The effects of uterine artery embolisation and surgical treatment on ovarian function in woman with uterine fibroids

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Abstract

Uterine artery embolisation (UAE) is a recognised alternative to surgery for treatment of uterine fibroids and maintains fertility for the majority of women. Premature ovarian failure (POF) can occur in a small proportion of women undergoing UAE (1-3%). Identification of prognostic factors for POF following UAE would allow accurate and informed counselling for those patients wishing to retain fertility and avoid a premature menopause. The aim of this study was to evaluate and compare ovarian functional outcomes following surgical treatment (hysterectomy or myomectomy) and UAE.

The randomised trial of embolisation versus surgery (REST) recruited 157 patients (UAE 106, 51 surgery). Of these patients, 96 (73 UAE, 23 surgery with retained ovaries) had serum FSH and LH measurements taken on day 3 of the menstrual cycle prior to treatment and at 6 and 12 months post-treatment. Data on menstrual cycle characteristics were also collected.

The median increase in FSH levels (from baseline to 12 months) was 1.7 IU/L ($p = 0.01$) following UAE and 2.4 IU/L ($p = 0.09$) after surgery. There was no significant difference in the median change in FSH at 12 months between UAE and surgical patients ($p=0.54$). In patients aged >45 years, the surgical group had a higher median increase in FSH level compared to the UAE group (34 v 4 IU/L; $p = 0.01$) from baseline to one year post treatment. UAE patients had a decrease of 1.4 days (95% CI 0.6 to 2.2; $P=0.001$) in the mean duration of menstrual flow from baseline (mean 7; SD 3) to six months post- embolisation. However, there was no change (-0.2 days; 95%CI -1.1 to 0.6; $p=0.56$) in the mean cycle length from baseline values (mean 27.4; SD 2.8). Ovarian failure (FSH > 40 IU/L up to 2 years after treatment) did not occur in either treatment arm in women under 40 years of age.

UAE and surgery both cause a small change in ovarian function at 1 year with no significant difference between the two groups. Patients over the age of 45 years are at much greater risk. Changes in ovarian function are not reflected in the length of the menstrual cycle following UAE.

Introduction

Uterine fibroids are common benign tumours which occur in 20-30% of women during reproductive life, rising to 40% in women above the age of fifty years who are still menstruating[1]. Although the majority of cases are asymptomatic, fibroids can grow to a considerable size, causing problems such as menorrhagia, dysmenorrhoea, pelvic pressure symptoms and infertility[1]. Up until recently, the standard surgical treatment for fibroids was either hysterectomy or myomectomy. The latter has been the principal option for those wishing to retain their fertility however myomectomy can be associated with pre and post-operative complications such as adhesion formation which may further decrease reproductive capacity. In 1995 Ravina introduced uterine artery embolisation (UAE), an alternative non-surgical technique for the treatment of fibroids. This procedure significantly decreases fibroid related symptoms[2] and is also used to control post-partum haemorrhage and post surgical bleeding[3].

Numerous studies, including randomised controlled trials have demonstrated the safety and efficacy of UAE. It is associated with low morbidity rates[4] and complication rates are similar to or less than those associated with surgery[5,6]. In addition, compared with surgical treatment, UAE necessitates a significantly shorter hospital stay and faster recovery of lifestyle milestones[6-9]. Other benefits include a decrease of up to 50% in fibroid diameter[10,11] with larger reductions in uterine volume[12] and a significant decrease in fibroid related symptoms[10, 13-17]. Emerging midterm data estimates new fibroids occur in up to 10% of cases at 2 years after UAE[18], which is significantly lower than those reported after myomectomy[19]. Longer term data are just emerging but current data suggest that 15-25% require further invasive treatment (repeat UAE, hysterectomy or myomectomy) at 5 years for recurrent symptoms. Nevertheless, several complications associated with UAE have also been reported[4, 14, 17, 20-23] including pelvic infection, premature ovarian failure (POF) and emergency hysterectomy, all of which severely compromise fertility.

