriate for the review question?	Yes	MRgFUS, uterine artery embolization (UAE), abdominal myomectomy, hysterectomy, and pharmacotherapy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US, a high income setting
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	Societal perspective
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Time horizon: Lifetime Costs discounted at 3% in base case (note deviation from NICE reference case of 3.5% for both costs and benefits).
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	Societal perspective is limited to health care and productivity
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov structure with the following health states; symptomatic, asymptomatic,
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Not clear	Published and unpublished data
2.5 Are the estimates of relative intervention effects from the best available source?	Not clear	See 2.4

2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Not clear	Expert opinion, Medical database and Bureau of Labour Statistics
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Mainly assessed through one-way sensitivity analysis but also some mult-way sensitivity analysis
2.11 Is there any potential conflict of interest?	Yes	Research funded by GE Healthcare
2.12 Overall assessment: Potentially serious limitations		

Appendix C – Research recommendations

Research recommendation 2. Effectiveness of the progestogen-only pill, injectable progestogens, or progestogen implants in alleviating HMB

How effective are the progestogen-only pill, injectable progestogens or progestogen implants in alleviating HMB?

Why is this important?

Many women use LNG-IUS as the first-line pharmacological treatment for HMB, but it is not acceptable to all women. Combined oral contraceptives have also been shown to be effective for treating HMB, but their use is contraindicated in some women. Other progestogens used for contraception have far fewer contraindications than combined contraceptives, but their effectiveness as a treatment for HMB has not been studied.

A randomised controlled trial or cohort prospective observational study could compare the effectiveness of progestogens with other pharmacological treatments for HMB.

Table 25: Research recommendation rationale

Research question	Effectiveness of the progestogen-only pill, injectable progestogens, or progestogen implants in alleviating heavy menstrual bleeding
Why this is needed	
Importance to 'patients' or the population	Heavy menstrual bleeding (HMB) is one of the commonest reasons for gynaecological consultation in both primary and secondary care. About 1 in 20 women aged 30 to 49 consult their GP each year for heavy periods and menstrual problems (Middleton 2010). Menstrual disorders comprise 12% of all referrals to gynaecology services (NICE 2015). Heavy periods affect women's quality of life and can restrict participation in the workplace and socially (Lukes 2008). The 2007 NICE guideline on HMB noted that progestogens used for contraception also suppress menstruation but no studies on their use in women with heavy menstrual bleeding were identified. During the update to this guideline in 2017 no new evidence was found. Progestogens in their licenced role as contraceptives are well studied and accepted by women, and the preparations are widely available and cheap. If they are effective in treating symptoms of HMB then they could offer additional cost-effective options to those currently available.
Relevance to NICE guidance	There is evidence showing that combined oral contraceptives are effective in the management of HMB, but they are associated with side effects in some women. There are alternative progestogens used for contraception, but there is no evidence from RCTs or comparative studies evaluating their effectiveness as treatment for HMB. The results from these studies could help to inform future guidance.
Relevance to the NHS	HMB is a common cause for presentation to primary care and for referral to secondary care gynaecological services. Progestogens are widely used as contraception, are readily available in primary care and cheap.
National priorities	Women's health.
Current evidence base	The NICE HMB guideline update 2017 did not identify any relevant research in women with HMB, although the 2007 guideline noted that data is available on reduction in mean blood loss and amenorrhoea rates for injectable progestogens in the population using it for long acting contraception.

Research question	Effectiveness of the progestogen-only pill, injectable progestogens, or progestogen implants in alleviating heavy menstrual bleeding
	Since then, both implants and better oral preparations (e.g. desogestrel) have become more widely used and are also known to suppress menstruation.
Equality	If effective, progestogens may be particularly useful in women in whom combined oral contraceptives are contraindicated or where surgery may be expected to be more hazardous (e.g. in populations who are obese, have medical co-morbidities, thrombo-embolic disease, smokers).
Feasibility	Progestogens are largely out of patent and not licensed for treatment of HMB, so manufacturers are unlikely to want to invest in research or in amending the drugs' licence. The research itself would be feasible if conducted within a well organised primary care research network. Recruitment should be reasonable as the preparations are well known and understood by women and clinicians.
Other comments	It is essential that definitive outcome measures are used – the NICE HMB update committee prioritised quality of life measures and discontinuation rates as of primary importance. Capture of additional treatment would be necessary for cost-effectiveness analysis. References: • Lukes, A. S., Baker, J., Eder, S., et al. Daily menstrual blood loss and quality of life in women with heavy menstrual bleeding, Womens Health 8, 503-11, 2012 • Middleton, L. J., Champaneria, R., Daniels, J. P., 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, 16, 341:c3929, 2010 • National Institute for Health and Care Excellence (NICE), NICE Clinical Knowledge Summaries on Menorrhagia, London: NICE, 2015 Available from: http://cks.nice.org.uk/menorrhagia#!backgroundsub:1

Table 26: Research recommendation PICO

Criterion	Explanation
Population	Women presenting to primary or secondary care with heavy menstrual bleeding where contraception is either desired or not problematic.
Intervention	• Medroxyprogesterone acetate 150 mg injection every 12 weeks • Desogestrel 75 µg tablet daily • Etonorgestrel 68 mg implant every 3 years
Comparators	• Other medical treatments (NSAIDs, tranexamic acid, LNG-IUS, combined oral contraceptives) • No treatment
Outcomes	• Primary outcome at 12 months: Quality of life (condition-specific); longer term effects measured at two years and 5 years. • Secondary outcomes: Other clinical (e.g. need for further treatment; satisfaction) qualitative (e.g. patient acceptability and preferences)
Study design	• Randomised controlled trial • Data could also be obtained through a cohort prospective observational study – although an inferior trial design, large numbers of participants may potentially be available from a well-structured academic primary care research network.
Timeframe	5 years.

Research recommendation 3. Long-term outcomes of pharmacological and uterine-sparing surgical treatments for women with HMB associated with adenomyosis

What are the long-term clinical outcomes of pharmacological and uterine-sparing surgical treatments in women with HMB associated with adenomyosis?

Why is this important?

Adenomyosis is common, and the symptoms cause significant morbidity, including restriction of daily activities. A wide range of incidences have been suggested, but most studies report a prevalence of between 20 and 35%. Despite this, there is little evidence about the impact of adenomyosis on symptoms of HMB or the best treatment for this condition. Optimising treatment can lead to better patient satisfaction and the avoidance of unnecessary investigations and treatments. In order to do this, a better understanding of the impact of adenomyosis in causing HMB, pain and subfertility is needed.

A prospective clinical registry would allow long-term clinical outcomes such as patient satisfaction and re-intervention for refractory symptoms, to be recorded after pharmacological and uterine-sparing surgical treatments for women with adenomyosis.

Table 27: Research recommendation rationale

Research question	What are the long-term clinical outcomes of medical or uterine sparing surgical treatment in women with heavy menstrual bleeding associated with adenomyosis?
Why this is needed	
Importance to 'patients' or the population	Adenomyosis is defined as the presence of endometrial glands and stroma deep within the myometrium. The exact prevalence of histologically confirmed adenomyosis varies widely, ranging from 5% to 70% with most quoting 20-35% (Bergholt 2001, Curtis 2002, Yeniel 2007). The pathogenesis of adenomyosis has not been well-established. There are a number of theories and it is likely that there are multiple different pathophysiologies as with endometriosis. The most frequent mechanism described is the direct penetration of endometrium into the myometrium. This mechanism of action is consistent with risk factors that are well documented for adenomyosis, which include multi parity and termination of pregnancy (Vivillis 1997). Other risk factors for adenomyosis include greater oestrogen exposure, such as early menarche, short menstrual cycles, and obesity (Templeman 2008). Diagnosis of adenomyosis can only be confirmed histologically. Traditionally, this was a diagnosis that was only made after hysterectomy. Advances in imaging in ultrasound and MRI mean that non-invasive diagnosis of adenomyosis is now possible. The development of sonographic criteria means that increasingly adenomyosis is being diagnosed in women prior to hysterectomy. A meta-analysis published in 2010, concluded that both MRI and ultrasound scan give a higher accuracy for the non-invasive diagnosis of adenomyosis, although MRI was determined to be more accurate (Stoelinga 2014). Now that adenomyosis is being diagnosed prior to hysterectomy there is an opportunity to tailor management for women with this diagnosis. Women with adenomyosis may be asymptomatic and reliance on clinical symptoms is not sensitive or specific. Symptoms may include: painful periods, heavy menstrual bleeding, painful intercourse and infertility, which can be related to whether gynaecological conditions such as endometriosis or fibroids. On examination, women with adenomyosis may be found to have an enlarged painful uterus. There have been a number of studies looking for biomarkers, but these have proven not to be as successful as imaging technologies.

Research question	What are the long-term clinical outcomes of medical or uterine sparing surgical treatment in women with heavy menstrual bleeding associated with adenomyosis?
	The treatment for adenomyosis will depend on the presenting features, with treatments targeting: heavy menstrual bleeding, pain or infertility. Medical options such as NSAIDs and hormonal treatments are normally first-line. This is despite a lack of evidence to support treatment in patients with adenomyosis. There is also a lack of data on long-term outcomes such as the impact of adenomyosis on treatment failure and its effect on fertility. There are treatments being used with little supporting evidence such as partial excision or the use of high-intensity ultrasound and interventional radiological procedure. Ideally, randomised controlled trials comparing surgical conservative and medical treatments would be optimal. However, we first need to establish the impact of adenomyosis in causing heavy menstrual bleeding, pain and subfertility. Moreover, we need to understand impacts on outcomes such as patient satisfaction and re-intervention for refractory symptoms. To do this a prospective clinical registry is needed.
Relevance to NICE guidance	Adenomyosis is a structural abnormality that is part of the FIGO PALM-COIEN classification of abnormal uterine bleeding. Adenomyosis is increasingly detected during the diagnostic work up of women with heavy menstrual bleeding because of the wider availability of enhanced imaging using pelvic ultrasound scanning and MRI. There is little evidence of how a concurrent diagnosis of adenomyosis with heavy menstrual bleeding effects the short-term and long-term treatments outcomes.
Relevance to the NHS	Abnormal uterine bleeding and dysmenorrhoea are common and can seriously affect a women's quality of life. It causes a significant amount of sickness from work and utilises substantial health service resources. Abnormal uterine bleeding is caused by several different pathologies including adenomyosis, which is estimated to be present in 5-70% of cases. Traditionally adenomyosis was diagnosed at hysterectomy but advances in imaging mean that it is increasingly being diagnosed before surgical intervention. Now that this diagnosis is being made non-invasively there is an opportunity to adapt treatment specifically for women for this condition. Understanding the impact of the treatments for heavy menstrual bleeding in women with adenomyosis can optimise clinical outcomes. This will save health care resources by avoiding unnecessary investigations and treatment and improve patient satisfaction.
National priorities	Women's Health.
Current evidence base	There is limited current evidence on the effectiveness of treatment. A small RCT of 75 patient randomised between hysterectomy and LNG-IUS showed equivalence in bleeding outcomes with LNG-IUS slightly superior in some aspects of quality of life (Ozdegirmenci 2011). There remains a lack of data looking at other treatment modalities or comparing the LNG-IUS to no treatment.
Equality	Abnormal uterine bleeding, dysmenorrhea and adenomyosis affect women of all reproductive ages and races. Thus the optimising clinical outcomes through better diagnosis will benefit all women with this condition.
Feasibility	Advances in imaging technologies and diagnostic criteria mean adenomyosis is increasingly diagnosed prior to hysterectomy. As the imaging modalities are becoming more specific and sensitive, the diagnosis is becoming more common and it will be possible to build a large cohort quickly of this highly prevalent condition. The uncertainty regarding the impact of adenomyosis and the effectiveness of treatment along with technological advancement means a lot of treatment strategies are being employed. This will provide a range of scenarios that can be analysed as part of a cohort study.
Other comments	References:

Research question	What are the long-term clinical outcomes of medical or uterine sparing surgical treatment in women with heavy menstrual bleeding associated with adenomyosis?
	• Bergholt, T., Eriksen, L., Berendt, N., et al, Prevalence and risk factors of adenomyosis at hysterectomy, Human Reproduction, 16, 2418e21 2001 • Curtis, K. M., Hillis, S. D., Marchbanks, P. A., et al, Disruption of the endometrial-myometrial border during pregnancy as a risk factor for adenomyosis, American Journal of Obstetrics and Gynecology, 187, 543e4, 2002 • Ozdegirmenci, O., Kayikcioglu, F., Akgul, M. A., et al, Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis, Fertility and Sterility, 95, 497e502, 2011 • Stoelinga, B., Hehenkamp, W. J., Brolmann, H. A., et al, Real-time elastography for assessment of uterine disorders, Ultrasound in Obstetrics & Gynecology, 43, 218e26, 2014 • Templeman, C., Marshall, S. F., Ursin, G., et al, Adenomyosis and endometriosis in the California Teachers Study, Fertility and Sterility, 90, 415e24, 2008 • Vavilis, D., Agorastos, T., Tzafetas, J., et al, Adenomyosis at hysterectomy: prevalence and relationship to operative findings and reproductive and menstrual factors, Clinical and Experimental Obstetrics and Gynecology, 24, 36e8, 1997 • Yeniel, O., Cirpan, T., Ulukus, M., et al, Adenomyosis: prevalence, risk factors, symptoms and clinical findings, Clinical and Experimental Obstetrics and Gynecology, 34, 163e7, 2007

Table 28: Research recommendation PICO

Criterion	Explanation
Population	Women with heavy menstrual bleeding and typical features of adenomyosis identified by ultrasound or MRI, who are initially willing to have conservative or uterine sparing treatment.
Intervention	A case report form will be developed which will contain: risk factors, symptoms, imaging findings and treatment choices. Patients will be followed up for quality of life, menstrual symptom control, treatment failure and re-interventions and fertility.
Comparators	None
Outcomes	• Primary outcome at 12 months: Quality of life; longer term effects measured at two years and 5 years • Secondary outcomes: satisfaction, complications of treatment, treatment failure and fertility
Study design	Prospective multicentre observational cohort
Timeframe	5 years

Research recommendation 4. Hysteroscopic removal of submucosal fibroids compared with other uterine-sparing treatments for women with HMB

Is hysteroscopic removal of submucosal fibroids more effective and cost-effective than other uterine-sparing treatments for the management of HMB?

Why is this important?

HMB is thought to be caused by submucosal fibroids in around 15% of women. Such fibroids are amenable to minimally invasive surgical removal ('hysteroscopic myomectomy'), avoiding

the need for surgical incision. Non-comparative data have reported improvement in HMB symptoms and the avoidance of further pharmacological or surgical treatment in 70 to 80% of women treated with hysteroscopic myomectomy.

Specific hysteroscopic surgical skills are necessary to optimise surgical success and minimise complications. However, recent advances in endoscopic technologies have made hysteroscopic myomectomy potentially safer and more feasible. A randomised controlled trial comparing this technique with long-term pharmacological therapy or more invasive surgical intervention would provide information on long-term outcomes.

Table 29: Research recommendation rationale

Research question	**Is hysteroscopic removal of submucosal fibroids more effective and cost-effective than alternative uterine sparing treatments for the management of women with heavy menstrual bleeding?**
Why this is needed	
Importance to 'patients' or the population	Heavy menstrual bleeding (HMB) is common and associated with significant morbidity and use of health care resources. Fibroids (leiomyomas) are benign tumours of uterine smooth muscle and connective tissue and are found in up to 70% of women with HMB. Submucosal fibroids (SMFs) refer to fibroids that grow into the uterine cavity and distort its shape. SMFs are thought to be more significant in the causation of HMB and are amenable to minimally invasive, hysteroscopic treatment because they are readily accessible in contrast to other locations of fibroids. Removal of SMFs, known as hysteroscopic myomectomy, has conventionally be done using electrosurgical cutting loops attached to specially designed hysteroscopes (resectoscopes). This transcervical resection of submucosal fibroids (TCRF) has shown efficacy in uncontrolled, observational series. However, the availability of this minimally invasive, uterine sparing procedure has been limited because specific hysteroscopic surgical skills are required and there is a potential for serious complications. These include uterine and visceral trauma and electrolyte disturbance. The latter complication arises from vascular absorption of instilled fluids required during hysteroscopic surgery to distend the uterine cavity and maintain visualisation. Recent technological advances in instrumentation has led to potentially safer and more feasible and thereby effective hysteroscopic myomectomy. These advances include (i) the development of bipolar electrosurgery allowing physiological fluid media to be used minimising adverse effects of fluid overload and (ii) hysteroscopic tissue removal systems (TRS) which enable simultaneous mechanical cutting and aspiration of fibroid tissue potentially reducing the risk of uterine and pelvic trauma by avoiding the need for blind uterine instrumentation and the generation of heat from the use of electrical energy. Hysteroscopic myomectomy offers a potentially highly effective, minimally invasive, uterine and fertility sparing treatment for women with HMB avoiding the need for chronic medical (including hormonal) treatment. Indeed, intrauterine medical and surgical treatments such as the levonorgesterol releasing intrauterine system (LNG-IUS) and endometrial ablation may be less effective in the presence of uterine distortion by SMFs such that invasive surgery in the form of open myomectomy or hysterectomy are often required. An RCT to evaluate the effectiveness and cost-effectiveness of hysteroscopic myomectomy is important because of the high prevalence of HMB associated with SMFs and such a trial is feasible given the enhanced safety and feasibility of hysteroscopic myomectomy with recent advances in endoscopic technology.
Relevance to NICE guidance	Submucosal fibroids are being increasingly detected during the diagnostic work up of women with HMB because of the wider availability of enhanced imaging using pelvic ultrasound scanning or outpatient hysteroscopy. Whilst

Research question	Is hysteroscopic removal of submucosal fibroids more effective and cost-effective than alternative uterine sparing treatments for the management of women with heavy menstrual bleeding?
	hysteroscopic myomectomy is an accepted treatment for women with SMFs associated with HMB in current practice, only uncontrolled observational data were identified to inform the NICE guideline limiting the strength of recommendations in the current NICE guidance. More evidence is needed about the relative effectiveness and cost-effectiveness of hysteroscopic myomectomy compared to alternative uterine sparing treatments (medical treatments and endometrial ablation) in alleviating HMB associated with SMFs.
Relevance to the NHS	HMB is common and adversely affects women's quality of life and utilises significant health service resources. HMB is caused by several different pathologies of which SMFs are one of the most common, estimated to be present in 15% of cases. Such fibroids are accessible without the need for surgical incisions and removal can be completed as a day-case procedure. Thus, if hysteroscopic myomectomy can be shown to be effective and cost-effective compared to alternative medical and surgical modalities, then investment in the relevant surgical technologies can be recommended to allow wider availability of a simple, minimally invasive, non-hormonal, one-off surgical treatment, enhancing clinical outcomes and saving health care resources.
National priorities	Women's health.
Current evidence base	The NICE HMB guideline update 2017 did not identify evidence from randomised controlled trial.
Equality	HMB affects women of all reproductive ages and races. Thus the optimising clinical outcomes through better diagnosis will benefit all women with this condition.
Feasibility	HMB associated with SMFs is common. Hysteroscopic myomectomy has become more widespread with developments in technology especially the introduction of bipolar electrosurgery and bespoke fibroid tissue removal systems. There is uncertainty regarding the effectiveness of hysteroscopic myomectomy compared with alternative uterine sparing treatments such that clinical practice varies with some clinicians not investing in the relevant endoscopic equipment, nor acquiring the necessary surgical skills and preferring to prescribe chronic medical therapies or undertake more invasive surgery such as hysterectomy. Thus, in this climate of technological advancement, a lack of clinical consensus and a highly prevalent condition, an RCT comparing hysteroscopic myomectomy with alternative uterine sparing treatments is feasible.
Other comments	None.

Table 30: Research recommendation PICO

Criterion	Explanation
Population	Women with submucosal fibroids associated with heavy menstrual bleeding
Intervention	Hysteroscopic removal of submucosal fibroids
Comparators	NICE recommended medical therapies or endometrial ablation
Outcomes	Primary outcome at 12 months: Quality of life (condition specific); longer term effects measured at two years and 5 years Secondary outcomes: Other clinical (e.g. satisfaction, generic quality of life, complications and feasibility, impact of grade of SMF (FIGO 0-2); qualitative (e.g. patient acceptability and preferences); economic (cost-utility (cost/QALY)
Study design	Randomised controlled trial
Timeframe	5 years

Research recommendation 5. Second-generation endometrial ablation for HMB associated with myometrial pathology

Are outcomes after second-generation endometrial ablation for women with HMB associated with myometrial pathology (adenomyosis and/or uterine fibroids) equivalent to those for women without myometrial pathology?

Why is this important?

With the wider availability of high-resolution transvaginal pelvic ultrasound, adenomyosis and fibroids have been recognised as 2 of the most common uterine pathologies in women presenting with HMB. Pharmacological treatments appear to be less effective in the presence of these conditions, making referral to secondary care for surgery more likely.

Second-generation endometrial ablation is a minimally invasive, uterine-sparing surgical procedure, but its effectiveness in women with adenomyosis or uterine fibroids is unclear. Thus women with these conditions may be denied second-generation endometrial ablation and undergo unnecessary invasive surgery such as hysterectomy. On the other hand, women may be subjected to ineffective that delays more effective treatment such as hysterectomy. It is therefore important to evaluate the effectiveness of second-generation endometrial ablation in women with these conditions, and a cohort controlled study is suggested as the best approach for doing this.

Table 31: Research recommendation rationale

Research question	Are outcomes of second generation endometrial ablation in women with heavy menstrual bleeding associated with myometrial pathology (adenomyosis and/or uterine fibroids) equivalent to those of women without myometrial pathology?
Why this is needed	
Importance to 'patients' or the population	Heavy menstrual bleeding (HMB) is common and associated with significant morbidity and use of health care resources. Second generation endometrial ablation (SGEA) refers to semi-automated technologies that impart energy to the endometrial lining to thermally destroy it thereby alleviating HMB. SGEA is widely employed for the treatment of HMB in women who have no desire to retain their fertility. New technologies are being introduced but the currently available devices utilise a variety of energy sources including: radiofrequency, electrosurgical, heated saline, microwave, thermal heated glycine balloons and cryotherapy. Data support their effectiveness and safety but younger patient age, large uterine size and presence of intrauterine pathology are thought to reduce their efficacy. The widespread use of high resolution pelvic ultrasound imaging as part of the diagnostic work up of HMB prior to an endometrial ablation has revealed the high prevalence myometrial pathologies; adenomyosis and uterine fibroids. Adenomyosis refers to the presence of ectopic endometrial glands and stroma within the underlying myometrium whereas uterine fibroids are benign tumours of smooth muscle and connective tissue. The estimated prevalence of adenomyosis is between 20-30% (Meredith 2009, Naftalin 2012) but may be nearer to 50% (Gonzalez 2012) in women with endometriosis. Uterine fibroids are found in over 70% of hysterectomy specimens (Cramer 1990). The importance of these diagnoses is that they are thought to be causative of much HMB and they are thought to be conditions that are more likely to be refractory to medical therapies and minimally invasive surgery such as endometrial ablation and as a consequence hysterectomy is more likely to be ultimately undertaken. However, data relating to the prognostic outcome of women with these highly prevalent, benign myometrial disorders are lacking to inform practice.

Research question	Are outcomes of second generation endometrial ablation in women with heavy menstrual bleeding associated with myometrial pathology (adenomyosis and/or uterine fibroids) equivalent to those of women without myometrial pathology?
Relevance to NICE guidance	Evidence pertaining to the effectiveness of SGEA in the treatment of the highly prevalent myometrial conditions of adenomyosis and / or uterine fibroids is lacking such that recommendations for the use of SGEA in these circumstances cannot be made with any degree of certainty.
Relevance to the NHS	Adenomyosis and uterine fibroids are highly prevalent uterine conditions causing morbidity from HMB and utilising scarce, health care resources. Optimal timely treatment will improve sufferer's quality of life and save scant health service resources. HMB associated with these conditions does not respond as well to conventional medical treatments such that surgery is more likely. One type of surgery is SGEA which is minimally invasive and associated with rapid return to normal activities of daily living in contrast to more invasive surgery such as hysterectomy. If SGEA can be shown to be effective or conversely ineffective in these women then treatment pathways can be altered and treatments tailored.
National priorities	Women's health.
Current evidence base	A recent systematic review and network meta-analysis conducted for the NICE 2017 HMB guideline update nor a review by Canadian Agency for Drugs and Technologies in Health (Chen 2016) did not identify any evidence regarding the clinical outcomes of women with HMB associated with myometrial pathology (adenomyosis and uterine fibroids) undergoing SGEA. The outcomes of SGEA have been reported for various devices in observational studies and RCTs but few have stratified outcomes by the presence of underlying myometrial pathology. Thus, there is a dearth of high quality data to direct practice for women with HMB associated with these highly prevalent uterine conditions.
Equality	HMB associated with the myometrial conditions adenomyosis and uterine fibroids affects women of all reproductive ages and races. Thus the optimising clinical outcomes through better treatment will benefit all women with these conditions.
Feasibility	HMB associated with the myometrial conditions adenomyosis and uterine fibroids is common. Diagnosis of these conditions is easily made using a combination of clinical examination and subsequent pelvic ultrasound as part of routine diagnostic work up of women with HMB. In the absence of data pertaining to treatment outcomes in women with fibroids or adenomyosis and HMB, clinical practice varies. Thus, in this climate of uncertainty of the role of a common, simple surgical treatment (SGEA) in a highly prevalent condition (HMB associated with fibroids or adenomyosis), recruitment to a large observational controlled cohort study appears to be highly feasible.
Other comments	References: • Chen, S., Pitre, E., Kaunelis, D., Singh, S., Uterine-Preserving Interventions for the Management of Symptomatic Uterine Fibroids: A Systematic Review of Clinical and Cost-Effectiveness, Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 (Accessed 30 May 2017 at https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0086153/pdf/PubMedHealth_PMH0086153.pdf). • Cramer, S. F., Patel, A., The frequency of uterine leiomyomas, American Journal of Clinical Pathology, 94, 435-8, 1990 • Gonzalez, M., de Mattos, L., Gonçalves, M., Blasbalg, R., Dias, J., Podgaec, S., et al, Patients with adenomyosis are more likely to have deep endometriosis, Gynecol Surgery, 2012 • Meredith, S. M., Sanchez-Ramos, L., Kaunitz, A. M., Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic

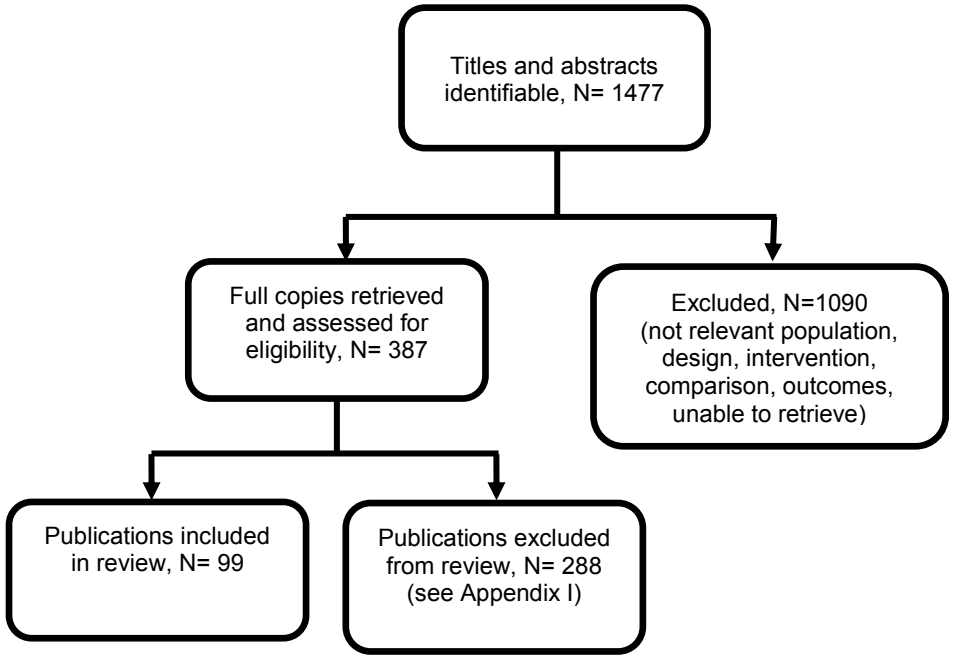
Research question	Are outcomes of second generation endometrial ablation in women with heavy menstrual bleeding associated with myometrial pathology (adenomyosis and/or uterine fibroids) equivalent to those of women without myometrial pathology?
	review and metaanalysis. American Journal of Obstetrics and Gynecology, 201, 107.e1–107.e6, 2009 • Naftalin, J., Hoo, W., Pateman, K., Mavrelos, D., Holland, T., Jurkovic, D., How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. Human Reproduction, 27, 3432-9, 2012

Table 32: Research recommendation PICO

Criterion	Explanation
Population	Women with heavy menstrual bleeding and myometrial pathology (adenomyosis and/or fibroids 3 cm or more in diameter not distorting the uterine cavity)
Intervention	Second generation endometrial ablation
Comparators	Women with heavy menstrual bleeding with no identified pathology or fibroids less than 3 cm in diameter not distorting the uterine cavity.
Outcomes	• Primary outcome at 12 months: Quality of life (condition-specific); longer term effects measured at two years and 5 years. • Secondary outcomes: Other clinical (e.g. need for further surgical intervention including hysterectomy rates; satisfaction, pelvic pain; generic quality of life, complications and feasibility of testing) qualitative (e.g. patient acceptability and preferences)
Study design	Cohort controlled study
Timeframe	5 years

Appendix D – Clinical evidence study selection

Figure 12: Flow diagram of clinical article selection for management of heavy menstrual bleeding review



Appendix E – Literature search strategies

Cochrane Library – Wiley

ID	Search
#1	MeSH descriptor: [Value of Life] explode all trees
#2	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#3	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#4	health economic* or cost* or (quality near life)
#5	MeSH descriptor: [Economics] explode all trees
#6	MeSH descriptor: [Economics, Hospital] explode all trees
#7	MeSH descriptor: [Economics, Medical] explode all trees
#8	MeSH descriptor: [Economics, Nursing] explode all trees
#9	MeSH descriptor: [Economics, Pharmaceutical] explode all trees
#10	MeSH descriptor: [Fees and Charges] explode all trees
#11	MeSH descriptor: [Budgets] explode all trees
#12	budget* or economic* or pharmaco?economic* or price* or pricing or financ* or fee or fees or (value near mone*) or (value near life)
#13	cost* near (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15	MeSH descriptor: [Menorrhagia] explode all trees
#16	Menorrhag* or hypermenorrh* or HMB or iron deficient anaemia or menometrorrhag* or metromenorrhag*
#17	menstru* near (excessive or heavy or abnormal or disorder)
#18	menstru* near (bleed* or blood loss)
#19	heavy near (period* or menses)
#20	dysfunction* near (uterine or uterus) near (bleed* or blood*)
#21	#15 or #16 or #17 or #18 or #19 or #20
#22	#14 and #21

OVID MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (last searched on 23/11/2016)

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	pragmatic clinical trial.pt.
4	randomi#ed.ab.
5	placebo.ab.
6	drug therapy.fs.
7	randomly.ab.
8	trial.ab.
9	groups.ab.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	Clinical Trials as topic.sh.

#	Searches
12	trial.ti.
13	or/1-5,7,11-12
14	Meta-Analysis/
15	Meta-Analysis as Topic/
16	(meta analy* or metanaly* or metaanaly*).ti,ab.
17	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
18	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
19	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
20	(search* adj4 literature).ab.
21	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
22	cochrane.jw.
23	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	13 or 23
25	exp Menorrhagia/
26	Menorrhagia.ti,ab.
27	hypermenorrhoea.ti,ab.
28	(menstrua* adj5 (excessive or heavy or abnormal or disorder)).ti,ab.
29	((uterine or dysfunctional) adj bleeding).ti,ab.
30	iron deficient anaemia.ti,ab.
31	or/25-30
32	exp Anti-Inflammatory Agents, Non-Steroidal/
33	NSAID*.ti,ab.
34	((Non?steroidal or Non steroidal) adj (anti inflammatory or anti?inflammatory)).ti,ab.
35	exp Antifibrinolytic Agents/
36	exp Progestins/
37	(progestin* or danazol or Mirena).ti,ab.
38	Progestogen*.ti,ab.
39	exp Hemostatics/
40	exp Flurbiprofen/
41	exp Contraceptives, Oral, Combined/ or exp Contraceptives, Oral/
42	exp Gonadotropin-Releasing Hormone/
43	GnRH*.ti,ab.
44	(Gonadorelin or gonadotrophin).ti,ab.
45	exp Drug Therapy/
46	exp Intrauterine Devices, Medicated/
47	exp Levonorgestrel/
48	(Levonorgestrel-releasing intrauterine system or LNG-IUS).ti,ab.
49	exp Prostaglandins/ or exp Cyclooxygenase Inhibitors/
50	(prostaglandin* or cyclooxygenase).ti,ab.
51	exp Tranexamic Acid/
52	exp Antifibrinolytic Agents/
53	antifibrinolytic.ti,ab.
54	exp Naproxen/

#	Searches
55	exp Ibuprofen/
56	exp Aspirin/
57	exp Mefenamic Acid/
58	exp Medroxyprogesterone Acetate/
59	exp Norethindrone/
60	exp Desogestrel/
61	Estradiol Valerate.ti,ab.
62	Dienogest.ti,ab.
63	exp Ethinyl Estradiol/
64	Leuprolide acetate.ti,ab.
65	Decapeptyl.ti,ab.
66	exp Goserelin/
67	Ulipristal acetate.ti,ab.
68	exp Ethamsylate/
69	exp Indomethacin/
70	exp Diclofenac/
71	(first?line or second?line or (first line or second line)).ti,ab.
72	or/32-71
73	exp Gynecologic Surgical Procedures/
74	exp Hysterectomy/
75	exp Laparoscopy/
76	exp Endometrial Ablation Techniques/
77	exp Hysteroscopy/
78	exp Catheter Ablation/
79	laser ablation*.ti,ab.
80	hyperthermia.ti,ab.
81	thermotherapy.ti,ab.
82	photodynamic.ti,ab.
83	radiofrequency.ti,ab.
84	saline irrigation*.ti,ab.
85	catheter ablation*.ti,ab.
86	vaginoscopy.ti,ab.
87	exp Uterine Myomectomy/
88	exp Uterine Artery Embolization/
89	exp High-Intensity Focused Ultrasound Ablation/
90	exp Electrosurgery/
91	exp Cryosurgery/
92	(first?line or second?line or (first line or second line)).ti,ab.
93	exp Laser Therapy/
94	(hysterectom* adj1 (laparoscop* or vaginal or robotic or open)).ti,ab.
95	(Endometri* adj3 (resect* or vapori?at* or ablat* or cryoablat*)).ti,ab.
96	(thermoablat* or Thermal Balloon).ti,ab.
97	transcervical resect*.ti,ab.

#	Searches
98	(rollerball or roller ball).ti,ab.
99	saline infusion.ti,ab.
100	catheter ablat*.ti,ab.
101	exp Ultrasonography/
102	(sonohysterography or ultraso*).ti,ab.
103	cavaterm.ti,ab.
104	ThermaChoice.ti,ab.
105	Menotreat.ti,ab.
106	Thermablate.ti,ab.
107	hysteroscop*.ti,ab.
108	(Uterine artery emboli?ation* or myomectom*).ti,ab.
109	transcutaneous ultraso*.ti,ab.
110	Electrosurg*.ti,ab.
111	(surgical or surger* or operat* or resect* or excis* or ablat*).ti,ab.
112	Ablation.ti,ab.
113	or/73-112
114	72 or 113
115	31 and 114
116	24 and 115
117	limit 116 to (english language and yr="2007 -Current")
118	letter/
119	editorial/
120	news/
121	exp historical article/
122	Anecdotes as Topic/
123	comment/
124	case report/
125	(letter or comment*).ti.
126	118 or 119 or 120 or 121 or 122 or 123 or 124 or 125
127	randomized controlled trial/ or random*.ti,ab.
128	126 not 127
129	animals/ not humans/
130	exp Animals, Laboratory/
131	exp Animal Experimentation/
132	exp Models, Animal/
133	exp Rodentia/
134	(rat or rats or mouse or mice).ti.
135	128 or 129 or 130 or 131 or 132 or 133 or 134
136	117 not 135

Embase 1980 to 2016 Week 48 (last searched on 23/11/2016)

#	Searches
1	random*.ti,ab.
2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	systematic review/
12	meta-analysis/
13	(meta analy* or metanaly* or metaanaly*).ti,ab.
14	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
15	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
16	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
17	(search* adj4 literature).ab.
18	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
19	((pool* or combined) adj2 (data or trials or studies or results)).ab.
20	cochrane.jw.
21	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	10 or 21
23	exp menorrhagia/
24	Menorrhagia.ti,ab.
25	hypermenorrhoea.ti,ab.
26	(menstrua* adj5 (excessive or heavy or abnormal or disorder)).ti,ab.
27	((uterine or dysfunctional) adj bleeding).ti,ab.
28	exp uterus bleeding/dt, su, th [Drug Therapy, Surgery, Therapy]
29	iron deficient anaemia.ti,ab.
30	or/23-29
31	NSAID*.ti,ab.
32	((Non?steroidal or Non steroidal) adj (anti inflammatory or anti?inflammatory)).ti,ab.
33	(progestin* or danazol or Mirena).ti,ab.
34	Progestogen*.ti,ab.
35	(Gonadorelin or gonadotrophin).ti,ab.
36	exp Drug Therapy/
37	(Levonorgestrel-releasing intrauterine system or LNG-IUS).ti,ab.
38	(prostaglandin* or cyclooxygenase).ti,ab.
39	exp Tranexamic Acid/
40	antifibrinolytic.ti,ab.
41	exp Naproxen/
42	exp Ibuprofen/
43	exp Mefenamic Acid/

#	Searches
44	exp Medroxyprogesterone Acetate/
45	exp Desogestrel/
46	exp Goserelin/
47	(first?line or second?line or (first line or second line)).ti,ab.
48	exp nonsteroid antiinflammatory agent/
49	exp antifibrinolytic agent/
50	exp gestagen/
51	exp hemostatic agent/
52	exp danazol/
53	exp flurbiprofen/
54	exp oral contraceptive agent/
55	exp gonadorelin/
56	(GnRH* or Gonadotropin-Releasing Hormone*).ti,ab.
57	exp gonadotropin/
58	exp levonorgestrel releasing intrauterine system/ or exp levonorgestrel/
59	exp prostaglandin/
60	exp prostaglandin synthase inhibitor/
61	exp antifibrinolytic agent/
62	exp acetylsalicylic acid/
63	Aspirin.ti,ab.
64	exp norethisterone/
65	Norethindrone.ti,ab.
66	exp estradiol valerate/
67	exp dienogest/
68	exp ethinylestradiol/
69	Ethinyl Estradiol.ti,ab.
70	exp leuprorelin/
71	Leuprolide acetate.ti,ab.
72	exp triptorelin/
73	Decapeptyl.ti,ab.
74	exp ulipristal/
75	Ulipristal acetate.ti,ab.
76	exp etamsylate/
77	Ethamsylate.ti,ab.
78	exp indometacin/
79	Indomethacin.ti,ab.
80	exp diclofenac/
81	or/31-80
82	laser ablation*.ti,ab.
83	hyperthermia.ti,ab.
84	thermotherapy.ti,ab.
85	photodynamic.ti,ab.
86	radiofrequency.ti,ab.

#	Searches
87	saline irrigation*.ti,ab.
88	catheter ablation*.ti,ab.
89	vaginoscopy.ti,ab.
90	exp Uterine Artery Embolization/
91	(first?line or second?line or (first line or second line)).ti,ab.
92	(hysterectom* adj1 (laparoscop* or vaginal or robotic or open)).ti,ab.
93	(Endometri* adj3 (resect* or vapori?at* or ablat* or cryoablat*)).ti,ab.
94	(thermoablat* or Thermal Balloon).ti,ab.
95	transcervical resect*.ti,ab.
96	(rollerball or roller ball).ti,ab.
97	saline infusion.ti,ab.
98	catheter ablat*.ti,ab.
99	(sonohysterography or ultraso*).ti,ab.
100	cavaterm.ti,ab.
101	ThermaChoice.ti,ab.
102	Menotreat.ti,ab.
103	Thermablate.ti,ab.
104	hysteroscop*.ti,ab.
105	(Uterine artery emboli?ation* or myomectom*).ti,ab.
106	transcutaneous ultraso*.ti,ab.
107	Electrosurg*.ti,ab.
108	(surgical or surger* or operat* or resect* or excis* or ablat*).ti,ab.
109	exp gynecologic surgery/
110	exp hysterectomy/ or exp vaginal hysterectomy/
111	exp laparoscopy/
112	exp endometrium ablation/
113	exp hysteroscopy/
114	exp catheter ablation/
115	exp laser surgery/
116	exp hyperthermia/
117	exp thermotherapy/
118	exp myomectomy/
119	exp high intensity focused ultrasound/
120	exp electrosurgery/
121	exp cryosurgery/
122	exp low level laser therapy/
123	exp echography/
124	exp gynecologic thermal ablation device/
125	exp ablation therapy/
126	or/82-125
127	81 or 126
128	30 and 127
129	22 and 128

#	Searches
130	limit 129 to (english language and yr="2007 -Current")
131	letter.pt. or letter/
132	note.pt.
133	editorial.pt.
134	case report/ or case study/
135	(letter or comment*).ti.
136	131 or 132 or 133 or 134 or 135
137	randomized controlled trial/ or random*.ti,ab.
138	136 not 137
139	animal/ not human/
140	nonhuman/
141	exp Animal Experiment/
142	exp Experimental Animal/
143	animal model/
144	exp Rodent/
145	(rat or rats or mouse or mice).ti.
146	138 or 139 or 140 or 141 or 142 or 143 or 144 or 145
147	130 not 146

Appendix F – Clinical evidence tables

The clinical evidence tables are presented in a separate document.

Appendix G – GRADE tables

1. Women with suspected or diagnosed fibroids

Table 33: Clinical evidence profile: Comparison 1: Ulipristal acetate versus placebo in women with suspected or diagnosed fibroids

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
SF-36: Health-related quality of life change from baseline after 3 cycles of treatment - Role physical score (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 5.7 higher (4.43 to 6.97 higher)	HIGH	CRITICAL
SF-36: Health-related quality of life change from baseline after 3 cycles of treatment - Role mental Component (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 6.3 higher (4.82 to 7.78 higher)	HIGH	CRITICAL
UFS-QOL: Symptom severity score change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 24.1 lower (28.12 to 20.08 lower)	HIGH	CRITICAL
UFS-QOL: Overall HRQL score change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 19.2 higher (15.74 to 22.66 higher)	HIGH	CRITICAL
UFS-QOL: Concern subscore change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 34 higher (29.73 to 38.27 higher)	HIGH	CRITICAL
UFS-QOL: Energy/mood subscore change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 15.5 higher (11.92 to	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate	Placebo	Relative (95% CI)	Absolute		
		risk of bias								19.08 higher)		
UFS-QOL: Self-conscious subscore change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	26	12	-	MD 3.2 higher (1.41 lower to 7.81 higher)	MODERATE	CRITICAL
UFS-QOL: Control subscore change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 11.2 higher (7.01 to 15.39 higher)	HIGH	CRITICAL
UFS-QOL: Sexual function subscore change from baseline after 3 cycles (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	26	12	-	MD 7 higher (1.75 to 12.25 higher)	MODERATE	CRITICAL
UFS-QOL: Activities subscore change from baseline after 3 cycles of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	12	-	MD 27.8 higher (23.49 to 32.11 higher)	HIGH	CRITICAL

CI: confidence interval; HRQL: health-related quality of life; MD: mean difference; MID: minimally important difference; SF-36: 36-Item Short Form Survey; UFS-QOL: Uterine Fibroid Symptom and Quality of Life questionnaire
1 The quality of the evidence was downgraded by 1 because the 95% CI crosses 1 default MID.

Table 34: Clinical evidence profile: Comparison 2.1: LNG-IUS versus norethisterone in women with suspected or diagnosed fibroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LNG-IUS**	**Norethisterone acetate**	**Relative (95% CI)**	**Absolute**		
PBAC score change from baseline after 6 months of treatment (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	30	30	-	MD 195.7 lower (237.47 to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Norethisterone acetate	Relative (95% CI)	Absolute		
										153.93 lower)		

AH: alkaline haematin; CI: confidence interval; HMB: heavy menstrual bleeding; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; PBAC: Pictorial Blood Loss Assessment Chart
1 The quality of evidence was downgraded by 2 because blinding was not possible, number of participants with outcome data was not reported, unclear if allocation concealment was done, and poor reporting of methodology.
2 The quality of evidence was downgraded by 1 because the proportion of women with HMB was not reported.

Table 35: Clinical evidence profile: Comparison 2.2: LNG-IUS versus COC in women with fibroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	COC	Relative (95% CI)	Absolute		
PBAC score change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious2	none	29	29	-	MD 77.9 lower (114.16 to 41.64 lower)	VERY LOW	IMPORTANT
Menstrual blood loss in ml (AH method) change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 210.8 lower (249.92 to 171.68 lower)	MODERATE	IMPORTANT
HRQoL-4: Self-rated health good or excellent at 12 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/29 (31%)	7/29 (24.1%)	RR 1.29 (0.55 to 2.99)	70 more per 1000 (from 109 fewer to 480 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	COC	Relative (95% CI)	Absolute		
HRQoL-4: No. of days in the previous 30 days feeling physically unwell, change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	29	-	MD 2.7 lower (3.86 to 1.54 lower)	VERY LOW	CRITICAL
HRQoL-4: No. of days in the previous 30 days feeling mentally unwell, change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 2.6 lower (3.67 to 1.53 lower)	LOW	CRITICAL
HRQoL-4: No. of lost days in the previous 30 days, change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 4.9 lower (6.08 to 3.72 lower)	LOW	CRITICAL

AH: alkaline haematin; CI: confidence interval; COC: combined oral contraceptives; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; MID: minimally important difference; PBAC: Pictorial Blood Loss Assessment Chart
1 The quality of evidence was downgraded by 2 because blinding was not possible and because there were substantial losses to follow-up.
2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
3 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.

.

Table 36: Clinical evidence profile: Comparison 3.1: UAE versus hysterectomy in women with suspected or diagnosed fibroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute		
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 6 weeks (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.013 lower, p=0.953	LOW	CRITICAL
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 6 months (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute		
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.06 lower, p=0.976	LOW	CRITICAL
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 12 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 1.34 lower, p=0.505	LOW	CRITICAL
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 18 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.08 lower, p=0.969	LOW	CRITICAL
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 1.46 lower, p=0.496	LOW	CRITICAL
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.56 lower, p=0.806	VERY LOW	CRITICAL
SF-36: Health-related quality of life - Mental Component Summary score change from baseline - At 10 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.13 lower, p=0.947	VERY LOW	CRITICAL
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 6 weeks (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 9.05 higher, p0.0001	LOW	CRITICAL
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 6 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 2.16 lower, p=0.192	LOW	CRITICAL
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 12 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 2.81 lower, p=0.104	LOW	CRITICAL
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 18 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 2.51 lower, p=0.131	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.1 higher, p=0.948	LOW	CRITICAL
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 1.27 higher, p=0.468	VERY LOW	CRITICAL
SF-36: Health-related quality of life - Physical Component Summary score change from baseline - At 10 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	not calculable[5]	none	81	75	-	MD 0.27 higher, p=0.900	VERY LOW	CRITICAL
Satisfaction with treatment (measured by asking women whether they would undergo the same treatment again) - Up to 24 months												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120/144 (83.3%)	109/122 (89.3%)	RR 0.94 (0.86 to 1.04)	54 fewer per 1000 (from 125 fewer to 36 more)	LOW	CRITICAL
Satisfaction with treatment (measured by asking women whether they would undergo the same treatment again)- At 5 years												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/81 (84%)	66/75 (88%)	RR 0.95 (0.84 to 1.08)	44 fewer per 1000 (from 141 fewer to 70 more)	LOW	CRITICAL
Satisfaction with treatment (measured by asking women whether they would undergo the same treatment again) - At 10 years												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	61/81 (75.3%)	63/75 (84%)	RR 0.9 (0.76 to 1.05)	84 fewer per 1000 (from 202 fewer to 42 more)	VERY LOW	CRITICAL
Length of hospital stay in days – Setting: Netherlands (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81	75	-	MD 3.10 lower (3.64 to 2.56 lower)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute		
Length of hospital stay in days – Setting: Finland (Better indicated by lower values)												
1	randomised trials	serious[4,6]	no serious inconsistency	serious indirectness7	no serious imprecision	none	27	26	-	MD 2.20 lower (2.80 to 1.60 lower)	LOW	IMPORTANT
Length of hospital stay in days – Setting: Spain (Better indicated by lower values)												
1	randomised trials	serious[4,8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	19	-	MD 4.14 lower (5.38 to 2.90 lower)	MODERATE	IMPORTANT
Adverse event: Blood transfusion												
2	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/121 (0%)	16/95 (16.8%)	RR 0.04 (0.01 to 0.32)	162 fewer per 1000 (from 115 fewer to 167 fewer)	MODERATE	IMPORTANT
Adverse event: Infection - Urinary tract infection within 30 days post-procedure												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	2/40 (5%)	2/20 (10%)	RR 0.5 (0.08 to 3.29)	50 fewer per 1000 (from 92 fewer to 229 more)	VERY LOW	CRITICAL
Adverse event: Infection - Urinary tract infection during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	0/81 (0%)	3/75 (4%)	RR 0.13 (0.01 to 2.52)	35 fewer per 1000 (from 40 fewer to 61 more)	LOW	CRITICAL
Adverse event: Infection - Urinary tract infection up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	5/81 (6.2%)	2/75 (2.7%)	RR 2.31 (0.46 to 11.57)	35 more per 1000 (from 14 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute		
										282 more)		
Adverse event: Infection - Vulvovaginitis within 30 days post-procedure												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/40 (2.5%)	0/20 (0%)	RR 1.54 (0.07 to 36.11)	-	VERY LOW	CRITICAL
Adverse event: Infection - Endometritis during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	N/A	-	-	HIGH	CRITICAL
Adverse event: Infection - Endometritis up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	2/81 (2.5%)	N/A	-	-	HIGH	CRITICAL
Adverse event: Infection - Pneumonia during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Infection - Pneumonia up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	1/81 (1.2%)	0/75 (0%)	RR 2.78 (0.12 to 67.22)	-	LOW	CRITICAL
Adverse event: Infection - Surgical wound abscess within 30 days post-procedure												
1	randomised trials	serious8	no serious inconsistency	no serious indirectness	very serious[10]	none	0/40 (0%)	3/20 (15%)	RR 0.07 (0 to 1.35)	140 fewer per 1000 (from 150 fewer to 53 more)	VERY LOW	CRITICAL
Adverse event: Infection - Wound abscess during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	1/81 (1.2%)	0/75 (0%)	RR 2.78 (0.12 to 67.22)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
Adverse event: Infection - Wound abscess up to 6 weeks post-procedure												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	0/81 (0%)	1/75 (1.3%)	RR 0.31 (0.01 to 7.47)	9 fewer per 1000 (from 13 fewer to 86 more)	LOW	CRITICAL
Adverse event: Infection - Intra-abdominal abscess within 30 days post-procedure												
1	randomised trials	serious8	no serious inconsistency	no serious indirectness	very serious[10]	none	0/40 (0%)	1/20 (5%)	RR 0.17 (0.01 to 4.01)	42 fewer per 1000 (from 49 fewer to 151 more)	VERY LOW	CRITICAL
Adverse event: Infection - Intra-abdominal infection during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Infection - Intra-abdominal infection up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Infection - Sepsis during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Infection - Sepsis up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	1/81 (1.2%)	0/75 (0%)	RR 2.78 (0.12 to 67.22)	-	LOW	CRITICAL
Adverse event: Venous thrombosis - Deep venous thrombosis within 30 days post-procedure												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/40 (2.5%)	1/20 (5%)	RR 0.5 (0.03 to 7.59)	25 fewer per 1000 (from 49 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute		
										330 more)		
Adverse event: Venous thrombosis - Thrombosis during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Venous thrombosis - Thrombosis up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Venous thrombosis - Pulmonary embolism during hospital stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	1/81 (1.2%)	1/75 (1.3%)	RR 0.93 (0.06 to 14.54)	1 fewer per 1000 (from 13 fewer to 181 more)	LOW	CRITICAL
Adverse event: Venous thrombosis - Pulmonary embolism up to 6 weeks post-discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	CRITICAL
Adverse event: Unscheduled re-admission rate within 4-6 weeks												
2	randomised trials	serious9	no serious inconsistency	no serious indirectness	serious[3]	none	41/121 (33.9%)	20/96 (20.8%)	RR 1.87 (1.2 to 2.9)	181 more per 1000 (from 42 more to 396 more)	LOW	IMPORTANT
Adverse event: Urinary stress incontinence at 2 years												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious1[0]	none	7/27 (25.9%)	13/30 (43.3%)	RR 0.6 (0.28 to 1.28)	173 fewer per 1000 (from 312 fewer to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Hysterectomy	Relative (95% CI)	Absolute		
										121 more)		
Adverse event: Death												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness7	not calculable[11]	none	0/81 (0%)	0/75 (0%)	-	-	HIGH	IMPORTANT

CI: confidence interval; HMB: heavy menstrual bleeding; MD: mean difference; MID: minimally important difference; N/A: not applicable; RR: relative risk; SF-36: 36-Item Short Form Survey; UAE: uterine artery embolisation
1 The quality of evidence was downgraded by 2 because blinding was not possible in any of the 3 studies, in one study only 75% of the women had HMB, one study did not report randomisation and allocation concealment clearly, one study used per protocol analysis, and one study did not carry out power calculations.
2 The quality of evidence was downgraded by 2 because blinding was not possible and there were substantial losses to follow-up.
3 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
4 The quality of evidence was downgraded by 1 because blinding was not possible.
5 The quality of evidence was downgraded by 1 because imprecision was not calculable because standard deviation in control arm was not reported.
6 The quality of evidence was downgraded by 1 because the study did not report clearly on randomisation and allocation concealment, and power calculations were not carried out.
7 The quality of evidence was downgraded by 1 because only 75% of the participants had HMB.
8 The quality of evidence was downgraded by 1 because the study used per protocol analysis.9 The quality of evidence was downgraded by 1 because blinding was not possible on either study and one study used per protocol analysis.
10 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.
11 Imprecision was not calculable because there were either zero events in both intervention groups or the outcome was not applicable to other intervention group.

