

# Fertility after uterine artery embolization of fibroids: a systematic review

K. Karlsen<sup>1</sup>  · A. Hrobjartsson<sup>2</sup> · M. Korsholm<sup>1</sup> · O. Mogensen<sup>3</sup> · P. Humaidan<sup>4</sup> · P. Ravn<sup>1</sup>

Received: 8 June 2017 / Accepted: 11 October 2017 / Published online: 20 October 2017  
© Springer-Verlag GmbH Germany 2017

## Abstract

**Purpose** The impact of uterine artery embolization (UAE) for the purpose of diminishing the effect of uterine fibroids on fertility is unclear. We have investigated the reported rates of pregnancy and miscarriage after treatment of uterine fibroids with UAE.

**Materials and methods** We searched for relevant information in PubMed and Embase for randomized controlled trials (RCT), controlled clinical trials, comparative before–after trials, cohort studies, case–control studies and case series where UAE treatment of premenopausal women was performed for uterine fibroids with and where a control intervention was included. The PRISMA guideline was used to do a systematic review using the main outcomes pregnancy rate and miscarriage rate. Risk of bias was assessed by the Cochrane risk of bias tool or by ROBINS-I. The quality of evidence was assessed by the GRADE approach.

**Results** We included 17 studies (989 patients): 1 RCT, 2 cohort studies, and 14 case series. Pregnancy rates after UAE were 50% in the RCT and 51 and 69% in the cohort studies. Among the case series median pregnancy rate was

29%. Miscarriage rates were 64% in the RCT. Miscarriage rates at 56 and 34% were found in the cohort studies after UAE. The median miscarriage rate was 25% in the case series.

**Conclusion** Pregnancy rate was found to be lower and miscarriage rate higher after UAE than after myomectomy. However, we found very low quality of evidence regarding the assessed outcomes and the reported proportions are uncertain. There is a need for improved prospective randomized studies to improve the evidence base.

Systematic review registration number: CRD42016036661.

**Keywords** Uterine artery embolization · Uterine fibroids · Fertility · Pregnancy rate · Miscarriage rate

## Introduction

The ideal treatment of uterine fibroids for women wanting to preserve fertility has yet to be determined. Treatment must also be effective and safe. Uterine fibroids occur in 70–80% of women in the fertile age and up to 25% have symptoms that require treatment [1–3], such as menorrhagia, pelvic pain, infertility, and bulk-related symptoms.

Surgical removal of fibroids (myomectomy) is the method of choice for women in childbearing age who may wish to become pregnant. However, large multiple fibroids with an unfavorable localization may be difficult or even impossible to remove without affecting fertility. In addition, a growing demand towards less invasive approaches and quick recovery has led to the development of alternative treatment modalities.

One of those alternative treatments is uterine artery embolization (UAE), a minimally invasive and uterus-preserving treatment. UAE is reported to be as effective

✉ K. Karlsen  
kamilla.karlsen@rsyd.dk

<sup>1</sup> Department of Gynaecology and Obstetrics, Odense University Hospital, University of Southern Denmark, Klørvænget 10, 10.sal, 5000 Odense C, Denmark

<sup>2</sup> Center for Evidence-Based Medicine, Odense University Hospital, University of Southern Denmark, Odense, Denmark

<sup>3</sup> Department of Gynaecology, Karolinska Institute Stockholm and the University of Southern Denmark, Karolinska University Hospital Stockholm, Stockholm, Sweden

<sup>4</sup> Faculty of Health, The Fertility Clinic, Skive Regional Hospital, Aarhus University, Skive, Denmark

as surgical removal regarding subjective symptoms, size of fibroids and patient satisfaction [4]. There are, however, concerns regarding the impact on fertility. UAE might affect endometrial receptivity and implantation through a possible negative impact on endometrial blood flow. UAE might also negatively impact ovarian blood flow, endocrine function and follicular development, leading to infertility and premature menopause. Since UAE was first introduced, the method has been refined in terms of embolic agents: the particle material, shape and size have been improved [5], which raises the question whether previous results apply to the present technology.

The National Institute of Health and Care Excellence (NICE) guideline from 2010 states that: "patients contemplating pregnancy should be informed that the effects on future fertility are uncertain" [6]. The Royal College of Obstetricians and Gynecologists guideline from 2013 concludes that there is poor evidence regarding UAE and fertility and, therefore, recommends that UAE treatment in women of childbearing age who wish, or might wish, to become pregnant in the near future should be offered UAE only after an informed discussion [7]. The Danish National Guideline is in agreement with those recommendations [8]. A Cochrane review from 2014 reviewed UAE in all aspects [9]. Regarding fertility, they concluded that the quality of evidence was very low. We made an updated, specific and focused review by reviewing medical publications with a focus only on fertility after UAE among premenopausal woman. We tried to broaden the potential pool of evidence by considering non-randomized studies of several types to estimate if this would affect the fertility estimates.

The primary aim of this systematic review was to investigate the effect of UAE for treatment of uterine fibroids on pregnancy rate and miscarriage rates. A secondary aim was to provide an overview of clinical studies conducted and their methodological characteristics.

## Methods

### Protocol and registration

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 18 March 2016, registration number CRD42016036661. The protocol was reported in accordance with the PRISMA–P statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) and the present article is presented in line with the PRISMA statement [10].

### Eligibility criteria

We included clinical studies assessing fertility after treatment of uterine fibroids with UAE. Inclusion criteria were based on predetermined criteria regarding study design, population, intervention and outcomes.