The impact of UAE on subsequent fertility and menstrual cyclicity is not well-characterised. POF is an undesirable complication of UAE for fibroids, although its occurrence is unusual when embolisation is performed in other circumstances e.g. post partum haemorrhage[24]. Despite the fact that resumption of normal menses has been reported in most women, numerous reports of amenorrhoea post UAE (both transient and permanent) have been documented throughout the

literature. Amenorrhoea rates vary from 1-2%[2, 12], 6-8%[13, 14, 16] and even 14%[26]. It appears that the incidence of POF may be age dependent since as many as 43% of woman above the age of 45 years become amennorhoeic after the procedure[26,27]. Thus POF seems to be uncommon in those who are most likely to wish to conceive.

During the menopausal transition, changes in the menstrual cycle are also observed reflecting the changes in gonadotrophin levels and output of ovarian steroids[28]. Thus it is important to examine the effect of UAE on menstrual cyclicity and duration of menstrual flow.

The purpose of this study is to investigate whether UAE causes a change in ovarian function (as assessed by gonadotrophin levels) which differs from that induced by surgical treatment in woman with uterine fibroids. The impact of age on ovarian function, and whether or not any changes in ovarian function are reflected by an alteration in~~whether any changes in ovarian function are reflected in an alteration in~~ menstrual ~~cyclicity~~characteristics, are also reported.

Material and Methods

Patients

The data for this study was taken from a multicentre randomised controlled trial comparing uterine artery embolisation with surgical treatment (REST trial)[6] for uterine fibroids. This trial recruited 157 patients, 106 of whom were randomised to embolisation and 51 to surgery, predominately hysterectomy, using a 2:1 randomisation and stratification for centre. Multi centre ethical approval was granted and local ethics approval was obtained by each participating centre. Each patient gave consent to the gathering of follow up data. Full details of this study have already been reported[6].

Procedures

Uterine artery embolisation (UAE) was performed using a variety of embolic agents. The preferred endpoint of embolisation was complete or near complete stasis of the uterine artery. The precise surgical technique (hysterectomy or myomectomy) was left to the individual operator. Post-procedural and follow-up protocol including clinical and quality of life outcomes have been reported elsewhere[6].

Study Design and Data Collection

For the purpose of the hormone study and to allow a comparison of gonadotrophin levels between women undergoing UAE and surgery, only patients with ovarian conservation at the time of surgery were included. Those already menopausal at the time of treatment, with measured FSH levels of 40 IU/l or greater in the early follicular phase of the cycle, were excluded from the study as were patients taking exogenous hormones at the time of pre- and post-treatment blood sampling. Data analysis was carried out on a final cohort of 96 patients (73 UAE and 23 surgical).

Baseline blood biochemistry results including follicle stimulating hormone (FSH) and lutenising hormone (LH) were obtained within 7 days of onset of menses, primarily on day 3 of the menstrual cycle. These measurements were made prior to treatment and repeated at 6 and 12 months after treatment. Hormone assays were performed with commercially available immunoassay kits. Basal FSH and LH levels were recorded in all patients. At the 6 month interval, serum FSH and LH results were available for 66 of 73 (90%) UAE patients and 22 of 23 (96%) surgical patients. At the 12 month interval, serum FSH results were available for 62 (85%) UAE patients and 17 (74%) surgical patients. LH results were available for 61 (84%) UAE patients and 16 (70%) surgical patients.

Patients' menstrual cycle data were collected from those women who underwent UAE and myomectomy. This included the duration of bleeding and the length of the menstrual cycle. Data were obtained from forms completed by hospital research nurses prior to the patients' treatment and at 6 and 12 month reviews. Patients' menstrual diaries were used to clarify the data. Bleeding data were available for 101 patients but 23 patients were excluded, leaving a cohort of 78 patients. Reasons for exclusion included missing data, irregular bleeding, continuous bleeding prior to treatment, amenorrhoea due to the menopause, the use of exogenous hormones and hysterectomy. Of the 78 cases, only 2 had myomectomy thus it was decided to report the menstrual cycle data only for the 76 UAE cases. Baseline menstrual data were available for all 76 patients. At the 6 month follow-up, data on the duration of bleeding and the length of the menstrual cycle were available for 75 (99%) patients and 73 (96%) patients, respectively. At the 12 months post-UAE, the corresponding figures were 69 (91%) patients and 66 (87%), respectively.