Table 37: Clinical evidence profile: Comparison 3.2: UAE versus myomectomy in women with suspected or diagnosed fibroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Myomectomy	Relative (95% CI)	Absolute		
Satisfaction with treatment (measured by asking the women if they obtained symptom relief) up to 24 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/52 (88.5%)	51/58 (87.9%)	RR 1.01 (0.88 to 1.15)	9 more per 1000 (from 106 fewer to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Myomectomy	Relative (95% CI)	Absolute		
										132 more)		
UFS-QOL: Symptom severity change score from baseline at 1 year (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 7.20 higher (2.14 lower to 16.54 higher)	VERY LOW	CRITICAL
UFS-QOL: Total HRQoL change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 7.6 lower (17.55 lower to 2.35 higher)	VERY LOW	CRITICAL
UFS-QOL: Concern subscale change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 4.9 lower (16.63 lower to 6.83 higher)	VERY LOW	CRITICAL
UFS-QOL: Activities subscale change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 7.20 lower (18.34 lower to 3.94 higher)	VERY LOW	CRITICAL
UFS-QOL: Mood subscale change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 3.20 lower (13.81 lower to 7.41 higher)	VERY LOW	CRITICAL
UFS-QOL: Control subscale change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 7.40 lower	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Myomectomy	Relative (95% CI)	Absolute	Quality	Importance
										(18.73 lower to 3.93 higher)		
UFS-QOL: Self control subscale change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 5.30 lower (16.30 lower to 5.70 higher)	VERY LOW	CRITICAL
UFS-QOL: Sex function subscale change score from baseline at 1 year (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	59	-	MD 13.20 lower (27.98 lower to 1.58 higher)	VERY LOW	CRITICAL
Length of hospital stay in days – Setting: UK (Better indicated by lower values)												
1	randomised trials	Serious[1, 4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	59	-	MD 4.00 lower (4.97 to 3.03 lower)	MODERATE	IMPORTANT
Length of hospital stay in days – Setting: Czech Republic (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	58	63	-	MD 1.10 lower (1.64 to 0.56 lower)	LOW	IMPORTANT
Adverse event: Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	0/58 (0%)	2/63 (3.2%)	RR 0.22 (0.01 to 4.43)	25 fewer per 1000 (from 31 fewer to 109 more)	LOW	IMPORTANT
Adverse event: Infection – Pneumonia within 1 year post-procedure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**UAE**	**Myomectomy**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/63 (0%)	1/59 (1.7%)	RR 0.31 (0.01 to 7.52)	12 fewer per 1000 (from 17 fewer to 111 more)	VERY LOW	CRITICAL
Adverse event: Infection – Sepsis within 1 year post-procedure												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/63 (0%)	1/59 (1.7%)	RR 0.31 (0.01 to 7.52)	12 fewer per 1000 (from 17 fewer to 111 more)	VERY LOW	CRITICAL
Adverse event: Infection - Urinary tract infection within 1 year post-procedure												
1	randomised trials	serious4	no serious inconsistency	no serious indirectness	serious[3]	none	0/63 (0%)	8/59 (13.6%)	RR 0.06 (0 to 0.93)	127 fewer per 1000 (from 9 fewer to 136 fewer)	LOW	CRITICAL
Adverse event: Infection - Need for antibiotics within 30 days post-procedure												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	8/58 (13.8%)	6/63 (9.5%)	RR 1.45 (0.53 to 3.92)	43 more per 1000 (from 45 fewer to 278 more)	LOW	CRITICAL
Adverse event: Pulmonary embolus within 1 year post-procedure												
1	randomised trials	serious4	no serious inconsistency	no serious indirectness	very serious5	none	0/63 (0%)	1/59 (1.7%)	RR 0.31 (0.01 to 7.52)	12 fewer per 1000 (from 17 fewer to 111 more)	VERY LOW	CRITICAL
Adverse event: Unscheduled readmission rate within 4-6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very seriou[s5]	none	2/58 (3.4%)	1/63 (1.6%)	RR 2.17 (0.2 to 23.33)	19 more per 1000 (from 13 fewer to	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE	Myomectomy	Relative (95% CI)	Absolute	Quality	Importance
										354 more)		

CI: confidence interval; MD: mean difference; MID: minimally important difference; RR: relative risk; UAE: uterine artery embolisation; UFS-QOL: Uterine Fibroid Symptom and Quality of Life questionnaire
1 The quality of evidence was downgraded by 1 because blinding was not possible.
2 The quality of evidence was downgraded by 2 because there was significant difference in the health-related quality of life scores at baseline between the intervention groups, blinding was not possible, there was substantial losses to follow-up.
3 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
4 The quality of evidence was downgraded by 1 because there were substantial losses to follow-up.
5 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.

Table 38: Clinical evidence profile: Comparison 3.3: UAE versus hysterectomy or myomectomy in women with suspected or diagnosed fibroids

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE versus hysterectomy or myomectomy	Control	Relative (95% CI)	Absolute	Quality	Importance
Satisfaction with treatment up to 12 months												
2	randomised trials	serious[1]	serious[2]	serious[3]	no serious imprecision	none	136/157 (86.6%)	87/107 (81.3%)	RR 1.04 (0.94 to 1.15)	33 more per 1000 (from 49 fewer to 122 more)	VERY LOW	CRITICAL
Satisfaction with treatment at 5 years												
1	randomised trials	serious[4]	no serious inconsistency	very serious[3]	no serious imprecision	none	83/93 (89.2%)	40/46 (87%)	RR 1.03 (0.9 to 1.17)	26 more per 1000 (from 87	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE versus hysterectomy or myomectomy	Control	Relative (95% CI)	Absolute		
										fewer to 148 more)		
SF-36: Quality of life score at 6 months - Physical function (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 8.3 higher (6.26 to 10.34 higher)	MODERATE	CRITICAL
SF-36: Quality of life score at 6 months - Social function (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	62	62	-	MD 8 higher (4.23 to 11.77 higher)	LOW	CRITICAL
SF-36: Quality of life score at 6 months - Mental health (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 14 higher (11.3 to 16.7 higher)	MODERATE	CRITICAL
SF-36: Quality of life score at 6 months - Emotional role (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 11.1 higher (8.72 to 13.48 higher)	MODERATE	CRITICAL
SF-36: Quality of life score at 6 months - Vitality (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 10.9 higher (8.04 to 13.76 higher)	MODERATE	CRITICAL
SF:36: Quality of life score at 1 year - Physical function (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	106	51	-	MD 3 higher (3.1 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE versus hysterectomy or myomectomy	Control	Relative (95% CI)	Absolute	Quality	Importance
										9.1 higher)		
SF:36: Quality of life score at 1 year - Social function (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	serious5	none	106	51	-	MD 3 lower (11.37 lower to 5.37 higher)	VERY LOW	CRITICAL
SF:36: Quality of life score at 1 year - Mental health (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	106	51	-	MD 0 higher (6.61 lower to 6.61 higher)	LOW	CRITICAL
SF:36: Quality of life score at 1 year - Emotional role (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	serious5	none	106	51	-	MD 6 lower (16.59 lower to 4.59 higher)	VERY LOW	CRITICAL
SF:36: Quality of life score at 1 year - Vitality (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	serious5	none	106	51	-	MD 5 lower (12.24 lower to 2.24 higher)	VERY LOW	CRITICAL
SF-36: Quality of life score at 5 years - Physical function (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	serious5	none	96	48	-	MD 3 higher (4.69 lower to 10.69 higher)	VERY LOW	CRITICAL
SF-36: Quality of life score at 5 years - Social function (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	96	48	-	MD 1 higher	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UAE versus hysterectomy or myomectomy	Control	Relative (95% CI)	Absolute	Quality	Importance
										(8.41 lower to 10.41 higher)		
SF-36: Quality of life score at 5 years - Mental health (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	96	48	-	MD 2 higher (5.59 lower to 9.59 higher)	LOW	CRITICAL
SF-36: Quality of life score at 5 years - Emotional role (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	96	48	-	MD 3 lower (14.9 lower to 8.9 higher)	LOW	CRITICAL
SF-36: Quality of life score at 5 years - Vitality (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	96	48	-	MD 0 higher (8.33 lower to 8.33 higher)	LOW	CRITICAL
Length of hospital stay in days (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	162	111	-	MD 3.14 lower (3.66 to 2.63 lower)	LOW	IMPORTANT
Adverse event: wound infection (during hospital stay)												
1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	-	2/51 (3.9%)	-	39 fewer per 1000 (from 39 fewer to 39 fewer)	LOW	IMPORTANT

CI: confidence interval; HMB: heavy menstrual bleeding; MD: mean difference; MID: minimally important difference; RR: relative risk; SF-36: 36-Item Short Form Survey; UAE: uterine artery embolisation
1 The quality of evidence was downgraded by 1 because blinding was not possible and because power calculation were not carried out.
2 The quality of evidence was downgraded by 1 because of a high level of heterogeneity (I squared statistic 76%)
3 The quality of evidence was downgraded by 1 because the proportion of women with HMB was not reported
4 The quality of evidence was downgraded by 1 because blinding was not possible
5 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.

Table 39: Clinical evidence profile: Comparison 3.4: TBA versus hysterectomy in women with suspected or diagnosed fibroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TBA	Hysterectomy	Relative (95% CI)	Absolute		
UFS-QOL: Symptom severity score at 6 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	not calculable[2]	none	20	20	-	MD 7.18 higher (1.29 to 13.07 higher)	LOW	CRITICAL
UFS-QOL: HRQoL score (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 5.87 lower (10.29 to 1.45 lower)	LOW	CRITICAL
Length of hospital stay in hours (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	not calculable[2]	none	20	20	-	MD 50.95 lower (46.2 to 55.7 lower)	LOW	IMPORTANT
Adverse event: Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	12/20 (60%)	RR 0.04 (0 to 0.63)	576 fewer per 1000 (from 222 fewer to 600 fewer)	HIGH	IMPORTANT

CI: confidence interval; HRQoL: Health-related quality of life; MD: mean difference; MID: minimally important difference; RR: relative risk; TBA: thermal balloon ablation; UFS-QOL: Uterine Fibroid Symptom and Quality of Life questionnaire
1 The quality of evidence was downgraded by 1 because blinding was not possible and it was unclear if allocation concealment was done.
2 The quality of evidence was downgraded by 1 because imprecision was not calculable because standard deviation in control arm was not reported.
3 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.

2. Women with suspected or diagnosed adenomyosis

Table 40: Clinical evidence profile: Comparison 1: LNG-IUS versus hysterectomy in women with suspected or diagnosed adenomyosis

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
Health-related quality of life (follow-up 12 months; measured with: WHOQOL-BREF TR - Physical; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[4]	none	43 Median = 68, IQR 59-77 (p-value = <0.001)	32 Median = 72, IQR 57-84 (p-value = <0.001)	-	p value 0.539	LOW	CRITICAL
Health-related quality of life (follow-up 12 months; measured with: WHOQOL-BREF TR - Psychological; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[4]	none	43 Median = 58, IQR 51-66 (p-value = 0.005)	32 Median = 62, IQR 50-75 (p-value = 0.146)	-	p value 0.440	LOW	CRITICAL
Health-related quality of life (follow-up 12 months; measured with: WHOQOL-BREF TR - Social; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[4]	none	43 Median = 67, IQR 59-75 (p-value = 0.005)	32 Median = 67, IQR 55-78 (p-value = 0.127)	-	p value 0.176	LOW	CRITICAL
Health-related quality of life (follow-up 12 months; measured with: WHOQOL-BREF TR - Environmental TR; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	32 Mean = 68 (SD 13)	-	MD 6 lower (12.36 lower to 0.36 higher)	VERY LOW	CRITICAL
Post-operative wound infection												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[4]	none	N/A	1/32 (3.1%)	-	31 fewer per 1000 (from 31 fewer to 31 fewer)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; MID: minimally important difference; N/A: not applicable; RR: relative risk; SD: standard seviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire Turkish version
1 The quality of evidence was downgraded by 1 because the allocation concealment was unclear, no blinding of outcome assessor, and substantial losses to follow-up in the hysterectomy arm.
2 The quality of evidence was downgraded by 1 because only 75% of the population were correctly diagnosed with adenomyosis.
3 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
4 Imprecision was not calculable because the outcome was not applicable to the other intervention group or the uncertainty around the outcome was not available.

3. Women with no identified pathology

Table 41: Clinical evidence profile: Comparison 2.3: Tranexamic acid versus progestogen in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Progestogen	Relative (95% CI)	Absolute	Quality	Importance
Health-Related Quality of Life change from baseline after 3 cycles of treatment - Menorrhagia Questionnaire (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	44	-	MD 6.51 lower (2.31 to 10.71 lower)	LOW	CRITICAL
Health-related quality of life - Physical domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	22	20	-	MD 0.97 higher (0.35 lower to 2.29 higher)	VERY LOW	CRITICAL
Health-related quality of life - Psychosocial domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	22	20	-	MD 0.62 higher (0.52	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Progestogen	Relative (95% CI)	Absolute	Quality	Importance
										lower to 1.76 higher)		
Health-related quality of life - Social domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	20	-	MD 0.12 lower (1.48 lower to 1.24 higher)	LOW	CRITICAL
Health-related quality of life - Environmental domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	22	20	-	MD 0.61 higher (0.36 lower to 1.58 higher)	VERY LOW	CRITICAL
Health-related quality of life - Environmental domain Turkey (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	22	20	-	MD 0.37 higher (0.54 lower to 1.28 higher)	VERY LOW	CRITICAL

CI: confidence interval; MD: mean difference; MID: minimally important difference; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire Turkish version

1 The quality of evidence was downgraded by 1 because randomisation, allocation concealment and blinding are unclear.

2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.

3 The quality of evidence was downgraded by 2 because blinding was not done, randomisation and allocation concealment were unclear, and there were considerable losses to follow-up.

Table 42: Clinical evidence profile: Comparison 2.4: LNG-IUS versus NSAIDs in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LNG-IUS**	**Mefenamic acid**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Adverse event: Chlamydial endometritis (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[1]	none	1/25 (4%)	N/A	-	-	HIGH	IMPORTANT
Adverse event: Expulsion (within 30 days post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[1]	none	1/25 (4%)	N/A	-	-	HIGH	IMPORTANT

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: nonsteroidal anti-inflammatory drugs
1 Imprecision was not calculable because the outcome is only relevant for one intervention arm.

Table 43: Clinical evidence profile: Comparison 2.5: LNG-IUS versus tranexamic acid in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Tranexamic acid	Relative (95% CI)	Absolute	**Quality**	**Importance**
Health-related quality of life - Physical domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious1	no serious inconsistency	no serious indirectness	serious2	none	20	22	-	MD 0.52 lower (1.59 lower to 0.55 higher)	VERY LOW	CRITICAL
Health-related quality of life - Psychosocial domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	22	-	MD 0.05 higher (1.15 lower to 1.25 higher)	LOW	CRITICAL
Health-related quality of life - Social domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious1	no serious inconsistency	no serious indirectness	serious2	none	20	22	-	MD 1.27 lower (2.49 to 0.05 lower)	VERY LOW	CRITICAL
Health-related quality of life - Environmental domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Tranexamic acid	Relative (95% CI)	Absolute		
1	randomised trials	very serious1	no serious inconsistency	no serious indirectness	serious2	none	20	22	-	MD 0.76 lower (1.67 lower to 0.15 higher)	VERY LOW	CRITICAL
Health-related quality of life - Environmental domain Turkey (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious1	no serious inconsistency	no serious indirectness	serious2	none	20	22	-	MD 0.42 lower (1.26 lower to 0.42 higher)	VERY LOW	CRITICAL

CI: confidence interval; MD: mean difference; MID: minimally important difference; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire Turkish version
1 The quality of evidence was downgraded by 2 because blinding was not done, randomisation and allocation concealment were unclear, and there were considerable losses to follow-up.
2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.

Table 44: Clinical evidence profile: Comparison 2.6: LNG-IUS versus progestogens in women with no identified pathology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Progestogen	Relative (95% CI)	Absolute		
Health-related quality of life - Physical domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 0.45 higher (0.86 lower to 1.76 higher)	VERY LOW	CRITICAL
Health-related quality of life - Psychosocial domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 0.67 higher (0.49 lower to 1.83 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Progestogen	Relative (95% CI)	Absolute		
Health-related quality of life - Social domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 1.39 lower (2.77 to 0.01 lower)	VERY LOW	CRITICAL
Health-related quality of life - Environmental domain (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 0.15 lower (1.13 lower to 0.83 higher)	LOW	CRITICAL
Health-related quality of life - Environmental domain Turkey (WHOQOL-BREF TR) after 6 months of treatment (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 0.05 lower (0.96 lower to 0.86 higher)	LOW	CRITICAL
Adverse event: Infection – Vaginitis within 6 months/cycles of treatment												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	9/80 (11.3%)	3/82 (3.7%)	RR 3.08 (0.86 to 10.95)	76 more per 1000 (from 5 fewer to 364 more)	MODERATE	IMPORTANT
Adverse outcome: Infection - Urinary tract infection within 6 months/cycles of treatment												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6/80 (7.5%)	3/82 (3.7%)	RR 2.05 (0.53 to 7.92)	38 more per 1000 (from 17 fewer to 253 more)	LOW	IMPORTANT
Adverse event: Expulsion within 6 months/cycles of treatment												
2	randomised trials	no serious risk of bias	not calculable4	no serious indirectness	not calculable[4]	none	5/102 (4.9%)	N/A	N/A	N/A	HIGH	IMPORTANT

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; MID: minimally important difference; RR: relative risk
1The quality of evidence was downgraded by 2 because blinding was not done, randomisation and allocation concealment were unclear, and there were considerable losses to follow-up.
2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
3 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.
4 Not calculable because the outcome is only relevant for one intervention arm.

Table 45: Clinical evidence profile: Comparison 2.7: LNG-IUS versus COC in women with no identified pathology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Low-dose COC	Relative (95% CI)	Absolute		
HRQoL-4: Self-rated health very good or excellent at 12 months												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/56 (26.8%)	13/56 (23.2%)	RR 1.15 (0.61 to 2.2)	35 more per 1000 (from 91 fewer to 279 more)	VERY LOW	CRITICAL
HRQoL-4: No. of days in previous 30 days feeling physically unwell, change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[4]	none	56	56	-	MD 0.9 lower (1.59 to 0.21 lower)	VERY LOW	CRITICAL
HRQoL-4: No. of days in previous 30 days feeling mentally unwell, change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	56	-	MD 2.6 higher (1.83 to 3.37 higher)	LOW	CRITICAL
HRQoL-4: No. on lost days in the previous 30 days, change from baseline at 12 months (Better indicated by lower values)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	56	-	MD 4.9 lower (5.59 to 4.21 lower)	LOW	CRITICAL

CI: confidence interval; COC: combined oral contraceptives; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; MID: minimally important difference; PBAC: pictorial blood loss assessment chart; RR: relative risk
1 The quality of evidence was downgraded by 1 because blinding was not possible.
2 The quality of evidence was downgraded by 1 because of substantial losses to follow-up.
3 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.
4 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.

Table 46: Clinical evidence profile: Comparison 2.8: LNG-IUS versus variety of pharmacological treatments in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Usual medical treatment	Relative (95% CI)	Absolute	Quality	Importance
Health-related quality of life: Menorrhagia Multi-Attribute Scale summary score change from baseline - At 6 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	222	212	-	MD 10.6 higher (7.82 to 13.38 higher)	MODERATE	CRITICAL
Health-related quality of life: Menorrhagia Multi-Attribute Scale summary score change from baseline - At 12 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	seriou[s1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	218	216	-	MD 14 higher (11.22 to 16.78 higher)	MODERATE	CRITICAL
Health-related quality of life: Menorrhagia Multi-Attribute Scale summary score change from baseline - At 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	225	208	-	MD 10.9 higher (8.11 to 13.69 higher)	MODERATE	CRITICAL
Health-related quality of life: Menorrhagia Multi-Attribute Scale summary score change from baseline - At 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	216	208	-	MD 0.7 higher (2.12 lower to 3.52 higher)	MODERATE	CRITICAL

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; RR: relative risk; usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, COCs (combined oral contraceptive), progesterone-only pill
1 The quality of evidence was downgraded by 1 because blinding was not possible.

Table 47: Clinical evidence profile: Comparison 3.1 LNG-IUS versus first generation endometrial resection/ablation in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	First generation resection/ablation (TCRE)	Relative (95% CI)	Absolute	Quality	Importance
Adverse event: Uterine perforation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/52 (0%)	1/52 (1.9%)	0.33 (0.01 to 8)	13 fewer per 1000 (from 19 fewer to 135 more)	LOW	IMPORTANT
Adverse event: Expulsion within 1 year post-procedure												
3	randomised trials	serious[2]	not calculable[3]	no serious indirectness	not calculable[3]	none	12/109 (11%)	N/A	-	-	MODERATE	IMPORTANT
Adverse event: Infection - Pelvic inflammatory disease or endometritis (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/30 (16.7%)	4/29 (13.8%)	RR 1.22 (0.35 to 4.21)	30 more per 1000 (from 90 fewer to 443 more)	LOW	IMPORTANT
Adverse event: Infection – Vaginitis (post-procedure)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/30 (13.3%)	2/30 (6.7%)	RR 2 (0.4 to 10.11)	67 more per 1000 (from 40 fewer to 607 more)	VERY LOW	IMPORTANT
Adverse event: Infection – Endometritis (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/19 (15.8%)	0/22 (0%)	RR 8.05 (0.44 to 146.59)	-	LOW	IMPORTANT
Adverse event: Infection – Myometritis (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/19 (0%)	1/22 (4.5%)	RR 0.38 (0.02 to 8.89)	28 fewer per 1000 (from 45 fewer to 359 more)	LOW	IMPORTANT

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; MD: mean difference; MID: minimally important difference; N/A: not applicable; RR: relative risk; TCRE: transcervical endometrial resection

1 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.
2 The quality of evidence was downgraded by 1 because there was substantial losses to follow-up in 1 study.
3 Not calculable because the outcome is only relevant for one intervention arm.
4 The quality of evidence was downgraded by 1 because blinding and allocation process was not possible.

Table 48: Clinical evidence profile: Comparison 3.2 LNG-IUS versus second generation endometrial resection/ablation in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	second generation resection/ablation	Relative (95% CI)	Absolute	Quality	Importance
Adverse event: Expulsion (times of follow-up varied between the studies from 3 months to 2 years)												
4	randomised trials	serious[1]	not calculable[2]	no serious indirectness	not calculable[2]	none	9/127 (7.1%)	N/A	-	-	MODERATE	IMPORTANT
Adverse event: Infection - Post-operation antibiotics for possible endometritis												
1	randomised trials	no serious risk of bias	not calculable[2]	no serious indirectness	not calculable[2]	none	N/A	5/39 (12.8%)	-	-	HIGH	CRITICAL

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; N/A: not applicable
1 The quality of evidence was downgraded by 1 because of considerable losses to follow-up.
2 Not calculable because the outcome was only relevant for one intervention arm.

Table 49: Clinical evidence profile: Comparison 3.3 LNG-IUS versus hysterectomy in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
Adverse event: Infection - Wound infection (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/117 (1.7%)	12/115 (10.4%)	RR 0.16 (0.04 to 0.72)	88 fewer per 1000 (from 29 fewer to 100 fewer)	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Hysterectomy	Relative (95% CI)	Absolute		
Adverse event: Infection - Infected pelvic haematoma (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	9/117 (7.7%)	6/115 (5.2%)	RR 1.47 (0.54 to 4.01)	25 more per 1000 (from 24 fewer to 157 more)	LOW	CRITICAL
Adverse event: Infection - Peritonitis (post-procedure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/117 (0%)	1/115 (0.87%)	RR 0.33 (0.01 to 7.96)	6 fewer per 1000 (from 9 fewer to 61 more)	LOW	CRITICAL
Adverse event: Perforation - **Bladder perforation**												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/117 (0%)	3/115 (2.6%)	RR 0.14 (0.01 to 2.69)	22 fewer per 1000 (from 26 fewer to 44 more)	LOW	IMPORTANT
Adverse event: Perforation - Bowel perforation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/117 (0%)	1/115 (0.87%)	RR 0.33 (0.01 to 7.96)	6 fewer per 1000 (from 9 fewer to 61 more)	LOW	IMPORTANT
Adverse event: Thromboembolic event (timeframe not clear)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/117 (0.85%)	0/115 (0%)	RR 2.95 (0.12 to 71.65)	-	LOW	CRITICAL
Adverse event: Vesicovaginal fistula												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/117 (0%)	1/115 (0.87%)	RR 0.33 (0.01 to 7.96)	6 fewer per 1000 (from 9 fewer to 61 more)	LOW	CRITICAL
Adverse event: Ureter lesion												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUS	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/117 (0%)	1/115 (0.87%)	RR 0.33 (0.01 to 7.96)	6 fewer per 1000 (from 9 fewer to 61 more)	LOW	CRITICAL
Long-term complication: Stress urinary incontinence (timeframe not clear)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23/68 (33.8%)	74/153 (48.4%)	RR 0.7 (0.48 to 1.01)	145 fewer per 1000 (from 252 fewer to 5 more)	MODERATE	IMPORTANT
Long-term complication: Urge urinary incontinence (timeframe not clear)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious1	none	11/68 (16.2%)	34/153 (22.2%)	RR 0.73 (0.39 to 1.35)	60 fewer per 1000 (from 136 fewer to 78 more)	LOW	IMPORTANT

CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; MID: minimally important difference; RR: relative risk
1 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MID.
2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MIDs.

Table 50: Clinical evidence profile: Comparison 4. Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medical management	TCRE with pre-op GnRHa	Relative (95% CI)	Absolute	Quality	Importance
Health-related quality of Life: SF-36 - Physical Functioning - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93	93	-	mean 5.32 lower (10.1 to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medical management	TCRE with pre-op GnRHa	Relative (95% CI)	Absolute	Quality	Importance
										0.54 lower)		
Health-related quality of Life: SF-36 - Physical Functioning - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	86	-	mean 1.27 lower (6.67 lower to 4.13 higher)	MODERATE	CRITICAL
Health-related quality of Life: SF-36 - Physical Functioning - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious2	none	71	73	-	MD 6.69 lower (13.38 lower to 0 higher)	VERY LOW	CRITICAL
Health-related quality of life: SF-36 - Energy/fatigue - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious2	none	93	93	-	MD 13.46 lower (19.35 to 7.57 lower)	LOW	CRITICAL
Health-related quality of life: SF-36 - Energy/fatigue - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	86	-	MD 4.52 lower (10.72 lower to 1.68 higher)	MODERATE	CRITICAL
Health-related quality of life: SF-36 - Energy/fatigue - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious2	none	70	73	-	MD 6.69 lower (13.45 lower to 0.07 higher)	VERY LOW	CRITICAL
Health-related quality of life: SF-36 - Physical Role - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious2	none	93	93	-	MD 16.94 lower (29.22 to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medical management	TCRE with pre-op GnRHa	Relative (95% CI)	Absolute	Quality	Importance
										4.66 lower)		
Health-related quality of life: SF-36 - Physical Role - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	86	-	MD 5.65 lower (19.11 lower to 7.81 higher)	MODERATE	CRITICAL
Health-related quality of life: SF-36 - Physical Role - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious2	none	71	73	-	MD 16.48 lower (28.46 to 4.5 lower)	VERY LOW	CRITICAL
Health-related quality of life: SF-36 - Social Function - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93	93	-	MD 9.87 lower (16.17 to 3.57 lower)	LOW	CRITICAL
Health-related quality of life: SF-36 - Social Function - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	87	86	-	MD 6.65 lower (14.37 lower to 1.07 higher)	LOW	CRITICAL
Health-related quality of life: SF-36 - Social Function - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	71	73	-	MD 7.28 lower (15.74 lower to 1.18 higher)	VERY LOW	CRITICAL
Health-related quality of life: SF-36 - Emotional Role - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93	93	-	MD 22.58 lower (36.37 to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medical management	TCRE with pre-op GnRHa	Relative (95% CI)	Absolute	Quality	Importance
										8.79 lower)		
Health-related quality of life: SF-36 - Emotional Role - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	87	86	-	MD 11.23 lower (25.51 lower to 3.05 higher)	LOW	CRITICAL
Health-related quality of life: SF-36 - Emotional Role - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	71	73	-	MD 19.46 lower (31.73 to 7.19 lower)	VERY LOW	CRITICAL
Health-related quality of life: SF-36 - Mental Health - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93	93	-	MD 10.23 lower (15.37 to 5.09 lower)	LOW	CRITICAL
Health-related quality of life: SF-36 - Mental Health - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	86	-	MD 2.81 lower (8.52 lower to 2.9 higher)	MODERATE	CRITICAL
Health-related quality of life: SF-36 - Mental Health - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	71	73	-	MD 9.64 lower (15.39 to 3.89 lower)	VERY LOW	CRITICAL
Health-related quality of life: SF-36 - Pain - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93	93	-	MD 12.78 lower (21.11 to 4.45 lower)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medical management	TCRE with pre-op GnRHa	Relative (95% CI)	Absolute		
Health-related quality of life: SF-36 - Pain - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	86	-	MD 0.96 lower (9.26 lower to 7.34 higher)	MODERATE	CRITICAL
Health-related quality of life: SF-36 - Pain - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	73	-	MD 2.83 lower (10.84 lower to 5.18 higher)	LOW	CRITICAL
Health-related quality of life: SF-36 - General Health - at 4 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93	93	-	MD 10.74 lower (16.08 to 5.4 lower)	LOW	CRITICAL
Health-related quality of life: SF-36 - General Health - at 2 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	86	-	MD 2.36 lower (7.3 lower to 2.58 higher)	MODERATE	CRITICAL
Health-related quality of life: SF-36 - General Health - at 5 years (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	71	73	-	MD 10.85 lower (17.92 to 3.78 lower)	VERY LOW	CRITICAL
Totally or generally satisfied with treatment - at 4 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/93 (26.9%)	70/93 (75.3%)	RR 0.36 (0.25 to 0.51)	482 fewer per 1000 (from 369 fewer to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medical management	TCRE with pre-op GnRHa	Relative (95% CI)	Absolute	Quality	Importance
										565 fewer)		
Totally or generally satisfied with treatment - at 2 years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/86 (55.8%)	68/87 (78.2%)	RR 0.71 (0.57 to 0.89)	227 fewer per 1000 (from 86 fewer to 336 fewer)	LOW	CRITICAL
Totally or generally satisfied with treatment - at 5 years												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	49/69 (71%)	55/72 (76.4%)	RR 0.93 (0.76 to 1.13)	53 fewer per 1000 (from 183 fewer to 99 more)	VERY LOW	CRITICAL
Would recommend the treatment - at 4 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/93 (40.9%)	84/93 (90.3%)	RR 0.45 (0.35 to 0.58)	497 fewer per 1000 (from 379 fewer to 587 fewer)	MODERATE	CRITICAL
Would recommend the treatment - at 2 years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/86 (24.4%)	68/87 (78.2%)	RR 0.31 (0.21 to 0.46)	539 fewer per 1000 (from 422 fewer to 617 fewer)	MODERATE	CRITICAL
Would recommend the treatment - at 5 years												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/70 (20%)	57/72 (79.2%)	RR 0.25 (0.16 to 0.41)	594 fewer per 1000 (from 467 fewer to 665 fewer)	LOW	CRITICAL

CI: confidence interval; GnHR: gonadotropin-releasing hormone; MD: mean difference; MID: minimally important difference; RR relative risk; SF-36: 36-Item Short Form Survey; TCRE: transcervical endometrial resection
1 The quality of evidence was downgraded by 1 because the blinding was not possible.
2 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
3 The quality of evidence was downgraded by 2 because the blinding was not possible and there were substantial losses to follow- up.

Table 51: Comparison 5.1 first generation resection/ablation versus hysterectomy in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First generation ablation/resection	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
Length of hospital stay in days - Setting: UK (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	119	57	-	MD 5 lower (5.54 to 4.46 lower)	MODERATE	IMPORTANT
Length of hospital stay in days - Setting: UK (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	not calculable2	none	99	97	-	Resection: median 2 (range 1-8) Hysterectomy: median 6 (range 5-10)	MODERATE	IMPORTANT
Length of hospital stay in days - Setting: US (Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	53	118	-	MD 1.82 lower (2 to 1.64 lower)	LOW	IMPORTANT
Length of hospital stay in days - Setting: Italy (Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	92	-	MD 0.3 lower (0.68 lower to 0.08 higher)	MODERATE	IMPORTANT
Adverse event: Blood Transfusion												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness[3]	no serious imprecision	none	3/304 (0.99%)	12/245 (4.9%)	RR 0.23 (0.07 to 0.71)	38 fewer per 1000 (from 14 fewer to 46 fewer)	MODERATE	IMPORTANT
Adverse event: Infection - Urinary tract infection (post-operative)												
3	randomised trials	very serious	no serious inconsistency	serious[4]	no serious imprecision	none	2/241 (0.8%)	19/307 (6.2%)	RR 0.17 (0.05	51 fewer per 1000 (from 25 fewer to 59 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First generation ablation/resection	Hysterectomy	Relative (95% CI)	Absolute		
									to 0.59)			
Adverse event: Infection - Abdominal wound infection												
2	randomised trials	serious[3]	not calculable9	serious[4]	not calculable[8]	none	N/A	16/215 (7.4%)	-	74 fewer per 1000 (from 74 fewer to 74 fewer)	LOW	CRITICAL
Adverse event: Infection - Endometritis (within 42 days post-procedure)												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	not calculable[8]	none	1/53 (1.9%)	N/A		-	LOW	CRITICAL
Adverse event: Infection - Pelvic Infection (post-operative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	2/99 (2%)	5/97 (5.2%)	RR 0.39 (0.08 to 1.97)	31 fewer per 1000 (from 47 fewer to 50 more)	LOW	CRITICAL
Adverse event: Infection - Sepsis (before discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	0/116 (0%)	2/56 (3.6%)	RR 0.1 (0 to 2)	32 fewer per 1000 (from 36 fewer to 36 more)	LOW	CRITICAL
Adverse event: Infection - Sepsis (after discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/116 (7.8%)	16/56 (28.6%)	RR 0.27 (0.13 to 0.58)	209 fewer per 1000 (from 120 fewer to 249 fewer)	HIGH	CRITICAL
Adverse event: Thromboembolic event (perioperative)												
1	randomised trials	Serious[3]	no serious inconsistency	Serious[4]	very serious[6]	none	0/53 (0%)	3/118 (2.5%)	RR 0.31 (0.02 to 5.99)	18 fewer per 1000 (from 25 fewer to 127 more)	VERY LOW	CRITICAL
								2.5%		17 fewer per 1000 (from 25 fewer to 125 more)		
Adverse event: Readmission or return to theatre (within up to 6 weeks post-procedure)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First generation ablation/resection	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
3	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[7]	none	2/268 (0.75%)	10/271 (3.7%)	RR 0.27 (0.08 to 0.93)	27 fewer per 1000 (from 3 fewer to 34 fewer)	VERY LOW	IMPORTANT
Adverse event: Internal organ injury - Cervical tear												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[8]	none	2/116 (1.7%)	N/A	-	-	HIGH	CRITICAL
Adverse event: Internal organ injury - Uterine Perforation												
3	randomised trials	serious[3]	not calculable[9]	serious4	not calculable[8]	none	8/268 (3%)	N/A	-	-	LOW	CRITICAL

CI: confidence interval; HMB: heavy menstrual bleeding; MD: mean difference; MID: minimally important difference; N/A: not applicable; RR: relative risk
1 The quality of evidence was downgraded by 1 because of the lack of blinding for outcome assessment.
2 Imprecision was not calculable because the results were reported in median values.
3 The quality of evidence was downgraded by 1 because loss to follow-up was not reported.
4 The quality of evidence was downgraded by 1 because the population was defined as dysfunctional uterine bleeding and % of HMB was not defined.
5 The quality of evidence was downgraded by 1 because of unclear allocation concealment and unclear selective reporting.
6 The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.
7 The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
8 Imprecision was not calculable because there were either zero events in both intervention groups or the outcome was not applicable to the other intervention group.
9 Inconsistency was not calculable because the outcome was not applicable to the other intervention group.

Table 52: Comparison 5.2 Second generation resection/ablation versus hysterectomy in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	second generation ablation/resection	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
Length of hospital stay in days (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	57	118	-	MD 1.81 lower	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	second generation ablation/resection	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
										(2 to 1.62 lower)		
Adverse event: Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	not calculable[3]	none	0/34 (0%)	0/34 (0%)	-	-	HIGH	IMPORTANT
Adverse event: Infection - Urinary tract infection (within 42 days post-procedure)												
1	randomised trials	serious [1]	no serious inconsistency	serious[1]	very serious[4]	none	1/57 (1.8%)	6/118 (5.1%)	RR 0.35 (0.04 to 2.8)	33 fewer per 1000 (from 49 fewer to 92 more)	VERY LOW	CRITICAL
Adverse event: Infection - Abdominal wound infection (post-operative)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable3	none	N/A	5/118 (4.2%)	-	42 fewer per 1000 (from 42 fewer to 42 fewer)	LOW	CRITICAL
Adverse event: Infection – Endometritis (within 42 days post-procedure)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[3]	none	0/57 (0%)	N/A		-	LOW	CRITICAL
Adverse event: Thromboembolic event (within 42 days post-procedure)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious4	none	0/57 (0%)	3/118 (2.5%)	RR 0.29 (0.02 to 5.58)	18 fewer per 1000 (from 25 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	second generation ablation/resection	Hysterectomy	Relative (95% CI)	Absolute	Quality	Importance
										to 116 more)		
Adverse event: Readmission or return to theatre (within up to 42 days post-procedure)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious4	none	0/91 (0%)	3/152 (2%)	RR 0.29 (0.02 to 5.58)	14 fewer per 1000 (from 19 fewer to 90 more)	VERY LOW	IMPORTANT
Adverse event: Internal organ damage - Uterine perforation												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	not calculable[3]	none	2/57 (3.5%)	N/A		-	LOW	CRITICAL

CI: confidence interval; MD: mean difference; MID: minimally important difference; N/A: not applicable; RR: relative risk
[1] The quality of evidence was downgraded by 1 because loss to follow-up was not reported.
[2] The quality of evidence was downgraded by 1 because the population was defined as dysfunctional uterine bleeding and % of HMB was not defined.
[3] Imprecision was not calculable because there were either zero events in both intervention groups or the outcome was not applicable to the other intervention group.
[4] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.

Table 43: Comparison 5.3 first generation resection/ablation versus second generation resection/ablation in women with no identified pathology

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First generation ablation/resection	second generation ablation/resection	Relative (95% CI)	Absolute	Quality	Importance
Adverse event: Infection - Post-operative infection												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/148 (1.4%)	0/270 (0%)	RR 4.93 (0.53 to 45.9)	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First generation ablation/resection	second generation ablation/resection	Relative (95% CI)	Absolute		
Adverse event: Infection - Endometritis or UTI (post-operative)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/411 (1.5%)	11/633 (1.7%)	RR 0.95 (0.38 to 2.34)		VERY LOW	CRITICAL
Adverse event: Internal organ injury - Cervical laceration												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/325 (1.2%)	0/440 (0%)	RR 5.03 (0.88 to 28.63)	-	LOW	CRITICAL
Adverse event: Internal organ injury - Uterine Perforation												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/384 (1.6%)	0/523 (0%)	RR 5.26 (1.13 to 24.43)	-	LOW	CRITICAL

CI: confidence interval; MID: minimally important difference; RR: relative risk; UTI: urinary tract infection

[1] *The quality of evidence was downgraded by 1 because of unclear random sequence generation and allocation concealment.*

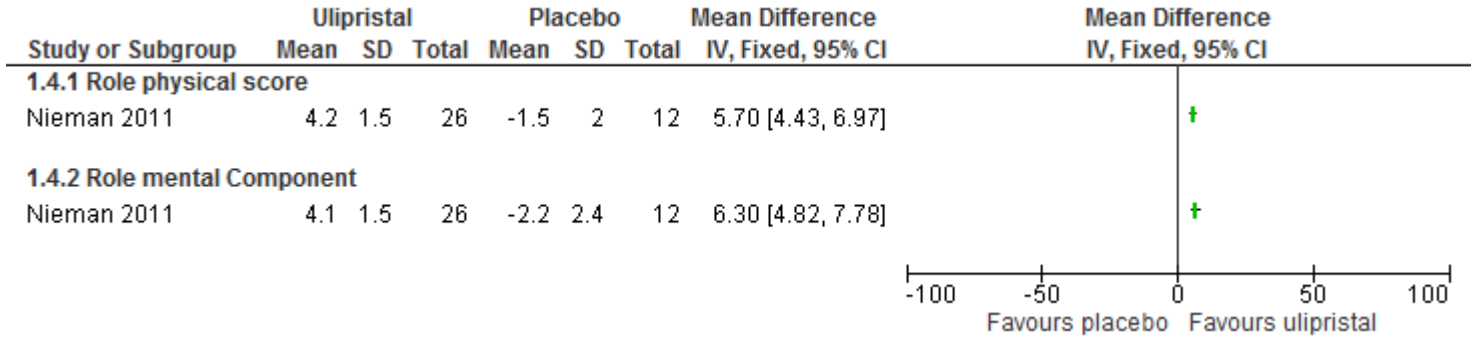
[2] *The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.*

[3] *The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.*

Appendix H – Forest plots

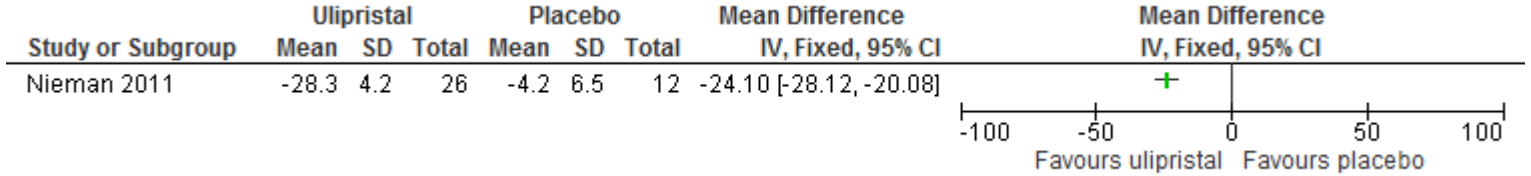
1. Women with suspected or diagnosed fibroids

Figure 13: Comparison 1: Ulipristal acetate versus placebo – SF-36 Health-related quality of life change from baseline after 3 cycles of treatment in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



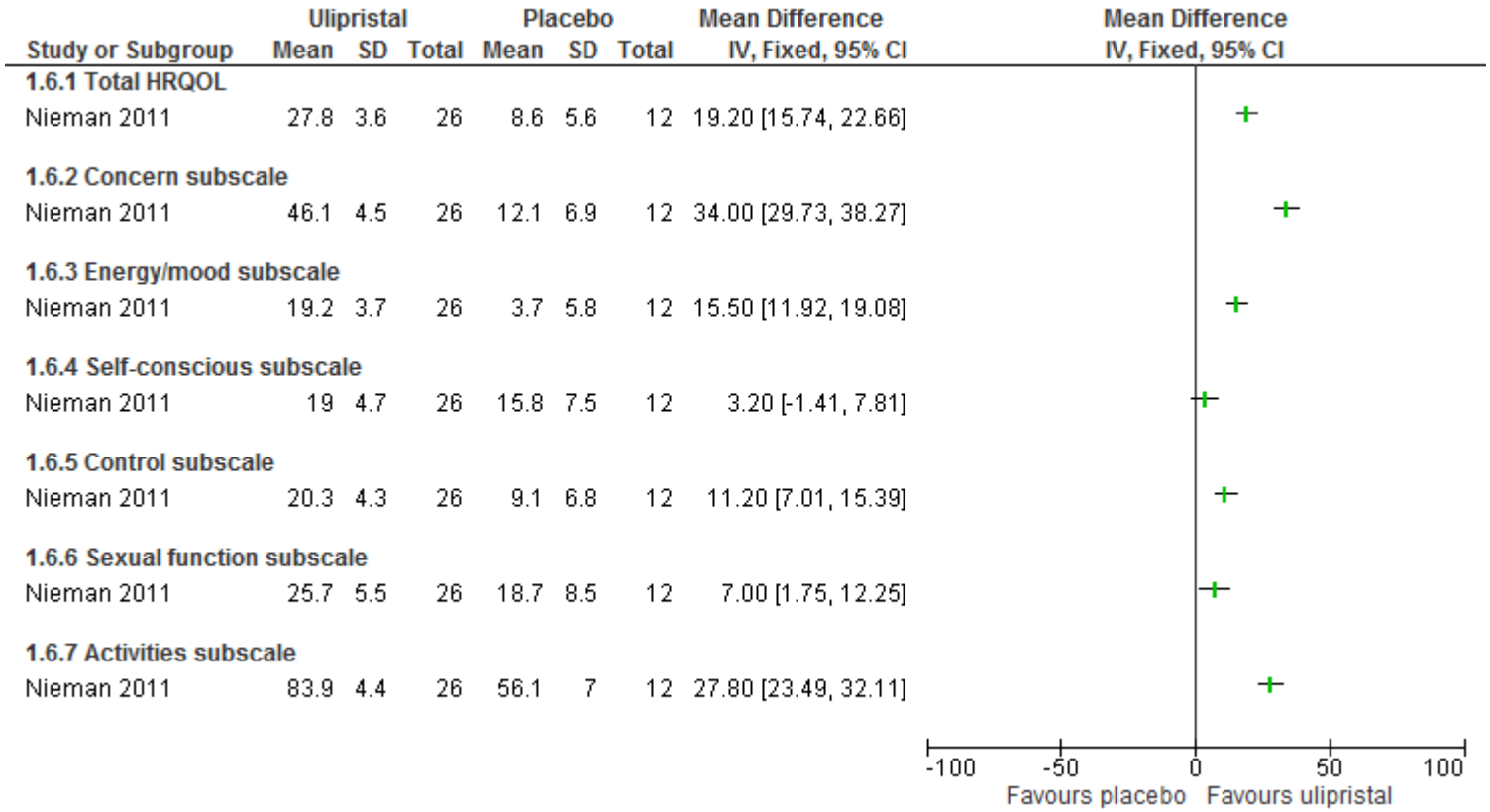
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey

Figure 14: Comparison 1: Ulipristal acetate versus placebo – UFS-QOL Symptom severity score change from baseline after 3 cycles of treatment in women with fibroids (range of scores 0-100, better indicated by lower values)



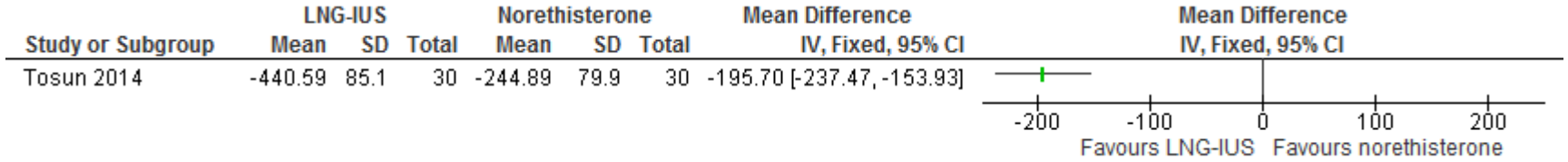
CI: confidence interval; IV: inverse variance; SD: standard deviation; UFS-QOL: Uterine Fibroid Symptom and Quality of Life questionnaire

Figure 15: Comparison 1: Ulipristal acetate versus placebo – UFS-QOL Health-related quality of life change score from baseline after 3 cycles of treatment in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



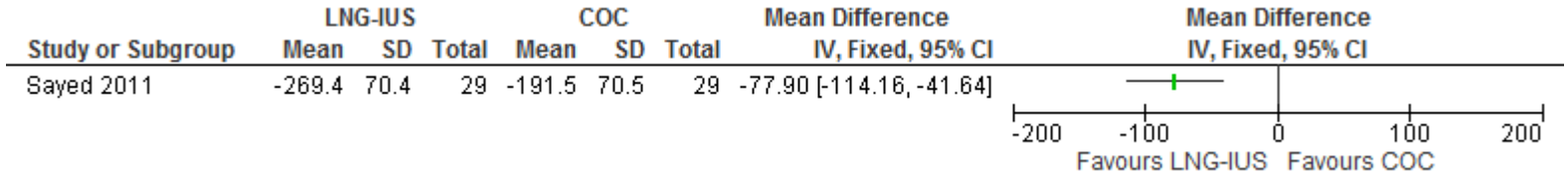
CI: confidence interval; HRQOL: health-related quality of life; IV: inverse variance; SD: standard deviation; UFS-QOL: Uterine Fibroid Symptom and Quality of Life questionnaire

Figure 16: Comparison 2.1: LNG-IUS versus norethisterone – PBAC score change from baseline after 6 months of treatment in women with suspected or diagnosed fibroids (better indicated by lower values)



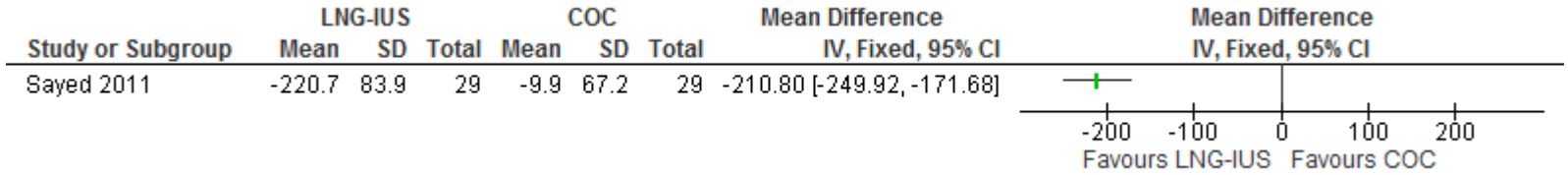
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; PBAC: Pictorial Blood Loss Assessment Chart; SD: standard deviation

Figure 17: Comparison 2.2: LNG-IUS versus COC – PBAC score change from baseline at 12 months in women with fibroids (better indicated by lower values)



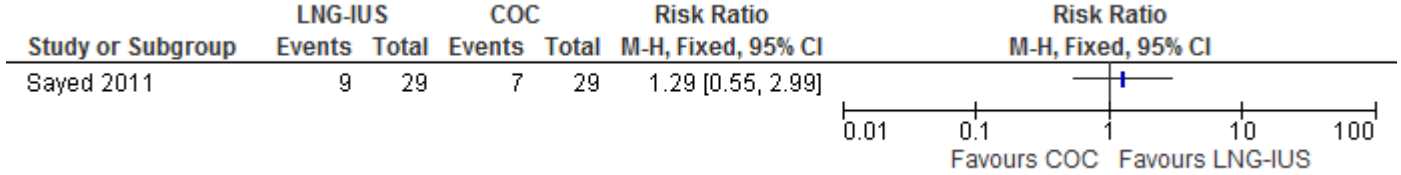
CI: confidence interval; COC: combined oral contraceptives; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; PBAC: Pictorial Blood Loss Assessment Chart; SD: standard deviation

Figure 18: Comparison 2.2: LNG-IUS versus COC – Menstrual blood loss in ml (AH method) change from baseline at 12 months in women with suspected or diagnosed fibroids (better indicated by lower values)



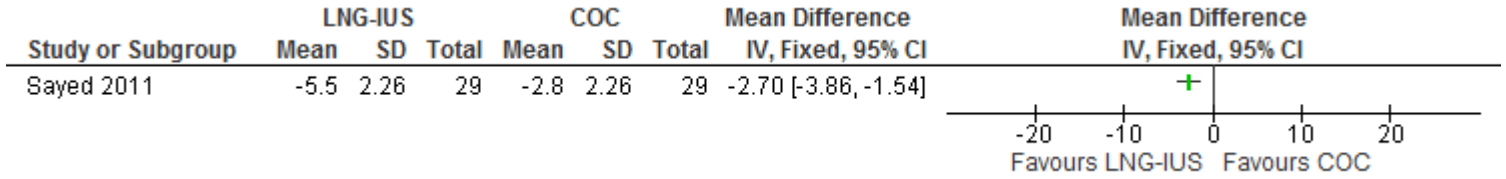
AH: alkaline haematin; CI: confidence interval; COC: combined oral contraceptives; IV: inverse variance; SD: standard deviation

Figure 19: Comparison 2.2: LNG-IUS versus COC – HRQoL-4 Self-rated health good or excellent at 12 months in women with fibroids



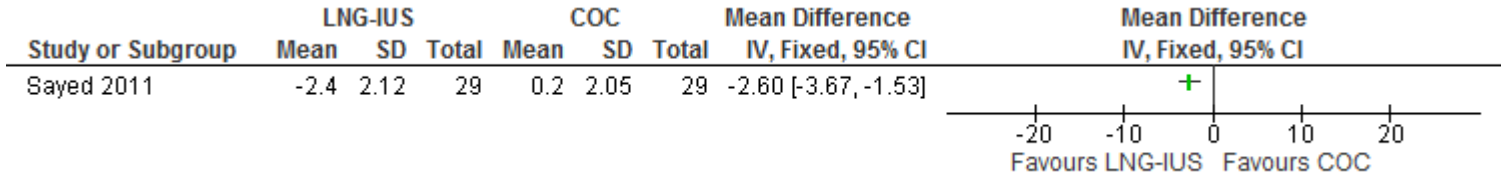
CI: confidence interval; COC: combined oral conbtraceptives; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; M-H: Mantel-Haenszel method

