Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-232 Linzagolix

Stand: Oktober 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Linzagolix
zur Behandlung der Symptome bei Gebärmutter-Myomen

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht II „Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Hysterektomie Myomenukleation (perkutane Transkatheter-)Embolisation (stationär)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss über die Aufnahme der Uterus-Ballon-Therapie (Behandlung der Menorrhagie/ Hypermenorrhoe) in Anlage B der Richtlinie über die Bewertung ärztlicher Untersuchungs- und Behandlungsmethoden (BUB): „Methoden, die nicht als vertragsärztliche Leistung zu Lasten der Krankenkassen erbracht werden dürfen.“ – vom 16. Oktober 2000 Bewertung der Methode „Ultraschallgesteuerter hoch-intensiver fokussierter Ultraschall zur Behandlung von Leiomyomen des Uterus“ nach § 137h SGB V (16. März 2017) Beschluss über die Nutzenbewertung von Arzneimitteln nach §35a SGB V zu Relugolix/E2/NETA (17. Februar 2022)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Linzagolix H01CC04 Yselty	Zugelassenes Anwendungsgebiet: Yselty® wird angewendet bei erwachsenen Frauen im gebärfähigen Alter zur Behandlung mäßiger bis starker Symptome von Uterusmyomen.
GnRH-Analoga	
Goserelin L02AE03 Zoladex®-Gyn	Symptomatischer Uterus myomatosus, wenn eine Unterdrückung der ovariellen Hormonbildung angezeigt ist zur Volumenreduktion einzelner Myome bei vorgesehener Myomenukleation oder Hysterektomie. (Stand FI: April 2015) *Aus Abschnitt 4.2 der Fachinformation: […] Die Behandlung des Uterus myomatosus sollte 6 Monate nicht überschreiten, da über einen längeren Zeitraum noch keine ausreichenden klinischen Erfahrungen vorliegen.*
Leuprorelin L02AE02 Trenantone®-Gyn	Symptomatischer Uterus myomatosus, wenn eine Unterdrückung der Hormonbildung in den Eierstöcken angezeigt ist, als präoperative Maßnahme zur Volumenreduktion einzelner Myome bei vorgesehener Myomenukleation oder Hysterektomie. (Stand FI: August 2018) *Aus Abschnitt 4.2 der Fachinformation: […] Die Dauer der Anwendung ist auf einen Zeitraum von 6 Monaten zu begrenzen.*
Triptorelin L02AE04 Decapeptyl Gyn	Bei symptomatischem Uterus myomatosus, wenn eine Unterdrückung der ovariellen Hormonbildung angezeigt ist, als präoperative Maßnahme zur Verkleinerung einzelner Myome bei vorgesehener Myomenukleation oder Hysterektomie. (Stand FI: März 2015) *Aus Abschnitt 4.2 der Fachinformation: […] Wegen der möglichen Wirkung auf die Knochendichte sollte die Behandlungsdauer 6 Monate nicht überschreiten (siehe Abschnitt 4.4.).*
GnRH-Antagonisten	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Relugolix/Estradiol /Norethistosteron H01CC5 Ryeqo®	Ryeqo wird angewendet bei erwachsenen Frauen im gebärfähigen Alter zur Behandlung mäßiger bis starker Symptome von Uterusmyomen. (Stand FI: Oktober 2021)
Progesteron-Rezeptor-Antagonisten	
Ulipristalacetat G03XB02 Esmya®	Ulipristalacetat ist indiziert zur Intervall-Therapie mittlerer bis starker Symptome durch Gebärmuttermyome bei erwachsenen Frauen, die noch nicht die Menopause erreicht haben und für die eine Embolisation von Gebärmuttermyomen und/oder der chirurgische Eingriff nicht geeignet oder fehlgeschlagen sind. (FI Stand: Januar 2021) *Aus Abschnitt 4.2 der Fachinformation:* *„[…] Der behandelnde Arzt sollte die Patientin über die Notwendigkeit von Behandlungspausen aufklären.* *Es liegen Untersuchungen für wiederholte Intervall-Behandlungen von bis zu 4 Intervall-Behandlungen vor."*
Gestagene	
Chlormadinon G03DB06 Chlormadinon-Jenapharm	unregelmäßige Zyklen und Menstruationsbeschwerden, z. B. Oligomenorrhoe, Polymenorrhoe, Hypermenorrhoe, Zwischenblutungen, prämenstruelle Schmierblutungen und Dysmenorrhoe. (Stand FI: April 2018) *Aus Abschnitt 4.4. der Fachinformation: Die Patientinnen sollten engmaschig überwacht werden, wenn eine der folgenden Situationen bzw. Erkrankungen vorliegt oder früher vorlag bzw. sich während einer Schwangerschaft oder einer zurückliegenden Hormonbehandlung verschlechtert hat. […]* - *Leiomyom (Uterusmyom) oder Endometriose*
Levonorgestrel G02BA03 Mirena®	Kontrazeption, Hypermenorrhoe (Stand FI: Mai 2020) *Aus Abschnitt 4.3 der Fachinformation (Gegenanzeigen):*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	[…] Angeborene oder erworbene Fehlbildungen des Uterus einschließlich Uterusmyome, wenn sie das Cavum uteri verformen. […]
Andere	
Tranexamsäure B02AA02 (Cyklokapron®)	Bei Hypermenorrhoe (zu starke Monatsblutung). (Stand FI: Juli 2016) *Aus Abschnitt 4.2 der Fachinformation: Die empfohlene Dosierung beträgt 3x täglich 2 Filmtabletten, solange eine Behandlung erforderlich ist, höchstens jedoch für die Dauer von 4 Tagen. […]*

Quellen: Amice-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-232 (Linzagolix)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	15. September 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
COCP	combined oral contraceptive pill
CVR	Contraceptive vaginal ring
EA	endometrial ablation
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GnRHa	Gonadotropin-releasing hormone agonists
GoR	Grade of Recommendations
HMB	Heavy menstrual bleeding
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LIUS	levonorgestrel intrauterine system
LoE	Level of Evidence
MBL	Menstrual blood loss
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSAIDs	non-steroidal anti-inflammatory drugs
OR	Odds Ratio
PBAC	Pictorial Bleeding Assessment Chart
QoL	Quality of Life
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SPRM	Selective progesterone receptor modulators
TA	tranexamic acid
TRIP	Turn Research into Practice Database
UAE	uterine artery embolisation
UPA	Ulipristalacetat
WHO	World Health Organization

1 Indikation

Zur Behandlung erwachsener Frauen im gebärfähigen Alter mit mäßigen bis starken Symptomen von Uterusmyomen.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Uterusmyome durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 02.06.2022 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 512 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 8 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Bofill Rodriguez M et al., 2020 [1].

Progestogen-releasing intrauterine systems for heavy menstrual bleeding.

Fragestellung

To determine the effectiveness, acceptability and safety of progestogen-releasing intrauterine devices in reducing heavy menstrual bleeding.

Methodik

Population:

- Women of reproductive years with regular heavy periods measured either objectively (by the alkaline haematin method), semi-objectively (by PBAC score) or subjectively (patient perception)

Intervention/Komparator:

- Progestogen-releasing intrauterine devices versus no treatment, placebo or any other medical or surgical treatment for the reduction of HMB.

