NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline
CG44: Heavy menstrual bleeding: investigation and treatment

Publication date
January 2007

Previous review dates
July 2010

Surveillance report for GE
March 2015

Surveillance recommendation
GE is asked to consider the proposal to update the following area of guideline CG44: Heavy menstrual bleeding using the Standing Committee for Updates via the Clinical Guidelines Update Team:

- Medical management of women with uterine fibroids: 'What is the clinical and cost effectiveness of medical treatments for fibroids greater than 3cm in diameter.'

GE is asked to consider the proposal to update the following areas of guideline CG44: Heavy menstrual bleeding using the standard update process:

- Diagnosis of women with heavy menstrual bleeding
- Management of women with heavy menstrual bleeding, including:
    - Pharmacological managment
    - Surgical management, including hysterectomy and endometrial ablation and resection.
- The diagnosis and management of women with adenomyosis

GE are asked to note that this 'yes to update' proposal will not be consulted on.

Key findings

	Potential impact on guidance	
	Yes	**No**
Evidence identified from Evidence Update		✓
Evidence identified from literature search	✓	
Feedback from Guideline Development Group	✓	

Anti-discrimination and equalities considerations				✓
Feedback from Triage Panel meeting			✓	
No update	**CGUT update**	**Standard update**	Transfer to static list	Change review cycle
	✓	✓		

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Surveillance review of CG44: Heavy menstrual bleeding

Recommendation for Guidance Executive

Background information

Guideline issue date: 2007
3 year review: 2010 (no update)
5 year review: 2012 (review postponed)

NCC: Women's and Children's Health

Main conclusions from previous surveillance review

1. CG44 previously underwent a surveillance review in 2010 when the review recommendation was that the guideline should not be considered for an update.

2. Guidance Executive (GE) acknowledged that there was ongoing research relevant to the guideline at the 3 year surveillance review in 2010 which was considered likely to inform a future update of the guideline as well as an update of NICE TA78: fluid filled thermal balloon and microwave endometrial ablation for menstrual bleeding (recommendations from which are incorporated into CG44). Therefore, GE recommended that the next surveillance review be in 18 months time to enable the results of ongoing trials to be evaluated. The first ongoing trial published in 2011 and this was evaluated through the review of TA78. It was decided that this study would not impact on the TA and it was proposed that TA78 be added to the static guidance list. In light of this decision, it was agreed in 2012 that CG44 revert back to its three year cycle and the surveillance review scheduled for 2012 was postponed. The surveillance review was not carried out in 2013 due to reconfiguration of the surveillance process.

Current eight year surveillance review

3. A literature search for systematic reviews and randomised controlled trials (RCTs) was carried out between December 2011 and December 2014 and relevant abstracts were assessed. Clinical feedback on the guideline was obtained from 4 members of the GDG through a questionnaire. Three out of the 4 respondents indicated that new evidence had become available that meant an update of the guideline was needed.

4. New evidence that may impact on recommendations was identified relating to the following areas within the guideline:

Clinical area 1: Diagnosis		
Diagnostic strategies for heavy menstrual bleeding		
Evidence summary	**GDG/clinical perspective**	**Impact**
One UK based cost-effectiveness analysis[11] compared diagnostic strategies (transvaginal scanning, endometrial biopsy, saline infusion sonography and outpatient hysteroscopy) for HMB. The study identified outpatient hysteroscopy as the most cost effective option for women referred to secondary care for investigation of HMB. Endometrial biopsy in addition to hysteroscopy had a cost effectiveness ratio of £21000 per additional satisfied patient.	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	New evidence has possible impact on current recommendations. Evidence from one study suggested that hysteroscopy was the most cost-effective diagnostic strategy, although cost effectiveness was not assessed in terms of cost per quality adjusted life year, as is the usual NICE approach. However, current recommendations recommend ultrasound as the first-line diagnostic tool, with hysteroscopy only used when ultrasound results are inconclusive. Given that the guideline recommended ultrasound as first line, based on cost-effectiveness modelling, these recommendations are likely to require reviewing.
Clinical area 2: Treatment options for heavy menstrual bleeding		
Endometrial ablation vs hysterectomy vs levonorgestrel inter-uterine device		

Evidence summary	GDG/clinical perspective	Impact
One UK-based cost effectiveness analysis [12] developed an economic model based on cost and outcome data from an individual patient data meta-analysis to compare the cost effectiveness of the levonorgestrel interuterine system, first or second generation endometrial ablation, and hysterectomy. The authors concluded that hysterectomy was the favoured treatment because although it was most expensive, it also was associated with the highest quality of life and the incremental cost effectiveness ratios comparing interventions were all under £1500 per QALY. Three randomised controlled trials [13-15] compared the levonorgestrel interuterine system to hysterectomy for the treatment of HMB. One trial [13] (72 participants) reported that menstrual blood loss and quality of life improved in both groups but did not report comparative data. One trial [14] (236 participants) reported that there was no significant difference in premenstrual symptoms between groups, except for breast tenderness at 12 months, which was lower in the levonorgestrel interuterine system group. One trial [15] (236 participants) reported that there was no difference in health-related quality of life and psychosocial wellbeing between levonorgestrel interuterine system and hysterectomy groups. One systematic review [16] compared endometrial resection or ablation with hysterectomy for the treatment of HMB. Bleeding symptoms and satisfaction rates favoured hysterectomy, both at short and long term (4 years) follow up. Repeat surgery following treatment was more likely following endometrial ablation/resection than hysterectomy. However, adverse events, including sepsis, blood transfusion, pyrexia, haematoma and infection following discharge from hospital were more likely with hysterectomy than endometrial ablation/resection. One randomised controlled trial [17] (68 participants) compared thermal balloon ablation with laparoscopic hysterectomy for treatment of HMB. Post-operative pain was significantly lower in the endometrial ablation groups. Other outcomes were not reported comparatively between	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	New evidence may have an impact on guideline recommendations. The new evidence found that hysterectomy was the most cost-effective treatment for HMB. This may contradict current recommendations, which state that hysterectomy should not be offered as a first line treatment and that endometrial ablation is preferable to hysterectomy for women with a uterus no bigger than a 10-week pregnancy. These recommendations may also be inconsistent with new evidence from randomised controlled trials, which did not clearly favour either endometrial ablation/resection or hysterectomy (some outcomes favoured one treatment, and some the other). Currently the guidelines recommend that endometrial ablation/resection can be offered as a first line treatment, whereas hysterectomy should not be offered as a first line treatment, which may be inconsistent with this evidence. As such it may be appropriate to reassess these approaches as treatment options for HMB.

groups. One randomised controlled trial [18] (110 participants) compared the levonorgestrel interuterine system with endometrial ablation (NovaSure) and hysteroscopic endometrial resection for the treatment of HMB. Hemorrahage was significantly lower in the levonorgestrel interuterine system group than the other groups. The number of participants for which there was no interaction between HMB and normal activity was significantly lower in the levonorgestrel interuterine system group than the other groups. It was not clear, from an assessment of the abstract, exactly what 'interaction' refers to. Patient satisfaction was significantly greater in the endometrial ablation group than the other two groups. One randomised controlled trial[19] (58 participants) compared the levonorgesterel interuterine system with endometrial ablation (thermal balloon ablation) for the treatment of HMB. After 5 years, the thermal balloon ablation group had higher levels of hysterectomy than the levonorgestrel interuterine system group, due to significantly higher levels of treatment failure. Menstrual blood loss was significantly lower in the levonorgestrel interuterine system group, and patient acceptability, perceived improvement and overall satisfaction rates were significantly higher.		
Comparison of endometrial ablation methods		
Evidence summary	**GDG/clinical perspective**	**Impact**
One randomised controlled trial [41] (126 participants) compared bipolar endometrial ablation with thermal balloon ablation for the treatment of HMB. At 10 years follow up, they found amenorrhea rates, further treatment rates following initial ablation, and patient satisfaction were not significantly different between the two groups. One randomised controlled trial [42] (160 participants) compared bipolar ablation with hydrothermablation for the treatment of HMB. At 5 years follow up, amenorrhoea rates were significantly higher and re-	GDG members indicated that microwave endometrial ablation is no longer available, and that new ablation techniques have been developed that can be done under local anaesthetic and may be more clinically and cost effective.	New evidence is consistent with current recommendations. Currently, the following techniques are recommended: bipolar radiofrequency ablation, thermal balloon ablation, microwave ablation and free-fluid thermal endometrial ablation. Out of these techniques, the least expensive option is recommended. This is consistent with the new evidence which does not show any significant differences in outcome for the