Figure 20: Comparison 2.2: LNG-IUS versus COC – HRQoL-4 No. of days in the previous 30 days feeling physically unwell, change from baseline at 12 months in women with suspected or diagnosed fibroids



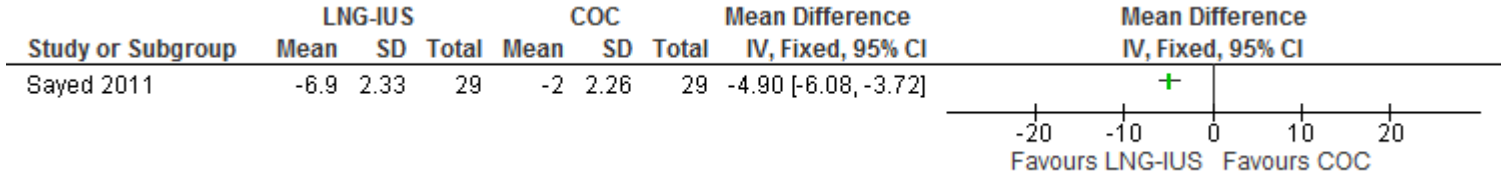
CI: confidence interval; COC: combined oral contraceptives; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

Figure 21: Comparison 2.2: LNG-IUS versus COC – HRQoL-4 No. of days in the previous 30 days feeling mentally unwell, change from baseline at 12 months in women with suspected or diagnosed fibroids (better indicated by lower values)



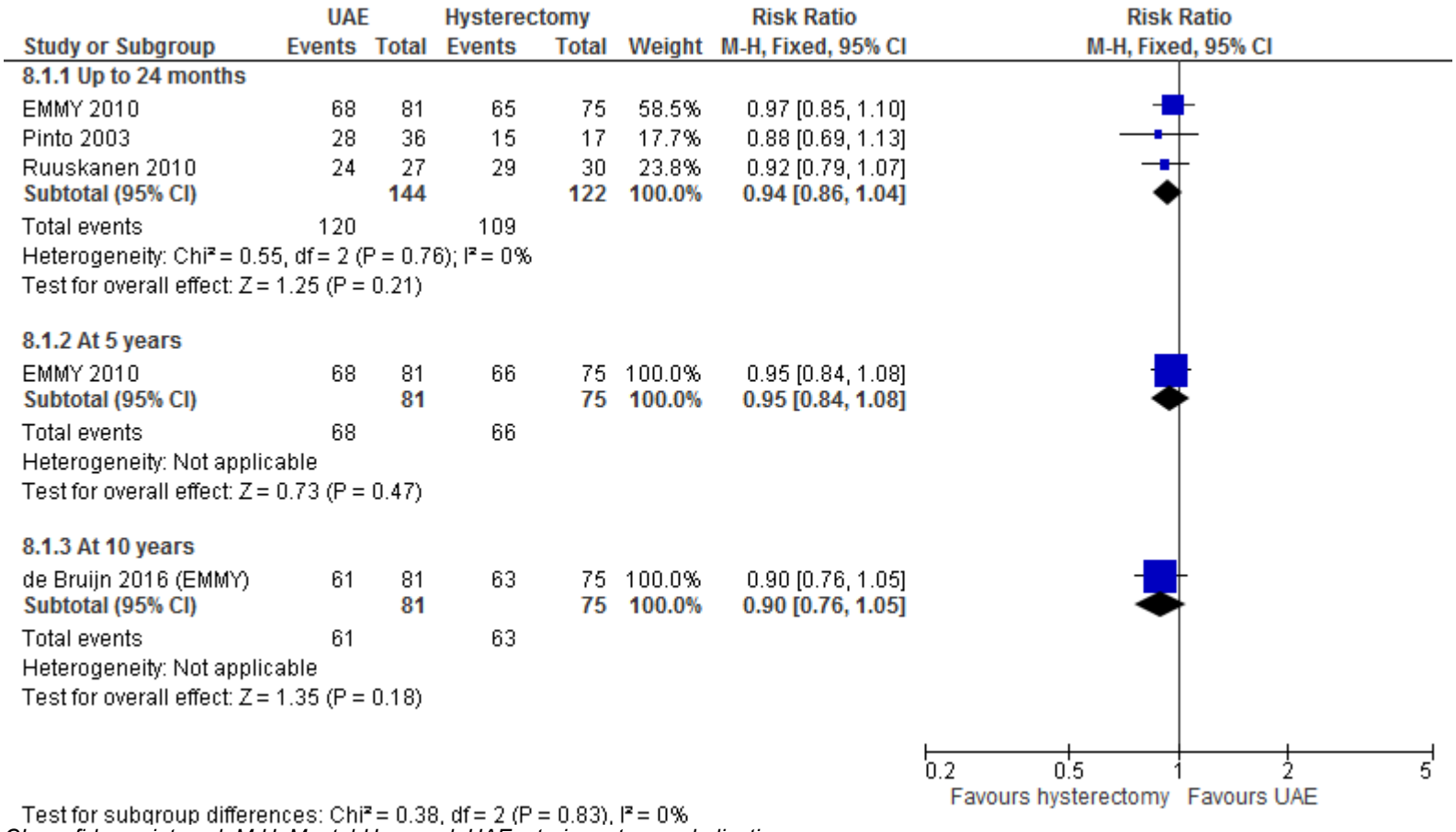
CI: confidence interval; COC: combined oral contraceptives; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

Figure 22: Comparison 2.2: LNG-IUS versus COC – HRQoL-4 No. of lost days in the previous 30 days, change from baseline at 12 months in women with suspected or diagnosed fibroids (better indicated by lower values)



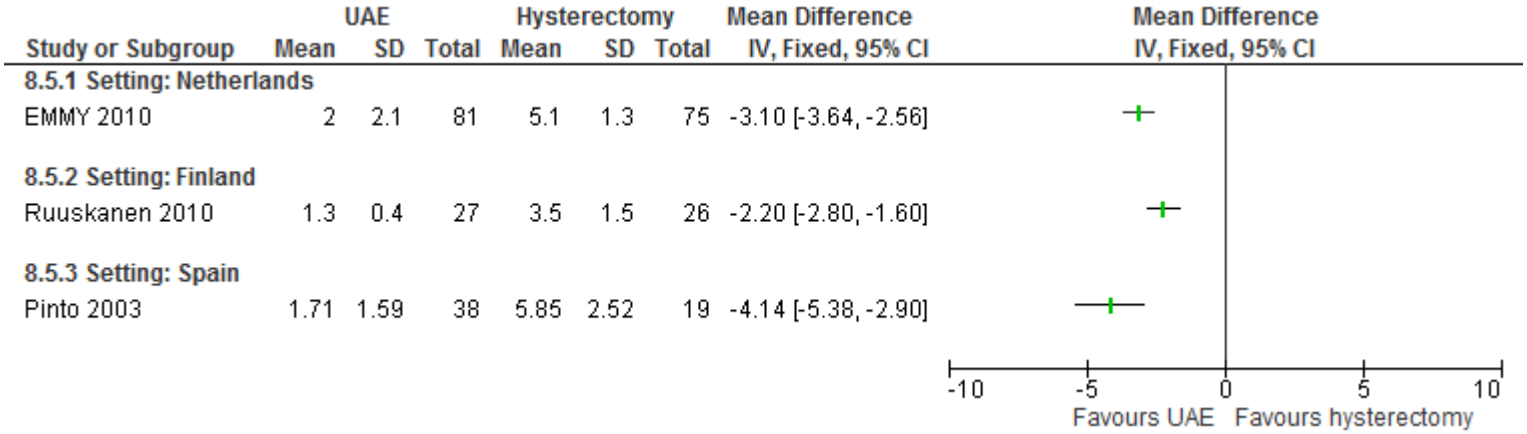
CI: confidence interval; COC: combined oral contraceptives; HRQoL-4: Health-related Quality of Life – 4 questionnaire by the Centers for Disease Control and Prevention; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

Figure 23: Comparison 3.1: UAE versus hysterectomy – Satisfaction with treatment (measured by asking women whether they would undergo the same treatment again) in women with suspected or diagnosed fibroids



CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

Figure 24: Comparison 3.1: UAE versus hysterectomy – Length of hospital stay in days in women with suspected or diagnosed fibroids (better indicated by lower values)

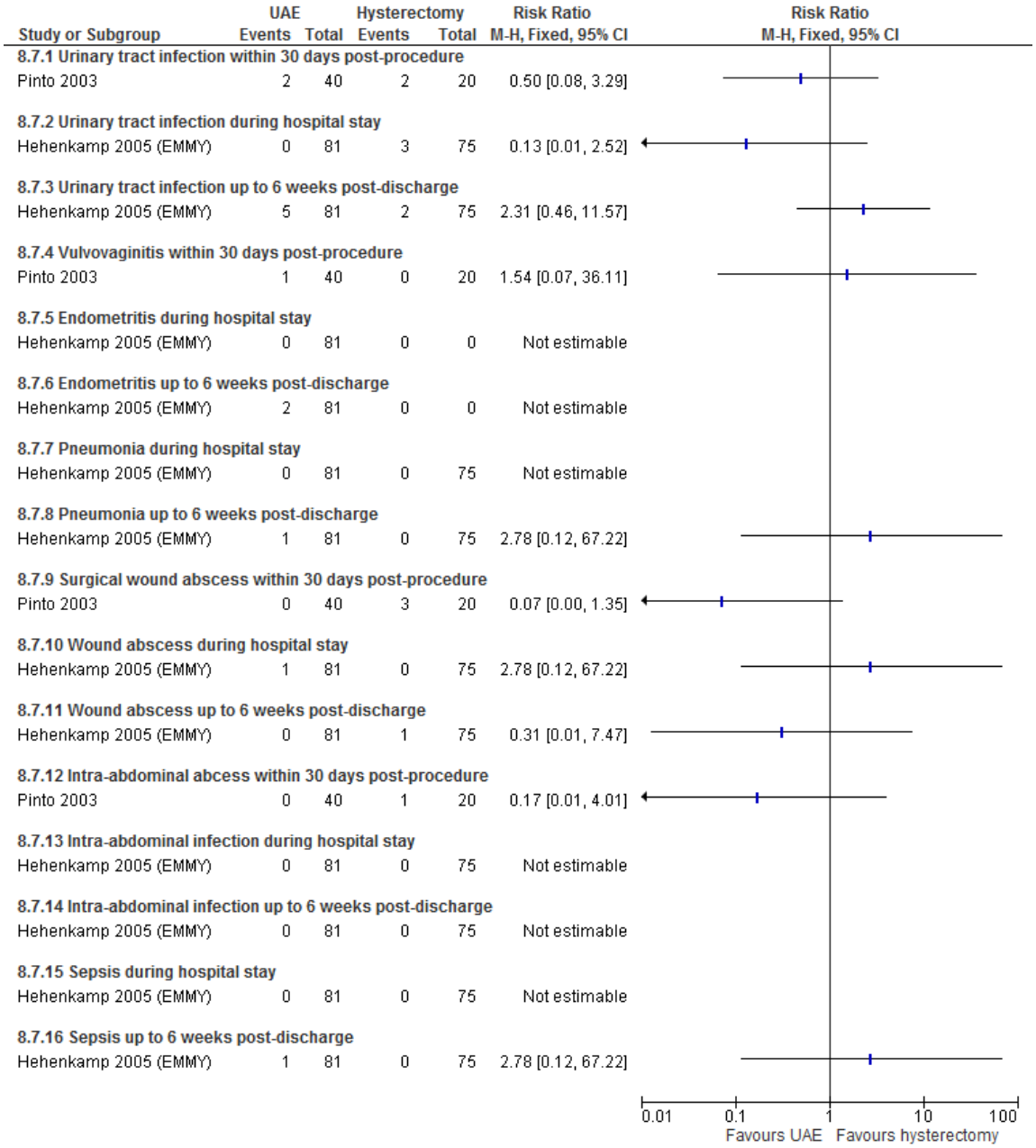


CI: confidence interval; IV: inverse variance; SD: standard deviation; UAE: uterine artery embolisation

Figure 25: Comparison 3.1: UAE versus hysterectomy – Blood transfusion in women with suspected or diagnosed fibroids

CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

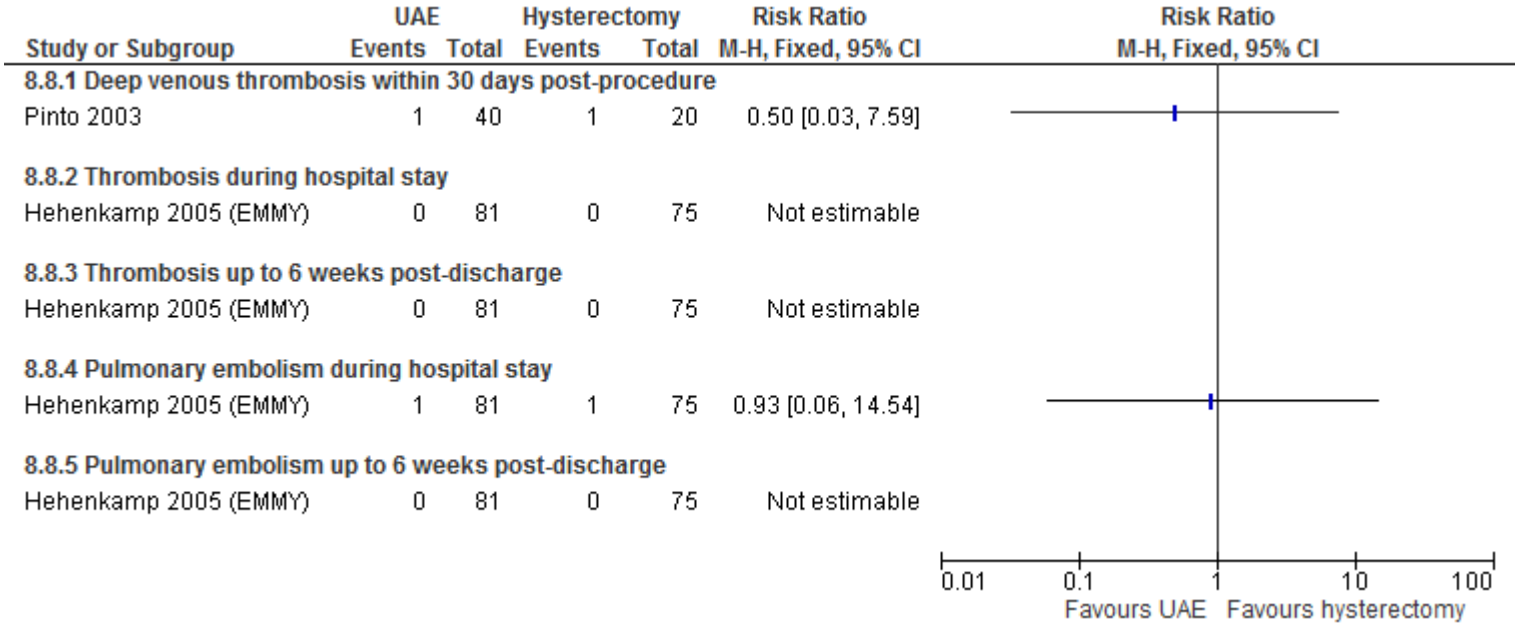
Figure 26: Comparison 3.1: UAE versus hysterectomy – Infection in women with suspected or diagnosed fibroids



Some risk ratios are not estimable for some outcomes because the outcome is either only relevant for one intervention arm, or there were no events in either intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

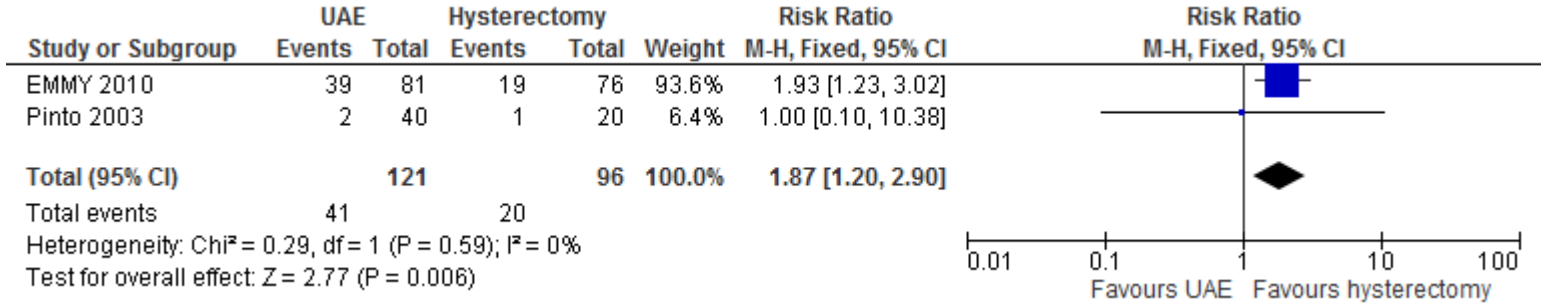
.

Figure 27: Comparison 3.1: UAE versus hysterectomy – Venous thrombosis in women with suspected or diagnosed fibroids



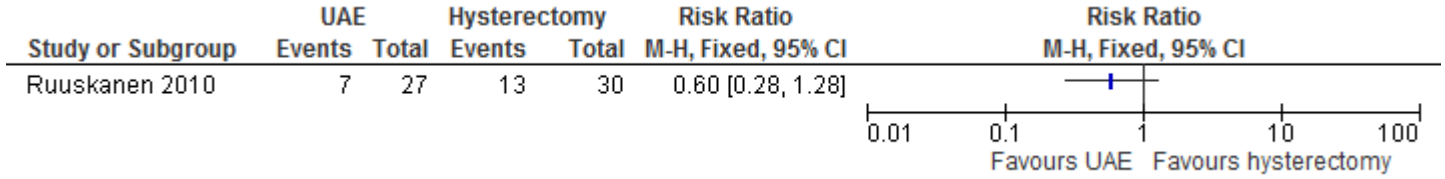
Some risk ratios are not estimable for some outcomes because there were no events in either intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

Figure 28: Comparison 3.1: UAE versus hysterectomy – Unscheduled readmission rate within 4-6 weeks in women with suspected or diagnosed fibroids



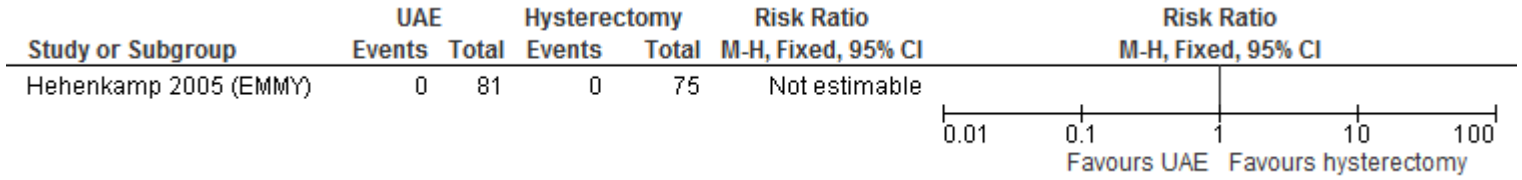
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

Figure 29: Comparison 3.1: UAE versus hysterectomy – Urinary stress incontinence at 2 years in women with suspected or diagnosed fibroids



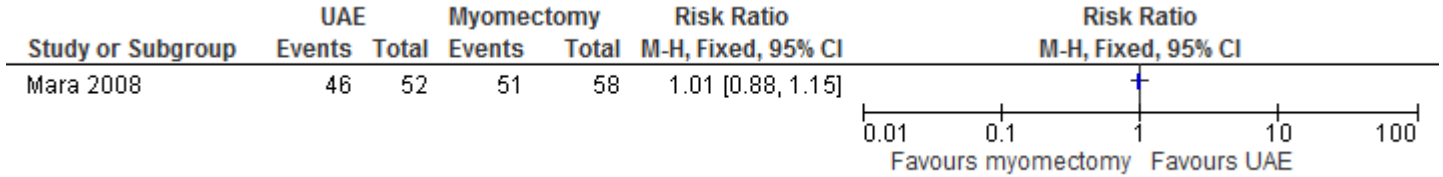
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

Figure 30: Comparison 3.1: UAE versus hysterectomy – Death in women with suspected or diagnosed fibroids



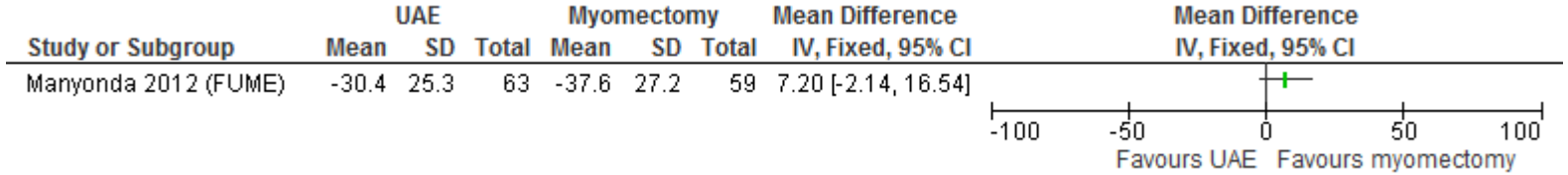
The risk ratio is not estimable because there were no events in either intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

Figure 31: Comparison 3.2: UAE versus myomectomy – Satisfaction with treatment (measured by asking the women if they obtained symptom relief) up to 24 months in women with suspected or diagnosed fibroids



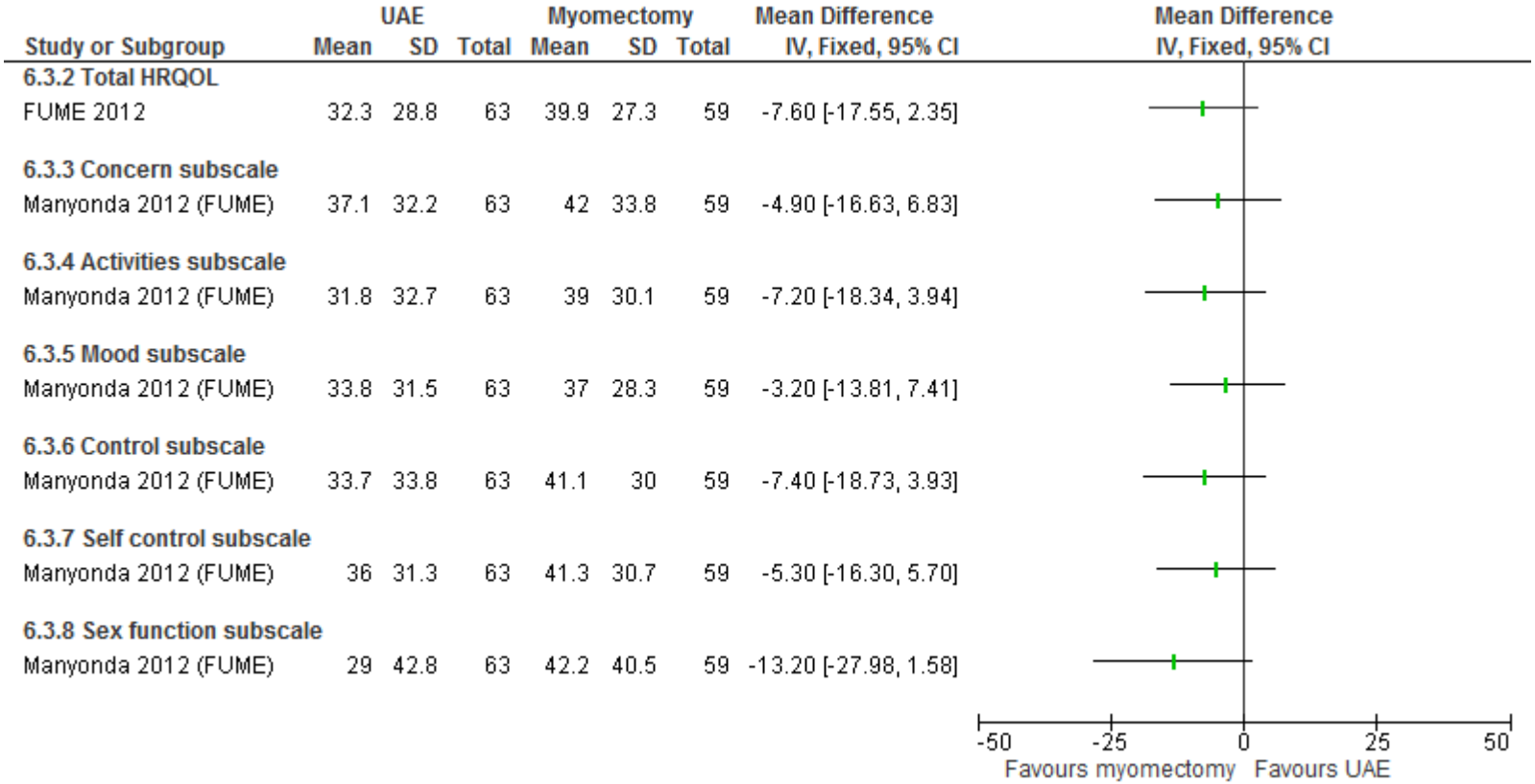
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolisation

Figure 32: Comparison 3.2: UAE versus myomectomy – UFS-QOL Symptom severity change score from baseline at 1 year in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by lower values)



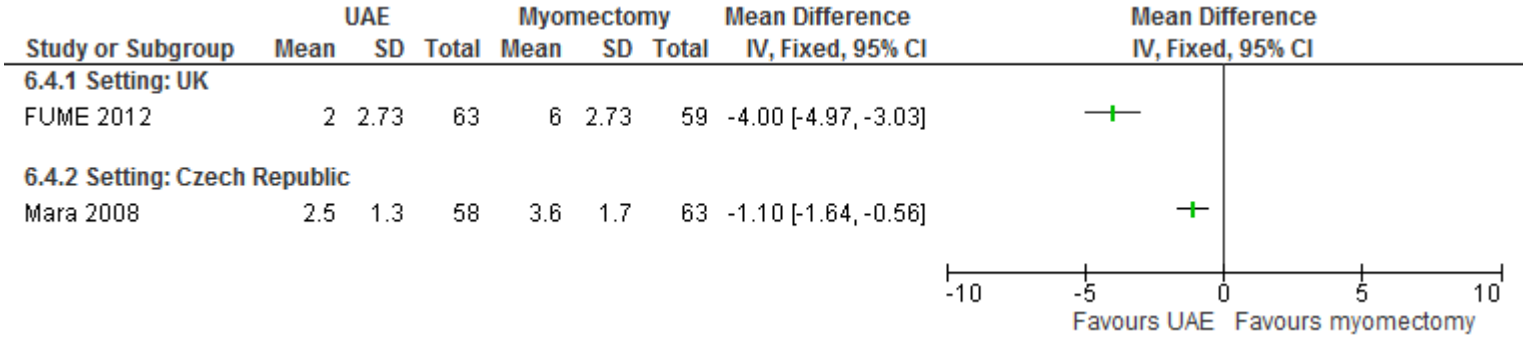
CI: confidence interval; IV: inverse variance; SD: standard deviation; UAE: uterine artery embolization; UFS-QOL: Uterine fibroid symptom and health-related quality of life

Figure 33: Comparison 3.2: UAE versus myomectomy – UFS-QOL Health-related quality of life change score from baseline at 1 year in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



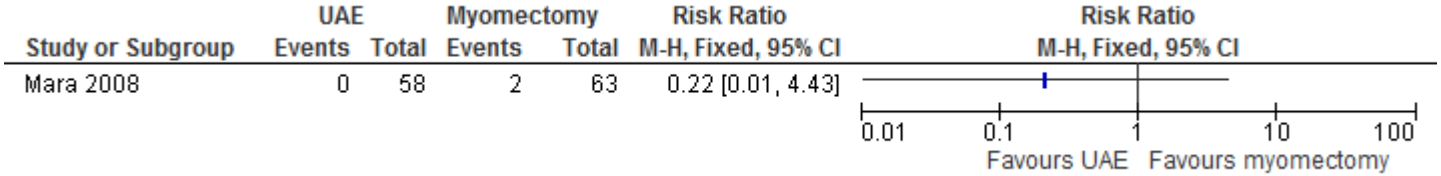
CI: confidence interval; HRQOL: health-related qualiy of life; IV: inverse variance; SD: standard deviation; UAE: uterine artery embolization; UFS-QOL: Uterine fibroid symptom and health-related quality of life

Figure 34: Comparison 3.2: UAE versus myomectomy – Length of hospital stay in days in women with suspected or diagnosed fibroids (better indicated by lower values)



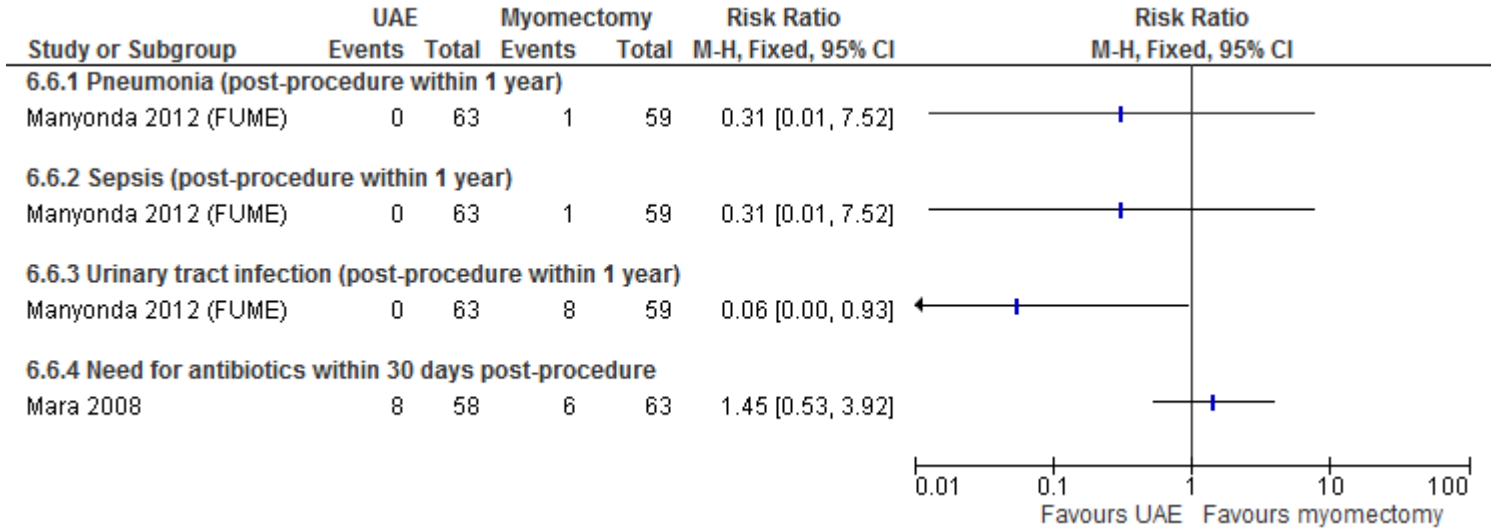
CI: confidence interval; IV: inverse variance; SD: standard deviation; UAE: uterine artery embolization

Figure 35: Comparison 3.2: UAE versus myomectomy – Blood transfusion in women with suspected or diagnosed fibroids



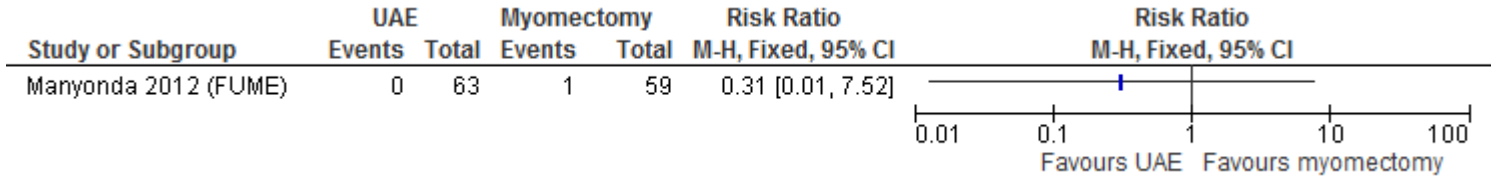
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 36: Comparison 3.2: UAE versus myomectomy – Infection in women with suspected or diagnosed fibroids



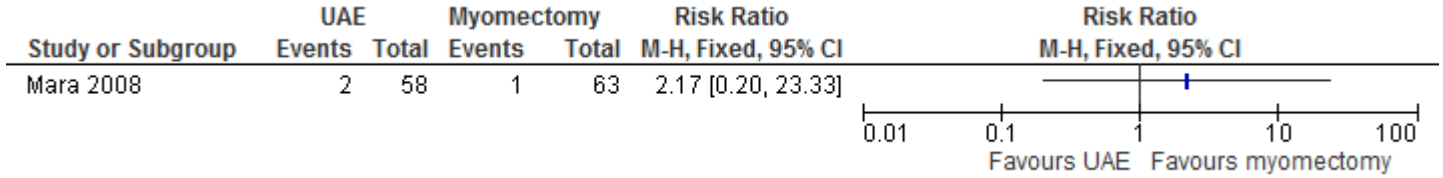
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 37: Comparison 3.2: UAE versus myomectomy – Pulmonary embolus within 1 year post-procedure in women with suspected or diagnosed fibroids



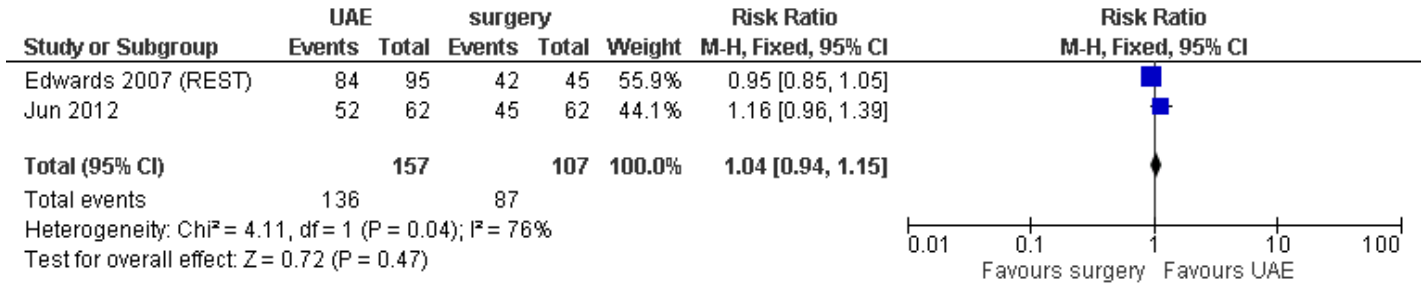
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 38: Comparison 3.2: UAE versus myomectomy – Unscheduled readmission rate within 4-6 weeks in women with suspected or diagnosed fibroids



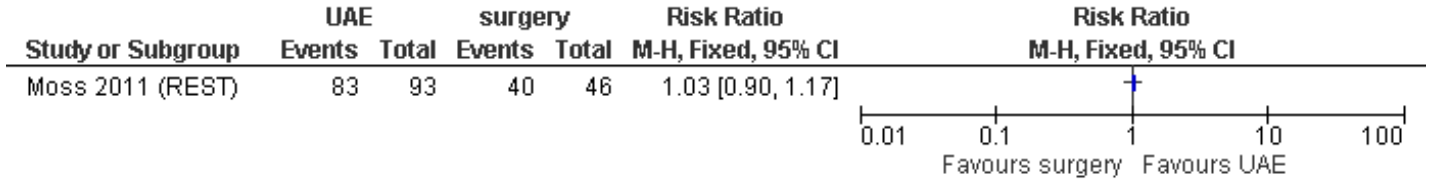
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 39: Comparison 3.3: UAE versus hysterectomy or myomectomy – Satisfaction with treatment (measurement method not specified) up to 12 months in women with suspected or diagnosed fibroids



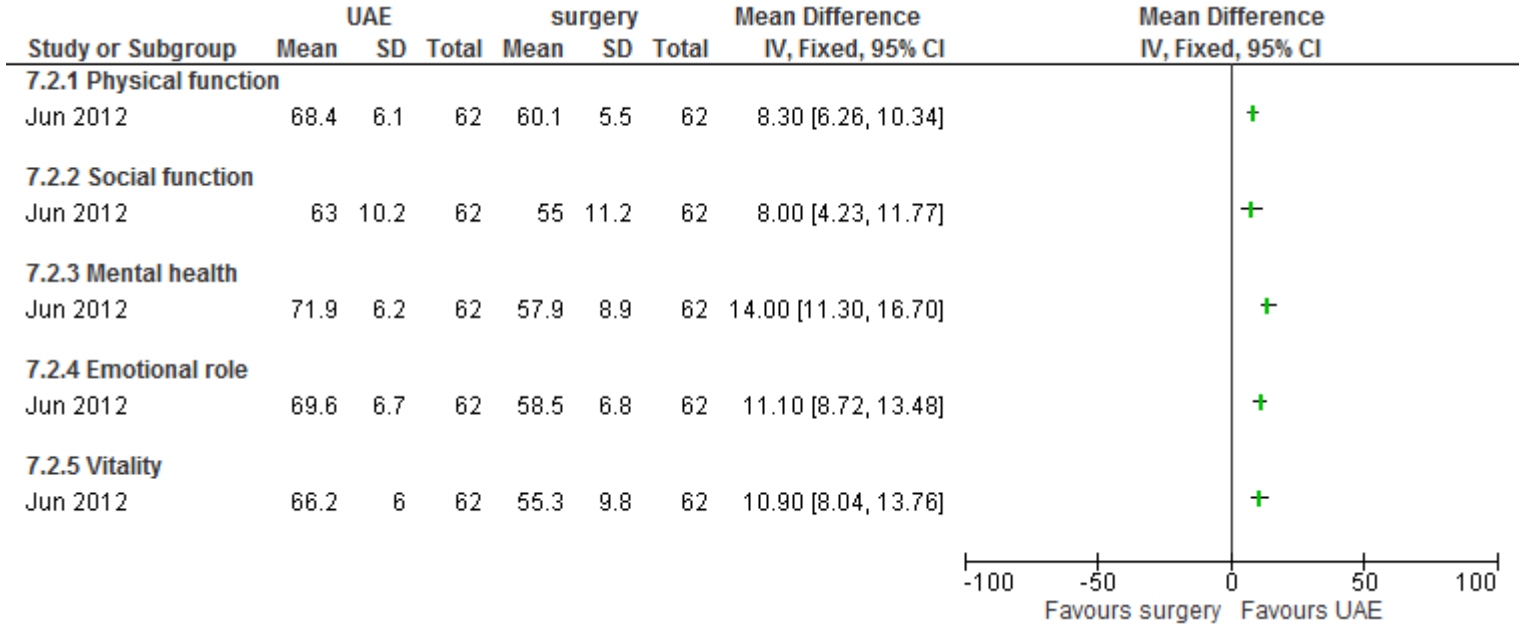
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 38: Comparison 3.3: UAE versus hysterectomy or myomectomy – Satisfaction with treatment (measurement method not specified) at 5 years in women with suspected or diagnosed fibroids



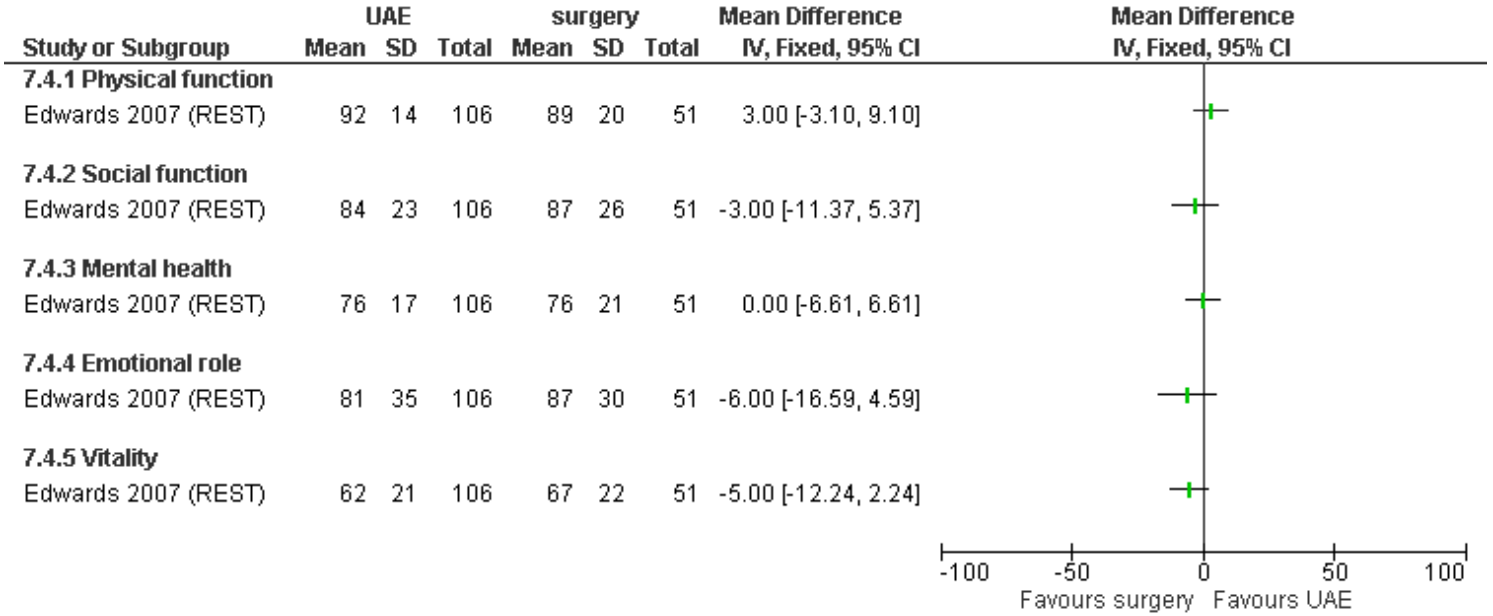
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 39: Comparison 3.3: UAE versus hysterectomy or myomectomy – SF-36 Health-related quality of life score at 6 months in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



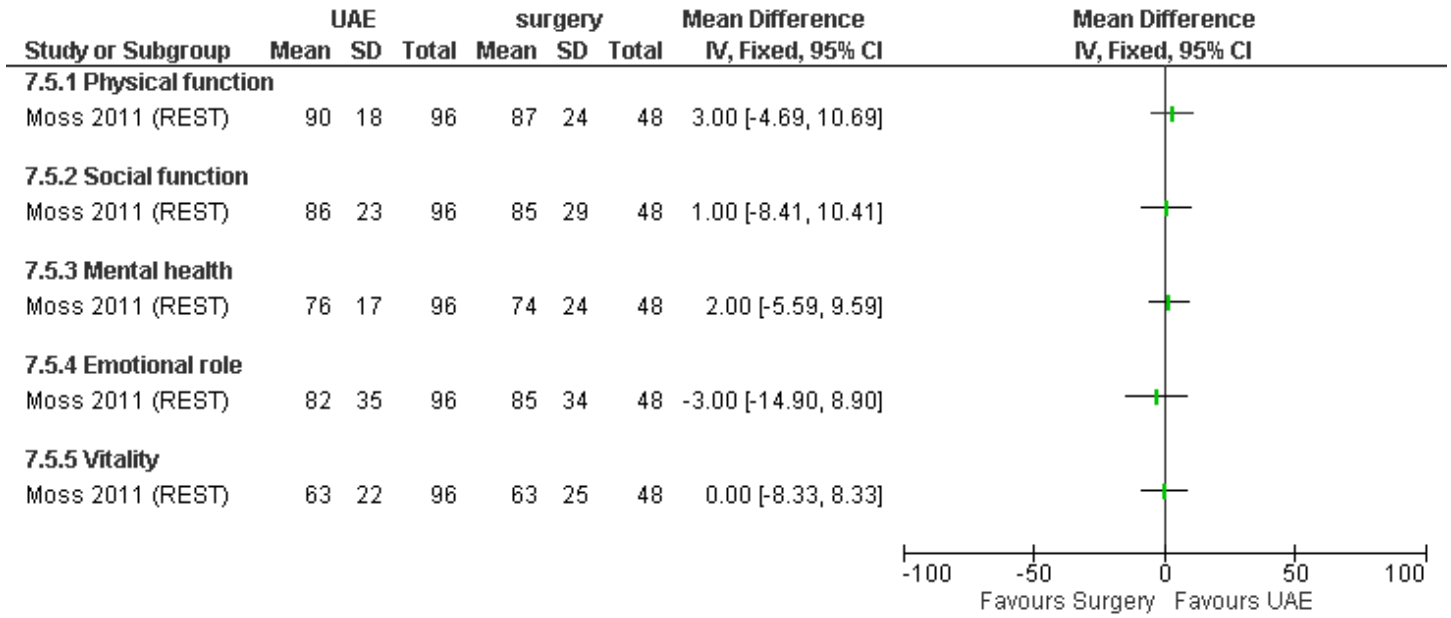
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; UAE: uterine artery embolization

Figure 40: Comparison 3.3: UAE versus hysterectomy or myomectomy – SF-36 Health-related quality of life score at 12 months in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



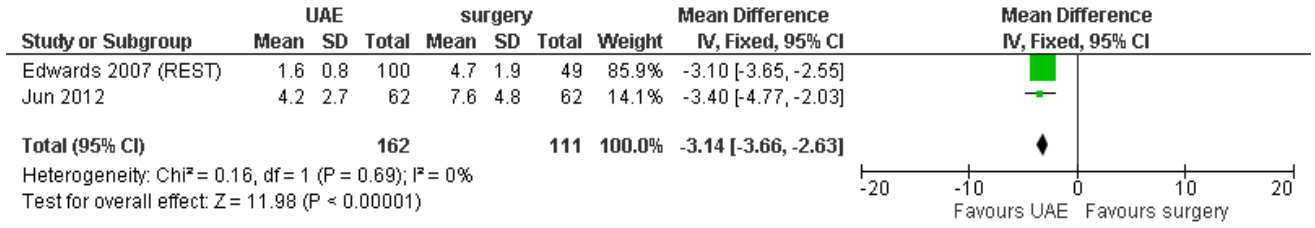
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; UAE: uterine artery embolization

Figure 41: Comparison 3.3: UAE versusu hysterectomy or myomectomy – SF-36 Health-related quality of life score at 5 years in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



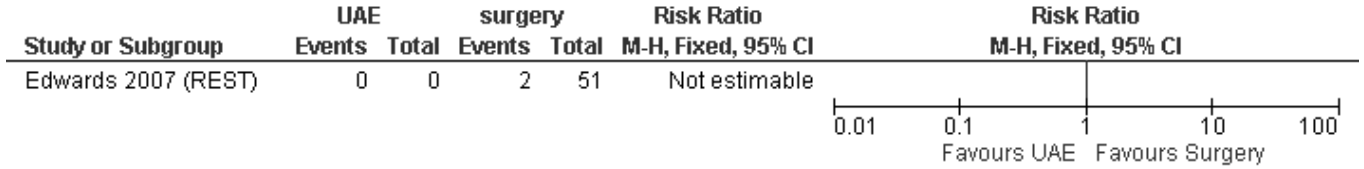
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; UAE: uterine artery embolization

Figure 42: Comparison 3.3: UAE versus hysterectomy or myomectomy – Length of hospital stay in days in women with suspected or diagnosed fibroids (better indicated by lower values)



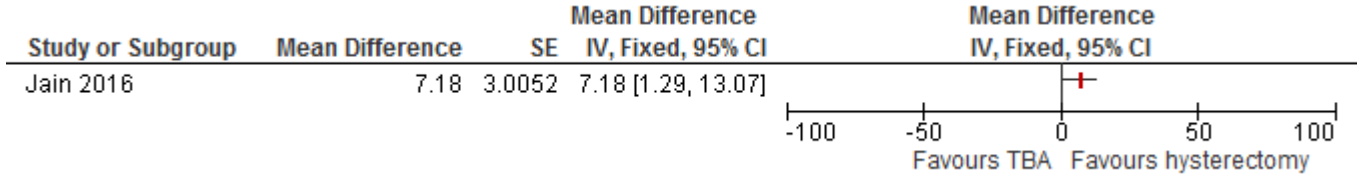
CI: confidence interval; IV: inverse variance; SD: standard deviation; UAE: uterine artery embolization

Figure 43: Comparison 3.3: UAE versus hysterectomy or myomectomy – Adverse event: wound infection (during hospital stay) in women with diagnosed or confirmed fibroids



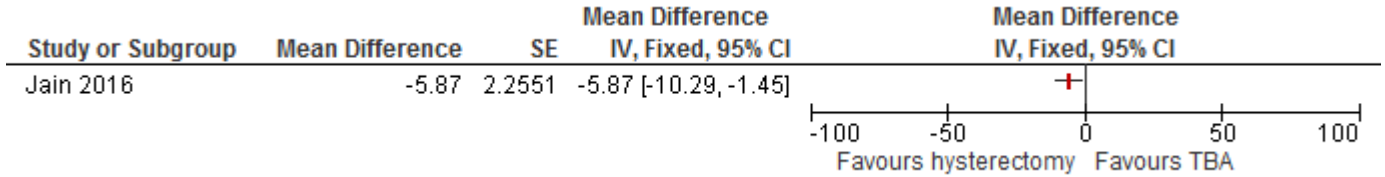
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel; UAE: uterine artery embolization

Figure 44: Comparison 3.4: Thermal balloon ablation versus hysterectomy – UFS-QOL Symptom severity score at 6 months in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by lower values)



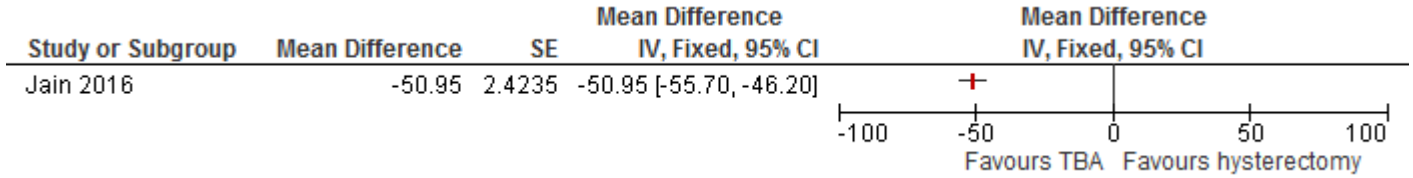
CI: confidence interval; IV: inverse variance; SE: standard error; TBA: thermal balloon ablation; UFS-QOL: Uterine fibroid symptom and health-related quality of life

Figure 45: Comparison 3.4: Thermal balloon ablation versus hysterectomy – UFS-QOL Health-related quality of life score at 6 months in women with suspected or diagnosed fibroids (range of scores 0-100, better indicated by higher values)



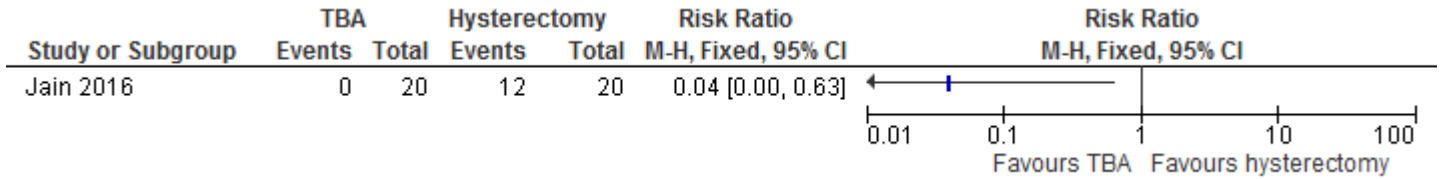
CI: confidence interval; IV: inverse variance; SE: standard error; TBA: thermal balloon ablation; UFS-QOL: Uterine fibroid symptom and health-related quality of life

Figure 46: Comparison 3.4: Thermal balloon ablation versus hysterectomy – Length of hospital stay in hours in women with suspected or diagnosed fibroids (better indicated by lower values)



CI: confidence interval; IV: inverse variance; SE: standard error; TBA: thermal balloon ablation; UFS-QOL: Uterine fibroid symptom and health-related quality of life

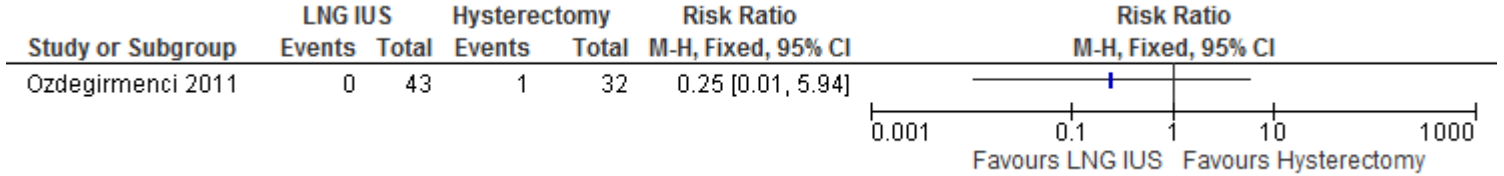
Figure 47: Comparison 3.4: Thermal balloon ablation versus hysterectomy – Blood transfusion in women with suspected or confirmed fibroids



CI: confidence interval; M-H: Mantel-Haenszel; TBA: thermal balloon ablation

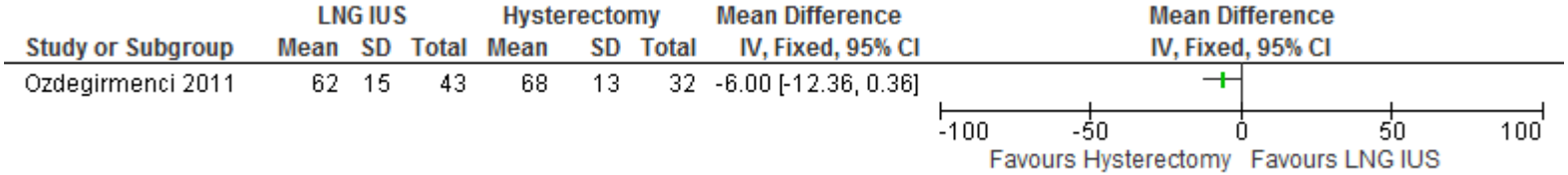
2. Women with suspected or diagnosed adenomyosis

