Anti-Mullerian hormone before and after uterine artery embolisation in reproductive-age women seeking treatment for symptomatic fibroids

C M Muteshi, MB ChB, MMed (Obstet Gynaecol); A Murage, MRCOG (UK); S Ngugi, MMed (Obstet Gynaecol)

Nuffield Department of Women’s and Reproductive Health, University of Oxford, UK
Department of Obstetrics and Gynaecology, Aga Khan University, Nairobi, Kenya

Corresponding author: C M Muteshi (murwa2006@yahoo.co.uk)

Background. Uterine fibroids are the most common benign gynaecological tumours, the definitive traditional treatment for which is either myomectomy or hysterectomy. Uterine artery embolisation (UAE) offers an alternative non-invasive option for treatment. There remain concerns as to the effects of UAE on ovarian reserve in women desirous of preserving ovarian function.

Objectives. To determine the effect of UAE on ovarian reserve, as assessed by anti-Mullerian hormone (AMH) measured before and after embolisation, and to assess the trend in serum AMH in the medium term, up to 12 months post UAE.

Methods. A cohort study between October 2012 and May 2015 recruited 40 women with symptomatic uterine fibroids. Serum AMH was measured prior to embolisation and post embolisation, at 2 weeks, 6 months and 12 months. Using descriptive statistics and bivariate analysis, pre-embolisation and post-embolisation AMH concentrations were compared. P<0.05 was considered statistically significant.

Results. The median participant age was 38.5 years (range 31 - 45). Of the women recruited, 47.5% (19) were nulliparous, and 72.5% (29 women) of the total desired a pregnancy in the future. The median (standard deviation) AMH immediately prior to embolisation was 1.3 ng/mL (1.53), and post embolisation at 2 weeks, 0.9 ng/mL (1.98); at 6 months, 2.2 ng/mL (2.63); and 12 months, 3.5 ng/mL (1.54) (p= 0.96).

Conclusion. In the short to medium term, UAE for treatment of symptomatic fibroids was not found to be detrimental to ovarian reserve. There is a need for longer-term studies evaluating its effects on fecundity, considering that most women in the present study had a strong desire to maintain their fertility.

sterilisation, or had no desire for future fertility, or were not willing to return for follow-up blood tests.

Study protocol
The protocol and procedures for UAE at the Aga Khan University Hospital are reported elsewhere.[17] Blood was collected in plain vacutainers, and delivered to the biochemistry laboratory within 60 minutes. This was centrifuged, and sera frozen at –20°C until analysis using the Beckman Coulter Gen. II assay (Beckman Coulter Inc., USA). Samples were collected immediately prior to UAE, and at 2 weeks, 6 months and 12 months following UAE.

Outcome measures
The primary outcome was change in the median concentration of serum AMH from baseline to 2 weeks following UAE. The secondary outcome was the trend in AMH concentration up to 12 months following UAE.

Sample size calculation and statistical analysis
A power calculation determined that a sample size of 65 women was needed to demonstrate a 10% difference in the before-and-after AMH concentration, with 80% power and a 5% significance threshold. Using univariate and bivariate analysis, data were analysed and presented as proportions, median and standard deviation. Student’s t-test was used to compare differences, p<0.05 was considered significant. All statistical analysis was performed using the statistical software SPSS version 24.0 (IBM, USA).

Results
Forty women with symptomatic uterine fibroids undergoing UAE were recruited to participate in the study. Their median age at recruitment was 38.5 years (range 31 - 45) (Table 1).

Immediately prior to UAE, the baseline median (standard deviation (SD) serum AMH was 1.3 ng/mL (1.53). The serum AMH showed progressive decline with woman’s increasing age at baseline (Pearson’s correlation coefficient r=−0.417). Measured 2 weeks after the UAE, the correlation coefficient between AMH and age was r²=−0.52, which was not significantly different to that prior to UAE (p=0.622) (Fig. 1). When the median concentration of serum AMH prior to UAE was compared with the concentration immediately after embolisatation, there was no statistically significant difference (p=0.99), with the trend showing an initial slight dip, followed by a recovery at 6 months, and no return to the former levels at 12 months (Fig. 2).

Discussion
Assessment of ovarian reserve in reproductive-age women is usually performed using various static and dynamic biomarkers, with various degrees of diagnostic accuracy. Serum FSH, oestradiol and inhibin B are less specific, cycle-dependent and are not able to reliably differentiate women with poor ovarian reserve from those with normal ovarian reserve.[9] Transvaginal ultrasound scanning for estimating ovarian antral follicle count is reliable, cycle-independent and performs well in the differentiation of low-ovarian-reserve from normal-ovarian-reserve women. Ultrasound scanning, however, is dependent on probe resolution, and requires trained operators and easy access to the ovary through the transvaginal approach.[9] In women with large or multiple uterine fibroids, assessment of antral follicle count may be suboptimal. AMH is a serum biomarker for ovarian reserve testing that is reliable, cycle-independent and stable in various laboratory conditions.[3] Our study assessed AMH values before and after UAE, showing that serum AMH levels consistently decreased immediately following UAE procedures, as early as 2 weeks later. Interestingly, AMH values had recovered on further follow-up at 6 months, and had not returned to the former levels 12 months later, showing that the initial depression is only temporary.