intervention rates were significantly lower in the bipolar group than the hydrothermablation group. Satisfaction rates were also significantly higher in the bipolar group. One randomised controlled trial [43] (320 participants) compared microwave endometrial ablation and thermal balloon ablation for women eligible for ablation (criteria not specified). Satisfaction, amenorrhoea rates, and hysterectomy rates were not significantly different between the two groups. One randomised controlled trial [44] assessed the effectiveness of pre-operative curettage in women undergoing endometrial thermal ablation for HMB which had not responded to treatment for at least 6 months. Patient satisfaction was significantly higher in the curettage than no curettage group, and persistence of HMB was significantly lower. However, endometrial scarring was significantly higher in the curettage than the no curettage group.		listed techniques, and also finds that bipolar ablation gives better outcomes than hydrothermablation, which is not currently recommended. However, GDG members noted that microwave endometrial ablation is no longer available (this was also highlighted during consultation for the HMB quality standard), and so the recommendation may need to be refreshed to remove this option.
Uterine artery embolization for adenomysosis		
Evidence summary	**GDG/clinical perspective**	**Impact**
No relevant evidence identified relating to this area.	GDG members noted that uterine artery embolization for HMB due to adenomyosis alone or with fibroids is recommended by NICE IPG473 but is only recommended for the treatment of HMB associated with fibroids in CG44. This was also identified in the intelligence gathering exercise.	New information (from GDG and initial intelligence gathering) may have an impact on current recommendations. CG44 specifically excludes conditions for which HMB is not primary presenting symptom from the scope – it is not clear whether adenomyosis falls into this category. If adenomyosis is within the remit of CG44 then this guidance may need to be incorporated, as CG44 currently only recommends uterine artery embolization for the treatment of uterine fibroids.
Clinical area 3: Treatment of uterine fibroids		
Progesterone receptor modulators for the treatment of uterine fibroids		
Evidence summary	**GDG/clinical perspective**	**Impact**

One randomised controlled trial[1] compared the progesterone-receptor modulator ulipristal acetate with placebo for the treatment of uterine fibroids, and found that the majority of the ulipristal acetate group experience amenorrhea, whereas the placebo group continued to experience HMB at similar levels to the beginning of the study. The majority of the ulipristal acetate group who did not experience amenorrhoea had infrequent or irregular bleeding, although around 12% had frequent or prolonged bleeding during treatment. Two systematic reviews[2,3] and one randomised controlled trial [4] investigated the effectiveness of the progesterone receptor modulator mifepristone for the treatment of fibroids. One review[2] concluded that mifepristone reduces menstrual bleeding compared to placebo and increases specific quality of life outcomes, but that there was no evidence of an effect of mifepristone on fibroid volume or uterine volume. Adverse events (abnormal endometrial histology) and endometrial hyperplasia and cystic glandular dilatation were significantly higher with mifepristone than placebo. The other review [3] concluded that mifepristone reduced uterine and fibroid volume and alleviated symptoms including hypermenorrhea, menstrual blood loss, pelvic pain, pelvic pressure, anaemia and dysmenorrhea. The review found no difference in atypical endometrial hyperplasia between mifepristone and placebo groups. One randomised controlled trial[4] (124 participants) compared the progesterone-receptor antagonist mifepristone with placebo for the treatment of uterine fibroids. There was a significantly greater reduction in fibroid volume in the mifepristone group, as well as significantly lower pelvic pain, pelvic pressure, rectal pain, hypermenorrhea and HMB. Quality of life was also significantly higher in terms of 'symptoms' and 'activity' in the mifepristone group. Four randomised controlled trials compared different doses of mifepristone for the treatment of women with uterine fibroids. One trial[5] (143 participants) compared doses of 10 and 25 mg. There was a greater reduced in fibroid size with the higher dose. Other outcome measures (leg cramps, hot flushes, endometrial hyperplasia/atypia, amenorrhea and blood loss were similar between groups,though the	GDG members identified progesterone-receptor modulators as a potential new non-surgical alternative for the treatment of uterine fibroids.	New evidence may have impact on current recommendations. The included studies indicate that overall there is evidence for the effectiveness of progesterone receptor modulators (ulipristal acetate or mifepristone) compared with placebo for the treatment of HMB associated with uterine fibroids. Progesterone receptor modulators were also identified as a potential new treatment by members of the GDG. The guideline currently does not recommend any non-surgical alternatives for the treatment of HMB associated with uterine fibroids, and so this treatment may warrant consideration for inclusion in the guideline.

statistical significance of differences were not reported). Another trial[6] (220 participants) compared does of 2.5 and 5 mg. Fibroid volume decrease and amenorrhoea was greater in the higher dose group. There were no significant differences in side effects between groups and quality of life improvement was similar. Two trials[7,8] compared doses of 5 and 10 mg. One trial[7] (70 participants) found that there was no significant difference in endometrial changes, but endometrial thickness was greater in the 10 mg group. Hot flushes were more frequent and irregular bleeding was more common in the 10 mg group. Another trial [8] (176 participants) found that the reduction in fibroid and uterus volume was similar between the two groups.		
Pre-surgical medical treatment of uterine fibroids (progesterone receptor modulaters and gonadotrophin releasing hormone analogues)		
Evidence summary	**GDG/clinical perspective**	**Impact**
One randomised controlled trial [9] found that, for women with HMB awaiting surgery for fibroids, significantly more women had their uterine bleeding 'controlled' in the ulipristal acetate group than the placebo group with the majority of women in the treatment group experiencing amenorrhoea. Median change in fibroid volume during treatment was also significantly higher in the ulipristal acetate group. Adverse events (serious and non-serious) did not occur at significantly different rates between groups. One randomised controlled trial [10] compared ulipristal acetate with leuprolide acetate (a gonadotropin-releasing hormone analogue) for the treatment of symptomatic uterine fibroids in women awaiting myomectomy. There was no significant difference between groups for bleeding control, however hot flashes were significantly less common in the ulipristal acetate group.	GDG members identified progesterone-receptor modulators as a potential new pre-surgical alternative for the treatment of uterine fibroids	New evidence may impact guideline recommendations. Currently, the guideline recommends that gonadotrophin releasing hormone should be considered as a pre-treatment for uterine fibroids before myomectomy. The new evidence may favour ulipristal acetate over gonadotrophin releasing hormone analogue for some, but not all outcomes, and so ulipristal acetate may need to be considered as a possible treatment option.

Ongoing research

5. National Institute for Health Research Health Technology Assessment Programme funded randomised trial comparing myomectomy and uterine artery embolization for women with uterine fibroids who wish to retain or improve their fertility (FEMME trial). Relevant to review question 44.30. Completion due June 2016.
6. Medical research council funded randomised trial comparing ulipristal acetate (a progesterone-receptor modulator) and conventional management for the treatment of HMB (UCON trial). Relevant to review question 44.23. Completion date unknown.

Anti-discrimination and equalities considerations

7. None identified.

Implications for other NICE programmes

8. This guideline is related to interventional procedure guidance, which may need to be considered for incorporation into the guideline:
    a. IPG473: Uterine artery embolization for treating adenomyosis. Issued December 2013

9. This guideline relates to a Quality Standard on Heavy menstrual bleeding (QS47: Heavy menstrual bleeding. Published September 2013).

10. The following quality statement may be affected by the proposed areas for update.
    a. Statement 5. Women with heavy menstrual bleeding and a normal uterus or small uterine fibroids who choose surgical intervention have a documented discussion about endometrial ablation as a preferred treatment to hysterectomy.
    b. Statement 6. Women with heavy menstrual bleeding related to large uterine fibroids who choose surgical or radiological intervention have a documented discussion about uterine artery embolisation, myomectomy and hysterectomy.

Triage panel recommendations

11. The new evidence identified through the 8 year surveillance review of CG44 which may potentially impact on guideline recommendations was considered by the Triage Panel to determine the most appropriate route to commission an update.

12. Diagnostic strategies for heavy menstrual bleeding
    a. The Triage Panel agreed that the results of the health technology assessment on diagnostic strategies for heavy menstrual bleeding could have an important impact on the recommendations in CG44. The panel noted that altering recommendations on

diagnosis could affect whether women are treated in primary and secondary care, and could have large economic implications. The panel considered it important to update the health economic model associated with this aspect of the guideline, which they acknowledged would be a substantial piece of work that would be best carried out via the standard updates process.

b. **Decision:** NICE to update this area of the guideline using the standard updates process.

13. Treatment options for heavy menstrual bleeding
    a. The Triage Panel agreed that new evidence comparing hysterectomy with other treatment options for heavy menstrual bleeding is not consistent with current recommendations, and that this area of the guideline should be updated. The original guideline considered each treatment option separately, whereas the panel agreed that a better approach would be to consider all treatment options with each other. Therefore the panel suggested that all sections of the guideline on the management of heavy menstrual bleeding should be updated.
    b. **Decision:** NICE to update this area of the guideline using the standard updates process.

