

SYSTEMATIC REVIEW

The impact of uterine artery embolization on ovarian reserve: A systematic review and meta-analysis

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Abstract

Introduction: Uterine artery embolization (UAE) has been gaining increasing popularity as an effective and minimally invasive treatment for uterine fibroids. However, there has been growing concern over the risk of unintended embolization of the utero-ovarian circulation, leading to reduction of ovarian blood supply with subsequent impairment of ovarian reserve. The purpose of this study was to investigate the impact of UAE on circulating anti-Müllerian hormone (AMH) and other markers of ovarian reserve.

Material and methods: This meta-analysis included all published cohort, cross-sectional and case-control studies, as well as randomized trials that investigated the impact of UAE on circulating AMH. Data sources included MEDLINE, EMBASE, Dynamed Plus, ScienceDirect, TRIP database, ClinicalTrials.gov and the Cochrane Library from January 2000 to June 2019. All identified articles were screened, and articles were selected based on the inclusion and exclusion criteria. AMH and other data were extracted from the eligible articles and entered into RevMAN software to calculate the weighted mean difference between pre- and post-embolization values. PROSPERO registration number: CRD42017082615.

Results: This review included 3 cohort and 3 case-control studies (n = 353). The duration of follow up after UAE ranged between 3 and 12 months. Overall pooled analysis of all studies showed no significant effect of UAE on serum AMH levels (weighted mean difference -0.58 ng/mL; 95% CI -1.5 to 0.36, $I^2 = 95%$). Subgroup analysis according to age of participants (under and over 40 years) and according to follow-up duration (3, 6 and 12 months) showed no significant change in post-embolization circulating AMH. Pooled analysis of serum follicle-stimulating hormone (FSH) concentrations (4 studies, n = 248) revealed no statistically significant change after UAE (weighted mean difference 4.32; 95% CI -0.53 to 9.17; $I^2 = 95%$). Analysis of 2 studies (n = 62) measuring antral follicle count showed a significant decline at 3-month follow up (weighted mean difference -3.28; 95% CI -5.62 to -0.93; $I^2 = 94%$).

Conclusions: Uterine artery embolization for uterine fibroids does not seem to affect ovarian reserve as measured by serum concentrations of AMH and FSH.

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; UAE, uterine artery embolization; WMD, weighted mean difference.

KEYWORDS

anti-Müllerian hormone, antral follicle count, follicle-stimulating hormone, ovarian reserve, uterine artery embolization

1 | INTRODUCTION

Uterine fibroids are the most common benign pelvic neoplasm in women with a wide variation in reported prevalence (25%-80%) in the literature.^{1,2} The wide variation in prevalence of fibroids is due to differences in populations (age, race, etc.) studied.³ Although the majority are asymptomatic, about 25% of women with fibroids have symptoms that significantly impact on their quality of life such as menorrhagia, dysmenorrhea, bloating, pressure symptoms and fatigue.¹ Other reproductive problems include subfertility or adverse pregnancy outcome depending on the location, size and number of the fibroids.⁴ Treatment options for uterine fibroids include expectant management, symptomatic treatment, hormonal therapy, hysteroscopic resection, myomectomy, hysterectomy and uterine artery embolization (UAE).

Uterine artery embolization was first introduced in 1995 as a minimally invasive and uterus-sparing treatment option for premenopausal women with symptomatic fibroids.⁵ Since then, UAE has been successfully employed in the management of other obstetric and gynecologic problems such as adenomyosis,⁶ uterine vascular malformations⁷ and postpartum hemorrhage.⁸ Furthermore, health-related quality of life results following UAE were reported to be comparable to hysterectomy.⁹

The procedure is performed using a percutaneous transfemoral approach to access both internal iliac arteries. After confirming the position of the catheter in the internal iliac artery, a guide wire is fed into the uterine artery and the catheter is threaded over the guide wire. After that, angiography is performed to assess the vascularity and size of the fibroid before the embolic agent is injected.¹⁰ The reported improvements in menorrhagia, pelvic pain and pelvic pressure after UAE are 90%, 80% and 90%, respectively.^{9,11}

