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: 2020-B-330 Relugolix / Estradiol / Norethisteronacetat

Stand: Dezember 2020

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

Relugolix / Estradiol / Norethisteronacetat
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 Es liegen keine Beschlüsse über die Nutzenbewertung von Arzneimitteln nach §35a SGB V vor.
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:	
Relugolix / Estradiol / Norethisteron-acetat H01CC54 Ryeqo®	Ryeqo 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.).*
Progesteron-Rezeptor-Antagonisten	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Ulipristalacetat G03XB02 Esmya®	Ulipristalacetat ist indiziert für ein Behandlungsintervall zur präoperativen Behandlung mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter, für die eine Operation vorgesehen ist. Ulipristalacetat ist indiziert zur Intervall-Therapie mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter, für die eine Operation nicht infrage kommt (Stand FI: Juli 2018) *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):* *[…] 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: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-330 (Relugolix/Estradiol/NETA)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	30. Oktober 2020

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

Behandlung der Symptome durch Gebärmutter-Myome.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Gebärmutter-Myome* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.09.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 416 Quellen. 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 Quellen 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 12 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2001 [5].

Zusammenfassender Bericht des Arbeitsausschusses "Ärztliche Behandlung" des Bundesausschusses der Ärzte und Krankenkassen über die Beratungen gemäß §135 Abs.1 SGB V: Uterus-Ballon-Therapie.

Fazit

Antragsstellung: Gemäß 2.2. der Verfahrensrichtlinie ist zur Beratung nach § 135 Abs. 1 SGB V ein Antrag der Kassenärztlichen Bundesvereinigung, einer Kassenärztlichen Vereinigung oder eines Spitzenverbandes der Krankenkassen im Arbeitsausschuss zu stellen.

Die Beratung der Behandlungsmethode Uterus-Ballon-Therapie geht zurück auf einen Antrag der Spitzenverbände der Krankenkassen. Der ordnungsgemäße Beratungsantrag und die Begründung zu diesem Antrag wurden in der 22. Sitzung des Arbeitsausschusses „Ärztliche Behandlung“ am 23.09.1999 vom Vorsitzenden der Krankenkassenseite schriftlich in den Ausschuss eingebracht.

Zusammenfassende Bewertung

Chronische Blutungsstörungen bedeuten erhebliche Einschränkungen sowohl der Leistungsfähigkeit als auch der Lebensqualität der betroffenen Frauen.

Zur Behandlung dieser Blutungsstörungen werden deshalb im Rahmen der Vertragsärztlichen Versorgung verschiedene konservative (in der Regel medikamentöse), minimal-invasive und andere operative Behandlungsmethoden vorgehalten.

Für einen Teil dieser Patientinnen kann nach erfolgloser konservativer Therapie die Verödung oder Abtragung der Gebärmutterschleimhaut die geeignete Therapieform darstellen, um die Blutungsstärke und –häufigkeit zu reduzieren. Hierfür stehen mit der hysteroskopischen Schleimhautverödung oder hysteroskopischen Schleimhautabtragung bewährte Therapien zur Verfügung, die derzeit als der Goldstandard in diesem Bereich angesehen werden und zum Leistungsumfang der Vertragsärztlichen Versorgung gehören. Die Gebärmutter bleibt dabei als Organ erhalten und eine Gebärmutterentfernung kann so ggf. vermieden werden.

Das gleiche therapeutische Ziel verfolgen neuere Therapieformen wie die Uterus-Ballon-Therapie. Bisher konnte eine therapeutische Überlegenheit gegenüber den zur Verfügung stehenden, oben genannten, minimal-invasiven Verfahren nicht belegt werden.

Da etablierte Standardtherapien zur Verfügung stehen, die ebenso wie die UBT die Gebärmutterentfernung vermeiden, wird die medizinische Notwendigkeit für die zusätzliche Einführung dieser Therapieform nicht festgestellt. Hinsichtlich ihres Nutzens erreicht die UBT etwa die gleichen Behandlungsergebnisse wie die etablierten Standardverfahren.

Allerdings verursacht die UBT gegenüber den hysteroskopischen Verfahren deutlich höhere Kosten infolge der finanzaufwendigen Einwegmaterialien. Der Arbeitsausschuss kommt deshalb zu dem Fazit, dass bei fehlendem überlegenem Nutzen und höherem Kostenaufwand eine zusätzliche Einführung dieser Behandlungsmethode in die vertragsärztliche Versorgung gegenwärtig nicht begründet ist.

3.2 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)

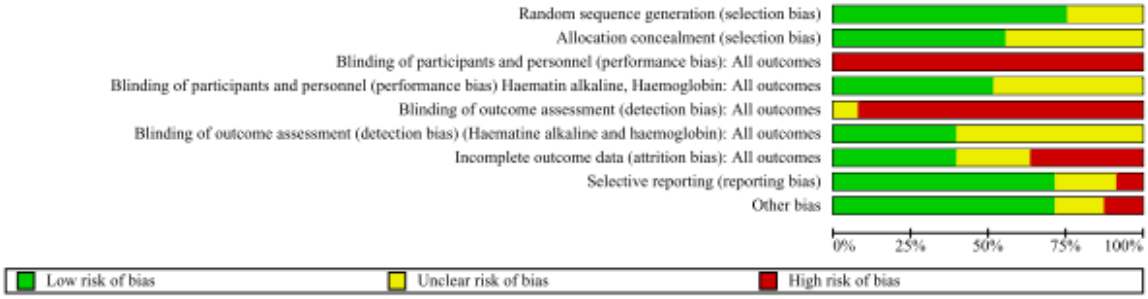
Charakteristika der Population:

- 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.

Lethaby A et al., 2019 [9].

