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Full length article

Uterine artery embolization versus surgical treatment in patients with symptomatic uterine fibroids: Protocol for a systematic review and meta-analysis of individual participant data

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ABSTRACT

Objective: Uterine fibroids are the most common benign tumours in women of the reproductive age. Symptoms of heavy menstrual bleeding, abdominal discomfort and infertility may seriously affect a woman's quality of life. Uterine artery embolization is a safe and effective alternative treatment to hysterectomy or myomectomy for symptomatic uterine fibroids. Which treatment provides the highest quality of life, least complications, symptom reduction and least chance intervention, has not been established and might depend on strict patient selection. This study aims to identify which specific subgroups benefit most of each treatment by analyzing individual participant data derived from randomized controlled trials of women undergoing embolization or surgical treatment. This study will primarily assess the effectiveness of both treatment groups by evaluating the effect on quality of life of embolization in comparison to surgery on specific patient and fibroid characteristics and the possible need for re-intervention for fibroid-related symptoms.
Data sources: PubMed/MEDLINE, Embase and The Cochrane Library were searched up to August 2020.
Study eligibility criteria: We will collect individual participant data from randomized controlled trials that studied clinical and procedural outcomes of premenopausal women with symptomatic uterine fibroids, who were randomized between uterine artery embolization and surgery.
Study appraisal and synthesis methods: Individual participant data from all eligible trials will be sought and analysed according to intention-to-treat principle. Risk of Bias will be done by using version 2 of the Cochrane tool for Risk of Bias in randomized trials. Subgroup analyses to explore the effect of e.g. age, fibroid characteristics and fibroid complaints will be performed, if data is available. This individual patient data meta-analysis will be analysed according to a one-stage model.

Introduction

Uterine fibroids are the most common benign tumours in women of the reproductive age, with a reported prevalence ranging from 5% up to 69%, depending on population and diagnostic method [1]. Although these neoplasms rarely show malignant transformations, the impact on a woman's quality of life can be significant. Heavy

Abbreviations: IPD-MA, individual participant data meta-analysis; QoL, quality of life; RCT(s), randomized controlled trials; RoB, risk of bias; UAE, uterine artery embolization.

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menstrual bleeding, dysmenorrhea, dyspareunia, and pressure complaints may prevent women from participating in normal daily activities and significantly decrease their quality of life (QoL) [2,3]. The impact of fibroids on fertility depends on their location [4]. Treatment options range from medicinal treatment, to minimally invasive procedures such as uterine artery embolization (UAE), and more invasive surgical treatment in the form of myomectomy or hysterectomy [5]. Patient preference may be influenced by a wish to preserve fertility, avoid radical surgery, or the need for a permanent solution. Treatment options can depend on fibroid characteristics, which can complicate the counselling of patients [6]. Multiple randomized controlled trials (RCTs) have proven UAE to be a safe and effective alternative to surgical treatment for symptomatic uterine fibroids [7–11], up to ten years after treatment [12], but balanced by a significant risk of re-intervention, which is estimated to be 15–32% [13].

Uncertainty remains with regards to whether specific patient characteristics and the underlying nature of the fibroid impact treatment outcomes. Volkers et al. attempted to identify risk factors for technical failure or complications of UAE and found that patients with single fibroid tumours and/or small uterine volumes have a higher risk of procedural failure, such as incomplete infarction [14]. Identification of predictive factors for effectiveness and safety has thus far been complicated by the small sample sizes and non-comparable patient baseline characteristics of the individual studies, often including a non-randomized setting [15].

Rationale for a systematic review with individual participant data meta-analysis comparing UAE with surgical treatment

The current evidence has highlighted the trade-off between the less invasive nature of UAE and the need for re-intervention, compared with surgical procedures. Many clinical guidelines recommend that the choice of procedures should lie with the informed patient [6,16]. To enable that women requiring treatment make informed choices, it is essential to identify which patients experience greatest benefit for either treatment method.

Collaborative approach

This individual participant data meta-analysis (IPD-MA) will be an international collaboration involving all trial investigators who conducted eligible RCTs and the IPD-MA research team (MAM; WH; BWM; JM, OW) to evaluate all available data.

Objectives

This study aims to assess the efficacy of UAE compared with surgical treatment in women with uterine fibroids. In particular, this study aims to determine how the patient and disease characteristics may predict clinical and QoL outcomes, thereby offering clinicians selection criteria to make recommendations on treatment success.