Traditionally, uterine fibroids are managed surgically, either by hysterectomy or, for women concerned about future fertility, by myomectomy. Hysterectomy is a major operation that carries significant risks and a variable period of convalescence.[30] In

<table>
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<tr>
<th>Table 1. Participant characteristics (N=40)</th>
<th>Value</th>
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<tr>
<td>Characteristic</td>
<td>Value</td>
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<tr>
<td>Age, mean (range)</td>
<td>38.5 (31 - 45)</td>
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<tr>
<td>Parity, n (%)</td>
<td>0</td>
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<td></td>
<td>≥1</td>
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<td>Fertility desired, n (%)</td>
<td>Yes</td>
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In our study, the median (SD) female age was 38.5 (6.5) years, with a median serum AMH of 1.3 (1.53) ng/mL before embolisation, and future fertility aspirations in up to 72.5% of the participants. It is not surprising that nearly three-quarters of the women still had fertility aspirations, as is comparable with other studies that report that many of those considering options for fibroid management usually opt for fertility preservation or conservative procedures. The effect of fibroids on infertility is, however, less clear, and may be indistinguishable from age-related effects on fecundity, considering that the incidence of fibroids increases with age, with studies reporting varying findings. Generally, the chance of natural conception is inversely proportional to female age, with a proportionate increase in the risk of miscarriage. Women being investigated for subfertility and found to have fibroids must consider this very carefully, particularly when choosing which treatment to pursue. Whereas the cohort of women in our study only indicated a desire for future pregnancy, information on those who had had previous fertility investigations was not sought. Reassuringly, the mean AMH levels prior to embolisation were within the expected normal range for age. It would therefore be expected that women aged <40 years would have an 80% chance of conceiving a pregnancy after trying for 12 months with no other cause for delay identified. UAE did not result in decreased concentration of AMH in the short term, but we were unable to determine reproductive outcome owing to a lack of follow-up information. Considering that ovarian failure following UAE is reported more commonly in women aged ≥45 years, and in younger women whose AMH concentration falls below the fifth percentile, consideration should be given to options for fibroid treatment other than embolisation, as these women have the highest risk of ovarian failure. In addition, concerns have also been raised about increased risks of pregnancy complications in women who have had UAE.

Our study benefitted from measuring serum AMH before and after UAE at fixed time points. AMH is a robust biomarker and independent of the ovarian cycle, with high predictability of both ovarian reserve and reproductive ageing. The inclusion of women up to the age of 45 years in this trial allows for generalisability of the findings, as changing sociodemographic characteristics of reproductive-age women embarking on their first pregnancy in their late 30s or early 40s become a reality.

Our study was limited by recruiting fewer women than initially anticipated. This renders the results subject to cautious interpretation; however, the general trend observed in AMH values conforms with that found in other trials, and is likely to represent a true biological phenomenon after embolisation. In trials using other markers of ovarian function, a similar observation was reported. Whereas a single-point AMH measurement of ovarian reserve is predictive of reproductive function, it is essential to design trials with longer-term follow-up to establish whether the trajectory in AMH decline is maintained at the same rate, or whether it accelerates beyond the first year. This will be especially informative for younger women with significant fibroid symptoms and normal ovarian reserve, who wish to avoid an operative procedure such as myomectomy. It is likely that younger women whose AMH values fall below the fifth percentile will have the highest risk of ovarian failure following UAE; however, a study to test this hypothesis would be ethically unsound, and conclusions can only be made from logical reasoning.

Conclusion

From this study, we can conclude that in women with symptomatic uterine fibroids and normal ovarian reserve estimated using AMH, UAE does not compromise ovarian function in the shorter to medium term. For women with fibroids seeking treatment who have future fertility aspirations, part of the investigations should include ovarian reserve testing, to ensure that they receive adequate and complete information to make an informed decision on the most appropriate management. It will be interesting to see whether the neutral effect of UAE on ovarian reserve is maintained in the longer term, and what its impact might be on female reproductive biology.
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Author contributions. CM developed the study protocol, applied for funding, analysed data and wrote the initial draft manuscript. AM developed the draft protocol, applied for funding, collected data and reviewed the draft manuscript. SN collected data and reviewed the draft manuscript. All authors approved the final manuscript for submission.

Conflicts of interest. None.

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