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Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy

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BACKGROUND: Ovarian failure as a complication of uterine artery embolization (UAE) for symptomatic uterine fibroids has raised concerns about this new treatment modality. METHODS: We investigated the occurrence of ovarian reserve reduction in a randomized trial comparing UAE and hysterectomy by measuring follicle stimulating hormone (FSH) and anti-Mullerian hormone (AMH). A total of 177 pre-menopausal women with menorrhagia due to uterine fibroids were included (UAE: $n=88$; hysterectomy: $n=89$). FSH and AMH were measured at baseline and at several time-points during the 24 months follow-up period. Follow-up AMH levels were also compared to the expected decrease due to ovarian ageing during the observational period. RESULTS: FSH increased significantly compared to baseline in both groups after 24 months follow-up (within group analysis: UAE: +12.1; $P=0.001$; hysterectomy: +16.3; $P<0.0001$). No differences in FSH values between the groups were found ($P=0.32$). At 24 months after treatment the number of patients with FSH levels >40 IU/l was 14/80 in the UAE group and 17/73 in the hysterectomy group (relative risk = 0.75; $P=0.37$). AMH was measured in 63 patients (UAE: $n=30$; hysterectomy: $n=33$). After treatment AMH levels remained significantly decreased during the entire follow-up period only in the UAE group compared to the expected AMH decrease due to ageing. No differences were observed between the groups. CONCLUSIONS: This study shows that both UAE and hysterectomy affect ovarian reserve. This results in older women becoming menopausal after the intervention. Therefore, the application of UAE in women who still wish to conceive should only be considered after appropriate counselling.

Keywords: anti-Müllerian hormone/hysterectomy/menopause/uterine artery embolization/ovarian reserve

Introduction

Since its introduction in 1995 uterine artery embolization (UAE) has become increasingly popular for the treatment of fibroid-related menorrhagia (Ravina *et al.*, 1995). UAE has been proposed by some enthusiasts to replace hysterectomy altogether as a final solution for fibroid disease in selected patients. Safety and efficacy have been evaluated in several large case-series (McLucas *et al.*, 2001; Spies *et al.*, 2001; Walker and Pelage, 2002; Pron *et al.*, 2003), but well designed randomized trials are lacking. Therefore, we initiated the randomized EMMY (EMbolization versus hysterectoMY) trial. Some short-term and long-term results of the EMMY trial have been published earlier (Hehenkamp *et al.*, 2005, 2006a; Volkers *et al.*, 2006a, 2006b).

Reduction of ovarian reserve after hysterectomy leading to (early) menopause has been described (Siddle *et al.*, 1987; Kaiser *et al.*, 1989; Derksen *et al.*, 1998; Cooper and Thorp, 1999; Nahas *et al.*, 2003; Chan *et al.*, 2005). Since early menopause is associated with an increased risk for osteoporosis and cardiovascular disease (Kritz-Silverstein and Barrett-Connor, 1993; van der Schouw *et al.*, 1996; Hu *et al.*, 1999), UAE might provide a benefit. However, also after UAE the onset of menopause has been described (Chrisman *et al.*, 2000; Stringer *et al.*, 2000; Messina *et al.*, 2002; Tulandi *et al.*, 2002). The true incidence of persistent ovarian failure after UAE is unknown but has been estimated to be <2% (Goodwin *et al.*, 1999). No randomized controlled trials have focused on this subject. Permanent ovarian failure can be demonstrated by increased FSH and LH levels, increased

menopausal symptoms and decreased estradiol (E_2) levels, which all occur typically after the onset of menopause (Speroff and Fritz, 2005).

To test the extent of ovarian reserve reduction (i.e. loss of oocytes) FSH, LH, E_2 and menopausal symptoms are of no use, since they only change or occurs after the actual onset of the menopausal transition (Soules *et al.*, 2001; Speroff and Fritz, 2005). Ovarian reserve reduction can better be tested by measuring anti-Müllerian-hormone (AMH). AMH in women reaches its highest level after puberty (Hudson *et al.*, 1990) and gradually decrease over time in normo-ovulatory women (de Vet *et al.*, 2002). Furthermore AMH is cycle independent (Cook *et al.*, 2000; Hehenkamp *et al.*, 2006b). AMH has been acknowledged as being a reliable marker of ovarian reserve, especially in relation to the quantity of remaining follicles in the ovaries (van Rooij *et al.*, 2002, 2004). To the best of our knowledge, relative damage to the ovaries has not been tested after both hysterectomy and UAE.

This report focuses on the occurrence of ovarian reserve reduction after UAE in comparison to hysterectomy as determined by clinical (i.e. menopausal symptoms) and hormonal markers (i.e. FSH, LH, E_2 and AMH).

Materials and Methods

Study design

The EMMY study is a multi-centre, randomized controlled trial, conducted in the Netherlands. A detailed description of the study has been provided earlier (Hehenkamp *et al.*, 2005) and will be discussed here only briefly.

Patients were included when their predominant complaint was menorrhagia, they had uterine fibroids and were to be scheduled for hysterectomy. Patients who desired future pregnancy were excluded. After written informed consent had been obtained, computer-based randomization was carried out, assigning patients 1:1 to either UAE or hysterectomy.

The study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by the local ethics committees of all participating hospitals.