Primary outcomes

The primary questions of our individual patient data meta-analysis is which patients undergoing UAE compared to surgical treatment, have:

1 The highest improvement of QoL, or if unavailable, the greatest symptom reduction.
2 The least chance of re-intervention.
   a Re-intervention is defined as any intervention after initial treatment to treat persisting or recurring symptoms in either groups.
   b Any non-scheduled re-intervention to treat short and long-term complications in either groups.

Secondary outcomes

1 Subgroup analyses of the primary outcomes will be done for the separate surgical treatment groups (myomectomy and hysterectomy).
2 Multivariate analysis to identify patient characteristics, that are of:
   o Highest improvement of QoL
   o Least chance for re-intervention
   o Symptom reduction
3 Subgroup analysis will be done for different patient characteristics to identify possible predictors for secondary myomectomy or hysterectomy in the UAE group.
4 Multivariate analysis will be done for different patient characteristics to identify possible predictors for a chance on a best possible outcome, defined as: no re-intervention and $\geq$ 10 points improvement on any QoL scale or symptom reduction scale.

Primary outcomes will be measured at 12 months of follow up. Different time points will be explored for the secondary outcomes. If sufficient data are available, a network meta-analysis will compare all treatment options (UAE, hysterectomy and myomectomy) and patient characteristics.

Methods

Protocol development and registration

This protocol was registered in PROSPERO (CRD42018098676) and is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA-P) 2015 statement [17]. Investigators from all identified trials were invited to contribute or comment on this protocol. All correspondence regarding the development of this protocol has been recorded. Ultimately, the IPD-MA team was responsible for making methodological decisions. The IPD meta-analysis will be conducted according to the Cochrane Collaboration methodology and reported in line with the PRISMA IPD statement.

Eligibility criteria

We will include RCTs that report on clinical and procedural outcomes (outcomes) of women with symptomatic uterine fibroids (population) who underwent either uterine artery embolization (intervention) or surgical treatment (comparison). Surgical treatment include myomectomy and hysterectomy, both laparoscopic and open approach or (combined) vaginal approach in case of hysterectomy. Hysteroscopic surgery is excluded. There will be no restrictions on dates or language. We aim to include all relevant RCTs, irrespective of whether they were published, had completed recruitment or had completed their analyses.

Information sources and search strategy

To identify all trials eligible for inclusion in this IPD, preliminary literature searches and screening were conducted (Appendix 1: Study characteristics and Appendix 2: Search strategy). These searches were conducted as part of the development of this protocol so that the protocol could be sent to the investigators of the trials, along with an invitation to join this project.

More detailed searches will be conducted in PubMed/MEDLINE (MeSH terms and tiab searches), The Cochrane Library (Cochrane Database of Systematic Reviews), and EMBASE (Emtree and tiab searches). To increase the likelihood of identifying all relevant studies, the reference lists of eligible studies will be searched for additional studies. The meta-register of controlled trials and the ISRCTN will be searched to identify any ongoing RCTs. We will contact the corresponding author of all published studies, and the named registry contract for unpublished studies, to retrieve individual participant data.

The search strategy include terms relating to or describing the population, intervention, comparison, and study design. The search terms are adapted for use in the distinct bibliographic databases as well as the database-specific filters. The full search strategy as applied in Pubmed/MEDLINE format can be found in Appendix 2.

Study selection

Literature search is aimed at identifying trials. Titles and abstracts of studies retrieved from the search strategy will be screened independently by two reviewers. Articles will be included or excluded according to the stated criteria. Any discrepancies between the two reviewers in this process will be discussed, and full text accessed for further clarification when needed. If discrepancies continue to exist, a third independent reviewer will be consulted and the article will be discussed among the researchers until consensus is reached. All duplicate articles included for full-text screening will be removed. A manual revision of duplicates to be deleted will be performed for verification. Trials that were excluded from the IPD-MA will be listed with their reason for exclusion.

Data acquisition and management

The data centre is located in the Department of Obstetrics and Gynaecology at the Amsterdam University Medical Centers, the Netherlands, who will manage transferring and sharing of the data. Corresponding authors of the included articles will be asked to share their individual participant data. When the author is either not willing to share the data or no contact could be established after repeated attempts (post/email/telephone/personal contact), two independent reviewers will extract published data from manuscripts following standardized data extraction forms. All collected data will be stored in a master database constructed for this IPD. These data will be cleaned and cross-checked against published results in the articles. When discrepancies exist, the authors will be contacted for clarification.