We defined clinical studies as randomized controlled trials (RCT, women randomized for either UAE or another treatment/no treatment), controlled clinical trials (CCT, women allocated to UAE or another treatment/no treatment without randomization), comparative before–after studies (CBA, observations made before and after UAE, and before and after intervention in a control group), cohort studies (a group of women with fibroids who were followed over time to examine associations between different interventions), case–control studies (observations on women who have been treated with UAE and women who have had other treatment/no treatment) and case series (observations on women who have been treated with UAE). Case reports were excluded.

Population was defined to be fertile women with uterine fibroids.

Intervention was defined to be the treatment of uterine fibroids with UAE and studies were excluded if UAE was used as an emergency management for hemostasis or for other or unclear indications.

The primary outcome was the pregnancy rate. Pregnancy rate was defined as number of pregnant women among the included women. The secondary outcome was miscarriage rate, defined as number of miscarriages among number of pregnancies.

### Search strategy

The electronic databases, PubMed and EMBASE were searched. Searches were performed during April 2016, updated on 21 March 2017.

### Search

The search strategy was designed in collaboration with a research librarian from University of Southern Denmark. We used medical subject headings (MeSH) and free text words 'UAE', 'uterine artery embolization' and 'uterine artery embolizations'. After the PubMed strategy was finalized, it was adapted in syntax and used in the other database. We also scanned the reference lists of included studies, relevant reviews and national clinical recommendations for additional references. There were no limits regarding publication date. We read articles in which the full text was available in English or Danish, or where translation to English or Danish was possible. To obtain high sensitivity, no study design filters were used during the search. An overview of our PubMed search strategy is shown in Appendix 1.

## Study selection

Studies were selected regarding inclusion and exclusion criteria. Two authors (K.K and M.K) independently screened the titles and abstracts. Selected studies were subsequently reviewed by the same two authors independently based on full text. Discrepancies were solved by discussion or by a third member (P.R) of the study team.

## Data collection process/data items

Data from the included studies were extracted based on: study design, number of participants, age, characteristics of the population, characteristics of the fibroids, in- and exclusion criteria, follow-up time, intervention and outcome (pregnancy, miscarriage). An adapted Cochrane data collection form was used.

Data extracted included mean uterine size, age, number of participants, number of women trying to conceive, number of women who became pregnant, number of pregnancies, number of miscarriages and follow-up time. Pregnancy and miscarriage rates were extracted directly or calculated from the original numbers if possible. Authors were contacted if outcome data were unclear.

## Risk of bias in individual studies

To determine the risk of bias in RTCs, the Cochrane risk of bias tool was used [11]. Selection bias, performance bias, detection bias, attritions bias, reporting bias, and other biases were assessed for main outcomes. For non-RTCs and observational studies, we used Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) [12]. Studies were assessed to be of low risk, low to moderate risk, serious risk or critical risk of bias.

## Synthesis of results

Pregnancy rate was defined as number of pregnant women among all included women. We defined miscarriage rate as number of miscarriages among pregnant women.

Pregnancy and miscarriage rates for all studies were reported in a forest plot, stratified by study design, with confidence intervals of 95%.  $I^2$  were measured to quantify the heterogeneity with a range from 0 to 100%, where 0% indicate no inconsistency or heterogeneity.

We had planned to perform sub-group analyses based on mean BMI, age, size of fibroids and follow-up time when possible. The low number of comparative studies made such subgrouping not meaningful.

The statistical software Stata IC14.2 was used for data analysis.

We assessed the quality of evidence for each outcome inspired by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [13–20]. The quality of evidence was graded as: very low, low, moderate or high quality.

## Results

### Study selection (Fig. 1, PRISMA flow chart)

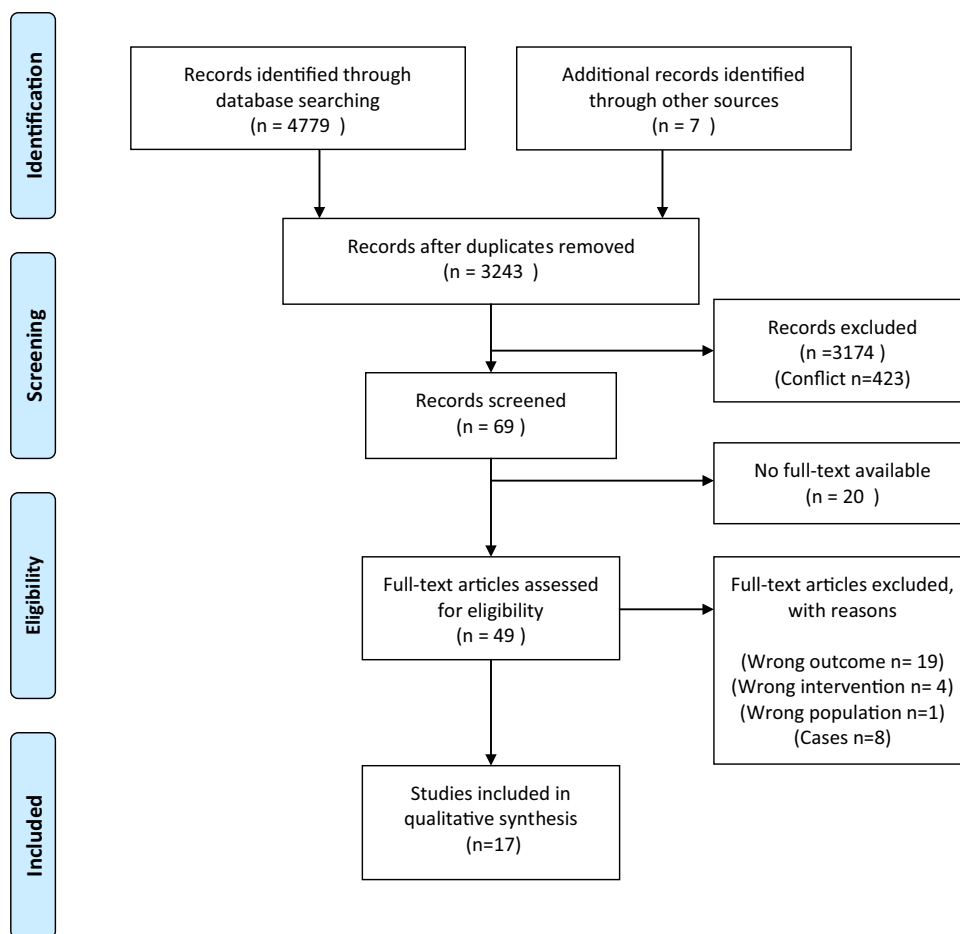
The searches in PubMed and Embase provided 4779 records. In all 3243 remained after duplicates were removed, and these were subsequently screened by two authors. In all, 69 studies met the inclusion criteria and 49 were available in full text and reviewed by the same two co-authors (K.K. and M.K.). 32 studies were excluded. 19 had wrong outcome, 4 had wrong interventions, 1 had wrong population and 8 were case reports. A total of 17 studies were included (Fig. 1).