Figure 48: Comparison 1: LNG-IUS versus hysterectomy – Adverse event: Wound infection (post-procedure) in women with suspected or diagnosed adenomyosis



CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

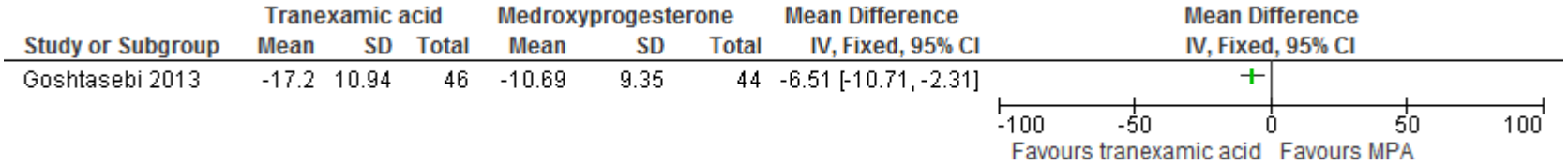
Figure 49: Comparison 1: LNG-IUS versus hysterectomy - Health-related quality of life – environmental domain (WHOQOL-BREF TR) at 1 year in women with suspected or diagnosed adenomyosis (range of scres 0-100, better indicated by higher values)



CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

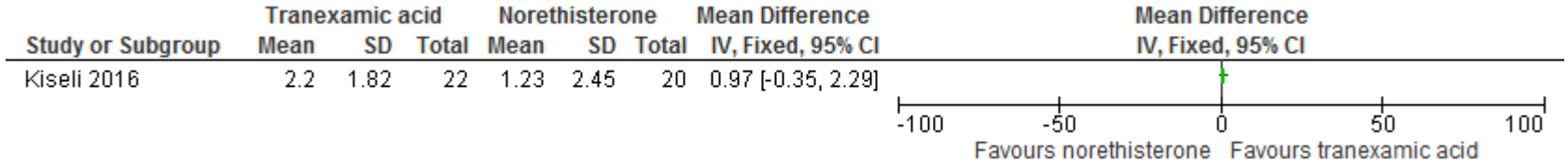
3. Women with no identified pathology

Figure 50: Comparison 2.3: Tranexamic acid versus progestogen – Health-related quality of life change from baseline after 3 cycles of treatment - Menorrhagia Questionnaire in women with no identified pathology (range of scores 0-100, better indicated by lower values)



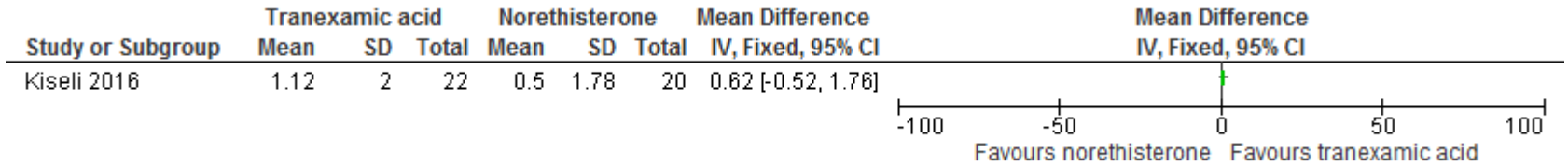
CI: confidence interval; IV: inverse variance; MPA: medroxyprogesterone; SD: standard deviation;

Figure 51: Comparison 2.3: Tranexamic acid versus progestogen – Health-related quality of life – Physical domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



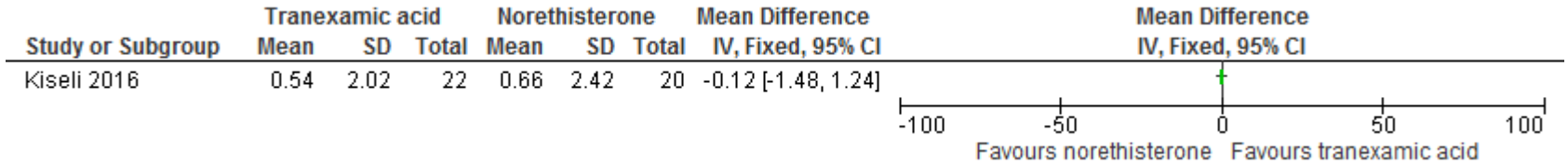
CI: confidence interval; IV: inverse variance; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 52: Comparison 2.3: Tranexamic acid versus progestogen – Health-related quality of life – Psychosocial domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



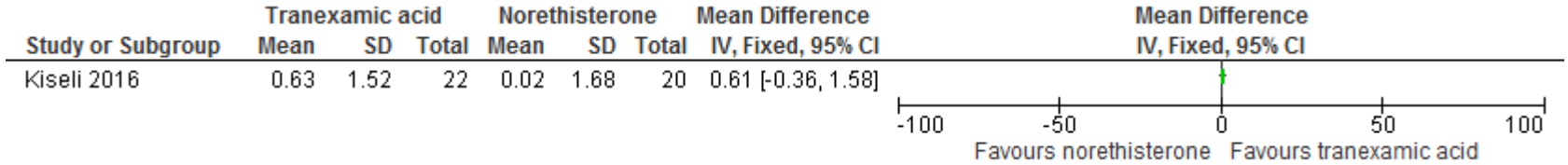
CI: confidence interval; IV: inverse variance; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 53: Comparison 2.3: Tranexamic acid versus progestogen – Health-related quality of life – Social domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



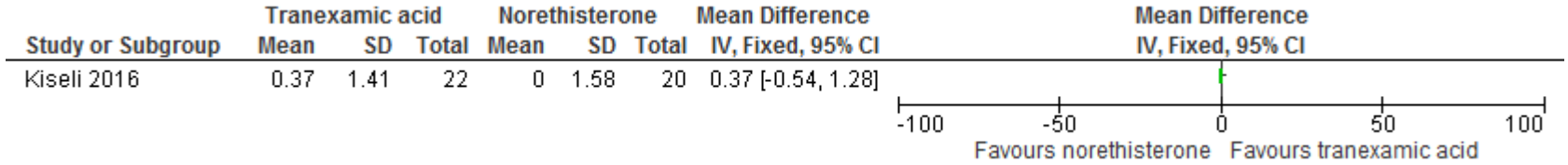
CI: confidence interval; IV: inverse variance; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 54: Comparison 2.3: Tranexamic acid versus progestogen – Health-related quality of life – Environmental domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



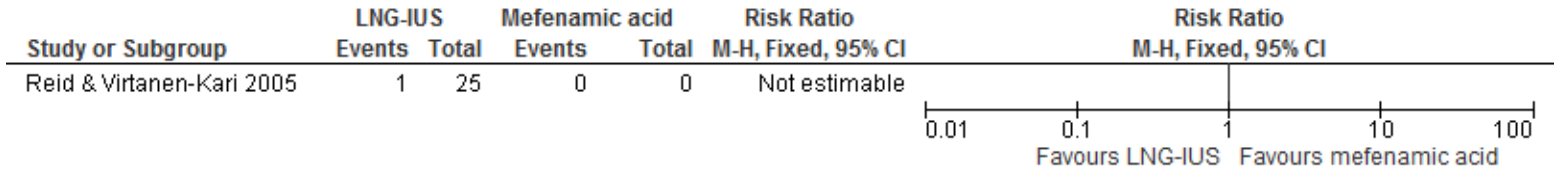
CI: confidence interval; IV: inverse variance; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 55: Comparison 2.3: Tranexamic acid versus progestogen – Health-related quality of life – Environmental domain (Turkey-specific) (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



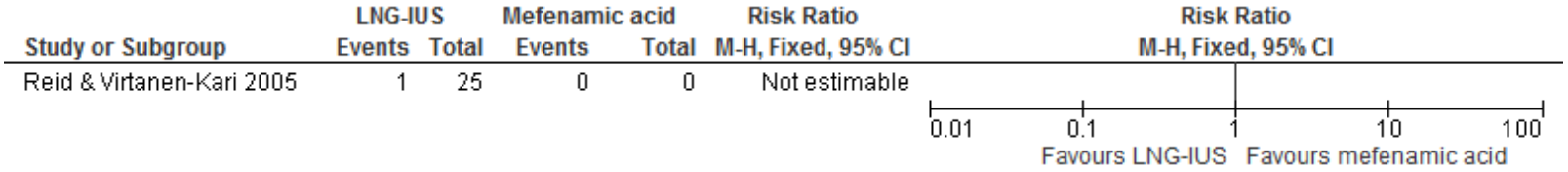
CI: confidence interval; IV: inverse variance; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 56: Comparison 2.4: LNG-IUS versus NSAIDs – Chlamydial infection (post-procedure) in women with no identified pathology



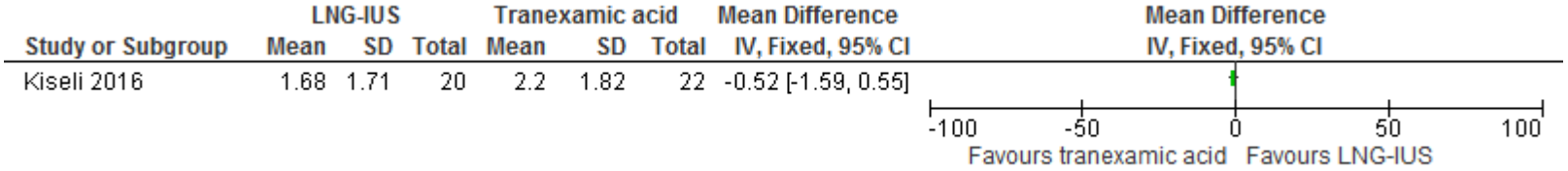
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; NSAIDs: non-steroidal anti-inflammatory drugs

Figure 57: Comparison 2.4: LNG-IUS versus NSAIDs – Expulsion (within 30 days) in women with no identified pathology



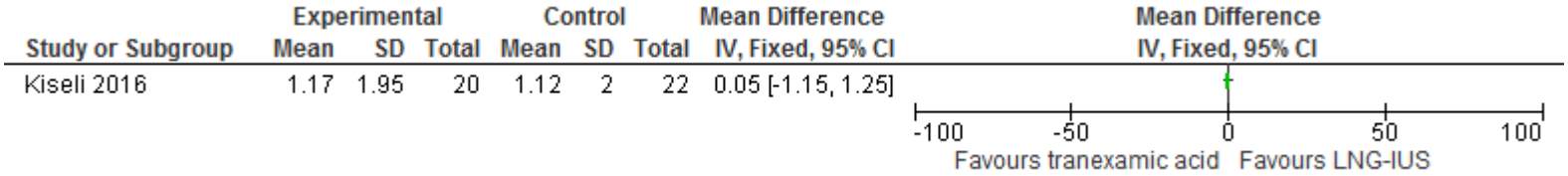
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; NSAIDs: non-steroidal anti-inflammatory drugs

Figure 58: Comparison 2.5: LNG-IUS versus tranexamic acid – Health-related quality of life – Physical domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



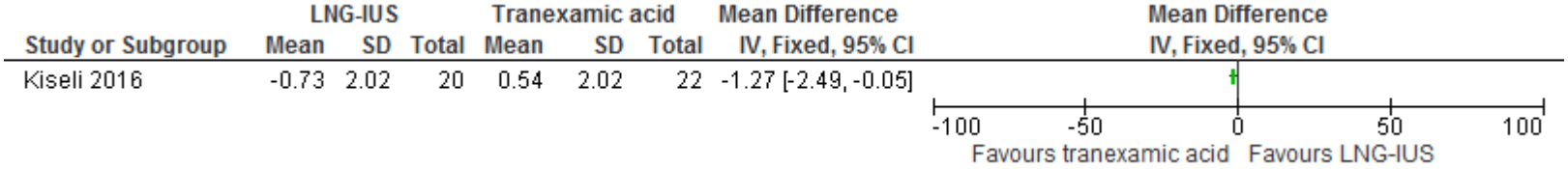
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 59: Comparison 2.5: LNG-IUS versus tranexamic acid – Health-related quality of life – Psychosocial domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



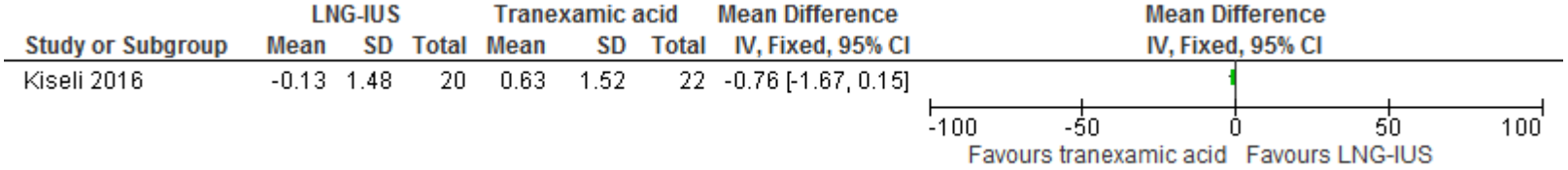
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 60: Comparison 2.5: LNG-IUS versus tranexamic acid – Health-related quality of life – Social domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identifiable pathology (range of scores 0-100, better indicated by higher values)



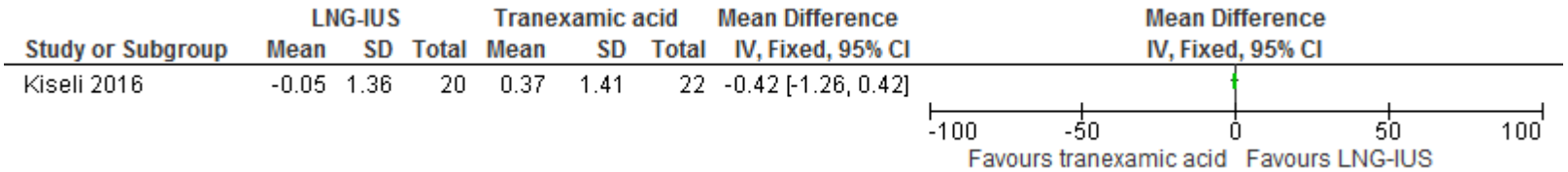
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 61: Comparison 2.5: LNG-IUS versus tranexamic acid – Health-related quality of life – Environmental domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



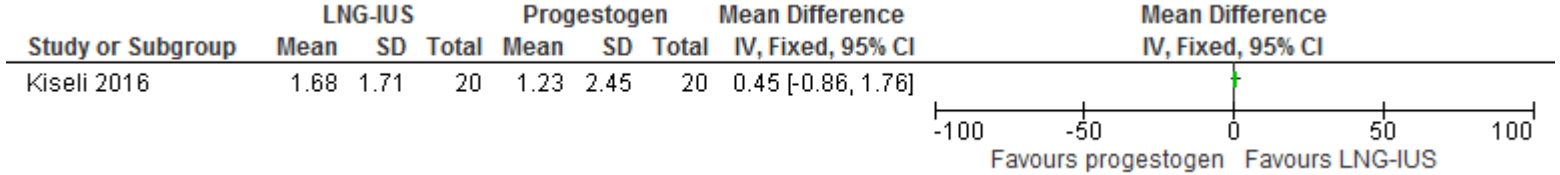
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 62: Comparison 2.5: LNG-IUS versus tranexamic acid – Health-related quality of life – Environmental domain (Turkey-specific) (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identifiable pathology (range of scores 0-100, better indicated by higher values)



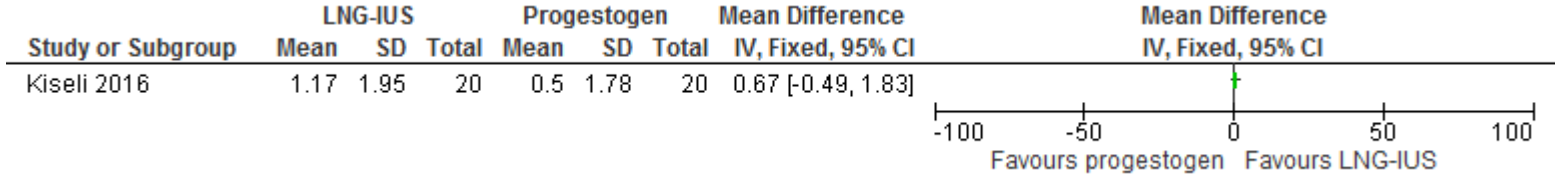
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 63: Comparison 2.6: LNG-IUS versus progestogens – Health-related quality of life – Physical domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



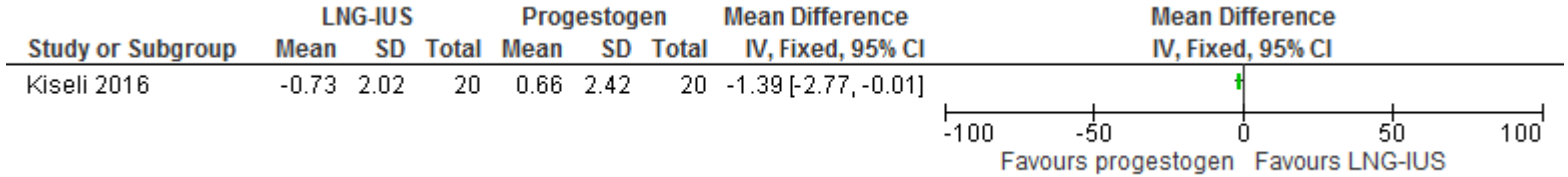
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 64: Comparison 2.6: LNG-IUS versus progestogens – Health-related quality of life – Psychosocial domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



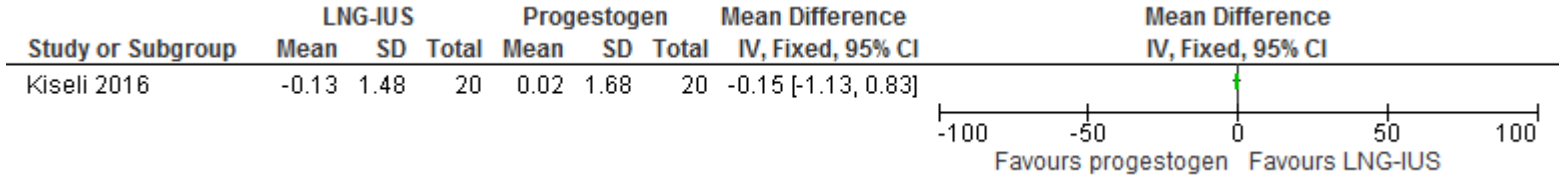
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 65: Comparison 2.6: LNG-IUS versus progestogens – Health-related quality of life – Social domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



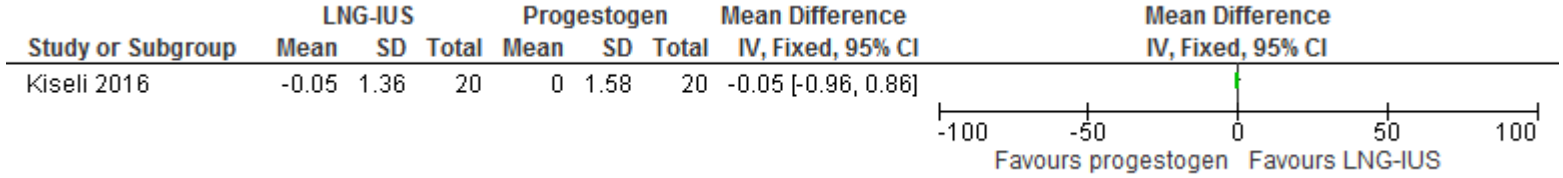
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 66: Comparison 2.6: LNG-IUS versus progestogens – Health-related quality of life – Environmental domain (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



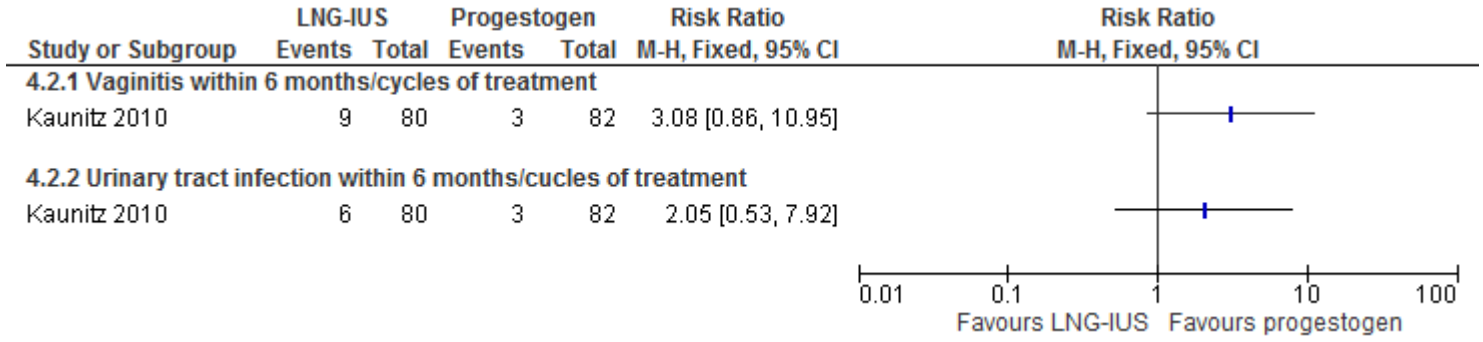
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 67: Comparison 2.6: LNG-IUS versus progestogens – Health-related quality of life – Environmental domain (Turkey-specific) (WHOQOL-BREF TR) after 6 cycles of treatment in women with no identified pathology (range of scores 0-100, better indicated by higher values)



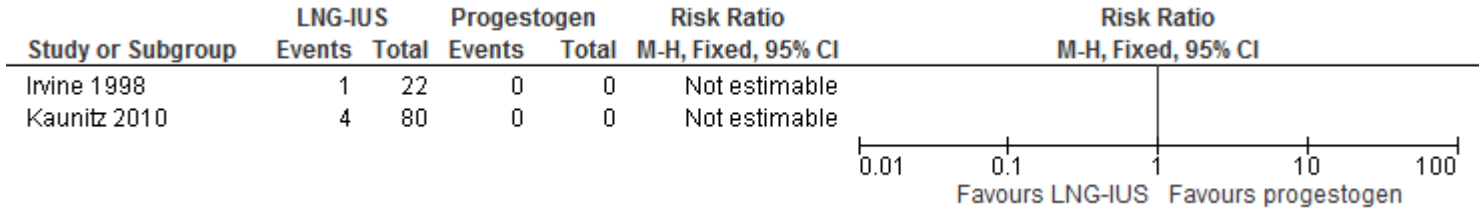
CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation; WHOQOL-BREF TR: World Health Organization Quality of Life abbreviated questionnaire (Turkish version)

Figure 68: Comparison 2.6: LNG-IUS versus progestogens – Infection in women with no identified pathology



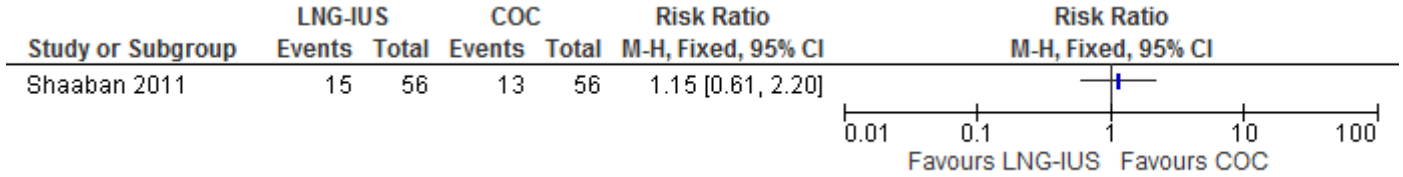
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 69: Comparison 2.6: LNG-IUS versus progestogens – Expulsion (within 6 months/cycles of treatment) in women with no identified pathology



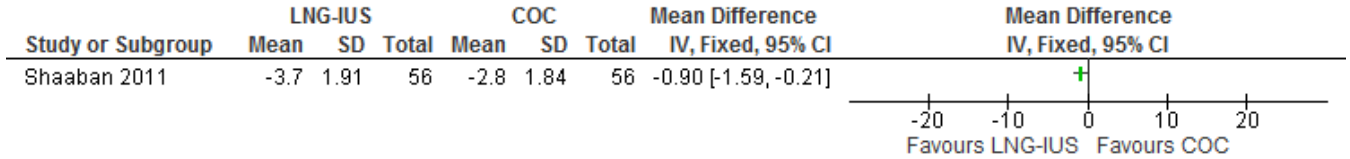
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 70: Comparison 2.7: LNG-IUS versus low-dose COC – HRQoL-4: Self-rated health very good or excellent at 12 months in women with no identified pathology



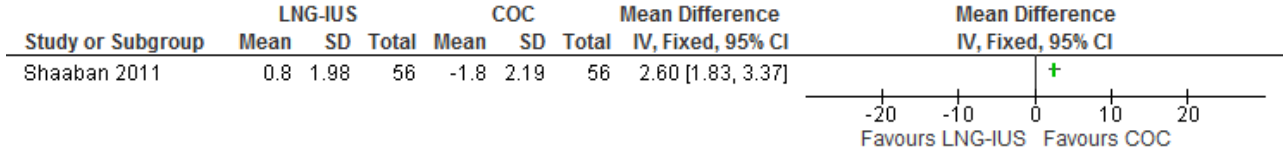
CI: confidence interval; COC: combined oral contraceptive; HRQoL-4: Health-related Quality of Life – 4; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 71: Comparison 2.7: LNG-IUS versus low-dose COC – HRQoL-4: No. of days in previous 30 days feeling physically unwell, change from baseline at 12 months in women with no identified pathology (better indicated by lower values)



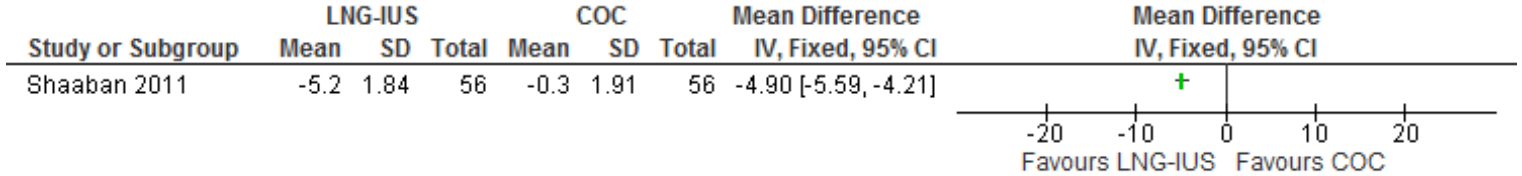
CI: confidence interval; COC: combined oral contraceptive; HRQoL-4: Health-related Quality of Life – 4; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

Figure 72: Comparison 2.7: LNG-IUS versus low-dose COC – HRQoL-4: No. of days in previous 30 days feeling mentally unwell, change from baseline at 12 months in women with no identified pathology (better indicated by lower values)



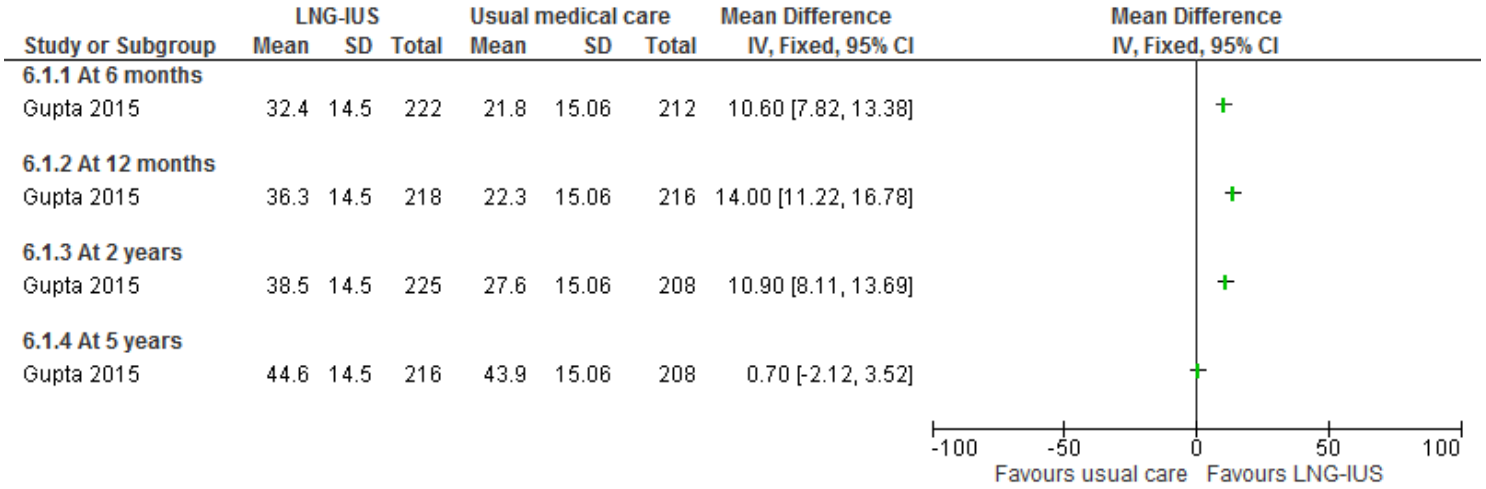
CI: confidence interval; COC: combined oral contraceptive; HRQoL-4: Health-related Quality of Life – 4; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

Figure 73: Comparison 2.7: LNG-IUS versus low-dose COC – HRQoL-4: No. on lost days in the previous 30 days, change from baseline at 12 months in women with no identified pathology (better indicated by lower values)



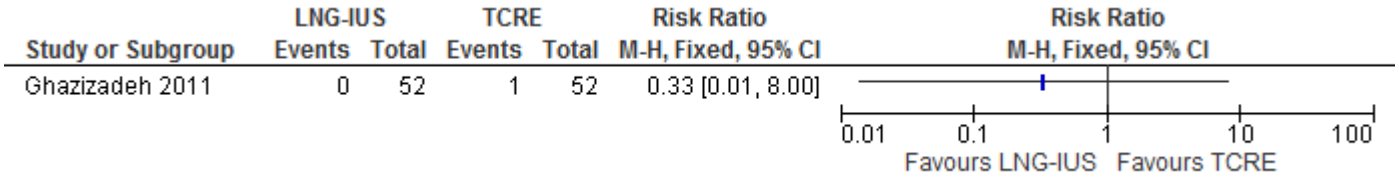
CI: confidence interval; COC: combined oral contraceptive; HRQoL-4: Health-related Quality of Life – 4; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

Figure 74: Comparison 2.8: LNG-IUS versus variety of pharmacological treatments - Health-related quality of life: Menorrhagia Multi-Attribute Scale summary score change from baseline in women with no identified pathology (range of scores 0-100, better indicated by higher values)



CI: confidence interval; IV: inverse variance; LNG-IUS: levonorgestrel-releasing intrauterine system; SD: standard deviation

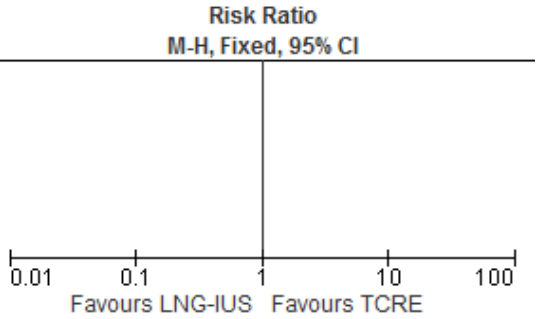
Figure 75: Comparison 3.1: LNG-IUS versus first generation endometrial resection/ablation (TCRE) – Uterine perforation in women with no identified pathology



CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; TCRE: transcervical resection of endometrium

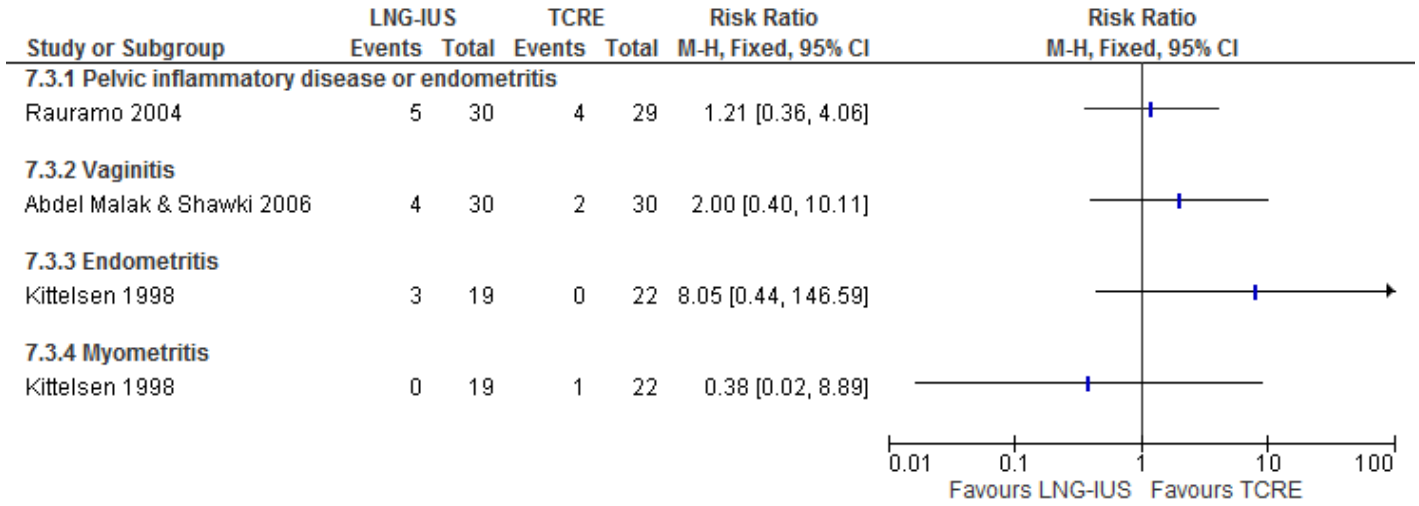
Figure 76: Comparison 3.1: LNG-IUS versus first generation endometrial resection/ablation (TCRE) - Expulsion (within 1 year) in women with no identified pathology

	LNG-IUS		TCRE			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Crosignani 1997	2	34	0	0		Not estimable
Ghazizadeh 2011	9	45	0	0		Not estimable
Rauramo 2004	1	30	0	0		Not estimable
Total (95% CI)		**109**		**0**		**Not estimable**
Total events	12		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



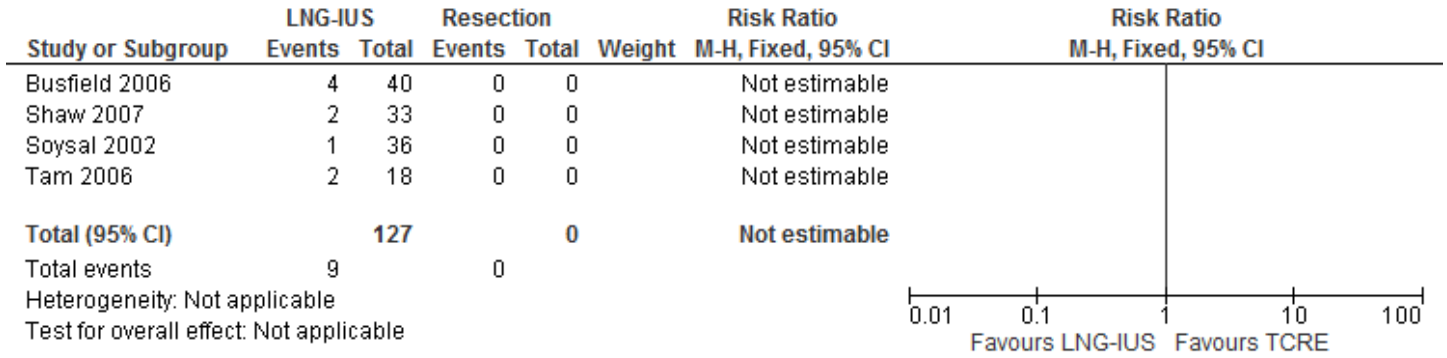
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; TCRE: transcervical resection of endometrium

Figure 77: Comparison 3.1: LNG-IUS versus first generation endometrial resection/ablation (TCRE) - Infection (post-procedure) in women with no identified pathology



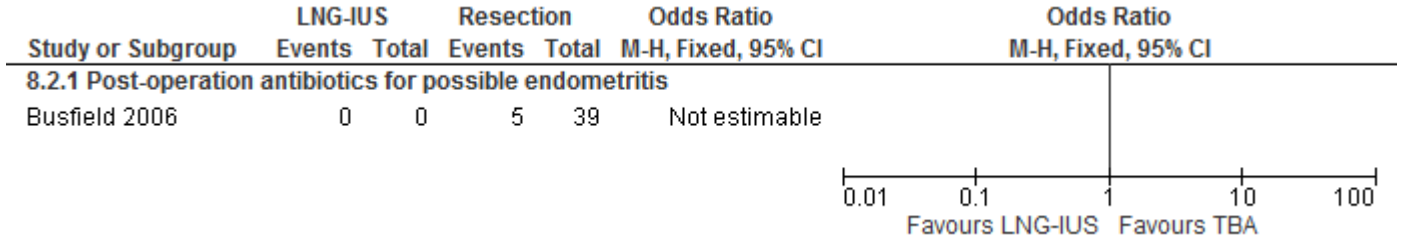
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; TCRE: transcervical resection of endometrium

Figure 78: Comparison 3.2: LNG-IUS versus second generation endometrial resection/ablation - Expulsion (within 3 to 24 months post-procedure depending on the study) in women with no identified pathology



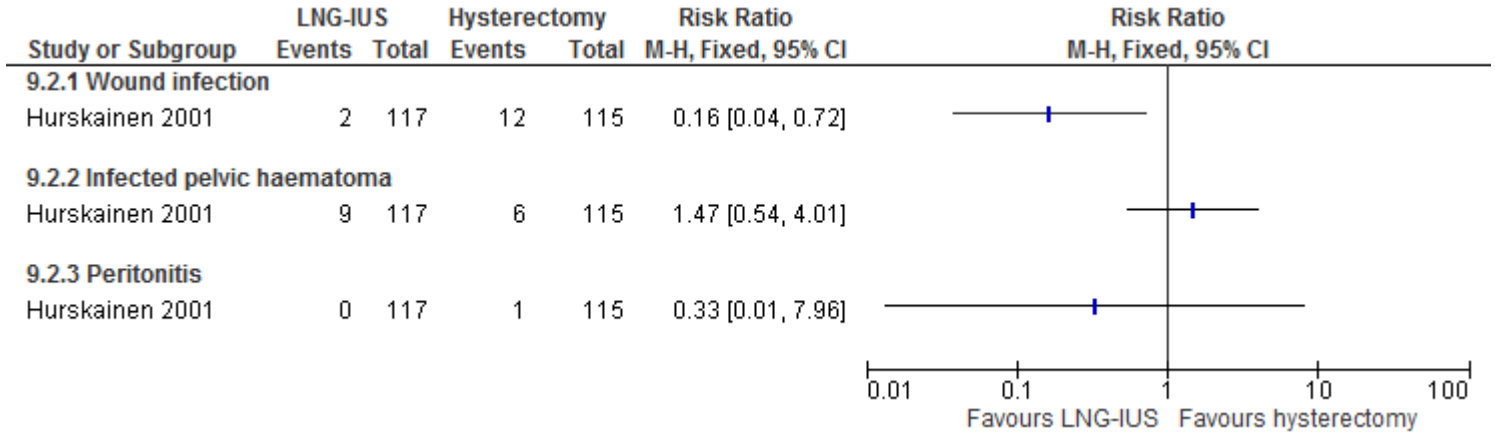
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; TCRE: transcervical resection of endometrium

Figure 79: Comparison 3.2: LNG-IUS versus second generation endometrial resection/ablation – Post operation antibiotics for possible endometritis in women no identified pathology



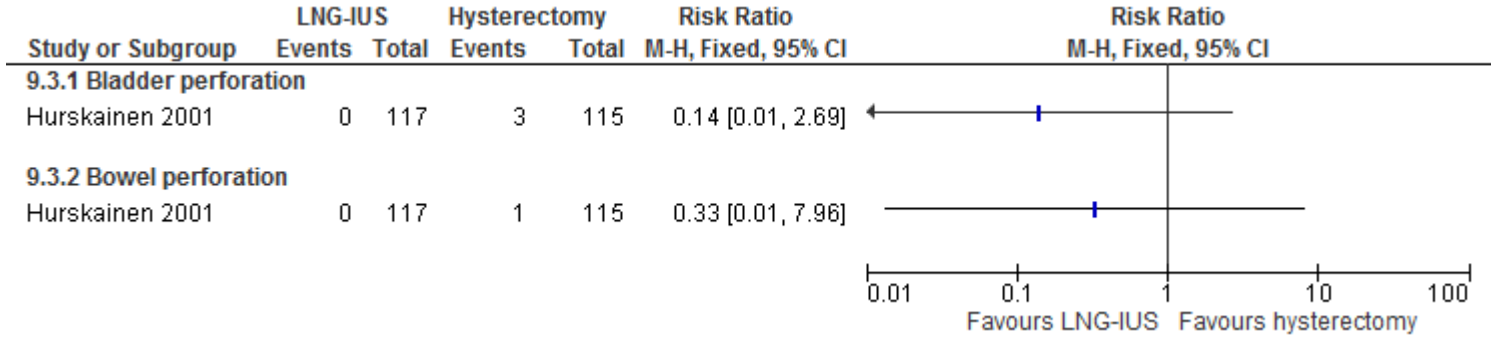
The risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel; TBA: thermal balloon ablation

Figure 80: Comparison 3.3: LNG-IUS versus hysterectomy – Infection (post-operative) in women with no identified pathology



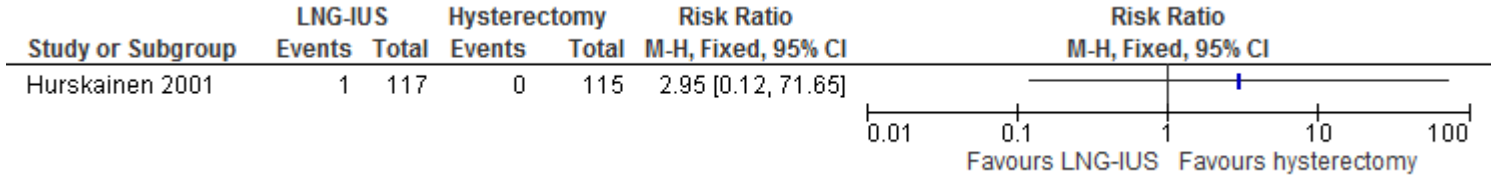
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 81: Comparison 3.3: LNG-IUS versus hysterectomy – Perforation in women with no identified pathology



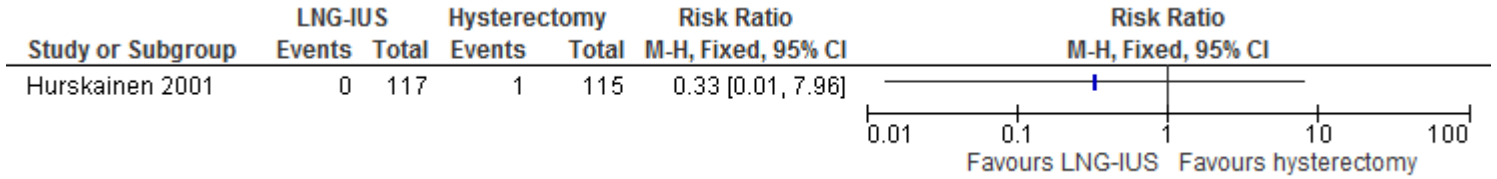
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 82: Comparison 3.3: LNG-IUS versus hysterectomy – Thromboembolic event (timeframe not clear) in women with no identified pathology



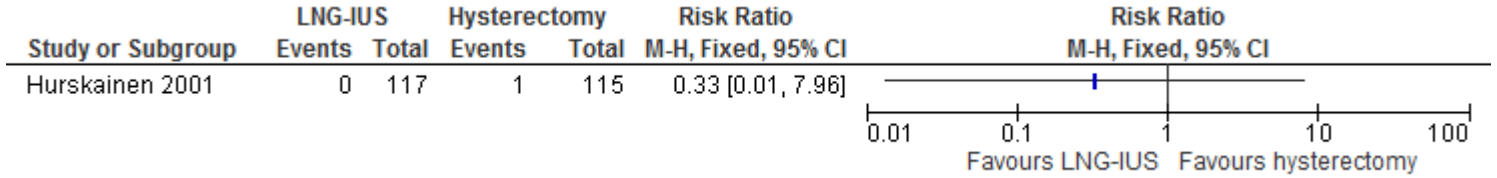
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 83: Comparison 3.3: LNG-IUS versus hysterectomy – Vesicovaginal fistula in women with no identified pathology



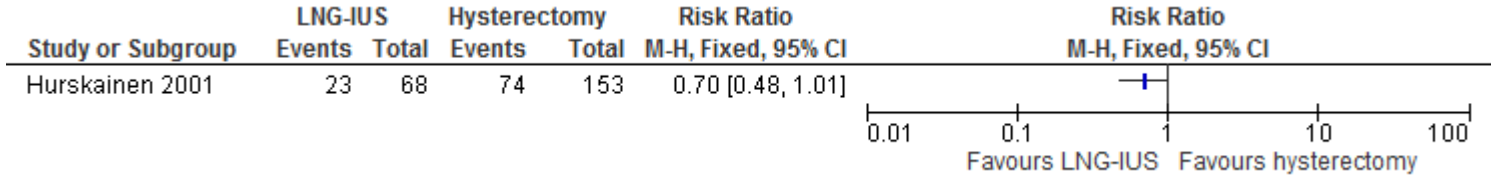
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 84: Comparison 3.3: LNG-IUS versus hysterectomy – Ureter lesion in women with no identified pathology



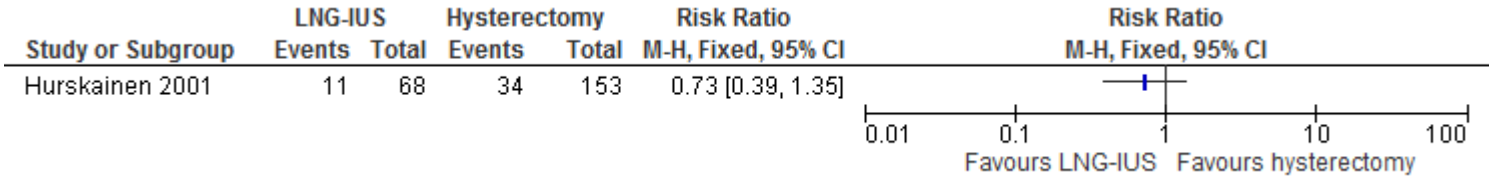
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 85: Comparison 3.3: LNG-IUS versus hysterectomy – Long term complication: Stress urinary incontinence (timeframe not clear) in women with no identified pathology



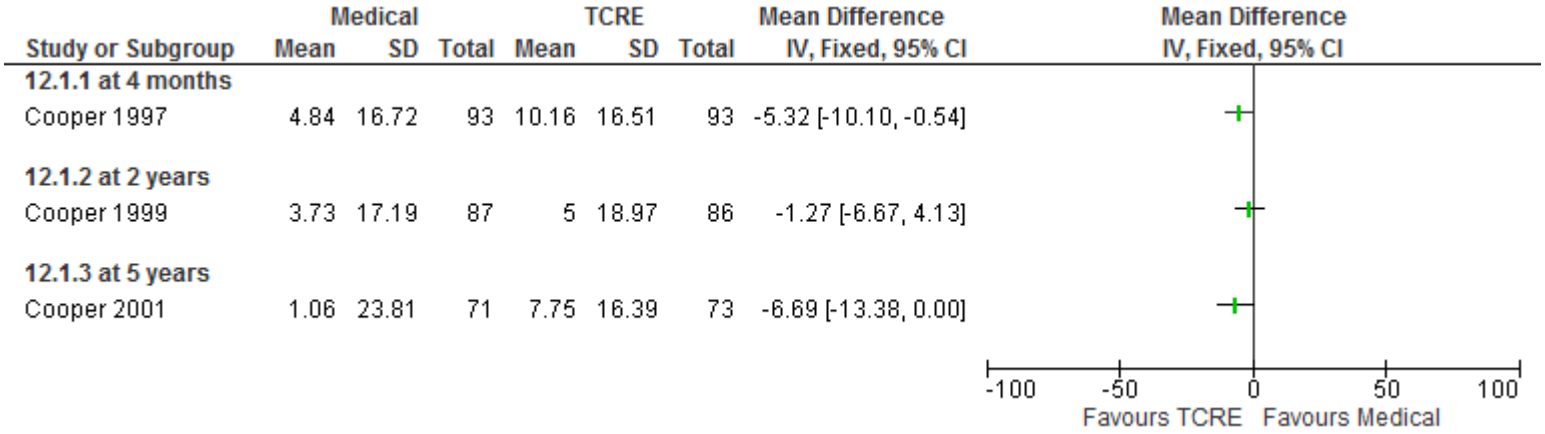
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 86: Comparison 3.3: LNG-IUS versus hysterectomy – Long term complication: Urge urinary incontinence (timeframe not clear) in women with no identified pathology



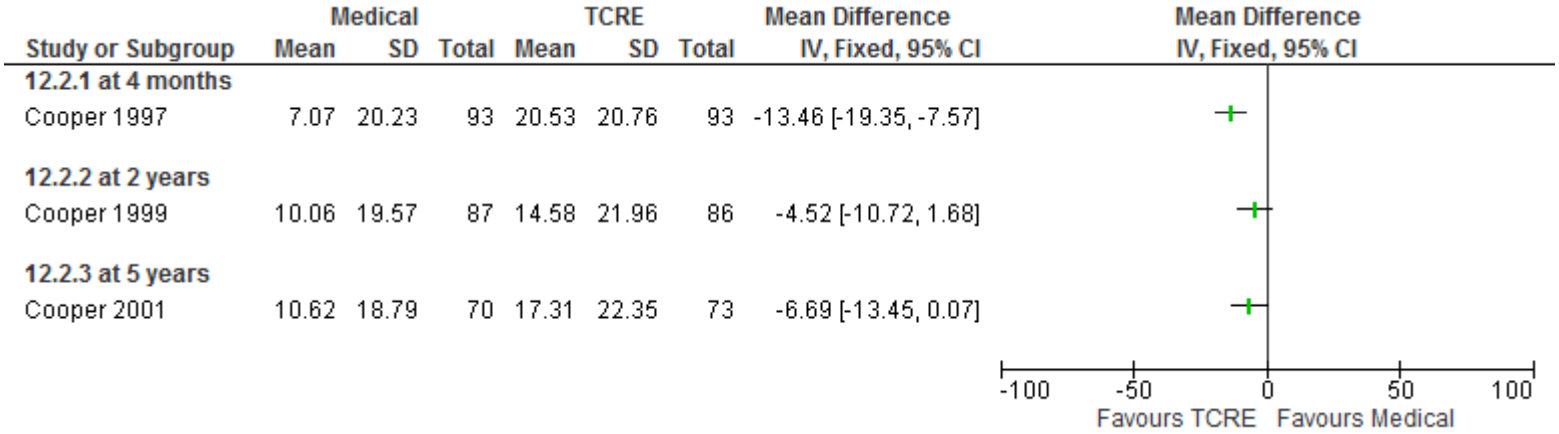
CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; M-H: Mantel-Haenszel

Figure 87: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Physical functioning in women with no identified pathology (range of scores 0-100, better indicated by higher values)



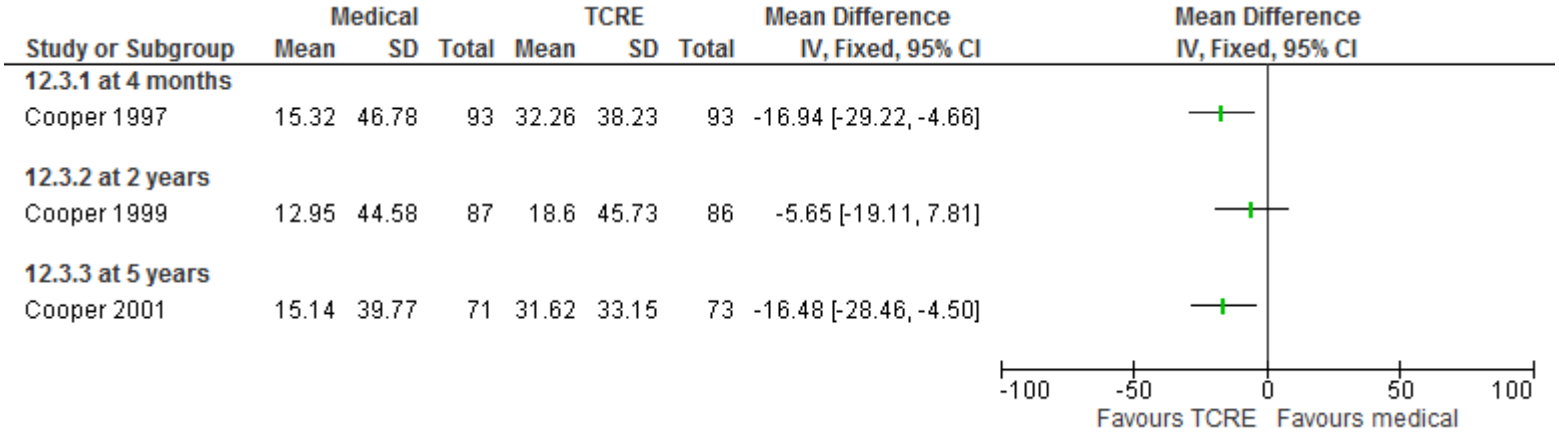
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 88: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Energy/fatigue in women with no identified pathology (range of scores 0-100, better indicated by higher values)