The participating investigators will be able to supply their data via a secure data transfer platform. We will also request trial protocols, forms, data dictionaries, and statistical analysis plans for the included trials. We will request a minimum list of data items (Appendix 3). An investigator is welcome to supply the data, whether limited to the minimum items or the complete dataset, in any manner that suits their convenience. The data must be anonymized before transfer. No attempts will be made by the IPD-MA team to re-identify participants. Access to the database will be limited to the IPD-MA team.

The quality assurance will be done when the data is received by the IPD-MA team. The data will be checked for consistency against the data dictionary or form, baseline differences and if correct randomization was done. The raw baseline data, trial flow chart (Consort diagram) and primary analyses will be repeated using the IPD received and compared to the reported data in the study publication. Any inconsistencies will be noted, and discussed with the investigator of the study and the IPD-MA team. Trials where the reported baseline characteristics, trial flow chart and primary analyses cannot be replicated from the IPD will be exclude from the IPD-MA.

Assessment of risk of bias

All selected trials will be assessed for risk of bias (RoB) using the received datasets and the reported information. Risk of bias will be assessed in all articles using version 2 of the Cochrane Risk of Bias in randomized trials (RoB 2) [18]. For each outcome, each study is assessed for a specific result on 6 points: 1) Specify results being assessed; 2) Specify effect of interest; 3) List sources of information used to inform assessment; 4) Answer signaling questions; 5) Judge RoB for each domain; 6) Judge overall RoB for the result. For the complete syntheses these judgements are integrated into results and conclusions. The different domains regard the bias arising from randomization process, intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and eventually the overall bias. Concluding in a RoB judgement: low or high RoB or 'some concerns'. The assessment will be conducted by one member of the IPD-MA research team and independently checked by a second member of the IPD-MA team.

Data synthesis

Before the data is synthesized, all data will be checked to ensure only appropriate data is used and all available data for subgroup and predictor analyses is incorporated. We will report the gathered data according to the PRISMA guidelines for a systematic review and meta-analysis of individual participant data.

Statistical analysis

Descriptive tables will be developed to outline the study and population characteristics by intervention (UAE) and comparator arms (surgery). Appendix 3 lists the data items that will be requested. All data will be checked for missing data, assessed for distribution and analysed in order to reproduce the initial published results. Data will be analysed according to an intention to treat principle, so that each participant will be analysed in conformance with the allocated treatment. All statistical analyses will be performed using STATA (SE 14.1).

Outcome measures

The difference between treatment arms will be reported as mean with standard deviation (or median in case of a non-normal distribution) for continuous outcomes (e.g. quality of life). Dichotomous outcomes (e.g. re-intervention yes/no) will be analysed by calculating the risk ratio for the effect of embolization compared to surgical treatment of uterine fibroids. When a risk ratio cannot be calculated, an odds ratio will be used. The relationship between continuous variables and the main outcome (QoL) will be explored through application of generalized linear mixed models [19]; linear mixed models will be applied to continuous outcomes, and logistic mixed-effect models to calculate a relative risk or odds ratio for dichotomous outcomes.

One-stage and two-stage model

The IPD will be analysed according to the 'one-stage' model, where we analyse the individual data of all studies combine with a single model, but take clustering into account. We will use multilevel logistics regression models with random effects models, thereby clustering on individual study level to account for heterogeneity and avoid between-study covariance [20,21].

Analysis of the data will focus on the robustness of the outcome in all subgroups. In order to do this, we will develop generalized linear mixed models to test how various patient characteristics relate to the outcome, while accounting for potential heterogeneity across trials. The variables to be tested and outcomes to be addressed in these multilevel models will depend on the available data from the participating studies. If sufficient data are available, a network meta-analysis will compare all treatment options (UAE, hysterectomy and myomectomy) and patient characteristics.

When possible, a two-stage model will be performed to do a sensitivity analysis with the aggregated data from the trials that did not provide data.

Analysis of potential effect modifiers

To find which patients derive greater benefit (or harm) from intervention (UAE) compared to surgery, we will investigate potential effect modifiers at intervention and patient level. The patients included in this IPD will be divided into groups according to intervention- or trial level, and a multivariate meta-regression approach will be performed. One-stage models will then be used to analyse the effect of the potential effect modifiers by adding them to existing one-stage models, enabling assessment of multiple interventions and patient level characteristics.