Although UAE has been established as an effective and minimally invasive treatment option for uterine fibroids, there have been concerns over its impact on ovarian reserve in women desiring future pregnancy. It has been postulated that unintended embolization of the utero-ovarian collateral circulation during UAE could lead to impairment of the blood supply to the ovaries with subsequent decline in ovarian reserve.¹²

The impact of UAE on ovarian function in women wishing to retain their fertility remains controversial.¹² Some authors suggest that UAE should not be offered to women desiring future pregnancy,^{13,14} but others report that UAE has insignificant effects on ovarian reserve and should be considered a feasible treatment option for women wishing to remain fertile.¹⁵⁻¹⁷ Tulandi et al reported a harmful effect on ovarian reserve after UAE.¹² However, more recent studies using anti-Müllerian hormone (AMH) as a marker for ovarian reserve revealed no significant decline in ovarian reserve after UAE.¹⁸⁻²⁰ Given the relatively small size of these

Key message

This systematic review analyzed six studies investigating the effect of uterine artery embolization on ovarian reserve in 353 women. Ovarian reserve was determined by circulating anti-Müllerian hormone. The review found that this procedure had no detrimental effect on ovarian reserve.

studies, further evidence is required to draw a firm conclusion. Therefore, the aim of this systematic review and meta-analysis was to investigate the impact of uterine artery embolization on ovarian reserve as determined by circulating serum AMH levels.

2 | MATERIAL AND METHODS**2.1 | Criteria for study selection**

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines²¹ and was prospectively registered in PROSPERO (CRD42017082615). All published cohort, cross-sectional, case-control studies and randomized controlled trials that investigated the impact of UAE on ovarian reserve as determined by serum AMH concentration were included in this systematic review.

2.2 | Outcome measures**2.2.1 | Primary outcome**

This was changes in serum AMH concentration after UAE.

2.2.2 | Secondary measures

These included post-embolization changes in serum follicle-stimulating hormone (FSH) concentration and antral follicle count (AFC).

2.3 | Search strategy

An extensive electronic database search was performed using MEDLINE, Scopus, EMBASE, Dynamed, TRIP, ScienceDirect and the Cochrane Library to identify research articles published between January 2000 and December 2018, on the impact of UAE on ovarian reserve as determined by serum AMH concentration. A combination of the following search terms was used: uterine artery embolization, uterine artery embolization, fibroid embolization, ovarian reserve,

anti-Müllerian hormone, antral follicle count, ovarian volume, follicle-stimulating hormone, ovarian function and pregnancy rate. For a more comprehensive search, we have also searched different databases using terms relating to the population (patients with fibroid) and intervention (UAE) regardless of the outcomes, as recommended by Cochrane methodology. All searches were carried out by the first author (TE) and then independently repeated using the same criteria by an accredited clinical librarian (CJ). All relevant reports were retrieved, and their reference lists were reviewed manually to identify further studies. The included studies should have been published in a peer-reviewed journal, with full-text available in English. We also considered published abstracts from conferences.

2.4 | Screening and selection of studies

All the identified papers were screened for relevance to the review by reading the title and abstract. Relevant studies were read in full for eligibility according to inclusion/exclusion criteria. They were evaluated according to a standardized format including study design, methods, participant characteristics, intervention and results. Two investigators (TE and AM) reviewed the articles and collected the information independently. In the case of discrepancies in scoring between the two investigators, a consensus was reached after discussion or after involvement of the senior investigators (SA and KJ).

