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ORIGINAL ARTICLE *Infertility*

Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve†

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STUDY QUESTION: Do the presence of endometriomas and their laparoscopic excision lead to a decrease in ovarian reserve as assessed by serum anti-Müllerian hormone (AMH) levels?

SUMMARY ANSWER: Both the presence and excision of endometriomas cause a significant decrease in serum AMH levels, which is sustained 6 months after surgery.

WHAT IS KNOWN ALREADY: No previous comparison of serum AMH levels between women with and without endometrioma has been reported. However, studies have suggested a decline in serum AMH levels 1–3 months after endometrioma excision but long-term data are needed.

STUDY DESIGN, SIZE, DURATION: A prospective cohort study including 30 women with endometrioma >2 cm were age matched with 30 healthy women without ovarian cysts.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with endometrioma underwent laparoscopic excision with the stripping technique. Serum AMH level and antral follicle count (AFC) were determined preoperatively, 1 and 6 months after surgery. Correlation analyses were undertaken in order to identify determinants of surgery-related change in ovarian reserve.

MAIN RESULTS AND THE ROLE OF CHANCE: Compared with controls at baseline, women with endometrioma had lower AMH levels (4.2 ± 2.3 versus 2.8 ± 2.2 ng/ml, respectively, $P = 0.02$) and AFC (14.7 ± 4.1 versus 9.7 ± 4.8, respectively, $P < 0.01$). Serum AMH levels were further decreased 6 months after surgery (2.8 ± 2.2 versus 1.8 ± 1.3 ng/ml, $P = 0.02$), while AFC remained unchanged (9.7 ± 4.8 versus 10.4 ± 4.2, $P = 0.63$). The rate of decline in AMH was not correlated with age, laterality of endometrioma, cyst diameter or the number of primordial follicles on the surgical specimens. The preoperative serum AMH level was positively correlated with the rate of decline in serum AMH after surgery ($r = 0.47$, $P = 0.02$).

LIMITATIONS, REASONS FOR CAUTION: The absence of a non-treated group of women with endometriomas as a further control prevents comment on the presence of a progressive decline in ovarian reserve related to endometrioma *per se*. The sample size may be too small for detection of factors correlated with the extent of ovarian damage.

WIDER IMPLICATIONS OF THE FINDINGS: While the findings are mostly in agreement with previous studies, the present study is the first to show that the presence of endometrioma *per se* is associated with a decrease in ovarian reserve. The extent of surgery-related decline in ovarian reserve is not predictable using preoperative or perioperative factors. It may be prudent to measure AMH levels preoperatively and delay/avoid surgical excision as far as is possible if subsequent fertility is a concern. Additional studies are required to further investigate whether the endometrioma-related decline in ovarian reserve *per se* is progressive in nature and whether it exceeds the surgery-related decline.

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Key words: endometriosis / anti-Müllerian hormone / antral follicle count / ovarian reserve / laparoscopy

Introduction

Endometriosis affects 0.8–2% of women of reproductive age (Moen and Schei, 1997; Leibson *et al*., 2004; Ballard *et al*., 2008; Gylfason *et al*., 2010; Abbas *et al*., 2012) and endometriomas are present in 20–40% of women with endometriosis (Jenkins *et al*., 1986; Redwine, 1999; Vercellini *et al*., 2003). Despite the failure to demonstrate a causal relationship between endometriosis and infertility, there seems to be an association. It has been reported that 30–50% of women with endometriosis experience fertility problems and endometriomas are frequently encountered during infertility work-up. Although indications for surgical excision of endometriomas are controversial, surgical removal is commonly undertaken. (Gelbaya *et al*., 2010; Raffi *et al*., 2012a,b). Besides the usual risks of anaesthesia and surgery in general, another major concern associated with surgical management of endometriomas in subfertile women is the potential detrimental impact of surgical excision on ovarian reserve, which can already be diminished in these women.

Although the literature is abound in studies investigating the effect of endometrioma removal on ovarian reserve, some controversy still exists and there is a gap in knowledge regarding the long-term (i.e. ≥6 months after surgery) effects of endometrioma excision on ovarian reserve, as pointed out by a recent systematic review (Raffi *et al*., 2012a,b). Another recent systematic review has also concluded that studies investigating risk factors associated with a surgery-related decline in ovarian reserve were needed (Somigliana *et al*., 2012).

