ORIGINAL ARTICLE: ENDOMETRIOSIS

Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study

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Objective: To evaluate whether endometrioma is associated with a progressive decline in ovarian reserve, and to compare the rate of decline with natural decline in ovarian reserve.
Design: Prospective, observational study.
Setting: Tertiary university hospital, endometriosis clinic.
Patient(s): Forty women with endometrioma and 40 age-matched healthy controls.
Intervention(s): Women with endometriomas who did not need hormonal/surgical treatment at the time of recruitment and were expectantly managed. Controls were age-matched, healthy women. All participants underwent serum antimüllerian hormone (AMH) testing twice, 6 months apart. Sexually active patients with endometrioma also underwent antral follicle count.
Main Outcome Measure(s): Change in serum AMH levels.
Result(s): Median (25th–75th percentile) serum AMH level at recruitment was 2.83 (0.70–4.96) ng/mL in the endometrioma group and 4.42 (2.26–5.57) ng/mL in the control group. The median percent decline in serum AMH level was 26.4% (11.36%–55.41%) in the endometrioma group and 7.4% (−11.98%, 29.33%) in the control groups. Twenty-two women with endometrioma who had antral follicle count (AFC) had median AFC of 10 (8–12) at recruitment and 8 (6.3–10) at 6 months.
Conclusion(s): Women with endometrioma experience a progressive decline in serum AMH levels, which is faster than that in healthy women.
Clinical Trial Registration Number: NCT02438735. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Antimüllerian hormone, endometrioma, endometriosis, ovarian reserve

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Endometriosis is a chronic disorder that affects approximately 1.5% of reproductive-age women (1–3). Despite an association between endometriosis and subfertility, the causal link remains elusive except for bilateral tubal blockage. Immunologic perturbations and poor oocyte and/or embryo quality could contribute to subfertility (4, 5). Approximately 40% of subfertile women with endometriosis are diagnosed with ovarian endometriomas (4, 6).

A possible impact of endometrioma on ovarian reserve is concerning. The majority of the prior studies focused on a possible effect of surgical removal of endometriomas on ovarian reserve (7–9). The totality of available evidence suggests a permanent decline in ovarian reserve after endometrioma excision. Studies comparing assisted reproduction technology outcomes between women who had endometriomas and women who underwent endometrioma excision reported similar pregnancy and live birth rates (10). Thus, surgical excision is not routinely recommended before assisted reproduction technology (11, 12).

In a cross-sectional study, we formerly reported that women with endometrioma had lower ovarian reserve as demonstrated by lower antral follicle count (AFC) and serum antimüllerian hormone (AMH) levels than healthy women (9). However, whether this decline in ovarian reserve is progressive is unknown. Moreover, how a possible progressive decline in ovarian reserve would compare with the natural decline in healthy women without endometrioma is also unknown.

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The present study aimed to evaluate whether endometrioma-associated decline in ovarian reserve is progressive in the absence of an intervention and is greater in magnitude than the natural decline over time.

MATERIALS AND METHODS

This prospective observational study was approved by the research ethics committee of the Uludag University School of Medicine (2015-7/12). The protocol was registered at clinicaltrials.gov (NCT02438735).

The participants were recruited from the endometriosis clinic of Uludag University Hospital between May 2015 and January 2017, and they all provided written informed consent for participation.

Women between 18 and 40 years of age who had at least one endometrioma >3 cm were offered participation, if they did not need hormonal or surgical treatment at the time of diagnosis (i.e., there was no suspicion of an ovarian malignancy or organ involvement, such as hydroureteronephrosis or bowel obstruction requiring surgical exploration) and if pain symptoms were absent or minimal, which could be controlled with occasional or intermittent nonsteroidal anti-inflammatory medication. An endometrioma was defined by the visualization of an ovarian cyst with regular margins and ground-glass echogenicity on transvaginal/transabdominal ultrasound examination or by magnetic resonance imaging of the pelvis (13, 14). The presence of the cysts was confirmed on at least two separate examinations done at least 1 month apart.

Exclusion criteria were irregular menstrual periods, endocrine disorders, polycystic ovarian syndrome, taking drugs that could have affected markers of ovarian reserve (e.g., GnRH analogues, oral contraceptives) during the 6 months before recruitment, history of ovarian surgery ever, and presence of any sonographic, clinical, or biochemical findings suggesting malignancy.