2.5 | Quality of included studies and risk of bias assessment

The quality and risk of bias of the included studies were assessed using a modified Newcastle-Ottawa scale for assessing the quality of nonrandomized studies. The original Newcastle-Ottawa scale for nonrandomized studies assesses three main categories including selection, comparability and outcomes giving a maximum of four, two and three stars for each category, respectively.²² This scale was modified to suit the nature of this study giving a maximum of three stars for selection, four for comparability and 2 for outcome criteria.^{23,24} Selection was rated according to recruitment bias, selection of consecutive participants and power calculation. Comparability was assessed based on studies adjusting their analysis for four confounders including participants' age (<40 years), dominant fibroid volume, baseline serum AMH and laterality of the UAE procedure. Outcome was scored according to completeness of at least 3-month follow up after embolization. It is generally accepted that a limit of 5 stars

could identify studies at low risk of bias.^{25,26} However, in our study, we have set the cut-off level at six stars.²³ Table 1 shows the results of quality scores of the studies included in this analysis.

2.6 | Data extraction and analysis

Pre- and post-embolization data including mean \pm SD serum concentrations AMH (ng/mL) and FSH (IU/L) and ovarian volume were extracted from the individual studies and entered into REVIEW MANAGER version 5.1 software, The Cochrane Collaboration, 2011 (The Nordic Cochrane Center). The weighted mean difference (WMD) between pre- and post-embolization values was calculated.

Statistical heterogeneity was assessed by chi-squared test and I^2 statistics. A chi-squared statistic larger than its degree of freedom or an I^2 higher than 50% was indicative of significant heterogeneity (moderate to high level) between studies. When heterogeneity was significant, a random-effect model was used for meta-analysis. Fixed effect meta-analysis was used when there was no significant heterogeneity.²⁷

The initial analysis included data from all studies, irrespective of length of follow up. In studies with multiple postoperative measurements at different follow-up points, we used the latest AMH level. Further subgroup analyses of AMH levels were then performed based on duration of follow up.

3 | RESULTS

Our initial search identified a total of 131 articles, of which nine were considered relevant as described above (Figure 1). Our more comprehensive search including population and intervention regardless of the outcome identified 1977 articles. Screening of these articles did not reveal any more relevant studies.

3.1 | Excluded studies

After the initial screening on the basis of the title and abstract, 122 studies were deemed irrelevant to the topic of systematic review and were therefore excluded (Figure 1). Three further studies were excluded due to missing data, including pre- and/or post-embolization serum AMH levels.²⁸⁻³⁰ The authors of these 3 studies were contacted by email to provide the missing data but did not respond despite several reminders.

TABLE 1 The results of quality scores of the studies included in the analysis

Author	Year	Selection	Comparability	Outcome	Score
Torre et al ³¹	2014	**	***	**	7
Keshavarzi et al ¹⁹	2015	**	**	**	6
Kim et al ³²	2016	*	***	**	6
McLucas et al ¹⁵	2017	**	**	**	6
Tsikouras et al ²⁰	2017	**	***	**	6
Czuczwar et al ³³	2018	*	****	**	7