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:

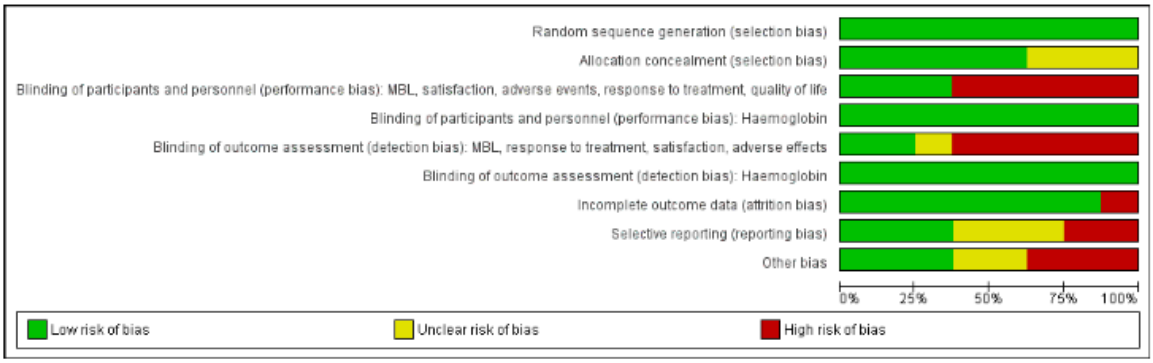
- Eight studies with 805 participants were included in this update of the review.

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)

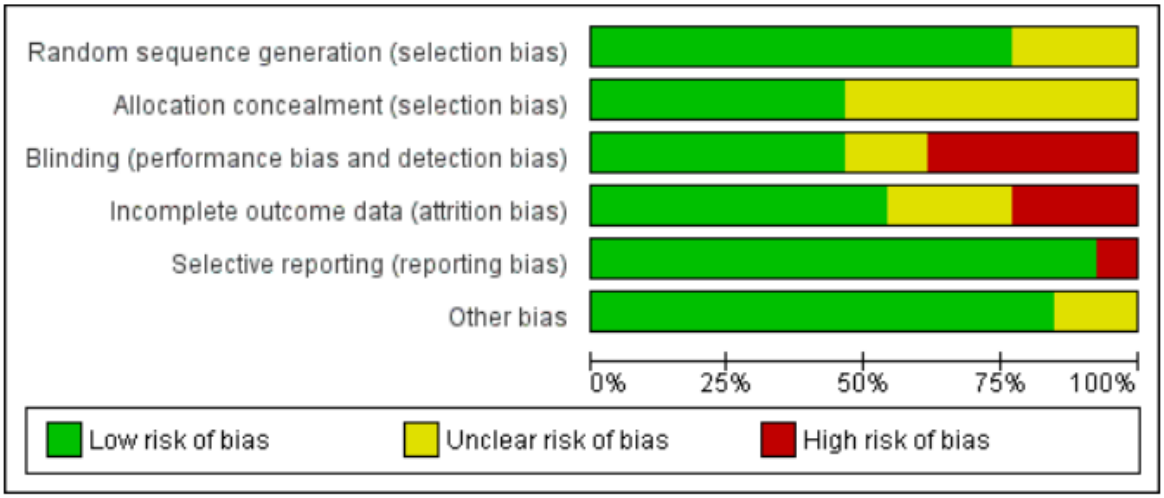
Charakteristika der Population:

- 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.

Murji A et al., 2017 [10].

Selective progesterone receptor modulators (SPRMs) for uterine fibroids.

Fragestellung

To evaluate the effectiveness and safety of SPRMs for treatment of premenopausal women with uterine fibroids.

Methodik

Population:

- Premenopausal women with uterine fibroids, with or without symptoms. The presence of fibroids was confirmed surgically (laparoscopy, laparotomy or hysteroscopy) or through at least one of the following imaging modalities: ultrasonography, computed tomography or magnetic resonance imaging (MRI).

Intervention/Komparator:

- Treatment with any SPRM for at least three months versus:
  - placebo; no treatment; another medical therapy (another SPRM, a GnRHa or another class of medication); surgery (myomectomy or hysterectomy); or uterine artery embolisation (UAE)

Endpunkte:

- Change in fibroid-related symptoms: QoL, Abnormal uterine bleeding, Pain and pelvic pressure, Change in fibroid or uterine size, SPRM-related effects

Recherche/Suchzeitraum:

- Cochrane Gynaecology and Fertility Group, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and clinical trials registries from database inception to May 2016.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

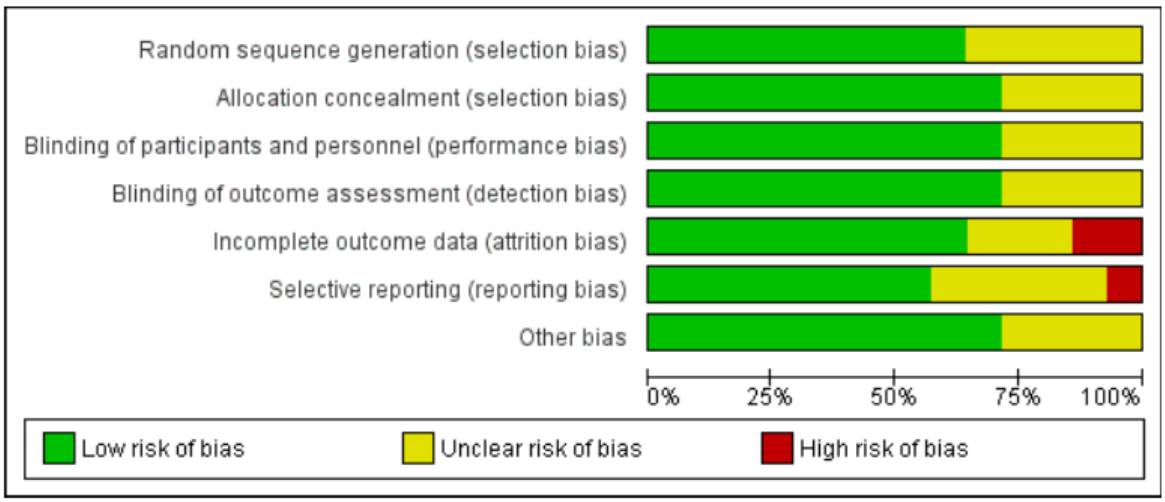
- 14 RCTs with a total of 1215 study participants
- We could not extract complete data from three studies. We included in the meta-analysis 11 studies involving 1021 study participants: 685 received SPRMs and 336 were given a control intervention (placebo or leuprolide).
- Investigators evaluated three SPRMs: mifepristone (five studies), ulipristal acetate (four studies) and asoprisnil (two studies).