Study Aims

The primary aim of the study was to determine if there was any difference in ovarian function post-treatment (as reflected by gonadotrophin levels) between those undergoing UAE and surgery, and to determine if the age of the patient influenced any effect that UAE might have on ovarian function. A secondary aim was to determine if UAE had an effect on the duration of menstrual flow and the length of the menstrual cycle.

Statistical Analysis

Changes in gonadotrophin levels (baseline to post-treatment) in each treatment group were analysed using the Wilcoxon Signed rank test. Comparisons of the change in hormone levels between groups were carried out using the Mann-Whitney test. For the menstrual cycle characteristics (duration of bleeding and length of menstrual cycle), paired t-tests and 95% confidence intervals were used to examine the differences between baseline and post-treatment values. A p-value of <0.05 was considered statistically significant. All analyses were carried out using the statistical software package Minitab, versions 15.

Results

Hormone Study

The final patient cohort for the hormone study consisted of 96 patients (73 UAE and 23 surgery). The hormone levels of the patients are summarised in Table 1. Both treatment groups were well-matched for age. The mean (SD) age of the patients was 43.8 (5.4) years in the UAE group and 42.5 (5.2) years in the surgery group.

The effect of treatment on gonadotrophin levels

The change in FSH and LH levels from baseline to 6 and to 12 months after treatment are shown in Table 2. There were significant increases in FSH and LH levels at both 6 months and 12 months for the UAE patients. Although the increases in levels in the surgical patients were generally of a similar or greater magnitude, the smaller sample size meant that the increases were not statistically significant.

UAE versus Surgery

There was no significant difference in the median change in either hormone level at 6 and 12 months between the UAE and surgery groups (Table 2).

The impact of age

Women aged 45 years and over showed a larger median increase in both FSH and LH at both 6 months and 12 months after treatment compared to women under the age of 45 years (Table 3) although this difference was only statistically significant at 12 months.

Table 4 shows change in FSH / LH levels as in Table 2 splitting the group into age ≥45 years and < 45 years. In women <45 years there were no statistically significant changes in hormone level. In women ≥45 years there were statistically significant increases in FSH levels at 1 year in both the UAE and surgery groups. In a comparison of UAE and surgery in women under 45 years there were no statistically significant differences between UAE and surgery in the median change in hormone levels after treatment. In women ≥45 years the surgical cases had a significantly greater increase in FSH level at 1 year compared with UAE; no other comparisons were statistically significant

Ovarian Failure after Treatment

Ovarian failure after treatment, defined as an FSH in excess of 40IU/l, developed in a total of 16 patients ((13 UAE and 3 surgery (2 myomectomy, 1 hysterectomy)) of whom 14 were aged ≥ 45 years. Both younger patients (43 and 44 years; received UAE) and 4 of the patients aged ≥ 45 years (all underwent UAE) had an elevated basal FSH at the time of treatment (>19 IU/l) indicating their peri-menopausal status. Follow-up review indicated that all 15 patients (16^{th} patient underwent hysterectomy) had menstrual bleeding in the year following treatment.

Menstrual Cycle Study

The menstrual cycle length and menstrual flow data are summarised in Table 1.

The effect of UAE on menstrual cycle characteristics

The effect of treatment on menstrual cycle is shown in Table 5. The mean duration of menstrual flow, assessed by the number of days bleeding, decreased significantly from baseline to 6 and 12 months by 1.4 days (SD 3.7) and 1.7 days (SD 3.8), respectively. There was no statistically significant change in the mean cycle length at both 6 months (-0.3days (SD 3.8)) and 12 months (0.7days (SD 4.9)).

Discussion

The issue of possible ovarian dysfunction as a consequence of UAE has been raised following reports of amenorrhoea and increased FSH levels (within the menopausal range) post-treatment[20, 26, 27], suggesting ovarian failure as a cause of amenorrhoea.

Data from the EMMY study confirm that there is an increase in FSH levels associated with a decrease in ovarian reserve following both surgical treatment and UAE, although it is unclear to what extent increasing age as opposed to the procedures themselves, contribute to this[27]. It should be noted that the majority of those in the EMMY study were over 40 years of age and antimullerian hormone (AMH) which was used to assess ovarian reserve, becomes undetectable in most women at that age. Consequently, changes in AMH could not be detected and conclusions regarding diminished ovarian reserve therefore, cannot be drawn. Since all the women in the surgical arm of that study had hysterectomy, the impact of treatment on bleeding pattern could not be determined as it can be following myomectomy. These reports have raised concerns about the potential impact of UAE on reproductive function, an aspect of treatment which is particularly important for those wishing to conceive. Bearing this in mind, some authors suggest that reproductive function should be assessed using gonadotrophin measurements prior to the procedure[14, 26].