### Study characteristics and results (Table 1, characteristics and results)

#### RCT

One RCT was included [21]. Inclusion criteria were intramural fibroids measuring at least 4 cm, age < 40 years, serum FSH < 30 IU/L and plans of pregnancy. 58 women were randomized to UAE and 63 women to myomectomy. Women previously treated with UAE or myomectomy were excluded. The intervention was standardized; bilateral with free flow and particle size > 500  $\mu$ m. Myomectomy was either performed by laparotomy or laparoscopy (67%) based on clinical assessment. Fibroids larger than 8 cm, multiple fibroids or fibroids with unfavorable localization were accessed by laparotomy. Patients were all recommended to wait at least 6 months before trying to conceive.

Groups were comparable in terms of age [32 years (UAE) and 32 years (myomectomy)] and fibroid mean size [62 mm (UAE) and 60 mm (myomectomy)]. Sterility was reported in 11 of 58 (19%) women in the UAE group and 24 women of 63 (38%) in the myomectomy group ( $p < 0.05$ ). Definition of sterility was not further described/defined. The mean duration of follow-up was 26.2 months (6–55) and 23.7 months (6–54), respectively. All included women had reproductive plans when randomized, but only 26 women in the UAE group and 40 women in the myomectomy group actually tried to conceive during follow-up. The reasons for that were not reported. Of these, 13 (50% CI 29, 70) women became pregnant after UAE and 31 (78% CI 62, 89) women after myomectomy. Pregnancy rates calculated from the original

**Fig. 1** PRISMA flow diagram

randomized groups were 22% (UAE, CI 14, 39) and 49% (myomectomy, CI 36, 62). Miscarriage rates were reported to be 64% (UAE) and 23% (myomectomy). The number of miscarriages was nine (UAE) and six (myomectomy), ectopic pregnancies one UAE and one myomectomy, terminations one UAE and one myomectomy out of respectively 17 and 32 reported pregnancies. It was not possible for the authors to reproduce the miscarriage rates from the reported numbers in the article. We found miscarriage rates at 60% (9/15) after UAE and 20% (6/30) after myomectomy. We contacted the authors of the article repeatedly without response.

Overall assessment of risk of bias in the RCT was assessed to be high. Selection bias was assessed to be low, but performance bias, detection bias, and attrition bias were all assessed to be high.

#### Cohort studies

Two prospective cohort studies compared UAE to laparoscopic uterine artery occlusion LUAO [22, 23].

In the Holub study from 2008, the objective was to assess reproductive outcomes after UAE and LUAO in women with

symptomatic fibroids [22]. Patients were assigned to one or the other treatment based on shared decision-making. Interventions were standardized and reported in detail. In total, 39 (UAE) and 81 (LUAO) women were included; all patients had a wish to conceive within 1–3 years after treatment. Follow-up time was not reported. Pregnancies were reported in 20 women after UAE and in 38 women after LUAO. Baseline characteristics on these women did not differ significantly regarding age, BMI, parity, reproductive history, or size of fibroids. Baseline characteristics of the women who did not conceive were not reported. The pregnancy rates were 51% (UAE, CI 35, 68) and 47% (LUAO, CI 36, 58) (difference NS). The miscarriage rates were 56% (UAE, CI 35, 76) and 11% (LUAO, CI 3, 26) ( $p < 0.001$ ).