Endpunkte:

- Menstrual bleeding (primärer Endpunkt), QoL, adverse events

Recherche/Suchzeitraum:

- Cochrane Gynaecology and Fertility Specialised Register, CENTRAL, MEDLINE, EMBASE, PsycINFO and CINAHL (from inception to June 2019)

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 25 RCTs (2511 women)

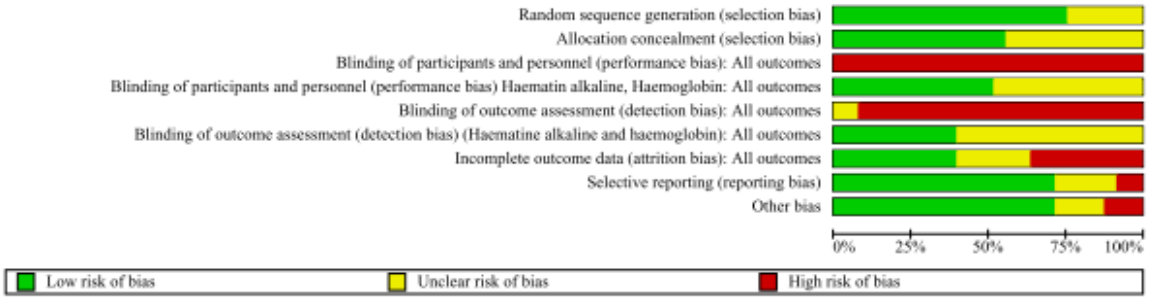
Charakteristika der Population:

- A majority of trials excluded women with fibroids of any kind or either those greater than a certain diameter or those large enough to distort the uterine cavity. One research group investigated the effects of treatments separately in women with fibroids (but excluding submucous fibroids of any size distorting the uterine cavity or intramural or subserous fibroids greater than 5 cm in diameter) and women without any evidence of fibroids (in two separate publications). Many studies required women to have completed their families. Menstrual blood loss was usually confirmed by the alkaline haematin method or Pictorial Bleeding Assessment Chart (PBAC) scores prior to the initiation of treatment in consecutive menstrual cycles but in two trials, women were eligible if they considered their menstrual blood flow excessive. In one trial, participants complaining of HMB were only included if they had confirmed adenomyosis, but in two other trials adenomyosis was an exclusion criterion. One trial investigated the effects of

treatments for HMB in women taking anticoagulant medication after cardiac valve replacement.

Qualität der Studien:

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Studienergebnisse:

- LNG-IUS versus other medical therapy
  - The other medical therapies were norethisterone acetate, medroxyprogesterone acetate, oral contraceptive pill, mefenamic acid, tranexamic acid or usual medical treatment (where participants could choose the oral treatment that was most suitable).
  - The LNG-IUS may improve HMB, lowering menstrual blood loss according to the alkaline haematin method (mean difference (MD) 66.91 mL, 95% confidence interval (CI) 42.61 to 91.20; 2 studies, 170 women; low-certainty evidence); and the Pictorial Bleeding Assessment Chart (MD 55.05, 95% CI 27.83 to 82.28; 3 studies, 335 women; low-certainty evidence).
  - We are uncertain whether the LNG-IUS may have any effect on women's satisfaction up to one year (RR 1.28, 95% CI 1.01 to 1.63; 3 studies, 141 women; I2 = 0%, very low-certainty evidence). The LNG-IUS probably leads to slightly higher quality of life measured with the SF-36 compared with other medical therapy (MD 2.90, 95% CI 0.06 to 5.74; 1 study: 571 women; moderate-certainty evidence) or with the Menorrhagia Multi-Attribute Scale (MD 13.40, 95% CI 9.89 to 16.91; 1 trial, 571 women; moderate-certainty evidence).
  - The LNG-IUS and other medical therapies probably give rise to similar numbers of women with serious adverse events (RR 0.91, 95% CI 0.63 to 1.30; 1 study, 571 women; moderate-certainty evidence). Women using other medical therapy are probably more likely to withdraw from treatment for any reason (RR 0.49, 95% CI 0.39 to 0.60; 1 study, 571 women, moderate-certainty evidence) and to experience treatment failure than women with LNG-IUS (RR 0.34, 95% CI 0.26 to 0.44; 6 studies, 535 women; moderate-certainty evidence).
- LNG-IUS versus endometrial resection or ablation (EA)
  - Bleeding outcome results are inconsistent. We are uncertain of the effect of the LNG-IUS compared to EA on rates of amenorrhoea (RR 1.21, 95% CI 0.85 to 1.72; 8 studies, 431 women; I2 = 21%; low-certainty evidence) and hypomenorrhoea (RR 0.98, 95% CI 0.73 to 1.33; 4 studies, 200 women; low-certainty evidence) and eumenorrhoea (RR 0.55, 95% CI 0.30 to 1.00; 3 studies, 160 women; very low-certainty evidence). We are uncertain whether both treatments may have similar rates of satisfaction with treatment at 12 months (RR 0.95, 95% CI 0.85 to 1.07; 5 studies, 317 women; low-certainty evidence).

- We are uncertain if the LNG-IUS compared to EA has any effect on quality of life, measured with SF-36 (MD −14.40, 95% CI −22.63 to -6.17; 1 study, 33 women; very low-certainty evidence). Women with the LNG-IUS compared with EA are probably more likely to have any adverse event (RR 2.06, 95% CI 1.44 to 2.94; 3 studies, 201 women; moderate-certainty evidence). Women with the LNG-IUS may experience more treatment failure compared to EA at one year follow up (persistent HMB or requirement of additional treatment) (RR 1.78, 95% CI 1.09 to 2.90; 5 studies, 320 women; low-certainty evidence); or requirement of hysterectomy may be higher at one year follow up (RR 2.56, 95% CI 1.48 to 4.42; 3 studies, 400 women; low-certainty evidence).

- LNG-IUS versus hysterectomy
  - We are uncertain whether the LNG-IUS has any effect on HMB compared with hysterectomy (RR for amenorrhoea 0.52, 95% CI 0.39 to 0.70; 1 study, 75 women; very low-certainty evidence).
  - We are uncertain whether there is difference between LNG-IUS and hysterectomy in satisfaction at five years (RR 1.01, 95% CI 0.94 to 1.08; 1 study, 232 women; low-certainty evidence) and quality of life (SF-36 MD 2.20, 95% CI −2.93 to 7.33; 1 study, 221 women; low-certainty evidence).
  - Women in the LNG-IUS group may be more likely to have treatment failure requiring hysterectomy for HMB at 1-year follow-up compared to the hysterectomy group (RR 48.18, 95% CI 2.96 to 783.22; 1 study, 236 women; low-certainty evidence).

Anmerkung/Fazit der Autoren

The levonorgestrel-releasing intrauterine system (LNG-IUS) results in a larger reduction in menstrual blood loss from baseline in women with HMB compared to other medical treatment or placebo, including selected women with fibroids. It appears to be more effective than oral medical therapies and results in better quality of life, higher satisfaction with treatment and lower withdrawal from treatment at two years.

There is very limited and low-quality evidence that the LNG-IUS appeared to have similar effectiveness to endometrial ablation methods; and quality of life outcomes were similar. The LNG-IUS is associated with adverse events such as breast or pelvic pain and bloating when compared with other treatments, which are not directly comparable to the adverse events encountered with surgery. Both the LNG-IUS and hysterectomy improved health related quality of life, which was most apparent within the five years after treatment. Although many women treated with the LNG-IUS eventually had hysterectomy (up to 46% within 10 years), the LNGIUS remained cost effective.