Procedures

Uterine artery embolization

UAE was performed by an interventional radiologist. For UAE, polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355–500 μm were used. Only if an anastomosis with the ovarian artery was observed particles with a size of 500–700 μm were used to prevent migration of particles into the ovarian artery. PVA was injected into each uterine artery until there was no parenchyma filling of the fibroids anymore (target embolization) or until the main uterine artery was blocked and there was stasis of contrast (selective embolization). No embolization of ovarian arteries was carried out, because of the assumed high risk for ovarian damage. In case of extensive collaterals of the uterine artery to the cervix and vaginal wall, the procedure was stopped.

Hysterectomy

The type of hysterectomy and the route of access were left at the discretion of the attending gynaecologist. We did not establish consensus guidelines for concomitant adnexal surgery. If adnexa were removed, note was made.

Endpoints of the study

To assess the impact of both treatments on the menopausal transition FSH, LH and E_2 were measured in both groups at baseline and at 6 weeks and 6, 12 and 24 months follow-up. Also menopausal symptoms were assessed at these time points, with an additional questionnaire at 18 months follow-up.

Impact of treatments on ovarian reserve was tested by measuring AMH at baseline and 1 day, 6 weeks and 6, 12 and 24 months after treatment. AMH was measured in a subset of patients for logistic reasons. These patients were recruited in the four hospitals (Academic Medical Centre, Amsterdam; Onze Lieve Vrouwe Gasthuis, Amsterdam; Universitary Medical Centre, Utrecht and Rijnstate hospital, Arnhem) that were expected to contribute the largest number of patients to the trial and that could reliably store the samples before collecting them for analysis in a central laboratory.

Comparisons were made between the groups at all time points and within the groups compared to baseline.

Blood sampling and laboratory assays

Blood samples were preferably taken on the 3 day of the menstrual cycle.

All blood samples were assayed for levels of FSH (Abbott, Bager, DPC and Roche), LH (Bayer, DPC and Rochc) and E_2 (Abbott, Bager, DPC and Roche) using each hospital laboratory's own assay. Blood samples taken for measurement of AMH were allowed to clot, centrifuged, serum collected, frozen at -20°C within 3 h and stored until assayed in a central laboratory. The samples were assayed in a number of consecutive assays during a short period after all samples had been collected (Laboratory for Internal Medicine, Erasmus Medical Centre) using an enzyme-immunometric assay (DSL Webster, TX, USA). Inter- and intra-assay coefficients of variation were below 5% at the level of 3 μg/l, and below 11% at the level of 13 μg/l. The detection limit of the assay was 0.026 μg/l. Repeated freezing and thawing of the samples or storage at 37°C for 1 h did not significantly affect results. A comparison of this assay with the ultrasensitive version of the assay method provided by Immunotech-Coulter (Marseilles, France) in 82 samples with AMH concentrations between 0 and 15 μg/l yielded a correlation coefficient of 0.85. The formula of the regression line was AMH (DSL) $= 0.495 \times$ AMH(ic) $- 0.03$. In order to keep results comparable with earlier published data, we multiplied all results by a factor 2.0 (van Rooij *et al.*, 2002, 2004, 2005).

Questionnaires on menopausal transition status (Table 1)

Standardized questionnaires (Table 1) were used to measure menopausal symptoms: the Kupperman score (Kupperman *et al.*, 1953), the Kupperman score as modified by Wiklund *et al*. (1992) and a score developed by Oldenhave *et al.* (1993) yielding 3D: vasomotor complaints, atypical symptoms and vaginal dryness.

This resulted in scores ranging from 0–51 (original and modified Kupperman), 0–6 (vasomotor symptoms Oldenhave) and 0–63 (atypical symptoms Oldenhave). The Oldenhave vaginal dryness score reflects the weight of the individual score yielding a score ranging from 0 to 3. For all instruments higher scores represented more menopausal symptoms.

At the outpatient clinic visits (6 weeks and 6/12/24 months after treatment), UAE patients were asked if and when menstrual periods had resumed.

Statistical analysis

Outcomes were analysed according to the intention to treat principle unless stated otherwise. A P-value <0.05 was considered statistically

Table 1: Questionnaires for scoring menopausal symptoms

Kupperman (0–51)	Wiklund (0–51)	Oldenhave
Vasomotor symptoms (×4)	Hot flushes (×4)	Vasomotor complaints (0–6)
Paraesthesia (×2)	Sweating (×2)	Fushes
Insomnia (×2)	Sleep disturbance (×2)	Sweating
Nervousness (×2)	Nervousness (×2)	Atypical symptoms (0–63)
Melancholia	Depression	Tenseness
Vertigo	Nertigo	Palpitations
Weakness/fatigue	Fatigue	Irritability
Arthralgia/myalgia	Athralgia	Pins and needles
Headaches	Hadache	Restless legs
Palpitations	Tchycardia	Dizziness
Formication*	Vaginal dryness	Tiredness
		Tiredness on waking
Question		Depression
In the last month, did you experience.....		Forgetfulness
		Lack of energy
Answering options + weights		Shortness of breath
Absent = 0		Muscle or joint pain
Slight = 1		Lack of self-confidence
Moderate = 2		Insomnia
Severe = 3		Headache
		Migraine
Scoring		Burning micturition
The sum of weights (sometimes multiplied by a number in parentheses, e.g. multiplies by 4 for 'hot flushes' in the wiklund score) yields the score		Itching labia
		Vaginal discharge
		Urine loss
		Vaginal dryness (0–3)
		Vaginal dryness