In the Mara study from 2012, women were assigned to UAE or LUAO according to patient preferences [23] including 100 women in each group. Laparotomy access was chosen if fibroids had a risky location (uterine margins or isthmus), or in case of  $\geq 5$  fibroids with a diameter  $\geq 2$  cm, a dominating fibroid with a diameter  $> 7$  cm, or if a myomectomy had previously been performed. Groups differed in several characteristics: women in the UAE group were older and had higher BMI and larger fibroids. Only 42 women (UAE)

**Table 1** Characteristics and results of the included studies

Authors/ publication	Design	Population	Uterus/ volume/ size or volume of dominant fibroid	No women trying to conceive	Age	Intervention	Compara- son	Follow-up (month)	Preg- nant women	Pregnan- cies	Miscar- riage	Preg- nancy rate after UAE/ Com- pari- son	Miscar- riage rate after UAE/ Compari- son	
Mara et al. [21]	RCT	Women with reproductive plans who presented with an intramural fibroid larger than 4 cm Randomized for UAE or myomectomy Recommended to wait 6 month before attempting to conceive	/6.23 cm	58	26	32.8	UAE Bilateral Free flow particles > 500 µm First 5 with 300–900 µm before they knew better	Laparo- scopic myomec- tomy Open myomec- tomy	26.2 (6–55)	13	17	9	13/26 50% 31/40 78% UAE/ Compari- son	9/15 60% 6/30 20%
Holub et al. [22]	Prospective Cohort studies	Women treated for uterine fibroid by LUAO or UAE Women with submucous fibroids were excluded Women with desire for pregnancy Recommended to wait 6 month before attempting to conceive	/6.19 cm	39	39	32	UAE Particles of > 500 µm	LUAO	Unknown	20	28	14	20/39 51% 38/81 47%	14/25 56% 4/36 11%
Mara et al. [23]	Prospective Cohort studies	Pre-menopausal women with symptomatic fibroids who preferred minimally invasive procedure were screened Women who were not eligible for LM, because of risky location (uterine margin or isthmus), > 5 cm, > 7 cm or a history of myomectomy The decision about type of treatment is made before inclusion Women who attempted to conceive	/6.82 cm	100	42	33.1	UAE Bilateral Free flow Trisacryl gelatin micro- spheres > 500 µm	LUAO	45.5 (8–84)	29	42	13	29/42 69% 32/48 67%	13/29 45% 12/32 38%

Table 1 (continued)

Authors/ publication	Design	Population	Uterus volume/ size or volume of dominant fibroid	No women trying to conceive	Age	Intervention	Compara- son	Follow-up (month)	Preg- nant women	Pregnan- cies	Miscar- riage	Preg- nancy rate after UAE/ Com- pari- son	Miscar- riage rate after UAE/ Compari- son
Ravina et al. [2]	Prospective case series	Women who got pregnant after UAE UAE because of sympto- matic fibroids	455 cm <sup>3</sup>	12	36	UAE Highly selec- tive, Bilateral, polyvinyl alcohol 150/300 to 300/600 µm particles	Non	Unknown	9	12	5	14/52 27%	5/12 42%
McLucas et al. [25]	Prospective case series	Symptomatic fibroids, menorrhagia Trying for pregnancy < 40 years	71.5 cm	52	<40	UAE unknown method	Non	Unknown	14	17	5	14/52 27%	5/17 29%
Walker and Pelage [24]	Prospective case series	Women with heavy bleeding or pressure symptoms. Indication for intervention decided by experienced gyn If they had fertility wish, it was discussed every time. If multi/difficult myomectomy was the only surgical option, UAE was performed	Unknown	24	43.2	UAE Polyvinyl alcohol particles First 66 women- 150–200 or 355–500 µm From 1998 all 355–500 µm	Non	16.7	12	13	2	12/24 50%	2/13 15%
Pron et al. [26]	Prospective case series	Symptomatic fibroids Trying for pregnancy	426 cm <sup>3</sup>	35	34	UAE Polyvinyl alco- hol particles 355–500 µm Bilateral in 98% cases	Non	24	21	24	4	21/35 60%	4/24 17%
Pabon et al. [27]	Prospective case series	Symptomatic fibroids Trying for pregnancy	602 ml	57	39.7	UAE 500–1200 µm trisacryl gelatin microspheres	Non	Up till 60	10	11	3	10/57 18%	3/11 27%
Firouznia et al. [28]	Prospective case series	Symptomatic fibroids Trying for pregnancy Recommended to wait 12 month before attempting to conceive	552 cm <sup>3</sup> / 228 cm <sup>3</sup>	23	31.2	UAE Single entry- right femoral approach Particles 500- 700 µm	Non	Unknown	14	15	2	14/23 61%	2/15 13%

Table 1 (continued)

Authors/ publication	Design	Population	Uterus volume/ size or volume of dominant fibroid	No women trying to conceive	Age	Intervention	Compara- son	Follow-up (month)	Preg- nant women	Pregnan- cies	Miscar- riage	Preg- nancy rate after UAE/ Com- pari- son	Miscar- riage rate after UAE/ Compari- son
Redecha et al. [29]	Prospect- ive. Case series	Patient with symptomatic fibroids, bleeding, pain, bulky syndrome Women with subserosal myoma > 50% of its vol- ume above the uterine surface was excluded UAE treatment Pregnancy desire	/129 cm <sup>3</sup>	21	38.7	UAE Bilateral 300–500µ polyvinyl alcohol particles	Non	24	6	7	1	6/21 29%	1/7 14%
Torre et al. [30]	Prospect- ive case series	Symptomatic fibroids, menorrhagia, metror- rhagia, pain, bulking symptoms All as treatment for infertility	577 cm <sup>3</sup> / 97 cm <sup>3</sup>	31	37.3	UAE Bilateral, acryl microspheres of > 500 µm	Non	28.9(± 16.2)	1	1	1	1/31 3%	1/1 100%
Carpenter and Walker [31]	Retrospec- tive case series	Symptomatic fibroids Trying for pregnancy	Unknown	79	37	UAE Unknown method	Non	Unknown	26	26	7	26/79 33%	7/26 27%
Walker and McDowell [32]	Retrospec- tive case series	UAE for symptomatic uterine fibroids + preg- nancy desire	Unknown	108	37	UAE unknown method	Non	Unknown	33	56	17	33/10 31%	17/56 30%
Dutton et al. [33]	Retrospec- tive case series Part of hopeful study	Symptomatic fibroids Trying for pregnancy	Unknown	187	38	UAE unknown method	Non	Unknown	27	37	15	27/187 14%	15/37 41%