Sangkomkamhang UA et al., 2020 [8].

Progestogens or progestogen-releasing intrauterine systems for uterine fibroids (other than preoperative medical therapy).

Fragestellung

To determine the eHectiveness of progestogens or progestogen-releasing intrauterine systems in treating premenopausal women with uterine fibroids.

Methodik

Population:

- premenopausal women with uterine fibroids

Intervention:

- Experimental interventions included oral progestogens, depot medroxyprogesterone acetate (DMPA) intramuscular injections, or progestin-releasing intrauterine devices (IUS)

Komparator:

- no treatment, placebo, medical therapy, or surgical procedures

Endpunkte:

- Uterine fibroid-related symptoms, abnormal uterine bleeding (blood loss), measured by objective disease measures, such as haemoglobin, haematocrit, or ferritin levels; pain assessed subjectively by the individual or with a visual analogue scale (VAS)
- Fibroid size
- Quality of life
- Recurrence rate, with the possibility of needing additional therapy
- Adverse events, such as acne, weight gain, bloating, breast tenderness, and expulsion of the IUS
- Cost effectiveness

Recherche/Suchzeitraum:

- We searched the Cochrane Gynaecology and Fertility Group Specialised Register, CENTRAL, MEDLINE, Embase, and PsycINFO databases to July 2020.

Qualitätsbewertung der Studien:

- GRADE approach

Ergebnisse

Anzahl eingeschlossener Studien:

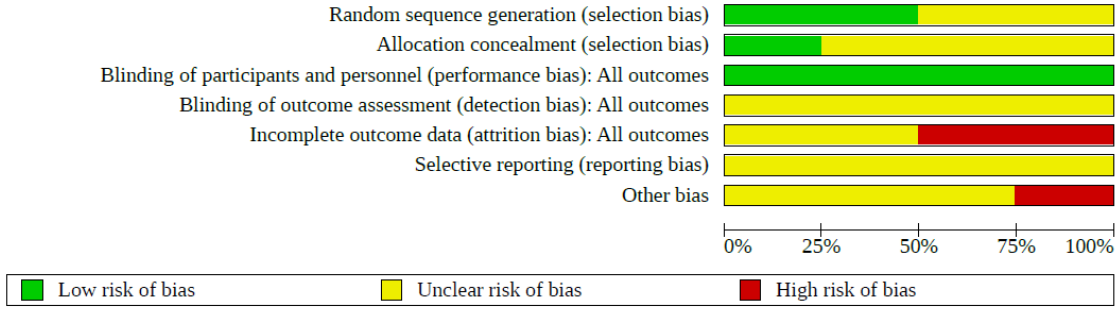
- four studies with 221 women

Charakteristika der Population:

- The four studies included a total of 221 women, who ranged in age between 25 and 49 years. Two studies included 131 women with fibroids with heavy menstruation or menorrhagia (Inki 2002; Sayed 2011). Two studies included 90 with abnormal uterine bleeding secondary to uterine fibroids (Brito 2017; Tosun 2014).

Qualität der Studien:

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Studienergebnisse:

- Levonorgestrel-releasing intrauterine device (LNG-IUS) versus hysterectomy
  - There was no information on the outcomes of interest, including adverse events.
- LNG-IUS versus low dose combined oral contraceptive (COC)
  - At 12 months, we are uncertain whether LNG-IUS reduced the percentage of abnormal uterine bleeding, measured with the alkaline hematin test (mean diHerence (MD) 77.50%, 95% confidence interval (CI) 70.44 to 84.56; 1 RCT, 44 women; very low-quality evidence), or the pictorial blood assessment chart (PBAC; MD 34.50%, 95% CI 11.59 to 57.41; 1 RCT, 44 women; very low-quality evidence); increased haemoglobin levels (MD 1.50 g/dL, 95% CI 0.85 to 2.15; 1 RCT, 44 women; very low-quality evidence), or reduced fibroid size more than COC (MD 1.90%, 95% CI -12.24 to 16.04; 1 RCT, 44 women; very low-quality evidence). The study did not measure adverse events.
- LNG-IUS versus oral progestogen (norethisterone acetate (NETA))
  - Compared to NETA, we are uncertain whether LNG-IUS reduced abnormal uterine bleeding more from baseline to six months (visual bleeding score; MD 23.75 points, 95% CI 1.26 to 46.24; 1 RCT, 45 women; very low-quality evidence); increased the percentage of change in haemoglobin from baseline to three months (MD 4.53%, 95% CI 1.46 to 7.60; 1 RCT, 48 women; very low-quality evidence), or from baseline to six months (MD 10.14%, 95% CI 5.57 to 14.71; 1 RCT, 45 women; very low-quality evidence). The study did not measure fibroid size. Spotting (adverse event) was more likely to be reported by women with the LNG-IUS (64.3%) than by those taking NETA (30%; 1 RCT, 45 women; very low-quality evidence).
- Oral progestogen (dienogest, desogestrel) versus goserelin acetate
  - Compared to goserelin acetate, we are uncertain whether abnormal uterine bleeding was reduced at 12 weeks with dienogest (PBAC; MD 216.00 points, 95% CI 149.35 to 282.65; 1 RCT, 14 women; very low-quality evidence) or desogestrel (PBAC; MD 78.00 points, 95% CI 28.94 to 127.06; 1 RCT, 16 women; very low-quality evidence). Vasomotor symptoms (adverse events, e.g. hot flashes) are only associated with goserelin acetate (55%), not with dienogest (1 RCT, 14 women; very low-quality evidence) or with desogestrel (1 RCT, 16 women; very lowquality evidence). The study did not report fibroid size.

Anmerkung/Fazit der Autoren

Because of very low-quality evidence, we are uncertain whether the LNG-IUS reduces abnormal uterine bleeding or increases haemoglobin levels in premenopausal women with uterine fibroids, compared to COC or norethisterone acetate. There was insufficient evidence to determine whether the LNG-IUS reduces the size of uterine fibroids compared to COC. We are uncertain whether oral progestogens reduce abnormal uterine bleeding as effectively as goserelin acetate, but women reported fewer adverse events, such as hot flashes.

Lethaby A et al., 2019 [6].

Combined hormonal contraceptives for heavy menstrual bleeding.

Fragestellung

To determine the efficacy of combined hormonal contraceptives (pills, vaginal ring or patch) compared with other medical therapies, placebo, or no therapy in the treatment of HMB. A secondary objective was to compare the COCP with the CVR.

Methodik

Population:

- Women of reproductive years
- Regular heavy periods measured either objectively or subjectively assessed at baseline for at least one-month follow-up
- Type of settings: primary care, family planning, or specialist clinic

Intervention/Komparator:

- Combined hormonal contraceptives (pills, ring, or patch) versus other methods of medical treatment, no treatment or placebo for heavy menstrual bleeding. All types and dosages of combined hormonal contraceptives were considered.