The present study was conducted prospectively to determine (i) whether women with endometriomas had a lower ovarian reserve than women without endometriomas, (ii) whether surgical excision of endometriomas led to a sustained loss in ovarian reserve and (iii) which factors could be related to a change in serum anti-Müllerian hormone (AMH) levels after endometrioma excision.

Materials and Methods

The study population was recruited from women presenting to the gynaecology clinic of a tertiary care hospital in Bursa, Turkey, between March 2008 and June 2011.

Women of reproductive age who had an ultrasonographic diagnosis of endometrioma measuring ≥2 cm and were to undergo surgical excision due to pain or subfertility were offered participation. The exclusion criteria were prior ovarian surgery, irregular menstrual periods, presence of polycystic ovary syndrome or any endocrine disorder, and having used any medication that could affect ovarian function, e.g. GnRH analogues or oral contraceptives, during the 6 months preceding scheduled surgery. The control group comprised women of reproductive age who did not have ovarian cysts. To exclude other pathology that could affect ovarian reserve, control subjects were not recruited from patients presenting to gynaecology clinic but were recruited from age-matched female medical residents and nurses working in the same hospital. The same exclusion criteria were applied to the controls. The study protocol was approved by the research ethics committee of the Uludag University School of Medicine and all participants provided written informed consent.

Assessment of ovarian reserve

Venous blood samples were collected for determination of serum AMH levels. All samples were collected during early follicular phase of a spontaneous cycle, i.e. between cycle days 3 and 5. Following centrifugation at 2000*g* for 10 min serum was frozen at −80°C for later analysis. Serum AMH levels were determined using a commercially available ELISA kit (*Active*® MIS/AMH ELISA kit, DSL, Webster, USA) according to the manufacturer's instructions. Measurements were performed in duplicate and the results were averaged. The AMH concentration in each sample was determined by interpolation from a standard curve and calculated as ng/ml as recommended. The minimum detectable level of human AMH in serum is 0.006 ng/ml. Recovery of MIS/AMH in this ELISA was 98–109%. Although AMH analyses were run in several rounds as patients accrued during the course of the study, preoperative and post-operative samples of each participant were analysed together with the same kit.

All women underwent a transvaginal ultrasound examination to determine antral follicle count (AFC) on the same day as sample collection. The total number of antral follicles measuring 2–9 mm diameter in both ovaries was recorded for each participant. Women with endometriomas underwent laparoscopic surgery during the follicular phase of the same menstrual cycle in which the ultrasonographic assessment of AFC and blood sampling were performed.

All operations were done by two surgeons (G.U. and K.O.), who have extensive experience in laparoscopic surgery for endometriosis. The surgical technique involved sharp dissection on the ovarian surface to identify the cleavage plane followed by blunt dissection and traction—counter traction for stripping the pseudocapsule from the ovary. Laparoscopic scissors were used to break fibrotic adhesions between the pseudocapsule and the ovary. Hemostasis was achieved by cautious micro-bipolar cauterization whenever necessary. Cauterization was avoided as far as possible, especially near the hilus, to prevent undue damage to ovarian tissue. The ovarian cortex was left open and not approximated with sutures. Any other endometriotic lesions identified in the abdominal cavity were destroyed by cauterization and adhesiolysis was performed.

To assess the extent of inadvertent removal of ovarian tissue during surgical excision of endometriomas, the number of ovarian follicles was counted on surgical specimens from each patient with an optical microscope.

GnRH analogues were not used in post-operative management of participants. Women who underwent surgery due to pelvic pain were allowed to use oral contraceptive pills (OCP) if pain recurred at least 1 month after surgery and the pain was not responsive to non-steroidal anti-inflammatory drugs.

Additional blood samples were collected 1 and 6 months after endometrioma excision for determination of serum AMH levels. Serum was separated and frozen, as above, until analysis. Women undergoing surgery also had a transvaginal ultrasonography to determine AFC 1 month after surgery.