Table 1 (continued)

Authors/ publication	Design	Population	Uterus volume/ size or volume of dominant fibroid	No women trying to conceive	Age	Intervention	Compara- son	Follow-up (month)	Preg- nant women	Pregnan- cies	Miscar- riage	Preg- nancy rate after UAE/ Com- pari- son	Miscar- riage rate after UAE/ Compari- son
Bonduki et al. [34]	Retro- spective case series	Symptomatic uterine fibroids, menorrhagia, pain, compressive symp- toms, infertility related to fibroids Subserosal and submu- cosal fibroids were excluded	Unknown	75	34.3	UAE PVA 500–900 µm Bilateral	Non	42	15	15	2	15/75 20%	2/15 13%
Pisco et al. [35]	Retro- spective case series	Treated with UAE for fibroids Women who wanted to become pregnant Recommended to wait 6 month before attempt- ing to conceive	347.6 ml	74	36	UAE Single artery. Rand- omized for 500 or 700 µm particles.	Non	54	44	44	4	44/74 60%	4/44 9%
McLucas and Voorhees III [36]	Retro- spec- tive case series	Symptomatic fibroids; heavy menstruation, pain, pressure, bulk- related symptoms	550 cm <sup>3</sup> / 7.0 cm	104	33	UAE unknown method	Non	40 (6–145)	23	27	6	23/10 22%	6/27 2%

NO number, UAE uterine artery embolization, LVAO laparoscopic uterine artery occlusion, RCT randomized controlled trials, CCT clinical controlled trials



and 48 women (LUAO) tried to conceive during follow-up. Of these, women in the UAE subgroup were younger, had higher BMI, larger fibroids and fewer had multiple fibroids. Mean length of follow-up was 46 months (UAE, 8–84) and 40 months (LUAO, 6–82) (difference NS).

In total, 29 women in the subgroup of women trying to conceive became pregnant after UAE and 32 after LUAO giving pregnancy rates of 69% (UAE, CI 53, 82) and 67% (LUAO, CI 52, 80) (difference NS). The pregnancy rate calculated from the original included group was 29% (UAE, CI 20, 39) and 32% (LUAO, CI 29, 49) (difference NS).

The miscarriage rates were 34% (UAE) and 33% (LUAO) with 13 miscarriages after UAE and 12 after LUAO. It was not possible for the authors to reproduce the miscarriage rates from the reported numbers in the article. We found miscarriage rate at 45% (13/29) after UAE and 38% (12/32) after LUAO. We contact the authors of the article repeatedly without response.

Pregnancy and miscarriage rates [22, 23] were assessed by Robins-I to be with a moderate risk of bias, which means that results cannot be compared with results from a well-performed RTC. Generally, the non-RTCs were incomplete in terms of report of blinding, attempts of blinding, confounders, adjustments for confounders, lost to follow-up, and mean follow-up time.

#### Case series

Fourteen case series have been included in the present analysis, eight prospective [2, 24–30] and six [31–36] retrospective. All studies included women who underwent UAE due to symptomatic uterine fibroids. Six authors reported itemized symptoms and characteristics and location of the uterine fibroids, whereas eight did not specify this information. Further, UAE methods differed between studies. Most studies performed bilateral embolization and used particles > 500  $\mu\text{m}$  [2, 24, 26–28, 30, 34, 35]. Five studies did not specify the UAE method [25, 31–33, 36] and follow-up time varied from 17 to 60 months.

Pregnancy rate ranged from 14 to 61% and miscarriage rate ranged from 2 to 100%.

The case series had various methodological limitations, which made risk of bias high. Types of fibroids and outcome differed. None of the studies were designed to evaluate pregnancy or miscarriage rates. All studies had a large risk of selection, performance and reporting bias.

**Table 2** Median pregnancy rate and median miscarriage rate

Included studies	Pregnancy rate		Miscarriage rate	
	UAE (%)	Com- parison (%)	UAE (%)	Com- parison (%)
<b>RCT</b>				
Mara et al. [21]	50	78	60	23
<b>Cohort studies</b>				
Holub et al. [22]	60	50	45	25
Mara et al. [23]				
<b>Case series</b>				
Ravina et al. [2]	29		25	
McLucas et al. [25]				
Walker and Pelage [24]				
Pron et al. [26]				
Pabon et al. [27]				
Firouznia et al. [28]				
Redecha et al. [29]				
Torre et al. [30]				
Carpenter and Walker [31]				
Walker and McDowell [32]				
Dutton et al. [33]				
Bonduki et al. [34]				
Pisco et al. [35]				
McLucas and Voorhees III [36]				