Endpunkte:

- Menstrual blood loss (MBL), QoL, adverse events

Recherche/Suchzeitraum:

- Gynecology and Fertility Group trials register, MEDLINE, EMBASE, CENTRAL, CINAHL and PsycINFO (search dates: Oct 1996, May 2002, June 2004, April 2006, June 2009, July 2017 and September 2018)

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

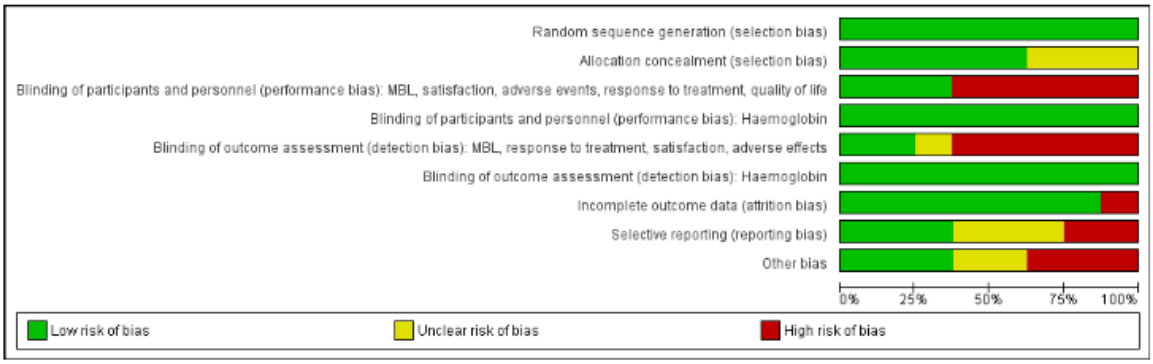
- Eight studies with 805 participants were included in this update of the review.

Charakteristika der Population:

- (…) Three of the eight studies did not exclude participants if they had small fibroids (Agarwal 2016; Dahiya 2016; Endrikat 2009). Two trials (Fraser 2011; Jensen 2011) also included women with prolonged bleeding; however, most of the women had HMB (91% and 93% in Fraser 2011 and 76% and 86% in Jensen 2011). In these two studies, where possible, outcome data were restricted to the subgroup in the trials that had confirmed HMB. (…)

Qualität der Studien:

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Studienergebnisse:

- COCP versus placebo
  - COCP, with a step-down oestrogen and step-up progestogen regimen, improved response to treatment (return to menstrual 'normality') (OR 22.12, 95% CI 4.40 to 111.12; 2 trials; 363 participants; I2 = 50%; moderate-quality evidence), and lowered MBL (OR 5.15, 95% CI 3.16 to 8.40; 2 trials; 339 participants; I2 = 0%; moderate-quality evidence) when compared to placebo. The results suggested that, if the chance of 'successful' treatment was 3% in women taking placebo, then COCP increased this chance from 12% to 77% in women with unacceptable HMB. Minor adverse events, in particular breast pain, were more common with COCP. No study in this comparison reported semi-objectively assessed MBL or participant satisfaction with treatment.
- COCP versus other medical treatments
  - Non-steroidal anti-inflammatory drugs (NSAIDs): There was insufficient evidence to determine whether the COCP reduced MBL when compared to NSAIDs (mefenamic acid and naproxen). No study in this comparison reported semi-objectively assessed MBL, subjectively assessed MBL, participant satisfaction with treatment or adverse events.
  - Levonorgestrel-releasing intrauterine system (LNG IUS): The LNG IUS was more effective than COCP in reducing MBL (OR 0.21, 95% CI 0.09 to 0.48; 2 trials; 151 participants; I2 = 0%; low-quality evidence) but it was not clear whether satisfaction with treatment or adverse effects varied according to which treatment was used. No study in this comparison reported semi-objectively assessed MBL or subjectively assessed MBL.
- Contraceptive vaginal ring (CVR) versus other medical treatments
  - COCP: COCP was compared with CVR in two trials. There were discrepancies between some of the findings and there was no evidence of a benefit for one treatment compared to the other for response to treatment, MBL or participant satisfaction with treatment. There was a greater likelihood of nausea with COCP. No study in this comparison reported objectively assessed MBL or subjectively assessed MBL.
  - Progestogens: CVR was compared to long course progestogens in one trial. It is possible that CVR increased the odds of satisfaction; but we are uncertain whether CVR improved MBL. The evidence was based on small numbers of participants and was very low quality, so definitive conclusions could not be reached. No study in this comparison reported objectively assessed MBL, subjectively assessed MBL, or adverse events.

Anmerkung/Fazit der Autoren

Moderate-quality evidence suggests that the combined oral contraceptive pill over six months reduces HMB in women with unacceptable HMB from 12% to 77% (compared to 3% in women taking placebo). When compared with other medical options for HMB, COCP was less effective than the LNG IUS. Limited evidence suggested that COCP and CVR had similar effects. There was insufficient evidence to determine comparative efficacy of combined hormonal contraceptives with NSAIDs, or long course progestogens.

Bryant-Smith AC et al., 2018 [2].

Antifibrinolytics for heavy menstrual bleeding.

Fragestellung

To determine the effectiveness and safety of antifibrinolytic medications as a treatment for heavy menstrual bleeding.

Methodik

Population:

- Women of reproductive age, who are having regular heavy periods (measured either objectively or subjectively), undertake at least two months' follow-up whilst on treatment, and who are recruited from primary care, family planning, or a specialist clinic setting were eligible for inclusion.

Intervention/Komparator:

- We included trials comparing antifibrinolytic agents (e.g. tranexamic acid and its precursors) versus no treatment, placebo, or any other medical (non-surgical) therapy. We excluded studies that used combined treatments (e.g. a LIUS with concurrent oral TXA)

Endpunkte:

- Menstrual blood loss (MBL) (primärer Endpunkt), QoL, adverse events

Recherche/Suchzeitraum:

- Cochrane Gynaecology and Fertility (CGF) Group trials register, CENTRAL, MEDLINE, Embase, PsycINFO and 2 trials registers in November 2017.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

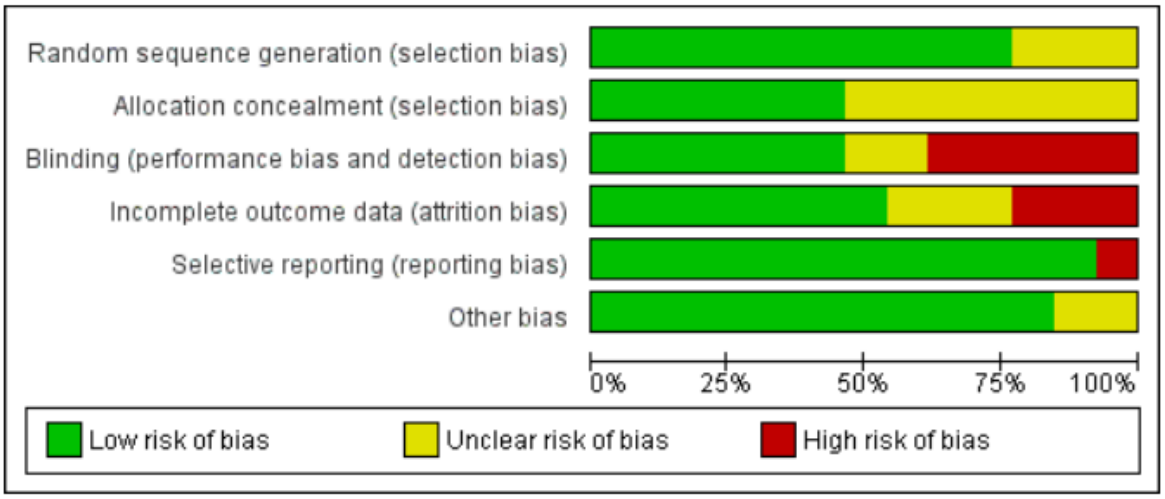
- 13 RCTs (1312 participants analysed)