The study was arbitrarily designed to include 30 women with endometriomas in order to ensure a normal distribution of most variables and to complete data collection in 2 years. The absence of age-based AMH nomograms and any prior publications reporting the change in AMH levels following endometrioma excision prevented a proper sample size calculation when this study was designed in 2007. Continuous data were defined with the mean and SD or median and interquartile range (IQR) depending on the distribution characteristics of a particular variable. Preoperative AFC and AMH levels were compared by the Mann–Whitney *U*-test between women who had endometrioma and women who did not have ovarian cysts. Preoperative and post-operative AFC and AMH levels were compared by Wilcoxon signed rank test in women who underwent laparoscopic endometrioma excision. The same comparisons were repeated in subgroups based on the laterality of endometriomas, i.e. unilateral or bilateral. The rate of decline in the serum AMH level was calculated as (serum AMH level before surgery − serum AMH levels at 6 months after surgery)/serum AMH level before surgery, and was expressed as a percentage. Bivariate correlation analysis was used to identify factors associated with the rate of decline in serum AMH levels 6 months after surgery. A two-sided *P* value of ≤0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp., USA) was used for statistical analyses.

Results

The study population included a total of 60 women, 30 with endometrioma and 30 women without endometrioma (controls).

The mean (SD) age was 29.0 (5.4) and 30.1 (4.4) years in endometrioma and control groups, respectively ($P = 0.39$).

Fifteen women (50%) in the endometrioma group had unilateral and 15 (50%) had bilateral cysts. Eighteen women (60%) had multiple endometriomas. The median (IQR) diameter of the larger endometriomas in patients was 42.5 mm (38.6–51.7 mm). Indication for surgery was subfertility in 9 and pelvic pain in 21 women. A total of 55 endometriomas were excised. Pathological examination confirmed the diagnosis in all cases. There were no major complications after surgery. Three women (10%) were found to have recurrent endometriomas 6 months after surgery.

Comparison of ovarian reserve between women with and without endometrioma

Compared with the controls, women with endometrioma had significantly lower AFC ($P < 0.01$) and serum AMH levels ($P = 0.02$). Results are presented in Table I.

Impact of endometrioma excision on ovarian reserve

One month after the surgery there was a tendency for serum AMH levels to decrease ($P = 0.18$) and for total AFC to increase ($P = 0.28$), but both changes did not reach statistical significance, as presented in Table II.

Four women were lost to follow-up at 6 months after surgery. Compared with preoperative values while serum AMH was significantly decreased ($P = 0.02$), the AFC remained unchanged in these 26 women (Table II).

Six months after the surgery AMH levels had declined in 16 women, were unchanged in 2 women and had increased in 6 women. Three of the four women who were lost to follow-up before 6 months had lower AMH levels than baseline at the first study visit 1 month after the surgery.

When the results were broken down according to laterality of endometriomas, serum AMH levels did not decline significantly after excision of unilateral endometriomas. On the other hand, serum AMH levels were significantly lower 1 and 6 months after excision of bilateral endometriomas (Table III). Six months after the surgery, serum AMH levels had decreased by 7 and 14.6% on average following excision of unilateral and bilateral endometriomas, respectively. However, the rate of decline was not significantly correlated with the laterality of endometriomas, i.e. unilateral or bilateral. The median (25th–75th percentiles) decline was 37.9% (+4.1% to −58.5%) and 44.2% (0–69.0%) for unilateral and bilateral excision, respectively ($P = 0.86$).

The rate of decline in serum AMH levels was not significantly correlated with patient age ($r = 0.01$, $P = 0.96$), baseline AFC ($r = 0.18$, $P = 0.38$), diameter of the largest endometrioma removed ($r = 0.15$, $P = 0.47$) or the number of follicles removed during surgery ($r = -0.23$, $P = 0.27$). However, the preoperative serum AMH level was positively correlated with the rate of decline in serum AMH after surgery ($r = 0.47$, $P = 0.02$).

Table I Ovarian reserve in women with or without endometrioma.

	Endometrioma (*n* = 30)	Control (*n* = 30)	*P* value
Age (in years)	29.0 (5.4)	30.1 (4.4)	0.39
Nulligravid (%)	15 (50)	10 (33.3)	0.19
AMH (in ng/ml)	2.81 (2.15)	4.20 (2.26)	0.02
Total AFC	9.73 (4.77)	14.7 (4.11)	<0.01

Values are the mean (SD). AMH, anti-Müllerian hormone; AFC, antral follicle count.

Table II Markers of ovarian reserve in women before and after endometrioma excision.

	Preoperative (*n* = 30)	1 month after surgery (*n* = 30)	6 months after surgery (*n* = 26)
AMH (in ng/ml)	2.81 (2.15)	$2.07 (1.47)^{0.18}$	$1.82(1.29)^{0.02}$
Total AFC	9.73 (4.77)	$11.0 (5.37)^{0.28}$	$10.4 (4.16)^{0.63}$

Values are mean (SD). Superscripts are *P* values compared with preoperative values.