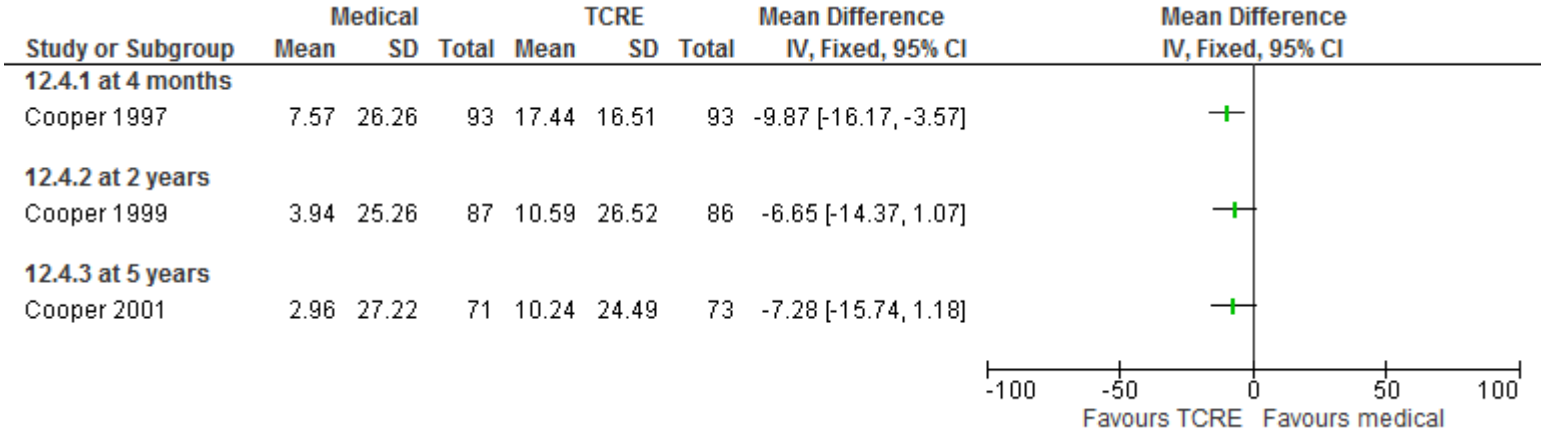
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 89: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Physical role in women with no identified pathology (range of scores 0-100, better indicated by higher values)



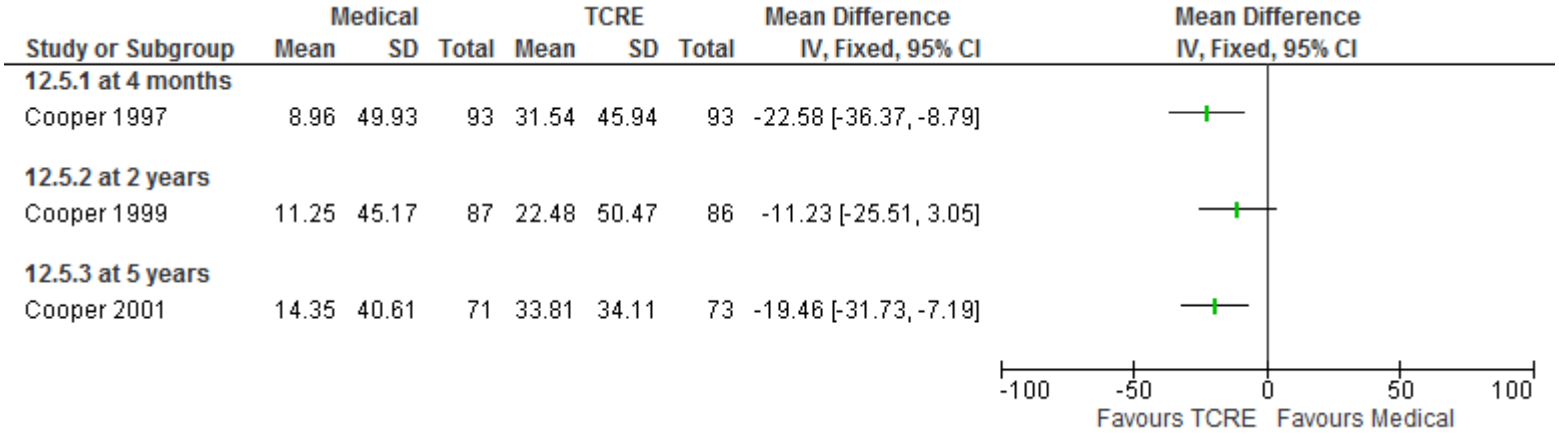
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 90: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Social function in women with no identified pathology (range of scores 0-100, better indicated by higher values)



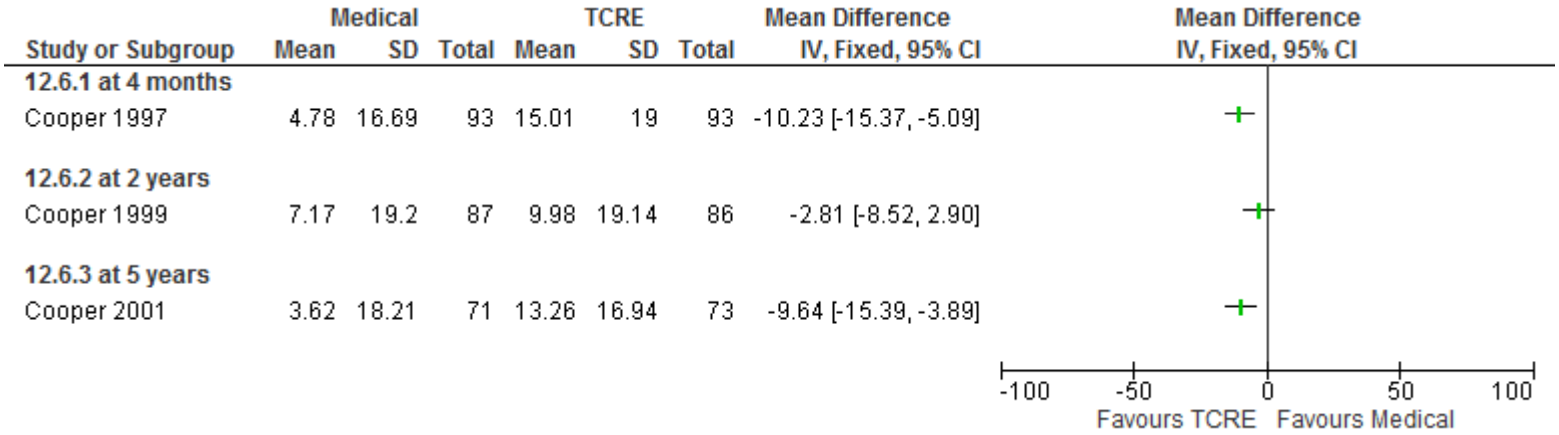
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 91: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Emotional role in women with no identified pathology (range of scores 0-100, better indicated by higher values)



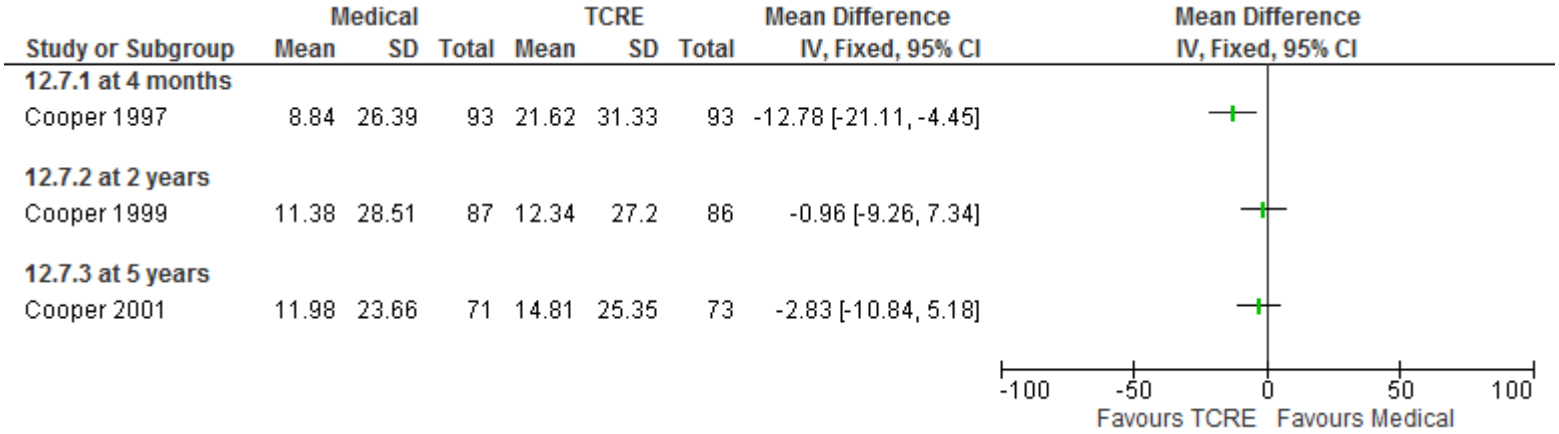
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 92: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Mental health in women with no identified pathology (range of scores 0-100, better indicated by higher values)



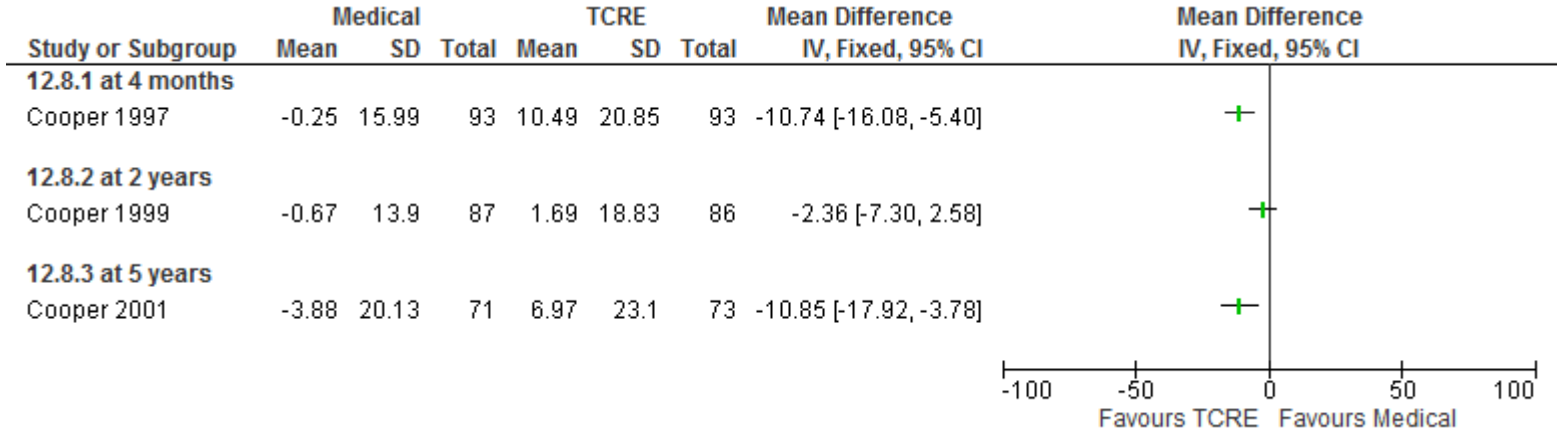
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 93: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – Pain in women with no identified pathology (range of scores 0-100, better indicated by higher values)



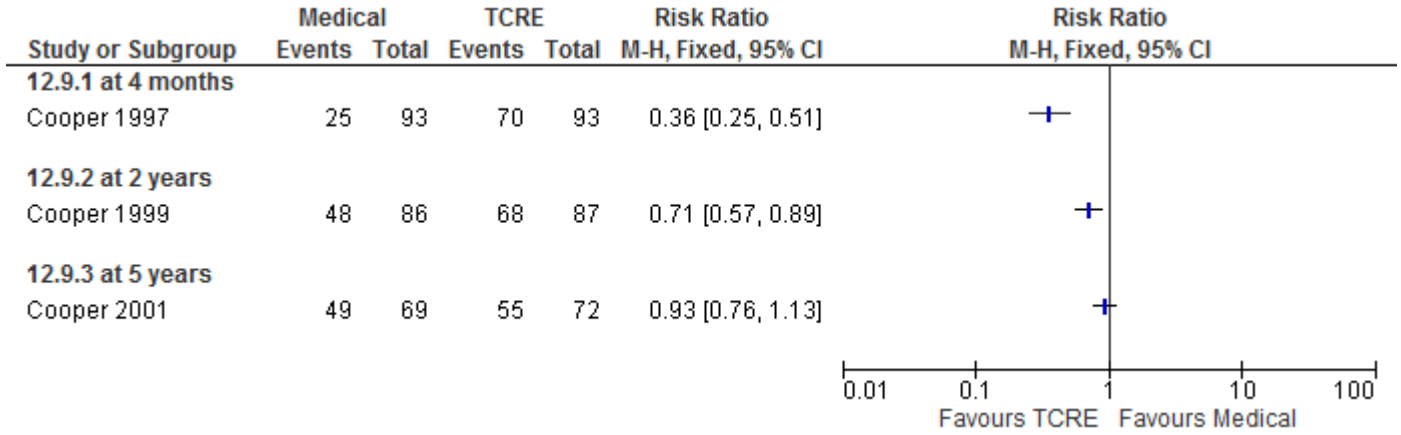
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 94: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Health-related quality of life: SF-36 – General health in women with no identified pathology (range of scores 0-100, better indicated by higher values)



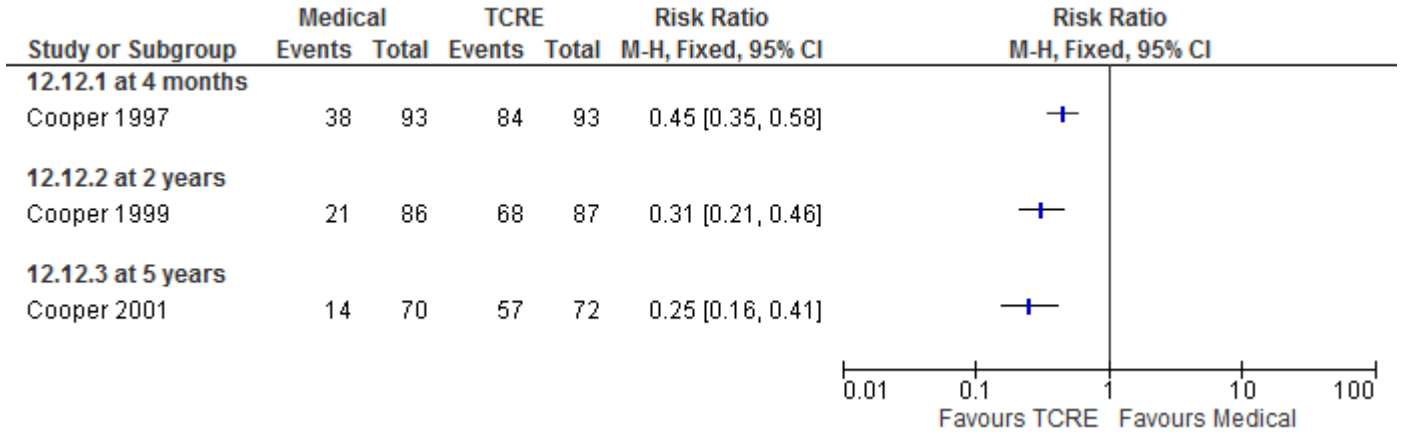
CI: confidence interval; IV: inverse variance; SD: standard deviation; SF-36: 36-Item Short Form Survey; TCRE: transcervical resection of endometrium

Figure 95: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Treatment satisfaction 'Totally or generally satisfied with treatment' in women with no identified pathology



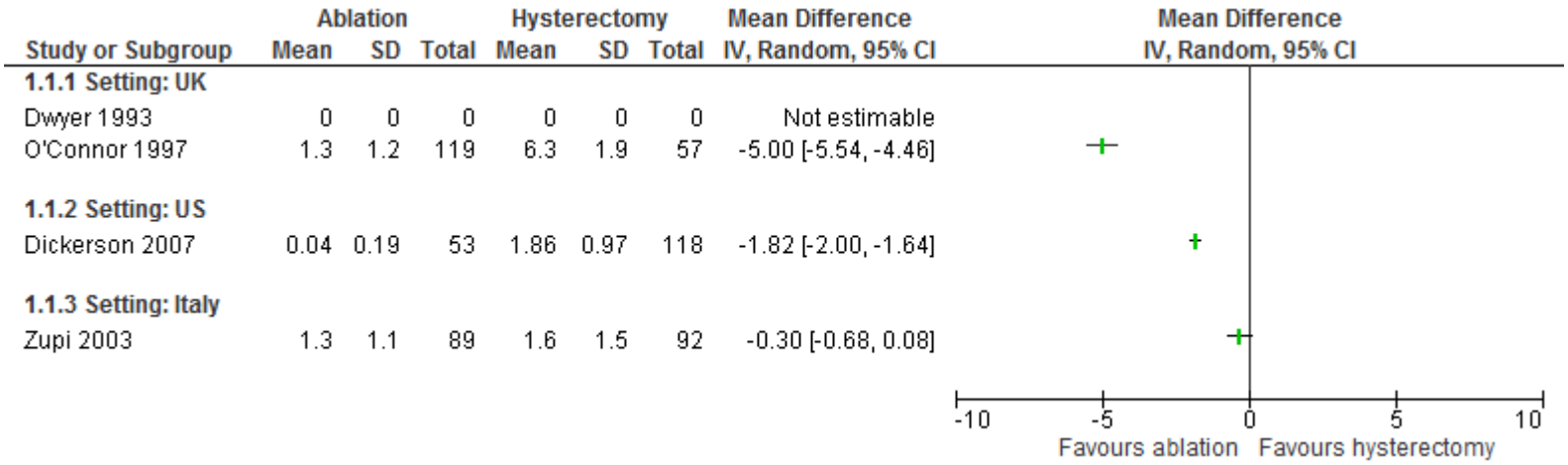
CI: confidence interval; M-H: Mantel-Haenszel; TCRE: Transcervical resection of endometrium

Figure 96: Comparison 4: Medical management versus transcervical endometrial resection with pre-operative gonadotrophin-releasing hormone injection – Treatment satisfaction 'Would recommend the treatment' in women with no identified pathology



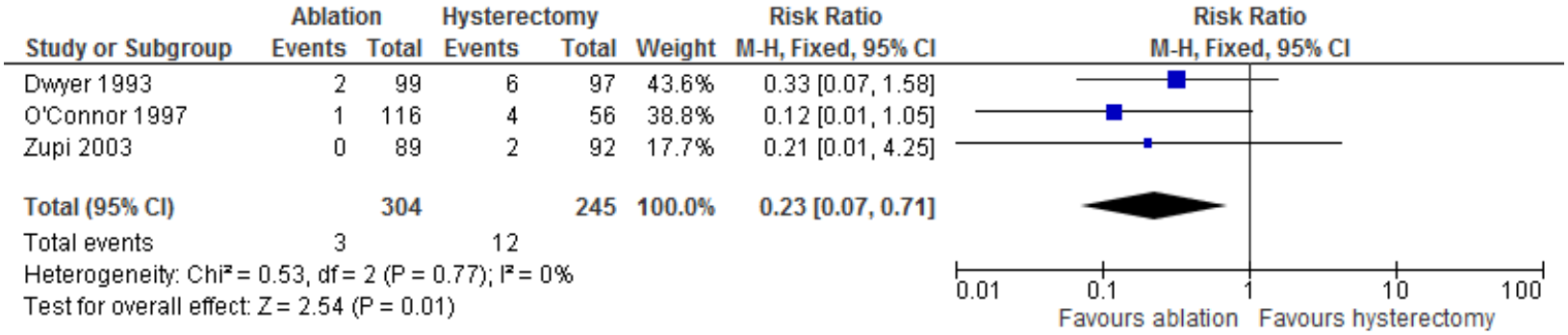
CI: confidence interval; M-H: Mantel-Haenszel; TCRE: Transcervical resection of endometrium

Figure 97: Comparison 5.1: First generation ablation/resection versus hysterectomy – Length of hospital stay in days in women with no identified pathology (better indicated by lower values)



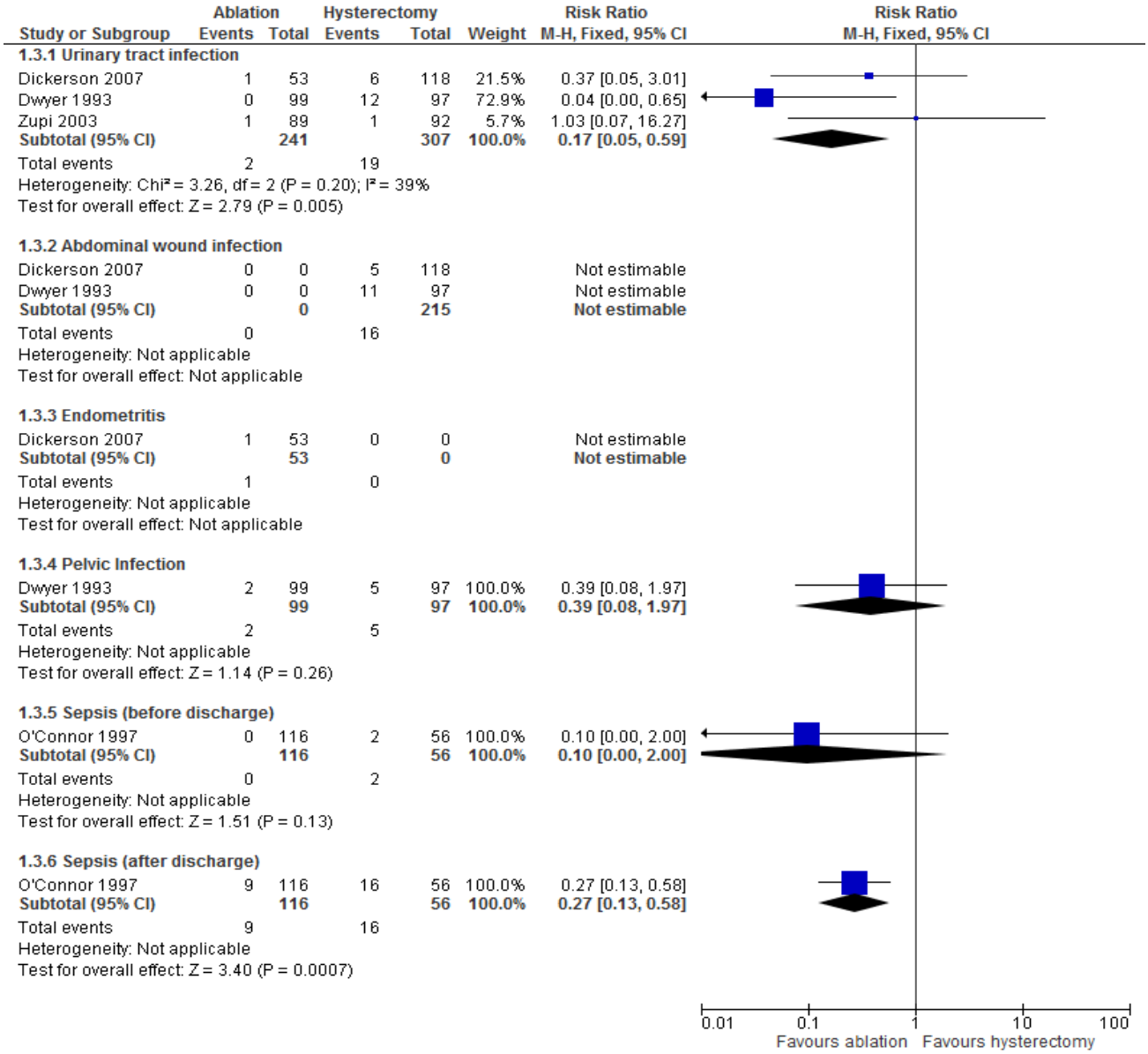
Risk ratios for Dwyer 1993 were not estimable because the length of hospital days were reported as median values.
CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 98: Comparison 5.1: First generation ablation/resection versus hysterectomy – Blood Transfusion in women with no identified pathology



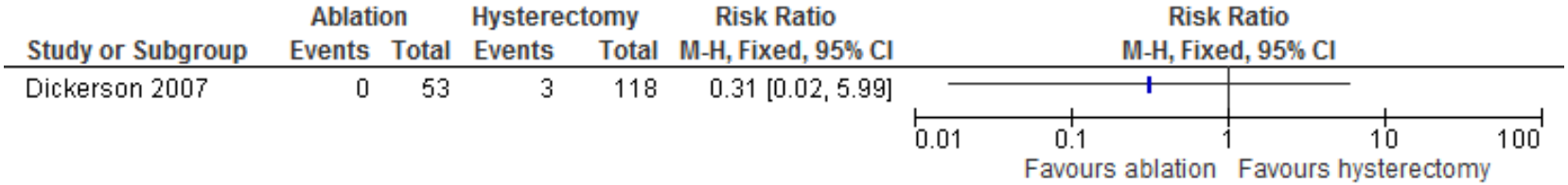
CI: confidence interval; M-H: Mantel-Haenszel

Figure 99: Comparison 5.1: First generation ablation/resection versus hysterectomy – Infection (post-operative) in women with no identified pathology



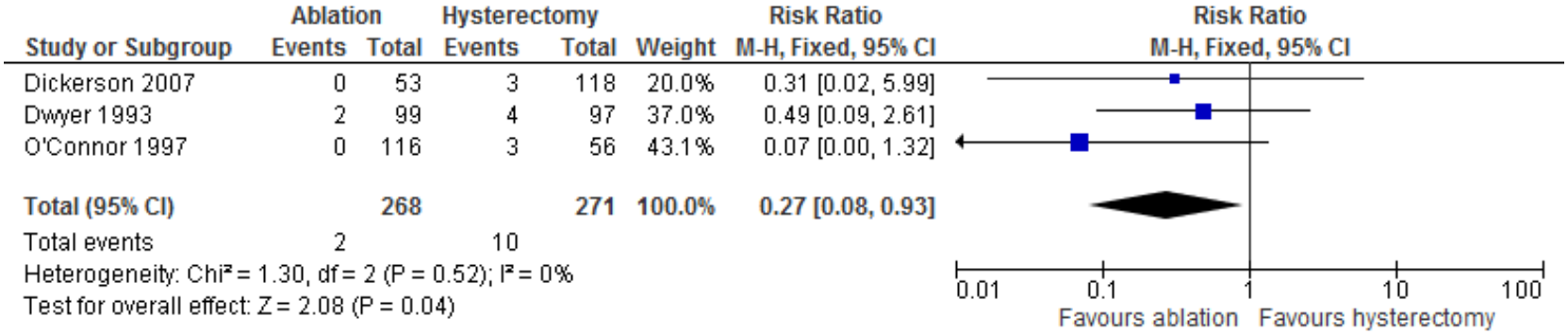
Some risk ratios are not estimable for some outcomes because the outcome is only relevant for one intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel

Figure 100: Comparison 5.1: First generation ablation/resection versus hysterectomy – Thromboembolic event (within 42 days) in women with no identified pathology



CI: confidence interval; M-H: Mantel-Haenszel

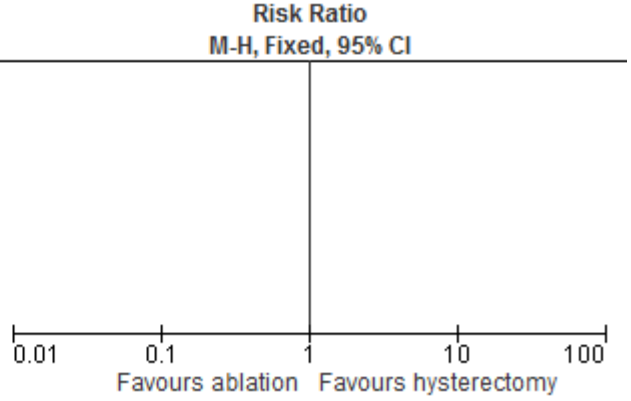
Figure 101: Comparison 5.1: First generation ablation/resection versus hysterectomy – Readmission or return to theatre (within up to 6 weeks) in women with no identified pathology



CI: confidence interval; M-H: Mantel-Haenszel

Figure 102: Comparison 5.1: First generation ablation/resection versus hysterectomy – Internal organ injury in women with no identified pathology

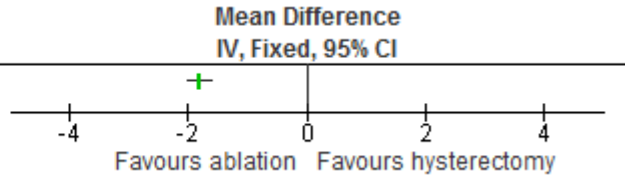
Study or Subgroup	Ablation Events	Ablation Total	Hysterectomy Events	Hysterectomy Total	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Cervival tear					
O'Connor 1997	2	116	0	0	Not estimable
1.6.2 Uterine Perforation					
Dickerson 2007	1	53	0	0	Not estimable
Dwyer 1993	4	99	0	0	Not estimable
O'Connor 1997	3	116	0	0	Not estimable



Risk ratios are not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel

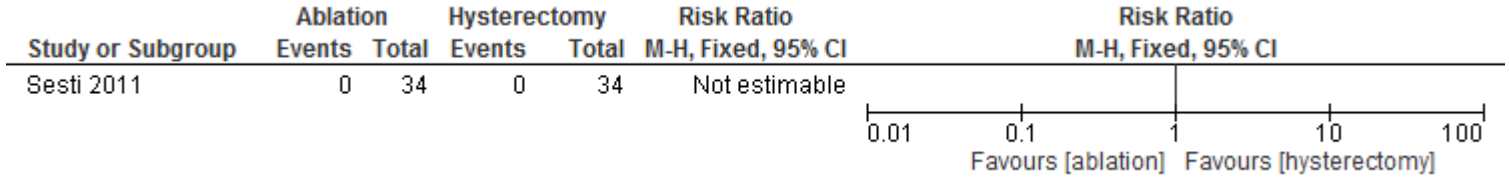
Figure 103: Comparison 5.2: Second generation ablation/resection versus hysterectomy – Length of hospital stay in days in women with no identified pathology (better indicated by lower values)

Study or Subgroup	Ablation Mean	Ablation SD	Ablation Total	Hysterectomy Mean	Hysterectomy SD	Hysterectomy Total	Mean Difference IV, Fixed, 95% CI
Dickerson 2007	0.05	0.29	57	1.86	0.97	118	-1.81 [-2.00, -1.62]



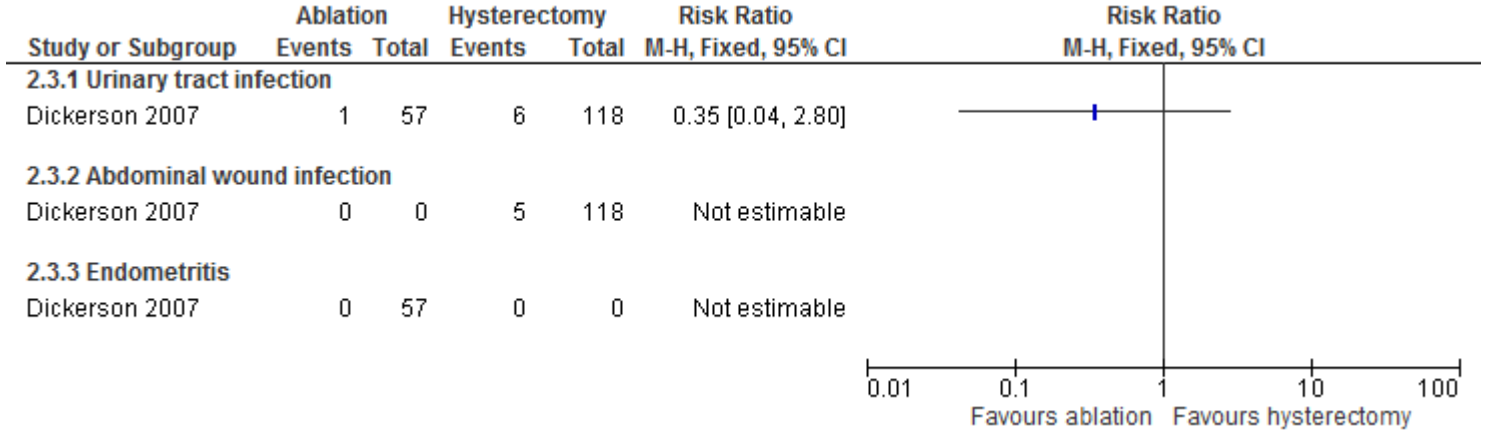
CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 104: Comparison 5.2: Second generation ablation/resection versus hysterectomy – Blood transfusion in women with no identified pathology



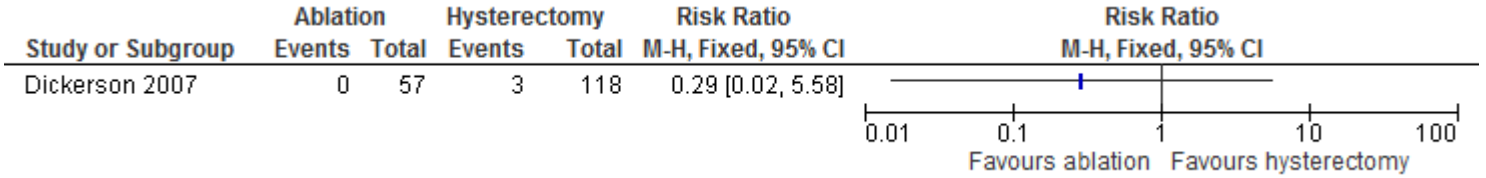
The risk ratio is not estimable because there were no events in either intervention arm.

Figure 105: Comparison 5.2: Second generation ablation/resection versus hysterectomy – Infection (post-operative) in women with no identified pathology



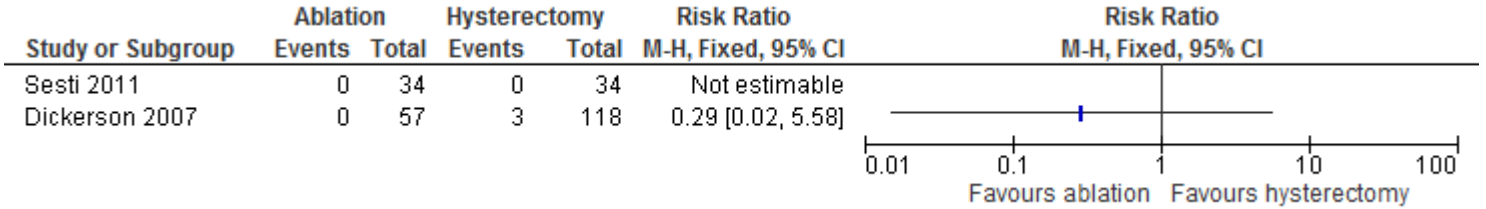
Some risk ratios are not estimable for some outcomes because the outcome is only relevant for one intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel

Figure 106: Comparison 5.2: Second generation ablation/resection versus hysterectomy – Thromboembolic event (within 42 days) in women with no identified pathology



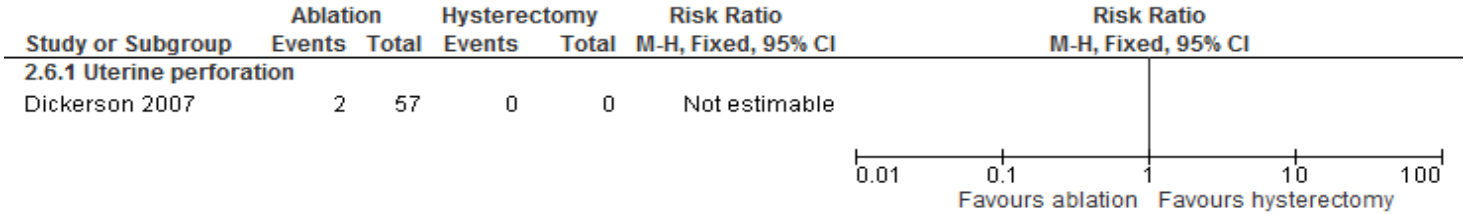
CI: confidence interval; M-H: Mantel-Haenszel

Figure 107: Comparison 5.2: Second generation ablation/resection versus hysterectomy – Readmission or return to theatre (within up to 42 days) in women with no identified pathology



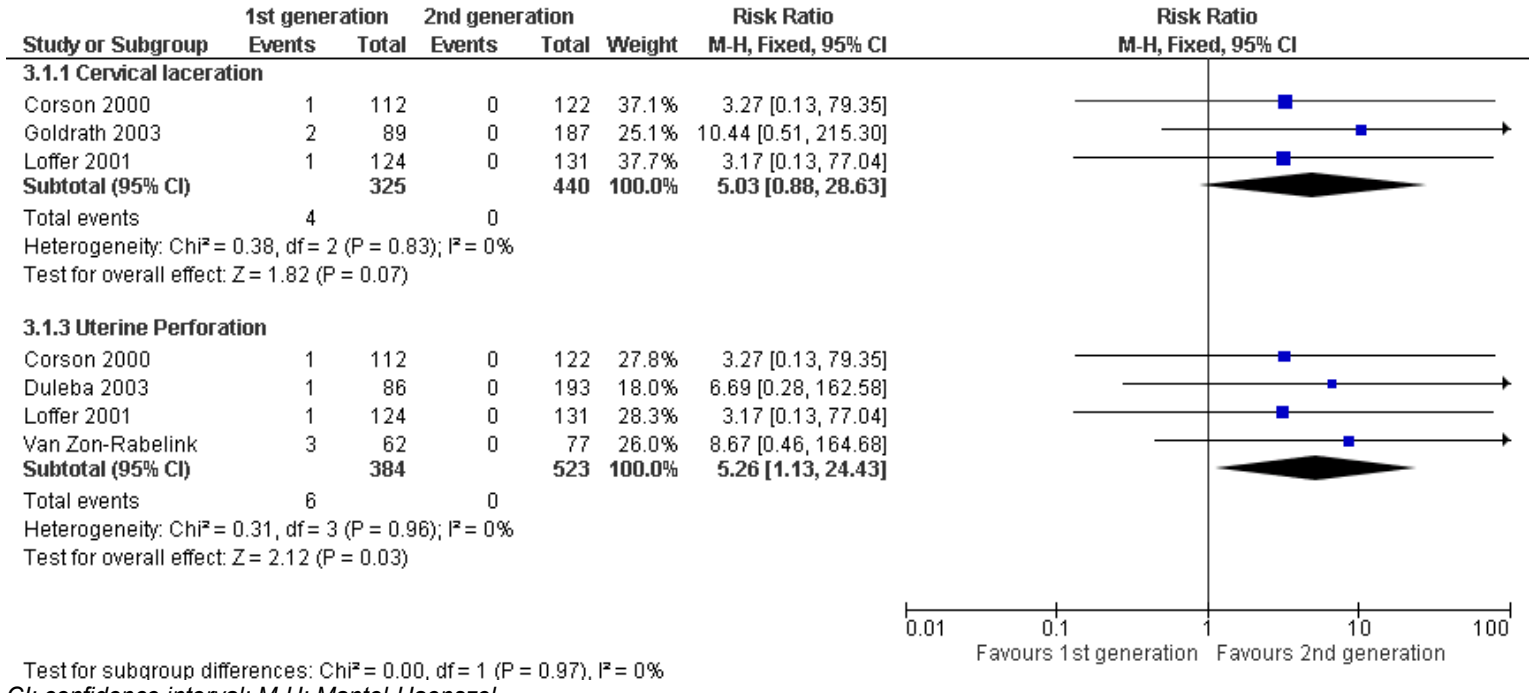
CI: confidence interval; M-H: Mantel-Haenszel

Figure 108: Comparison 5.2: Second generation ablation/resection versus hysterectomy – Uterine perforation in women with no identified pathology



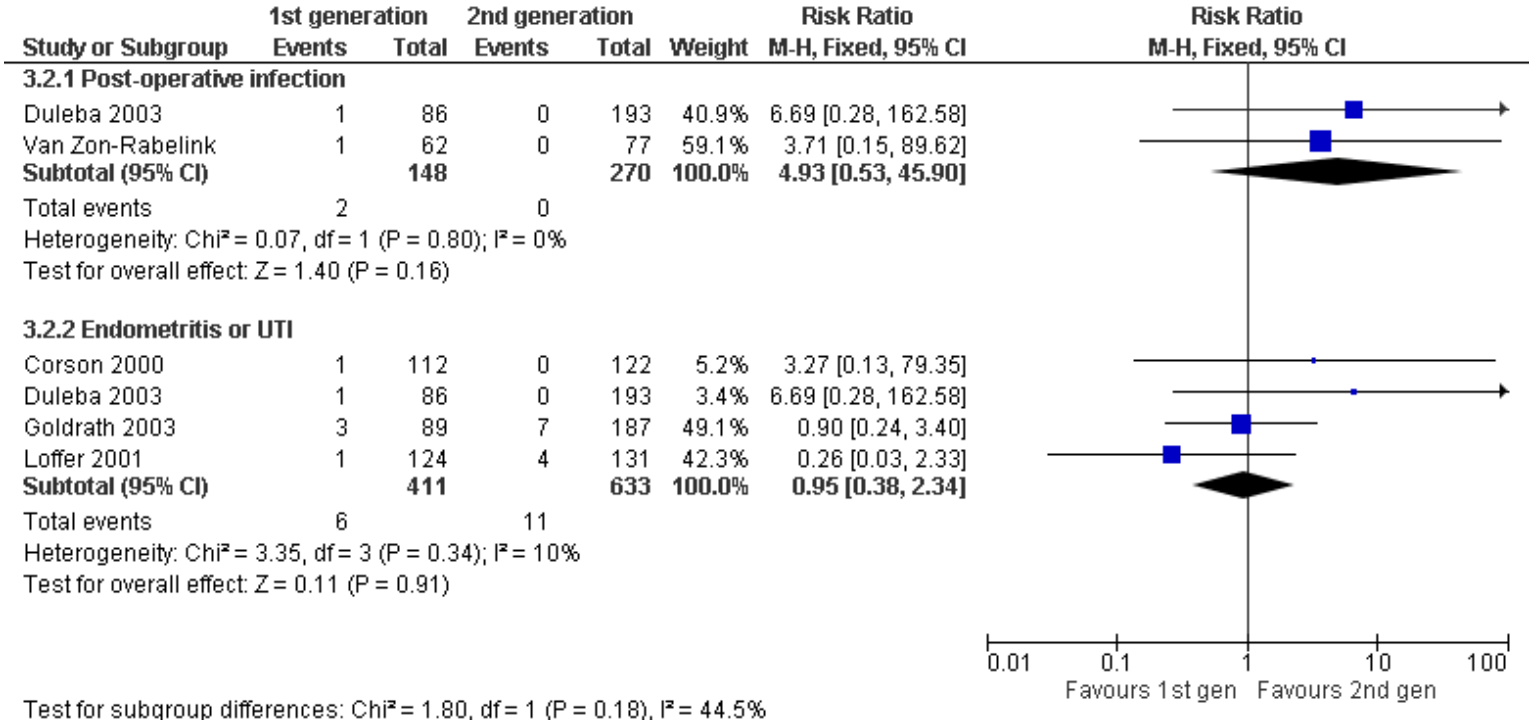
A risk ratio is not estimable because the outcome is only relevant for one intervention arm.
CI: confidence interval; M-H: Mantel-Haenszel

Figure 109: Comparison 5.3: First generation ablation/resection versus second generation ablation/resection – Internal organ injury in women with no identified pathology



CI: confidence interval; M-H: Mantel-Haenszel

Figure 110: Comparison 5.3: First generation ablation/resection versus second generation ablation/resection – Infection (post-operative) in women with no identified pathology



CI: confidence interval; M-H: Mantel-Haenszel

Appendix I – Excluded studies

Clinical studies

Table 53: Studies excluded from the clinical evidence review for the most clinically and cost-effective treatment (pharmacological/surgical) for heavy menstrual bleeding in women with: suspected or diagnosed fibroids, suspected or diagnosed adenomyosis, no identified pathology.

Reference	Reason for exclusion
SOGC clinical practice guidelines. Uterine fibroid embolization (UFE). Number 150, October 2004, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 89, 305-318, 2005	A clinical practice guideline.
Abbott, J. A., Hawe, J., Garry, R., Quality of life should be considered the primary outcome for measuring success of endometrial ablation, J Am Assoc Gynecol Laparosc, 10, 491-5; discussion 495, 2003	Incorrect study type: cohort study.
Abd, El Hameed Aa, Endometrial thermal balloon ablation by a simple technique using Foley's catheter with or without pre ablation endometrial curettage to treat cases with intractable menorrhagia, Middle East Fertility Society Journal, 17, 116-21, 2012	Pre-ablation curettage not an intervention of interest according to protocol.
Agostini, A., Ronda, I., Franchi, F., Bretelle, F., Roger, V., Cravello, L., Blanc, B., Oxytocin during myomectomy: a randomized study, Eur J Obstet Gynecol Reprod Biol, 118, 235-8, 2005	Treatment duration less than 3 months.
Alborzi, S., Parsanezhad, ME., Dehbashi, S., A comparison of hysteroscopic endometrial ablation for abnormal uterine bleeding in two groups of patients with or without endometrial preparation., Middle East Fertility Society Journal, 7, 135-9, 2002	Specific Endometrial preparation not an intervention of interest according to protocol.
Ambat, S., Mittal, S., Srivastava, D. N, Misra, R., Dadhwal, V., Ghosh, B., Uterine artery embolization versus laparoscopic occlusion of uterine vessels for management of symptomatic uterine fibroids, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 105, 162-5, 2009	Laparoscopic occlusion is used as addition to myomectomy, not intervention of interest according to protocol.
Andersch, B., Milsom, I., Rybo, G., An objective evaluation of flurbiprofen and tranexamic acid in the treatment of idiopathic menorrhagia, Acta Obstet Gynecol Scand, 67, 645-8, 1988	Treatment given for 2 cycles only. Fluribiprofen used as intervention, not an intervention of interest according to protocol.
Angioni, S., Pontis, A., Nappi, L., Sedda, F., Sorrentino, F., Litta, P., Haimovich, S., Melis, G. B., Endometrial ablation: first- vs. second-generation techniques, Minerva ginecologica, 68, 143-53, 2016	Narrative review.

Reference	Reason for exclusion
Anonymous,, Microwave = Thermal balloon endometrial ablation, Journal of the National Medical Association, 101, 975, 2009	Abstract of study included in NMA (Sambrook 2009).
Agarwal, N.,Gupta, M., Kriplani, A., Bhatla, N., Singh, N. Comparison of combined hormonal vaginal ring with ultralow-dose combined oral contraceptive pills in the management of heavy menstrual bleeding: A pilot study. J Obstet Gynaecol, 36, 71-5, 2016	Comparison of 2 types of combined hormonal contraceptives, inter group comparisons were not of interest for this review.
Badawy, A. M., Elnashar, A. M., Mosbah, A. A., Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial, Acta Obstetricia et Gynecologica Scandinavica, 91, 489-95, 2012	No outcomes of interest for this review.
Barlow, D. H., Lumsden, M. A., Fauser, B. C. J. M., Terrill, P., Bestel, E., Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo, Human Reproduction, 29, 480-489, 2014	Women with at least one fibroid more than or equal to 3 cm, this trial was included in the rapid update of management of fibroids larger than 3 cm in diameter.
Beaumont, H., Augood, C., Duckitt, K., Lethaby, A., Danazol for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, CD001017, 2007	Systematic review, no additional studies found.
Beaumont,H., Augood,C., Duckitt,K., Lethaby,A., Danazol for heavy menstrual bleeding, Cochrane database of systematic reviews (Online), 2002. Date of Publication, -, 2002	Updated 2007 Cochrane review available.
Berman, J. M., Guido, R. S., Garza Leal, J. G., Pemueller, R. R., Whaley, F. S., Chudnoff, S. G., Halt Study, Group, Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas, Journal of Minimally Invasive Gynecology, 21, 767-74, 2014	No comparison group.
Bhattacharya, S, Middleton, Lj, Tsourapas, A, Lee, Aj, Champaneria, R, Daniels, Jp, Roberts, T, Hilken, Nh, Barton, P, Gray, R, Khan, Ks, Chien, P, O'Donovan, P, Hysterectomy, endometrial ablation and Mirena for heavy menstrual bleeding: a systematic review of clinical effectiveness and costeffectiveness analysis (Structured abstract), Health Technology Assessment Database, 1, 2011	Cost-effectiveness study.
Bhattacharya, S., Mollison, J., Pinion, S., Parkin, D. E., Abramovich, D. R., Terry, P., Kitchener, H. C., A comparison of bladder and ovarian function two years following hysterectomy or endometrial ablation, Br J Obstet Gynaecol, 103, 898-903, 1996	No outcomes of interest.
Bitzer, J., Heikinheimo, O., Nelson, A. L., Calaf-Alsina, J., Fraser, I. S., Medical management of heavy menstrual bleeding: a comprehensive review of the literature, Obstetrical & Gynecological Survey, 70, 115-30, 2015	Review article.
Blake, J., Costescu, D., Dunn, S., Leyland, N., Rheault, K., Health technology assessment at health quality Ontario, Ontario Health Technology Assessment Series, 16, 2016	Non-Cochrane systematic review; references checked for relevant studies.

Reference	Reason for exclusion
Blumenthal, Pd, Dawson, L, Hurskainen, R, Cost-effectiveness and quality of life associated with heavy menstrual bleeding among women using the levonorgestrel-releasing intrauterine system (Provisional abstract), International Journal of Gynecology and Obstetrics, 112, 171-178, 2011	Non-Cochrane systematic review; references checked for relevant studies.
Bonduelle, M., Walker, J. J., Calder, A. A., A comparative study of danazol and norethisterone in dysfunctional uterine bleeding presenting as menorrhagia, Postgrad Med J, 67, 833-6, 1991	Intervention not relevant for the review. Treatments not connected to the network in the NMA.
Bongers, M. Y., Mol, B. W., Brolmann, H. A., Prognostic factors for the success of thermal balloon ablation in the treatment of menorrhagia, Obstet Gynecol, 99, 1060-6, 2002	Incorrect study type: case series.
Borgelt-Hansen,L., Oral contraceptives: an update on health benefits and risks, Journal of the American Pharmaceutical Association (Washington,D.C, 1996). 41, 875-886, 2001	Narrative review of combined oral contraceptives.
Boujida, V. H., Philipsen, T., Pelle, J., Joergensen, J. C., Five-year follow-up of endometrial ablation: endometrial coagulation versus endometrial resection, Obstet Gynecol, 99, 988-92, 2002	No outcomes of interest for NMA; compared two types of first line endometrial surgery.
Bourdrez, P., Bongers, M. Y., Mol, B. W., Treatment of dysfunctional uterine bleeding: patient preferences for endometrial ablation, a levonorgestrel-releasing intrauterine device, or hysterectomy, Fertil Steril, 82, 160-6, quiz 265, 2004	Incorrect study type: observational study.
Broder, M. S., Goodwin, S., Chen, G., Tang, L. J., Costantino, M. M., Nguyen, M. H., Yegul, T. N., Erberich, H., Comparison of long-term outcomes of myomectomy and uterine artery embolization, Obstet Gynecol, 100, 864-8, 2002	Incorrect study type: cohort study.
Brown, P. M., Farquhar, C. M., Lethaby, A., Sadler, L. C., Johnson, N. P., Cost-effectiveness analysis of levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding, BJOG, 113, 797-803, 2006	Cost-effectiveness analysis based on Busfield 2006, which is included in review.
Bruno, J., Sterbis, K., Flick, P., McCullough, M., Cramp, M., Murphy-Skrynarz, K., Spies, J. B., Recovery after uterine artery embolization for leiomyomas: a detailed analysis of its duration and severity, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 15, 801-7, 2004	Incorrect study type: cohort study.
Bushnell, Dm, Martin, Ml, Moore, Ka, Richter, He, Rubin, A, Patrick, Dl, Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life, Current medical research and opinion, 26, 2745-55, 2010	Menorrhagia Impact Questionnaire validation study.
Callender, S. T., Warner, G. T., Cope, E., Treatment of menorrhagia with tranexamic acid. A double-blind trial, Br Med J, 4, 214-6, 1970	No outcomes of interest.
Cameron, I. T., Haining, R., Lumsden, M. A., Thomas, V. R., Smith, S. K., The effects of mefenamic acid and norethisterone on measured menstrual blood loss, Obstetrics & Gynecology, 76, 85-8, 1990	Pharmacological treatment only given for 8 weeks (2 cycles).
Cameron, I. T., Leask, R., Kelly, R. W., Baird, D. T., The effects of danazol, mefenamic acid, norethisterone and a progesterone-impregnated coil on endometrial prostaglandin concentrations in women with menorrhagia, Prostaglandins, 34, 99-110, 1987	Treatment given for 2 cycles only; less than 10 participants in each arm.