Charakteristika der Population:

- The studies (1312 participants) included 582 women in the control (non-antifibrinolytic) groups and 778 in the intervention (i.e. tranexamic acid) groups. Their age ranged across studies from 15 to 50 years
- (…) Fathima 2012 included women with leiomyomata. Goshtasebi 2013 and Kriplani 2006 excluded women found to have uterine leiomyomata, whilst Freeman 2011 and Lukes 2010 only excluded women with fibroids thought to warrant surgical management. Goshtasebi 2015 excluded women with fibroids greater than 3 cm in diameter, and Kiseli 2016 excluded women with fibroids that were greater than 2 cm or indented the uterine cavity on ultrasound. (…)

Qualität der Studien:

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Studienergebnisse:

- Antifibrinolytics (TXA or Kabi) versus no treatment or placebo
  - When compared with a placebo, antifibrinolytics were associated with reduced mean blood loss (MD −53.20 mL per cycle, 95% CI −62.70 to −43.70; I2 = 8%; 4 RCTs, participants = 565; moderate-quality evidence) and higher rates of improvement (RR 3.34, 95% CI 1.84 to 6.09; 3 RCTS, participants = 271; moderate-quality evidence). This suggests that if 11% of women improve without treatment, 43% to 63% of TXA was associated with reduced mean blood loss (MD −73.00 mL per cycle, 95% CI −123.35 to −22.65; 1 RCT, participants = 49; low-quality evidence) and higher likelihood of improvement (RR 1.43, 95% CI 1.18 to 1.74; 12 = 0%; 2 RCTs, participants = 161; low-quality evidence). This suggests that if 61% of women improve with NSAIDs, 71% to 100% of women will do so with TXA. Adverse events were uncommon and no comparative data were available. No thromboembolic events were reported.
- TXA versus ethamsylate
  - TXA was associated with reduced mean blood loss (MD 100 mL per cycle, 95% CI −141.82 to −58.18; 1 RCT, participants = 53; low-quality evidence), but there was insufficient evidence to determine whether the groups differed in rates of improvement (RR 1.56, 95% CI 0.95 to 2.55; 1 RCT, participants = 53; very low quality evidence) or withdrawal due to adverse events (RR 0.78, 95% CI 0.19 to 3.15; 1 RCT, participants = 53; very low quality evidence).
- TXA versus herbal medicines (Safoof Habis and Punica granatum)
  - TXA was associated with a reduced mean PBAC score after three months' treatment (MD −23.90 pts per cycle, 95% CI −31.92 to −15.88; I2 = 0%; 2 RCTs, participants = 121; low-quality evidence). No data were available for rates of improvement. TXA was associated with a reduced mean PBAC score three months after the end of the treatment phase (MD −10.40 points per cycle, 95% CI −19.20 to −1.60; I2 not applicable; 1 RCT, participants = 84; very low quality evidence). There was insufficient evidence to determine whether the groups differed in rates of adverse events (RR 2.25, 95% CI 0.74 to 6.80; 1 RCT, participants = 94; very low quality evidence). No thromboembolic events were reported.
- TXA versus levonorgestrel intrauterine system (LIUS)

- TXA was associated with a higher median PBAC score than LIUS (median difference 125.5 points; 1 RCT, participants = 42; very low quality evidence) and a lower likelihood of improvement (RR 0.43, 95% CI 0.24 to 0.77; 1 RCT, participants = 42; very low quality evidence). This suggests that if 85% of women improve with LIUS, 20% to 65% of women will do so with TXA. There was insufficient evidence to determine whether the groups differed in rates of adverse events (RR 0.83, 95% CI 0.25 to 2.80; 1 RCT, participants = 42; very low quality evidence). No thromboembolic events were reported.

Anmerkung/Fazit der Autoren

Antifibrinolytic treatment (such as TXA) appears effective for treating HMB compared to placebo, NSAIDs, oral luteal progestogens, ethamsylate, or herbal remedies, but may be less effective than LIUS. There were too few data for most comparisons to determine whether antifibrinolytics were associated with increased risk of adverse events, and most studies did not specifically include thromboembolism as an outcome.

3.2 Systematische Reviews

Ghonim M et al., 2019 [3].

A systematic review and meta-analysis of ulipristal acetate for symptomatic uterine fibroids.

Fragestellung

To assess the effectiveness of UPA in women with symptomatic uterine fibroids.

Methodik

Population:

- women of reproductive age with symptomatic uterine fibroids

Intervention:

- UPA

Komparator:

- placebo/no treatment/any pharmacological intervention

Endpunkte:

- Amenorrhea, Uterine Fibroid Symptom and Quality of Life (UFSQOL) assessment: symptom severity, control of heavy menstrual blood loss, and adverse events including endometrial changes

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE, EMBASE, and CINHAL on December 31, 2018

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- six RCTs (1121 participants)

Charakteristika der Population:

- All studies included women of reproductive age (ranging from 18 to 50 years), who had symptomatic fibroids (menorrhagia, pelvic pressure).

Qualität der Studien:

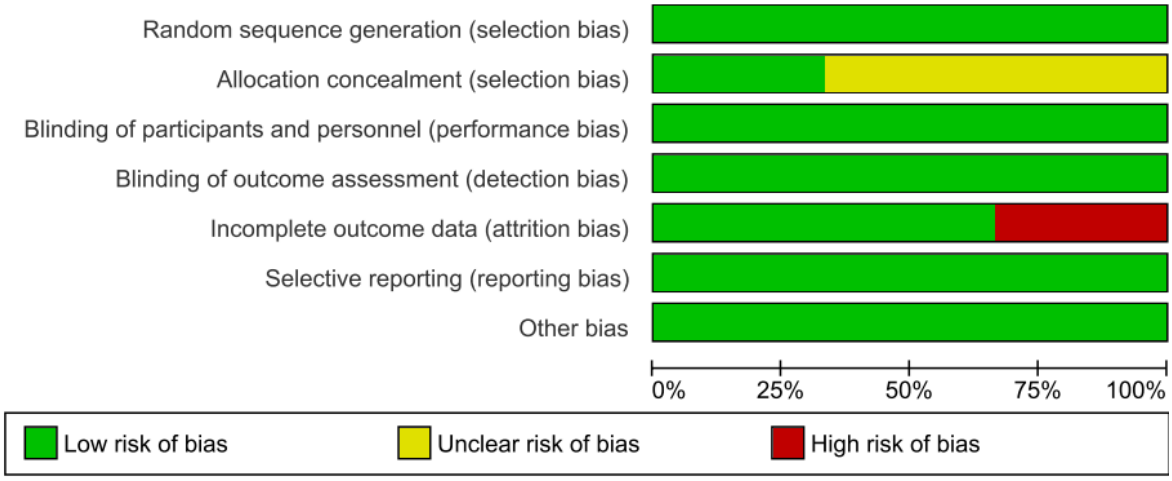


FIGURE 3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Studienergebnisse:

- Five studies (882 participants) compared UPA with placebo. UPA significantly achieved amenorrhea (RR 24.54; 95% CI, 10.82–55.64), reduced blood loss, and improved quality of life with insufficient evidence from RCTs for adverse events.
- There was insufficient evidence for improved outcomes when UPA was compared with leuprolide acetate.

Anmerkung/Fazit der Autoren

In conclusion, evidence suggests that a 3- month treatment with oral UPA, compared with placebo, induces amenorrhea, improves fibroid- related symptom severity, and controls heavy menstrual bleeding. There is low- certainty evidence about undesirable effects and there is still insufficient evidence regarding UPA versus leuprolide acetate.