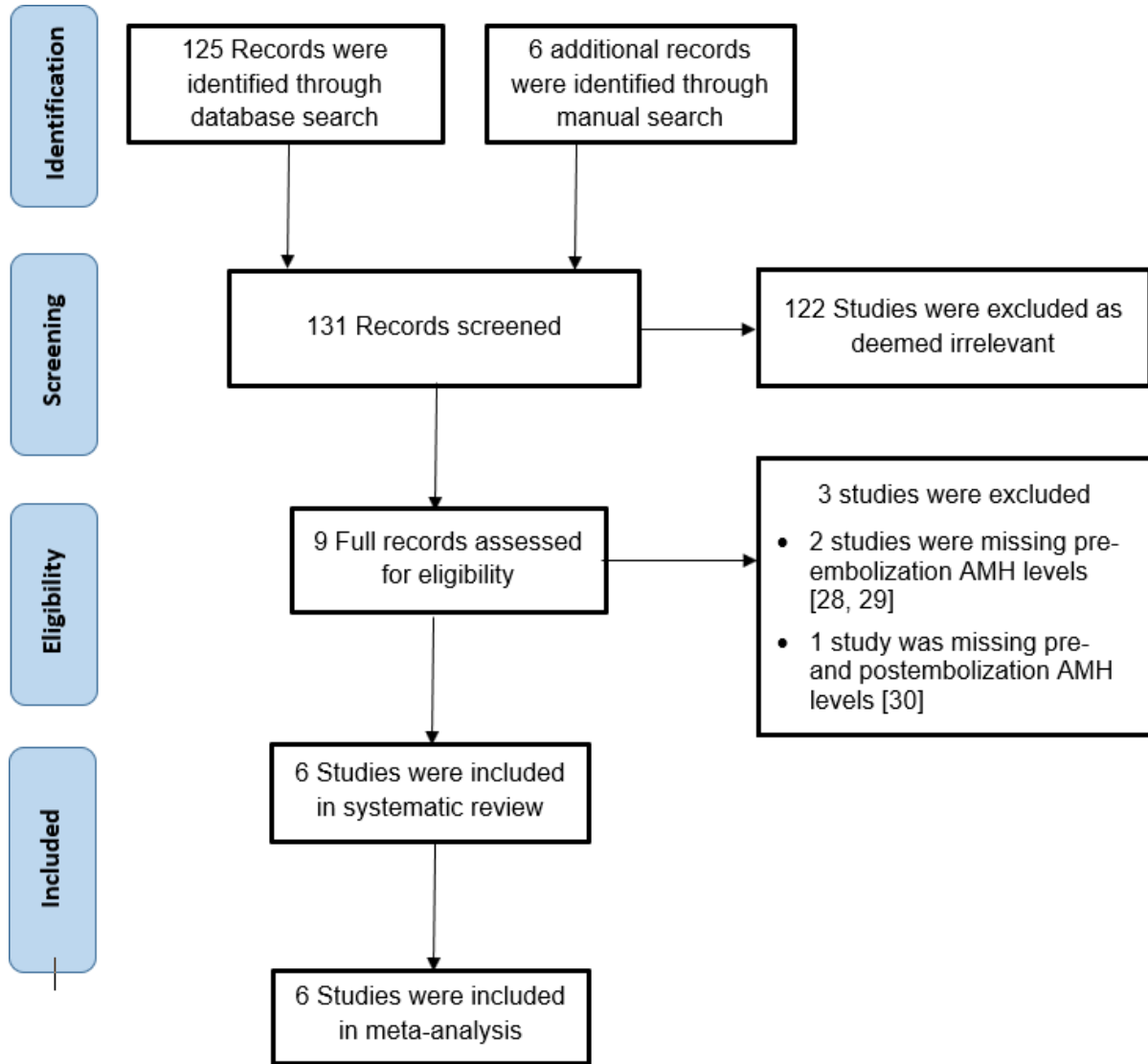


FIGURE 1 PRISMA flow chart of the study selection process [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Included studies

The remaining six studies were eligible for our review and included all required data. These are summarized in Table 2. All studies scored ≥ 6 on the modified Newcastle-Ottawa scale and the sensitivity analysis was not carried out.

3.3 | Study design

The review included two prospective cohort studies,^{15,31} retrospective cohort study³² and three case-control studies.^{19,20,33}

3.4 | Participants

Selection criteria were appropriate for all studies. All studies reported inclusion and exclusion criteria that were appropriate except one.¹⁹

With regards to the laterality of UAE, five studies reported bilateral UAE and one did not specify the laterality.¹⁹ The embolic agent was polyvinyl alcohol in two studies,^{15,33} Tris-acryl gelatin microspheres in one study,³¹ gelatin sponge particles in one study,³² and was not reported in one study.¹⁹ One study presented pre- and post-embolization AMH concentrations in median and range. We contacted the corresponding author who provided the mean \pm SD of AMH.³³

The length of follow up was up to 3 months in one study,³³ 6 months in one study,¹⁹ 10 months in one study¹⁵ and 12 months in three studies.^{20,31,32}