Reference	Reason for exclusion
Carr, B. R., Marshburn, P. B., Weatherall, P. T., Bradshaw, K. D., Breslau, N. A., Byrd, W., Roark, M., Steinkampf, M. P., An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial, J Clin Endocrinol Metab, 76, 1217-23, 1993	No outcomes of interest.
Cash, C, Garza-Leal, J, Donovan, A, Guidry, C, Romanowski, C, Patel, B, Clinical evaluation of long-term safety and effectiveness of a third-generation thermal uterine balloon therapy system for heavy menstrual bleeding, Journal of Minimally Invasive Gynecology, 19, 469-76, 2012	Third generation UBT versus first generation UBT, not of interest according to protocol.
Celik, H., Sapmaz, E., Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy, Fertil Steril, 79, 1207-10, 2003	Treatment duration less than 3 months.
Cetin, Nn, Karabacak, O, Korucuoglu, U, Karabacak, N, Gonadotropin-releasing hormone analog combined with a low-dose oral contraceptive to treat heavy menstrual bleeding, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 104, 236-9, 2009	No outcomes of interest.
Chamberlain, G., Freeman, R., Price, F., Kennedy, A., Green, D., Eve, L., A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding, Br J Obstet Gynaecol, 98, 707-11, 1991	Treatment duration less than 3 cycles; ethamsylate not a relevant intervention according to protocol.
Chang, Pt, Vilos, Ga, Abu-Rafea, B, Hollett-Caines, J, Abyaneh, Zn, Edris, F, Comparison of Clinical Outcomes with Low-Voltage (Cut) Versus High-Voltage (Coag) Waveforms during Hysteroscopic Endometrial Ablation with the Rollerball: A Pilot Study, Journal of Minimally Invasive Gynecology, 16, 350-3, 2009	Intervention not of interest according to protocol.
Chelmow, D., Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding: a randomized controlled trial, Obstetrics & GynecologyObstet Gynecol, 116, 1455-6; author reply 1456, 2010	Author reply, not a study.
Chimbira, T. H., Anderson, A. B., Naish, C., Cope, E., Turnbull, A. C., Reduction of menstrual blood loss by danazol in unexplained menorrhagia: lack of effect of placebo, Br J Obstet Gynaecol, 87, 1152-8, 1980	Treatment duration less than 3 cycles; Danazol not an intervention of interest according to protocol.
Chimbira, T. H., Cope, E., Anderson, A. B., Bolton, F. G., The effect of danazol on menorrhagia, coagulation mechanisms, haematological indices and body weight, Br J Obstet Gynaecol, 86, 46-50, 1979	Incorrect study type: case series.
Clark, Tj, Middleton, Lj, Cooper, Na, Diwakar, L, Denny, E, Smith, P, Gennard, L, Stobert, L, Roberts, Te, Cheed, V, Bingham, T, Jowett, S, Brettell, E, Connor, M, Jones, Se, Daniels, Jp, A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding, Health technology assessment (Winchester, England), 19, 1-194, 2015	Intervention (polypectomy) not of interest according to protocol.

Reference	Reason for exclusion
Clarke, A., Judge, A., Herbert, A., McPherson, K., Bridgman, S., Maresh, M., Overton, C., Altman, D., Readmission to hospital 5 years after hysterectomy or endometrial resection in a national cohort study, Qual Saf Health Care, 14, 41-7, 2005	Incorrect study type: cohort study.
Cooke, I., Lethaby, A., Farquhar, C., Antifibrinolytics for heavy menstrual bleeding, CD000249, 2000	Superseded by an updated Cochrane review (2013).
Cooper, Na, Clark, Tj, Middleton, L, Diwakar, L, Smith, P, Denny, E, Roberts, T, Stobert, L, Jowett, S, Daniels, J, Outpatient versus inpatient uterine polyp treatment for abnormal uterine bleeding: randomised controlled non-inferiority study, BMJ (Clinical research ed.), 350, h1398, 2015	Intervention (polypectomy) not of interest according to protocol.
Corson, S. L., Brooks, P. G., Serden, S. P., Batzer, F. R., Gocial, B., Effects of vasopressin administration during hysteroscopic surgery, J Reprod Med, 39, 419-23, 1994	Duration of treatment less than 3 months.
Coulter, A., Kelland, J., Peto, V., Rees, M. C., Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice, Int J Technol Assess Health Care, 11, 456-71, 1995	Systematic review; references checked for relevant studies.
Creatsas, G., Cardamakis, E., Deligeoroglou, E., Hassan, E., Tzingounis, V., Tenoxicam versus lynestrenol-ethinyl estradiol treatment of dysfunctional uterine bleeding cases during adolescence, J Pediatr Adolesc Gynecol, 11, 177-80, 1998	Treatment duration less than 3 cycles; intervention (Tenoxicam) not of interest according to protocol.
Cunningham, E, Barreda, L, Ngo, M, Terasaki, K, Munro, Mg, Uterine artery embolization versus occlusion for uterine leiomyomas: a pilot randomized clinical trial, Journal of Minimally Invasive Gynecology, 15, 301-7, 2008	Laparoscopic occlusion is used as addition to myomectomy, not an intervention of interest according to protocol.
Daniels, J. P., The long-term outcomes of endometrial ablation in the treatment of heavy menstrual bleeding, Current Opinion in Obstetrics and Gynecology, 25, 2013	Non-Cochrane systematic review; references checked for relevant studies.
Daniels, Jp, Middleton, Lj, Champaneria, R, Cooper, K, Khan, Ks, Mol, Bwj, Bhattacharya, S, Second generation endometrial ablation techniques for heavy menstrual bleeding: A network metaanalysis, Bjog, 120, 390, 2013	Non-Cochrane review; references checked for relevant studies.
De Blok, S., Dijkman, A.B., Hemrika, D.J, Transcervical resection of fibroids (TCRM): Results related to hysteroscopic classification, 4, 246, 1995	Incorrect study type: cohort study.
de Souza, S. S., Camargos, A. F., de Rezende, C. P., Pereira, F. A., Araujo, C. A., Silva Filho, A. L., A randomized prospective trial comparing the levonorgestrel-releasing intrauterine system with thermal balloon ablation for the treatment of heavy menstrual bleeding, Contraception, 81, 226-31, 2010	No relevant data reported.
Deng, Linyu, Wu, Taixiang, Chen, Xiao Y, Xie, Lingxia, Yang, Jinrong, Selective estrogen receptor modulators (SERMs) for uterine leiomyomas, Cochrane Database of Systematic Reviews, 2012	Incorrect population, not with HMB.
Dequesne,J.H., Gallinat,A., Garza-Leal,J.G., Sutton,C.J., van der Pas,H.F., Wamsteker,K., Chandler,J.G., Thermoregulated radiofrequency endometrial ablation, International Journal of Fertility and Womens Medicine, 42, 311-318, 1997	Incorrect study type: non-comparative cohort study.

Reference	Reason for exclusion
Derman, S. G., Rehnstrom, J., Neuwirth, R. S., The long-term effectiveness of hysteroscopic treatment of menorrhagia and leiomyomas, Obstet Gynecol, 77, 591-4, 1991	Incorrect study type: case series.
Dockeray, C. J., Sheppard, B. L., Bonnar, J., Comparison between mefenamic acid and danazol in the treatment of established menorrhagia, British Journal of Obstetrics & Gynaecology, 96, 840-4, 1989	Treatment duration less than 3 months/cycles; Danazol not an intervention of interest according to protocol.
Donnez, J, Donnez, O, Matule, D, Ahrendt, Hj, Hudecek, R, Zatik, J, Kasilovskiene, Z, Dumitrascu, Mc, Fernandez, H, Barlow, Dh, Bouchard, P, Fauser, Bc, Bestel, E, Loumaye, E, Long-term medical management of uterine fibroids with ulipristal acetate, Fertility and sterility, 105, 165-173.e4, 2016	Compares two different dosages of the same drug. Not relevant for this review.
Donnez, J, Hudecek, R, Donnez, O, Matule, D, Arhendt, H-J, Zatik, J, Kasilovskiene, Z, Dumitrascu, Mc, Fernandez, H, Barlow, Dh, Bouchard, P, Fauser, Bcjm, Bestel, E, Terrill, P, Osterloh, I, Loumaye, E, Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids, Fertility and sterility, 103, 519-527.e3, 2015	Compares two different dosages of the same drug. Not relevant for this review.
Donnez, J, Tatarchuk, Tf, Bouchard, P, Puscasiu, L, Zakharenko, Nf, Ivanova, T, Ugocsai, G, Mara, M, Jilla, Mp, Bestel, E, Terrill, P, Osterloh, I, Loumaye, E, Ulipristal acetate versus placebo for fibroid treatment before surgery, The New England journal of medicine, 366, 409-20, 2012	Women with at least one fibroid more than or equal to 3 cm, this study was included in the rapid update of management of fibroids larger than 3 cm in diameter.
Donnez, J., Polet, R., Rabinovitz, R., Ak, M., Squifflet, J., Nisolle, M., Endometrial laser intrauterine thermotherapy: the first series of 100 patients observed for 1 year, Fertil Steril, 74, 791-6, 2000	Incorrect study type: case series.
Donnez, J., Tomaszewski, J., Vazquez, F., Bouchard, P., Lemieszczuk, B., Baro, F., Nouri, K., Selvaggi, L., Sodowski, K., Bestel, E., Terrill, P., Osterloh, I., Loumaye, E., Ulipristal acetate versus leuprolide acetate for uterine fibroids, New England Journal of MedicineN Engl J Med, 366, 421-432, 2012	Women with at least one fibroid more than or equal to 3 cm, this study was included in the rapid update of management of fibroids larger than 3 cm in diameter.
Dutton, C., Ackerson, L., Phelps-Sandall, B., Outcomes after rollerball endometrial ablation for menorrhagia, Obstet Gynecol, 98, 35-9, 2001	Incorrect study type: case series.
Eder, S., Baker, J., Gersten, J., Mabey, R. G., Adomako, T. L., Efficacy and safety of oral tranexamic acid in women with heavy menstrual bleeding and fibroids, Women's health, 9, 397-403, 2013	Post-hoc analysis of 2 RCTs.
Edlund, M., Nonhormonal treatments for heavy menstrual bleeding, Journal of Women's HealthJ Womens Health (Larchmt), 20, 1645-53, 2011	Non-Cochrane review; references checked for relevant studies.
Edlund, M., Andersson, K., Rybo, G., Lindoff, C., Astedt, B., von Schoultz, B., Reduction of menstrual blood loss in women suffering from idiopathic menorrhagia with a novel antifibrinolytic drug (Kabi 2161), Br J Obstet Gynaecol, 102, 913-7, 1995	Kabi is a pro-drug of tranexamic acid and not used in clinical practice.
Edwards, R.G., Moss, J.G, Murray, L, Randomised Study of Embolisation and Surgical Treatment for Uterine Fibroids (REST). No. CZH/4/1, Edinburgh: Chief Scientist Office, 2006	Duplicate study of Edwards 2007

Reference	Reason for exclusion
El Behery, M. M., Saleh, H. S., Ibrahiem, M. A., Kamal, E. M., Kassem, G. A., Mohamed Mel, S., Levonorgestrel-releasing intrauterine device versus dydrogesterone for management of endometrial hyperplasia without atypia, Reproductive SciencesReprod Sci, 22, 329-34, 2015	Less than 2/3 of participants with HMB.
El-Toukhy, T., Chandakas, S., Grigoriadis, T., Hill, N., Erian, J., Outcome of the first 220 cases of endometrial balloon ablation using Cavaterm plus, J Obstet Gynaecol, 24, 680-3, 2004	Incorrect study type: case series; Cavaterm not an intervention of interest according to protocol.
English, J., Daly, S., McGuinness, N., Kiernan, E., Prendiville, W., Medical preparation of the endometrium prior to resection: Decapeptyl SR (triptorelin) versus danazol versus placebo, Minimally Invasive Therapy & Allied Technologies, 7, 251-256, 1998	Medical preparation of the endometrium not an intervention of interest according to protocol.
Engman, M, Granberg, S, Williams, Ar, Meng, Cx, Lalitkumar, Pg, Gemzell-Danielsson, K, Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial, Human reproduction (Oxford, England), 24, 1870-9, 2009	Treatment duration less than 3 months.
Erian, M. M., Goh, J. T., Transcervical endometrial resection, J Am Assoc Gynecol Laparosc, 3, 263-6, 1996	Incorrect study type: non-comparative cohort of women undergoing hysteroscopic endometrial resection.
Erian,J., Endometrial ablation in the treatment of menorrhagia, British Journal of Obstetrics and Gynaecology, 101 Suppl 11, 19-22, 1994	No outcomes relevant to NMA. Laser ablation not an intervention of interest for the pairwise analysis according to protocol.
Erian,M.M., Thomas,I.L., Buck,R.J., Lewin,M.W., Coglan,M., Battistutta,D., The effects of danazol after endometrial resection--results of a randomized, placebo-controlled, double-blind study, Australian and New Zealand Journal of Obstetrics and Gynaecology, 38, 210-214, 1998	No outcomes relevant to NMA. Danazol not an intervention of interest for the pairwise analysis according to protocol.
Esteve, J. L. C., Acosta, R., Perez, Y., Rodriguez, B., Seigler, I., Sanchez, C., Tomasi, G., Mifepristone versus placebo to treat uterine myoma: A double-blind, randomized clinical trial, International journal of women's health, 5, 361-369, 2013	Treatment duration less than 3 months.
Esteve, J. L., Acosta, R., Perez, Y., Campos, R., Hernandez, A. V., Texido, C. S., Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 161, 202-8, 2012	Treatment duration less than 3 months.
Farquhar,Cindy, Brown,Julie, Oral contraceptive pill for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, -, 2009	Systematic review with only 1 RCT included; less than 10 participants in some arms.

Reference	Reason for exclusion
Fawzy, M., Mesbah, Y., Comparison of dienogest versus triptorelin acetate in premenopausal women with adenomyosis: a prospective clinical trial, Archives of Gynecology & ObstetricsArch Gynecol Obstet, 292, 1267-71, 2015	Incorrect study type: not a RCT.
Fedele, L., Vercellini, P., Bianchi, S., Brioschi, D., Dorta, M., Treatment with GnRH agonists before myomectomy and the risk of short-term myoma recurrence, Br J Obstet Gynaecol, 97, 393-6, 1990	Less than 10 participants per arm.
Feitoza, S. S., Gebhart, J. B., Gostout, B. S., Wilson, T. O., Cliby, W. A., Efficacy of thermal balloon ablation in patients with abnormal uterine bleeding, Am J Obstet Gynecol, 189, 453-7, 2003	Incorrect study type: case series.
Ferry, J., Rankin, L., Transcervical resection of the endometrium using intracervical block only. A review of 278 procedures, Aust N Z J Obstet Gynaecol, 34, 457-61, 1994	Incorrect study type: case series.
Fletcher, H., Frederick, J., Hardie, M., Simeon, D., A randomized comparison of vasopressin and tourniquet as hemostatic agents during myomectomy, Obstet Gynecol, 87, 1014-8, 1996	Single dose intraoperative medication as intervention, not relevant for this review.
Fraser, I. S., Treatment of ovulatory and anovulatory dysfunctional uterine bleeding with oral progestogens, Aust N Z J Obstet Gynaecol, 30, 353-6, 1990	Treatment duration less than 3 cycles; less than 10 participants in each arm.
Fraser, I. S., McCarron, G., Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia, Australian & New Zealand Journal of Obstetrics & Gynaecology, 31, 66-70, 1991	Treatment duration less than 3 months.
Fraser, I. S., Pearse, C., Shearman, R. P., Elliott, P. M., McIlveen, J., Markham, R., Efficacy of mefenamic acid in patients with a complaint of menorrhagia, Obstetrics and gynecology, 58, 543-51, 1981	Treatment duration less than 3 months.
Frederick, J., Fletcher, H., Simeon, D., Mullings, A., Hardie, M., Intramyometrial vasopressin as a haemostatic agent during myomectomy, Br J Obstet Gynaecol, 101, 435-7, 1994	Single dose intraoperative medication as intervention, not relevant for this review.
Friberg, Britt, Ahlgren, Mats, Thermal balloon endometrial destruction: the outcome of treatment of 117 women followed up for a maximum period of 4 years, Gynaecological Endoscopy, 9, 389-395, 2000	Incorrect study type: non-comparative cohort study.
Friedman, A. J., Barbieri, R. L., Doubilet, P. M., Fine, C., Schiff, I., A randomized, double-blind trial of a gonadotropin releasing-hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri, 49, 404-9, 1988	No outcomes of interest.
Friedman, A. J., Daly, M., Juneau-Norcross, M., Rein, M. S., Fine, C., Gleason, R., Leboff, M., A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen-progestin or progestin "add-back" regimens for women with leiomyomata uteri, J Clin Endocrinol Metab, 76, 1439-45, 1993	No outcomes of interest.
Friedman, A. J., Hoffman, D. I., Comite, F., Browneller, R. W., Miller, J. D., Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Leuprolide Study Group, Obstet Gynecol, 77, 720-5, 1991	No outcomes of interest.

Reference	Reason for exclusion
Fürst, Sn, Philipsen, T, Joergensen, Jc, Ten-year follow-up of endometrial ablation, Acta Obstetricia et Gynecologica Scandinavica, 86, 334-8, 2007	Less than 2/3 of participants with HMB.
Gallinat, Adolf, Cosgriff, Ned, Endometrial ablation by electroballoon coagulation: long-term results, Gynaecological Endoscopy, 10, 37-43, 2001	Incorrect study type: case series.
Gallinat,A., NovaSure impedance controlled system for endometrial ablation: three-year follow-up on 107 patients, American Journal of Obstetrics and Gynecology, 191, 1585-1589, 2004	Incorrect study type: case series.
Gandhi, Saurabh V., Fear, Kenneth B. C., Sturdee, David W., Endometrial resection: factors affecting long-term success, Gynaecological Endoscopy, 8, 41-50, 1999	Incorrect study type: retrospective cohort; non-comparative study.
Gannon, M. J., Holt, E. M., Fairbank, J., Fitzgerald, M., Milne, M. A., Crystal, A. M., Greenhalf, J. O., A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia, Bmj, 303, 1362-4, 1991	No outcomes of interest.
Garry, R., Erian, J., Grochmal, S. A., A multi-centre collaborative study into the treatment of menorrhagia by Nd-YAG laser ablation of the endometrium, Br J Obstet Gynaecol, 98, 357-62, 1991	Incorrect study type: case series.
Garry,R., Shelley-Jones,D., Mooney,P., Phillips,G., Six hundred endometrial laser ablations, Obstetrics and Gynecology, 85, 24-29, 1995	Incorrect study type: case series.
Garza-Leal, J, Pena, A, Donovan, A, Cash, C, Romanowski, C, Ilie, B, Lin, L, Clinical evaluation of a third-generation thermal uterine balloon therapy system for menorrhagia coupled with curettage, Journal of Minimally Invasive Gynecology, 17, 82-90, 2010	Interventions not of interest according to protocol.
Gervaise, A., Fernandez, H., Capella-Allouc, S., Taylor, S., La Vieille, S., Hamou, J., Gomel, V., Thermal balloon ablation versus endometrial resection for the treatment of abnormal uterine bleeding, Hum Reprod, 14, 2743-7, 1999	Incorrect study type: cohort study.
Ginsburg, E. S., Benson, C. B., Garfield, J. M., Gleason, R. E., Friedman, A. J., The effect of operative technique and uterine size on blood loss during myomectomy: a prospective randomized study, Fertil Steril, 60, 956-62, 1993	Compares two methods of blood loss reduction with myomectomy- tourniquet or vasopressin, not of interest according to protocol.
Goodwin, S. C., Bradley, L. D., Lipman, J. C., Stewart, E. A., Nosher, J. L., Sterling, K. M., Barth, M. H., Siskin, G. P., Shlansky-Goldberg, R. D., U. A. E. versus Myomectomy Study Group, Uterine artery embolization versus myomectomy: a multicenter comparative study, Fertil Steril, 85, 14-21, 2006	Incorrect study type: cohort study.
Grimbizis, G. F., Mikos, T., Tarlatzis, B., Uterus-sparing operative treatment for adenomyosis, Fertility and Sterility, 101, 472-487.e8, 2014	Incorrect study type: review of cases or case series.
Grover, V., Usha, R., Gupta, U., Kalra, S., Management of cyclical menorrhagia with prostaglandin synthetase inhibitor, Asia Oceania J Obstet Gynaecol, 16, 255-9, 1990	No outcomes of interest reported; blood loss reported in days of bleeding or number of pads.

Reference	Reason for exclusion
Guido, Rs, Macer, Ja, Abbott, K, Falls, Jl, Tilley, Ib, Chudnoff, Sg, Radiofrequency volumetric thermal ablation of fibroids: A prospective, clinical analysis of two years' outcome from the Halt trial, Health and quality of life outcomes, 11, 1-8, 2013	Intervention not of interest according to protocol.
Gupta, J, Kai, J, Middleton, L, Pattison, H, Gray, R, Daniels, J, Levonorgestrel intrauterine system versus medical therapy for menorrhagia, The New England journal of medicine, 368, 128-37, 2013	Full data available in Gupta 2015
Gupta, J. K., Hickey, M., Lumsden, M. A., Broder, M., Tsatsi, L. D. R., Uterine artery embolisation for symptomatic uterine fibroids, The Cochrane Database of Systematic Reviews, 2005	Updated version of Cochrane review available.
Gupta, Jk, Kai, J, Middleton, Lj, Pattison, Hm, Gray, R, Gennard, L, Daniels, Jp, Randomised trial of levonorgestrel intrauterine system compared to usual medical treatment for heavy menstrual bleeding: The ECLIPSE Trial, Bjog, 120, 379, 2013	Abstract, no full text.
Hahn, M., Brucker, S., Kraemer, D., Wallwiener, M., Taran, F. A., Wallwiener, C. W., Kramer, B., Radiofrequency volumetric thermal ablation of fibroids and laparoscopic myomectomy: Long-term follow-up from a randomized trial, Geburtshilfe und FrauenheilkundeGeburtshilfe Frauenheilkd, 75, 442-449, 2015	Intervention not of interest according to protocol.
Hald, K, Kløw, Ne, Qvigstad, E, Istre, O, Laparoscopic occlusion compared with embolization of uterine vessels: a randomized controlled trial, Obstetrics and Gynecology, 109, 20-7, 2007	Laparoscopic occlusion is used as addition to myomectomy, not intervention of interest according to protocol.
Hall, P., Maclachlan, N., Thorn, N., Nudd, M. W., Taylor, C. G., Garrioch, D. B., Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid, Br J Obstet Gynaecol, 94, 554-8, 1987	Treatment duration less than 3 cycles.
Halmesmaki,K., Hurskainen,R., Tiitinen,A., Teperi,J., Grenman,S., Kivela,A., Kujansuu,E., Yliskoski,M., Paavonen,J., A randomized controlled trial of hysterectomy or levonorgestrel-releasing intrauterine system in the treatment of menorrhagia-effect on FSH levels and menopausal symptoms, Human Reproduction, 19, 378-382, 2004	No outcomes of interest.
Hayes,, Inc,, Laparoscopic electromechanical morcellation of uterine fibroids during myomectomy or hysterectomy (Structured abstract), Health Technology Assessment Database, 2014	Abstract.
Hayes,, Inc,, Hysteroscopic morcellation (Truclear Morcellator System; Smith & Nephew Inc.) for treatment of uterine submucosal fibroids and endometrial polyps (Structured abstract), Health Technology Assessment Database, 2014	Abstract.
Haynes, P. J., Hodgson, H., Anderson, A. B., Turnbull, A. C., Measurement of menstrual blood loss in patients complaining of menorrhagia, Br J Obstet Gynaecol, 84, 763-8, 1977	Incorrect study type: cohort study.

Reference	Reason for exclusion
Hehenkamp, W. J., Volkers, N. A., Birnie, E., Reekers, J. A., Ankum, W. M., Pain and return to daily activities after uterine artery embolization and hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial, Cardiovasc Intervent Radiol, 29, 179-87, 2006	No outcomes of interest.
Hehenkamp, Wj, Volkers, Na, Broekmans, Fj, Jong, Fh, Themmen, Ap, Birnie, E, Reekers, Ja, Ankum, Wm, Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy, Human reproduction (Oxford, England), 22, 1996-2005, 2007	Included in Gupta 2014 Cochrane systematic review as part of the EMMY trial, however, no outcomes of interest for the current review.
Heikinheimo, O, Vani, S, Carpén, O, Tapper, A, Härkki, P, Rutanen, Em, Critchley, H, Intrauterine release of progesterone antagonist ZK230211 is feasible and results in novel endometrial effects: a pilot study, Human reproduction (Oxford, England), 22, 2515-22, 2007	No outcomes of interest.
Helal, A, Mashaly, Ael-M, Amer, T, Uterine artery occlusion for treatment of symptomatic uterine myomas, JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons, 14, 386-90, 2010	Laparoscopic occlusion is used as addition to myomectomy, not intervention of interest according to protocol.
Heliovaara-Peippo, S., Hurskainen, R., Teperi, J., Aalto, A. M., Grenman, S., Halmesmaki, K., Jokela, M., Kivela, A., Tomas, E., Tuppurainen, M., Paavonen, J., Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: A 10-year randomized controlled trial, Obstetrical and Gynecological Survey, 69, 204-205, 2014	Follow-up duration too long for NMA inclusion, no outcomes relevant to pairwise
Herman, M. C., van den Brink, M. J., Geomini, P. M., van Meurs, H. S., Huirne, J. A., Eising, H. P., Timmermans, A., Pijnenborg, J. M. A., Klinkert, E. R., Coppus, S. F., Nieboer, T. E., Catshoek, R., van der Voet, L. F., van Eijndhoven, H. W. F., Graziosi, G. C. M., Veersema, S., van Kesteren, P. J., Langenveld, J., Smeets, N. A. C., van Vliet, H. A. A. M., van der Steeg, J. W., Lisman-van Leeuwen, Y., Dekker, J. H., Mol, B. W., Berger, M. Y., Bongers, M. Y., Levonorgestrel releasing intrauterine system (Mirena) versus endometrial ablation (Novasure) in women with heavy menstrual bleeding: A multicentre randomised controlled trial, BMC women's health, 13 (1) (no pagination), 2013	Protocol of an RCT.
Herman, Mc, Penninx, Jp, Mol, Bw, Bongers, My, Ten-year follow-up of a randomised controlled trial comparing bipolar endometrial ablation with balloon ablation for heavy menstrual bleeding, BJOG : an international journal of obstetrics and gynaecology, 120, 966-70, 2013	Balloon ablation versus bipolar ablation (both second generation ablation techniques), not relevant for the pairwise analysis and 10-year follow-up too long for the NMA.
Hickey, M., Marino, J. L., Brownfoot, F. C., Uterine artery embolisation associated with greater need for reintervention than surgical treatment for symptomatic uterine fibroids; quality of life similar though study underpowered, Evidence-based medicine, 17, 87-88, 2012	Commentary.
Higham, J. M., Shaw, R. W. A comparative study of danazol, a regimen of decreasing doses of danazol, and norethindrone in the treatment of objectively proven unexplained menorrhagia. American Journal of Obstetrics & Gynecology, 169, 1134-9, 1993	Intervention (danazol) not relevant for the pairwise analysis according to protocol, does not connect to the network in the NMA.

Reference	Reason for exclusion
Hoaglin, Dc, Filonenko, A, Glickman, Me, Wasiak, R, Gidwani, R, Use of mixed-treatment-comparison methods in estimating efficacy of treatments for heavy menstrual bleeding (Provisional abstract), European Journal of Medical Research, 18, 17, 2013	Non-Cochrane review; references checked for relevant studies
Huang, J. Y., Kafy, S., Dugas, A., Valenti, D., Tulandi, T., Failure of uterine fibroid embolization, Fertility & Sterility, 85, 30-5, 2006	Incorrect study type: cohort study
Hutchins, F. L., Jr., Worthington-Kirsch, R., Berkowitz, R. P., Selective uterine artery embolization as primary treatment for symptomatic leiomyomata uteri, J Am Assoc Gynecol Laparosc, 6, 279-84, 1999	Incorrect study type: non-comparative cohort.
Iyer, V., Farquhar, C., Jepson, R., Oral contraceptive pills for heavy menstrual bleeding, Cochrane Database Syst Rev, CD000154, 2000	Updated 2009 version of Cochrane review available.
Jack,S.A., Cooper,K.G., Seymour,J., Graham,W., Fitzmaurice,A., Perez,J., A randomised controlled trial of microwave endometrial ablation without endometrial preparation in the outpatient setting: patient acceptability, treatment outcome and costs, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1109-1116, 2005	Compares 2 types of microwave ablation, not relevant for this review.
Jakubowicz, Diana L., Wood, Carl, The Use of the Prostaglandin Synthetase Inhibitor Mefenamic Acid in the Treatment of Menorrhagia, Australian and New Zealand Journal of Obstetrics and Gynaecology, 18, 135-138, 1978	Treatment duration less than 3 cycles; blood loss measured as sanitary towel use.
Jasonni, V. M., D'Anna, R., Mancuso, A., Caruso, C., Corrado, F., Leonardi, I., Randomized double-blind study evaluating the efficacy on uterine fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate depot treatment before myomectomy, Acta Obstet Gynecol Scand, 80, 956-8, 2001	Less than 2/3 of population with HMB.
Jensen, J, Machlitt, A, Mellinger, U, Schaefers, M, Fraser, Is, A multicenter, double-blind, randomized, placebo-controlled study of oral estradiol valerate/dienogest for the treatment of heavy and/or prolonged menstrual bleeding, Fertility and sterility, 92 Suppl 1, S32, 2009	Abstract.
Jensen, J. T., Parke, S., Mellinger, U., Machlitt, A., Fraser, I. S., Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest: a randomized controlled trial, Obstetrics & Gynecology, 117, 777-87, 2011	Not outcomes of interest for pairwise; PBAC scores reported dichotomously thus excluded from NMA.
Jiang, W., Shen, Q., Chen, M., Wang, Y., Zhou, Q., Zhu, X., Levonorgestrel-releasing intrauterine system use in premenopausal women with symptomatic uterine leiomyoma: A systematic review, Steroids, 86, 69-78, 2014	Systematic review which only includes 1 RCT which was captured in the search.
Kalampokas, T., Kamath, M., Boutas, I., Kalampokas, E., Ulipristal acetate for uterine fibroids: a systematic review and meta-analysis, Gynecological endocrinology, 32, 91-6, 2016	Systematic review. Included studies are being considered individually for inclusion.
Karakilic, I. D., Karabacak, O., Karabacak, N., Guler, I., Korucuoglu, U., Gonadotropin-releasing hormone analog combined with depot medroxyprogesterone acetate in the management of endometrial	No outcomes of interest.

Reference	Reason for exclusion
hyperplasia: A prospective randomized clinical study, Journal of Reproductive MedicineJ Reprod Med, 61, 361-367, 2016	
Karakus, S, Kiran, G, Ciralik, H, Efficacy of micronised vaginal progesterone versus oral dydrogestrone in the treatment of irregular dysfunctional uterine bleeding: a pilot randomised controlled trial, The Australian & New Zealand journal of obstetrics & gynaecology, 49, 685-8, 2009	Study does not link to the NMA. Dydrogesterone not available in the UK.
Karimi Zarchi, M., Dehghani Firoozabadi, R., Dehghani Firoozabadi, Z., Teimoori, S., Roohi, M., A comparison of the effect of levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation, International Journal of Fertility and Sterility, Conference, 2013	Conference abstract.
Katsumori, T., Kasahara, T., Akazawa, K., Long-term outcomes of uterine artery embolization using gelatin sponge particles alone for symptomatic fibroids, AJR Am J Roentgenol, 186, 848-54, 2006	Incorrect study type: case review.
Katsumori, T., Nakajima, K., Mihara, T., Is a large fibroid a high-risk factor for uterine artery embolization?, AJR Am J Roentgenol, 181, 1309-14, 2003	Incorrect study type: retrospective cohort
Kaunitz, A. M., Inki, P., The levonorgestrel-releasing intrauterine system in heavy menstrual bleeding: A benefit-risk review, Drugs, 72, 193-215, 2012	Non-Cochrane systematic review; references checked for relevant studies.
Kelekci, S., Kelekci, K. H., Yilmaz, B., Effects of levonorgestrel-releasing intrauterine system and T380A intrauterine copper device on dysmenorrhea and days of bleeding in women with and without adenomyosis, Contraception, 86, 458-63, 2012	Treatment indication was contraception in 69% of participants; HMB not part of inclusion criteria and not reported.
Komaram, R., Palla, J., Swamy Chintada, G., A study of efficacy of ormeloxifene in the pharmacological management of dysfunctional uterine bleeding, Journal of Clinical and Diagnostic Research, 7, 2534-2536, 2013	Ormeloxifene not available in the UK and unlicensed.
Kriplani, A., Manchanda, R., Monga, D., Takkar, D., Depot medroxy progesterone acetate: a poor preparatory agent for endometrial resection, Gynecol Obstet Invest, 52, 180-3, 2001	Preparation for resection/treatment duration less than 3 months.
Kriplani, A., Srivastava, A., Kulshrestha, V., Kachhawa, G., Agarwal, N., Bhatla, N., Hari, S., Efficacy of ormeloxifene versus oral contraceptive in the management of abnormal uterine bleeding due to uterine leiomyoma, Journal of Obstetrics & Gynaecology ResearchJ Obstet Gynaecol Res, 20, 20, 2016	Ormeloxifene not licensed for use in the UK.
Kriplani,A., Manchanda,R., Nath,J., Takkar,D., A randomized trial of danazol pretreatment prior to endometrial resection, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 103, 68-71, 2002	Preparation for resection; Danazol not an intervention of interest according to protocol.
Kroft, J., Liu, G., First- versus second-generation endometrial ablation devices for treatment of menorrhagia: a systematic review, meta-analysis and appraisal of economic evaluations, Journal of Obstetrics & Gynaecology Canada: JOGC, 35, 1010-9, 2013	Non-Cochrane RCT; references checked for relevant studies.

Reference	Reason for exclusion
Kucuk, T., Ertan, K., Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomized, prospective, controlled clinical trial in female smokers, Clinical & Experimental Obstetrics & GynecologyClin Exp Obstet Gynecol, 35, 57-60, 2008	Results reported for 2 treatment cycles only (8 weeks).
Kulshrestha, V, Kriplani, A, Agarwal, N, Sareen, N, Garg, P, Hari, S, Thulkar, J, Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India, The Indian journal of medical research, 137, 1154-62, 2013	Treatment duration less than 3 cycles.
Kuppermann, M., Varner, R. E., Summitt, R. L., Jr., Learman, L. A., Ireland, C., Vittinghoff, E., Stewart, A. L., Lin, F., Richter, H. E., Showstack, J., Hulley, S. B., Washington, A. E., Ms Research, Group, Effect of hysterectomy vs medical treatment on health-related quality of life and sexual functioning: the medicine or surgery (Ms) randomized trial, JAMA, 291, 1447-55, 2004	No outcomes of interest for pairwise; only satisfaction and HRQoL summaries reported, inappropriate for NMA imputation.
Laberge, P., Garza-Leal, J., Fortin, C., Basinski, C., Thiel, J., Leyland, N., Presthus, J., Johns, A., Grainger, D., Adkins, T., Swarup, M., Gimpelson, R., Harris, M., A prospective, randomized, multi-center, controlled, international clinical study of the safety and efficacy of the minerva endometrial ablation system. 6 & 12-months follow-up results, Journal of Minimally Invasive Gynecology, Conference, 2014	Conference abstract.
Laberge, P., Leyland, N., Murji, A., Fortin, C., Martyn, P., Vilos, G., Clinical Practice-Gynaecology, Committee, Leyland, N., Wolfman, W., Allaire, C., Awadalla, A., Dunn, S., Heywood, M., Lemyre, M., Marcoux, V., Potestio, F., Rittenberg, D., Singh, S., Yeung, G., Society of, Obstetricians, Gynaecologists of, Canada, Endometrial ablation in the management of abnormal uterine bleeding, Journal of Obstetrics & Gynaecology Canada: JOGCJ Obstet Gynaecol Can, 37, 362-79, 2015	Practice guideline.
Lahteenmaki, P., Haukkamaa, M., Puolakka, J., Riikonen, U., Sainio, S., Suvisaari, J., Nilsson, C. G., Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy, BMJ, 316, 1122-6, 1998	No outcomes of interest reported.
Lamb, M. P., Danazol in menorrhagia: a double blind placebo controlled trial, Journal of Obstetrics and Gynaecology, 7, 212-216, 1987	Danazol not an intervention of interest according to protocol; incomplete data reported for NMA
Learman, L. A., Summitt, R. L., Jr., Varner, R. E., Richter, H. E., Lin, F., Ireland, C. C., Kuppermann, M., Vittinghoff, E., Showstack, J., Washington, A. E., Hulley, S. B., Medicine or Surgery Research, Group, Hysterectomy versus expanded medical treatment for abnormal uterine bleeding: clinical outcomes in the medicine or surgery trial, Obstet Gynecol, 103, 824-33, 2004	No outcomes of interest reported.
Lefler,H.T.,Jr., Long-term follow-up of endometrial ablation by modified loop resection, Journal of the American Association of Gynecologic Laparoscopists, 10, 517-520, 2003	Incorrect study type: non-comparative cohort study of women treated with rollerball ablation and loop resection of endometrium.

Reference	Reason for exclusion
Leminen, H., Hurskainen, R., Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety, International journal of women's health, 4, 413-21, 2012	Narrative review.
Lethaby, A. E., Cooke, I., Rees, M., Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding, Cochrane Database Syst Rev, CD002126, 2005	Updated version of Cochrane review available.
Lethaby, A., Augood, C., Duckitt, K., Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 1998	Updated version of Cochrane review available.
Lethaby, A., Irvine, G., Cameron, I., Cyclical progestogens for heavy menstrual bleeding, Cochrane Database Syst Rev, CD001016, 2000	Updated version of Cochrane review available.
Lethaby, Anne, Farquhar, Cindy, Cooke, Inez, Antifibrinolytics for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 2000	Only one relevant study which is included in another Cochrane review.
Lethaby,Anne, Duckitt,Kirsten, Farquhar,Cindy, Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, -, 2013	Cochrane systematic review with two relevant studies, however, both are included in other Cochrane systematic reviews which are included in the review.
Levens, E. D., Potlog-Nahari, C., Armstrong, A. Y., Wesley, R., Premkumar, A., Blithe, D. L., Blocker, W., Nieman, L. K., CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial, Obstet Gynecol, 111, 1129-36, 2008	Less than 10 participants in each arm.
Lissak,A., Fruchter,O., Mashiach,S., Brandes-Klein,O., Sharon,A., Kogan,O., Abramovici,H., Immediate versus delayed treatment of perimenopausal bleeding due to benign causes by balloon thermal ablation, Journal of the American Association of Gynecologic Laparoscopists, 6, 145-150, 1999	Treatment duration less than 3 months.
Liu,W.M., Tzeng,C.R., Yi-Jen,C., Wang,P.H., Combining the uterine depletion procedure and myomectomy may be useful for treating symptomatic fibroids, Fertility and Sterility, 82, 205-210, 2004	Incorrect study type: controlled study with no randomisation.
Luisi, S., Ciani, V., Gabbanini, M., Sollazzi, S., Torricelli, M., Calonaci, F., Petraglia, F., Oral contraceptives after myomectomy: a short term trial, International Journal of Endocrinology PrintInt, 2009, 476897, 2009	No outcomes of interest.
Lukes, A. S., Baker, J., Eder, S., Adomako, T. L., Daily menstrual blood loss and quality of life in women with heavy menstrual bleeding, Women's Health, 8, 503-11, 2012	Post-hoc analysis of 2 RCTs.
Lukes, A. S., Freeman, E. W., Van Drie, D., Baker, J., Adomako, T. L., Safety of tranexamic acid in women with heavy menstrual bleeding: An open-label extension study, Women's Health, 7, 591-598, 2011	Tranexamic acid MR 650mg not available in the UK; extension study with no control group (excluded from NMA).
Lukes, A. S., Moore, K. A., Muse, K. N., Gersten, J. K., Hecht, B. R., Edlund, M., Richter, H. E., Eder, S. E., Attia, G. R., Patrick, D. L., Rubin, A., Shangold, G. A., Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial, Obstetrics & Gynecology, 116, 865-75, 2010	Tranexamic acid 650 mg not available in the UK; mainly narrative/figure reporting, statistical analysis cannot be done because of limited reporting.

Reference	Reason for exclusion
Mara, M., Fucikova, Z., Maskova, J., Kuzel, D., Haakova, L., Uterine fibroid embolization versus myomectomy in women wishing to preserve fertility: preliminary results of a randomized controlled trial, Eur J Obstet Gynecol Reprod Biol, 126, 226-33, 2006	Data from this trial reported in Mara 2008 included in this review. This publication with smaller sample (shorter recruitment time of the same trial) does not report any additional outcomes, therefore, not relevant.
Marjoribanks, J., Lethaby, A., Farquhar, C., Surgery versus medical therapy for heavy menstrual bleeding, Cochrane Database Syst Rev, CD003855, 2006	Updated 2016 version of Cochrane review available.
Marret, H., Cottier, J. P., Alonso, A. M., Giraudeau, B., Body, G., Herbreteau, D., Predictive factors for fibroids recurrence after uterine artery embolisation, BJOG, 112, 461-5, 2005	Incorrect study type: case series.
Marsh, F, Thewlis, J, Duffy, S, Randomized controlled trial comparing Thermachoice III* in the outpatient versus daycase setting, Fertility and sterility, 87, 642-50, 2007	No outcomes of interest.
Marziani, R., Mossa, B., Ebano, V., Perniola, G., Melluso, J., Napolitano, C., Transcervical hysteroscopic myomectomy: long-term effects on abnormal uterine bleeding, Clin Exp Obstet Gynecol, 32, 23-6, 2005	Incorrect study type: non-comparative cohort study.
Matteson, K. A., Abed, H., Wheeler, T. L., Sung, V. W., Rahn, D. D., Schaffer, J. I., Balk, E. M., A systematic review comparing hysterectomy with less-invasive treatments for abnormal uterine bleeding, Journal of Minimally Invasive Gynecology, 19, 13-28, 2012	Non-Cochrane systematic review; references checked for relevant studies.
Matteson, Ka, Rahn, Dd, Wheeler, Tl, Casiano, E, Siddiqui, Ny, Harvie, Hs, Mamik, Mm, Balk, Em, Sung, Vw, Nonsurgical management of heavy menstrual bleeding: a systematic review (Provisional abstract), Obstetrics and Gynecology, 121, 632-643, 2013	Non-Cochrane systematic review; references checked for relevant studies.
Mawet, M., Nollevaux, F., Nizet, D., Wijzen, F., Gordenne, V., Tasev, N., Segedi, D., Marinescu, B., Enache, A., Parhomenko, V., Frankenne, F., Foidart, J. M., Impact of a new levonorgestrel intrauterine system, Levosert(), on heavy menstrual bleeding: results of a one-year randomised controlled trial, European Journal of Contraception & Reproductive Health Care, 19, 169-79, 2014	Comparisons between different kinds of LNG-IUSs, not of interest according to protocol.
McCausland, A. M., McCausland, V. M., Hysteroscopic Endometrial Resection Versus Laparoscopic Supracervical Hysterectomy for Abnormal Uterine Bleeding: Long-Term Follow-Up of a Randomized Trial, Journal of Minimally Invasive Gynecology, 23, 136-7, 2016	Letter to editor.
McClure, N., Mamers, P.M., Healy, D.L., A quantitative assessment of endometrial electrocautery in the management of menorrhagia and a comparative report of argon laser endometrial ablation., Gynaecological Endoscopy, 1, 199-202, 1992	Laser ablation not an intervention of interest according to protocol; small sample size n=22
McLucas, B., Adler, L., Perrella, R., Uterine fibroid embolization: nonsurgical treatment for symptomatic fibroids, J Am Coll SurgJournal of the American College of Surgeons, 192, 95-105, 2001	Incorrect study type: case series.

Reference	Reason for exclusion
McLucas, B., Adler, L., Perrella, R., Predictive factors for success in uterine fibroid embolisation, Minimally Invasive Therapy & Allied Technologies, 8, 429-432, 1999	Incorrect study type: case series.
McLucas, N., Adler, L., Uterine artery embolization as therapy for myomata., Infertility and Reproductive Medicine Clinics of North America, 11, 77-94, 2000	Incorrect study type: non-comparative cohort study of UAE.
McPherson, K., Herbert, A., Judge, A., Clarke, A., Bridgman, S., Maresh, M., Overton, C., Self-reported bladder function five years post-hysterectomy, J Obstet Gynaecol, 25, 469-75, 2005	Incorrect study type: cohort study.
McPherson,K., Herbert,A., Judge,A., Clarke,A., Bridgman,S., Maresh,M., Overton,C., Psychosexual health 5 years after hysterectomy: population-based comparison with endometrial ablation for dysfunctional uterine bleeding, Health Expectations, 8, 234-243, 2005	Incorrect study type: cohort study.
Middleton, Lj, Champaneria, R, Daniels, Jp, Bhattacharya, S, Cooper, Kg, Hilken, Nh, O'Donovan, P, Gannon, M, Gray, R, Khan, Ks, Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients (Structured abstract), Bmj, 341:c3929, 2010	Non-Cochrane systematic review; references checked for relevant studies.
Milsom, I., The levonorgestrel-releasing intrauterine system as an alternative to hysterectomy in peri-menopausal women, Contraception, 75, S152-4, 2007	Review article.
Milsom, I., Andersson, K., Andersch, B., Rybo, G., A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia, American Journal of Obstetrics and Gynecology, 164, 879-83, 1991	Treatment duration less than 3 cycles.
Moroni, R. M., Vieira, C. S., Ferriani, R. A., Reis, R. M., Nogueira, A. A., Brito, L. G., Presentation and treatment of uterine leiomyoma in adolescence: a systematic review, BMC women's health, 15, 4, 2015	Incorrect study type: review of cases or case series.
Mousa, H. A., Abou El Senoun, G. M., Mahmood, T. A., Medium-term clinical outcome of women with menorrhagia treated by rollerball endometrial ablation versus abdominal hysterectomy with conservation of at least one ovary, Acta Obstet Gynecol Scand, 80, 442-6, 2001	Incorrect study type: comparative cohort study.
Munro, Mg, Dickersin, K, Clark, Ma, Langenberg, P, Scherer, Rw, Frick, Kd, The Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding: Summary of an Agency for Health Research and Quality-sponsored randomized trial of endometrial ablation versus hysterectomy for women with heavy menstrual bleeding, Menopause (New York, N.Y.), 18, 445-52, 2011	Synopsium paper.
Najam, R, Agarwal, D, Tyagi, R, Singh, S, Comparison of traneximic acid with a combination of traneximic acid and mefenamic acid in reducing menstrual blood loss in ovulatory dysfunctional uterine bleeding (DUB), Journal of Clinical and Diagnostic Research, 4, 3020-5, 2010	Results are unclear - authors use the terms ‘mean’, ‘median’ and ‘average’ interchangeably for PBAC.
Nakayama, H., Yano, T., Sagara, Y., Kikuchi, A., Ando, K., Wang, Y., Watanabe, M., Matsumi, H., Osuga, Y., Momoeda, M., Taketani, Y., Estriol add-back therapy in the long-acting gonadotropin-releasing hormone agonist treatment of uterine leiomyomata, Gynecol Endocrinol, 13, 382-9, 1999	Less than 10 patients in each arm.

Reference	Reason for exclusion
Nilsson, Lennart, Rybo, Göran, Treatment Of Menorrhagia With An Antifibrinolytic Agent, Tranexamic Acid (Amca): A Double Blind Investigation, Acta Obstetricia et Gynecologica Scandinavica, 46, 572-580, 1967	No outcomes of interest.
Nooh, Am, Abdeldayem, Hm, Girbash, Ef, Arafa, Em, Atwa, K, Abdel-Raouf, Sm, Depo-Provera Versus Norethisterone Acetate in Management of Endometrial Hyperplasia Without Atypia, Reproductive sciences (Thousand Oaks, Calif.), 23, 448-54, 2016	No outcomes of interest.
Nor, Azlin Mi, Maryasalwati, I, Norzilawati, Mn, Mahdy, Za, Jamil, Ma, Zainul, Rashid Mr, The efficacy of etoricoxib vs mefenamic acid in the treatment of primary dysmenorrhoea: a randomised comparative trial, Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology, 28, 424-6, 2008	No outcomes of interest; HMB not part of inclusion criteria; % with HMB not reported.
O'Connor, H., Magos, A., Endometrial resection for the treatment of menorrhagia, N Engl J Med, 335, 151-6, 1996	Incorrect study type: case series.
Olufowobi, O., Sharif, K., Papaionnou, S., Neelakantan, D., Mohammed, H., Afnan, M., Are the anticipated benefits of myomectomy achieved in women of reproductive age? A 5-year review of the results at a UK tertiary hospital, Journal of Obstetrics and Gynaecology, 24, 434-440, 2004	Incorrect study type: retrospective chart review.
Palomba, S., Orio, F., Jr., Morelli, M., Russo, T., Pellicano, M., Nappi, C., Mastrantonio, P., Lombardi, G., Colao, A., Zullo, F., Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism, J Clin Endocrinol Metab, 87, 4476-81, 2002	Raloxifene used as an adjunct in intervention, not relevant.
Palomba, S., Orio, F., Jr., Russo, T., Falbo, A., Amati, A., Zullo, F., Gonadotropin-releasing hormone agonist with or without raloxifene: effects on cognition, mood, and quality of life, Fertil Steril, 82, 480-2, 2004	Raloxifene used as an adjunct in intervention, not relevant.
Palomba,S., Affinito,P., Tommaselli,G.A., Nappi,C., A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata, Fertility and Sterility, 70, 111-118, 1998	Tibolone used as an adjunct in intervention, not relevant.
Parkin, David E., Meatm Users' Group, Microwave endometrial ablation (MEATM): a safe technique? Complication data from a prospective series of 1400 cases, Gynaecological Endoscopy, 9, 385-388, 2000	Incorrect study type: prospective case series; microwave endometrial ablation technique not an intervention of interest according to protocol.
Parveen, T, Kausar, T, Iqbal, T, Batool, A, Comparison of outcome between vaginal and abdominal hysterectomy, Pakistan Journal of Medical and Health Sciences, 7, 1150-3, 2013	Mixed population including women with prolapse; 65.79% fibroids or HMB.
Peitsidis, P., Koukoulomati, A., Tranexamic acid for the management of uterine fibroid tumors: A systematic review of the current evidence, World Journal of Clinical CasesWorld j, 2, 893-8, 2014	Systematic review of tranexamic acid, included studies considered individually.

Reference	Reason for exclusion
Pelage, J. P., Le Dref, O., Soyer, P., Kardache, M., Dahan, H., Abitbol, M., Merland, J. J., Ravina, J. H., Rymer, R., Fibroid-related menorrhagia: treatment with superselective embolization of the uterine arteries and midterm follow-up, Radiology, 215, 428-31, 2000	Incorrect study type: non-comparative cohort study.
Perez-Medina, T., Haya, J., Frutos, L. S., Arenas, J. B., Factors influencing long-term outcome of loop endometrial resection, J Am Assoc Gynecol Laparosc, 9, 272-6, 2002	Incorrect study type: non-comparative cohort of women undergoing loop resection.
Phillips, D. R., Nathanson, H. G., Meltzer, S. M., Milim, S. J., Haselkorn, J. S., Johnson, P., Transcervical electrosurgical resection of submucous leiomyomas for chronic menorrhagia, J Am Assoc Gynecol Laparosc, 2, 147-53, 1995	Incorrect study type: non-comparative cohort study.
Pinion, S. B., Parkin, D. E., Abramovich, D. R., Naji, A., Alexander, D. A., Russell, I. T., Kitchener, H. C., Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding, Bmj, 309, 979-83, 1994	Incorrect population: women with dusfunctional uterine bleeding with less than 2/3 with HMB.
Pooley, A. S., Ewen, S. P., Sutton, C. J., Does transcervical resection of the endometrium for menorrhagia really avoid hysterectomy? Life table analysis of a large series, J Am Assoc Gynecol Laparosc, 5, 229-35, 1998	Incorrect study type: case series.
Preston, J. T., Cameron, I. T., Adams, E. J., Smith, S. K., Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia, British journal of obstetrics and gynaecology, 102, 401-6, 1995	Treatment duration less than 3 cycles.
Prollius, A., de Vries, C., Loggenberg, E., du Plessis, A., Nel, M., Wessels, P. H., Uterine artery embolisation for symptomatic fibroids: the effect of the large uterus on outcome, BJOG, 111, 239-42, 2004	Incorrect study type: case control.
Pron, G., Bennett, J., Common, A., Wall, J., Asch, M., Sniderman, K., Ontario Uterine Fibroid Embolization Collaboration, Group, The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids, Fertil Steril, 79, 120-7, 2003	Incorrect study type: cohort study.
Pron, G., Cohen, M., Soucie, J., Garvin, G., Vanderburgh, L., Bell, S., Ontario Uterine Fibroid Embolization Collaboration, Group, The Ontario Uterine Fibroid Embolization Trial. Part 1. Baseline patient characteristics, fibroid burden, and impact on life, Fertil Steril, 79, 112-9, 2003	Incorrect study type: cohort study.
Pron, G., Mocarski, E., Bennett, J., Vilos, G., Common, A., Zaidi, M., Sniderman, K., Asch, M., Kozak, R., Simons, M., Tran, C., Kachura, J., Ontario, U. F. E. Collaborative Group, Tolerance, hospital stay, and recovery after uterine artery embolization for fibroids: the Ontario Uterine Fibroid Embolization Trial, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 14, 1243-50, 2003	Incorrect study type: cohort study.