The control group comprised women of reproductive age who did not have any ovarian cysts. To exclude other pathology that could affect ovarian reserve, control subjects were not recruited from patients presenting to the gynecology clinic but were recruited from age-matched female residents and nurses working in the same hospital. Presence of ovarian cysts was ruled out by either a transvaginal or a transabdominal ultrasound (with a full bladder to ensure ovarian visualization) in control volunteers.

Assessment of Ovarian Reserve

Serum AMH levels were measured twice, at recruitment and on the 6th month of follow-up. Venous blood samples were collected during the early follicular phase of a spontaneous cycle (i.e., between cycle days 3 and 5). The Beckman Coulter Automated Access AMH assay was used according to the manufacturer's instructions in the reference laboratory of Uludag University. The Access AMH assay has a limit of detection of ≤0.02 ng/mL (0.14 pmol/L) and a limit of quantitation of ≤0.08 ng/mL (0.57 pmol/L). The Access AMH assay showed good performance across the measuring range for both intra-assay (coefficient of variation 4.87%) and interassay (coefficient of variation 5.09 %) precision during the study period.

Statistical Considerations

Seifer et al. (15) reported the rate of decline in mean serum AMH levels to be 0.2 ng/mL/y among reproductive-aged women younger than 35 years and 0.1 ng/mL/y thereafter. On the basis of our previous observation in women without endometriomas with a mean age of 30 years, average serum AMH levels could be expected be approximately 4.0 ng/mL in our population (9). An anticipated 0.2-ng/mL/y decline corresponds to a decline of approximately 2.5% over 6 months. According to our same study, women undergoing endometrioma excision had a decline of 35% 6 months after surgery. Attributing some of this decline to ovarian damage during surgery, we assumed women with endometrioma could have a decline of as low as 10% during the same period. According to a sample size calculation with SD ranging between 0.01 and 0.1, β error between 10% and 20% (i.e., power 90%–80%), and α error rate of 0.05, the required sample size ranged between 2 and 76. We decided to recruit 80 women: 40 with and 40 without endometriomas.

Continuous data were defined with mean and SD or median and interquartile range, depending on the distribution characteristics. Continuous variables were compared between groups by the independent samples *t* test or Mann-Whitney *U* test, as appropriate. Subgroup analyses based on laterality (i.e. unilateral or bilateral) were done. The rate of decline in the serum AMH level was calculated as (initial serum AMH level − serum AMH levels at 6 months control/initial serum AMH level) and expressed as a percentage. Bivariate correlation analyses were used to identify factors associated with the rate of decline in serum AMH levels 6 months after follow-up. A multivariate logistic regression analysis was done to isolate independent effects of age, baseline AMH level, cyst size, or laterality on the change in AMH levels. A related samples Wilcoxon signed rank test was used to compare AFC at recruitment and at 6 months in the untreated endometrioma group. A two-sided *P* value of ≤.05 was considered statistically significant. Statistical Package for Social Sciences version 20 (IBM) was used for statistical analyses.

RESULTS

The study population included a total of 80 women, 40 in the endometrioma and 40 in the control groups. The mean (SD) age was 32.7 (4.2) and 32.1 (4.2) years in endometrioma and control groups (*P*=.49), respectively. Thirty-one women (77.5%) had unilateral and nine (22.5%) had bilateral endometriomas. The mean diameter of the cysts was 4.6 (1.7) cm (Table 1).

Median (25th–75th percentile) serum AMH level at recruitment was 2.83 (0.70–4.96) ng/mL in the endometrioma group and 4.42 (2.26–5.57) ng/mL in the control group (*P*=.04). Median serum AMH level 6 months after recruitment was 1.86 (0.57–3.77) ng/mL in the endometrioma group and 3.2 (2.45–5.59) ng/mL in the control group (*P*=.002). The median percent decline in serum AMH level was 26.4% (11.36%–55.41%) in the endometrioma group and 7.4% (−11.98%,

TABLE 1

Comparison of women with in situ endometriomas and women without endometriomas.