14. Comparison of endometrial ablation methods
    a. Feedback from the GDG received during the surveillance process indicated that microwave endometrial ablation was no longer available in the UK. The Triage Panel confirmed that this was the case and agreed that the endometrial ablation methods recommended in the guideline should be reviewed as part of the update on treatment options for heavy menstrual bleeding described in point 13. above.
    b. **Decision:** NICE to update this area of the guideline using the standard updates process.

15. Use of uterine artery embolization in adenomyosis
    c. The Triage Panel noted that adenomyosis is not included in the current guideline on heavy menstrual bleeding, but that heavy menstrual bleeding was a common symptom of this condition. Adenomyosis will not be included in the scope of the Endometriosis guideline which is currently in development. Therefore the panel agreed that the interventional procedure on uterine artery embolization should be considered for incorporation into the guideline, as part of the guidline update.
    d. **Decision:** NICE to update this area of the guideline using the standard updates process.

16. Progesterone receptor modulators for the treatment of uterine fibroids
    e. Progesterone receptor modulators are not included in the current guideline because they were not available when the guideline was developed. The panel agreed that medical treatments for fibroids should be considered for inclusion in the guideline. The panel decided that all treatments for fibroids should be considered as part of a standard guideline update of treatment options for heavy menstrual bleeding (see point 13. above). However, medical treatments for fibroids (including progesterone receptor

modulators) greater than 3 cm should be considered for immediate update using the Standing Committee for updates, as this is an important area where immediate guidance is needed. The panel agreed that the update should include both definitive treatment and pre-treatment before surgery.

f. **Decision:** NICE to update this area of the guideline using the Standing Committee for Updates via the Clinical Guidelines Update Team.

Conclusion

17. Through the review of CG44 new evidence which may potentially impact guideline recommendations was identified in the following areas:
    g. Diagnostic strategies for heavy menstrual bleeding
    h. Treatment options for heavy menstrual bleeding
    i. Endometrial ablation methods
    j. Uterine artery embolization for adenomyosis
    k. Treatment options for uterine fibroids

18. All of the above areas were considered by the Triage Panel, who agreed that all areas should be updated. The panel decided that the medical management of uterine fibroids should be updated by the Standing Committee for Updates via the Clinical Guidelines update Team. All other areas should be updated using the standard update process.

19. For all other areas of the guideline no evidence was identified which would impact on recommendations.

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Centre for Clinical Practice
March 2015

Appendix 1 Decision matrix

Surveillance and identification of triggers for updating CG44. The table below provides summaries of the evidence for key questions for which studies were identified.

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
44.01: How is HMB defined?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.02 What risk factors are associated with developing HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.03 How is clinical effectiveness of treatment for HMB defined?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.04 What impact does HMB have on quality of life of the women? (Why do women consult for HMB?)		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.05 What are the current trends in treatment for HMB in the UK?		
No relevant evidence identified	GDG members noted that there was an increase in the number of ‘one stop’ clinics for the diagnosis and treatment of HMB	New evidence is unlikely to have an impact on current recommendations, as current recommendations do not cover the organisation of services.

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
44.06 What are the indications for, effectiveness of, and cost-effectiveness of menstrual blood loss estimation in the diagnosis and management of HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.07 What is the effectiveness of patient education/information provision/counselling on patient satisfaction with treatment for HMB		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.08 How much should patient choice influence management?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.09 Do lifestyle indications/interventions affect HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.10 What questions need to be asked in routine history taking for HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.11 Physical examination on women with HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
44.12 What are the indications for, effectiveness of, and cost-effectiveness of imaging for excluding other conditions?		
No relevant evidence identified relating only to this question, but see bottom row of table for a study comparing diagnostic testing strategies for HMB (including both imaging and tests)	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.13 What are the indications for, effectiveness of, and cost-effectiveness of tests for excluding other conditions?		
No relevant evidence identified relating only to this question, but see bottom row of table for a study comparing diagnostic testing strategies for HMB (including both imaging and tests)	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.14 What are the indications for, effectiveness of, and cost-effectiveness of a full blood count to test for anaemia?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.15 What are the indications for, effectiveness of, and cost-effectiveness of using antifibrinolytics for treating HMB?		
One systematic review [20] compared tranexamic acid with placebo in women with idiopathic heavy menstrual bleeding, and found evidence from 10 included studies that tranexamic acid significantly reduced menstrual blood loss. One study [21] reported a pooled analysis of two previous trials comparing tranexamic acid and placebo for women with HMB with and without fibroids. The results of the pooled analysis showed a significant reduction in menstrual blood loss which was greater in women with fibroids than without fibroids. There was no significant difference in adverse events between groups.	Clinical feedback indicated that tranexamic acid is now available over the counter [confirmed on MHRA website].	New evidence is consistent with current recommendations, as tranexamic acid is currently recommended as a treatment option. This is consistent with the evidence identified, which suggests that tranexamic acid is an effective treatment for HMB compared with placebo.
44.16 What are the indications for, effectiveness of, and cost-effectiveness of using NSAIDs for treating HMB?		
One randomised controlled trial [22] (120 participants) compared mefenamic acid, naproxen (2 non-steroidal anti-inflammatories, NSAIDs) with placebo for the treatment of women with heavy menstrual bleeding. The reduction in	No clinical feedback was provided through the GDG questionnaire that was related to	New evidence is consistent with current recommendations, as NSAIDs are currently recommended as a treatment

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
menstrual blood loss was significantly greater for naproxen than mefenamic acid, and significantly greater with both treatments than placebo.	this section of the guideline.	option. This is consistent with the evidence identified, which suggests that NSAIDS are an effective treatment for HMB compared with placebo.
44.17 What are the indications for, effectiveness of, and cost-effectiveness of using etamsylate for treating HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.18 What are the indications for, effectiveness of, and cost-effectiveness of using the combined oral contraceptive pill for treating HMB?		
Two randomised controlled trials [23,24] and one study which presented a pooled analysis of two trials [25] compared an estradiol valterate/dienogest combined oral contraceptive with placebo for the treatment of heavy menstrual bleeding. The combined analysis reported that estradiol valterate/dienogest was associated with significantly less menstrual blood loss after treatment, and a significantly greater number of treatment responders (menstrual blood loss reduction > 50%) than placebo. Both randomised controlled trials [23,24] reported greater work productivity and a positive impact on activities of daily living with estradiol valterate/dienogest than placebo.	GDG feedback identified a new combined oral contraceptive (estradiol valerate/dienogest) with HMB as a licenced indication.	New evidence is consistent with current recommendations, as combined oral contraceptives are currently recommended as a treatment option, and the type of combined contraceptive is not specified in the recommendations. The evidence identified suggests that estradiol valerate/dienogest is effective for the treatment of HMB compared with placebo, but there is no evidence that it is better than other combined oral contraceptives, so referring to combined oral contraceptives as a group in the recommendations is still justified.
44.19 What are the indications for, effectiveness of, and cost-effectiveness of using oral progestogens for treating HMB?		
One randomised controlled trial [26] (71 participants) compared long-acting progestogens (route of administration not described) with no further treatment for women with HMB who had undergone hysteroscopic transcervical endometrial resection. Progestogen treatment was associated with reduction in the number of bleeding days, increased cycle length,	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	New evidence is consistent with current recommendations, as oral progestogens are currently recommended as a treatment option. This is consistent with the evidence identified, which suggests that

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
reduced dysmenorrhea, reduced premenstrual symptom score and a reduction in the need for repeat surgery.		oral progestogens are an effective treatment for HMB compared with no treatment.
44.20 What are the indications for, effectiveness of, and cost-effectiveness of using injected/depot progestogens for treating HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.21 What are the indications for, effectiveness of, and cost-effectiveness of using intrauterine levonorgestrel-releasing systems for treating HMB?		
One systematic review [27] investigated the effectiveness of the levonorgestrel interuterine system for the treatment of symptomatic uterine fibroids. The comparator was not specified. The review concluded that the levonorgestrel interuterine system was associated with decreased uterine volume, endometrial thickness, and uterine blood flow, increased blood haemoglobin, ferritin and haematocrit, but no decrease in fibroid volume. **Levonorgestrel-releasing interuterine system vs standard medical management** One randomised controlled trial [28] (571 participants) and one UK based economic analysis [29] alongside the same trial compared the levonorgestrel interuterine system with usual medical care for HMB (the ECLIPSE trial, identified as ongoing at the previous surveillance review). The randomised controlled trial [28] found that improvements in the menorrhagia multi-attribute scale (a patient-reported measure of menorrhagia severity) was greater in the levonorgestrel interuterine system group and the number of women still using the same treatment after 2 years was also greater. However, there was no significant difference in rates of surgical intervention, sexual activity score, or adverse events between groups. The economic analysis [29] found that the levongestrel interuterine system was the more cost effective, with an incremental cost effectiveness ratio of £1600 per QALY. One systematic review [30] compared the levonorgestrel interuterine system	GDG members noted that 'Mirena' is about to come off patent and new, cheaper levonorgestrel-releasing interuterine devices may mean that this treatment is more cost effective. Note however the drugs search for this surveillance review found that there was no patent associated with Mirena in the UK.	New evidence is consistent with current recommendations. Overall the identified evidence suggests that the levonorgestrel interuterine system is effective compared with standard medical management for the treatment of HMB and that levonorgestrel interuterine devices may be less costly in the future. Levongestrel-releasing interuterine systems are currently recommended as a first line treatment for HMB, which is consistent with this evidence. There was evidence showing no-significant difference between different levonorgstrel interuterine systems – current recommendations do not distinguish between interuterine systems, which is consistent with this evidence.