RCT randomized controlled trials, UAE uterine artery embolisation

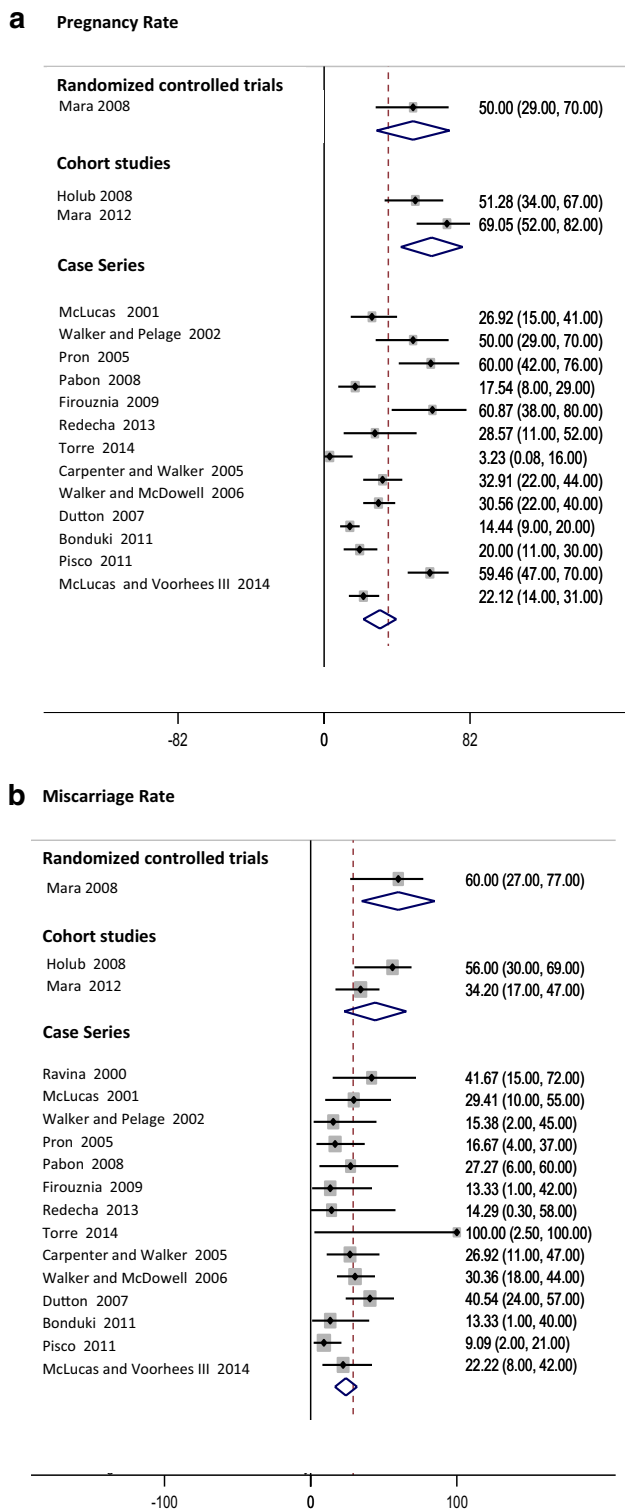
#### Synthesis of results (Table 2; Fig. 2a, b)

##### RCT

The included RCT found a pregnancy rate of 50% (13/26) after UAE and 78% (31/40) after myomectomy (difference NS). Miscarriage rate was found to be 60% (9/15) after UAE and 20% (6/15) after myomectomy [Statistically significant different ( $p < 0.05$ )].

##### Cohort studies

The two included cohort studies reported pregnancy rates of, respectively, 51% (CI 35, 68) and 69% (CI 53, 82) after UAE, and, respectively, 47% (CI 36, 58) and 67% (CI 52, 80) after LUAO (difference NS). Miscarriage rates were found to be, respectively, 56% (CI 35, 76) and 45% after UAE, and respectively, 11% (CI 3, 26) and 38% after LUAO ( $p < 0.001$ ).



**Fig. 2 a** pregnancy rates, **b** miscarriage rate. Pregnancy rates from included studies expressed in percent

The median pregnancy rate after UAE among the included cohort studies is 60% ( $I^2$  59.0%). The median miscarriage rate after UAE among the included cohort studies is 45% ( $I^2$  66.8%).

*Case series*

For the fourteen included case series, the median pregnancy rate after UAE is 29% ( $I^2$  89.7%) and the median miscarriage rate is 25% ( $I^2$  54.4%).

**Grade**

We graded the quality of evidence regarding both pregnancy and miscarriage rates to be low, which means that the true effect may be substantially different from the estimate of the effect. We downgraded the quality due to study limitations (high risk of bias) and inconsistency of results.

**Discussion**

In this systematic review, investigating studies on treatment of uterine fibroids with UAE, we found very low quality of the evidence.

UAE was introduced by Ravina et al. in 1995 as a radiological treatment for uncontrolled onco-gynecologic and obstetric uterine bleeding [37]. Since then, UAE has become an alternative to surgical removal of uterine fibroids. During the initial years after the introduction, UAE was considered an attractive method for improving symptoms from fibroids, but after a few years, reports of possible negative impacts on future fertility emerged. Case series reported a high rate of miscarriage, which subsequently resulted in a restricted approach towards UAE in fertile women. It is believed that UAE can result in ischemia of the endometrium and cause endometrial damage [38]. In a study including hysteroscopy and endometrial histology 6 months after UAE, 90% of included women revealed a normal functional endometrium by histological evaluation, but only 37% revealed entirely normal hysteroscopy findings. Intrauterine protrusion of fibroid/s, yellowish coloration of the endometrium, intrauterine or cervical adhesions and communication between the myoma and the uterine cavity were reported [39]. The women were only assessed after treatment and it remains unknown whether the findings were caused by UAE or the fibroids *per se*. Fibroids are removed completely by surgical treatment, whereas even successful UAE result in up to 40% fibroid mass remaining after the procedure. Since fibroids are known to cause decreased pregnancy rates and increased miscarriage rates [40], it is unknown whether the negative

results reported after UAE are caused by a remaining fibroid mass or endometrial damage.