Charakteristika der Population:

- (…) All studies, with one exception, included only patients with symptomatic fibroids. In Chwalisz 2007, although participants were not expected to be symptomatic at baseline, most of them experienced symptoms (76% had abnormal uterine bleeding and 94% had bulk symptoms). Three studies scheduled participants for surgery for their symptomatic fibroids (Engman 2009; Esteve 2013; Wilkens 2008). (…)

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:

- SPRM versus placebo
  - SPRM treatment resulted in improvements in fibroid symptom severity (MD -20.04 points, 95% confidence interval (CI) -26.63 to -13.46; four RCTs, 171 women, I2 = 0%; moderate-quality evidence) and health-related quality of life (MD 22.52 points, 95% CI 12.87 to 32.17; four RCTs, 200 women, I2 = 63%; moderate-quality evidence) on the Uterine Fibroid Symptom Quality of Life Scale (UFS-QoL, scale 0 to 100). Women treated with an SPRM showed reduced menstrual blood loss on patient-reported bleeding scales, although this effect was small (SMD -1.11, 95% CI -1.38 to -0.83; three RCTs, 310 women, I2 = 0%; moderate-quality evidence), along with higher rates of amenorrhoea (29 per 1000 in the placebo group vs 237 to 961 per 1000 in the SPRM group; OR 82.50, 95% CI 37.01 to 183.90; seven RCTs, 590 women, I2 = 0%; moderate-quality evidence), compared with those given placebo.
  - We could draw no conclusions regarding changes in pelvic pain owing to variability in the estimates. With respect to adverse effects, SPRM-associated endometrial changes were more common after SPRM therapy than after placebo (OR 15.12, 95% CI 6.45 to 35.47; five RCTs, 405 women, I2 = 0%; low-quality evidence).
- SPRM versus leuprolide acetate
  - In comparing SPRM versus other treatments, two RCTs evaluated SPRM versus leuprolide acetate. One RCT reported primary outcomes. No evidence suggested a difference between SPRM and leuprolide groups for improvement in quality of life, as measured by UFS-QoL fibroid symptom severity scores (MD -3.70 points, 95% CI -9.85 to 2.45; one RCT, 281 women; moderate-quality evidence) and health-related quality of life scores (MD 1.06 points, 95% CI -5.73 to 7.85; one RCT, 281 women; moderate-quality evidence). It was unclear whether results showed a difference between SPRM and leuprolide groups for reduction in menstrual blood loss based on the pictorial blood loss assessment chart (PBAC), as confidence intervals were wide (MD 6 points, 95% CI -40.95 to 50.95; one RCT, 281 women; low-quality evidence), or for rates of amenorrhoea (804 per 1000 in the placebo group vs 732 to 933 per 1000 in the SPRM group; OR 1.14, 95% CI 0.60 to 2.16; one RCT, 280 women; moderate-quality evidence). No evidence revealed differences between groups in pelvic pain scores based on the McGill Pain Questionnaire (scale 0 to 45) (MD -0.01 points, 95% CI -2.14 to 2.12; 281 women; moderate-quality evidence). With respect to adverse effects, SPRM-associated endometrial changes were more common after SPRM therapy than after leuprolide treatment (OR 10.45, 95% CI 5.38 to 20.33; 301 women; moderate-quality evidence).

Anmerkung/Fazit der Autoren

Short-term use of SPRMs resulted in improved quality of life, reduced menstrual bleeding and higher rates of amenorrhoea than were seen with placebo. Thus, SPRMs may provide effective treatment for women with symptomatic fibroids. Evidence derived from one RCT showed no difference between leuprolide acetate and SPRM with respect to improved quality of life and bleeding symptoms. Evidence was insufficient to show whether effectiveness was different between SPRMs and leuprolide. Investigators more frequently observed SPRM associated endometrial changes in women treated with SPRMs than in those treated with placebo or leuprolide acetate. As noted above, SPRM-associated endometrial changes are benign, are not related to cancer and are not precancerous. Reporting bias may impact the conclusion of this meta-analysis. Well-designed RCTs comparing SPRMs versus other treatments are needed.

Lethaby A et al., 2017 [8].

Preoperative medical therapy before surgery for uterine fibroids.

Fragestellung

To assess the effectiveness and safety of medical treatments prior to surgery for uterine fibroids.

Methodik

Population:

- Premenopausal women, without any other underlying uterine pathology, intending to undergo any surgery for uterine fibroids: either hysterectomy (abdominal, vaginal or laparoscopic), myomectomy (laparotomy or laparoscopy) or resection for uterine fibroids.

Intervention/Komparator:

- GnRHa versus no pretreatment or placebo;
- GnRHa versus other pretreatment (progestin, SPRM, SERM, dopamine agonist, oestrogen receptor antagonist); and
- SPRMs versus placebo

Endpunkte:

- Preoperative assessment: Reduction in uterine volume or fibroid volume or both (as reported in the primary study); Preoperative haemoglobin, Preoperative bleeding
- Operative difficulties and postoperative assessment: Duration of surgery, Intraoperative blood loss, frequency of blood transfusions
- Postoperative morbidity (complications such as pyrexia, haematoma formation and incidence of postoperative adhesions).
- Adverse events (related to the preoperative treatment), Quality of life

Recherche/Suchzeitraum:

- Cochrane Gynaecology and Fertility Group specialised register, CENTRAL, MEDLINE, Embase, PsycINFO and CINAHL in June 2017

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

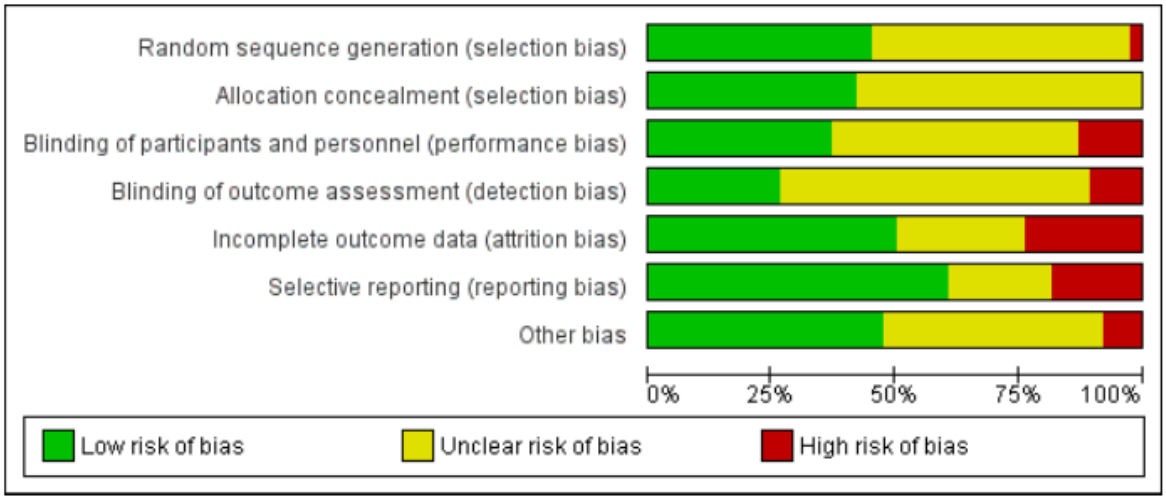
- 38 RCTs, including 3623 women

Charakteristika der Population:

- Participants in all studies had symptomatic fibroids, mostly diagnosed by ultrasound, and were scheduled for surgery

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:

- GnRHa versus no treatment or placebo
  - GnRHa treatments were associated with reductions in both uterine (MD -175 mL, 95% CI -219.0 to -131.7; 13 studies; 858 participants; I2 = 67%; low-quality evidence) and fibroid volume (heterogeneous studies, MD 5.7 mL to 155.4 mL), and increased preoperative haemoglobin (MD 0.88 g/dL, 95% CI 0.7 to 1.1; 10 studies; 834 participants; I2 = 0%; moderate-quality evidence), at the expense of a greater likelihood of adverse events, particularly hot flushes (OR 7.68, 95% CI 4.6 to 13.0; 6 studies; 877 participants; I2 = 46%; moderate-quality evidence).
  - Duration of hysterectomy surgery was reduced among women who received GnRHa treatment (-9.59 minutes, 95% CI 15.9 to -3.28; 6 studies; 617 participants; I2 = 57%; low-quality evidence) and there was less blood loss (heterogeneous studies, MD 25 mL to 148 mL), fewer blood transfusions (OR 0.54, 95% CI 0.3 to 1.0; 6 studies; 601 participants; I2 = 0%; moderate-quality evidence), and fewer postoperative complications (OR 0.54, 95% CI 0.3 to 0.9; 7 studies; 772 participants; I2 = 28%; low-quality evidence).
  - GnRHa appeared to reduce intraoperative blood loss during myomectomy (MD 22 mL to 157 mL). There was no clear evidence of a difference among groups for other primary outcomes after myomectomy: duration of surgery (studies too heterogeneous for pooling), blood transfusions (OR 0.85, 95% CI 0.3 to 2.8; 4 studies; 121 participants; I2 = 0%; low-quality evidence) or postoperative complications (OR 1.07, 95% CI 0.43 to 2.64; I2 = 0%; 5 studies; 190 participants; low-quality evidence). No suitable data were available for analysis of preoperative bleeding.
- GnRHa versus other medical therapies
  - GnRHa was associated with a greater reduction in uterine volume (-47% with GnRHa compared to -20% and -22% with 5 mg and 10 mg ulipristal acetate) but was more likely to cause hot flushes (OR 12.3, 95% CI 4.04 to 37.48; 5 studies; 183 participants; I2 = 61%; low-quality evidence) compared with ulipristal acetate. There was no clear evidence of a difference in bleeding reduction (ulipristal acetate 5 mg: OR 0.71, 95% CI 0.3 to 1.7; 1 study; 199 participants; moderate-quality evidence; ulipristal acetate 10 mg: OR 0.39,

95% CI 0.1 to 1.1; 1 study; 203 participants; moderate-quality evidence) or haemoglobin levels (MD -0.2, 95% CI -0.6 to 0.2; 188 participants; moderate-quality evidence).

- There was no clear evidence of a difference in fibroid volume between GnRHa and cabergoline (MD 12.71 mL, 95% CI -5.9 to 31.3; 2 studies; 110 participants; I2 = 0%; low-quality evidence).
- The included studies did not report usable data for any other primary outcomes.

- SPRMs versus placebo
  - SPRMs (mifepristone, CDB-2914, ulipristal acetate and asoprisnil) were associated with greater reductions in uterine or fibroid volume than placebo (studies too heterogeneous to pool) and increased preoperative haemoglobin levels (MD 0.93 g/dL, 0.5 to 1.4; 2 studies; 173 participants; I2 = 0%; high-quality evidence). Ulipristal acetate and asoprisnil were also associated with greater reductions in bleeding before surgery (ulipristal acetate 5 mg: OR 41.41, 95% CI 15.3 to 112.4; 1 study; 143 participants; low-quality evidence; ulipristal acetate 10 mg: OR 78.83, 95% CI 24.0 to 258.7; 1 study; 146 participants; low-quality evidence; asoprisnil: MD -166.9 mL; 95% CI -277.6 to -56.2; 1 study; 22 participants; low-quality evidence). There was no evidence of differences in preoperative complications. No other primary outcomes were measured.

Anmerkung/Fazit der Autoren

A rationale for the use of preoperative medical therapy before surgery for fibroids is to make surgery easier. There is clear evidence that preoperative GnRHa reduces uterine and fibroid volume, and increases preoperative haemoglobin levels, although GnRHa increases the incidence of hot flushes. During hysterectomy, blood loss, operation time and complication rates were also reduced. Evidence suggests that ulipristal acetate may offer similar advantages (reduced fibroid volume and fibroid-related bleeding and increased haemoglobin levels) although replication of these studies is advised before firm conclusions can be made. (…)

3.3 Systematische Reviews

Ghonim M et al., 2019 [6].