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
with standard medical management for the treatment of HMB. The levonorgestrel interuterine system was associated with greater menstrual blood loss, greater satisfaction, lower discontinuation, and fewer treatment failures. There was no significant difference in serious adverse events between treatments. **Comparison of levonorgestrel-releasing interuterine devices** One randomised controlled trial [31] (280 participants) compared a new levonorgestrel-release interuterine device 'Levosert' with the device 'Mirena' for the treatment of HMB. There was no significant difference in any of the outcomes that were measured, including, bleeding patterns, insertion ease, explusion rates. There were no perforations for either device.		
44.22 What are the indications for, effectiveness of, and cost-effectiveness of using HRT for treating HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.23 Medical management of HMB using other pharmaceutical interventions?		
Progesterone receptor modulators for the treatment of uterine fibroids One randomised controlled trial[1] compared the progesterone-receptor modulator ulipristal acetate with placebo for the treatment of uterine fibroids, and found that the majority of the ulipristal acetate group experience amenorrhea, whereas the placebo group continued to experience HMB at similar levels to the beginning of the study. The majority of the ulipristal acetate group who did not experience amenorrhoea had infrequent or irregular bleeding, although around 12% had frequent or prolonged bleeding during treatment. Two systematic reviews[2,3] and one randomised controlled trial [4] investigated the effectiveness of the progesterone receptor modulator mifepristone for the treatment of fibroids. One review[2] concluded that mifepristone reduces	GDG members identified progesterone-receptor modulators as a potential new non-surgical alternative for the treatment of uterine fibroids (both as a stand-alone treatment and a pre-treatment before myomectomy).	**Progesterone receptor modulators for the treatment of uterine fibroids** New evidence may have impact on current recommendations. The included studies indicate that overall there is evidence for the effectiveness of progesterone receptor modulators (ulipristal acetate or mifepristone) compared with placebo for the treatment of HMB associated with uterine fibroids. Progesterone receptor modulators were also identified as a potential new treatment by members of the GDG. The guideline currently does not

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
menstrual bleeding compared to placebo and increases specific quality of life outcomes, but that there was no evidence of an effect of mifepristone on fibroid volume or uterine volume. Adverse events (abnormal endometrial histology) and endometrial hyperplasia and cystic glandular dilatation were significantly higher with mifepristone than placebo. The other review [3] concluded that mifepristone reduced uterine and fibroid volume and alleviated symptoms including hypermenorrhea, menstrual blood loss, pelvic pain, pelvic pressure, anaemia and dysmenorrhea. The review found no difference in atypical endometrial hyperplasia between mifepristone and placebo groups. One randomised controlled trial[4](124 participants) compared the progesterone-receptor antagonist mifepristone with placebo for the treatment of uterine fibroids. There was a significantly greater reduction in fibroid volume in the mifepristone group, as well as significantly lower pelvic pain, pelvic pressure, rectal pain, hypermenorrhea and HMB. Quality of life was also significantly higher in terms of 'symptoms' and 'activity' in the mifepristone group. Four randomised controlled trials compared different doses of mifepristone for the treatment of women with uterine fibroids. One trial[5] (143 participants) compared doses of 10 and 25 mg. There was a greater reduced in fibroid size with the higher dose. Other outcome measures (leg cramps, hot flushes, endometrial hyperplasia/atypia, amenorrhea and blood loss were similar between groups (though the statistical significance of differences were not reported). Another trial[6] (220 participants) compared does of 2.5 and 5 mg. Fibroid volume decrease and amenorrhoea was greater in the higher dose group. There were no significant differences in side effects between groups and quality of life improvement was similar. Two trials[7,8] compared doses of 5 and 10 mg. One trial[7] (70 participants) found that there was no significant difference in endometrial changes, but endometrial thickness was greater in the 10 mg group. Hot flushes were more frequent and irregular bleeding was more common in the 10 mg group. Another trial [8]		recommend any non-surgical alternatives for the treatment of HMB associated with uterine fibroids, and so this treatment may warrant consideration for inclusion in the guideline. **Pre-surgical medical treatment of uterine fibroids (progesterone receptor modulators and gonadotrophin releasing hormone analogues)** New evidence may impact guideline recommendations. Currently, the guideline recommends that gonadotrophin releasing hormone should be considered as a pre-treatment for uterine fibroids before myomectomy. The new evidence may favour ulipristal acetate over gonadotrophin releasing hormone analogue for some, but not all outcomes, and so ulipristal acetate may need to be considered as a possible treatment option. **Oestrogen receptor modulators for the treatment of uterine fibroids** New evidence unlikely to have an impact on current recommendations. Although oestrogen-receptor modulators are not currently included in the guideline, the new evidence in the single identified systematic review was mixed, and there is unlikely to be a robust enough body of evidence to

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
(176 participants) found that the reduction in fibroid and uterus volume was similar between the two groups. **Pre-surgical medical treatment of uterine fibroids (progesterone receptor modulaters and gonadotrophin releasing hormone analogues)** One randomised controlled trial [9] found that, for women with HMB awaiting surgery for fibroids, significantly more women had their uterine bleeding 'controlled' in the ulipristal acetate group than the placebo group with the majority of women in the treatment group experiencing amenorrhoea. Median change in fibroid volume during treatment was also significantly higher in the ulipristal acetate group. Adverse events (serious and non-serious) did not occur at significantly different rates between groups. One randomised controlled trial [10] compared ulipristal acetate with leuprolide acetate (a gonadotropin-releasing hormone analogue) for the treatment of symptomatic uterine fibroids in women awaiting myomectomy. There was no significant difference between groups for bleeding control, however hot flashes were significantly less common in the ulipristal acetate group. **Oestrogen receptor modulators for the treatment of uterine fibroids** One systematic review [32] reported the effectiveness of selective oestrogen receptor modulators for the treatment of uterine fibroids. The review reported that three studies investigating the effectiveness of the selective oestrogen modulator raloxifene, compared with placebo were included. Two of the studies showed a significant benefit from raloxifene, while the 3rd did not. **Herbal preparations for uterine fibroids** One systematic review [33] investigated the effectiveness of herbal preparations for the treatment of uterine fibroids. Tripterygium wilfordii was associated with a greater reduction in fibroid and uterine volume compared with mifepristone. There was no significant difference in fibroid or uterine		support a recommendation. **Herbal preparations for the treatment of uterine fibroids** New evidence unlikely to have an impact on current recommendations. Although herbal preparations are not currently included in the guideline, the new evidence in the single identified systematic review compared different herbal preparations with other medical treatments that are also not currently recommended in the guideline for the treatment of fibroids. Therefore, the effectiveness of herbal preparations is difficult to determine from this evidence and there is unlikely to be a robust enough body of evidence to support a recommendation. **Vitamin K for adjuvant treatment of HMB** New evidence unlikely to have an impact on current recommendations. Although evidence from one small trial showed a beneficial effect of vitamin k treatment for one outcome, there is unlikely to be a robust enough body of evidence to support a recommendation. **Single vs double dose misoprostol before myomectomy**

