# Uterine artery embolisation versus myomectomy for premenopausal women with uterine fibroids wishing to avoid hysterectomy: the FEMME RCT

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## Scientific summary

### The FEMME RCT

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# Scientific summary

## Background

Uterine fibroids are the most common tumour in women of reproductive age and are associated with heavy menstrual bleeding (HMB), abdominal discomfort, subfertility and reduced quality of life. For women seeking to retain their uterus and who do not respond to medical treatment, myomectomy and uterine artery embolisation (UAE) are therapeutic options.

Surgery, either myomectomy or hysterectomy, has traditionally been the main approach for management of symptomatic fibroids. Myomectomy involves the surgical removal of the fibroid, preserving the uterus, and, although significantly reducing heavy bleeding symptoms, can involve myometrial trauma. To the best of our knowledge, there are no reliable randomised trial data to confirm a benefit on reproductive outcomes. UAE involves temporary occlusion of the arteries supplying the uterus using biocompatible particles and is usually performed under local anaesthetic. Concern around the potential impact of UAE on ovarian and uterine function has resulted in recommendations against the procedure for women seeking pregnancy, but a recent meta-analysis suggested no appreciable impact on ovarian reserve (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.).

## Objectives

The primary aim of this randomised trial of treating Fibroids with either Embolisation or Myomectomy to Measure the Effect on quality of life among women wishing to avoid hysterectomy (the FEMME trial) was to examine the effect of these interventions on quality of life at 6 months and at 1, 2 and 4 years.

The secondary objectives were to compare the two interventions with respect to:

- relative cost-effectiveness at 2 and 4 years from the perspective of the NHS
- HMB symptoms
- pregnancy rates and outcomes
- adverse events and post-procedure complications
- reintervention rates.
- hormones associated with ovarian reserve at 6 weeks and 6 and 12 months post procedure.

## Design

A multicentre, open, randomised trial with a parallel economic evaluation.

## Setting

Twenty-nine UK hospitals.

## Participants

Premenopausal women who had symptomatic uterine fibroids amenable to myomectomy or UAE were recruited. Women were excluded if they had significant adenomyosis, had any malignancy or pelvic inflammatory disease or had already had a previous open myomectomy or UAE.

## Interventions

Online randomisation was performed centrally using minimisation to balance the study group allocations in a 1 : 1 ratio and according to the longest dimension of the largest fibroid (i.e. $\leq 7$ cm or $> 7$ cm), number of fibroids (i.e. 1–3, 4–10 or $> 10$) and whether or not the woman wanted to get pregnant.

Myomectomy could be open abdominal, laparoscopic or hysteroscopic according to the location of the fibroid and the preference of the operating gynaecologist.

Bilateral UAE was performed under fluoroscopic guidance. The embolic agent was at the discretion of the interventional radiologist and the end point of the embolisation procedure was complete or near-complete stasis of blood flow in the uterine artery.

## Main outcome measures

The primary outcome measure was the condition-specific quality-of-life domain score from the Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire at 2 years post randomisation [with scores ranging from 0 (worst) to 100 (best)].

The following prespecified secondary outcomes were collected at 6 months and at 1, 2 and 4 years (unless otherwise stated):

- health-related quality-of-life (HRQoL) domain from the UFS-QOL at 6 months and 1 and 4 years
- symptom severity domain from the UFS-QOL
- EuroQol-5 Dimensions, three-level version (EQ-5D-3L), score
- EuroQol-5 Dimensions (EQ-5D) visual analogue scale
- menstrual blood loss using the pictorial bleeding assessment chart
- pregnancy and associated outcomes, specifically the ability to conceive (i.e. overall and in the population of women who at the time of randomisation reported that they wanted to get pregnant) and the subsequent pregnancy outcome (i.e. live birth, miscarriage, stillbirth and termination)
- participant acceptability, as defined by responses to 'Would you have your operation again?'
- participant acceptability, as defined by responses to 'Would you recommend operation to a friend?'
- length of hospital stay
- further treatment for fibroids or recurrence of symptoms, including hysterectomies
- measure of ovarian reserve by assay of follicle-stimulating hormone, anti-Müllerian hormone and luteinising hormone at 6 weeks, 6 months and 12 months post procedure
- serious adverse events and procedural complications considered to be related to the study protocol or intervention.

The economic evaluation estimated quality-adjusted life-years (QALYs) derived from EQ-5D-3L and costs from the NHS perspective over the time horizons of 2 and 4 years. Cost-effectiveness was expressed as incremental cost per QALY gained. Cost-effectiveness acceptability curves were used to present uncertainty in the decision regarding cost-effectiveness over a range of thresholds of willingness to pay (WTP) for a gain of 1 QALY.