To assess the effect of UAE and surgery on ovarian function, basal gonadotrophin values obtained in the early follicular phase of the menstrual cycle were used as indicators of ovarian function[29]. In our study, UAE patients had a statistically significant increase in median FSH and LH values post-treatment compared with baseline values. These findings correlate with previous reports[30] and suggest that UAE has an adverse effect on ovarian function. Surgical patients also

had higher median FSH and LH levels post-treatment but the increase from baseline levels, although of a similar magnitude, was not statistically significant. The surgical group was small and the gonadotrophin levels highly variable in spite of all the samples being collected in the early follicular phase of the cycle. Although our study was underpowered, the data suggest that the impact of surgery on hormone levels is similar to that of UAE. There was no significant difference in median change in gonadotrophin levels at 6 and 12 months post-treatment between UAE and surgical patients

Age had a significant impact on the results. Both UAE and surgical patients ≥45 years had significantly higher median levels of FSH and LH at 12 months post-treatment compared to baseline whilst women < 45 years of age did not. Previous studies have reported an age-related susceptibility to menopause post-UAE[16, 26, 31]. Spies et al[31] also reported that woman over the age of 45 have a 15% chance of an increase in basal FSH levels into the menopausal range after UAE. Although patients in our study over the age of 45 demonstrated statistically significant increases in gonadotrophin levels, the median FSH values at 6 and 12 months post-UAE were 10.2 IU/l and 14.0 IU/l, respectively - values that were still in the pre-menopausal range 1 year after treatment. Surgical patients over 45 years of age had a higher median increase in FSH value at 12 months post-treatment than UAE patients of the same age category (the median FSH value in the surgical group of women ≥45 years of age was 37.5 IU/l at 12 months, which is within the menopausal range). This was despite the fact that all surgical patients reported in this paper had conservation of their ovaries.

Studies which have examined the effect of surgery on ovarian function have reported similar observations. Beavis et al[32] studied a group of pre-menopausal patients who underwent total abdominal hysterectomy with ovarian conservation and found a rate of hysterectomy-induced ovarian failure of 15% which is very similar to that reported with UAE by both Chrisman[26] and Siddle et al[33]. This study and others[34] have emphasised the importance of the role of a viable uterus, or an intact blood supply, on normal ovarian function. Several mechanisms have been proposed in an attempt to explain the apparent change in ovarian function after UAE. Anastomoses between uterine and ovarian vessels have been described in up to 10% of women undergoing UAE[35]. Subsequently, there have been reports of non-target embolisation with embolic particles in the ovarian circulation, causing a decrease in the blood supply to the ovaries[36]. The increased risk of ovarian dysfunction in older women undergoing UAE could be due to the fact that older women are more sensitive to disruptions in vascular supply. It could also be postulated that an increase in gonadotrophins in women over the age of 45 is the result of

natural ageing. No surgical patients were classified as postmenopausal (FSH > 40 IU/L level) prior to treatment. Less than 10% of women in the UAE arm were postmenopausal pre-embolisation, most of whom were aged > 45 years. At follow up, both surgical and UAE patients had a statistically significant increase in median gonadotrophin levels from pre- to post-treatment. When examining the effect of age on gonadotrophin levels in this study, it may have been of greater value to compare patients over and under 40 years of age since FSH levels start rising around the age of 37 years[28] and fertility is usually less of an issue for women over 40 years. However, this was not possible due to the small number of patients under 40 years of age in both treatment groups. Despite the fact that there have been reports of POF post-UAE in younger woman[10, 37], no women in our study under the age of 40 years became menopausal during the 1 year follow up period. In addition, there was little deviation from baseline values of gonadotrophins in women < 45 years of age after treatment. Thus, in our study population, UAE does not have an effect on ovarian function in younger women.