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
volume between Nona Roguy and gonadotropin-releasing hormone agonist. Guizhi Fuling with mifepristone was associated with a greater reduction in fibroid volume and uterine size than mifepristone alone. No adverse events were reported for herbal preparations. **Vitamin K for adjuvant treatment of HMB** One randomised controlled trial [34] (80 participants) investigated the use of vitamin K as an adjuvant to standard treatment for benign causes of HMB. The vitamin K group had significantly greater improvement in haemoglobin levels, but there was no significant difference in haematocrit, menstrual blood loss, patient acceptance, compliance and quality of life. **Single vs double dose misoprostol before myomectomy** One randomised controlled trial [35] (69 participants) investigated the effectiveness of single vs double dose misoprostol (a synthetic prostaglandin) before myomectomy for multiple uterine fibroids. A double dose was associated with significantly lower operative time, less operative blood loss, and a significant rise in body temperature. There was no significant difference in haemoglobin levels, post-operative febrile morbidity or length of hospital stay.		New evidence is unlikely to have an impact on current recommendations. Although current recommendations recommend myomectomy in some circumstances, they do not recommend particular surgical techniques or preparatory treatments. Therefore the new evidence is only of indirect relevance to this surveillance review.
44.24 What are the indications for, effectiveness of, and cost-effectiveness of using gonadotrophin-releasing hormone analogue for treating HMB?		
Gonadotrophin-releasing hormone analogue before endometrial ablation One systematic review [36] reported the effectiveness of endometrial thinning agents, including gonadotrophin releasing hormone analogues and danazol (which suppresses the action of gonadotrophin releasing hormone), for pre-treatment before endometrial ablation for women with HMB. Gonadotrophin-releasing hormone analogue use before hysteroscopic resection was associated with a significantly higher rate of amenorrhea at 12 and 24 months, significantly shorter surgery duration, ease of surgery, and a reduction in post-surgical dysmenorrhea. There was no significant difference	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	**Gonadotrophin-releasing hormone analogue before endometrial ablation** New evidence is unlikely to have an impact on current recommendations. The current recommendations do not recommend particular endometrial thinning agents before endometrial ablation, which is consistent with new evidence showing that for almost all outcomes, there is no significant

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
in intraoperative complications or patient satisfaction. When comparing gonadotrophin-releasing hormone analogues with danazol, gonadotrophin-releasing hormone analogues were associated with significantly greater endometrial atrophy, but no significant differences on other intra or post-operative outcomes (although both treatments were associated with adverse effects). One randomised controlled trial [37] (30 participants) investigated the efficacy of a pre-surgical gonadotrophin-releasing hormone injection before endometrial ablation by hydrothermoablation for recurrent HMB. After 12 months, the gonadotrophin-releasing hormone group had a significantly lower failure rate than the control group.		difference between gonadotrophin release hormone analogues and danazol for the purpose of endometrial thinning before endometrial ablation. There was some evidence of a beneficial effect of gonadotrophin-releasing hormone before hydrothermoablation. However, this type of ablation is not currently recommended, and so this evidence is of limited applicability.
44.25 What are the indications for surgery?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.26 Are there situations where non-pharmaceutical treatment should not be the first line of treatment for HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.27 What are the indications for, effectiveness of, and cost-effectiveness of using dilatation and curettage for treating HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.28 What are the indications for, effectiveness of, and cost-effectiveness of using endometrial ablation/resection for treating HMB?		
First vs second generation techniques for endometrial ablation One systematic review [38] and network meta-analysis compared second	GDG members indicated that microwave endometrial ablation	**First vs second generation techniques for endometrial ablation**

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
generation endometrial ablation techniques for heavy menstrual bleeding. Amenorrhoea rates were highest with endometrial laser thermotherapy, followed by cryoablation, free fluid ablation, radio frequency and microwave ablation and then thermal balloon ablation. There was no convincing evidence for a difference between the thermal balloon, radio frequency and microwave ablation methods in terms of the number of women dissatisfied with treatment or still experiencing HMB, but evidence of higher dissatisfaction and higher rates of women still experiencing HMB with free fluid ablation than with radio-frequency ablation. One systematic review [39] compared first and second endometrial ablation techniques for the treatment of HMB, There was no significant different in amenorrhoea between groups. Second generation devices had a significantly lower complication rate, operating time and could more commonly be used with local anaesthesia. One systematic review [40] compared endometrial ablation and resection techniques for HMB. There was no significant difference in improvements in HMB or patient satisfaction between first and second generation techniques. Surgery was significantly shorter for second than first generation techniques, and local anaesthesia was more likely. Equipment failure, uterine cramping and nausea were more likely with second generation techniques, but adverse events (fluid overload, uterine perforation, cervical laceration, hematometra) were less likely. The risk of requiring further surgery or hysterectomy was lower with second generation techniques. Pair-wise comparisons of individual ablation methods did not show any significant differences between methods. **Comparison of ablation methods** One randomised controlled trial [41] (126 participants) compared bipolar endometrial ablation with thermal balloon ablation for the treatment of HMB,	is no longer available, and that new ablation techniques have been developed that can be done under local anaesthetic and may be more clinically and cost effective.	New evidence is consistent with current recommendations. Currently second generation techniques are recommended, consistent with the new evidence which overall favours second generation over first generation techniques. **Comparison of ablation methods** New evidence is consistent with current recommendations. Currently, the following techniques are recommended: bipolar radiofrequency ablation, thermal balloon ablation, microwave ablation and free-fluid thermal endometrial ablation. Out of these techniques, the least expensive option is recommended. This is consistent with the new evidence which does not show any significant differences in outcome for the listed techniques, and also finds that bipolar ablation gives better outcomes than hydrothermablation, which is not currently recommended. However, GDG members noted that microwave endometrial ablation is no longer available (this was also highlighted during consultation for the HMB quality standard), and so the recommendation may need to be refreshed to remove this option.

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
At 10 years follow up, they found amenorrhea rates, further treatment rates following initial ablation, and patient satisfaction were not significantly different between the two groups. One randomised controlled trial [42] (160 participants) compared bipolar ablation with hydrothermablation for the treatment of HMB. At 5 years follow up, amenorrhoea rates were significantly higher and re-intervention rates were significantly lower in the bipolar group than the hydrothermablation group. Satisfaction rates were also significantly higher in the bipolar group. One randomised controlled trial [43] (320 participants) compared microwave endometrial ablation and thermal balloon ablation for women eligible for ablation (criteria not specified). Satisfaction, amenorrhoea rates, and hysterectomy rates were not significantly different between the two groups. One randomised controlled trial [44] assessed the effectiveness of pre-operative curettage in women undergoing endometrial thermal ablation for HMB which had not responded to treatment for at least 6 months. Patient satisfaction was significantly higher in the curettage than no curettage group, and persistence of HMB was significantly lower. However, endometrial scarring was significantly higher in the curettage than the no curettage group.		
44.29 What are the indications for, effectiveness of, and cost-effectiveness of using radiological interventions for treating HMB?		
No relevant evidence identified relating only to this question, but see bottom row of table for studies comparing uterine artery embolization with other treatments.	GDG members noted that uterine artery embolization for HMB due to adenomyosis alone or with fibroids is recommended by NICE IPG473 but is only recommended for the treatment of HMB associated with fibroids in CG44. This was also identified in the intelligence gathering exercise.	New information (from GDG and initial intelligence gathering) may have an impact on current recommendations. CG44 specifically excludes conditions for which HMB is not primary presenting symptom from the scope – it is not clear whether adenomyosis falls into this category. If adenomyosis is within the remit of CG44 then this guidance may need to be incorporated, as CG44

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
		currently only recommends uterine artery embolization for the treatment of uterine fibroids.
44.30 What are the indications for, effectiveness of, and cost-effectiveness of using myomectomy for treating HMB?		
Effectiveness of myomectomy (reproductive outcomes) One systematic review [45] compared myomectomy to no treatment or different myomectomy procedures for infertile women with uterine fibroids. There was no significant difference between myomectomy and no treatment for clinical pregnancy rate or miscarriage rate. There was no significant difference between open and laparoscopic myomectomy on live birth rate, clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate, preterm labour rate or caesarean section rate. **Minimally invasive vs open techniques for myomectomy** One systematic review [46] compared myomectomy using minimally invasive (hysteroscopic or laparoscopic) techniques to an open procedure for the treatment of symptomatic uterine fibroids. The review found that post-operative pain scores at 6 and 48 hrs after surgery were significantly lower in the laparoscopic than the open group, but that there was no significant difference at 24 hours. There was no significant difference in the rate of return to theatre or laparoconversion between laparoscopic and open surgery. Rates of post-operative fever were significantly lower in the laparoscopic groups than the open groups. **Treatments for haemorrhage during myomectomy** One systematic review [47] investigated the effectiveness of treatments (compared with placebo or no treatment) for haemorrhage during myomectomy for uterine fibroids. Significant reductions in blood loss were found for vaginal misprostol, intramyometrial vasopressin, intramyometrial bupivacaine plus epinephrine,intravenous tranexamic acid, gelatin-thrombin matrix, intravenous ascorbic acid, vaginal dinoprostone, loop ligation of the	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	**Effectiveness of myomectomy (reproductive outcomes)** New evidence is unlikely to have an impact on current recommendations. The new evidence suggests that there is no impact of myomectomy compared with no treatment for uterine fibroids. Myomectomy is currently recommended as a possible treatment option. However, the new evidence only considered specific reproductive outcomes, and did not consider key outcomes such as satisfaction, bleeding reduction or quality of life. Therefore the new evidence is unlikely to be inconsistent with current recommendations. **Minimally invasive vs open techniques for myomectomy** New evidence is unlikely to have an impact on current recommendations. The new evidence favours minimally invasive over open techniques for myomectomy. Although the current recommendations suggest that myomectomy should be offered as a possible treatment, no recommendations are made about how