3.5 | UAE techniques

Apart from one study,¹⁹ all others described the methods and the material used for UAE including polyvinyl alcohol particles 500 μm ,^{15,33} gelatin sponge particles (500-710 μm , then changed to 710-1000 μm),³² spherical nonresorbable hydrogel-coated microspheres (700 and

TABLE 2 Characteristics of the six studies included in the meta-analysis

Author	Country	Design	n	Age (mean ± SD)	Laterality and method of UAE	Dominant fibroid volume (mL)	Follow up (mo)	AMH Kit	Secondary outcomes (ovarian reserve markers)
Torre et al., 2014 ³¹	France	Prospective cohort	64	37.3 ± 3.9	Bilateral (Tris-acryl microspheres 500-1200 µm)	97 ± 103	3, 6, 12 ^a	NS	FSH, LH, E ₂ , Inhibin B, fertility
Keshavarzi et al., 2015 ¹⁹	Iran	Case-control	20	34.6 ± 3.9	NS	NS	6	Monobinal kit	—
Kim et al., 2016 ³²	South Korea	Retrospective cohort	32	39.4 ± 4.8	Bilateral (gelatin sponge) ^b	265.26 ± 339.0	3, 12	NS	FSH, LH, E ₂ , AFC, OV
McLucas et al., 2017 ¹⁵	USA	Prospective cohort	87	35.5 ± 3.8	Bilateral (PVA ≥ 500 µm)	NS	Variable ^c	NS	—
Tsikouras et al., 2017 ²⁰	Greece	Case-control	120	43.6 ± 2.05	Bilateral (Hydrogel coated micro-spheres 700-900 µm)	NS	1, 3, 6, 12	NS	FSH, LH, E ₂
Czuczwar et al., 2018 ³³	Poland	Case-control	30	35 (33-40)	Bilateral (PVA)	108.5 ± 12.6	3	ELISA (USCN-E90228Hu)	FSH, AFC, inhibin B, E ₂

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; E₂, estradiol; ELISA, enzyme-linked immunosorbent assay; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NS, not specified; OV, ovarian volume; PVA, polyvinyl alcohol.

^aFirst follow up was 2 weeks after surgery.

^bGelatin sponge 500-710 µm then changed to 710-1000 µm.

^c190 ± 290 days.

900 µm in diameter)²⁰ and calibrated Tris-acryl microspheres (>500 µm in diameter).³¹ In all these studies, one experienced interventional radiologist performed the UAE bilaterally by inserting an angiographic catheter into the femoral artery through an incision in the right groin. Two studies described the embolization end-point as the complete stasis of contrast agent in the ascending segment of the uterine artery.^{20,32} One study defined the embolization end-point as the pruned-tree appearance corresponding to limited UAE targeting the peri-fibroid arterial plexus and sparing normal adjacent myometrial arteries.³¹

3.6 | AMH assays

Only two studies provided the type of AMH kit used (without giving any details) including E90228Hu AMH ELISA (Wuhan USCN Business Co., Ltd., Wuhan, China)³³ and AMH Monobinal kit.¹⁹ The remaining four studies did not specify the type of AMH kit used.

3.7 | Overall pooled results for all studies

Analysis of all six studies including 353 participants showed no significant change in post-embolization serum AMH concentrations (WMD -0.60 ng/mL; 95% CI -1.51 to 0.31). Heterogeneity between studies was high ($I^2 = 94%$) (Figure 2).^{15,19,20,31-33}

3.8 | Sensitivity analysis

No sensitivity analysis was performed because all studies scored ≥6 on the modified Newcastle-Ottawa scale.

