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

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ABSTRACT

Introduction: In the recent years, uterine artery embolisation (UAE) has been gaining increasing popularity as an effective and minimally invasive treatment for uterine fibroids. However, there has been a 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 a 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 three cohort and three case-control studies (n=353). The duration of follow up after UAE ranged between three 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-month) showed no significant change in post-embolization circulating AMH. Pooled analysis of serum follicle stimulating hormone (FSH) concentrations (four studies, n=248) revealed no statistically significant change after UAE (weighted mean difference 4.32; 95% CI -0.53 to 9.17; I2= 95%). Analysis of two studies (n=62) measuring antral follicle count

showed a significant decline at 3-months 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.

Keywords:

Uterine artery embolization; Ovarian reserve; Anti-Müllerian Hormone; Antral Follicle Count; follicle stimulating hormone

Abbreviations:

AFC, antral follicle count;

AMH anti-Müllerian hormone

FSH, follicle stimulating hormone,

UAE, uterine artery embolization;

WMD weighted mean difference

Key message:

This systematic review analysed 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.

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, dysmenorrhoea, 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).

UAE was first introduced in 1995 as a minimally invasive and uterine 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 malformations[7] and postpartum haemorrhage.[8] Furthermore, health-related quality of life results following UAE were reported to be comparable to hysterectomy.[9]

The procedure is performed utilizing 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 improvement in menorrhagia, pelvic pain, pelvic pressure after UAE is 90%, 80% and 90% respectively.[9,11]

While 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]

To date, the impact of UAE on ovarian function in women wishing to retain fertility remains controversial.[12] While some authors suggested that UAE should not be offered to women desiring future pregnancy,[13,14] others reported that UAE has insignificant effect on ovarian reserve and should be considered a feasible treatment option for women wishing to remain

fertile.[15–17] Tulandi and co-workers reported a harmful effect on ovarian reserve after UAE.[12] However, more recent studies utilizing 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 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.

MATERIAL AND METHODS

Criteria for study selection

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[21] 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.

Outcome measures

Primary outcome

This included changes in serum AMH concentration after UAE.

Secondary measures

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

Search strategy

An extensive electronic database search was performed using MEDLINE, Scopus, EMBASE, Dynamed, TRIP, ScienceDirect and the Cochrane library to identify published research articles 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 embolisation, 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.

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 & 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 & KJ).

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 (NOS) 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 suite the nature of this study giving a maximum of three stars for selection, four for comparability, and two 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), dominant fibroid volume, baseline serum AMH and laterality of the UAE procedure. Outcome was scored

according to completeness of at least three-month follow-up after embolisation. It is generally accepted that a limit of five 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.

Data extraction and analysis

Pre- and post-embolization data including mean ± 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 Centre, Copenhagen, Denmark). The weighted mean difference (WMD) between pre- and post-embolization values was calculated.

Statistical heterogeneity was assessed by chi-squared (χ^2, or Chi^2) test and I^2 statistics. A Chi^2 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 post-operative measurements at different follow up points, we utilized the latest AMH level. Further subgroup analyses of AMH levels were then performed based on duration of follow-up.

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.

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 three studies were contacted via email to provide the missing data but did not respond despite several reminders.

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.

Study design

The review included two prospective cohort,[15,31] one retrospective cohort[32] and three case-control studies.[19,20,33]

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±SD of AMH.[33]

The length of follow up was up to three months in one study,[33] six months in one study,[19] 10 months in one study[15] and 12 months in three studies.[31,32,20]

UAE techniques

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

AMH assays

Only two studies provided the type of AMH kit used (without giving any details) including E90228Hu AMH ELISA (Uscn Life Science Inc., Wuhan, Hubei, China)[33] and AMH Monobinal kit.[19] The remaining four studies did not specify the type AMH kit used.