A significant decrease in the mean duration of menstrual flow from pre- to post-treatment has also been reported in other studies[16, 38]. This is of clinical benefit to women undergoing UAE for fibroids as the majority present with heavy menses and an increased duration of menstrual bleeding. In contrast, there was no statistically significant difference in the mean cycle length before and after UAE. This is rather surprising and suggests that the changes in gonadotrophins induced by UAE were not reflected by changes in the menstrual cycle.

In conclusion, this study has shown that both UAE and surgery cause a statistically significant change in ovarian function post-treatment as assessed by gonadotrophin levels in women over 45 years of age. It has also demonstrated that there is no significant difference in the increase in post-treatment gonadotrophin levels between patients undergoing UAE compared to surgery. Our results in women under the age of 45 years were reassuring and suggest that ovarian function may be preserved in such women after UAE. In addition, UAE offers symptomatic relief by causing a statistically significant decrease in the mean duration of menstrual flow. Whilst there is a statistically significant increase in gonadotrophin levels post UAE, this does not appear to have a clinically significant effect.

Further studies, with age-controlled comparisons between UAE and surgery, need to be carried out in larger patient cohorts to determine the likelihood of premature ovarian failure in women

undergoing UAE. In particular, the real possibility of iatrogenic ovarian failure after UAE merits careful consideration in patients desiring future fertility.

Conclusions

1. Both UAE and surgery lead to small increases in gonadotrophin levels.
2. The increase in gonadotrophin levels is only significant in women over the age of 45 years.
3. Impaired ovarian function it is not reflected in an alteration in the length of the menstrual cycle although the length of the menses is shortened.
4. All women, particularly those in their 40s who desire future fertility, must be very carefully counselled regarding ovarian failure, prior to UAE.
5. The impact of myomectomy on ovarian function requires a larger study.

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Table 1. Hormone levels (n = 96) and menstrual cycle characteristics (n = 76) of women at baseline and at 6 and 12 months post-treatment.

Hormone Levels (n = 96)	**UAE (n = 73)**	**Surgery (n = 23)**
	FSH (IU/L)	**FSH (IU/L)**
	Median; range, (interquartile range)	**Median; range, (interquartile range)**
Baseline	6.7; 0.8 – 38.7, (4.4 – 11.3)	6.2; 2.2 – 14.7, (4.2 – 8.3)
6 months	7.5; 0.6 – 112, (4.3 – 16.0)	8.9; 0.5 – 28.1, (4.2 – 12.2)
12 months	7.8; 1.7 – 120, (5.4 – 14.7)	7.6; 4.3 – 81.0, (5.4 – 24.8)
	LH (IU/L)	**LH (IU/L)**
	Median; range, (interquartile range)	**Median; range, (interquartile range)**
Baseline	5.6; 0.5 – 45.8, (3.5 – 8.2)	4.2; 1.4 – 12.1, (2.9 – 6.3)
6 months	6.8; 1.4 – 103, (4.0 – 22.1)	4.8; 0.5 – 56.4, (3.0 – 10.6)
12 months	6.1; 2.1 – 60.8, (4.3 – 13.5)	7.9; 0.5 – 56.2, (13.4 – 19.1)
Menstrual cycle (n = 76) – UAE patients only		
Menstrual flow duration	**Mean (SD) - days**	
Baseline	7.1 (3.3)	
6 months	5.7 (2.7)	
12 months	5.6 (2.8)	
Length of menstrual cycle	**Mean (SD) - days**	
Baseline	27.4 (2.8)	
6 months	27.2 (3.3)	
12 months	28.0 (4.3)	

Table 2. Change in FSH and LH levels from baseline to 6 and 12 months after treatment for UAE and surgery and a comparison between UAE and surgery

	UAE (n = 73)	**Surgery (n = 23)**	**Difference UAE – Surgery**
Change in FSH (IU/L)	**median**; IQR (p-value for increase)	**median**; IQR (p-value for increase)	p – value (95% CI for median difference)
Increase at 6 months	**1.1**; -2.3 to 9.1 (p = 0.04)	**1.0**; -2.7 to 6.2 (p = 0.18)	0.81 (-3.2 to 3.6)
Increase at 12 months	**1.7**; -2.6 to 8.1 (p = 0.01)	**2.4;** -2.3 to 19.4 (p = 0.09)	0.54 (-8.7 to 3.7)
Change in LH (IU/L)			
Increase at 6 months	**2.0**; -0.8 to 12.8 (p = 0.001)	**0.8;** -2.1 to 4.5 (p = 0.30)	0.36 (-1.5 to 4.1)
Increase at 12months	**1.5**; -1.5 to 6.5 (p = 0.01)	**2.4;** -1.0 to 14.4 (p = 0.07)	0.50 (-7.1 to 2.2)

IQR – inter-quartile range

Table 3. Change in FSH and LH levels from baseline to 6 and 12 months after treatment in women ≥ 45 years compared to those < 45 years of age.