* The sensation of crawling ants under the skin.

significant. Plots were constructed for average values of FSH, LH, E_2, AMH and menopausal scores, using all available data at baseline, 6 weeks and at 6 months intervals after treatment (until 24 months). Missing values for laboratory results were not imputed. Both, within group and between group analysis was performed for all outcome parameters. For parametric data a Student's *t*-test was performed, while for non-parametric data a Mann–Whitney-U or a Wilcoxon test was used. Change from baseline was calculated for all visits after treatment. Differences between the groups were calculated by analysing change from baseline at 6 weeks and 6, 12 and 24 months. Longitudinal differences between groups were evaluated with repeated measurements analyses for all longitudinally available data (i.e. both for hormones and menopausal questionnaires).

FSH values were categorized for each outpatient visit (<10, 10–20, 20–30, 30–40 and >40 IU/l). Logistic regression analysis was performed to assess the risk of the occurrence of menopause. Since menopausal status cannot be determined by absence of menstrual flow in hysterectomy patients, we used FSH levels in excess of 40 IU/l at 24 months follow-up to assess menopause (Speroff and Fritz, 2005). The normal mid-follicular FSH peak does not reach these levels, and therefore this threshold value was assumed to indicate persistent ovarian arrest. The following co-variables were included in the logistic regression, whenever univariate analysis revealed *P*-values < 0.1: intended treatment (UAE/hysterectomy), age at baseline (>/<45 years), ethnicity (Caucasian, black or other), body mass index (continuous), uterus volume (continuous), parity (parous/non-parous), smoking (yes/no), comorbidity (yes/no) and previous surgical treatment (yes/no). This analysis was repeated for both groups (UAE/hysterectomy) separately as well. In the hysterectomy group the following variables were added: type of hysterectomy (abdominal/not abdominal) and duration of hysterectomy (continuous); in the UAE group the following variables were added: unilateral selective UAE (yes/no), bilateral selective UAE (yes/no), number of required vials of PVA (continuous), presence of anastomozing vessels between uterine and ovarian arteries as detected at angiography, either unilateral (yes/no) or bilateral (yes/no) and secondary hysterectomy after UAE (yes/no).

The natural decrease of AMH was calculated according to an earlier report (van Rooij *et al.*, 2005). Follow-up values of AMH measurements were compared to both baseline AMH values and the expected calculated AMH values. For AMH, a per-protocol analysis was performed to assess the exact impact of UAE on ovarian reserve: whenever a secondary hysterectomy was performed in the UAE group the subsequent AMH values were excluded from further analysis.

Subtle ovarian reserve reduction was explored by performing linear regression analysis with the change of AMH level (24 months AMH level minus baseline AMH level) as the dependent variable, with the same co-variables and the same procedure as the logistic regression analysis described above. For the questionnaires, the average individual score was used when only one question was missing. In case of >1 question missing or when only the question on 'hot flushes' was missing, the whole score was excluded from analysis.

Results

Patients

Between March 2002 and February 2004, 177 patients (out of 349 eligible patients) agreed to participate in the study. A total of 88 patients were randomized to the UAE group and 89 patients to the hysterectomy group. In the UAE group, 81 patients underwent the allocated procedure compared to 75 in the hysterectomy group (Fig. 1). Baseline characteristics did not differ between both groups (Table 2). At randomization, two patients had a unilateral oophorectomy previously (both >10 years ago). Their baseline FSH values were 6.0 and 8.5 IU/l. They were both randomized to the UAE group. In the UAE group, the procedure failed bilaterally in four cases. These patients subsequently had a hysterectomy, but were followed up in the UAE group (in the intention to treat analysis). In the follow-up period of 24 months, 15 additional patients had a secondary hysterectomy after UAE due to clinical failure (Volkers *et al.*, 2006a).

UAE patients resumed having menstrual periods on average 24.4 days (SD: 24.4; median: 24; range: 0–172 days) after the procedure. Two patients did not have menstrual periods anymore after undergoing UAE.

Hormonal parameters

Figure 2 displays mean values (with 95% confidence intervals (CI)) of FSH, LH and E_2 over time for each treatment. Pretreatment FSH measurements were not available for 3/75 hysterectomy patients. After treatment, FSH values increased in both groups, peaked at 6 weeks, decreased until 6 months and then increased again slowly until 24 months. FSH levels after treatment were consistently higher after hysterectomy than after UAE, but the repeated measurement analysis revealed no significant differences between the groups (FSH: $P = 0.41$; LH: $P = 0.16$; E_2: $P = 0.12$). Table 3 lists average differences between baseline values for each group and estimates at 6 weeks and 6, 12, 24 months after treatment. In general, FSH increased significantly over time within the