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:

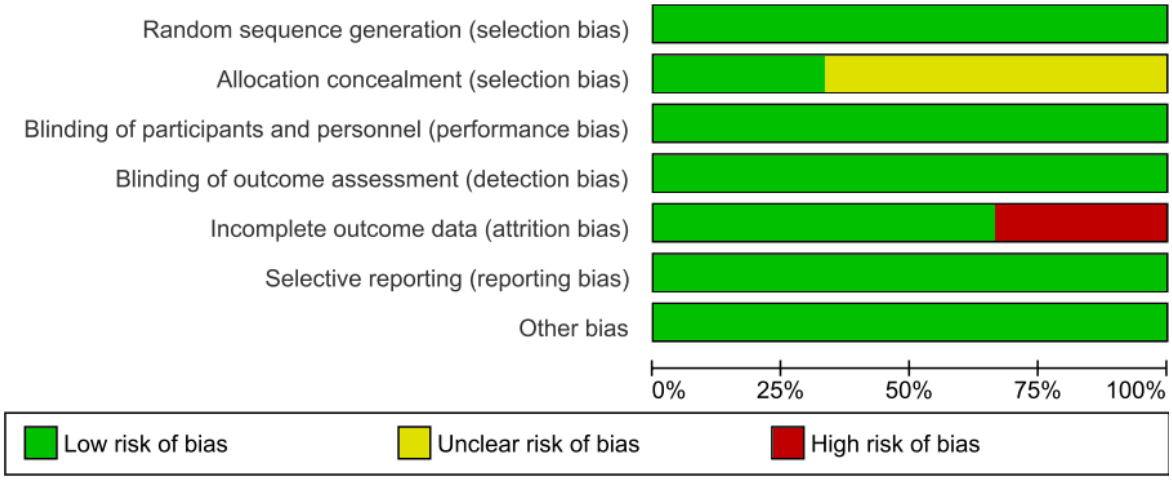


FIGURE 3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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.

De Milliano I et al., 2017 [3].

Pre-treatment with GnRHa or ulipristal acetate prior to laparoscopic and laparotomic myomectomy: A systematic review and meta-analysis.

Fragestellung

to study the effectiveness of medical pre-treatment with Gonadotropin-releasing hormone agonists (GnRHa) or ulipristal acetate prior to laparoscopic or laparotomic myomectomy on intra-operative and post-operative outcomes.

Methodik

Population:

- Participants were pre-menopausal women of18 years and older without no other underlying uterine pathology scheduled for a myomectomy (by laparoscopy or laparotomy).

Intervention/Komparator:

- Admission of pre-treatment using GnRHa or ulipristal acetate versus no pre-treatment, placebo or any other medical therapy prior to surgery. No exclusion criteria for duration of pre-treatment were used.

Endpunkte:

- Duration of surgery (min)
- Intra-operative assessments: Duration of enucleation (min), Blood loss intra-operative (ml), Degree of difficulty of surgery, Identification of cleavage planes, Proportion of vertical incisions (in case of laparotomy), Conversion rate (in case of laparoscopy)
- Post-operative assessments: Frequency of blood transfusions, Post-operative complications (e.g. fever, repeat surgery, pelvic hematomas), Duration of hospital stay (days), Frequency of recurrence of fibroids, Frequency of uterine adhesions (by second look laparoscopy), Recovery time (return to normal activities and return to work), Quality of Life (QoL) including Uterine Fibroid Symptoms and Quality of Life (UFS-QoL)

Recherche/Suchzeitraum:

- Embase.com, Wiley/Cochrane Library and PubMed were searched from inception (by IM and JK) up to 3 April 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's 'Risk of Bias' tool / STROBE

Ergebnisse

Anzahl eingeschlossener Studien:

- 23 studies

Qualität der Studien:

- For the included randomized clinical trials, the overall quality of the included studies was considered moderate (Figs 2 and 3). None of the studies reported clearly on allocation concealment which increases risk for selection bias. This was marked as an unclear risk. In only four of 15 included randomized trials, participants and personnel were blinded for allocation of pre-treatment. For this reason, possible performance bias cannot be excluded. None of the included studies published (a link) to their study protocol. Therefore, the risk for reporting bias is unclear. We added the item 'publication bias' to the quality assessment checklist, since we considered that a power analysis and the reporting of in-/exclusion criteria are essential items in a randomized trial. Unfortunately, only two studies reported on both items. Especially power analysis were frequently missed in the included studies. As a consequence, the findings were indicated as high risk of publication bias.
- The overall quality of the included cohort studies was considered moderate to good. Only one study did not score 'low risk of bias' on any of the selected items. The overall quality of this paper was marked as poor. Two items (bias (9) and study size/power analysis (10)) were reported very limited by the included studies. In general, the more recent studies reported a better overall quality.

Studienergebnisse:

- In laparotomic myomectomy, pre-treatment with GnRHa decreases intra-operative blood loss with 97.39ml (95% CI -111.80 to -82.97) compared to no pre-treatment or placebo.
- Pre-treatment with GnRHa before laparoscopic myomectomies also shows a reduction in intra-operative blood loss by 23.03ml (95% CI -40.79 to -5.27) and in the frequency of blood transfusions (OR 0.17, 95% CI 0.05 to 0.55) compared to no pre-treatment.
- Only two retrospective cohort studies reported on pre-treatment with ulipristal acetate compared to no pre-treatment before laparoscopic myomectomy showing a statistically significant reduction in intra-operative blood loss, duration of surgery and frequency of blood transfusions after pre-treatment with ulipristal acetate.

Anmerkung/Fazit der Autoren

There is high evidence from randomized trials and cohort studies that administration of GnRHa prior to laparotomic myomectomy reduces blood loss. It may also decrease uterine adhesion formation, however quality of evidence is considered moderate. Pre-treatment with GnRHa before laparoscopic myomectomy reduces blood loss, the frequency of blood transfusions and might increase recurrence rate of fibroids, however it should be taken into account that some results are mainly based on cohort studies and therefore quality of evidence is considered low. Besides, clinical relevance could be discussed for most significant results on intraoperative outcomes. Other pre-treatment agent ulipristal acetate has not been investigated sufficiently for relevant surgical outcomes and should not be prescribed routinely in order to improve surgical outcomes. Research on pre-treatment before myomectomy should focus on randomized comparisons with relevant outcomes.

Kommentar zum Review:

- Siehe auch: Vitale SG et al., 2020 [12]

Fusca L et al., 2019 [4].

The Effectiveness of Tranexamic Acid at Reducing Blood Loss and Transfusion Requirement for Women Undergoing Myomectomy: A Systematic Review and Meta-analysis.

Fragestellung

to determine the effectiveness of tranexamic acid (TA) in reducing perioperative blood loss in women undergoing myomectomy.

Methodik

Population:

- women of reproductive age with uterine fibroids who were undergoing myomectomy and who received TA or a comparator

Intervention:

- oral TA

Komparator:

- placebo, no treatment, or another active comparator.