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
myoma pseudocapsule, a fibrin sealant patch, a polyglactin suture, and a Foley catheter tied around the cervix. There was no evidence of a significant change in blood loss with oxytocin, morcellation, or clipping the uterine artery. Significant reductions in the need for blood transfusion were found with a polyglactin suture, peri-cervical tourniquet, gelatin-thrombin matrix and dinoprostone. There was no evidence of a significant change in the need for blood transfusion with misprostol, oxytocin, tranexamic acid, ascorbic acid, loop ligation of the myoma pseudocapsule and a fibrin sealant patch.		the surgery should be carried out. Therefore the new evidence is of limited applicability to the guideline. **Treatments for haemorrhage during myomectomy** New evidence is unlikely to have an impact on current recommendations. Although the current recommendations suggest that myomectomy should be offered as a possible treatment, no recommendations are made about how the surgery should be carried out, including the prevention of haemorrhage. Therefore the new evidence is of limited applicability to the guideline.
44.31 Are there any indications for using hysterectomy as first-line treatment for HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.32 What are the indications for, effectiveness of, and cost-effectiveness of using hysterectomy for treating HMB?		
No relevant evidence identified relating only to this question, but see bottom row of table for studies comparing hysterectomy with other treatments	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.33 What are the indications for, effectiveness of, and cost-effectiveness of removing ovaries during hysterectomy versus not removing?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to	No relevant evidence identified

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
	this section of the guideline.	
44.34 What are the competencies required by practitioners who wish to carry out surgical techniques and other interventions for HMB?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
44.35 Competencies for investigations?		
No relevant evidence identified	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	No relevant evidence identified
The evidence described below relates to two or more of the following clinical questions: 44.12 What are the indications for, effectiveness of, and cost-effectiveness of imaging for excluding other conditions? 44.13 What are the indications for, effectiveness of, and cost-effectiveness of tests for excluding other conditions? 44.15 What are the indications for, effectiveness of, and cost-effectiveness of using antifibrinolytics for treating HMB? 44.16 What are the indications for, effectiveness of, and cost-effectiveness of using NSAIDs for treating HMB? 44.18 What are the indications for, effectiveness of, and cost-effectiveness of using the combined oral contraceptive pill for treating HMB? 44.19 What are the indications for, effectiveness of, and cost-effectiveness of using oral progestogens for treating HMB? 44.21 What are the indications for, effectiveness of, and cost-effectiveness of using intrauterine levonorgestrel-releasing systems for treating HMB? 44.23 Medical management of HMB using other pharmaceutical interventions? 44.24 What are the indications for, effectiveness of, and cost-effectiveness of using gonadotrophin-releasing hormone analogue for treating HMB? 44.28 What are the indications for, effectiveness of, and cost-effectiveness of using endometrial ablation/resection for treating HMB? 44.29 What are the indications for, effectiveness of, and cost-effectiveness of using radiological interventions for treating HMB? 44.30 What are the indications for, effectiveness of, and cost-effectiveness of using myomectomy for treating HMB? 44.32 What are the indications for, effectiveness of, and cost-effectiveness of using hysterectomy for treating HMB?		
Diagnostic strategies for HMB One UK based cost-effectiveness analysis[11] compared diagnostic strategies (transvaginal scanning, endometrial biopsy, saline infusion sonography and outpatient hysteroscopy) for HMB. The study identified outpatient hysteroscopy as the most cost effective option for women referred to	No clinical feedback was provided through the GDG questionnaire that was related to this section of the guideline.	**Diagnostic strategies for HMB** New evidence has possible impact on current recommendations. Evidence from one study suggested that hysteroscopy was the most cost-effective diagnostic

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
secondary care for investigation of HMB. Endometrial biopsy in addition to hysteroscopy had a cost effectiveness ratio of £21000 per additional satisfied patient. **Network meta-analysis of treatments for HMB** One systematic review and network meta-analysis [48] compared pharmacological and surgical treatment options (combined oral contraceptives, danazol, endometrial ablation, levonorgestrel, placebo, progestogens given for less than 2 weeks out of 4 during the menstrual cycle, progestogens given for close to 3 weeks out of 4, and tranexamic acid) for HMB. At 3 months follow up, the treatment that was estimated to result in the greatest reduction in menstrual blood loss was the levonorgestrel interuterine system, and the treatment that resulted in the smallest reduction was progestogens administered for less than 2 weeks out of 4 in the menstrual cycle. **Antifibrinolytics vs progestogens** One randomised controlled trial [49] (90 participants) compared tranexamic acid with medroxyprogesterone acetate (MPA, an oral progestogen) for the treatment of HMB of endometrial origin. No significant difference in mean blood loss, duration of bleeding, haemoglobin values and quality of life was found between groups, but satisfaction was significantly lower, and drug complications were significantly higher in the MPA group. **Antifibrinolytics vs other pharmacological treatment** One randomised controlled trial [50] (52 participants) compared tranexamic acid with 'Safoof Habis' (which is made up of hydrated magnesium silicate, silicate of alumina, iron oxide and vateria indica). There was no significant difference between menstrual blood loss reduction between groups. **Non-steroidal anti-inflammatories vs other pharmacological treatment**		strategy. However, the guideline currently recommends ultrasound as the first-line diagnostic tool, with hysteroscopy only used when ultrasound results are inconclusive. Given that the guideline recommended ultrasound as first line, based on cost-effectiveness modelling, these recommendations are likely to require reviewing. **Network meta-analysis of treatments for HMB** New evidence is unlikely to have an impact on current recommendations. In the original guideline, the effectiveness of treatments was considered separately for each treatment (see review questions above). However, much of the new evidence compares different treatments that were not previously compared. It is unclear whether these data may have an impact on current recommendations without combining the data into a network meta-analysis. However, one published network meta-analysis appears to be broadly in line with the current recommendations in that the levonorgestrel interuterine system (which is the current 1st line recommended pharmaceutical treatment) was identified as the most effect in terms of reduction in

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
One systematic review [51] compared non-steroidal anti-inflammatories with other pharmacological treatments for HMB. Non-steroidal anti-inflammatories were better than placebo at reducing bleeding, but less effective than tranexamic acid, danazol or the levonorgestrel interuterine system. Non-steroidal anti-inflammatories were associated with a longer duration of menstruation than danazol, but fewer adverse events. There were no significant differences (outcomes not specified) between non-steroidal anti-inflammatories and oral progestogens, ethamsylate, combined oral contraceptives, and an older progestogen-releasing interuterine system. There were no significant differences between different types of non-steroidal anti-inflammatories. **Combined oral contraceptives vs levonorgestrel interuterine system** One systematic review [52] compared combined oral contraceptives, oral progestogens and the levonorgestrel interuterine system for women with fibroids. One study comparing combined oral contraceptives with the levonorgestrel interuterine system was identified, which showed a significantly greater reduction in menstrual blood loss in the levonorgestrel interuterine system group. Two studies were found comparing leuprorelin with progestogen lynestrenol (two oral progestogens). The reduction in fibroid size was significantly greater in the leuprorelin group. One randomised controlled trial [53] (112 patients) compared combined oral contraceptives with the levongestrel interuterine system for idiopathic HMB. Menstrual blood loss was significantly lower with the levonorgestrel interuterine system and time to treatment failure (defined as the need for medical or surgical treatment during follow up) was significantly longer. One randomised controlled trial [54] (58 patients) compared the levonorgestrel interuterine system with combined oral contraceptives for the treatment of HMB associated with fibroids. The reduction in menstrual blood loss was significantly greater in the levonorgestrel interuterine system group, although		menstrual blood loss. **Antifibrinolytics vs progestogens** New evidence is consistent with current recommendations. Evidence from one randomised controlled trial favours transexamic acid over medroxyprogesterone, and this is consistent with the guideline which recommends tranexamic acid, but not medroxyprogesterone as a treatment option. **Non-steroidal anti-inflammatories vs other pharmacological treatment** New evidence unlikely to have an impact on current recommendations. Currently, non-steroidal anti-inflammatories are only recommended as a second line treatment option following unsuccessful treatment with the levongestrel interuterine system, or if the women does not want hormonal treatment. However, the new evidence did not specifically consider second line treatment, and so it is of limited applicability. **Combined oral contraceptives vs levonorgestrel interuterine system** New evidence is consistent with guideline recommendations. The evidence favours