Kommentare zum Review

Es liegt ein weiterer SR zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Kounidas et al., 2021 [4]

3.3 Leitlinien

NICE, 2018 [7].

National Institute for Health and Care Excellence (NICE)

Heavy menstrual bleeding: assessment and management

Zielsetzung/Fragestellung

This guideline covers assessing and managing heavy menstrual bleeding (menorrhagia).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- In May 2021 we reviewed this guideline and reinstated recommendations on ulipristal acetate (Esmya) for uterine fibroids, including measures to mitigate the risk of serious liver injury.
- March 2020: In response to updated MHRA advice on the use of ulipristal acetate (Esmya) to say that healthcare professionals should contact patients currently taking Esmya for uterine fibroids as soon as possible and advise them to stop their treatment, we have amended recommendations 1.5.10, 1.5.13 and 1.5.17 and withdrawn recommendations 1.5.11 and 1.5.12. These recommendations may be reinstated or amended again at a later date depending on the outcome of the safety review now in progress.
- These recommendations are marked as [2007, amended 2020] if the evidence was reviewed in 2007, or [2018, amended 2020] if the evidence was reviewed in 2018.
- March 2018: This guideline is an update of NICE guideline CG44 (published January 2007) and replaces it.

LoE/GoR

- GRADE & Empfehlungen anhand ,,Formulierungen‘‘

Sonstige methodische Hinweise

- This guideline replaces CG44.
- This guideline is the basis of QS47.

Recommendations:

Women with suspected submucosal fibroids, polyps or endometrial pathology

- 1.3.4 Offer outpatient hysteroscopy to women with HMB if their history suggests submucosal fibroids, polyps or endometrial pathology because:
  - they have symptoms such as persistent intermenstrual bleeding or
  - they have risk factors for endometrial pathology (see recommendation 1.3.10). [2018]
- 1.3.5 Ensure that outpatient hysteroscopy services are organised and the procedure is performed according to best practice, including:
  - advising women to take oral analgesia before the procedure
  - vaginoscopy as the standard diagnostic technique, using miniature hysteroscopes (3.5 mm or smaller). [2018]
- 1.3.6 Ensure that hysteroscopy services are organised to enable progression to 'see-and-treat' hysteroscopy in a single setting if feasible. [2018]
- 1.3.7 Explain to women with HMB who are offered outpatient hysteroscopy what the procedure involves and discuss the possible alternatives. [2018]
- 1.3.8 If a woman declines outpatient hysteroscopy, offer hysteroscopy under general or regional anaesthesia. [2018]
- 1.3.9 For women who decline hysteroscopy, consider pelvic ultrasound, explaining the limitations of this technique for detecting uterine cavity causes of HMB. [2018]
- 1.3.10 Consider endometrial biopsy at the time of hysteroscopy for women who are at high risk of endometrial pathology, such as:
  - women with persistent intermenstrual or persistent irregular bleeding, and women with infrequent heavy bleeding who are obese or have polycystic ovary syndrome
  - women taking tamoxifen
  - women for whom treatment for HMB has been unsuccessful. [2007, amended 2018]
- 1.3.11 Obtain an endometrial sample only in the context of diagnostic hysteroscopy. Do not offer 'blind' endometrial biopsy to women with HMB. [2018]

Women with possible larger fibroids

- 1.3.12 Offer pelvic ultrasound to women with HMB if any of the following apply:
  - their uterus is palpable abdominally
  - history or examination suggests a pelvic mass
  - examination is inconclusive or difficult, for example in women who are obese. [2018]

(…)

1.4 Information for women about HMB and treatments

- 1.4.1 Provide women with information about HMB and its management. Follow the principles in the NICE guidelines on patient experience in adult NHS services and shared decision making in relation to communication, information and shared decision-making. [2018]
- 1.4.2 Provide information about all possible treatment options for HMB and discuss these with the woman (see section 1.5). Discussions should cover:
  - the benefits and risks of the various options
  - suitable treatments if she is trying to conceive
  - whether she wants to retain her fertility and/or her uterus. [2018]

Levonorgestrel-releasing intrauterine system (LNG-IUS)

- 1.4.3 Explain to women who are offered an LNG-IUS:
  - about anticipated changes in bleeding pattern, particularly in the first few cycles and maybe lasting longer than 6 months
  - that it is advisable to wait for at least 6 cycles to see the benefits of the treatment. [2007]
- Note that this is an off-label use for some LNG-IUSs.

Impact of treatments on fertility

- 1.4.4 Explain to women about the impact on fertility that any planned surgery or uterine artery embolisation may have, and if a potential treatment (hysterectomy or ablation) involves loss of fertility then opportunities for discussion should be made available. [2007]
- 1.4.5 Explain to women that uterine artery embolisation or myomectomy may potentially allow them to retain their fertility. [2007]

Endometrial ablation

- 1.4.6 Advise women to avoid subsequent pregnancy and use effective contraception, if needed, after endometrial ablation. [2007]

Hysterectomy

- 1.4.7 Have a full discussion with all women who are considering hysterectomy about the implications of surgery before a decision is made. The discussion should include:
  - sexual feelings
  - impact on fertility
  - bladder function
  - need for further treatment
  - treatment complications
  - her expectations
  - alternative surgery
  - psychological impact. [2007]
- 1.4.8 Inform women about the increased risk of serious complications (such as intraoperative haemorrhage or damage to other abdominal organs) associated with hysterectomy when uterine fibroids are present. [2007]
- 1.4.9 Inform women about the risk of possible loss of ovarian function and its consequences, even if their ovaries are retained during hysterectomy. [2007]

1.5 Management of HMB

- 1.5.1 When agreeing treatment options for HMB with women, take into account:
  - the woman's preferences
  - any comorbidities
  - the presence or absence of fibroids (including size, number and location), polyps, endometrial pathology or adenomyosis
  - other symptoms such as pressure and pain. [2018]

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

- 1.5.2 Consider an LNG-IUS as the first treatment for HMB in women with:

  - no identified pathology or
  - fibroids less than 3 cm in diameter, which are not causing distortion of the uterine cavity or
  - suspected or diagnosed adenomyosis. [2018] Note that this is an off-label use for some LNG-IUSs.
- 1.5.3 If a woman with HMB declines an LNG-IUS or it is not suitable, consider the following pharmacological treatments:
  - non-hormonal:
    - tranexamic acid
    - NSAIDs (non-steroidal anti-inflammatory drugs)
  - hormonal:
    - combined hormonal contraception
    - cyclical oral progestogens. [2018] Note that this is an off-label use for NSAIDs and some combined hormonal contraceptives.
- 1.5.4 Be aware that progestogen-only contraception may suppress menstruation, which could be beneficial to women with HMB. [2018]
- 1.5.5 If treatment is unsuccessful, the woman declines pharmacological treatment, or symptoms are severe, consider referral to specialist care for:
  - investigations to diagnose the cause of HMB, if needed (see section 1.3) taking into account any investigations the woman has already had and
  - alternative treatment choices, including:
    - pharmacological options not already tried (see recommendations 1.5.2 and 1.5.3)
    - surgical options:
      - second-generation endometrial ablation
      - hysterectomy. [2018]
- 1.5.6 For women with submucosal fibroids, consider hysteroscopic removal. [2018]