Discussion

The results of the present study demonstrate (i) the presence of endometriomas is associated with decreased ovarian reserve and (ii) surgical excision of endometriomas leads to a further decrease. The surgery-related decrease seems to be progressive and is more evident at 6 months after surgery than 1 month after surgery. Other than the preoperative AMH level, none of the evaluated parameters were significantly correlated with the decline in serum AMH levels 6 months after surgery.

The absence of a control group comprising women with endometriomas who would have undergone serial assessment of ovarian reserve without surgery is one of the limitations of the present study. Such a control group would enable us to know whether endometriomas

Table III Markers of ovarian reserve in women before and after endometrioma excision, according to laterality.

	Preoperative (n = 15)	1 month after surgery (n = 15)	6 months after surgery (n = 14)
Unilateral only			
AMH (in ng/ml)	2.04 (1.38)	2.03 (1.18)$^{0.50}$	1.76 (1.18)$^{0.40}$
Total AFC	11.73 (4.56)	12.0 (4.16)$^{0.91}$	10.57 (2.56)$^{0.31}$
	Preoperative (n = 15)	**1 month after surgery (n = 15)**	**6 months after surgery (n = 12)**
Bilateral only			
AMH (in ng/ml)	3.58 (2.53)	2.11 (1.76)$^{0.05}$	1.88 (1.45)$^{0.02}$
Total AFC	7.73 (4.22)	10.0 (6.35)$^{0.10}$	10.2 (5.67)$^{0.09}$

Values are the mean (SD). Superscripts are P values compared with preoperative values.

cause a progressive decrease in the AMH level and, if so, how would the endometrioma-related decrease in AMH compare with the decrease observed after surgical excision.

OCP use by some women between the first and the second postoperative assessments may have caused a decrease in the AFC but is unlikely to have affected serum AMH level significantly. AMH is secreted from pre-antral and early antral follicles, which are not dependent on FSH stimulation. Deb *et al*. (2012) prospectively compared serum AMH levels between women who had been on an OCP containing 30 μg ethinyl estradiol (Microgynon 30, Schering, Germany) for more than 1 year (average period on OCP was 3.6 years) with women who had not used any hormonal contraceptive and found that AMH levels were similar between users and non-users of OCP. However, it also should be noted that some studies suggest serum AMH levels can be decreased by OCP use (van den Berg *et al*., 2010; Kristensen *et al*., 2012).

Previous studies have evaluated indirectly the effect of endometriomas on ovarian reserve by comparing the number of oocytes collected from endometrioma-containing ovaries with contralateral ovaries following ovarian stimulation in IVF cycles (Somigliana *et al*., 2006; Almog *et al*., 2011; Esinler *et al*., 2012). While Esinler *et al*. (2012) and Almog *et al*. (2011) reported similar numbers of oocytes being collected from ovaries containing endometriomas and ovaries without endometriomas, Somigliana *et al*. (2006) reported that the number of co-dominant follicles was significantly decreased in ovaries containing an endometrioma. The number of oocytes collected was not reported by Somigliana *et al*. (2006). To the best of our knowledge the present study is the first to compare serum AMH levels between women with endometrioma(s) and similarly aged women who do not have ovarian cysts, and to clearly document an endometrioma-related loss of ovarian reserve.

Our finding of a surgery-related decline in serum AMH levels is consistent with the results of two recent meta-analyses (Raffi *et al*., 2012a,b; Somigliana *et al*., 2012). An important gap in knowledge, as pointed out in both meta-analyses, is whether the surgery-related loss is progressive in nature and whether it is sustained several months after surgery. Although there are several studies evaluating the effect of endometrioma excision on serum AMH levels, there are only three studies investigating the change in serum AMH levels ≥6 months after endometrioma excision by the 'stripping' technique (Tsolakidis *et al*., 2010; Biacchiardi *et al*., 2011; Celik *et al*., 2012). These studies included a total of 91 women and reported significantly lower AMH levels when compared with preoperative values. Our study substantially contributes to the available data and reaffirms that recovery of serum AMH levels over time, as suggested by Chang *et al*. (2010), is unlikely. Moreover, our observations suggest a progressive decline in serum AMH levels. This is in agreement with the Celik *et al*.'s (2012) observation of a progressive decline in serum AMH levels following endometrioma excision. The other three studies in which serum AMH levels were examined following endometrioma excision did not report a progressive decline (Chang *et al*., 2010; Biacchiardi *et al*., 2011; Lee *et al*., 2011). It should be noted that the period between serial measurements differed between these studies, and a shorter period between two consecutive measurements may have prevented demonstration of a progressive decline in serum AMH levels.