Several narrative reviews have been published on pregnancy rates and obstetric outcomes after treatment of uterine fibroids with UAE, but no systematic review with pregnancy rate as primary outcome has been published. In 2010, a systematic review on miscarriage rate was performed [41]. Homer et al. reviewed seven reports of outcomes of 227 completed pregnancies after UAE, five observational studies, one prospective cohort-controlled study, and one RCT. A control group of pregnant women with untreated fibroids was constructed with 1121 pooled pregnancies. The accumulated miscarriage rate was 16.5% among women with fibroids and 35.2% among women previously treated with UAE. The study concluded that UAE increases the risk of miscarriage.

Mohan et al. reviewed 21 studies, concluding that the impact on fertility was still unclear [42]. Age and type of fibroids were assessed to be strong confounders and no studies adjusted for this. A narrative review from 2014 found that UAE is a safe alternative to a surgical procedure for women who do not want to preserve fertility and/or for selected cases where the surgical risk is high [43]. In contrast to these studies, the latest review from 2016 concluded that UAE is a valid alternative to myomectomy for women who wish to conceive [44]. However, the review did not include the RCT by Mara et al. [21], which to our knowledge this is the only RCT.

It is important to include age and observation time as possible confounders in assessment of fertility. Fecundability (the probability of achieving pregnancy in one menstrual cycle) among 782 healthy couples is 40% among 27–34-year-old women and 30% among 35–39-year-old women [45]. The American Society for Reproductive Medicine published the fecundability among 30-year-old healthy women to be 20 and 5% among women older than 40 years [46]. None of the pregnancy rates reported in the review have been assessed based on the number of cycles. However, the results of our review are in favor of both UAE and myomectomy with pregnancy rates of 50 and 78% over a period of 6–55 months in 32–33-year-old women, respectively, i.e., comparable to reports in healthy couples. Women in the included case series after UAE were slightly older (36–37 years in average) compared to the women in the RCT and CCT's. Still, mean pregnancy rates were 35%. Miscarriage rates were 15% among 30–34-year-old women and 51% among 40–44-year-old women in a register-based study [47]. This outcome does not require a time frame making miscarriage more directly comparable. We found miscarriage rates after UAE to range from 45 to 60% among RCT/CCT in women aged 32–33 years, thus considerably higher than the spontaneous miscarriage rate in healthy women of comparable age. However, the increased miscarriage rate

reported in the RCT and CCT are not found among the included case series (miscarriage rates at 29%). The included women in the case series were even slightly older, and an increased miscarriage rate, therefore, expected.

### Strengths and limitations

The strength of this systematic review is the application of Cochrane methodology. A systematic search was applied with very few exclusion criteria, ensuring that all relevant studies were most likely identified. A challenge, as well as a main result, is the low quality of the evidence available: Only one RCT and two CCT met the inclusion criteria.

### Implications on research

There is considerable uncertainty as to whether UAE causes a higher degree of reduced fertility as compared with surgery, so there is a clear indication for a large RCT assessing fertility outcomes after UAE compared with myomectomy. An ideal RCT should include fertile women with symptomatic fibroids and a wish to conceive designed to randomize between UAE, myomectomy and no treatment with pregnancy, live birth and miscarriage as outcome before and after treatment.

This review leaves the question whether remaining fibroids or post-embolization ischemia of the endometrium is the causal reason for the negative impact on fertility, calling for research with focus on causality.

### Implication on practice

The Cochrane review update from 2014 concluded that there is very low quality evidence to suggest that myomectomy may be associated with better fertility outcomes than UAE [4]. By reviewing the literature with focus on UAE and fertility, we have made a very specific review. Only premenopausal women with desire for future pregnancy have been reviewed, and only based on specific outcomes (pregnancy and miscarriage rate). The conclusion in our review is in line with this previous conclusion regarding low quality of evidence and does not justify a major change in recommendations. On the other hand, we do not find evidence to suggest that future pregnancy is a contraindication against UAE. There is a need for improved studies to increase the quality of evidence. In the meantime, the NICE guidelines should be followed and for women with future pregnancy desire the considerable uncertainty and remaining risk of decreased fertility should be discussed.

## Conclusion

In conclusion, a total of 1 RCT, 2 CCT's, and 14 case series (989 included women) have been reviewed. We found that half the women (50%) achieved a pregnancy after UAE, which is lower than after myomectomy (78%). Miscarriage rates appear to be higher after UAE (60%) than after myomectomy (20%). However, we found very low quality of evidence and the reported proportions are uncertain. We see a clear need for future well-designed RCT's exploring possible differences in reproductive outcomes between the different treatments for uterine fibroids. This systematic review does not call for revision of existing guidelines. We do not recommend UAE as first choice treatment for women with future pregnancy plans.

**Acknowledgements** This review received an un-restricted Grant from The University of Southern Denmark.

**Author contributions** KK: Data curation, formal analysis, methodology, project administration, and writing original draft. AH: Methodology, supervision, writing review, and editing. MK: Data curation, formal analysis, writing review, and editing. OM: Supervision, writing review, and editing. PH: Supervision, writing review, and editing. PR: Formal analysis, supervision, writing review, and editing.

## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants performed by any of the authors.