<u>Treatments for women with fibroids of 3 cm or more in diameter</u>

- 1.5.7 Consider referring women to specialist care to undertake additional investigations and discuss treatment options for fibroids of 3 cm or more in diameter. [2018]
- 1.5.8 If pharmacological treatment is needed while investigations and definitive treatment are being organised, offer tranexamic acid and/or NSAIDs. [2007] Note that this is an off-label use for NSAIDs.
- 1.5.9 Advise women to continue using NSAIDs and/or tranexamic acid for as long as they are found to be beneficial. [2007] Note that this is an off-label use for NSAIDs.
- 1.5.10 For women with fibroids of 3 cm or more in diameter, take into account the size, location and number of fibroids, and the severity of the symptoms and consider the following treatments:
  - pharmacological:
    - non-hormonal:
      - tranexamic acid
      - NSAIDs
    - hormonal:
      - LNG-IUS

- combined hormonal contraception
- cyclical oral progestogens
- ulipristal acetate (this is only indicated for some premenopausal women; see recommendations 1.5.11 and 1.5.12 for more information) [amended 2021]

- uterine artery embolisation for fibroids
- surgical:
  - myomectomy
  - hysterectomy.

Note that this is an off-label use for NSAIDs and some LNG-IUSs. [2018]

- 1.5.11 Only think about ulipristal acetate for the intermittent treatment of moderate to severe symptoms of uterine fibroids in premenopausal women if:
  - surgery and uterine artery embolisation for fibroids are not suitable, for example, because the risks to a woman outweigh the possible benefits, or
  - surgery and uterine artery embolisation for fibroids have failed, or
  - the woman declines surgery and uterine artery embolisation for fibroids. [2021]
- 1.5.12 Discuss with the woman the risks and possible benefits of intermittent treatment with ulipristal acetate.
  - Advise that ulipristal acetate can be associated with serious liver injury leading to liver failure, and the signs and symptoms to look out for.
  - Measure liver function before starting ulipristal acetate, monthly for the first 2 courses and once before each new treatment course when clinically indicated.
  - If there is no underlying liver injury, and surgery and uterine artery embolisation for fibroids are unsuitable or have failed, consider ulipristal acetate 5 mg (up to 4 courses) for premenopausal women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, particularly if the haemoglobin level is 102 g per litre or below.
  - If a woman shows signs and symptoms of liver failure, stop ulipristal acetate and perform liver function tests urgently. [2021]
- 1.5.13 Be aware that the effectiveness of pharmacological treatments for HMB may be limited in women with fibroids that are substantially greater than 3 cm in diameter. [2018, amended 2020]
- 1.5.14 Prior to scheduling of uterine artery embolisation or myomectomy, the woman's uterus and fibroid(s) should be assessed by ultrasound. If further information about fibroid position, size, number and vascularity is needed, MRI should be considered. [2007]
- 1.5.15 Consider second-generation endometrial ablation as a treatment option for women with HMB and fibroids of 3 cm or more in diameter who meet the criteria specified in the manufacturers' instructions. [2018]
- 1.5.16 If treatment is unsuccessful:
  - consider further investigations to reassess the cause of HMB (see section 1.3), taking into account the results of previous investigations and
  - offer alternative treatment with a choice of the options described in recommendation 1.5.10. [2018]
- 1.5.17 Pretreatment with a gonadotrophin-releasing hormone analogue before hysterectomy and myomectomy should be considered if uterine fibroids are causing an

enlarged or distorted uterus. [2007, amended 2020] Note that this is an off-label use for some gonadotrophin-releasing hormone analogues.

Laberge PY et al., 2019 [5].

Guideline No. 389-Medical Management of Symptomatic Uterine Leiomyomas - An Addendum.

Zielsetzung/Fragestellung

The aim of this guideline is to provide clinicians with an update to the 2015 Clinical Practice Guideline on the Management of Uterine Fibroids.

Methodik

Die Leitlinie erfüllt nicht vollständig die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, zur Fragestellung von jeglichen Symptomen aufgrund von Gebärmuttermyomen, wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

Repräsentatives Gremium: unklar

Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: unklar

Systematische Suche, Auswahl und Bewertung der Evidenz;

Formale Konsensusprozesse und externes Begutachtungsverfahren unklar;

Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Published literature was retrieved through searches of PubMed, CINAHL, and Cochrane Systematic Reviews in February 2015 to April 2018

LoE/ GoR

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment[a]	Classification of Recommendations[b]
I: Evidence obtained from at least 1 properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action.
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than 1 centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision making.
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category.	D. There is fair evidence to recommend against the clinical preventive action.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action.
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making.

[a] The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

[b] Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in The Canadian Task Force on Preventive Health Care.

Recommendations

CHANGE IN PRACTICE

1. Prolonged medical management of fibroid symptoms is safe and effective.
2. Women treated with ulipristal acetate should undergo liver monitoring.
3. Attempts should be made to correct anemia (hemoglobin <120) prior to elective gynaecologic surgery.

KEY MESSAGES

1. Prolonged treatment with ulipristal acetate is efficacious and safe.
2. Women treated with ulipristal acetate should undergo liver enzyme monitoring.
3. Gonadotropin-releasing hormone agonists decrease fibroid size, improve anemia, and reduce blood transfusions.

Recommendations :

1. Prolonged intermittent administration of selective progesterone receptor modulators can be used to treat fibroid-related symptoms and is generally safe, well tolerated, and efficacious (I-B).
2. Women treated with ulipristal acetate should be screened for risk of liver impairment prior to commencing therapy and undergo liver enzyme monitoring monthly during treatment courses and 2 to 4 weeks following completion of the course of therapy. Physicians should be aware of the signs and symptoms of liver failure, and patients should be apprised of the symptoms of liver failure (III-C).
3. Gonadotropin-releasing hormone agonists have been shown to decrease fibroid size, improve anemia, and reduce the probability of perioperative blood transfusions (I-A).
4. Preoperative anemia (hemoglobin <120 g/dL) prior to elective gynaecologic surgery has been associated with adverse outcomes. Attempts should be made to correct anemia with menstrual suppression and/or iron therapy (II-A).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2022) am 02.06.2022

#	Suchfrage
1	[mh leiomyoma]
2	(leiomyoma* OR fibroid* OR fibromyoma* OR fibroleiomyoma*):ti,ab,kw
3	[mh myoma]
4	(myom* OR adenomyom* OR fibroma*):ti,ab,kw
5	#3 OR #4
6	[mh uterus]
7	(uterus OR uteri* OR cervic* OR cervix* OR intramural* OR subserosa* OR submucosa*):ti,ab,kw
8	#6 OR #7
9	#5 AND #8
10	[mh menorrhagia]
11	(Menorrhagia* OR (Heavy NEXT Menstrual NEXT Bleeding*) OR (Heavy NEXT Period*) OR Hypermenorrhea*):ti,ab,kw
12	[mh Dysmenorrhea]
13	(Dysmenorrhea* OR (pain* NEAR/3 menstruat*)):ti,ab,kw
14	#1 OR #2 OR #9 OR #10 OR #11 OR #12 OR #13
15	#14 with Cochrane Library publication date Between Jun 2017 and Jun 2022