Reference	Reason for exclusion
Qiu, J, Cheng, J, Wang, Q, Hua, J, Levonorgestrel-releasing intrauterine system versus medical therapy for menorrhagia: a systematic review and meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, 1700-1713, 2014	Non-Cochrane systematic review; references checked for relevant studies.
Quenby, S., Banahan, I., Farquharson, R., Listening to the patient: endometrial resection, Br J Hosp Med, 57, 508-11, 1997	Incorrect study type: non-comparative cohort.
Rajan, D. K., Beecroft, J. R., Clark, T. W., Asch, M. R., Simons, M. E., Kachura, J. R., Sved, M., Sniderman, K. W., Risk of intrauterine infectious complications after uterine artery embolization, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 15, 1415-21, 2004	Incorrect study type: retrospective cohort.
Rashid,S., Khaund,A., Murray,L.S., Moss,J.G., Cooper,K., Lyons,D., Murray,G.D., Lumsden,M.A., The effects of uterine artery embolisation and surgical treatment on ovarian function in women with uterine fibroids, BJOG: An International Journal of Obstetrics and Gynaecology, 117, 985-989, 2010	No outcomes of interest for the review.
Ravina, J. H., Ciraru-vigneron, N., Aymard, A., Ferrand, J., Merland, J. J., Uterine artery embolisation for fibroid disease: Results of a 6 year study, Minimally Invasive Therapy & Allied Technologies, 8, 441-447, 1999	Incorrect study type: cohort study.
Razavi, M. K., Hwang, G., Jahed, A., Modanlou, S., Chen, B., Abdominal myomectomy versus uterine fibroid embolization in the treatment of symptomatic uterine leiomyomas, AJR Am J Roentgenol, 180, 1571-5, 2003	Incorrect study type: cohort study.
Reilly, R.J., Nour, N., Abdominal myomectomy is associated with few surgical complications., Journal of Gynecologic Techniques, 4, 107-12, 1998	Incorrect study type: retrospective review of medical records.
Romer, T., [Therapy of recurrent menorrhagia--Cavaterm balloon coagulation versus roller-ball endometrium coagulation--a prospective randomized comparative study], Die Therapie rezidivierender Menorrhagien--Cavaterm-Ballon-Koagulation versus Roller-Ball-Endometriumkoagulation--eine prospektive randomisierte Vergleichsstudie., 120, 511-4, 1998	Full text in German language.
Roth, A. R., Spies, J. B., Walsh, S. M., Wood, B. J., Gomez-Jorge, J., Levy, E. B., Pain after uterine artery embolization for leiomyomata: can its severity be predicted and does severity predict outcome?, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 11, 1047-52, 2000	Incorrect study type: cohort study.
Sambrook, Am, Bain, C, Parkin, De, Cooper, Kg, A randomised comparison of microwave endometrial ablation with transcervical resection of the endometrium: follow up at a minimum of 10 years, BJOG : an international journal of obstetrics and gynaecology, 116, 1033-7, 2009	10-year follow up too long time-frame to include in NMA; microwave ablation technique not an intervention of interest according to protocol.
Sanghera, S, Roberts, Te, Barton, P, Frew, E, Daniels, J, Middleton, L, Gennard, L, Kai, J, Gupta, Jk, Levonorgestrel-releasing intrauterine system vs. usual medical treatment for menorrhagia: an economic evaluation alongside a randomised controlled trial, PloS one, 9, e91891, 2014	Economic model and cost-effectiveness evaluation; no relevant data reported.

Reference	Reason for exclusion
Sapmaz, E., Celik, H., Comparison of the effects of the ligation of ascending branches of bilateral arteria uterina with tourniquet method on the intra-operative and post-operative hemorrhage in abdominal myomectomy cases, Eur J Obstet Gynecol Reprod Biol, 111, 74-7, 2003	Less than 2/3 of participants with HMB.
Sawin, S. W., Pilevsky, N. D., Berlin, J. A., Barnhart, K. T., Comparability of perioperative morbidity between abdominal myomectomy and hysterectomy for women with uterine leiomyomas, Am J Obstet Gynecol, 183, 1448-55, 2000	Incorrect study type: cohort study.
Schlaff, W. D., Zerhouni, E. A., Huth, J. A., Chen, J., Damewood, M. D., Rock, J. A., A placebo-controlled trial of a depot gonadotropin-releasing hormone analogue (leuprolide) in the treatment of uterine leiomyomata, Obstet Gynecol, 74, 856-62, 1989	Less than 10 participants in each arm.
Sculpher, M. J., Dwyer, N., Browning, J., Horsley, S., Cullimore, J., A survey of women's preferences regarding alternative surgical treatments for menorrhagia, Health Expect, 1, 96-105, 1998	Incorrect study type: cohort study.
Seidman, D. S., Bitman, G., Mashiach, S., Hart, S., Goldenberg, M., The effect of increasing age on the outcome of hysteroscopic endometrial resection for management of dysfunctional uterine bleeding, J Am Assoc Gynecol Laparosc, 7, 115-9, 2000	Incorrect study type: non-comparative cohort study of women treated with hysteroscopic endometrial resection.
Seracchioli,R., Rossi,S., Govoni,F., Rossi,E., Venturoli,S., Bulletti,C., Flamigni,C., Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy, Human Reproduction, 15, 2663-2668, 2000	Incorrect population: HMB not an inclusion criteria.
Shan, H., Huang, M. S., Guan, S. H., Jiang, Z. B., Zhu, K. S., Li, Z. R., Superselective uterine arterial embolization with pingyangmycin-lipiodol emulsion for management of symptomatic uterine leiomyoma, Chin Med J (Engl), 117, 75-8, 2004	Incorrect study type: non-comparative cohort.
Sharma, B., Preston, J., Ray, C., Microwave endometrial ablation for menorrhagia: outcome at 2 years--experience of a district general hospital, Journal of Obstetrics & Gynaecology, 24, 916-9, 2004	Incorrect study type: cohort study.
Shawki,O., Hebert,A.S., Peters,A.J., Endometrial preparation before hysteroscopic surgery for uterine bleeding: A prospective randomized multicenter evaluation, Middle East Fertility Society Journal, 5, 48-52, 2000	Endometrial preparation not an intervention of interest according to protocol.
Shen, Q., Hua, Y., Jiang, W., Zhang, W., Chen, M., Zhu, X., Effects of mifepristone on uterine leiomyoma in premenopausal women: a meta-analysis, Fertility & Sterility, 100, 1722-6.e1-10, 2013	Treatment duration less than 3 cycles/months; mifepristone not licensed in the UK.
Shokeir, T., Eid, M., Abdel-Hady el, S., Does adjuvant long-acting gestagen therapy improve the outcome of hysteroscopic endometrial resection in women of low-resource settings with heavy menstrual bleeding?, Journal of Minimally Invasive Gynecology, 20, 222-6, 2013	Treatment duration less than 3 cycles/months.
Shravage, J, Mekhala, D, Bellad, Mb, Ganachari, Ms, Dhumale, Ha, Ormeloxifene versus medroxyprogesterone acetate (MPA) in the treatment of dysfunctional uterine bleeding: A double-blind randomized controlled trial, Journal of SAFOG, 3, 21-4, 2011	Ormeloxifene not licensed in the UK.

Reference	Reason for exclusion
Siskin, G. P., Shlansky-Goldberg, R. D., Goodwin, S. C., Sterling, K., Lipman, J. C., Nosher, J. L., Worthington-Kirsch, R. L., Chambers, T. P., U. A. E. versus Myomectomy Study Group, A prospective multicenter comparative study between myomectomy and uterine artery embolization with polyvinyl alcohol microspheres: long-term clinical outcomes in patients with symptomatic uterine fibroids, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 17, 1287-95, 2006	Incorrect study type: cohort study.
Smith, P. P., Malick, S., Clark, T. J., Bipolar radiofrequency compared with thermal balloon ablation in the office: A randomized controlled trial, Obstetrics and Gynecology, 124, 219-225, 2014	Two types of second line endometrial ablation techniques compared; no outcomes of interes for the NMA.
Song,Huan, Lu,DongHao, Navaratnam,Kate, Shi,Gang, Aromatase inhibitors for uterine fibroids, Cochrane Database of Systematic Reviews, -, 2013	Intervention not licensed in UK for HMB.
Soysal,M.E., Soysal,S.K., Vicdan,K., Thermal balloon ablation in myoma-induced menorrhagia under local anesthesia, Gynecologic and Obstetric Investigation, 51, 128-133, 2001	Exclude NMA: women with fibroids; exclude from pairwise analysis: no outcomes of interest.
Spies, J. B., Allison, S., Flick, P., Cramp, M., Bruno, J., Jha, R. C., Ascher, S. A., Spherical polyvinyl alcohol versus tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a limited randomized comparative study, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 16, 1431-7, 2005	Polyvinyl or tri-acetyl gelatin spheres not interventions of interest according to protocol.
Spies, J. B., Allison, S., Flick, P., McCullough, M., Sterbis, K., Cramp, M., Bruno, J., Jha, R., Polyvinyl alcohol particles and tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a randomized comparative study, J Vasc Interv RadiolJournal of vascular and interventional radiology : JVIR, 15, 793-800, 2004	Polyvinyl or tri-acetyl gelatin spheres not interventions of interest according to protocol.
Spies, J. B., Ascher, S. A., Roth, A. R., Kim, J., Levy, E. B., Gomez-Jorge, J., Uterine artery embolization for leiomyomata, Obstet Gynecol, 98, 29-34, 2001	Incorrect study type: case series.
Spies, J. B., Bruno, J., Czeyda-Pommersheim, F., Magee, S. T., Ascher, S. A., Jha, R. C., Long-term outcome of uterine artery embolization of leiomyomata, Obstet Gynecol, 106, 933-9, 2005	Incorrect study type: cohort study.
Spies, J. B., Cooper, J. M., Worthington-Kirsch, R., Lipman, J. C., Mills, B. B., Benenati, J. F., Outcome of uterine embolization and hysterectomy for leiomyomas: results of a multicenter study, Am J Obstet Gynecol, 191, 22-31, 2004	Incorrect study type: cohort study.
Spies, J. B., Roth, A. R., Jha, R. C., Gomez-Jorge, J., Levy, E. B., Chang, T. C., Ascher, S. A., Leiomyomata treated with uterine artery embolization: factors associated with successful symptom and imaging outcome, Radiology, 222, 45-52, 2002	Incorrect study type: one arm trial.
Spies, J. B., Spector, A., Roth, A. R., Baker, C. M., Mauro, L., Murphy-Skrynarz, K., Complications after uterine artery embolization for leiomyomas, Obstet Gynecol, 100, 873-80, 2002	Incorrect study type: cohort study.

Reference	Reason for exclusion
Srivaths, L. V., Dietrich, J. E., Yee, D. L., Sangi-Haghpeykar, H., Mahoney, D., Jr., Oral Tranexamic Acid versus Combined Oral Contraceptives for Adolescent Heavy Menstrual Bleeding: A Pilot Study, Journal of Pediatric & Adolescent GynecologyJ Pediatr Adolesc Gynecol, 28, 254-7, 2015	Less than 10 in intervention arm.
Steffensen, A. J., Schuster, M., Endometrial resection and late reoperation in the treatment of menorrhagia, J Am Assoc Gynecol Laparosc, 4, 325-9, 1997	Incorrect study type: retrospective study; non-comparative study of TCRE.
Stewart, A., Cummins, C., Gold, L., Jordan, R., Phillips, W., The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review, BJOG, 108, 74-86, 2001	Non-Cochrane systematic review; references checked for relevant studies.
Stringer, N. H., Walker, J. C., Meyer, P. M., Comparison of 49 laparoscopic myomectomies with 49 open myomectomies, J Am Assoc Gynecol Laparosc, 4, 457-64, 1997	Incorrect study type: retrospective chart review; compared open to laparoscopic myomectomy.
Tabatabaei, A, A clinical randomized single blind trial of medical therapies for menorrhagia using ibuprofen and tranexamic acid, International Journal of Fertility and Sterility, 7, 120, 2013	Conference abstract.
Takeuchi,H., Kobori,H., Kikuchi,I., Sato,Y., Mitsuhashi,N., A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis, Journal of Obstetrics and Gynaecology Research, 26, 325-331, 2000	Less than 2/3 of population with HMB.
Tan, Yu Hwee, Lethaby, Anne, Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding, Cochrane Database of Systematic Reviews, 2013	Systematic review with all trials included with treatment duration less than 3 cycles/months and 1 trial with 3 cycles/months but no outcomes of interest.
Taylor, A., Sharma, M., Tsirkas, P., Di Spiezio Sardo, A., Setchell, M., Magos, A., Reducing blood loss at open myomectomy using triple tourniquets: a randomised controlled trial, BJOG, 112, 340-5, 2005	Tourniquets not an intervention of interest according to protocol.
Thiel, J, Rattray, D, A randomized trial of uterine-sparing fibroid treatments in Canada: Laparoscopic radiofrequency volumetric thermal ablation (Rfvta) and myomectomy, Gynecological Surgery, 11, 184-5, 2014	Conference abstract.
Thijssen,R.F., Radiofrequency induced endometrial ablation: an update, British Journal of Obstetrics and Gynaecology, 104, 608-613, 1997	Incorrect study type: case series.
Thurkow, A., Van Baal, M., Van Eijndhoven, H., Final Results of a Multicenter Trial of Safety and Effectiveness of Endometrial Ablation With the AEGEA Vapor System for the Treatment of Menorrhagia, Journal of Minimally Invasive Gynecology, 22, S46, 2015	Conference abstract; non-randomized, single arm study.
Tristan, M., Orozco, L. J., Steed, A., Ramirez-Morera, A., Stone, P., Mifepristone for uterine fibroids, Cochrane Database of Systematic Reviews, 8, CD007687, 2012	Mifepristone not an intervention of interest according to protocol; not relevant for the NMA because population is women women with fibroids.
Tsaltas, J., Taylor, N., Healey, M., A 6-year review of the outcome of endometrial ablation, Aust N Z J Obstet Gynaecol, 38, 69-72, 1998	Incorrect study type: case series.

Reference	Reason for exclusion
Turnbull, A. C., Rees, M. C., Gestrinone in the treatment of menorrhagia, Br J Obstet Gynaecol, 97, 713-5, 1990	Incorrect study type: non-randomised trial.
Uhm, S., Perriera, L., Hormonal contraception as treatment for heavy menstrual bleeding: a systematic review, Clinical Obstetrics & GynecologyClin Obstet Gynecol, 57, 694-717, 2014	Non-Cochrane systematic review; references checked for relevant studies.
van der Kooij, S. M., Bipat, S., Hehenkamp, W. J., Ankum, W. M., Reekers, J. A., Uterine artery embolization versus surgery in the treatment of symptomatic fibroids: a systematic review and metaanalysis, American Journal of Obstetrics & Gynecology, 205, 317.e1-18, 2011	Systematic review, all included studies included in the Gupta 2014 Cochrane review and considered individually for inclusion.
van Dijk, M. M., van Hanegem, N., de Lange, M. E., Timmermans, A., Treatment of Women With an Endometrial Polyp and Heavy Menstrual Bleeding: A Levonorgestrel-Releasing Intrauterine Device or Hysteroscopic Polypectomy?, Journal of Minimally Invasive Gynecology, 22, 1153-62, 2015	Polypectomy not an intervention of interest according to protocol.
van Eijkeren, M. A., Christiaens, G. C., Geuze, H. J., Haspels, A. A., Sixma, J. J., Effects of mefenamic acid on menstrual hemostasis in essential menorrhagia, Am J Obstet Gynecol, 166, 1419-28, 1992	Treatment duration less than 3 cycles/months; less than 10 participants in each arm.
Vargyas, J. M., Campeau, J. D., Mishell, D. R., Jr., Treatment of menorrhagia with meclofenamate sodium, Am J Obstet Gynecol, 157, 944-50, 1987	Treatment duration less than 3 months/cycles.
Varner, R. E., Ireland, C. C., Summitt, R. L., Jr., Richter, H. E., Learman, L. A., Vittinghoff, E., Kuppermann, M., Washington, E., Hulley, S. B., Ms Research, Group, Medicine or Surgery (Ms): a randomized clinical trial comparing hysterectomy and medical treatment in premenopausal women with abnormal uterine bleeding, Controlled Clinical TrialsControl Clin Trials, 25, 104-18, 2004	Same trial as Kupperman 2004 which already included, this publication does not report any additional outcomes of relevance.
Vercellini, P., Trespidi, L., Zaina, B., Vicentini, S., Stellato, G., Crosignani, P. G., Gonadotropin-releasing hormone agonist treatment before abdominal myomectomy: a controlled trial, Fertil Steril, 79, 1390-5, 2003	Treatment duration less than 3 cycles.
Vermylen, J., Verhaegen-Declercq, M. L., Verstraete, M., Fierens, F., A double blind study of the effect of tranexamic acid in essential menorrhagia, Thromb Diath Haemorrh, 20, 583-7, 1968	No outcomes of interest.
Vilos, G. A., Fortin, C. A., Sanders, B., Pendley, L., Stabinsky, S. A., Clinical trial of the uterine thermal balloon for treatment of menorrhagia, J Am Assoc Gynecol Laparosc, 4, 559-65, 1997	Incorrect sutyd type: non-comparative cohort of thermal balloon ablation.
Vilos, G. A., Vilos, A. G., Abu-Rafea, B., Randomized Comparison of Goserelin Versus Suction Curettage Prior to Thermachoice II Balloon Endometrial Ablation: One-year Results, Journal of Obstetrics and Gynaecology Canada, 32, 2010	Treatment duration less than 3 cycles/months.
Vilos, G. A., Vilos, A. G., Abu-Rafea, B., Pron, G., Kozak, R., Garvin, G., Administration of goserelin acetate after uterine artery embolization does not change the reduction rate and volume of uterine myomas, Fertil Steril, 85, 1478-83, 2006	No outcomes of interest.
Vilos,G.A., Vilos,E.C., King,J.H., Experience with 800 hysteroscopic endometrial ablations, Journal of the American Association of Gynecologic Laparoscopists, 4, 33-38, 1996	Incorrect study type: retrospective record review; non-comparative study of endometrial ablation.

Reference	Reason for exclusion
Volkers, N. A., Hehenkamp, W. J. K., Smit, P., Ankum, W. M., Reekers, J. A., Birnie, E., Economic Evaluation of Uterine Artery Embolization versus Hysterectomy in the Treatment of Symptomatic Uterine Fibroids: Results from the Randomized EMMY Trial, Journal of Vascular and Interventional Radiology, 19, 1007-1016, 2008	Included in Gupta 2014 Cochrane systematic review as part of the EMMY trial, however, no relevant/new outcomes for the current review.
Vuorma, S., Rissanen, P., Aalto, A. M., Kujansuu, E., Hurskainen, R., Teperi, J., Factors predicting choice of treatment for menorrhagia in gynaecology outpatient clinics, Soc Sci Med, 56, 1653-60, 2003	Incorrect study type: cohort study.
Walker, W., Green, A., Sutton, C., Bilateral uterine artery embolisation for myomata: Results, complications and failures, Minimally Invasive Therapy & Allied Technologies, 8, 449-454, 1999	Incorrect study type: case series.
Walker,W.J., Pelage,J.P., Uterine artery embolisation for symptomatic fibroids: Clinical results in 400 women with imaging follow up, BJOG: An International Journal of Obstetrics and Gynaecology, 109, 1262-1272, 2002	Incorrect study type: observational study.
Wasiak, R, Filonenko, A, Vanness, Dj, Law, A, Jeddi, M, Wittrup-Jensen, Ku, Stull, De, Siak, S, Jensen, Jt, Impact of estradiol valerate/dienogest on work productivity and activities of daily living in women with heavy menstrual bleeding, Journal of women's health (2002), 22, 378-84, 2013	Same study as Jensen 2011; no additional outcomes of interest.
Watson, G. M., Walker, W. J., Uterine artery embolisation for the treatment of symptomatic fibroids in 114 women: reduction in size of the fibroids and women's views of the success of the treatment, BJOG, 109, 129-35, 2002	Incorrect study type: case series.
Wellington,K., Wagstaff,A.J., Tranexamic acid: A review of its use in the management of menorrhagia, Drugs, 63, 1417-1433, 2003	Narrative review; references checked for additional relevant studies.
West, C. P., Lumsden, M. A., Hillier, H., Sweeting, V., Baird, D. T., Potential role for medroxyprogesterone acetate as an adjunct to goserelin (Zoladex) in the medical management of uterine fibroids, Hum ReprodHuman reproduction (Oxford, England), 7, 328-32, 1992	Incorrect study type: cohort study.
Worthington-Kirsch, R., Spies, J. B., Myers, E. R., Mulgund, J., Mauro, M., Pron, G., Peterson, E. D., Goodwin, S., Fibroid Investigators, The Fibroid Registry for outcomes data (FIBROID) for uterine embolization: short-term outcomes, Obstet Gynecol, 106, 52-9, 2005	Incorrect study type: cohort study.
Wright, B., Gannon, M. J., Greenberg, M., House, A., Rutherford, T., Psychiatric morbidity following endometrial ablation and its association with genuine menorrhagia, BJOG, 110, 358-63, 2003	Incorrect study type: cohort study.
Xu,L., Lee,B.S., Asif,S., Kraemer,P., Inki,P., Satisfaction and health-related quality of life in women with heavy menstrual bleeding; results from a non-interventional trial of the levonorgestrel-releasing intrauterine system or conventional medical therapy, International Journal of Women's Health, 6, 547-554, 2014	Incorrect study type: observational study.

Reference	Reason for exclusion
Yang, B. Q., Xu, J. H., Teng, Y. C., Levonorgestrel intrauterine system versus thermal balloon ablation for the treatment of heavy menstrual bleeding: A meta-analysis of randomized controlled trials, Experimental & Therapeutic MedicineExperimental Ther, 10, 1665-1674, 2015	Non-Cochrane systematic review; references checked for relevant studies.
Ylikorkala, O., Pekonen, F., Naproxen reduces idiopathic but not fibromyoma-induced menorrhagia, Obstet Gynecol, 68, 10-2, 1986	Treatment duration less than 3 cycles/months.
Zapata, Lb, Whiteman, Mk, Tepper, Nk, Jamieson, Dj, Marchbanks, Pa, Curtis, Km, Intrauterine device use among women with uterine fibroids: a systematic review (Provisional abstract), Contraception, 82, 41-55, 2010	A systematic review with incorrect study type: not RCTs.
Zheng, J., Xia, E., Li, T. C., Sun, X., Comparison of combined transcervical resection of the endometrium and levonorgestrel-containing intrauterine system treatment versus levonorgestrel-containing intrauterine system treatment alone in women with adenomyosis: a prospective clinical trial, Journal of Reproductive Medicine, 58, 285-90, 2013	No outcomes of interest.
Zullo, F., Palomba, S., Corea, D., Pellicano, M., Russo, T., Falbo, A., Barletta, E., Saraco, P., Doldo, P., Zupi, E., Bupivacaine plus epinephrine for laparoscopic myomectomy: a randomized placebo-controlled trial, Obstet Gynecol, 104, 243-9, 2004	Treatment duration less than 3 months; peri-operative Bupivicane plus epinephrine as intervention, not of interest according to protocol.
Zupi, E, Centini, G, Lazzeri, L, Finco, A, Exacoustos, C, Afors, K, Zullo, F, Petraglia, F, Hysteroscopic Endometrial Resection Versus Laparoscopic Supracervical Hysterectomy for Abnormal Uterine Bleeding: Long-term Follow-up of a Randomized Trial, Journal of Minimally Invasive Gynecology, 22, 841-5, 2015	Excluded from NMA as a 15-year follow-up is too long to be modelled.

Economic studies

Table 54: Studies excluded from the ecomomic review for the management of HMB

Study	Reason for Exclusion
Ahonkallio, S., Santala, M., Valtonen, H., Martikainen, H., Cost-minimisation analysis of endometrial thermal ablation in a day case or outpatient setting under different anaesthesia regimens, European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 162, 102-4, 2012	Main focus is comparing a given technique in different settings. Whilst technique is within the scope the setting for this technique is not.
Bischoff-Everding, C., Soeder, R., Neukirch, B., Economic and clinical benefits of endometrial radiofrequency ablation compared with other ablation techniques in women with menorrhagia: A retrospective analysis with German health claims data, International journal of women's health, 8, 23-29, 2016	Cost analysis; not a full economic evaluation.

Study	Reason for Exclusion
Blumenthal, P. D., Dawson, L., Hurskainen, R., Cost-effectiveness and quality of life associated with heavy menstrual bleeding among women using the levonorgestrel-releasing intrauterine system, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 112, 171-8, 2011	Review article.
Bonafede, M. M., Miller, J. D., Laughlin-Tommaso, S. K., Slukes, A., Meyer, N. M., Lenhart, G. M., Retrospective database analysis of clinical outcomes and costs for treatment of abnormal uterine bleeding among women enrolled in US Medicaid programs, ClinicoEconomics and Outcomes Research, 6, 423-429, 2014	Conference abstract, cost analysis rather than full economic evaluation.
Bonafede, M. M., Miller, J., Meyer, N. M., Lenhart, G. M., Retrospective database analysis of clinical outcomes and costs for treatment of menorrhagia among women enrolled in medicaid programs in the united states, Value in HealthValue Health, 16 (3), A72, 2013	Conference abstract, cost analysis rather than full economic evaluation.
Bonafede, M. M., Miller, J., Meyer, N. M., Lenhart, G. M., Comparative direct and indirect costs of menorrhagia treatment with global endometrial ablation or hysterectomy, Value in HealthValue Health, 16 (3), A73, 2013	Conference abstract, cost analysis rather than full economic evaluation.
Brown, P M, Farquhar, C M, Lethaby, A, Sadler, L C, Johnson, N P, Cost-effectiveness analysis of levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding (Provisional abstract), BJOG. An International Journal of Obstetrics and Gynaecology, 113, 797-803, 2006	Pre-2007, more recent studies.
Buyuktuna, N., Sumer, F., Comparison of mirena intrauterine device with oral progesterone treatment and surgical treatment in idiopathic menorrhagia patients: Results of a cost-minimisation analysis, Value in HealthValue Health, 19 (7), A698, 2016	Conference abstract.
Cadth,, Clinical review report. Ulipristal Acetate (Fibristal - Actavis Specialty Pharmaceuticals Co.) indication: uterine fibroids (Structured abstract), Health Technology Assessment Database, 2014	Background - summary of pharmocoeconomic submission but not detail. Also, Ulipristal Acetate evaluated by CGUT.
Choi, Y. R., Lee, S., Choi, I., Suh, D., Cost-utility analysis of ulipristal acetate 5mg for treating patients with uterine fibroids in South Korea, Value in HealthValue Health, 19 (3), A177, 2016	Conference abstract.
Clark, T. J., Middleton, L. J., Cooper, N. A., Diwakar, L., Denny, E., Smith, P., Gennard, L., Stobert, L., Roberts, T. E., Cheed, V., Bingham, T., Jowett, S., Brettell, E., Connor, M., Jones, S. E., Daniels, J. P., A randomised controlled trial of outpatient versus inpatient polyp treatment (OPT) for abnormal uterine bleeding, Health Technology Assessment, 19, 2015	Polyps outside the scope.
Cooper, N. A. M., Barton, P. M., Breijer, M. C., Opmeer, B. C., Mol, B. W. J., Khan, K. S., Clark, T. J., Cost-effectiveness of diagnostic strategies for the management of heavy menstrual bleeding, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2013	Same analysis as included HTA study.

Study	Reason for Exclusion
Copher, R., Le Nestour, E., Zampaglione, E., Prezioso, A. N., Pocoski, J., Law, A. W., Heavy menstrual bleeding treatment patterns and associated health care utilization and costs, Journal of Clinical Outcomes Management, 19, 402-413, 2012	Burden of disease focus rather than a full economic evaluation.
de Bruijn, A. M., Ankum, W. M., Reekers, J. A., Birnie, E., van der Kooij, S. M., Volkers, N. A., Hehenkamp, W. J., Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 5, 5, 2016	Not an economic evaluation.
Garside, R, Stein, K, Wyatt, K, Round, A, Pitt, M, A cost-utility analysis of microwave and thermal balloon endometrial ablation techniques for the treatment of heavy menstrual bleeding (Structured abstract), BJOG. An International Journal of Obstetrics and Gynaecology, 111, 1103-1114, 2004	Pre 2007 Microwave technique not available in UK.
Hurskainen, R, Teperi, J, Rissanen, P, Aalto, A M, Grenman, S, Kivela, A, Kujansuu, E, Vuorma, S, Yliskoski, M, Paavonen, J, Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia (Structured abstract), Jama, 291, 1456-1463, 2004	Pre 2007, more recent economic evaluations.
Hurskainen, R, Teperi, J, Rissanen, P, Aato, A-M, Grenman, S, Kivela, A, Kujansuu, E, Vuorma, S, Yliskoski, M, Paavonen, J, Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial (Structured abstract), Lancet, 357, 273-277, 2001	Pre-2007, more recent economic evaluations of these technologies.
Hurskainen, R., Cost effectiveness of treatment modalities of heavy menstrual bleeding, International Journal of Gynecology and Obstetrics, 131, E52-E53, 2015	Conference abstract.
Kane, C. O., Chinnadurai, A., Beirne, J., Mc Ilwaine, P., Thompson, A., Johnston, K., Comparison of patient outcome in second generation ablation techniques. Microwave ablation and Mirena intrauterine system (IUS): Who wins and at what cost!, Gynecological SurgeryGynecol, 7, S88-S89, 2010	Conference abstract.
Kessel, S., Hucke, J., Goergen, C., Soeder, R., Roemer, T., Economic and clinical benefits of radiofrequency ablation versus hysterectomy in patients suffering from menorrhagia: a retrospective analysis with German health claims data, Expert Review of Medical DevicesExpert Rev Med Devices, 12, 365-72, 2015	Not full economic evaluation.
Kilonzo, M. M., Sambrook, A. M., Cook, J. A., Campbell, M. K., Cooper, K. G., A cost-utility analysis of microwave endometrial ablation versus thermal balloon endometrial ablation, Value in HealthValue Health, 13, 528-34, 2010	Microwave endometrial ablation not available in the UK.
Kroft, J., Ang, M., Liu, G., First-versus second-generation endometrial ablation for treatment of menorrhagia: A health technology assessment, Journal of Minimally Invasive Gynecology, 1), S137, 2013	Abstract only, review article with limited focus on health economics.

Study	Reason for Exclusion
Lee, K. K., Lee, V. W. Y., Tam, W. H., Cost-effectiveness assessment of levonorgestrel intrauterine system in patients with idiopathic menorrhagia in a Hong Kong public hospital, Value in health, 12 (3), A164-A165, 2009	Conference abstract.
Legit, C., Farooq, H., Seed, P., Kunde, K., Laparoscopic hysterectomy for the large uterus and associated costs, Gynecological Surgery, 8, S135, 2011	Cost comparison and route of hysterectomy not in scope.
Lete, I., Calaf, J., Crespo, C., Canals, I., Espinos, B., Cristobal, I., Cost-effectiveness analysis in the treatment of heavy menstrual bleeding in Spain, Value in HealthValue Health, 16 (7), A333, 2013	Conference abstract.
Lete, I., Cristobal, I., Canals, I., Crespo, C., Espinos, B., Calaf, J., Economic evaluation of oral treatments for heavy menstrual bleeding in Spain, Pharmacoeconomics - Spanish Research Articles, 12, 105-114, 2015	Full text in Spanish.
Louie, M., Spencer, J., Wheeler, S., Ellis, V., Toubia, T., Schiff, L. D., Siedhoff, M. T., Moulder, J. K., Levonorgestrel intrauterine device outperforms endometrial ablation by cost and utility metrics: A decision analysis, Journal of Minimally Invasive GynecologyJ Minim Invasive Gynecol, 23 (7 Supplement 1), S96, 2016	Conference abstract.
Miller, J. D., Costs of global endometrial ablation (GEA) for treatment of heavy menstrual bleeding (menorrhagia): Assimilation and comparison of results from published cost-effectiveness modeling studies, Value in HealthValue Health, 16 (3), A73, 2013	Review article.
Penketh, R. J. A., Griffiths, A. N., Bruen, E. M., Patwardhan, A., Lindsay, P., Hill, S., White, J., The Cardiff shine project. Outpatient operative hysteroscopy (resection of fibroids and polyps) using conventional monopolar resectoscopes with glycine under local anaesthetic: Excellent clinical success and patient satisfaction rates with major financial savings, Journal of Minimally Invasive Gynecology, Conference, 40th Global Congress of Minimally Invasive Gynecology, AAGL 2011. Hollywood, FL United States. Conference Start: 20111106. Conference End: 20111110. Conference Publication: (var.pagings). 18 (6 SUPPL. 1) (pp S81-S82), 2011	Cost analysis only.
Postlethwaite, D. A., Hung, Y. Y., Armstrong, M. A., Maloney, K., Trussell, J., Evaluation of cost savings of the LNG-IUD for treatment of dysfunctional uterine bleeding, and pelvic pain in an integrated health care setting, Journal of Women's HealthJ Womens Health (Larchmt), 22 (3), 17-18, 2013	Conference abstract of cost analysis - not a full economic evaluation.
Ratnavelu, N., Basu, S., Devlin, K., Elsapagh, K., McMurray, D., Allam, M., Laparoscopic subtotal hysterectomy: Implications and cost-effectiveness, Gynecological Surgery, 8, S137, 2011	Conference abstract.
Roberts, Te, Tsourapas, A, Middleton, Lj, Champaneria, R, Daniels, Jp, Cooper, Kg, Bhattacharya, S, Barton, Pm, Hysterectomy, endometrial ablation, and levonorgestrel releasing intrauterine system (Mirena) for treatment of heavy menstrual bleeding: cost effectiveness analysis (Structured abstract), BMJBmj, 342:d2202, 2011	Same analysis as included HTA study.

Study	Reason for Exclusion
Sanghera, S, Roberts, Te, Barton, P, Frew, E, Daniels, J, Middleton, L, Gennard, L, Kai, J, Gupta, Jk, Levonorgestrel-releasing intrauterine system vs. usual medical treatment for menorrhagia: an economic evaluation alongside a randomised controlled trial (Provisional abstract), PLoS ONE [Electronic Resource]PLoS ONE, 9, e91891, 2014	Same analysis as included HTA study.
Sanghera, S., Frew, E., Gupta, J. K., Kai, J., Roberts, T. E., Exploring the Use of Cost-Benefit Analysis to Compare Pharmaceutical Treatments for Menorrhagia, PharmacoeconomicsPharmacoeconomics, 33, 957-65, 2015	Different methodological approach to another included paper by same authors comparing same treatments.
Sanghera, S., Frew, E., Kai, J., Gupta, J., Elizabeth Roberts, T., An assessment of economic measures used in menorrhagia: a systematic review, Social Science & MedicineSoc Sci Med, 98, 149-53, 2013	Review article not an economic evaluation.
Sanghera, S., Roberts, T., Barton, P., Daniels, J., Middleton, L., Gennard, L., Kai, J., Gupta, J., Cost-effectiveness of levonorgestrel intrauterine system for menorrhagia, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 390-391, 2013	Conference abstract, analysis published in full in 2014 included paper.
Sculpher, M, A cost-utility analysis of abdominal hysterectomy versus transcervical endometrial resection for the surgical treatment of menorrhagia (Structured abstract), International Journal of Technology Assessment in Health Care, 14, 302-319, 1998	Pre 2007 and very dated.
Sculpher, M J, Bryan, S, Dwyer, N, Hutton, J, Stirrat, G M, An economic evaluation of transcervical endometrial resection versus abdominal hysterectomy for the treatment of menorrhagia (Structured abstract), British Journal of Obstetrics and Gynaecology, 100, 244-252, 1993	Too dated to be meaningful.
Sculpher, M J, Dwyer, N, Byford, S, Stirrat, G M, Randomised trial comparing hysterectomy and transcervical endometrial resection: effect on health related quality of life and costs two years after surgery (Structured abstract), British Journal of Obstetrics and Gynaecology, 103, 142-149, 1996	Very dated and doesn't appear to be full economic evaluation.
Taipale, K., Leminen, A., Rasanen, P., Heikkila, A., Tapper, A. M., Sintonen, H., Roine, R. P., Costs and health-related quality of life effects of hysterectomy in patients with benign uterine disorders, Acta Obstetricia et Gynecologica Scandinavica, 88, 1402-1410, 2009	Not a comparative analysis.
Tewary, S., Pattni, S., Saeed, M., First 50 cases of outpatient endometrial ablation at new cross hospital: Acceptability, tolerance and cost-saving when compared to inpatient treatment, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 42, 2014	Conference abstract, cost study and not full economic evaluation.
Volkers, N. A., Hehenkamp, W. J. K., Smit, P., Ankum, W. M., Reekers, J. A., Birnie, E., Economic Evaluation of Uterine Artery Embolization versus Hysterectomy in the Treatment of Symptomatic Uterine Fibroids: Results from the Randomized EMMY Trial, Journal of Vascular and Interventional Radiology, 19, 1007-1016, 2008	Cost analysis.

Study	Reason for Exclusion
Waters, H., Song, X., Pan, K., Subramanian, D., Sedgley, R., Raff, G. J., Laparoscopic supracervical hysterectomy versus laparoscopic-assisted vaginal hysterectomy: Post-surgical outcomes and costs, Value in Health, 14 (3), A89, 2011	Route of hysterectomy not included in scope.

Appendix J – NMA analysis protocol

Item	Details
Review question	What is the most clinically and cost-effective treatment for heavy menstrual bleeding (HMB) among pharmacological and surgical treatments?
Objective	The objective of these reviews is to identify effective pharmacological and surgical treatment classes and interventions to reduce heavy menstrual bleeding and improve quality of life for women with heavy menstrual bleeding.
Population	Women between menarche and menopause complaining of heavy menstrual bleeding with no significant pathology • Studies with more than 66% women with HMB, or where the proportion of women with HMB is not specified, will be included. If the analysis has been performed for the women with HMB separately then only this data will be extracted. Exclusions: • Women with fibroids 3 cm or more in diameter • Women with fibroids in the uterine cavity
Subgroup Analyses	Networks will be examined separately if the populations undergoing different types of treatments (e.g. pharmacological versus surgical) are considered to be substantially different: First-line treatments (pharmacological treatment will be considered to be first-line if not specified otherwise in the papers) Second-line treatments (surgery will be considered to be second-line if not specified otherwise in the papers) Other subgroup analyses Women with fibroids less than 3 cm in diameter located outside the uterine cavity Consider prior hormonal treatment as potential source of heterogeneity
Covariates	Covariates can sometimes be included to account for heterogeneity instead of running subgroup analyses, where data are available. These characteristics will also be assessed for similarity where studies deviate substantially from the results predicted by the model. • Baseline blood loss • Bias (e.g. blinding) • Age of participants • Body mass index

Interventions	All interventions in the following classes (in bold) will be considered, provided doses are within ranges specified by the committee (as below) or those within the BNF. Classes not reported below will still be included in the network if they provide information for the network.
	Pharmacological treatments
	• **NSAIDs**
	  ○ Ibuprofen
	  ○ Mefenamic acid
	  ○ Flurbiprofen
	• **Antifibrinolytics**
	  ○ Tranexamic acid
	• **Haemostatics**
	  ○ Ethamsylate
	• **Progestogens**
	  ○ Oral
	  - Medroxyprogesterone acetate

Item	Details
	- Norethisterone ○ Injectable - Depot medroxyprogesterone acetate ○ Implant • **Danazol** • **Combined hormonal contraceptives** ○ Estradiol valerate/dienogest ○ Noresthisterone acetate/ethinyl estradiol (EE) ○ others (EE/levonorgestrel EE/drospirenone etc.) • **Levonorgestrel-releasing intra-uterine device** (LNG-IUS) **Surgical treatments (check for heterogeneity between old/new studies due to improvements in surgical techniques)** • Hysterectomy • First generation (hysteroscopic-controlled endometrial resection) ○ Transcervical endometrial resection ○ Endometrial vaporization ○ Endometrial ablation - rollerball ○ Endometrial laser ablation • Second generation endometrial resection (non-hysteroscopic controlled endometrial resection) ○ Endometrial laser intrauterine thermo therapy ○ Cavaterm endometrial ablation ○ Novasure endometrial ablation (bipolar) ○ Endometrial cryoablation ○ Thermal balloon ablation (Thermachoice) ○ Hydrotherm endometrial ablation • Uterine artery embolization
Comparisons	• All interventions listed above • Combinations of those interventions • Placebo • No treatment
Outcomes	• Blood loss ○ Pictorial blood loss assessment chart (PBAC) ○ Alkaline-Haematin (AH) method • Quality of life ○ EQ-5D ○ SF-36 ○ SF-12 ○ RAND-36 (if possible) • Discontinuation (due to adverse events) • Discontinuation • Patient satisfaction/acceptability • The latest time point from each study will be used. • Maximum study duration will depend on whether relative effects change across different study follow-ups: • If change is found then we will include all study durations and model discontinuation as a rate ratio or HR, or split into long and short-term
Study design	Studies prior to the search in the original HMB guideline will be considered for inclusion in the NMA if they were included in the original guideline. All studies identified after this will be considered for inclusion in the NMA.

Item	Details
	Only RCTs will be considered for inclusion. Both periods of cross over RCTs will be considered if authors have used a suitable paired analysis and if they have tested for carryover effects or have used a suitable washout period. Exclusion criteria: studies of pharmacological treatments with a duration of less than 3 months (12 weeks), studies with less than two relevant treatments (non-relevant treatments include non UK licensed drugs).
Review strategy	Synthesis of data • Network meta-analysis will be conducted using Winbugs codes (Decision Support Unit, Bristol University) • We will use mean differences for reporting the results of continuous outcomes • We will use the ORs (95% cr.i.) for reporting the results of dichotomous outcomes • We will use rate ratios or HRs for reporting the results of rate outcomes. • We will impute SD (accounting for uncertainty in SD imputation) where it has not been reported • We will not use MIDs as outputs will feed directly into health economic model so MIDs will not be needed
Model Structure	• Treatments not included in the list of interventions will be included if they provide information to the network via a closed loop of treatment effects. • Class effect model to allow borrowing of evidence from other treatments if network is too sparse. The following investigations into which class effect model fits the data best will be performed. o Treatments of the same class grouped by route of administration (e.g. oral progestogen contraceptives would be an individual class) o Treatments of the same class grouped (e.g. progestogen contraceptives would be an individual class) • We will test for exchangeability of within-class treatments to assess if a class model is appropriate • We will consider mapping of treatment effects to a common scale using the method of Lu (2014) for correlated scales for which correlations are known o PBAC – AH correlation • We will consider using responder analysis as a means of standardising 'patient satisfaction' to a dichotomous measure where satisfaction is reported on a continuous scale. • Adjusted for covariate(s) (severity as primary) o For multivariate this requires assuming correlations are same in different covariate subgroups (e.g. more/less severe) • Use empirical priors (if available) where the ratio of studies to treatments is less than 3:1
Assumptions	• Standard NMA assumptions (refer to NMA methods chapter for more detail) o Similarity of included populations o Consistency o Transitivity • Means are normally distributed (central limit theorem) • If covariates are included we assume that there is no multiplicative effect of these with the different hormonal therapies (i.e. no interaction terms). This means that the effect of the covariate is the same irrespective of the treatment.
Sensitivity Analyses	• Treatment characteristics that have not been stratified/subgrouped (e.g. dose – high/low, if there is not enough data for subgroup analysis)

Item	Details
	• Using studies with mixed populations • Imputed SDs • Choice of prior distributions

AH: alkaline haematin; BNF: British National Formulary; cr.i.: credible interval; EE: ethinyl estradiol; EQ-5D: EuroQol five dimensions questionnaire; HMB: heavy menstrual bleeding; HR: hazard ratio; MID: minimally important difference; NMA: network meta-analysis; NSAIDs: nonsteroidal anti-inflammatory drugs; OR: odds ratio; PBAC: pictorial blood loss assessment chart; RCT: randomised controlled trial; SD: standard deviation; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey; RAND-36: 36-Item Short Form Health Survey

Appendix K – Network meta-analysis methods

The results of conventional pairwise meta-analyses of direct evidence alone do not help to fully inform which intervention is most effective in the treatment of HMB. The challenge of interpretation has arisen for two main reasons. In isolation, each pairwise comparison does not fully inform the choice between the different treatments (pharmacological, surgical and non-pharmacological) and having a series of discrete pairwise comparisons can be disjoint and difficult to interpret. In addition, direct comparisons of treatments of clinical interest are not fully available, for example, comparison between certain types of hormonal therapy. This makes choice difficult unless based on patient preference or price.

To overcome these issues, a hierarchical Bayesian network meta-analysis (NMA) was performed. Advantages of performing this type of analysis are as follows.

- It allows the synthesis of data from direct and indirect comparisons without breaking randomisation, to produce measures of treatment effect and ranking of different interventions. If treatment A has never been compared against treatment B head to head, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can use the relative effects of the two treatments versus the common comparator. Indirect estimates can be calculated whenever there is a path linking two treatments through a set of common comparators. All the randomised evidence is considered simultaneously within the same model
- For every intervention in a connected network, a relative effect estimate (with its 95% credible intervals, CrIs) can be estimated versus any other intervention. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all of the best available evidence, whilst appropriately accounting for uncertainty.
- Estimates from the NMA can be used to directly parameterise treatment effectiveness in cost-effectiveness modelling of multiple treatments.

Conventional fixed effect meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

NMA requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in an NMA, the assumption is that intervention A has the same effect across trials of A versus B, A versus C and so on.

The terms indirect treatment comparisons, mixed treatment comparisons, and NMA are used interchangeably. We use the term NMA as the network consists of both indirect treatment comparisons (some trials have a common comparator and some do not) and mixed

treatment comparisons (with at least one closed loop, combination of direct and indirect evidence).

Study selection and data collection

For full details see analysis protocol in Appendix M.

Outcome measures

The guideline committee identified HRQoL, adverse events, blood loss and patient satisfaction as critical outcomes for assessing the effectiveness of treatments. NMAs were performed on these outcomes where evidence was available.

Health-related quality of life (HRQoL)

HRQoL was reported on different scales, which complicated meta-analysis of evidence. The most commonly used scales were the EQ-5D, SF-36 and SF-12. To allow for NMA and to allow for subsequent use in the health economic analyses we mapped the SF-12 and SF-36 on to the EQ-5D probabilistically using a Bayesian model that accounted for the variation in the means from each subscale and the correlation between the subscales.

Mapping regression coefficients for the SF-36 were taken from Ara and Brazier (2008) and for the SF-12 were taken from Franks (2004). Means for the mapping model were drawn from multivariate normal distributions that accounted for correlations between subscales. These correlations were pooled estimates from 3 studies (Frempong-Ainguah & Hill 2014; Myles 2001; Zhou 2013). WinBUGS code for the mapping model is given in Appendix Q.

Seven included studies reported results on both the EQ-5D and the SF-36 or SF-12. By mapping the SF-36 and SF-12 to the EQ-5D for these studies and comparing the mapped results to the values for EQ-5D reported in the trial, these studies were used to confirm the accuracy of the mapping.

Results for HRQoL are presented as mean differences (MDs) on the EQ-5D.

Adverse events

As adverse events for hormonal treatments varied substantially depending on the treatment in question, the committee felt that the number of women discontinuing treatments due to adverse events was a more generalisable and useful outcome, as this also accounted for how severe women felt an adverse event to be (that is, it had to be sufficiently severe for them to discontinue treatment). Results for discontinuation due to adverse events are presented as ORs.

Blood loss

Blood loss was reported using two methods – the AH method and the PBAC (Higham 1990). Results in papers were frequently reported as medians and ranges / inter-quartile ranges, as blood loss was reported to have strong positive skew, following a log-normal distribution. Both blood loss measures were converted to the log scale using the method of Hoaglin (2013), meaning that they were approximately normally distributed.

For conversion of AH and PBAC measures to the log-scale, it was necessary for all study estimates to be reported as absolute means (rather than change from baseline). For studies which only reported change from baseline, results were converted to absolute means assuming a correlation between baseline and follow-up of 0.7.

In order to be able to use both AH and PBAC in the same NMA to maximise precision, and in order to generate results that were easily interpretable to the Committee, study means were pooled using MRs on the log-scale (Friedrich 2008).

MRs allow results to be expressed in a ratio form, similar to ORs and risk ratios, that are reasonably simple to interpret clinically. MRs are the ratio of the mean in the active group to the mean in the control group, and a MR of 2 would therefore be interpreted as participants in the active group have twice as much blood loss as in the control group.

Patient satisfaction

Patient satisfaction was reported in most studies as a dichotomous outcome (satisfied / not satisfied), though for a number of studies these two categories were created from a satisfaction scale (for example, a 5 point scale of satisfaction). As these satisfaction scales were not validated measurements, and the dichotomisation of them was not performed consistently, these NMAs were expected to have high heterogeneity. Results for patient satisfaction are presented as ORs.

Methodology

Data were available for a number of treatments and routes of administration. Due to the sparseness of the networks, it was necessary to group treatments within different classes and assume a common class effect (Table 55). The common class effects were assessed to identify if it was reasonable to assume similarity of treatment effects within classes. For NMAs where efficacy was consistently different between treatments within a class, the class was split and efficacy was estimated separately for the different treatments. Multi-level NMA models with treatments nested within classes were also examined, though this added complexity did not improve model fit for any of the analyses.

There are three key assumptions behind a NMA, similarity, transitivity and consistency.

Similarity across trials is the critical rationale for the consistency assumption to be valid as by ensuring the clinical characteristics of the trials are similar we ensure consistency in the data analysis.

More specifically, randomisation holds only within individual trials, not across the trials. Therefore, if the trials differ in terms of patient characteristics, measurement and/or definition of outcome, length of follow up across the direct comparisons, the similarity assumption is violated and this can bias the analysis. Potential sources of heterogeneity arising from trials of interventions for HMB, and attempts made to identify and account for heterogeneity are as follows.

- Different populations were considered to examine if this caused heterogeneity:
    - NMAs were stratified into studies including women who failed on first line therapy and those that did not.
    - NMAs were stratified into studies including women with small non-cavity uterine fibroids and those that did not..
- Different duration of treatment or study follow-up:
    - treatment effects were examined across different study follow-up; NMAs were stratified into short and long term study follow-up where substantial differences were found.
- Different dosages of pharmacological treatments (see Table 55)
    - these typically showed little variation and were within the dose ranges specified by the British National Formulary (BNF).

Transitivity is the assumption that an intervention A will have the same efficacy in a study comparing A versus B as it will in a study comparing A versus C. Another way of looking at

this, in terms of the study participants, is that we assume that it is equally likely that any patient in the network could have been given any of the treatments in the network, and would have responded to the treatments in the same way (depending on how efficacious the treatments are).

The final assumption is consistency/coherence of the network. It is important that for a network that contains closed loops of treatments (for example, with studies comparing A versus B, B versus C, and A versus C), the indirect comparisons are consistent with the direct comparisons. Discrepancies between direct and indirect estimates of effect may result from several possible causes. One possible cause is 'chance', and if this is the case then the NMA results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. However, a second possible cause could be differences between the trials included in terms of their clinical or methodological characteristics, which would therefore raise concerns about the validity of the network.

Table 55: Dose ranges of treatments in different classes of interventions, with abbreviations used in tables and figures within the network meta-analysis

Class	Treatment	Abbreviation
Placebo/no treatment	Placebo No treatment/Waiting list	-
Danazol	Danazol (200mg once a day)	Dan
Ethamsylate	Ethamsylate (500mg four times a day)	Etham
NSAIDs	Mefenamic acid (1g-1.5g per day in divided doses for up to 5 days) Naproxen (1g per day in divided doses for up to 5 days)	NSAID
Tranexamic acid	Tranexamic acid (2-4g per day in divided doses for up to 5 days)	TXA
Norethisterone acetate	Norethisterone acetate (5mg three times a day on days 5 to 26 of cycle)	NA
Medroxyprogesterone acetate	Medroxyprogesterone acetate (10mg once a day for 10 days from day 16 of cycle or 5mg twice a day for 21 days from day 5 of cycle)	MPA
Combined oral contraceptives	Oestradiol valerate + dienogest (Qlaira® manufacturers regimen) Ethinyl oestradiol + levonorgestrel (30 mcg + 150 mcg once a day for 21 days) Ethinyl oestradiol + norethindrone acetate (20mcg + 1mg once a day for 21 days)	COC
Combined contraceptive vaginal ring	Etonogestrel and ethinylestradiol (120 mcg and 1.5 mcg released every day)	Nuva
Levonorgestrel intrauterine device	Levonorgestrel intrauterine device (20 mcg released every day)	LNG-IUS
Usual medical treatment	Usual medical treatment (tranexamic acid, mefenamic acid, norethisterone, COC, progesterone-only pill)	Medical
Hysterectomy	Hysterectomy	Hyst

Class	Treatment	Abbreviation
Second generation endometrial ablation	Thermal balloon ablation Microwave endometrial ablation Endometrial laser intrauterine thermotherapy Cavaterm endometrial ablation Novasure endometrial ablation Hydrotherm endometrial ablation Multielectrode balloon ablation	Second gen TBA MEA ELIT Cava Nova HEA MBA
First generation endometrial ablation	Endometrial vaporisation Transcervical endometrial resection Endometrial laser ablation Rollerball endometrial ablation Transcervical endometrial resection + rollerball ablation Endometrial coagulation Hysteroscopic endometrial resection	firstgen

NMA: network meta-analysis
(a) Table only includes treatments included in the NMA

Imputation of missing standard errors

Missing standard errors (SE) for continuous outcomes were calculated from standard deviations (SDs) imputed using the median SD of study arms using the same treatment. This was only required for one study reporting blood loss (Endrikat 2009).