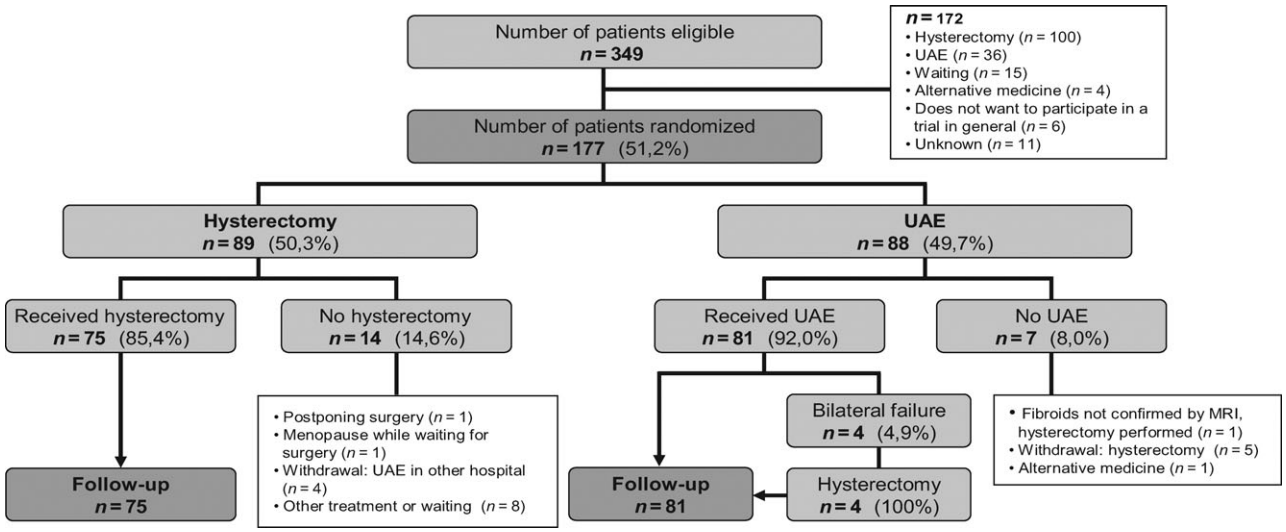

Figure 1: Trial profile of patients undergoing hysterectomy or UAE

groups compared to baseline values (except for 6 months in the UAE group). LH increased significantly at all times within both groups. Average E_2 levels increased significantly, except for 6 weeks after treatment in the UAE group. Table 4 lists number of patients by FSH levels, time and treatment group. No differences between the two groups were observed. FSH levels >40 U/l at 24 months follow-up were observed in 14/80 (17.5%) UAE patients compared to 17/73 (23.3%) hysterectomy patients (relative risk = 0.75; 95% CI: 0.40–1.41; $P = 0.37$). Hormonal replacement therapy was used at 24 months follow-up by five women (three in UAE group and two in hysterectomy group).

Multivariate logistic regression analysis on FSH >/< 40 IU/l revealed only age >45 years at baseline (odds ratio: 4.46; 95% CI: 1.79–11.14; $P = 0.001$) to be significantly associated with FSH levels >40 IU/l after treatment. Treatment allocation (UAE/hysterectomy) was not associated with this outcome ($P = 0.38$). Separate analyses per treatment group revealed no treatment-related variables to be predictive of ovarian failure (i.e. FSH >40 IU/l).

Analysis of AMH was based on 63 included patients (30 UAE versus 33 hysterectomy) of whom pretreatment serum was available. The mean age of these 63 patients was not significantly different between the groups (UAE: 45.0; hysterectomy: 45.2; $P = 0.84$). The same applies to mean baseline FSH (UAE: 7.7 IU/l; hysterectomy: 7.9 IU/l; $P = 0.95$). None of the patients in either group had had a uni- or bilateral oophorectomy previously or during hysterectomy. In the UAE group 6 women (20%) had a secondary hysterectomy between 12 and 24 months follow-up. Only AMH values after the secondary hysterectomy were excluded from further analysis. Figure 3 displays means (with SE) of AMH values over time, together with the natural decrease of AMH as expected for the age-range of our patients. Follow-up samples were available for 61/63 (97%) patients (at 6 months), 60/63 (95%) patients (at 12 months) and 53/63 (84%) patients (at 24 months). In hysterectomy patients, mean AMH values decreased until 6 weeks after treatment. Between 6 weeks and 12 months the mean AMH values recovered to the expected (normal) values and remained that way until 24 months follow-up. Mean AMH values of UAE patients decreased initially with a slight recovery between 6 weeks and 6 months, but remained significantly under the expected value range until 24 months follow-up. Repeated measurements analysis revealed no differences between the groups.

Table 3 displays mean change scores for AMH levels compared to baseline (except for the measurement 1 day after the procedure, which was only used for plotting purposes). AMH levels in the UAE group decreased significantly at all time points, both compared to baseline and compared to expected levels. In the hysterectomy group the change from baseline was only significant at 6 and 24 months ($P = 0.010$ and $P = 0.027$, respectively), while none of the observed values were significantly lower than the expected decrease. In the between group analysis, there was only a significant difference at 6 weeks ($P = 0.005$).

Univariate analysis on decrement of AMH 24 months after treatment revealed no variables to be predictive (all: $P > 0.10$). As demonstrated in Table 3 as well, treatment allocation was not associated with the outcome ($P = 0.27$).

Menopausal parameters

Baseline menopausal scores were not available for 11/81 (13.6%) UAE and 9/75 (12.0%) hysterectomy patients. Response rates to the follow-up questionnaire were 155/156 (99%, 6 weeks), 151/156 (97%, 6 months), 151/156 (97%, 12 months), 150/156 (96%, 18 months) and 154/156 (99%, 24 months), respectively.