Another important gap in knowledge is the identification of factors affecting the extent of ovarian damage following endometrioma excision (Somigliana *et al*., 2012). Although it is logical to assume that the extent of collateral damage to the ovarian tissue surrounding endometriomas, as measured by the number of ovarian follicles on surgical specimens, would be correlated with the decline in serum AMH levels, neither our study nor two previous studies were able to demonstrate such a correlation (Hirokawa *et al*., 2011; Celik *et al*., 2012). Similarly female age and cyst diameter were not related to the extent of AMH decline in any of the three studies, including the present study. While Hirokawa *et al*. (2011) reported that bilateral endometrioma excision caused a greater decline in serum AMH levels than the excision of a unilateral endometrioma, Celik *et al*. (2012) found that bilaterality was not an independent factor associated with the loss of ovarian reserve. Our results are in agreement with Celik *et al*. (2012), and although the relative decline in serum AMH levels was more prominent after bilateral endometrioma excision than unilateral excision in our study the difference between the two was not statistically significant. It is possible that this was a beta error due to the relatively small sample size in each group, i.e. unilateral versus bilateral, and bilateral excision can be more harmful. The preoperative serum AMH level was the only factor independently correlated with the extent of decline in serum AMH levels both in the present study and in the study by Celik *et al*. (2012). However, it should be noted that even if a woman with a high ovarian reserve (i.e. high AMH level) loses a higher proportion of this reserve, she may still have a higher residual reserve than a women who already had low AMH levels preoperatively.

It seems practically impossible to predict which women will have a severe decline in ovarian reserve following endometrioma excision.

Probably the extent of damage to the ovarian circulation is the most important determinant of the loss of ovarian reserve. However, neither preoperative nor perioperative features are helpful in predicting the impact of surgery on post-operative ovarian circulation.

It should be noted that 5 of the 30 women in the endometrioma group were found to have a preoperative serum AMH level <1 ng/ml, suggesting a severely decreased ovarian reserve. Neither preoperative serum FSH and estradiol levels nor AFC were useful in identifying these women. None of these five women experienced premature ovarian failure (POF) during the follow-up period of this study. While four of them had AMH levels <1 ng/ml 6 months after surgery, in one women AMH levels had increased to 1.94 ng/ml from a baseline value of 0.93 ng/ml. Yet, women with already decreased ovarian reserve should be warned about possible POF following a surgical intervention, especially bilateral cyst excision (Busacca *et al*., 2006). Given our inability to foresee the extent of damage to the ovary inflicted by surgery we believe it is prudent to measure serum AMH levels before taking the decision for surgical removal.

In conclusion, our results combined with the available data suggest that both the presence of endometriomas and their removal negatively affect ovarian reserve. The detrimental impact on ovarian reserve is not temporary but sustained over 6–9 months. Current data suggest a progressive decline following surgery. Although the factors determining the extent of ovarian damage are not clear, it should be noted that excision of bilateral endometriomas might be associated with a greater loss of ovarian reserve. Given the high recurrence rates following endometrioma excision and the unequivocal detrimental effects of repeated surgeries on ovarian reserve, we believe that it is prudent to delay/avoid surgical excision to the greatest possible extent, at least until women have completed their families. However, it should also be acknowledged that additional studies are required to further investigate whether the endometrioma-related decline in ovarian reserve *per se* is progressive in nature and whether it exceeds the surgery-related decline.

Authors' roles

G.U. contributed to conception and design of the study, surgical intervention, review of the manuscript and approval of the final version. I.K. contributed to sample collection, data collection, review of the manuscript and approval of the final version. K.O. contributed to surgical intervention, review of the manuscript and approval of the final version. A.S. contributed to critical review of the manuscript for intellectual content and approval of the final version. A.O.Y. contributed to laboratory analyses and approval of the final version. B.A. contributed to data analysis and interpretation, drafting the manuscript and approval of the final version.

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Conflict of interest

None of the authors have any conflict of interest associated with this study.

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