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
there was no significant difference in time to treatment failure between groups. **Oral progestogens vs levonorgestrel interuterine system** Two randomised controlled trials [55,56] compared oral progestogens with a levonorgestrel interuterine system. One randomised controlled trial [55] (165 patients) found that, for women with heavy menstrual bleeding, increase in haemoglobin levels from baseline and ferritin levels were greater in the levonorgesterel interuterine system group, as was the number of women who rated their bleeding as 'improved'. Another randomised controlled trial [56] (60 participants) found that for women with HMB associated with uterine fibroids, reduction in menstrual bleeding following treatment was higher in the levonorgestrel interuterine system group. **Progestogen-releasing vaginal ring vs oral progestogen** One randomised controlled trial [57] (95 participants) compared the progestogen-releasing vaginal ring with the oral progestogen norhisterone for the treatment of women with idiopathic HMB. There was no significant difference in reduction in blood loss, duration of menses, haemoglobin and serum ferritin levels between groups, although the ring group were significantly more satisfied and likely to continue with treatment. **Endometrial ablation vs hysterectomy vs levonorgestrel inter-uterine device** One UK-based cost effectiveness analysis [12] developed an economic model based on cost and outcome data from an individual patient data meta-analysis to compare the cost effectiveness of the levonorgestrel interuterine system, first or second generation endometrial ablation, and hysterectomy. The authors concluded that hysterectomy was the favoured treatment because although it was most expensive, it also was associated with the highest quality of life and the incremental cost effectiveness ratios comparing		the levonorgestrel interuterine system for the treatment of HMB associated with fibroids. The current guideline recommends the levonorgestrel interuterine system as a first line treatment option, consistent with this new evidence. **Oral progestogens vs levonorgestrel interuterine system** New evidence is consistent with guideline recommendations. The evidence favours the levonorgestrel interuterine system for the treatment of HMB associated with fibroids. The current guideline recommends the levonorgestrel interuterine system as a first line treatment option, consistent with this new evidence. **Progestogen-releasing vaginal ring vs oral progestogen** New evidence is unlikely to have an impact on current recommendations. Currently, norhisterone is only recommended as a third line treatment option following unsuccessful treatment with the levongestrel inter-uterine system and other pharmacological treatments. However, the new evidence did not specifically consider second line treatment, and so it is of limited applicability.

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
interventions were all under £1500 per QALY. Three randomised controlled trials [13-15] compared the levonorgestrel interuterine system to hysterectomy for the treatment of HMB. One trial [13] (72 participants) reported that menstrual blood loss and quality of life improved in both groups but did not report comparative data. One trial [14] (236 participants) reported that there was no significant difference in premenstrual symptoms between groups, except for breast tenderness at 12 months, which was lower in the levonorgestrel interuterine system group. One trial [15] (236 participants) reported that there was no difference in health-related quality of life and psychosocial wellbeing between levonorgestrel interuterine system and hysterectomy groups. One systematic review [16] compared endometrial resection or ablation with hysterectomy for the treatment of HMB. Bleeding symptoms and satisfaction rates favoured hysterectomy, both at short and long term (4 years) follow up. Repeat surgery following treatment was more likely following endometrial ablation/resection than hysterectomy. However, adverse events, including sepsis, blood transfusion, pyrexia, haematoma and infection following discharge from hospital were more likely with hysterectomy than endometrial ablation/resection. One randomised controlled trial [17] (68 participants) compared thermal balloon ablation with laparoscopic hysterectomy for treatment of HMB. Post-operative pain was significantly lower in the endometrial ablation groups. Other outcomes were not reported comparatively between groups. One randomised controlled trial [18] (110 participants) compared the levonorgestrel interuterine system with endometrial ablation (novasure) and hysteroscopic endometrial resection for the treatment of HMB. Hemorrahage was significantly lower in the levonorgestrel interuterine system group than the other groups. The number of participants for which there was no		**Endometrial ablation vs hysterectomy vs levonorgestrel inter-uterine device** New evidence may have an impact on guideline recommendations. The new evidence found that hysterectomy was the most cost-effective treatment for HMB. This may contradict current recommendations, which state that hysterectomy should not be offered as a first line treatment. This recommendation may also be inconsistent with new evidence from randomised controlled trials, which did not clearly favour either endometrial ablation/resection or hysterectomy (some outcomes favoured one treatment, and some the other). Currently the guidelines recommend that endometrial ablation/resection can be offered as a first line treatment, whereas hysterectomy should not be offered as a first line treatment, which may be inconsistent with this evidence. As such it may be appropriate to reassess these approaches as treatment options for HMB. **Uterine artery embolization vs surgery (hysterectomy or myomectomy)** New evidence is consistent with current recommendations. The new evidence does not clearly favour one treatment over another for the treatment of fibroids. This

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
interaction between HMB and normal activity was significantly lower in the levonorgestrel interuterine system group than the other groups. It was not clear, from an assessment of the abstract, exactly what 'interaction' refers to. Patient satisfaction was significantly greater in the endometrial ablation group than the other two groups. One randomised controlled trial[19] (58 participants) compared the levonorgesterel interuterine system with endometrial ablation (thermal balloon ablation) for the treatment of HMB. After 5 years, the thermal balloon ablation group had higher levels of hysterectomy than the levonorgestrel interuterine system group, due to significantly higher levels of treatment failure. Menstrual blood loss was significantly lower in the levonorgestrel interuterine system group, and patient acceptability, perceived improvement and overall satisfaction rates were significantly higher. **Uterine artery embolization vs surgery (hysterectomy or myomectomy)** Two systematic reviews [58,59] compared uterine artery embolization with surgery for uterine fibroids. One systematic review [58] found no significant difference in patient satisfaction at 2 or 5 years, quality of life at 1 year, major complication rates or long-term ovarian failure rate for uterine artery embolization and surgery. Uterine artery embolization was associated with significantly shorter length of procedure, shorter length of hospital stay, shorter time to resumption of routine activity and reduced likelihood of needing a blood transfusion than surgery. However, uterine artery embolization was also associated with higher rates of minor complication, more unscheduled readmissions, and increased surgical re-intervention rates. Uterine artery embolization resulted in significantly poorer fertility outcomes than myomectomy. A second systematic review [59] found that uterine artery embolization resulted in less blood loss, shorter hospital stay and quicker resumption of work than surgery. There was no significant difference in quality of life or patient satisfaction, but the rate of re-		is consistent with current recommendations, which recommend that uterine artery embolization, myomectomy and hysterectomy should all be considered as treatment options for uterine fibroids.

Is there any new evidence/intelligence identified during this 8-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2014)
intervention was higher in the uterine artery embolization group.		

References

1. Barlow DH, Lumsden MA, Fauser BC et al. (2014) 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.

2. Tristan M, Orozco LJ, Steed A et al. (2012) Mifepristone for uterine fibroids. Cochrane database of systematic reviews (Online).8 (pp CD007687), 2012.Date of Publication: 2012. CD007687.

3. Shen Q, Hua Y, Jiang W et al. (2013) Effects of mifepristone on uterine leiomyoma in premenopausal women: a meta-analysis. Fertility & Sterility 100:1722-1726.

4. Esteve JL, Acosta R, Perez Y et al. (2013) Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. International Journal of Women's Health 5:361-369.

5. Kulshrestha V, Kriplani A, Agarwal N et al. (2013) Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India. Indian Journal of Medical Research 137:1154-1162.

6. Carbonell JL, Acosta R, Perez Y et al. (2013) Treatment of uterine myoma with 2.5 or 5 mg mifepristone daily during 3 months with 9 months posttreatment followup: Randomized clinical trial. ISRN Obstetrics and Gynecology.2013 , 2013.Article Number: 649030.Date of Publication: 2013.

7. Carbonell JLL, Acosta R, Perez Y et al. (2013) Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: A double-blind randomized clinical trial. International Journal of Women's Health.5 (1) (pp 115-124), 2013.Date of Publication: 13 Mar 2013. 115-124.

8. Esteve JL, Acosta R, Perez Y et al. (2012) 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 161:202-208.

9. Donnez J, Tatarchuk TF, Bouchard P et al. (2-2-2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine 366:409-420.

10. Donnez J, Tomaszewski J, Vazquez F et al. (2-2-2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. New England Journal of Medicine 366:421-432.

11. Cooper NA, Barton PM, Breijer M et al. (20-1-2014) Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis. Health Technology Assessment (Winchester, England) 18:1-201.

12. Roberts TE, Tsourapas A, Middleton LJ et al. (2011) Hysterectomy, endometrial ablation, and levonorgestrel releasing intrauterine system (Mirena) for treatment of heavy menstrual bleeding: Cost effectiveness analysis. BMJ (Online) 342.

13. Sesti F, Piancatelli R, Pietropolli A et al. (2012) Levonorgestrel-releasing intrauterine system versus laparoscopic supracervical hysterectomy for the treatment of heavy menstrual bleeding: a randomized study. Journal of Women's Health 21:851-857.

14. Leminen H, Heliovaara-Peippo S, Halmesmaki K et al. (2012) The effect of hysterectomy or levonorgestrel-releasing intrauterine system on premenstrual symptoms in women treated for menorrhagia: secondary analysis of a randomized controlled trial. Acta Obstetricia et Gynecologica Scandinavica 91:318-325.