Endpunkte:

- perioperative blood loss, the need for red blood cell transfusion

Recherche/Suchzeitraum:

- From inception until June 3, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Three studies included

Charakteristika der Population:

Characteristics	Caglar et al. 2008[17]	Mousa et al. 2012[24]	Ngichabe et al. 2015[23]	Shaaban et al. 2016[18]
Country	Turkey	Egypt	Kenya	Egypt
Type of myomectomy	Abdominal	Hysteroscopic	Abdominal	Abdominal
Treatment	TA 10 mg/kg IV 15 min before incision and 1 mg/kg/h dissolved in 1 L saline for 10 h	TA 15 mg/kg IV 30 min before incision and 10 mg/kg/h in 500 mL Ringer's by infusion pump until end of procedure	TA 1 g/50 mL saline IV at 100 mL/h until end of procedure	TA 10 mg/kg in 20 mL dextrose 5% IV 10 min before incision and 1 mg/kg/h in 500 mL dextrose 5% for 6 h
Control	Saline bolus 15 min before incision and 1 L of saline for 10 h	Equal volume of saline IV 30 min before incision and 1 ampoule of oxytocin (10 U/mL/amp) in 500 mL Ringer's solution at 400 mU/min by infusion pump	50 mL saline IV	N/A
Co-intervention	None	N/R	Ornipressin 1 vial diluted to 60 mL infiltrated around fibroid	N/R
Blinding	Double blind	Double blind	Double blind	Open label
Fibroid characteristics				
Fibroid type	Intramural	Submucosal	Intramural or subserosal	Intramural
Symptomatic	N/R	Yes	Yes	N/R
Size of fibroid	<6 or ≥6 cm	N/R	N/R	N/R
No. of fibroids	Single or multiple	N/R	N/R	>3
Sample size, n				
Treatment	50	23	17	66
Control	50	24	17	66
Age, y				
Treatment	34.2 (5.5)	34.08 (6.43)	36.0 (4.3)	35.03 (5.43)
Control	36.5 (4.4)	35.24 (5.17)	35.0 (3.9)	34.60 (5.06)
BMI, kg/m^2				
Treatment	24.3 (3.5)	26.27 (3.28)	29.6 (2.8)	28.28 (2.06)
Control	26.2 (3.8)	26.21 (2.99)	29.2 (3.7)	28.59 (2.07)
Preoperative Hb, g/dL				
Treatment	11.4 (2.0)	11.95 (0.78)	12.6 (1.9)	10.77 (0.75)
Control	12.0 (1.6)	11.81 (0.74)	12.8 (1.3)	10.73 (0.62)
Measurement of blood loss	Weight of sponges Suction apparatus	N/A	Weight of sponges	Weight of sponges Suction apparatus

TA: tranexamic acid; Hb: hemoglobin; IV: intravenously; N/A: not applicable; N/R: not reported.

Data provided in means (standard deviation) unless otherwise indicated.

Qualität der Studien:

- Overall, the quality of individual studies was moderate. In all four studies, allocation concealment was inadequate or not reported.

Studienergebnisse:

- TA significantly reduced intraoperative blood loss by a mean difference of 213.1 ml (95% CI --242.4 to -183.7) and postoperative blood loss by a mean difference of 56.3 ml (95% CI -67.8 to -44.8) compared with control arms.
- However, no significant differences were seen in blood transfusion requirement (relative risk 0.58; 95% CI 0.33-1.00).
- In one study for women undergoing hysteroscopic myomectomy, TA was not associated with improved outcomes in transfusion requirement and resulted in reduced postoperative hemoglobin levels compared with oxytocin.

Table 2. Summary of findings of included studies

Outcomes	Caglar et al. 2008[17]	Mousa et al. 2012[24]	Ngichabe et al. 2015[23]	Shaaban et al. 2016[18]
Intraoperative blood loss, mL				
Treatment	654 (460)	N/R	251	346.67 (92.86)[a]
Control	820 (558)	N/R	398	560.76 (80.73)[a]
Postoperative blood loss, mL				
Treatment	150 (167)[a]	N/R	N/R	60.36 (35.87)[a]
Control	213 (113)[a]	N/R	N/R	116.36 (32.76)[a]
Need for transfusion				
Treatment	0.3 (0.8)	5 (21.7)[b]	2 (11.8)[b,c]	13 (19.7)[b,d]
Control	0.3 (0.7)	1 (4.1)[b]	3 (17.6)[b,c]	23 (34.8)[b,d]
Postoperative Hb, g/dL				
Treatment	9.97 (1.5)	10.18 (0.62)[a]	10.3 (1.9)	9.09 (0.79)[a]
Control	9.76 (1.4)	11.13 (0.70)[a]	10.2 (2.1)	8.23 (0.90)[a]
Surgery duration, min				
Treatment	73 (22)[a]	61.24 (15.97)	50.1	75.9 (14.3)[a]
Control	84 (29)[a]	61.48(14.47)	50.1	86.7 (13.4)[a]
Length of hospital stay, h				
Treatment	N/R	N/R	55.03 (21.22)	N/R
Control	N/R	N/R	67.88 (22.98)	N/R
Adverse effects	Respiratory distress postoperative day 1 (TA: n = 2/control: n = 0)	N/R	TA: n = 0 Control: n = 0	Nausea (TA: n = 8/ control: n = 1)[a] Vomiting (TA: n = 6/ control: n = 1)[a]

N/R: not reported; Hb: hemoglobin; TA: tranexamic acid.

Outcomes are given in means (standard deviation) unless otherwise indicated. [a]Statistically significant difference between treatment and control groups ($P < 0.05$); [b]Presented as n (%); [c]Not included in the published article but obtained by contacting study authors;. [d]$P = 0.051$ on reanalysis by review team.

Anmerkung/Fazit der Autoren

On the basis of a limited number of studies, among women undergoing abdominal myomectomy, TA was effective at reducing perioperative blood loss compared with no treatment or placebo, and non-significant trends were observed for reduction in need for blood transfusion. For women undergoing hysteroscopic myomectomy, TA was not associated with improved outcomes in transfusion requirement and resulted in reduced postoperative hemoglobin levels compared with oxytocin.

3.4 Leitlinien

NICE, 2018 [11].