In Fig. 4, the mean menopausal scores (95% CI) of both treatments are plotted over time for the Kupperman, Wiklund and Oldenhave (vasomotor, vaginal dryness and atypical symptoms) scores. Repeated measurement analysis revealed no differences between the groups (Kupperman: $P = 0.65$; Wiklund: $P = 0.83$; Oldenhave vasomotor: $P = 0.63$; Oldenhave vaginal dryness: 0.63 and Oldenhave atypical symptoms:

Table 2: Baseline characteristics of women undergoing hysterectomy or UAE

	UAE $n = 88$ *n* (%)	Hysterectomy, $n = 89$ *n* (%)
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
BMI (Weight (kg) / length $(m)^2$)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
≥1	58 (65.9)	69 (77.5)
Race		
Black	24 (27.3)	20 (22.5)
White	54 (61.4)	57 (64.0)
Other	10 (11.4)	12 (13.5)
Comorbid disease*	24 (27.3)	22 (24.7)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)
Number of fibroids**		
Median (range)	2 (1–20)	2 (1–9)
Uterine volume (cm^3)**		
Median (range)	321 (31–3005)	313 (58–3617)
Fibroid volume (dominant fibroid, cm^3)**		
Median (range)	59 (1–673)	87 (4–1641)
Type of UAE		
Target embolisation		
Left uterine artery	65	–
Right uterine artery	59	–
Selective embolisation		
Left uterine artery	8	–
Right uterine artery	12	–
Type of hysterectomy		
Abdominal hysterectomy	–	63
Vaginal hysterectomy	–	8
Vaginal hysterectomy with morcellator	–	1
LH with morcellator	–	2
LAVH****	–	1
Uterine-ovarian artery anastomosis	15***	Unkown
Other procedures		
Salpingo-oophorectomy		
Unilateral	–	2
Bilateral	–	1

*At least one of the following: hypertension; diabetes; asthma; systemic disease; **Ultrasound data; ***In 13 patients unilaterally, in 1 patient bilaterally; ****Laparoscopically assisted vaginal hysterectomy.

$P = 0.63$). The baseline scores did not differ significantly between groups.

Average differences with baseline values for each group at 6 weeks and 6, 12 and 24 months follow-up are listed in Table 3. Only the Oldenhave atypical symptoms at 12 months after treatment were significantly different between both groups.

Within group analysis revealed several significant changes compared to baseline (indicated by '*' in Table 3). The Kupperman and Wiklund scores decreased the most, with significant changes in the short term. The Oldenhave vasomotor score was significantly increased in both groups at 24 months follow-up. Vaginal dryness was only significantly increased at 18 months follow-up in the hysterectomy group and atypical symptoms decreased significantly in both groups at all occasions.

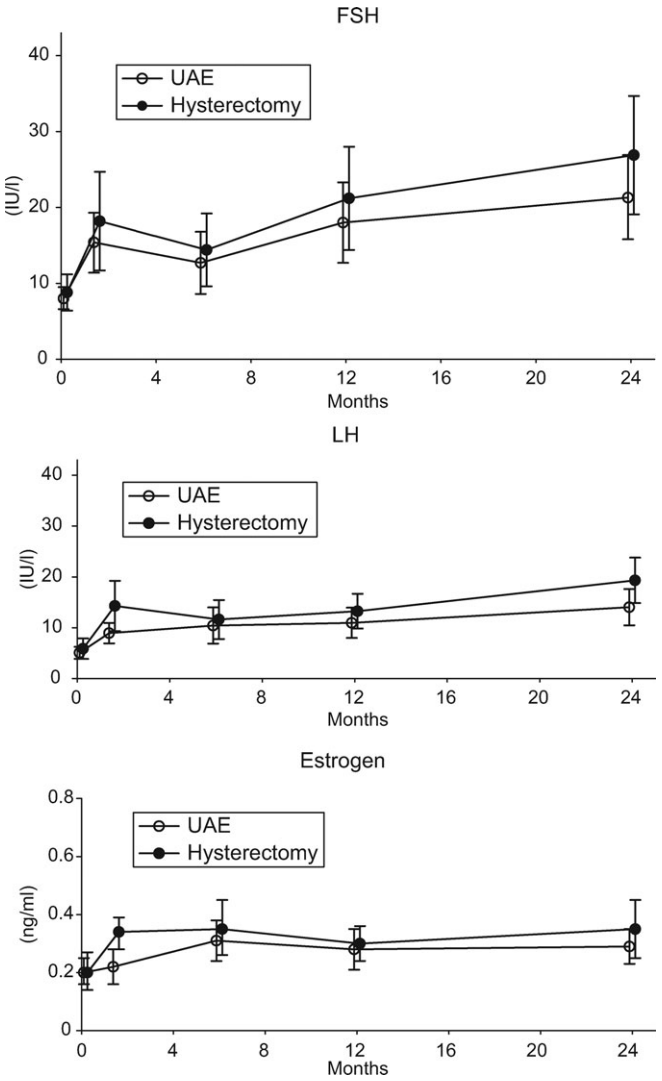

Figure 2: FSH, LH and E_2 over time

Discussion

The effect of UAE on the ovaries in comparison to hysterectomy has not been established earlier. Ovarian function after hysterectomy has been investigated extensively. Some studies have shown that hysterectomy affects the age at which the onset of menopause occurs (Siddle *et al.*, 1987) and that hysterectomy may increase the incidence of menopausal symptoms (Riedel *et al.*, 1986; Menon *et al.*, 1987; Oldenhave *et al.*, 1993; Hartmann *et al.*, 1995; Stadberg *et al.*, 2000). Also, FSH and/or LH levels have been shown to increase significantly after hysterectomy (Kaiser *et al.*, 1989; Derksen *et al.*, 1998; Cooper and Thorp, 1999; Nahas *et al.*, 2003; Chan *et al.*, 2005) although others did not confirm these findings (Stone *et al.*, 1975; Chalmers *et al.*, 2002).