Systematic Reviews in PubMed am 02.06.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	leiomyoma[MeSH Terms]
2	leiomyoma*[Title/Abstract] OR fibroid*[Title/Abstract] OR fibromyoma*[Title/Abstract] OR fibroleiomyoma*[Title/Abstract]
3	myoma[MeSH Terms]
4	myom*[Title/Abstract] OR adenomyom*[Title/Abstract] OR fibroma*[Title/Abstract]
5	#3 OR #4
6	uterus[MeSH Terms]
7	uterus[Title/Abstract] OR uteri*[Title/Abstract] OR cervic*[Title/Abstract] OR cervix*[Title/Abstract] OR intramural*[Title/Abstract] OR subserosa*[Title/Abstract] OR submucosa*[Title/Abstract]
8	#6 OR #7
9	#5 AND #8
10	#1 OR #2 OR #9

#	Suchfrage
11	(#10) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
12	(#11) AND ("2017/06/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 02.06.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	leiomyoma[MeSH Terms]
2	leiomyoma*[Title/Abstract] OR fibroid*[Title/Abstract] OR fibromyoma*[Title/Abstract] OR fibroleiomyoma*[Title/Abstract]
3	myoma[MeSH Terms]

#	Suchfrage
4	myom*[Title/Abstract] OR adenomyom*[Title/Abstract] OR fibroma*[Title/Abstract]
5	#3 OR #4
6	uterus[MeSH Terms]
7	uterus[Title/Abstract] OR uteri*[Title/Abstract] OR cervic*[Title/Abstract] OR cervix*[Title/Abstract] OR intramural*[Title/Abstract] OR subserosa*[Title/Abstract] OR submucosa*[Title/Abstract]
8	#6 OR #7
9	#5 AND #8
10	(menorrhagia[MeSH Terms]) OR (dysmenorrhea[MeSH Terms])
11	menorrhagia*[Title/Abstract] OR (heavy[Title/Abstract] AND menstrual[Title/Abstract] AND bleeding*[Title/Abstract]) OR heavy period*[Title/Abstract] OR hypermenorrhea*[Title/Abstract] OR dysmenorrhea*[Title/Abstract] OR (menstruat*[Title/Abstract] AND pain*[Title/Abstract])
12	#1 OR #2 OR #9 OR #10 OR #11
13	(#12) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
14	(#13) AND ("2017/06/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 02.06.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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2. **Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M.** Antifibrinolytics for heavy menstrual bleeding. Cochrane Database of Systematic Reviews [online]. 2018(4):Cd000249. URL: http://dx.doi.org/10.1002/14651858.CD000249.pub2.
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5. **Laberge PY, Murji A, Vilos GA, Allaire C, Leyland N, Sony S.** Guideline no. 389; medical management of symptomatic uterine leiomyomas: an addendum. J Obstet Gynaecol Can 2019;41(10):1525-1528.
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[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2022-B-232

Kontaktdaten

Bundesärztekammer, Bereich Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 06.10.2022

Indikation gemäß Beratungsantrag

…wird angewendet bei erwachsenen Frauen im gebärfähigen Alter zur Behandlung mäßiger bis starker Symptome von Uterusmyomen.

Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zunächst sollte definiert werden, welche Symptome bei Vorliegen von Myomen gemeint sind – am häufigsten treten wohl Blutungsstörungen auf im Sinne von Menorrhagien, oft deutlich anämisierend. Als Symptome können aber auch Schmerzen, Sterilität, Defäkationsstörungen o. Ä. je nach Anzahl, Lage und Größe von Myomen auftreten. Letztere Symptome sind allerdings nicht intermittierend (1;2).

Die Fragestellung „mäßige bis starke Symptome“ ist wenig spezifiziert und so auch nur sehr allgemein zu beantworten.

Die Fragestellung oben definiert die potenzielle Einsatzpopulation: Frauen im gebärfähigen Alter, sodass man potenziellen Kinderwunsch unterstellen darf und somit definitive operative Maßnahmen wie z. B. Hysterektomie oder andere ausgedehnte operative Eingriffe keine Option sind (3;4).

Zur Therapie sind medikamentöse, radiologische, operative und kurzfristig symptomatische Ansätze zu unterscheiden (5).

Die medikamentösen Möglichkeiten werden u. a. bei Blutungsstörungen (6) oder zur Schrumpfung von Myomen vor operativen Eingriffen (3) genutzt und umfassen:

- GnRH-Agonisten zur Blutungsreduktion, Schrumpfung der Myome (Einsatzdauer eher kurzfristig; vor OP),
- Relugolix/Estradiol/Norethisteronacetat (Blutungsreduktion und deutlich weniger stark auch Schrumpfung, kann längerfristig eingesetzt werden (7)),
- Progesteronrezeptorantagonist Ulipristalacetat (UPA; Blutungsreduktion und Schrumpfung – nach Rote-Hand-Brief (8) stark eingeschränkte Indikation/eingeschränktes Patientinnen-Klientel). Die Nutzung der medikamentösen Option UPA ist seit der Veröffentlichung der gefährlichen Nebenwirkungen im Rote-Hand-Brief stark zurückgegangen und erfordert bei gewünschter Nutzung eine aufwendige Aufklärung und Kontrolle.

Und sonstige:

- KOK-Therapie (Blutungsreduktion, Off-Label-Use in Bezug auf Myomtherapie)
- Gestagentherapie mit z. B. Chlormadinon (Blutungsreduktion, Off-Label-Use in Bezug auf Myomtherapie)
- LNG-IUD (Blutungsreduktion, Off-Label-Use in Bezug auf Myomtherapie)
- Tranexamsäure (deutlich Blutungsreduktion, Off-Label-Use in Bezug auf Myomtherapie)
- Ibuprofen (Schmerz- und Blutungsreduktion, Off-Label-Use in Bezug auf Myomtherapie)

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Radiologisch sind Embolisations- und fokussierte Ultraschallverfahren im Einsatz, die allerdings bei Frauen mit Kinderwunsch sehr zurückhaltend anzuwenden sind (9-11).

Operativ reichen die Möglichkeiten von organerhaltenden hysteroskopischen, laparaskopischen bis hin zu offenen Verfahren, wie der Entfernung von Myomen (3). Die teils sehr aufwendigen Operationen können zu deutlichem Blutverlust führen, sind allerdings von langfristigem Erfolg.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*wörtliches Zitat aus Antrag pU***“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Neben der Einschätzung von Symptomstärke, die bei Vorliegen einer Hypermenorrhö mit Anämie sicher leichter fällt als bei Vorliegen von Schmerzen oder Defäkationsbeschwerden, sind für die Wahl einer Therapie zu berücksichtigen:

- Alter der Patientin und Parität (und Frage nach aktuellem Kinderwunsch: aktuell, später, abgeschlossen oder gar nicht),
- Art der Symptome (Blutungsstörung, Schmerz u. a.),
- ob erstmalige Therapie oder Scheitern einer Vortherapie vorliegen,
- Lage, Anzahl und Größe von Myomen,
- Begleiterkrankungen.

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Indikation gemäß Beratungsantrag

…wird angewendet bei erwachsenen Frauen im gebärfähigen Alter zur Behandlung mäßiger bis starker Symptome von Uterusmyomen.

Literatur

1. Römer T, Doubek K, Foth D et al.: Symptomatischer Uterus myomatosus – zielgerichtete medikamentöse Therapie. Frauenarzt 2017; 58: 497-503.
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Die S3-Leitlinie zur Diagnostik und Therapie von benignen Erkrankungen der Gebärmutter ist unter der Register-Nr. 015-093 aktuell in Bearbeitung und wird für den 31.12.2023 erwartet (12).