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:

- 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 guideline on patient experience in adult NHS services 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
- uterine artery embolisation
- surgical:
  - myomectomy
  - hysterectomy. [2018, amended 2020]

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

(…)

- 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]
- 1.5.15 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 [7].

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 9 of 12, September 2020) am 22.09.2020

#	Suchfrage
1	MeSH descriptor: [Leiomyoma] explode all trees
2	(leiomyoma* OR fibroid* OR fibromyoma* OR fibroleiomyoma*):ti,ab,kw
3	MeSH descriptor: [Myoma] explode all trees
4	(myom* OR adenomyom* OR fibroma*):ti,ab,kw
5	MeSH descriptor: [Uterus] explode all trees
6	(uterus OR uteri* OR cervic* OR cervix* OR intramural* OR subserosa* OR submucosa*):ti,ab,kw
7	(#3 OR #4) AND (#5 OR #6)
8	MeSH descriptor: [Menorrhagia] explode all trees
9	MeSH descriptor: [Dysmenorrhea] explode all trees
10	#1 OR #2 OR #7 OR #8 OR #9
11	#10 with Cochrane Library publication date from Sep 2015 to present

Systematic Reviews in Medline (PubMed) am 22.09.2020

#	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	uterus[MeSH Terms]
6	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]
7	(#3 OR #4) AND (#5 OR #6)
8	#1 OR #2 OR #7
9	(#8) 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]))))))
10	(#9) AND ("2015/09/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 22.09.2020

#	**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	uterus[MeSH Terms]
6	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]
7	(#3 OR #4) AND (#5 OR #6)
8	(menorrhagia[MeSH Terms]) OR (dysmenorrhea[MeSH Terms])
9	menorrhagia*[Title/Abstract] OR hypermenorrhea*[Title/Abstract] OR "heavy menstrual bleeding"[Title/Abstract] OR dysmenorrhea*[Title/Abstract] OR (menstrua*[Title/Abstract] AND pain*[Title/Abstract])
10	#1 OR #2 OR #7 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
12	(#11) AND ("2015/09/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

1. **Bofill Rodriguez M, Lethaby A, Jordan V.** Progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database of Systematic Reviews [online]. 2020(6):Cd002126. URL: http://dx.doi.org/10.1002/14651858.CD002126.pub4.

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.

3. **De Milliano I, Twisk M, Ket JC, Huirne JA, Hehenkamp WJ.** Pre-treatment with GnRHa or ulipristal acetate prior to laparoscopic and laparotomic myomectomy: a systematic review and meta-analysis. PLoS One 2017;12(10):e0186158.

4. **Fusca L, Perelman I, Fergusson D, Boutet M, Chen I.** The effectiveness of tranexamic acid at reducing blood loss and transfusion requirement for women undergoing myomectomy: a systematic review and meta-analysis. J Obstet Gynaecol Can 2019;41(8):1185-1192.e1181.

5. **Gemeinsamer Bundesausschuss (G-BA).** Zusammenfassender Bericht des Arbeitsausschusses "Ärztliche Behandlung" des Bundesausschusses der Ärzte und Krankenkassen über die Beratungen gemäß §135 Abs.1 SGB V: Uterus-Ballon-Therapie [online]. Berlin (GER): G-BA; 2001. [Zugriff: 22.09.2020]. URL: https://www.g-ba.de/downloads/40-268-243/HTA-Uterus-Ballon-Therapie.pdf.

6. **Ghonim M, Magdy R, Sabbour M, Ghonim M, Nabhan A.** A systematic review and meta-analysis of ulipristal acetate for symptomatic uterine fibroids. Int J Gynaecol Obstet 2019;146(2):141-148.

7. **Laberge PY, Murji A, Vilos GA, Allaire C, Leyland N, Singh SS.** Guideline No. 389: Medical management of symptomatic uterine leiomyomas; an addendum. J Obstet Gynaecol Can 2019;41(10):1521-1524.

8. **Lethaby A, Puscasiu L, Vollenhoven B.** Preoperative medical therapy before surgery for uterine fibroids. Cochrane Database of Systematic Reviews [online]. 2017(11):Cd000547. URL: http://dx.doi.org/10.1002/14651858.CD000547.pub2.

9. **Lethaby A, Wise MR, Weterings MAJ, Bofill Rodriguez M, Brown J.** Combined hormonal contraceptives for heavy menstrual bleeding. Cochrane Database of Systematic Reviews [online]. 2019(2):Cd000154. URL: http://dx.doi.org/10.1002/14651858.CD000154.pub3.

10. **Murji A, Whitaker L, Chow TL, Sobel ML.** Selective progesterone receptor modulators (SPRMs) for uterine fibroids. Cochrane Database of Systematic Reviews [online]. 2017(4):Cd010770. URL: http://dx.doi.org/10.1002/14651858.CD010770.pub2.

11. **National Institute for Health and Care Excellence (NICE).** Heavy menstrual bleeding: assessment and management [online]. Last updated: 2020. London (GBR): NICE; 2018. [Zugriff: 17.09.2020]. (NICE Guideline; Band 88). URL: https://www.nice.org.uk/guidance/ng88/resources/heavy-menstrual-bleeding-assessment-and-management-pdf-1837701412549.

12. **Vitale SG, Ferrero S, Caruso S, Barra F, Marín-Buck A, Vilos GA, et al.** Ulipristal acetate before hysteroscopic myomectomy: a systematic review. Obstet Gynecol Surv 2020;75(2):127-135.

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

2020-B-330

Kontaktdaten

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

Indikation gemäß Beratungsantrag

„Zur **Therapie mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter**“

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei der Therapie mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter**? Wie sieht die Versorgungspraxis in Deutschland aus?**

Der symptomatische Uterus myomatosus ist eine mögliche Indikation für eine Hysterektomie. Im Einzelfall sollte abgewogen werden, ob ein uteruserhaltendes Verfahren möglich ist. 72% der symptomatischen Frauen, welche sich nach abgeschlossenem Kinderwunsch und frustranen konservativen Therapieversuchen einer Hysterektomie unterzogen, fühlten sich danach besser (1). Frauen mit großen Myomen haben ein erhöhtes Risiko für eine intraoperative hämodynamisch signifikante Blutung sowie für eine bereits bestehende Anämie. Vor einer geplanten Hysterektomie aufgrund eines Uterus myomatosus kann eine präoperative Vorbereitung mit GNRH-Analoga die Myome und den Uterus verkleinern, so dass die vaginale Hysterektomie größenbedingt einfacher wird und präoperativer Eisenmangel und Anämie günstig beeinflusst werden. Hierbei ist eine Dauer von 3 Monaten zu empfehlen. Die Therapie mit dem selektiven Progesteron-Rezeptor-Modulator Ulipristal-Acetat (Esmya®) wird aufgrund der berichteten Todesfälle bei akutem Leberversagen nicht mehr empfohlen (2).