Parameter	Endometrioma (n = 40)	Control (n = 40)	*P* value
Age (y), mean (SD)	32.7 (4.2)	32.1 (4.2)	.49
Cyst diameter (cm), mean (SD)	4.6 (1.7)	NA	
Serum AMH at recruitment (ng/mL)	2.83 (0.7–4.96)	4.42 (2.26–5.57)	.04
Serum AMH at 6 mo after recruitment (ng/mL)	1.86 (0.57–3.77)	3.2 (2.45–5.59)	.002
Decline in serum AMH (%)	26.4 (11.36–55.41)	7.4 (−11.98, 29.33)	.01
Decline in AMH (%)			
Bilateral endometriomas (n = 9)	34.62 (15.81–49.58)	7.4 (−11.98, 29.33)	.015
Unilateral endometriomas (n = 31)	22.35 (3.92–68.75)	7.4 (−11.98, 29.33)	.005

Note: Values are median (interquartile range) unless otherwise noted. AMH = antimüllerian hormone; SD = standard deviation.

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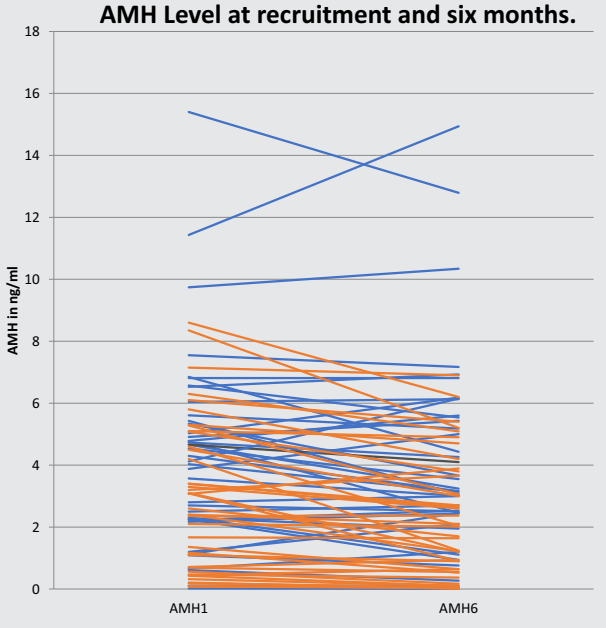
29.33%) in the control group (*P*=.01) (Table 1). When expressed as mean (SD), percent decline in AMH levels was 30.6% (32%) vs. 3.0% (38%) in the endometrioma and control groups, respectively (Table 1). Serum AMH levels at baseline and 6 months for all participants are presented in Figure 1 and Supplemental Table 1.

Subgroup analyses based on laterality showed similar results. Women with unilateral endometriomas (*P*=.005) and bilateral endometriomas (*P*=.015) had a significantly higher decline in serum AMH levels than healthy women (Table 1). The rate of decline in serum AMH level was 22.35% (3.92%–68.75%) and 34.62% (15.81%–49.58%) in women with unilateral and bilateral endometriomas, respectively.

FIGURE 1



Serum AMH levels at recruitment and 6 months later. Each line represents one participant. *Blue*, control; *red*, endometrioma.

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Overall, rate of decline in serum AMH level was not correlated with age ($r = 0.22$, *P*=.05), cyst diameter ($r = 0.081$, *P*=.60), or initial serum AMH level ($r = -0.20$, *P*=.08).

Multivariate regression analysis did not suggest a significant independent effect of age, baseline AMH level, cyst diameter, or laterality on the change in AMH level. The β values (95% confidence intervals) and *P* values were as follows; age, 0.19 (−1.6, 4.4), *P*=.35; AMH baseline, −0.9 (−6.6, 4.1), *P*=.64; diameter, 0.61 (−5.3, 6.8), *P*=.79; laterality, −0.02 (−35.7, 32.9) *P*=.93.

Regarding change in AFC in women with in situ endometriomas, 22 patients with endometrioma underwent AFC. Median (25th–75th percentile) AFC was 10 (8–12) at recruitment and 8 (6.3–10) at 6 months (*P*=.01).

DISCUSSION

Our results corroborate that the existence of endometrioma(s) is associated with a decrease in ovarian reserve compared with women without endometriomas (9). Moreover, we demonstrated for the first time that endometrioma(s) are associated with a faster decline in serum AMH levels than in healthy controls.