## References

- Baird DD et al (2003) High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 188(1):100–107
- Ravina JH et al (2000) Pregnancy after embolization of uterine myoma: report of 12 cases. *Fertil Steril* 73(6):1241–1243
- Stewart EA (2001) Uterine fibroids. *Lancet* 357(9252):293–298
- Gupta JK et al (2015) Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev* 5:Cd005073
- Spies JB et al (2007) Long-term outcome from uterine fibroid embolization with tris-acryl gelatin microspheres: results of a multicenter study. *J Vasc Interv Radiol* 18(2):203–207
- Guidance IP (2010) Uterine artery embolisation for fibroids
- RCOG (2013) Clinical recommendations on the use of uterine artery embolisation (UAE) in the management of fibroids
- Andersen JEA (2014) DSOG guideline
- Gupta JK et al (2014) Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev* 12:Cd005073
- Meta-analyses, T.R.o.S.R.a., PRISMA-statement. <http://www.prisma-statement.org/>
- Green JPHAS (2011) *Cochrane handbook for systematic reviews of interventions*. Wiley, New York
- IR, The risk of bias in non-randomized studies- of interventions (ROBINS I) assessment tool. <https://sites.google.com/site/riskofbiastool/welcome/home>
- Guyatt G et al (2011) GRADE guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 64(4):383–394
- Guyatt GH et al (2011) GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 64(4):395–400
- Balshem H et al (2011) GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 64(4):401–406
- Guyatt GH et al (2011) GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 64(4):407–415
- Guyatt GH et al (2011) GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* 64(12):1277–1282
- Guyatt GH et al (2011) GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol* 64(12):1283–1293
- Guyatt GH et al (2011) GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* 64(12):1294–1302
- Guyatt GH et al (2011) GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol* 64(12):1303–1310
- Mara M et al (2008) Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. *Cardiovasc Intervent Radiol* 31(1):73–85
- Holub Z et al (2008) Pregnancy outcomes after uterine artery occlusion: prospective multicentric study. *Fertil Steril* 90(5):1886–1891
- Mara M et al (2012) Uterine artery embolization versus laparoscopic uterine artery occlusion: the outcomes of a prospective, nonrandomized clinical trial. *Cardiovasc Intervent Radiol* 35(5):1041–1052
- Walker WJ, Pelage JP (2002) Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up. *BJOG* 109(11):1262–1272
- McLucas B et al (2001) Pregnancy following uterine fibroid embolization. *Int J Gynaecol Obstet* 74(1):1–7
- Pron G et al (2005) Pregnancy after uterine artery embolization for leiomyomata: the ontario multicenter trial. *Obstet Gynecol* 105(1):67–76
- Pinto Pabon I et al (2008) Pregnancy after uterine fibroid embolization: follow-up of 100 patients embolized using tris-acryl gelatin microspheres. *Fertil Steril* 90(6):2356–2360
- Firouznia K et al (2009) Pregnancy after uterine artery embolization for symptomatic fibroids: a series of 15 pregnancies. *Am J Roentgenol* 192(6):1588–1592
- Redecha M Jr et al (2013) Pregnancy after uterine artery embolization for the treatment of myomas: a case series. *Arch Gynecol Obstet* 287(1):71–76
- Torre A et al (2014) Uterine artery embolization for severe symptomatic fibroids: effects on fertility and symptoms. *Hum Reprod* 29(3):490–501
- Carpenter TT, Walker WJ (2005) Pregnancy following uterine artery embolisation for symptomatic fibroids: a series of 26 completed pregnancies. *BJOG* 112(3):321–325
- Walker WJ, McDowell SJ (2006) Pregnancy after uterine artery embolization for leiomyomata: a series of 56 completed pregnancies. *Am J Obstet Gynecol* 195(5):1266–1271
- Dutton S et al (2007) A UK multicentre retrospective cohort study comparing hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids (HOPEFUL study): main results on medium-term safety and efficacy. *BJOG* 114(11):1340–1351

34. Bonduki CE et al (2011) Pregnancy after uterine arterial embolization. *Clinics (Sao Paulo)* 66(5):807–810
35. Pisco JM et al (2011) Pregnancy after uterine fibroid embolization. *Fertil Steril* 95(3):1121.e5–1121.e8
36. McLucas B, Voorhees IWD (2014) Results of UAE in women under 40 years of age. *Minim Invasive Ther Allied Technol* 23(3):179–183
37. Ravina JH et al (1995) Arterial embolisation to treat uterine myomata. *Lancet* 346(8976):671–672
38. Tropeano G et al (2003) Permanent amenorrhea associated with endometrial atrophy after uterine artery embolization for symptomatic uterine fibroids. *Fertil Steril* 79(1):132–135
39. Mara M et al (2007) Hysteroscopy after uterine fibroid embolization in women of fertile age. *J Obst Gynaecol Res* 33(3):316–324
40. Pritts EA, Parker WH, Olive DL (2009) Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril* 91(4):1215–1223
41. Homer H, Saridogan E (2010) Uterine artery embolization for fibroids is associated with an increased risk of miscarriage. *Fertil Steril* 94(1):324–330
42. Mohan PP, Hamblin MH, Vogelzang RL (2013) Uterine artery embolization and its effect on fertility. *J Vasc Interv Radiol* 24(7):925–930
43. Mara M, Kubinova K (2014) Embolization of uterine fibroids from the point of view of the gynecologist: pros and cons. *Int J Womens Health* 6:623–629
44. McLucas B, Voorhees WD 3rd, Elliott S (2016) Fertility after uterine artery embolization: a review. *Minim Invasive Ther Allied Technol* 25(1):1–7
45. Dunson DB, Colombo B, Baird DD (2002) Changes with age in the level and duration of fertility in the menstrual cycle. *Hum Reprod* 17(5):1399–1403
46. Opinion C (2014) Female age-related fertility decline. *Fertil Steril* 101(3):633–634
47. Nybo Andersen AM et al (2000) Maternal age and fetal loss: population based register linkage study. *BMJ* 320(7251):1708–1712