Overall pooled results for all studies

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

Sensitivity analysis

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

Subgroup analysis

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]

According to duration of follow up

Pooled results of four studies (n=246) showed no significant drop in serum AMH concentration at three 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 six months follow up showed no statistically significant difference in post-embolization serum AMH concentration (WMD -0.17; 95%CL -0.43 to 0.13; I^2=0%).[19,20,31] Similarly, analysis of three studies (n=214) with 12 months follow-up revealed no statistically significant difference in post-embolization serum AMH concentration (WMD -0.09; 95%CL -0.32 to 0.14; I^2=0%).[20,31,32]

Secondary outcomes

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; I^2= 95%) (Figure 3).

Antral Follicle Count

Two studies included AFC (as a marker for ovarian reserve) as an outcome measure at three months follow up (n=62).[32,33] Pooled analysis of these two studies showed a significant decline in AFC at three months following UAE (WMD -3.28; 95% CI -5.62 to -0.93; I^2= 94%) (Figure 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 three months follow-up.[32,33] Interestingly, one of these two studies reported a partial recovery of AFC at 12 months follow-up.[32] This is in agreement with a previous study by Tropeano et al who reported no significant change in AFC at 12-month and up-to 5 years after UAE when compared with a control group.[13] Given the small number of the 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 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 due to 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 Ahmed 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 two studies including 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 and colleagues reported a significant decrease in mean AMH levels from 3.4ng/ml ± 0.39 to 1.32ng/ml ± 0.81 at 3-month follow-up after UAE.[33] This is in disagreemet with all the other five 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 to 7 ng/ml) compared to other reviewed studies. This 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 due to the difference in 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 recognised that many technical factors, including embolization material type & 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 endpoints. 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. While 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] Tsikouras et al included women with mean (±SD)

age of 43.58 (±2.05) years.[20] The mean (±SD) age 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 inter- 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 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 randomised studies with robust designs are required to verify the findings of this review.

CONCLUSION

UAE 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.

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Figure and table legends

Table 1. The results of quality scores of the studies included in the analysis

Table 2. Characteristics of the six studies included in the meta-analysis.

Figure 1. PRISMA Flow Chart of the study selection process

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

Figure 3. Weighted mean difference in serum follicle stimulating hormone concentrations after uterine artery embolization for symptomatic uterine fibroids: pooled results for four studies

Figure 4. Weighted mean difference in antral follicle count after uterine artery embolization for symptomatic uterine fibroids: pooled results for two studies

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

Table 1. The results of quality scores of the studies included in the analysis

Table 2. Characteristics of the six studies included in the meta-analysis.

Author	Country	Design	n	Age (mean±SD)	Laterality & method of UAE	Dominant fibroid volume (ml)	Follow up (Months)	AMH Kit	Secondary outcomes (ovarian reserve markers)
Torre et al., 2014 (31)	France	Prospective Cohort	64	37.3±3.9	Bilateral (Tris acryl microspheres 500-1200µm)	97±103	3, 6, 12*	NS	FSH, LH, E2, 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) **	265.26±339.0	3, 12	NS	FSH, LH, E2, AFC, OV
McLucas et al., 2017 (15)	USA	Prospective Cohort	87	35.5±3.8	Bilateral (PVA ≥500µm)	NS	Variable***	NS	-
Tsikouras et al., 2017 (20)	Greece	Case-control	120	43.6±2.05	Bilateral (Hydrogel coated microspheres 700µm-900µm)	NS	1, 3, 6, 12	NS	FSH, LH, E2
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, E2

* fist follow up was 2 weeks after surgery

** gelatin sponge 500-710µm then changed to 710-1000µm

*** 190±290 days

NS, Not specified**; PVA,** polyvinyl alcohol**; AMH** anti-Müllerian hormone**; FSH** follicle stimulating hormone; **LH,** luteinising hormone; E2 oestradiol; **AFC,** antral follicle count; OV, ovarian volume; **ELISA**, Enzyme-linked Immunosorbent Assay