A strength of the present work is the prospective comparison of the rate of AMH decline between women with endometriomas and age-matched healthy controls, after excluding women with other factors that could have affected ovarian reserve or its markers.

Endometriomas can affect ovarian reserve in two ways: [1] the compression of surrounding ovarian cortex by the cyst could hamper circulation and cause follicle loss; and [2] the inflammatory reaction in the endometriotic foci could cause follicular damage (5).

Indirect evidence supports both theories. The use of bipolar cauterization to achieve hemostasis after endometrioma excision seems to harm ovarian reserve more than the use of sutures or hemostatic sealants (16). Cauterization not only causes thermal damage but is also expected to impair vascularization of the ovarian tissue surrounding the cyst bed. Although the immediate decline in ovarian reserve after endometrioma excision (i.e. declining AMH levels as soon as 1 month after surgery) can be attributed to thermal damage,

progressive decline observed later (i.e., between 1 and 6 months after surgery) could be attributed to impaired vascularization (9,16–20). However, it should be noted that some other studies do not lend credit to a progressive decline in ovarian reserve after endometrioma excision (21–23). Yet it is logical to expect that impaired circulation would affect ovarian cortex as it would affect any tissue.

With regard to the inflammatory reaction, a high concentration of iron in the cyst mediates the production of reactive oxygen species (24). Reactive oxygen species along with transforming growth factor-β is a potent inducer of tissue fibrosis, which would cause follicle loss. Thus, it is reasonable to assume that the ongoing production of reactive oxygen species by the endometrioma could cause a progressive decline in ovarian reserve, which could be expected to occur at a higher rate than in healthy ovaries, as suggested by the present study.

Assessment of ovarian reserve with only serum AMH levels, and omitting other markers (e.g., serum FSH level) and AFC could be regarded as a limitation. However, serum FSH level has relatively higher intercyle variation than serum AMH and is not regarded to be as reliable a marker of ovarian reserve as AMH (25, 26). Our decision not to collect AFC data was a convenience choice made after the decision to include healthy controls. This was due to the perceived reluctance of hospital staff to undergo a vaginal ultrasound for personal/cultural reasons during a prior study at the same clinic (9). Likewise, sexually inactive patients with endometrioma were reluctant for transvaginal or transrectal ultrasound examination. Arguably, AFC could be counted with the transabdominal approach; however, because the value of AFC, even as assessed by transvaginal ultrasound, is limited as a marker of ovarian reserve in the presence of endometriomas (27–29), we deemed it would be even less reliable with transabdominal ultrasound in this study population. All in all, despite its own limitations, we regard serum AMH levels as the optimal marker of ovarian reserve in the presence of endometriomas, or other cysts possibly obscuring visibility of antral follicles.

What would be the implications of our observations? From a research perspective, we absolutely need other longitudinal studies, preferentially including other markers of ovarian reserve in addition to AMH to confirm or refute our observations. From a clinical perspective, there is evidence showing women with endometrioma already have decreased ovarian reserve compared with their healthy, age-matched counterparts (9), and our findings suggest more rapid decline of already decreased serum AMH levels in the presence of endometrioma. Therefore, women with endometriomas could be counseled about possible loss of reproductive potential and urged to consider their childbearing plans. Indeed, in two large-cohort studies, women with a history of endometriosis or endometriosis-related infertility are reported to experience menopause earlier than women without endometriosis (30, 31). Women who do not plan pregnancy in the near future could be informed about fertility preservation options, including oocyte and embryo freezing. However, this remains a subjective choice, and women could be informed but absolutely must not be terrorized, leading to unnecessary stress and interventions. Even though AMH is a predictor for ovarian response in assisted reproduction cycles, it has limited value (32). Moreover, the association between markers of ovarian reserve and chances of spontaneous conception is even weaker, and women with even very low ovarian reserve can conceive spontaneously (33).

In conclusion, the present study shows that women with endometrioma experience a progressive decline in serum AMH levels, which is faster than that in healthy women. Future studies prospectively comparing serial changes in markers of ovarian reserve between women with endometriomas and healthy controls, as well as women with in situ endometriomas and those undergoing surgical excision, are needed to direct clinical practice.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.fertnstert.2018.03.015.

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