3.9 | Subgroup analysis

3.9.1 | According to age of participants

A total of four studies provided data for women under/over 40 years of age including two studies with women ≤40 years (n = 50),^{19,33} one study including under 40 (n = 21) and over 40 (n = 11)³² and one study including women over 40 (n = 120).²⁰ The remaining two studies included women with an age range crossing 40 and did not provide separate data for under/over 40 years of age.^{15,31}

Pooled analysis of the three studies including participants aged ≤40 years (n = 71) showed no significant change in post-embolization serum AMH concentrations (WMD -0.93; 95% CI -2.39 to 0.53; $I^2 = 91%$).^{19,32,33}

Pooled analysis of the two studies including participants aged >40 years (n = 131) revealed no significant change in post-embolization serum AMH levels (WMD -0.10; 95% CI -0.92 to 0.09; $I^2 = 0%$).^{20,32}

3.9.2 | According to duration of follow up

Pooled results of four studies (n = 246) showed no significant drop in serum AMH concentration at 3 months after embolization (WMD -0.21; 95% CI -0.52 to 0.10; $I^2 = 96%$).^{20,31-33} Analysis of three studies (n = 204) with 6 months of follow up showed no statistically significant difference in post-embolization serum AMH concentration (WMD -0.17; 95% CI -0.43 to 0.13; $I^2 = 0%$).^{19,20,31} Similarly, analysis of three studies (n = 214) with 12 months of

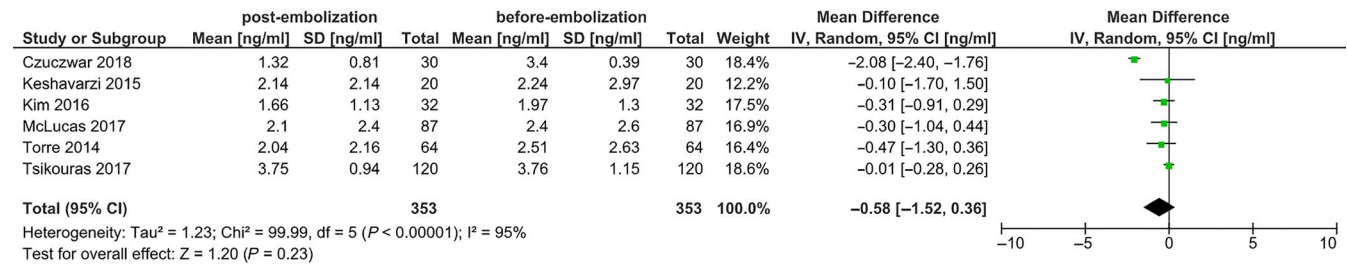


FIGURE 2 Weighted mean difference in serum anti-Müllerian hormone concentrations after uterine artery embolization for symptomatic uterine fibroids: pooled results for all six studies [Color figure can be viewed at wileyonlinelibrary.com]

follow up revealed no statistically significant difference in post-embolization serum AMH concentration (WMD -0.09; 95% CI -0.32 to 0.14; I² = 0%).^{20,31,32}

3.10 | Secondary outcomes

3.10.1 | Serum FSH concentrations

Four studies measured changes in serum FSH concentrations (n = 248).^{20,31-33} Pooled analysis of these four studies showed no significant change in circulating FSH following UAE (WMD 4.32; 95% CI -0.53 to 9.17; I² = 95%) (Figure 3).

3.10.2 | Antral follicle count

Two studies included AFC (as a marker for ovarian reserve) as an outcome measure at 3 months of follow up (n = 62).^{32,33} Pooled analysis of these two studies showed a significant decline in AFC at 3 months following UAE (WMD -3.28; 95% CI -5.62 to -0.93; I² = 94%) (Figure 4).

4 | DISCUSSION

To the best of our knowledge, this is the first systematic review to investigate the impact of UAE on ovarian reserve as determined by serum AMH concentration. The data from our meta-analysis showed no significant effect of UAE on ovarian reserve as measured by AMH levels up to 12 months after the procedure. Subgroup analysis to evaluate the degree of effect on ovarian reserve at 3 and 6 months also showed no significant drop in AMH levels after UAE. We have adopted an extensive electronic and manual search approach and we have examined the quality of the included studies through a modified Newcastle-Ottawa Quality Assessment Scale.