Appendix L – Summary and quality apprasial of studies included in the network meta-analysis

Table 56: Treatment arm-level details for included studies in the network meta-analysis

First Author	Year	Treatment			Number of women			Study follow-up (weeks)	Non-uterine fibroids less than 3 cm	Women who failed on firstline therapy	EQ5D short-term	EQ5D long-term	Discontinuation due to adverse events	Patient satisfaction	Blood loss	AH/ PBAC
		Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3									
Abbott	2003	Cavaterm endometrial ablation	Novasure endometrial ablation bipolar	N/A	18	37	N/A	52	Not reported	Not reported	1			1	1	PBAC
Aberdeen Group	1999	Hysterectomy	Endometrial ablation	N/A	73	78	N/A	208	Not reported	Not reported				1		N/A
Abu Hashim	2012	Norethisterone	Combined contraceptive vaginal ring	N/A	47	48	N/A	13	Not reported	Not reported				1	1	PBAC
Athanatos	2015	Microwave endometrial ablation	Novasure endometrial ablation bipolar	N/A	33	33	N/A	52	Not reported	All participants				1	1	PBAC
Barrington	2003	LNG-IUS	Thermal balloon ablation	N/A	25	25	N/A	26	Not reported	Not reported					1	PBAC
Bhattacharya	1997	Transcervical endometrial resection	Endometrial laser ablation	N/A	155	166	N/A	52	Not reported	Not reported				1		N/A
Bongers	2005	Thermal balloon ablation	Novasure endometrial ablation bipolar	N/A	85	40	N/A	52	Not reported	Not reported	1					N/A
Bongers	2004	Thermal balloon ablation	Novasure endometrial ablation bipolar	N/A	43	83	N/A	52	Not reported	Not reported				1		N/A
Bonnar & Sheppard	1996	Ethamsylate	Mefenamic acid	Tranexamic acid	27	23	26	13	Not reported	Not reported			1	1	1	AH

Brun	2006	Cavaterm endometrial ablation	Transcervical endometrial resection	N/A	28	19	N/A	52	Not reported	All participants				1	1	PBAC
Busfield	2006	LNG-IUS	Thermal balloon ablation	N/A	40	39	N/A	103	Yes (<3 cm)	Not reported				1	1	PBAC
Clark	2011	Thermal balloon ablation	Novasure endometrial ablation bipolar	N/A	39	42	N/A	26	Not reported	All participants	1			1		N/A
Cooper	1999	Microwave endometrial ablation	Transcervical endometrial resection	N/A	134	129	N/A	52	Mixed (<33%)	Not reported	1					N/A
Cooper	2002	Novasure endometrial ablation bipolar	Endometrial ablation-rollerball	N/A	154	82	N/A	52	Yes (<3 cm)	Not reported				1		N/A
Cooper	2004	Microwave endometrial ablation	Endometrial ablation-rollerball	N/A	196	97	N/A	52	Yes (<3 cm)	All participants				1	1	PBAC
Cooper	2005	Microwave endometrial ablation	Transcervical endometrial resection	N/A	116	120	N/A	260	Mixed (<33%)	Not reported				1		N/A
Corson	2000	Multielectrode balloon ablation (Vesta)	Transcervical endometrial resection plus rollerball	N/A	112	122	N/A	52	Not reported	All participants					1	PBAC
Corson	2001	Hydrotherm endometrial ablation	Endometrial ablation-rollerball	N/A	184	85	N/A	52	Not reported	All participants					1	PBAC
Crosignani	1997	LNG-IUS	Transcervical endometrial resection	N/A	34	35	N/A	52	Not reported	Not reported	1					N/A
Dunphy	1998	Danazol	Medroxyprogesterone acetate	N/A	10	10	N/A	13	Not reported	Not reported					1	PBAC
Endrikat	2009	Ethinyl oestradiol/norethindrone acetate	LNG-IUS	N/A	19	20	N/A	52	Not reported	Not reported			1		1	PBAC
Fraser	2011	Placebo	Estradiol valerate/dienogest	N/A	149	82	N/A	13	Not reported	Not reported			1			N/A

Ghazizadeh	2011	LNG-IUS	Transcervical endometrial resection	N/A	52	52	N/A	26	Not reported	Not reported					1	PBAC
Ghazizadeh	2014	LNG-IUS	Novasure endometrial ablation bipolar	Transcervical endometrial resection	48	30	32	26	Yes (% participants unknown)	All participants				1		N/A
Goldrath	2003	Hydrotherm endometrial ablation	Endometrial ablation-rollerball	N/A	135	68	N/A	156	Not reported	All participants				1		N/A
Goshtasebi	2013	Tranexamic acid	Medroxyprogesterone acetate	N/A	46	44	N/A	13	Not reported	Not reported			1		1	PBAC
Gupta	2013	LNG-IUS	Usual medical treatment	N/A	285	286	N/A	52	No	Not reported	1					
Hawe	2003	Cavaterm endometrial ablation	Endometrial laser ablation	N/A	37	34	N/A	26	Not reported	Not reported	1			1	1	PBAC
Hurskainen	2001	LNG-IUS	Hysterectomy	N/A	116	112	N/A	26	Mixed (33-66% of participants)	Not reported	1					N/A
Hurskainen	2004	LNG-IUS	Hysterectomy	N/A	117	115	N/A	260	Mixed (33-66% of participants)	Not reported		1				N/A
Irvine	1998	Norethisterone	LNG-IUS	N/A	22	22	N/A	13	Not reported	Not reported				1	1	AH
Istre & Trolle	2001	LNG-IUS	Transcervical endometrial resection	N/A	30	30	N/A	52	Not reported	Mixed (33-66% of participants)					1	PBAC
Kaunitz	2010	Medroxyprogesterone acetate	LNG-IUS	N/A	83	82	N/A	26	Not reported	Not reported			1		1	AH
Khajehei	2013	Placebo	Mefenamic acid	Naproxen	32	33	28	13	Not reported	Not reported					1	PBAC

Kiseli	2016	Tranexamic acid	Norethisterone	LNG-IUS	22	20	20	26	Not reported	Not reported				1	1	PBAC
Kittelsen & Istre	1998	LNG-IUS	Transcervical endometrial resection	N/A	24	29	N/A	52	Not reported	All participants					1	PBAC
Kriplani	2006	Tranexamic acid	Medroxyprogesterone acetate	N/A	49	45	N/A	13	No	Not reported			1	1		N/A
Loffer	2001	Thermal balloon ablation	Endometrial ablation-rollerball	N/A	114	100	N/A	156	Not reported	All participants				1		N/A
Abdel Malak & Shawki	2006	LNG-IUS	Transcervical endometrial resection	N/A	26	30	N/A	52	Yes (<3 cm)	Yes (>66%)					1	PBAC
OConnor	1997	Hysterectomy	Transcervical endometrial resection	N/A	46	104	N/A	52	No	Not reported				1		N/A
Pellicano	2002	Thermal balloon ablation	Transcervical endometrial resection	N/A	40	42	N/A	104	Not reported	All participants				1		N/A
Penninx	2010	Novasure endometrial ablation bipolar	Hydrotherm endometrial ablation	N/A	75	71	N/A	52	Not reported	Not reported				1		N/A
Penninx	2016	Thermal balloon ablation	Novasure endometrial ablation bipolar	N/A	52	52	N/A	52	No	Not reported				1		N/A
Perino	2004	Endometrial laser intrauterine thermotherapy	Hysteroscopic endometrial resection	N/A	55	56	N/A	156	Not reported	Not reported				1		N/A
Rauramo	2004	LNG-IUS	Transcervical endometrial resection	N/A	30	30	N/A	156	Not reported	Yes (>66%)					1	PBAC
Reid & Virtanen-Kari	2005	Mefenamic acid	LNG-IUS	N/A	26	25	N/A	56	Not reported	Not reported			1		1	PBAC
Sambrook	2009	Thermal balloon ablation	Microwave endometrial ablation	N/A	157	157	N/A	52	Not reported	Not reported	1				1	PBAC

Sambrook	2014	Thermal balloon ablation	Microwave endometrial ablation	N/A	157	157	N/A	260	Not reported	Not reported				1		N/A
Sculpher	1996	Hysterectomy	Transcervical endometrial resection	N/A	73	82	N/A	114	Not reported	'Not controlled by conservative means'				1		N/A
Sesti	2012	LNG-IUS	Hysterectomy	N/A	36	36	N/A	52	Not reported	All participants	1					N/A
Shaaban	2011	Ethinyl estradiol/levonorgestrel	LNG-IUS	N/A	56	56	N/A	52	No	Not reported					1	AH
Shaw	2007	LNG-IUS	Thermal balloon ablation	N/A	33	30	N/A	103	Not reported	All participants				1	1	PBAC
Silva-Filho	2013	LNG-IUS	Thermal balloon ablation	N/A	27	25	N/A	260	Not reported	All participants				1		N/A
Soysal	2002	LNG-IUS	Thermal balloon ablation	N/A	32	35	N/A	52	Not reported	Yes (% of participants unknown)				1	1	PBAC
van Zon-Rabelink	2004	Thermal balloon ablation	Endometrial ablation-rollerball	N/A	77	60	N/A	103	Not reported	Not reported				1	1	PBAC
Vercillini	1999	Endometrial vaporization	Transcervical endometrial resection	N/A	47	44	N/A	52	Yes (<3 cm)	Not reported				1	1	PBAC
Vihko	2003	Thermal balloon ablation	Cavaterm endometrial ablation	N/A	16	15	N/A	26	Not reported	Mixed (33-66% of participants)				1		N/A
Zupi	2003	Hysterectomy	Transcervical endometrial resection	N/A	89	92	N/A	52	No	Not reported	1					N/A

AH: alkaline haematin; LNG-IUS: levonorgestrel-releasing intrauterine system; N/A: not applicable; PBAC: pictorial blood loss assessment chart
Usual medical treatment: tranexamic acid, mefenamic acid, norethisterone, combined oral contraceptive, progesterone-only pill
Note: A '1' in each of the outcome columns indicates that data in this study could be included in the NMA for this outcome. The PBAC/AH column indicates whether a study reporting blood loss used the PBAC or AH for measuring blood loss.

Table 57: Risk of bias assessment for included studies in the network meta-analysis

	Sequence generation	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcomes	Selective reporting	Other bias
Abbott 2003	✓	✓	?	✓	✓	✓	✓
Aberdeen group 1999	?	?	X	X	✓	✓	✓
Abu Hashim 2012	✓	✓	?	✓	✓	✓	✓
Abdel Malak 2006	?	?	X	X	?	✓	?
Athanatos 2015	✓	✓	?	✓	✓	✓	✓
Barrington 2003	?	?	X	X	✓	✓	✓
Bhattacharya 1997	✓	✓	X	X	X	✓	?
Bongers 2004	✓	✓	✓	✓	✓	✓	?
Bongers 2005	✓	✓	✓	✓	✓	✓	✓
Bonnar & Sheppard 1996	?	?	?	?	✓	✓	✓
Brun 2006	✓	✓	X	X	X	✓	X
Busfield 2006	✓	✓	X	X	?	✓	✓
Clark 2011	✓	✓	?	X	X	✓	✓
Cooper 1999	✓	✓	?	X	✓	✓	✓
Cooper 2002	✓	?	X	X	?	✓	?

	Sequence generation	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcomes	Selective reporting	Other bias
Cooper 2004	✓	?	X	X	✓	✓	?
Cooper 2005	✓	✓	?	X	✓	✓	✓
Corson 2000	✓	✓	X	X	?	✓	?
Corson 2001	✓	?	X	X	?	✓	?
Crosignani 1997	✓	X	X	X	✓	✓	?
Dunphy 1998	?	?	?	?	X	✓	✓
Endrikat 2009	?	?	X	X	✓	✓	✓
Fraser 2011	✓	?	✓	✓	✓	✓	✓
Ghazizadeh 2014	?	?	X	X	✓	?	X
Ghazizadeh 2011	✓	✓	X	X	X	X	?
Goldrath 2003	✓	?	?	?	✓	✓	✓
Goshtasebi 2013	?	?	?	?	✓	✓	✓
Gupta 2013	✓	✓	X	X	✓	✓	?
Hawe 2003	✓	✓	✓	✓	✓	✓	✓
Hurskainen 2001	?	✓	X	X	✓	✓	✓
Hurskainen 2004	?	✓	X	X	✓	✓	✓
Irvine 1998	✓	✓	X	X	✓	✓	✓
Istre & Trolle 2001	✓	✓	X	X	X	✓	?
Kaunitz 2010	?	?	X	X	✓	✓	✓
Khajehei 2013	X	X	✓	✓	X	X	X
Kiseli 2016	?	?	?	X	X	✓	✓
Kittlesen & Istre 1998	✓	✓	X	X	X	✓	✓

	Sequence generation	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcomes	Selective reporting	Other bias
Kripliani 2006	?	?	?	?	X	✓	✓
Loffer 2001	?	?	X	X	?	✓	?
O'Connor 1997	✓	✓	X	X	X	✓	✓
Pellicano 2002	✓	?	X	X	?	✓	?
Penninx 2010	✓	✓	?	?	✓	?	✓
Penninx 2016	?	✓	?	✓	✓	✓	✓
Perino 2004	✓	?	X	X	✓	✓	✓
Rauramo 2004	✓	✓	X	X	✓	✓	✓
Reid & Virtanen-Kari 2005	✓	✓	X	X	✓	✓	✓
Sambrook 2009	✓	✓	?	?	✓	✓	✓
Sambrook 2014	✓	✓	?	?	✓	✓	✓
Sculpher 1996	?	✓	X	X	✓	?	✓
Sesti 2012	✓	✓	X	X	✓	✓	✓
Shabaan 2011	✓	✓	X	X	X	✓	✓
Shaw 2007	✓	✓	X	X	X	✓	✓
Silva-Filho 2013	✓	?	X	X	X	X	✓
Soysal 2002	✓	✓	X	X	✓	✓	✓
Van Zon-Rabelink 2004	?	?	X	X	✓	✓	?
Vercillini 1999	✓	✓	X	X	✓	✓	?

	Sequence generation	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcomes	Selective reporting	Other bias
Vihko 2003	?	?	?	X	✓	✓	✓
Zupi 2003	✓	?	X	X	✓	✓	✓

✓: low risk of bias; ?: unclear risk of bias; X: high risk of bias

Appendix M – Studies excluded from the network meta-analysis

Table 58: Table of studies excluded from the network meta-analysis for statistical reasons

First author	Year	Reason for exclusion
Bonduelle	1991	Treatments not connected to network
Cooper	1997	'Medical treatment' includes treatments not relevant for current practice and this comparison provides no indirect evidence
Duleba	2003	PBAC only reported as dichotomous
Heliovaara-Peippo	2013	Study duration too long for NMA inclusion
Herman	2013	Study duration too long for NMA inclusion
Higham & Shaw	1993	Treatments not connected to network
Jensen	2011	AH only reported as dichotomous
Kupperman	2004	Only reports summary scales of SF-36. Cannot be mapped to EQ-5D
Lukes	2010	Study reports mean with no SD/SE - PBAC scores cannot be converted to log-scale
McClure	1992	Sample size too small (N = 22)
Najam	2010	Details unclear - authors use terms 'average', 'median' and 'mean' interchangeably

AH: alkaline haematin; EQ-5D: EuroQol five dimensions questionnaire; NMA: network meta-analysis; PBAC: pictorial blood loss assessment chart; SD: standard deviation; SE: standard error; SF-36: 36-item short form survey

Appendix N – Supplementary results

Model fit characteristics

Table 59: Model fit characteristics for HRQoL measured on the EQ-5D for short-term follow-up

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	N/A	18.99	14.98	33.97
Random effects	0.02 (<0.01, 0.07)	19.23	16.66	35.89
Fixed effects allowing for incoherence	N/A	19.02	15.70	34.72

CrI: credible interval; DIC: deviance information criterion; EQ-5D: EuroQol five dimension questionnaire; HRQoL: health-related quality of life; N/A: not applicable; pD: effective number of parameters;
(a) Compared to 22 data points

Table 60: Model fit characteristics for HRQoL measured on the EQ-5D for long-term follow-up

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	N/A	15.3	10.97	26.27
Random effects	0.03 (<0.01, 0.22)	13.99	13.06	27.05

CrI: credible interval; DIC: deviance information criterion; EQ-5D: EuroQol five dimension questionnaire; HrQoL: health-related quality of life; N/A: not applicable; pD: effective number of parameters
(a) Compared to 14 data points

Table 61: Model fit characteristics for discontinuation of pharmacological treatment due to adverse events

Model	Between-study standard deviation (95% CrI)	Residual deviance[b]	pD	DIC
Fixed effects	N/A	14.22	12.60	68.22
Random effects	1.31 (0.05, 4.66)	14.77	13.26	69.43
Random effects with empirical prior[a]	0.19 (0.03, 1.00)	14.32	12.73	68.46
Fixed effects allowing for incoherence	N/A	13.88	12.73	68.01

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; pD: effective number of parameters
(a) Empirical prior from Turner et al (2012) – between-study variance followed a log-normal distribution with mean -3.23 and variance 3.53
(b) Compared to 16 data points

Table 62: Model fit characteristics for pharmacological treatments for blood loss

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD[b]	DIC[b]
Fixed effects	N/A	59.62	N/C	N/C
Random effects	0.19 (0.09, 0.44)	28.20	N/C	N/C
Random effects allowing for incoherence	0.13 (0.02, 0.81)	28.63	N/C	N/C

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; N/C: not calculable; pD: effective number of parameters
(a) Compared to 28 data points
(b) Not calculable using standard approach in WinBUGS for mean ratios

Table 63: Model fit characteristics for surgical treatments for blood loss in women with no identifiable fibroids

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD[b]	DIC[b]
Fixed effects	N/A	140.2	N/C	N/C
Random effects	0.56 (0.30, 1.26)	32.61	N/C	N/C
Random effects allowing for incoherence	0.47 (0.24, 1.14)	29.62	N/C	N/C

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; N/C: not calculable; pD: effective number of parameters
(a) Not calculable using standard approach in WinBUGS for mean ratios
(b) Compared to 30 data points

Table 64: Model fit characteristics for surgical treatments for blood loss in women with non-cavity fibroids less than 3 cm

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD[b]	DIC[b]
Fixed effects	N/A	7.19	N/C	N/C
Random effects	0.56 (0.01, 4.48)	7.877	N/C	N/C
Fixed effects allowing for incoherence	N/A	7.193	N/C	N/C

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; N/C: not calculable; pD: effective number of parameters
(a) Compared to 8 data points
(b) Not calculable using standard approach in WinBUGS for mean ratios

Table 65: Model fit characteristics for pharmacological treatments for patient satisfaction

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	N/A	11.34	11.09	64.42
Random effects	1.28 (0.05, 4.69)	11.95	11.72	65.65
Fixed effects allowing for incoherence	N/A	12.38	12.14	66.50

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; pD: effective number of parameters
(a) Compared to 12 data points

Table 66: Model fit characteristics for surgical treatments for patient satisfaction in women with no identifiable fibroids

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	N/A	55.73	29.807	235.527
Random effects	0.39 (0.02, 1.26)	51.19	35.092	236.271
Random effects allowing for incoherence	0.36 (0.02, 1.25)	49.77	37.437	240.44

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; pD: effective number of parameters
(a) Compared to 44 data points

Table 67: Model fit characteristics for surgical treatments for patient satisfaction in women with non-cavity fibroids less than 3 cm

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects	N/A	11.75	9.957	66.722
Random effects	0.68 (0.03, 3.62)	12.16	11.316	68.489

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	pD	DIC
Fixed effects allowing for incoherence	N/A	12.86	10.904	68.775

CrI: credible interval; DIC: deviance information criterion; N/A: not applicable; pD: effective number of parameters
(a) Compared to 8 data points

WinBUGS sample code

Mapping to the EQ-5D

```
model{                                  # *** PROGRAM STARTS
for(i in 1:N){

      # multivariate likelihood
      y[i,1:2] ~ dmnorm(mean.y[study[i],arm[i],1:2],omega[i,,])
      omega[i,1:2,1:2] <- inverse(cov.mat[i,,])# within-study
precision matrix

      #define elements of within-study covariance matrix
       cov.mat[i,1,1] <-  pow(sd[i,1],2)
       cov.mat[i,2,2] <-  pow(sd[i,2],2)
       cov.mat[i,1,2] <-  sd[i,1]*sd[i,2]*cor[1]
       cov.mat[i,2,1] <-  cov.mat[i,1,2]

      # mapping algorithm from SF-12 to EQ-5D (can allow for OLS
uncertainty)
      pcs[i] <- (mean.y[study[i],arm[i],1]-49.9)
      mcs[i] <- (mean.y[study[i],arm[i],2]-51.5)

      eq5d[i] <- inter + (pcs[i]*bpcs) + (mcs[i]*bmcs) +
(pow(pcs[i],2)*bpcs2) + (pow(mcs[i],2)*bmcs2) +
(pcs[i]*mcs[i]*binteract)

      # Priors
      mean.y[study[i],arm[i],1] ~ dnorm(49.9, 0.0001)
      mean.y[study[i],arm[i],2] ~ dnorm(51.5, 0.0001)

      }

      # Model coefficients (#SE)
      # Source: Model with SF-12 items only from Franks et al (2004)
            inter <- 0.8469
            bpcs <- 0.01261
            bmcs <- 0.00759
            bpcs2 <- -0.00009
            bmcs2 <- -0.00015
            binteract <- -0.00015

}                                       # *** PROGRAM ENDS
```

EQ-5D fixed effects NMA – normal likelihood, identity link

```
model{                                  # *** PROGRAM STARTS
for(i in 1:N){

      # multivariate likelihood
      y[i,1:2] ~ dmnorm(mean.y[study[i],arm[i],1:2],omega[i,,])
      omega[i,1:2,1:2] <- inverse(cov.mat[i,,])# within-study
precision matrix

      #define elements of within-study covariance matrix
       cov.mat[i,1,1] <-  pow(sd[i,1],2)
       cov.mat[i,2,2] <-  pow(sd[i,2],2)
       cov.mat[i,1,2] <-  sd[i,1]*sd[i,2]*cor[1]
       cov.mat[i,2,1] <-  cov.mat[i,1,2]

      # mapping algorithm from SF-12 to EQ-5D (can allow for OLS
uncertainty)
      pcs[i] <- (mean.y[study[i],arm[i],1]-49.9)
      mcs[i] <- (mean.y[study[i],arm[i],2]-51.5)

      eq5d[i] <- inter + (pcs[i]*bpcs) + (mcs[i]*bmcs) +
(pow(pcs[i],2)*bpcs2) + (pow(mcs[i],2)*bmcs2) +
(pcs[i]*mcs[i]*binteract)

      # Priors
      mean.y[study[i],arm[i],1] ~ dnorm(49.9, 0.0001)
      mean.y[study[i],arm[i],2] ~ dnorm(51.5, 0.0001)

      }

      # Model coefficients (#SE)
      # Source: Model with SF-12 items only from Franks et al (2004)
            inter <- 0.8469
            bpcs <- 0.01261
            bmcs <- 0.00759
            bpcs2 <- -0.00009
            bmcs2 <- -0.00015
            binteract <- -0.00015

}                                       # *** PROGRAM ENDS
```

Blood loss random effects NMA – normal likelihood, log link

```
model{

          # *** NMA PROGRAM STARTS
for(i in 1:ns) {        # LOOP THROUGH THREE-ARM STUDIES
           w[i,1] <- 0
           delta[i,1] <- 0
           mu[i] ~ dnorm(0,.0001)    # vague priors for all trial
baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
        var.nma[i,k] <- pow(se[i,k],2)   # calculate variances
        prec[i,k] <- 1/var.nma[i,k]      # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood

# Model the linear predictor ON THE LOG SCALE for mean ratios
        log(theta[i,k]) <- mu[i] + delta[i,k]   # model for linear
predictor

#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-
theta[i,k])*prec[i,k]
      }

#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])

      for (k in 2:na[i]) {
                  delta[i,k] ~ dnorm(md[i,k],taud[i,k])
                  md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
           taud[i,k] <- tau *2*(k-1)/k
                  w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
                  sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }

  }

totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)
tau <- pow(sd,-2)

# all pairwise mean ratios
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        MR[c,k]<- exp(d[k]-d[c])
      }
  }

# all treatments to be used for ranking
for(k in 1:nt){ dR[k] <- d[k] }

# ranking on relative scale
for (k in 1:ntR) {
```

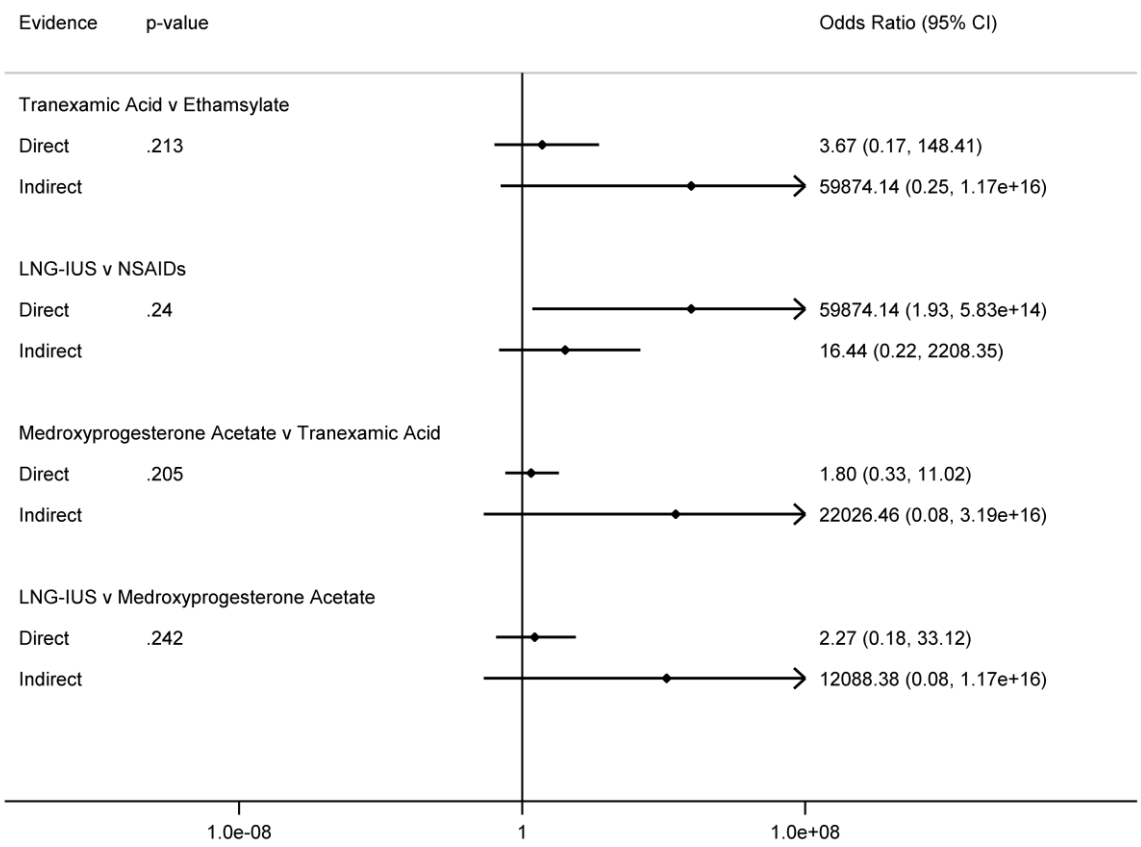
```
    rk[k]<- rank(dR[],k)              # events are "bad"
    best[k] <- equals(rk[k],1)        # rank=1 is best

#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
  }
}                                     # *** PROGRAM ENDS
```

Incoherence

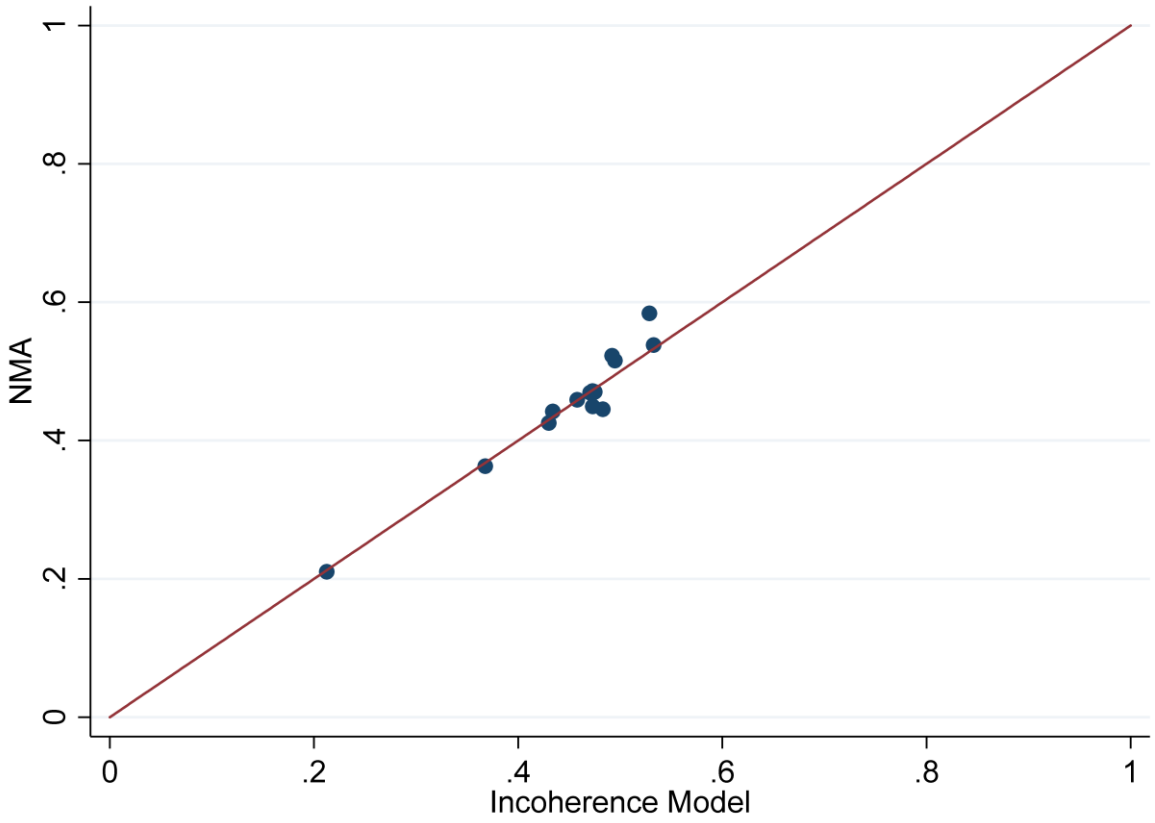
Discontinuation of treatment due to adverse events

Figure 40: Forest plot of node-splitting to estimate direct and indirect contributions to NMA for discontinuation due to adverse events



CI: confidence interval; LNG-IUS: levonorgestrel-releasing intrauterine system; NMA: network meta-analysis; NSAIDs: no-steroidal anti-inflammatory drugs

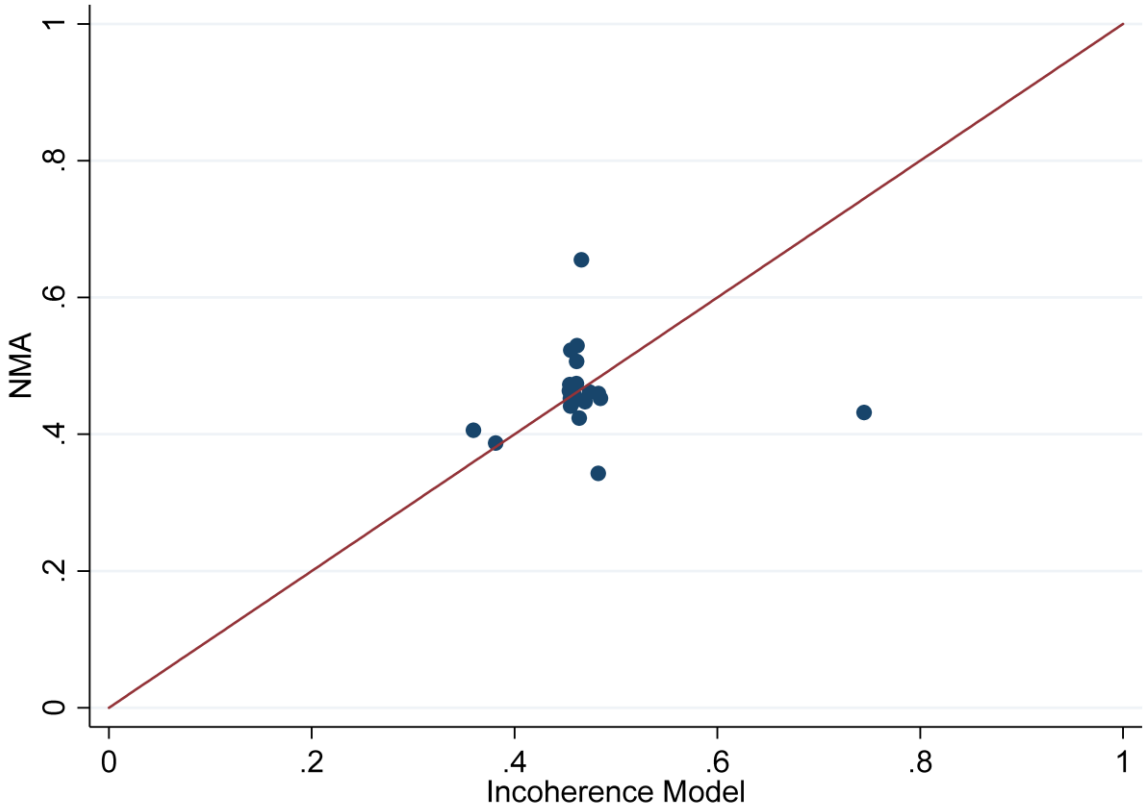
Figure 41: Residual deviances for direct comparisons from a pairwise (incoherence) model and NMA model for pharmacological treatments for blood loss



NMA: network meta-analysis
Note: Incoherence can be expected to be present where residual deviances are substantially different between NMA and incoherence (pairwise) models

Blood loss

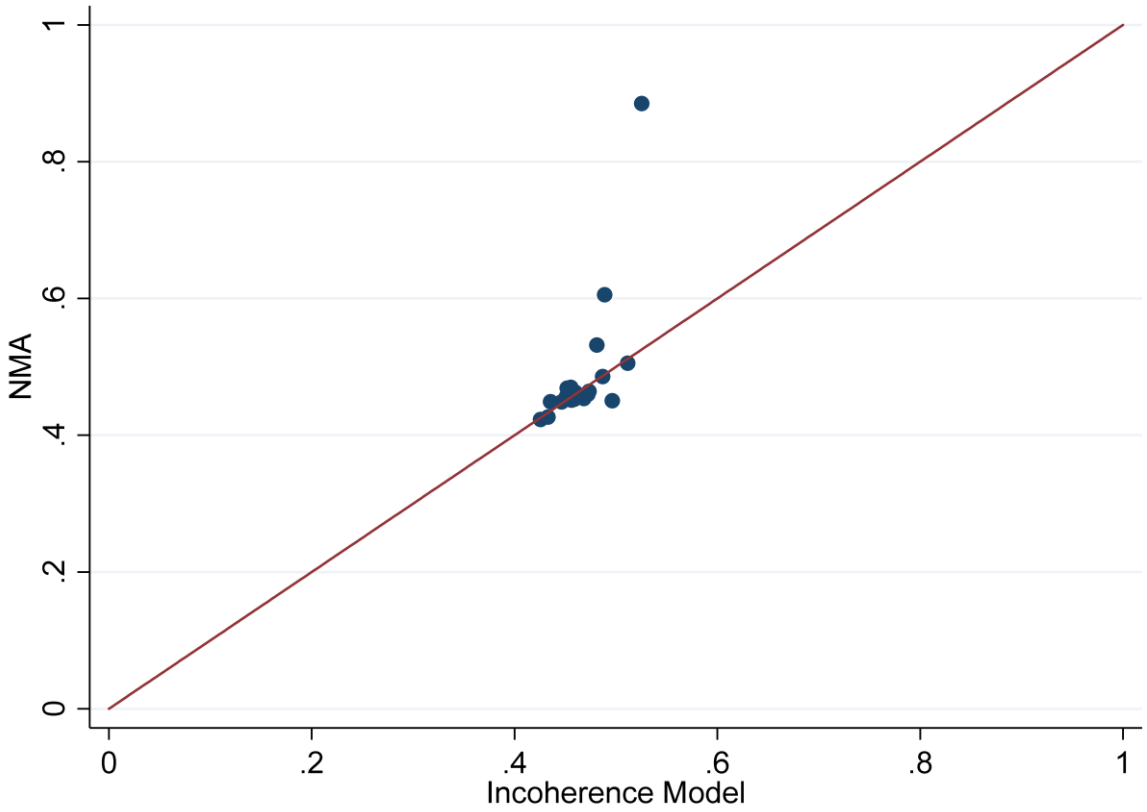
Figure 42: Residual deviances for direct comparisons from a pairwise (incoherence) model and NMA model for pharmacological treatments for blood loss



NMA: network meta-analysis

Note: Incoherence can be expected to be present where residual deviances are substantially different between NMA and incoherence (pairwise) models

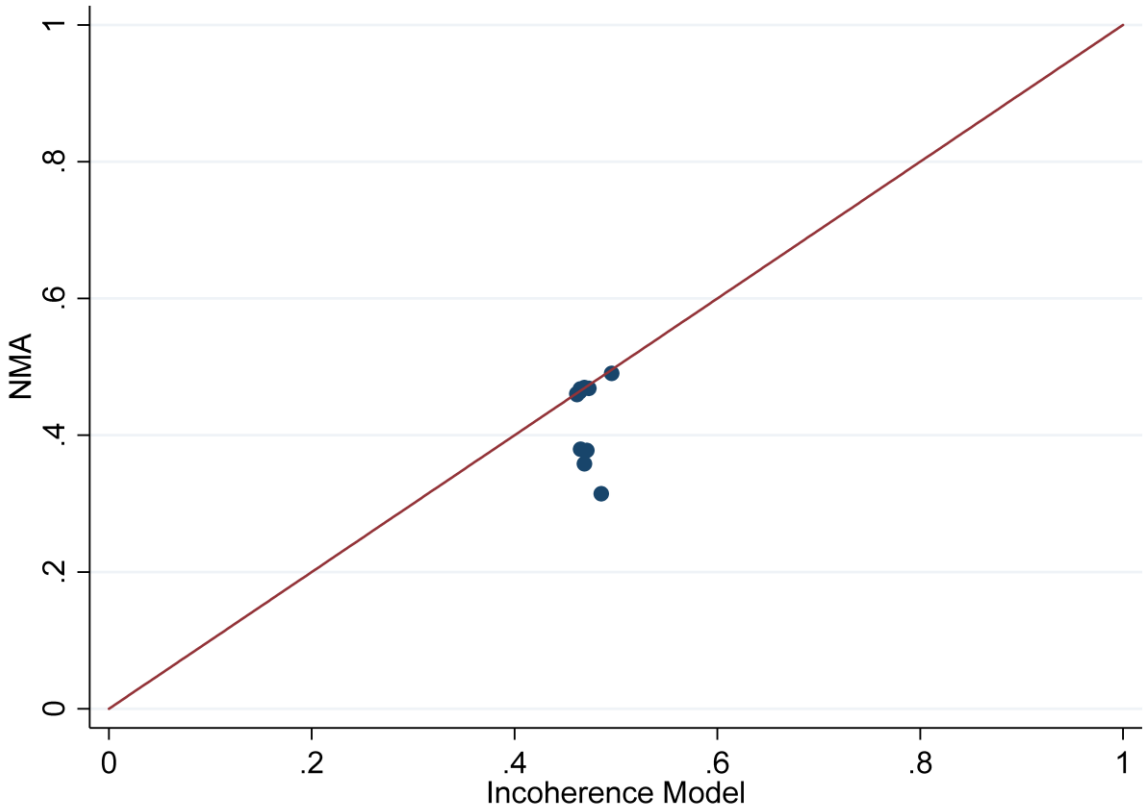
Figure 43: Residual deviances for direct comparisons from a pairwise (incoherence) model and NMA model for surgical treatments for blood loss in women with no identifiable fibroids



NMA: network meta-analysis
Note: Incoherence can be expected to be present where residual deviances are substantially different between NMA and incoherence (pairwise) models

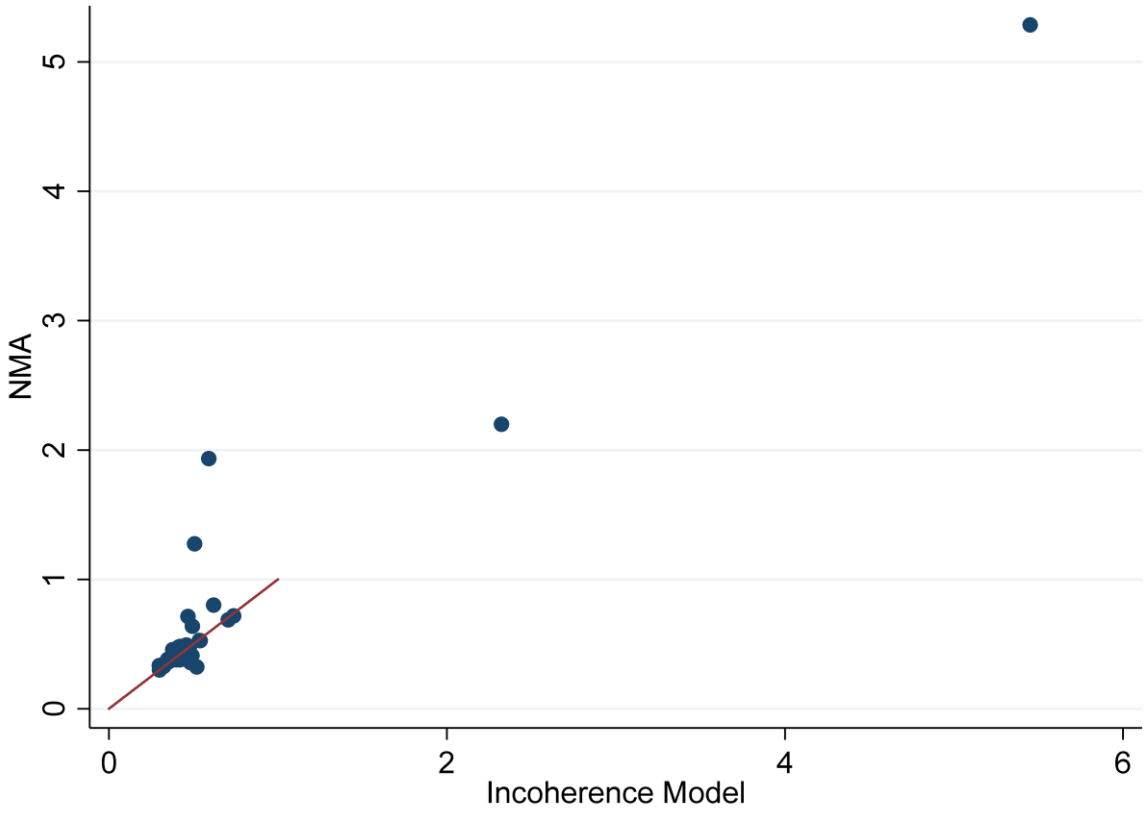
Patient satisfaction

Figure 44: Residual deviances for direct comparisons from a pairwise (incoherence) model and NMA model for pharmacological treatments for patient satisfaction



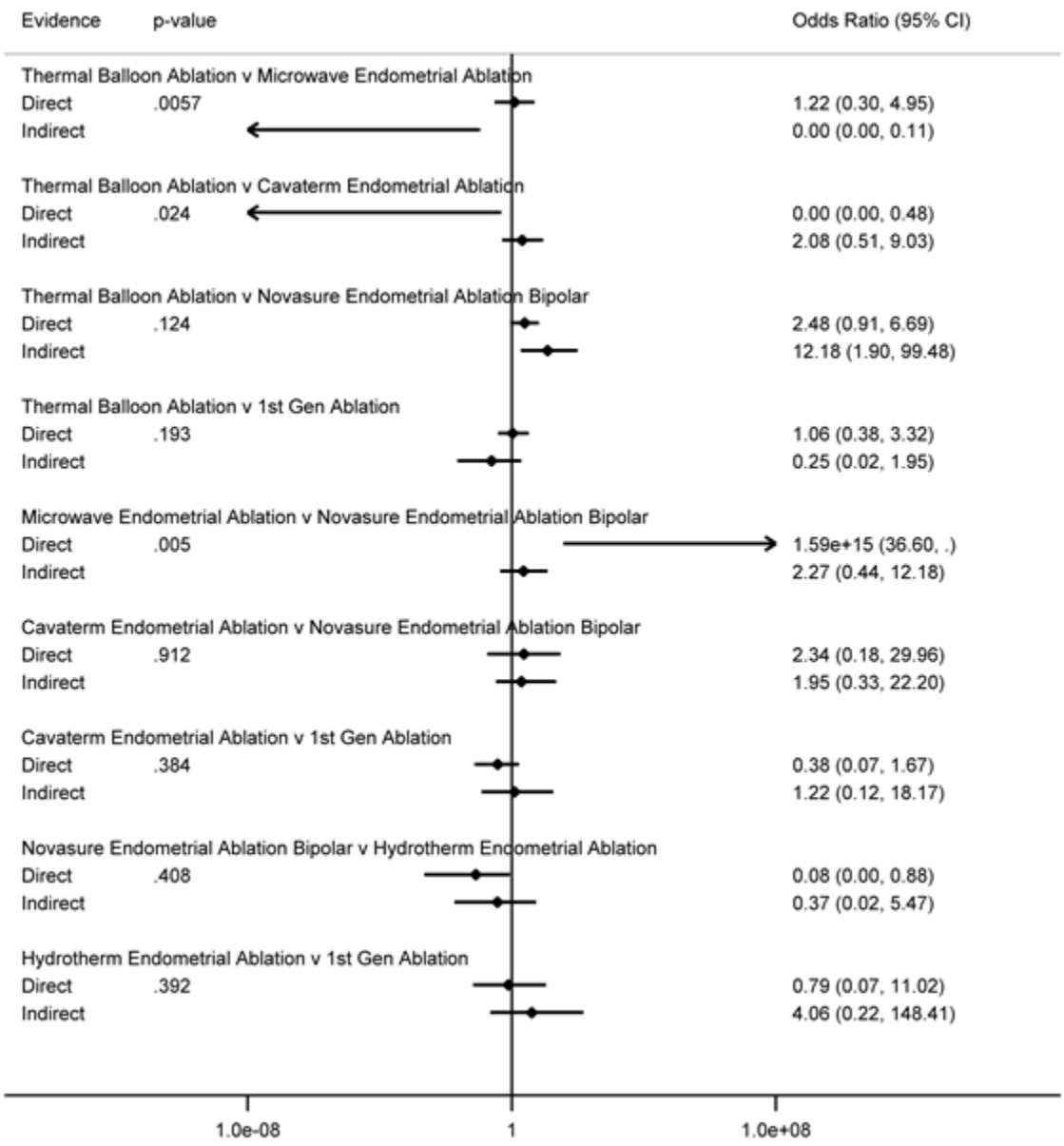
NMA: network meta-analysis
Note: Incoherence can be expected to be present where residual deviances are substantially different between NMA and incoherence (pairwise) models

Figure 45: Residual deviances for direct comparisons from a pairwise (incoherence) model and NMA model for surgical treatments for patient satisfaction in women with no identifiable fibroids



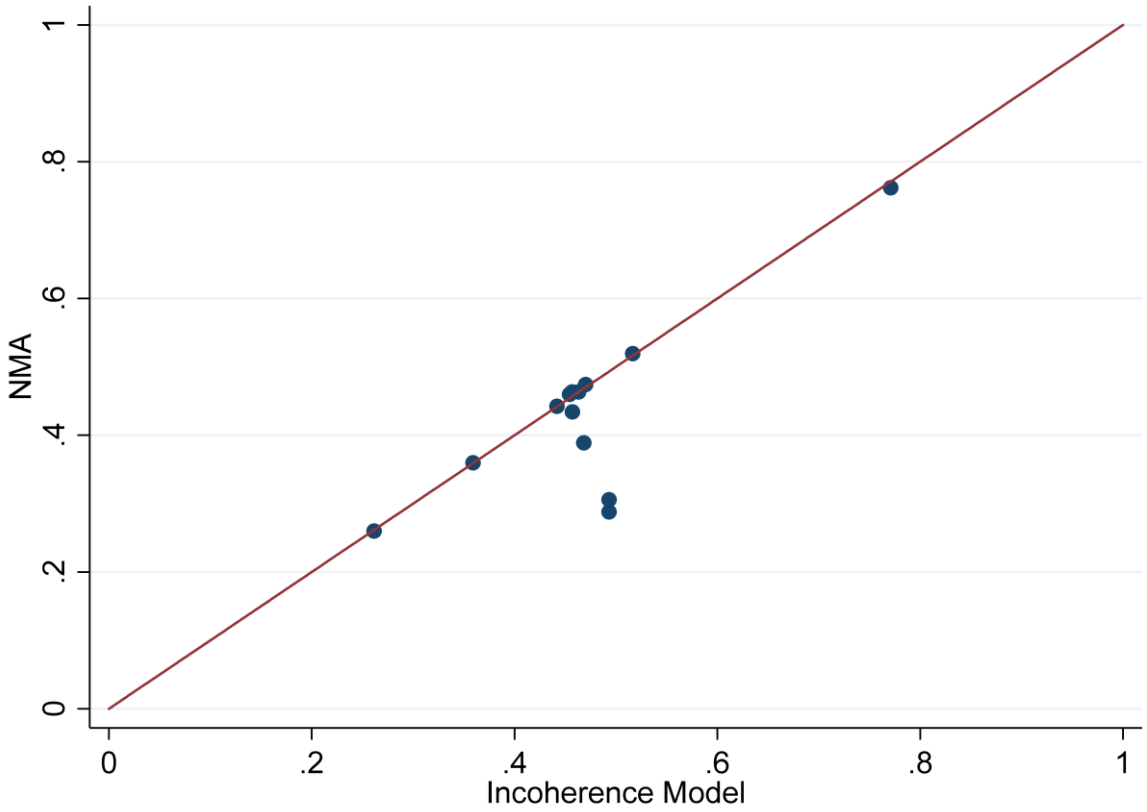
NMA: network meta-analysis
Note: Incoherence can be expected to be present where residual deviances are substantially different between NMA and incoherence (pairwise) models

Figure 46: Forest plot of node-splitting to estimate direct and indirect contributions to NMA for patient satisfaction in women with no identifiable fibroids



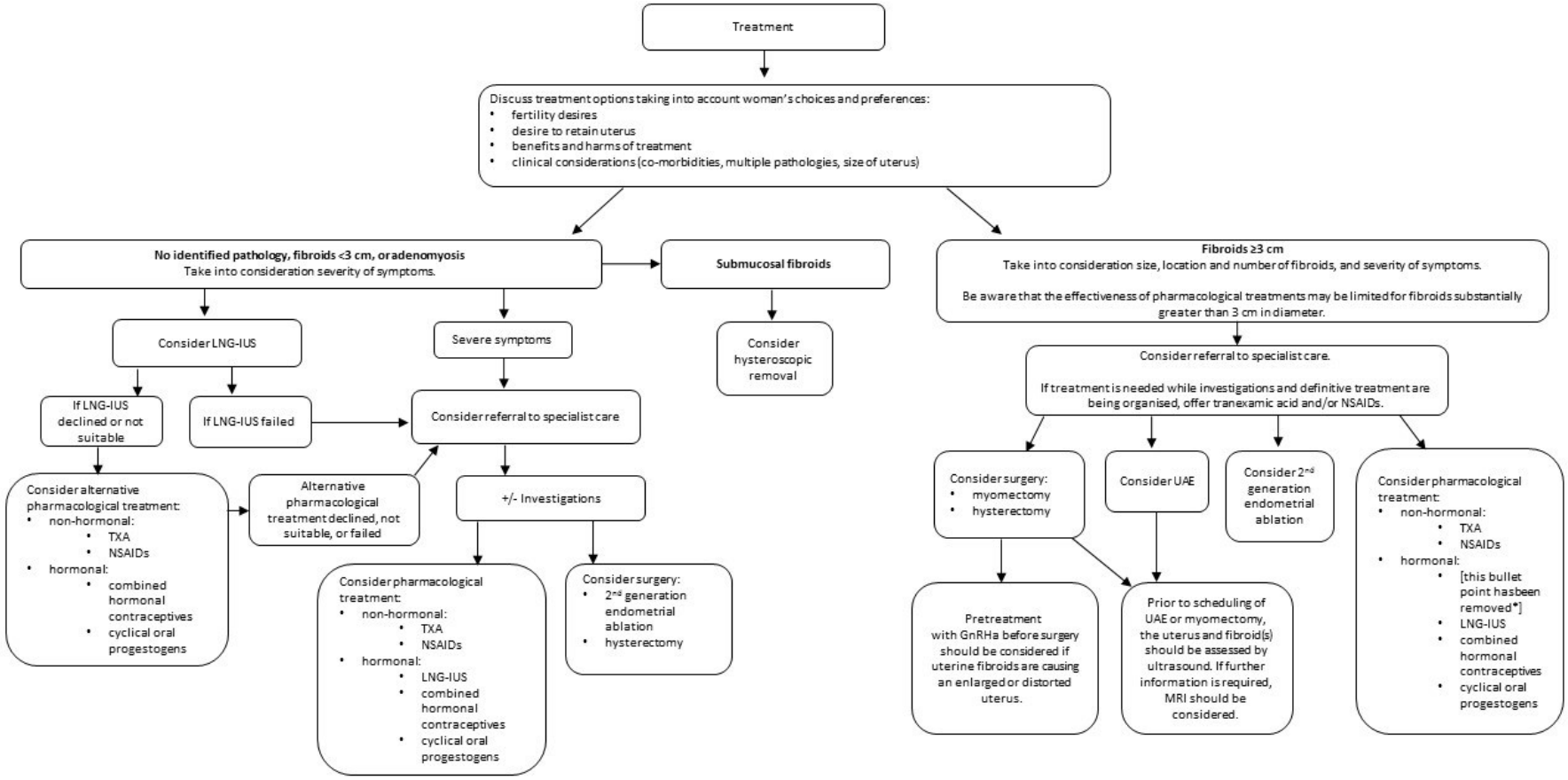
1st Gen Ablation: first generation endometrial ablation; CI: confidence interval; NMA: network meta-analysis

Figure 47: Residual deviances for direct comparisons from a pairwise (incoherence) model and NMA model for surgical treatments for patient satisfaction in women with non-cavity fibroids less than 3 cm



Note: Incoherence can be expected to be present where residual deviances are substantially different between NMA and incoherence (pairwise) models

Appendix O – Care pathway



GnRHa: gonadotrophin-releasing hormone analogue; LNG-IUS: levonorgestrel-releasing intrauterine system; NSAIDs: nonsteroidal anti-inflammatory drugs; TXA: tranexamic acid; UAE: uterine artery embolization

*See information on EMA review and safety measures for ulipristal acetate (Esmya)