In contrast, the present knowledge on the effect upon ovarian function after UAE is limited, and derives mainly from case reports and small series. Permanent loss of ovarian function after UAE resulting in menopause has been reported in several studies (Chrisman *et al.*, 2000; Stringer *et al.*, 2000; Messina *et al.*, 2002; Tulandi *et al.*, 2002). This complication

Table 3: Change of menopausal scores, FSH, LH, E_2 and AMH at 6 weeks and 6, 12, 18 and 24 months compared to baseline

	6 weeks change				6 months change				12 months change				18 months change				24 months change			
	UAE	Hyst.	difference (95% CI)	*P*-value	UAE	Hyst.	difference (95% CI)	*P*-value	UAE	Hyst.	difference (95% CI)	*P*-value	UAE	Hyst.	difference (95% CI)	*P*-value	UAE	Hyst.	difference (95% CI)	*P*-value
Menopause questionnaires																				
Kupperman (0–51)	−2.5*	−2.4*	0.1 (−2.2 to 2.5)	0.91	−2.0*	−3.0*	−1.0 (−3.3 to 1.3)	0.40	−0.5	−1.9*	−1.4 (−4.0 to 1.1)	0.28	−0.9	−1.7	−0.8 (−3.4 to 1.8)	0.56	−0.5	−0.23	0.3 (−2.6 to 3.2)	0.84
Wiklund (0–51)	−2.2*	−2.5*	−0.3 (−2.9 to 2.2)	0.80	−1.5	−3.0*	−1.5 (−4.2 to 1.2)	0.27	−0.4	−1.9	−1.5 (−4.4 to 1.4)	0.31	−0.5	−1.2	−0.6 (3.7 to 2.5)	0.68	−0.05	0.05	0.1 (−3.1 to 3.3)	0.95
Oldenhave																				
Vasomotor (0–6)	0.1	−0.4	−0.5 (−1.0 to 0.01)	0.053	0.2	−0.1	−0.3 (−0.8 to 0.3)	0.30	0.4*	0.1	−0.3 (−0.9 to 0.3)	0.32	0.5*	0.12	−0.4 (−1.0 to 0.2)	0.22	0.6*	0.5*	−0.1 (−0.7 to 0.5)	0.71
Vaginal dryness (0–3)	−0.1	−0.2	−0.1 (−0.4 to 0.2)	0.61	−0.1	0.1	0.2 (−0.1 to 0.4)	0.24	−0.02	0.1	0.2 (−0.1 to 0.4)	0.25	−0.1	0.2*	0.2 (−0.02 to 0.5)	0.07	−0.01	0.1	0.1 (−0.2 to 0.4)	0.64
Atypical symptoms (0–63)	−3.6*	−4.5*	−0.9 (−3.5 to 1.8)	0.53	−4.0*	−5.6*	−1.6 (−4.3 to 1.0)	0.22	−3.0*	−6.1*	−3.1 (−5.7 to −0.5)	0.02	−3.7*	−6.0*	−2.3 (−5.2 to 0.6)	0.11	−3.9*	−5.1*	−1.2 (−4.2 to 1.8)	0.42
Hormone levels																				
FSH (IU/l)	7.2*	9.8*	2.7 (−4.2 to 9.5)	0.44	4.8	6.6*	1.9 (−4.5 to 8.2)	0.56	9.6*	13.0*	−3.4 (−4.2 to 11.1)	0.38	NA	NA	NA	NA	13.3*	17.8*	4.6 (−4.1 to 13.3)	0.30
LH (IU/l)	3.8*	8.0*	4.2 (−0.6 to 9.0)	0.09	5.3*	5.8*	0.5 (−4.8 to 5.8)	0.86	5.8*	7.3*	−1.5 (−2.9 to 5.9)	0.50	NA	NA	NA	NA	8.9*	12.5*	3.5 (−2.0 to 9.0)	0.21
Oestrogen (nmol/l)	0.03	0.13*	0.10 (−0.01 to 0.21)	0.07	0.12*	0.15*	0.03 (−0.10 to 0.17)	0.63	0.09*	0.11*	−0.02 (−0.08 to 0.12)	0.69	NA	NA	NA	NA	0.09*	0.15*	0.06 (−0.08 to 0.19)	0.42
AMH (μg/l)	−0.63*	−0.08	0.54 (0.18 to 0.92)	0.005**	−0.27*	−0.14*	0.14 (−0.40 to 0.69)	0.60	−0.41*	−0.01	0.40 (−0.16 to 0.95)	0.16	NA	NA	NA	NA	−0.61*	−0.31*	0.30 (−0.24 to 0.85)	0.27
AMH (μg/l) versus expected	−0.62*	−0.07	0.54 (0.18 to 0.92)	0.005**	−0.23*	−0.09	0.14 (−0.40 to 0.68)	0.61	−0.31*	−0.09	0.39 (−0.16 to 0.94)	0.16	NA	NA	NA	NA	−0.42*	−0.12	0.29 (−0.24 to 0.83)	0.28

Hyst., hysterectomy; *Statistically significant ($P < 0.05$) change in within group analysis (Wilcoxon test); **between group difference.