Two of the reviewed studies showed a significant reduction of AFC at 3 months follow up.^{32,33} Interestingly, one of these two studies reported a partial recovery of AFC at 12 months of follow up.³² This is in agreement with a previous study by Tropeano et al, who reported no significant change in AFC at 12 months and up to 5 years after UAE when compared with a control group.¹³ Given the small number of women included in the reviewed studies it is difficult to draw a firm conclusion on the short-term effect of UAE on AFC. A possible

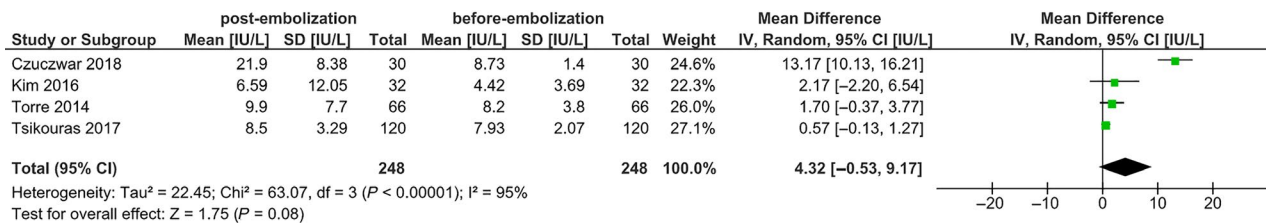


FIGURE 3 Weighted mean difference in serum follicle-stimulating hormone concentrations after uterine artery embolization for symptomatic uterine fibroids: pooled results for four studies [Color figure can be viewed at wileyonlinelibrary.com]

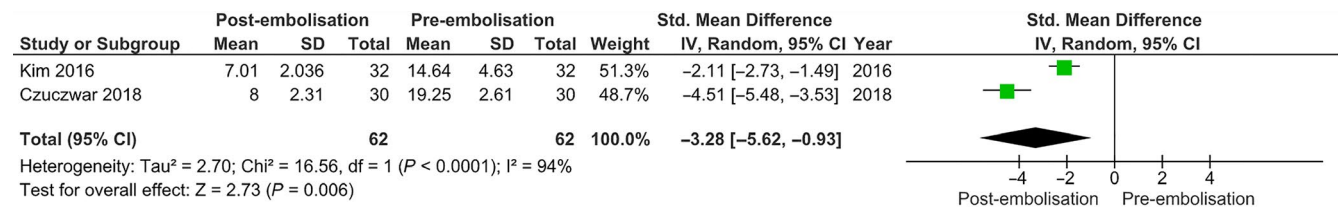


FIGURE 4 Weighted mean difference in antral follicle count after uterine artery embolization for symptomatic uterine fibroids: pooled results for two studies [Color figure can be viewed at wileyonlinelibrary.com]

explanation of the observed decline in AFC could be an untargeted occlusion of the uterine collateral artery contributing to the ovarian blood flow as a result of UAE.¹⁶ The later increase in AFC may be the result of recovery of the ovarian blood flow due to compensation from the ovarian artery.¹⁴

Pooled analyses of the secondary outcome "FSH concentration" of four studies showed no change in FSH level following UAE. This finding is similar to previous reports by Ahmad et al and Healey et al which have not demonstrated any significant impact by UAE on FSH levels.^{34,35} The trend of increasing FSH levels after UAE (WMD 4.32; 95% CI -0.53 to 9.17), albeit statistically insignificant, may be partially explained by the increased age of participants in the two studies by Tsikouras et al (age, 43.58 ± 2.05 years) and Kim et al (age, 39.4 ± 4.8 years).^{20,32}

The study by Czuczwar et al reported a significant decrease in mean AMH levels from 3.4 ng/mL ± 0.39 to 1.32 ng/mL ± 0.81 at the 3-month follow up after UAE.³³ This is in disagreement with all five other studies, which reported no statistically significant change in post-UAE AMH at 3-month follow up.^{15,19,20,31,32} When looking at the AMH data of Czuczwar et al, we noted that some of their participants had relatively higher baseline AMH levels (ranging between 5 and 7 ng/mL) compared with other reviewed studies. These high AMH levels could be related to high prevalence of polycystic ovary syndrome in the studied population. In other words, the discrepancies between this study and the other publications could be the result of differences between the study populations.