15. Heliovaara-Peippo S, Hurskainen R, Teperi J et al. (2013) 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 & Gynecology 209:535 E1-535 E14.

16. Fergusson RJ, Lethaby A, Shepperd S et al. (2013) Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database of Systematic Reviews .

17. Sesti F, Ruggeri V, Pietropolli A et al. (2011) Thermal balloon ablation versus laparoscopic supracervical hysterectomy for the surgical treatment of heavy menstrual bleeding: a randomized study. Journal of Obstetrics & Gynaecology Research 37:1650-1657.

18. Ghazizadeh S, Panahi Z, Ghanbari Z et al. (2014) 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 (4) (pp 215-218), 2014.Date of Publication: 01 Aug 2014. 215-218.

19. Silva-Filho AL, Pereira FA, de Souza SS et al. (2013) 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 87:409-415.

20. Naoulou B and Tsai MC. (2012) Efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding: a systematic review. [Review]. Acta Obstetricia et Gynecologica Scandinavica 91:529-537.

21. Eder S, Baker J, Gersten J et al. (2013) Efficacy and safety of oral tranexamic acid in women with heavy menstrual bleeding and fibroids. Women's health 9:397-403.

22. Khajehei M, Abdali K, and Tabatabaee H. (2013) The effect of mefenamic acid and naproxen on heavy menstrual bleeding: A placebo-controlled study. South African Journal of Obstetrics and Gynaecology.19 (2) (pp 31-34), 2013.Date of Publication: 2013. 31-34.

23. Wasiak R, Filonenko A, Vanness DJ et al. (2012) Impact of estradiol-valerate/dienogest on work productivity and activities of daily living in European and Australian women with heavy menstrual bleeding. International Journal of Women's Health 4:271-278.

24. Wasiak R, Filonenko A, Vanness DJ et al. (2013) Impact of estradiol valerate/dienogest on work productivity and activities of daily living in women with heavy menstrual bleeding. Journal of Women's Health 22:378-384.

25. Fraser IS, Jensen J, Schaefers M et al. (2012) Normalization of blood loss in women with heavy menstrual bleeding treated with an oral contraceptive containing estradiol valerate/dienogest. Contraception 86:96-101.

26. Shokeir T, Eid M, and Abdel-Hady e. (2013) 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 20:222-226.

27. Jiang W, Shen Q, Chen M et al. (2014) Levonorgestrel-releasing intrauterine system use in premenopausal women with symptomatic uterine leiomyoma: a systematic review. Steroids 86:69-78.

28. Gupta J, Kai J, Middleton L et al. (10-1-2013) Levonorgestrel intrauterine system versus medical therapy for menorrhagia. New England Journal of Medicine 368:128-137.

29. Sanghera S, Roberts TE, Barton P et al. (2014) Levonorgestrel-releasing intrauterine system vs. usual medical treatment for menorrhagia: an economic evaluation alongside a randomised controlled trial. PLoS ONE [Electronic Resource] 9:e91891.

30. Qiu J, Cheng J, Wang Q et al. (2014) Levonorgestrel-releasing intrauterine system versus medical therapy for menorrhagia: a systematic review and meta-analysis. Medical Science Monitor 20:1700-1713.

31. Mawet M, Nollevaux F, Nizet D et al. (2014) 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 19:169-179.

32. Deng L, Wu T, Chen XY et al. (2012) Selective estrogen receptor modulators (SERMs) for uterine leiomyomas. Cochrane Database of Systematic Reviews .

33. Liu JP, Yang H, Xia Y et al. (2013) Herbal preparations for uterine fibroids. The Cochrane database of systematic reviews.4 (pp CD005292), 2013.Date of Publication: 2013.

34. Loo CV, Noor Azmi MA, and Isahak M. (2012) A randomised controlled trial using vitamin K as adjuvant treatment for benign causes of menorrhagia. BJOG 119:228.

35. Ragab A, Khaiary M, and Badawy A. (2014) The use of single versus double dose of intra-vaginal prostaglandin E 2 "misoprostol" prior to abdominal myomectomy: A randomized controlled clinical trial. Journal of Reproduction and Infertility.15 (3) (pp 152-156), 2014.Date of Publication: July-September 2014. 152-156.

36. Tan YH and Lethaby A. (2013) Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. [Review]. Cochrane Database of Systematic Reviews 11:CD010241.

37. Litta P, Saccardi C, Tommasi L et al. (2014) Risk of recurrent menorrhagia after hydrothermoablation: role of GnRH analogues neoadjuvant treatment in long-term successful rate. Clinical & Experimental Obstetrics & Gynecology 41:426-431.

38. Daniels JP, Middleton LJ, Champaneria R et al. (2012) Second generation endometrial ablation techniques for heavy menstrual bleeding: network meta-analysis. [Review]. BMJ 344:e2564.

39. Kroft J and Liu G. (2013) First- versus second-generation endometrial ablation devices for treatment of menorrhagia: a systematic review, meta-analysis and appraisal of economic evaluations. [Review]. Journal of Obstetrics & Gynaecology Canada: JOGC 35:1010-1019.

40. Lethaby A, Penninx J, Hickey M et al. (2013) Endometrial resection and ablation techniques for heavy menstrual bleeding. The Cochrane database of systematic reviews.8 (pp CD001501), 2013.Date of Publication: 2013.

41. Herman MC, Penninx JP, Mol BW et al. (2013) 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 & Gynaecology 120:966-970.

42. Penninx JP, Herman MC, Mol BW et al. (2011) Five-year follow-up after comparing bipolar endometrial ablation with hydrothermablation for menorrhagia. Obstetrics & Gynecology 118:1287-1292.

43. Sambrook AM, Elders A, and Cooper KG. (11-5-0014) Microwave endometrial ablation versus thermal balloon endometrial ablation (MEATBall): 5-year follow up of a randomised controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology 121:747-753.

44. Abd El Hameed AA. (2012) 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 (2) (pp 116-121), 2012.Date of Publication: June 2012. 116-121.

45. Metwally M, Cheong YC, and Horne AW. (2012) Surgical treatment of fibroids for subfertility. Cochrane Database of Systematic Reviews .

46. Bhave CP, Franik S, Pouwer AW et al. (2014) Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. Cochrane Database of Systematic Reviews .

47. Kongnyuy EJ and Wiysonge CS. (2014) Interventions to reduce haemorrhage during myomectomy for fibroids. Cochrane Database of Systematic Reviews .

48. Hoaglin DC, Filonenko A, Glickman ME et al. (2013) Use of mixed-treatment-comparison methods in estimating efficacy of treatments for heavy menstrual bleeding. European Journal of Medical Research 18:17.

49. Goshtasebi A, Moukhah S, and Gandevani SB. (2013) Treatment of heavy menstrual bleeding of endometrial origin: randomized controlled trial of medroxyprogesterone acetate and tranexamic acid. Archives of Gynecology & Obstetrics 288:1055-1060.

50. Fathima A and Sultana A. (2012) Clinical efficacy of a Unani formulation 'Safoof Habis' in menorrhagia: A randomized controlled trial. European Journal of Integrative Medicine.4 (3) (pp e315-e322), 2012.Date of Publication: September 2012. e315-e322.

51. Lethaby A, Duckitt K, and Farquhar C. (2013) Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane database of systematic reviews (Online).1 (pp CD000400), 2013.Date of Publication: 2013. CD000400.

52. Sangkomkamhang US, Lumbiganon P, Laopaiboon M et al. (2013) Progestogens or progestogen-releasing intrauterine systems for uterine fibroids. [Review]. Cochrane Database of Systematic Reviews 2:CD008994.

53. Shaaban MM, Shabaan MM, Zakherah MS et al. (2011) Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial. Contraception 83:48-54.

54. Sayed GH, Zakherah MS, El-Nashar SA et al. (2011) 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 112:126-130.

55. Kaunitz AM, Bissonnette F, Monteiro I et al. (2012) Levonorgestrel-releasing intrauterine system for heavy menstrual bleeding improves hemoglobin and ferritin levels. Contraception 86:452-457.

56. Tosun AK, Tosun I, and Suer N. (2014) 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 30:834-839.

57. Abu HH, Alsherbini W, and Bazeed M. (2012) Contraceptive vaginal ring treatment of heavy menstrual bleeding: a randomized controlled trial with norethisterone. Contraception 85:246-252.

58. Gupta JK, Sinha A, Lumsden MA et al. (2012) Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database of Systematic Reviews .

59. van der Kooij SM, Bipat S, Hehenkamp WJ et al. (2011) Uterine artery embolization versus surgery in the treatment of symptomatic fibroids: a systematic review and metaanalysis. [Review]. American Journal of Obstetrics & Gynecology 205:317-318.