	≥45 years n =48	**< 45 years n =48**	**Difference (≥45 years – <45 years)**
Change in FSH (IU/L)	**median**; IQR	**median**; IQR	p – value (95%CI for median difference)
Increase at 6 months	**2.1**; -3.2 to 21.7	**0.8**; -2.3 to 3.6	0.33 (-1.7 – 5.5)
Increase at 12 months	**6.8**; -2.6 to 21.8	**0.3**; -2.4 to 4.2	0.01 (1.3 – 12.5)
Change in LH (IU/L)			
Increase at 6 months	**1.8**; -0.6 to 20.5	**1.4**; -2.3 to 3.6	0.28 (-1.0 – 5.5)
Increase at 12months	**2.2**; 0.6 to 13.8	**0.2**; -2.1 to 3.9	0.04 (0.2 – 6.7)

IQR – inter-quartile range

Table 4. Change in FSH and LH levels from baseline to 6 and 12 months after treatment for UAE and surgery and a comparison between UAE and surgery for women ≥ 45 years and for those < 45 years of age.

	UAE	**Surgery**	**Difference UAE - Surgery**
45 years and over	**n = 41**	**n = 7**	
Change in FSH (IU/L)	median; IQR (p-value for increase)	median; IQR (p-value for increase)	p-value (95%CI for median difference)
Increase at 6 months	**1.1**; -3.6 to 28.9 (0.12)	**4.6**; 1.1 to 10.0 (0.05)	0.43 (-15.1 to 11.2)
Increase at 12 months	**4.4**; -3.2 to 18.2 (0.03)	**33.7**; 3.5 to 58.9 (0.04)	0.01 (6.9 to 51.3)
Change in LH (IU/L)			
Increase at 6 months	**1.9**; -0.3 to 22.1 (0.01)	**0.8**; -1.5 to 4.0 (0.45)	0.38 (-20.6 to 2.5)
Increase at 12months	**2.0**; 0.3 to 10.2 (0.01)	**14.9**; 6.9 to 32.4 (0.06)	0.06 (-0.1 to 26.6)
Under 45 years	**n = 32**	**n = 16**	p-value (95% CI for median difference)
Change in FSH (IU/L)	median; IQR (p-value for increase)	median; IQR (p-value for increase)	
Increase at 6 months	**1.0**; -1.0 to 4.0 (0.09)	**-0.8**; -2.7 to 3.2 (1.0)	0.21 (-4.4 to 1.3)
Increase at 12 months	**0.7**; -2.0 to 4.8 (0.18)	**-0.7**; -3.0 to 2.4 (0.56)	0.27 (-5.4 to 1.5)
Change in LH (IU/L)			
Increase at 6 months	**2.1**; -2.4 to 3.5 (0.130	**0.8**; -2.3 to 6.1 (0.49)	0.80 (-3.5 to 4.0)
Increase at 12months	**1.1**; -2.2 to 3.6 (0.55)	**-0.3**; -1.7 to 4.8 (0.76)	0.86 (-3.1 to 5.3)

IQR – inter-quartile range

Table 5. Change in menstrual cycle characteristics from baseline to 6 and 12 months after treatment

	Change at 6 months	**Change at 12 months**
	mean (SD) (p-value; 95%CI)	**mean** (SD) (p-value; 95%CI)
Decrease in duration of menstrual flow (days)	**1.4** (3.7) (p = 0.001; 0.6 to 2.2)	**1.7** (3.8) (p = 0.001); 0.8 to 2.6)
Change in length of menstrual cycle (days)	**-0.3** (3.8) (p = 0.50; -1.2 to 0.6)	**0.7** (4.9) (p = 0.25; -0.5 to 1.9)