Table 4: Comparison of ranges of FSH values between treatment groups at 6 weeks and 6, 12, 24 months after treatment

FSH (IU/l)	6 weeks after treatment			6 months after treatment			12 months after treatment			24 months after treatment		
	UAE $n = 79$ n(%)	Hyst. $n = 69$ n (%)	p-value*	UAE $n = 78$ n (%)	Hyst. $n = 69$ n (%)	P-value*	UAE $n = 74$ n (%)	Hyst. $n = 73$ n (%)	P-value*	UAE $n = 80$ n (%)	Hyst. $n = 73$ n (%)	P-value*
<10	48 (61)	45 (65)	0.66	57 (73)	48 (70)	0.99	43 (58)	42 (58)	0.48	41 (51)	38 (52)	0.87
10–20	11 (14)	10 (15)		9 (12)	9 (13)		12 (16)	12 (16)		12 (15)	9 (12)	
20–30	5 (6)	1 (1)		2 (3)	2 (3)		3 (4)	4 (5)		8 (10)	6 (8)	
30–40	5 (6)	3 (4)		3 (4)	3 (4)		7 (9)	2 (3)		5 (6)	3 (4)	
>40	10 (13)	10 (15)		7 (9)	7 (10)		9 (12)	13 (18)		14 (18)	17 (23)	

*Fisher's exact.

seems to occur mainly in women >45 years of age (Chrisman *et al.*, 2000; Spies *et al.*, 2001). Transient ovarian failure has also been described (Amato and Roberts, 2001; Hascalik *et al.*, 2004) but other studies did not show any untoward effects on ovarian function from UAE (Ahmad *et al.*, 2002; Salomon *et al.*, 2003; Descargues *et al.*, 2004; Healey *et al.*, 2004; Tropeano *et al.*, 2004). Ovarian damage is thought to occur after UAE because of passage of embolization particles through anastomotic vessels between uterine and ovarian arteries, causing hypoxic ovarian damage and tissue loss (Tulandi *et al.*, 2001). Indeed, it has been confirmed that embolization particles can be found at histopathologic examination of ovarian tissue after UAE (Payne *et al.*, 2002). Furthermore, loss of ovarian perfusion, as demonstrated by sonographic assessment, directly after treatment in a substantial number of patients has been observed (Ryu *et al.*, 2001).

In our study, very few differences in effect on ovarian reserve were found between UAE and hysterectomy: both treatments cause damage to the ovaries, as substantiated by a significant rise in FSH and LH serum levels. The drop in AMH levels immediately after treatment represents the loss of ovarian tissue, probably as a result of vascular compromise with ensuing ischaemia, either by inadvertent embolization of ovarian vasculature in UAE, or by compromising ovarian bloodflow by ligating anastomozing vessels during hysterectomy. Results of indicators of ovarian reserve tests tend to partially recover after both treatments, supporting earlier observations that ovarian failure may be transient (Amato and Roberts, 2001; Hascalik *et al.*, 2004). After the (partial) recovery of ovarian function, the decrement is only significant after UAE when compared to the expected decrement due to ageing, thereby indicating that UAE might be even more harmful to ovarian reserve status than hysterectomy.

Multivariate regression analysis revealed that higher age (>45 years of age) predicted the occurrence of elevated, post-

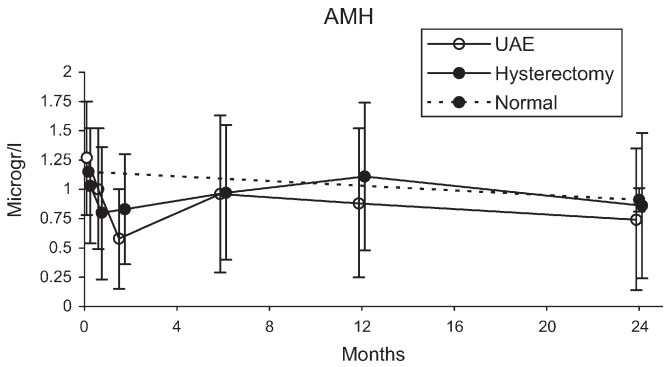

Figure 3: AMH over time. Data for the normal decrease were derived from van Rooij *et al.* (2005)