## Sample size

A sample size of 250 participants had 90% power to detect a moderate difference between groups [i.e. 12 points, 0.55 of a standard deviation (SD)] in the UFS-QOL HRQoL domain, allowing for approximately 20% loss of primary outcome data. The analysis of the primary outcome was performed according to the intention-to-treat (ITT) principle and analyses were performed on (1) complete

observed data and (2) all randomised participants at all assessment times through imputation of missing responses.

## Results

The randomisation of participants commenced on 6 February 2012 and the last woman was randomised on 21 May 2015. A total of 254 women were randomised: 127 to myomectomy (105 underwent myomectomy) and 127 to UAE (98 underwent embolisation). Information on the primary outcome at 2 years was available for 81% ($n = 206$) of women. Of the 123 women randomised to myomectomy for whom initial treatments details were known, 105 (85%) had a myomectomy as their initial operation. Similarly, 98 of the 122 (80%) women in the UAE group underwent UAE. Women were, on average, 41 years old and classed as overweight by their body mass index.

The average UFS-QOL HRQoL score at 2 years was 84.6 (SD 21.5) in the myomectomy group and 80.0 (SD 22.0) in the UAE group [ITT complete-case analysis mean-adjusted difference 8.0, 95% confidence interval (CI) 1.8 to 14.1, $p = 0.01$; mean-adjusted difference using multiple imputation for missing responses 6.5, 95% CI 1.1 to 11.9]. Sensitivity analysis returned comparable results. The mean difference in the primary outcome at the 4-year follow-up time point was 5.0 (95% CI −1.4 to 11.5) in favour of myomectomy.

The UFS-QOL symptom severity domain scores at 6 months and 1 year were higher in the UAE group than in the myomectomy group, indicating more residual symptoms in the former group. Small, but consistent, differences were seen for the two EQ-5D instrument domains that favoured myomectomy. Over the 2 years of follow-up, there were no apparent and sustained differences between the two groups in the bleeding scores, or in the proportions of women reporting amenorrhoea or heavy bleeding. Perioperative and postoperative complications from all initial procedures occurred in similar percentages of women in both groups (29% in the myomectomy group vs. 24% in the UAE group). The cumulative repeat procedure rate to 4 years was 24% in the UAE group and 13% in the myomectomy group (hazard ratio 0.53, 95% CI 0.27 to 1.05).

There were 15 pregnancies in the UAE group and seven in the myomectomy group, with a cumulative pregnancy rate to 4 years of 15% and 6%, respectively (hazard ratio 0.48, 95% CI 0.18 to 1.28). There was no evidence of any material difference between the levels of hormones associated with ovarian reserve in each group. There were no apparent differences in the participants' rating of their operation by 4 years, which remained high overall.

Over a 2-year time horizon, UAE was associated with higher costs than myomectomy (£7958, 95% CI £6304 to £9612, vs. £7314, 95% CI £5854 to £8773), but with fewer QALYs gained (0.74, 95% CI 0.70 to 0.78, vs. 0.83, 95% CI 0.79 to 0.87). The differences in costs (difference £645, 95% CI −£1381 to £2580) and QALYs (difference −0.09, 95% CI −0.11 to −0.04) were small. Similar results were observed over the 4-year time horizon. At a £20,000 WTP threshold, the probability of myomectomy being cost-effective is 98% at 2 years and 96% at 4 years.

## Conclusions

Although both procedures improved participant-reported HRQoL scores, women assigned to myomectomy reported higher scores (i.e. a mean difference of 8 points on a 100-point scale) than those in the UAE group. Menstrual bleeding scores appeared similar in both groups. Overall, complication rates from all initial procedures occurred in a similar proportion of women in both groups. The hospital stay was shorter in the UAE group, but the need for reintervention was higher in the UAE group. There were no consistent differences between groups in biomarkers of ovarian reserve.

There were 15 pregnancies in the UAE group and seven in the myomectomy group, but these numbers were too small to draw a conclusion on the effect of the procedures on fertility. The economic evaluation showed that UAE was associated with higher costs and fewer QALYs than myomectomy. Future research should involve younger women who want to get pregnant.

Both UAE and myomectomy are effective treatments for improving the quality of life of women with symptomatic uterine fibroids. Women with fibroids, including those wanting to get pregnant in the future, should be provided with the evidence generated by the FEMME trial to enable a fully informed decision regarding their fibroid treatment.

The most important research now required is the investigation of the impact of UAE and myomectomy on fertility. The lack of compelling evidence for adverse effects of myomectomy and UAE from the FEMME trial and other sources should reduce the barriers to a new randomised trial in women seeking to get pregnant naturally or undergoing assisted reproduction treatment.

## Trial registration

This trial is registered as ISRCTN70772394.

## Funding

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### This report

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