Potential effect modifiers on intervention level

- Type of surgical intervention: myomectomy, or hysterectomy
- Type of surgical approach: abdominal, vaginal, laparoscopic

Potential effect modifiers on patient and fibroid level

- Uterine volume (cm^3)
- Number of fibroids
- Fibroid volume (dominant fibroid, cm^3)
- Location of dominant fibroid: submucosal, intramural and subserosal
- Symptoms: menorrhagia, dysmenorrhea, pain, urinary symptoms, defecation problems, anaemia, pressure symptoms
- Age
- Ethnicity
- BMI

Time to event analyses

The association between the time to first re-intervention and subsequent re-interventions and patient level risk factors can be calculated within each trial by using an appropriate time-to-event-analysis.

Missing data

If data from trials are missing because the investigators decided not to participate or did not respond to our invitation to join this IPD-MA collaboration, we will extract aggregate data from the published article and combine these with the results from the IPD-MA in a sensitivity analysis.

If covariate data are missing for some participants, these patients will in the first instance be excluded from the analysis. In case there is substantial missing data (>10% for an outcome or variable), multiple imputation will be used. Imputation will only be performed for missing data in individual trials that recorded this particular outcome or covariate, not to impute an outcome or covariate that was never recorded: in this case the trial will not contribute to that particular analyses. The impact of missing outcome data across the trials will be compared by performing sensitivity analyses with and without these studies.

Ethics approval and consent to participate

All individual studies to be included in this individual participant data meta-analysis should have obtained ethical approval from their respective ethics committees. Only anonymous data will be analysed. The results of this study will be published in a peer-reviewed journal and presented at an international conference.

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Author contribution

MAM, MJH, WJKH, OW, JM made substantial contributions to the design and drafting of this article. BWJM provided project supervision as well as review and editing of the manuscript. WJKH, IM, MM, AR, JD, JM and WJKH are the initial investigators of the participating trials and responsible for the available data. They all reviewed this manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.11.027.

References

[1] Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG 2017;124(10):12.
[2] Fortin C, Flyckt R, Falcone T. Alternatives to hysterectomy: the burden of fibroids and the quality of life. Best Pract Res Clin Obstet Gynaecol 2018;46:31–42.
[3] Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. Int J Womens Health 2014;6:95–114.
[4] Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91(4):1215–23.
[5] Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update 2016;22(6):665–86.
[6] Expert Panel on Interventional R, Knuttinen MG, Stark G, et al. ACR appropriateness criteria((R)) radiologic management of uterine leiomyomas. J Am Coll Radiol 2018;15(5S):S160–70.
[7] Hehenkamp WJ, Volkers NA, Birnie E, Reekers JA, Ankum WM. Symptomatic uterine fibroids: treatment with uterine artery embolization or hysterectomy–results from the randomized clinical Embolisation versus Hysterectomy (EMMY) Trial. Radiology 2008;246(3):823–32.
[8] Moss JG, Cooper KG, Khaund A, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG 2011;118(8):936–44.
[9] Manyonda I, Belli AM, Lumsden MA, et al. Uterine-artery embolization or myomectomy for uterine fibroids. N Engl J Med 2020;383(5):440–51.
[10] Manyonda IT, Bratby M, Horst JS, Banu N, Gorti M, Belli AM. Uterine artery embolization versus myomectomy: impact on quality of life–results of the FUME (Fibroids of the Uterus: myomectomy versus Embolization) Trial. Cardiovasc Intervent Radiol 2012;35(3):530–6.
[11] Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Intervent Radiol 2008;31(1):73–85.
[12] de Bruijn AM, Ankum WM, Reekers JA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial. Am J Obstet Gynecol 2016;215(6)745 e741-745 e712.
[13] Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev 2014(12)CD005073.

[14] Volkers NA, Hehenkamp WJ, Birnie E, et al. Uterine artery embolization in the treatment of symptomatic uterine fibroid tumors (EMMY trial): periprocedural results and complications. J Vasc Interv Radiol 2006;17(3):471–80.
[15] Chen S, Pitre E, Kaunelis D, Singh S. Uterine-preserving interventions for the management of symptomatic uterine fibroids: a systematic review of clinical and cost-effectiveness Ottawa (ON). 2016.
[16] Radiologists TRCoOaGaTRCo. Clinical recommendations on the use of uterine artery embolisation (UAE) in the management of fibroids. London: RCOG and RCR; 2013. p. 24.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4)264–9 W264.
[18] Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[19] Hastie T, Tibshirani R, Friedman J. The elements of statistical learning data mining, inference, and prediction. second edition ed. 2008 California.
[20] Debray TP, Moons KG, Abo-Zaid GM, Koffijberg H, Riley RD. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? PLoS One 2013;8(4)e60650.
[21] Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221.