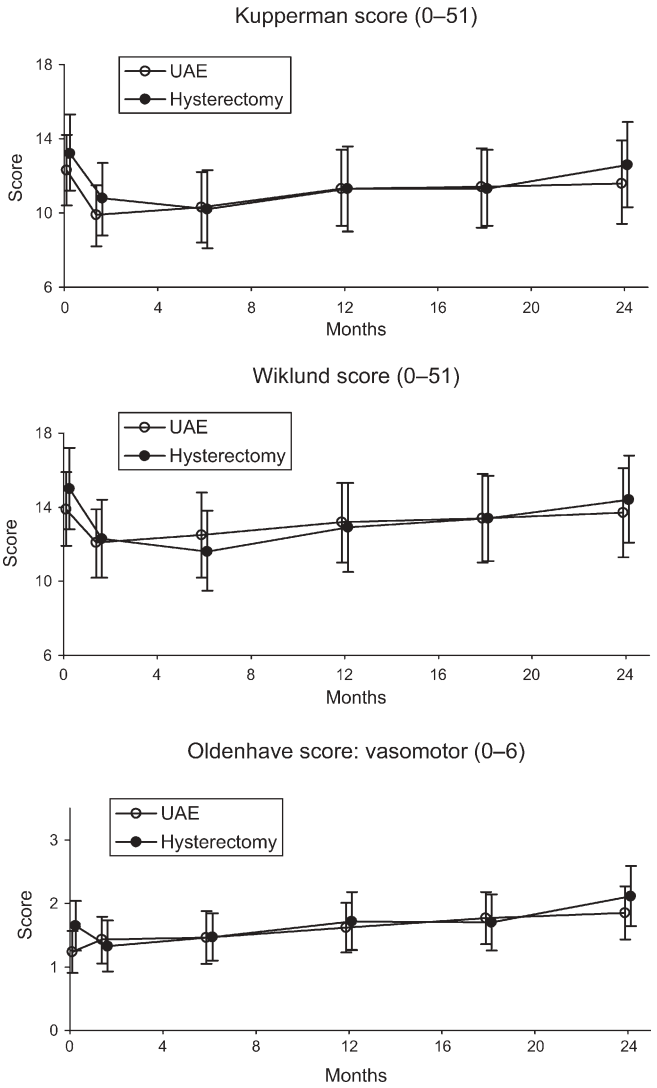

Figure 4: Menopause scores over time (Kupperman, Wiklund and Oldenhave)

menopausal FSH values. This indicates that women with low ovarian reserve (older women and women with higher FSH values at baseline) are prone to develop a menopausal state. However, the decrease in AMH in the first 24 months, which was not correlated with age, indicates that every woman experiences loss of ovarian reserve. For older women with less ovarian reserve, this means that menopause is more likely to occur. For younger women, however, relative damage occurs, which does not result in menopause, but which might impair ovarian reserve and may affect future prospects of becoming pregnant. Although this damage may be missed altogether by low-sensitivity diagnostic tests, such as FSH measurements and by assessment of clinical signs and symptoms, analysis of AMH patterns, however, reveal its presence.

Reduction of ovarian reserve is of special importance when UAE is used in the treatment of women desiring future fertility, which is now still being discouraged (Tulandi *et al.*, 2001; ACOG Committee Opinion 2004; Andrews *et al.*, 2004; Hascalik *et al.*, 2004). The impact on future fertility was not the scope of our trial, which excluded women with a desire for future pregnancy. Although UAE has been advocated by some to be used in women who do wish to conceive, our results discourage this view.

Our patients had no alternative other than hysterectomy, since other treatment options (i.e. medical therapy, endometrium ablation or myomectomy) were not possible or had already provided insufficient clinical results. Therefore, ovarian damage could not be avoided. With the proper indication, UAE might provide a suitable alternative for hysterectomy, since no differences in impact on ovarian reserve between the treatments were found. For patients with less severe fibroid-related complaints or patients with the desire for future fertility, one should keep in mind that ovarian damage may occur when UAE is undertaken, and might be avoided with other treatment choices.

In contrast to a rise in average FSH levels, no significant increase in menopausal symptoms was observed, except for the Oldenhave vasomotor symptoms. This is probably consistent with the absence of low E_2 levels as found in the present study. In contrast, E_2 levels increased, probably as a result of hyper-stimulation of the ovaries by elevated FSH values as found in our study (Speroff and Fritz, 2005).

A limitation of our study was the inability to obtain serum samples strictly at the 3 day of the menstrual cycle to obtain a standardized parameter for ovarian reserve (Scott *et al.*, 1989). This standardization was sometimes impossible because of permanent vaginal blood loss prior to the intervention, absence of menstrual bleeding in post-hysterectomy patients or irregular menstrual cycles. Therefore average FSH values might be higher by inclusion of mid-cycle samples. However, FSH values normally do not reach the threshold level we used as indicator of menopause (i.e. >40 IU/l, Speroff and Fritz, 2005).

Furthermore, we did not have a control group for the occurrence of ovarian ageing over time. However, AMH values in both groups dropped dramatically immediately after treatment in comparison to the normal (expected) decrease of AMH for our patients' age group (Fig. 3). This indicates instant ovarian damage that may have been caused by demise of the follicle cohort responsible for the AMH levels. The mechanism of (partial) recovery of the AMH levels thereafter may be attributed to restoration of the follicle cohort from the primordial follicle pool. However, since AMH levels do not reach the expected level over time for the UAE group, it may be suggested that the primordial pool has also suffered irreparable damage in this group.

Furthermore, our study population was relatively old compared to the population of women who have a desire for future pregnancy. The occurrence of a significant and permanent drop in AMH levels in the UAE group might be different in a younger age group, i.e. the age group of particular interest when desire for future fertility is at stake. We encourage future studies to address these matters.

In conclusion, both UAE and hysterectomy affect ovarian reserve. No differences between treatments on ovarian function were observed, however. Especially when future pregnancy is desired, UAE should only be offered after appropriate counselling.

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