Myome können je nach Lage, Größe und Zahl hysteroskopisch, laparoskopisch, laparoskopisch-assistiert oder per (Mini-)Laparotomie entfernt werden. Eine operative Myomentfernung stellt derzeit die einzige evidenzbasierte Option für Frauen dar, die aktuell oder perspektivisch Kinderwunsch haben. Der therapeutische Goldstandard für submuköse Myome ist die hysteroskopische Abtragung. Einige Autoren empfehlen bereits für Myome > 3 cm, andere ab 4 cm Größe eine ein- bis dreimonatige GnRH-Analoga-Vorbehandlung zur Verkleinerung und damit Optimierung der Operationsbedingungen (3). Eine weitere

Kontaktdaten

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

Indikation gemäß Beratungsantrag

„Zur **Therapie mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter**“

Therapiemethode ist die transzervikale Radiofrequenzablation mit intrauteriner Ultraschallführung zur Behandlung von submukösen und intramuralen Myomen (4).

Der hochenergetische fokussierte Ultraschall unter NMR-Kontrolle zur Myomdestruktion ist eine neue Methodik, die einem raschen Innovationsprozess unterliegt und daher einer kontinuierlichen Reevaluierung bedarf Aufgrund ihrer Lage können nicht alle Myome mit fokussiertem Ultraschall behandelt werden. Die Methodik sollte derzeit eher ausgewählten Fällen vorbehalten werden, zudem variiert die Dauer der einzelnen Therapiesitzung je nach Myomgröße (5).

Die UAE (uterine artery embolization) ist eine Alternative zu chirurgischen Optionen bei entsprechend aufgeklärten Frauen mit dem Wunsch nach Uteruserhalt und abgeschlossenem Kinderwunsch. Im Vergleich zur vaginalen Hysterektomie zeigt die Literatur, dass die Komplikationsraten zwar nicht unterschiedlich sind, allerdings bei der UAE eine höhere Rezidivrate besteht (6) (7).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter**“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen.**

Ein Grenzwert bzgl der Anzahl oder Größe der Myome als Hilfestellung für die Entscheidung des Verfahrens existiert nicht (8).

Weniger als 5% der „rasch wachsenden“ Leiomyome sind tatsächlich Sarkome. Wir verweisen hierzu auch auf die DGGG Stellungnahme von 2015 (9), welche eine individuelle Bewertung der Indikation zum Morcellement empfiehlt und insbesondere darauf hinweist, dass eine genaue Aufklärung der Patientin über

Kontaktdaten *Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)*
Indikation gemäß Beratungsantrag „Zur **Therapie mittlerer bis starker Symptome durch Gebärmutter-Myome bei erwachsenen Frauen im fortpflanzungsfähigen Alter**“
mögliche Auswirkung auf die Prognose im Falle eines Uterussarkoms erfolgen und dokumentiert werden muss. Bei der Entscheidung bezüglich des Morcellements ist insbesondere das Alter der Patientin sowie die Größenprogredienz zu berücksichtigen. Ein sehr großer Uterus myomatosus mit zahlreichen Myomen und/ oder sehr große, tief intra- oder transmural gelegene Myome erfordern auch heute zumeist einen offenen Zugang. Der mehrschichtige Verschluss der Uterotomie kann über eine Minilaparotomie von 4 bis 5 cm oder die laparoskopisch assistierte Myomektomie (Myompräparation per laparoscopiam, Myomentfernung und Naht per Minilaparotomieinzision) erfolgen. Die Lokalisation und die Größe der vorhandenen Myome sind die Hauptdeterminanten für die Entscheidung für oder gegen ein laparoskopisches Vorgehen. Die Vorteile der Laparoskopie gegenüber der Laparotomie sollten, wann immer möglich, genutzt werden: geringerer Blutverlust, weniger postoperative Schmerzen, kürzere Hospitalisation, schnellere Rekonvaleszenz, weniger Adhäsionen (5).

1. Carlson KJ, Miller BA, Fowler FJ, Jr. The Maine Women's Health Study: II. Outcomes of nonsurgical management of leiomyomas, abnormal bleeding, and chronic pelvic pain. Obstet Gynecol. 1994;83(4):566-72.
2. Rote-Hand-Brief Esmya® 5 mg Tabletten: Indikationseinschränkung, neue Kontraindikation sowie die Notwendigkeit zur Überwachung der Leberfunktion. 2018.
3. Mukhopadhaya N, De Silva C, Manyonda IT. Conventional myomectomy. Best Pract Res Clin Obstet Gynaecol. 2008;22(4):677-705.
4. 245. Stellungnahme der DGGG. "Transzervikale Radiofrequenzablation mit intrauteriner Ultraschallführung bei Uterusmyomen". 2017.
5. S3 Leitlinie Indikation und Methodik der Hysterektomie bei benignen Erkrankungen. AWMF Nummer 015/070. 2015.

6. Jun F, Yamin L, Xinli X, et al. Uterine artery embolization versus surgery for symptomatic uterine fibroids: a randomized controlled trial and a meta-analysis of the literature. Arch Gynecol Obstet. 2012;285(5):1407-13.
7. van der Kooij SM, Hehenkamp WJ, Volkers NA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2010;203(2):105 e1-13.
8. Yoo EH, Lee PI, Huh CY, et al. Predictors of leiomyoma recurrence after laparoscopic myomectomy. J Minim Invasive Gynecol. 2007;14(6):690-7.
9. Beckmann MW, Juhasz-Boss I, Denschlag D, et al. Surgical Methods for the Treatment of Uterine Fibroids - Risk of Uterine Sarcoma and Problems of Morcellation: Position Paper of the DGGG. Geburtshilfe Frauenheilkd. 2015;75(2):148-64.