The lack of any effect on ovarian reserve, as measured by AMH and FSH levels, could be explained by the fact that UAE does not affect the utero-ovarian collateral circulation, with no subsequent impairment of the ovarian blood supply. Another possible explanation is that any unintended embolization of the utero-ovarian collateral circulation during UAE does not cause significant compromise to the ovarian blood supply.

Our study is limited by the small sample size of the included studies (n = 353) and the high heterogeneity between studies. A major source of this heterogeneity is the variation in the operators' experiences and UAE techniques. It is well recognized that many technical factors, including embolization material type and size, extent of embolization, and embolization end-point, could influence the extent of arterial occlusion and the chances of occluding the utero-ovarian anastomosis with a potential negative impact on the ovarian reserve.^{32,36} For instance Kim et al explained in a previous publication that they changed the embolization particles to larger sizes (from 500-710 µm to 710-1000 µm) in order to avoid nontarget embolization of the ovarian parenchyma.³⁷ They, however, admitted that the reflux to the utero-ovarian anastomoses was unavoidable at times when trying to achieve the embolization end-points. They recommended that embolization should be aborted if this reflux reaches the ovarian parenchyma.

Another important factor contributing to the heterogeneity is the variation in the age of the participants and the duration of the follow up in different studies. Czuczwar et al and McLucas et al included women with median (range) age of 35 (33-40) years and mean (±SD) age of 35.5 (±3.8) years, respectively,^{15,33} but Tsikouras et al included women with mean (±SD) age of 43.58 (±2.05) years.²⁰ The mean (±SD) ages of

women in Kim et al, Keshavarzi et al and Torre et al were 39.4 (±4.8), 34.55 (±3.94) and 37.3 (±3.9) years, respectively.^{19,31,32} Therefore, further research is needed with a larger population of women less than 40 years of age to allow a firm conclusion on the impact of UAE on ovarian reserve. Furthermore, as AMH levels decline with age, future studies should undertake regression analysis to investigate the influence of the varied ages of participants on the levels of AMH.

Another weakness in the reviewed studies is the lack of information on the AMH kits used. Over the last decade, several AMH kits have been developed with a wide variation in sensitivities and intra- and inter-assay coefficients of variation. It is now well established that different AMH kits give varied results. Furthermore, inter-laboratory variations and sample instability further complicate the interpretation and clinical implications of AMH values.

This review provides preliminary evidence for the safety of UAE in young women wishing to retain their fertility. This is further supported by recent reports of successful pregnancies following UAE in women under 40 years old.^{15,38} However, further high-quality prospective randomized studies with robust designs are required to verify the findings of this review.

5 | CONCLUSION

Uterine artery embolization does not seem to affect ovarian reserve, as measured by AMH and FSH levels. Given the low quality of studies included in this review, further research is needed with a larger population of women under 40 years of age to allow a firm conclusion to be drawn.

ACKNOWLEDGMENTS

We are grateful to all librarians and other staff in the Library at the University Hospitals of Derby and Burton NHS Foundation Trust for their help with the literature search and obtaining the full text of selected articles. We are also grateful to Ms Louise Levitt, Librarian at Patricia Bowen Library & Knowledge Service, Chelsea and Westminster Hospital NHS Foundation Trust.

CONFLICT OF INTEREST

None.

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How to cite this article: El Shamy T, Amer SAK, Mohamed AA, James C, Jayaprakasan K. The impact of uterine artery embolization on ovarian reserve: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand.* 2020;99:16-23. <https://doi.org/10.1111/aogs.13698>