ORIGINAL ARTICLE: ENDOMETRIOSIS

Serum antimüllerian hormone concentration increases with ovarian endometrioma size

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Objective: To examine whether serum antimüllerian hormone (AMH) levels correlate with the size of ovarian endometrioma (OMA).
Design: An observational cross-sectional study.
Setting: A university hospital.
Patient(s): Two hundred and sixty-seven nonpregnant women, aged 18–42 years, with no prior history of surgery for endometriosis and a histologically documented ovarian cyst.
Intervention(s): Surgical management for a benign ovarian cyst.
Main Outcome Measure(s): Correlation between serum AMH concentration and cyst size according to OMA and non-OMA benign cyst.
Result(s): Women with OMA were compared with a control group of women who had non-OMA benign ovarian cysts. The AMH assay samples were collected less than a month before the surgery. Between January 2004 and September 2016, 148 women were allocated to the OMA group and 119 to the non-OMA benign cyst group. The AMH concentrations were not statistically significantly different between the two groups (3.7 ± 2.8 ng/mL vs. 4.1 ± 3.3 ng/mL). A multiple linear regression model accounting for potential confounders revealed that the log10 of the serum AMH concentration positively correlated with the log10 of the OMA cyst volume ($R^2 = 0.23$; coefficient = 0.05; 95% CI, 0.007–0.10).
Conclusion(s): In women no prior history of surgery for endometriosis, serum AMH levels increased with cyst size in cases of OMA. (Fertil Steril® 2019;■:■–■. ©2019 by American Society for Reproductive Medicine.)
Key Words: Benign ovarian cyst, endometrioma, serum AMH level, surgery

Antimüllerian hormone (AMH) is used in daily practice as a biochemical marker of the ovarian reserve (1, 2) whereas the actual ovarian function can be clinically characterized by the occurrence of a regular menstrual cycle (3). In assisted reproductive technologies (ART), AMH is a predictive tool of the ovarian response to gonadotropin stimulation in infertile women (4, 5), although it does not reflect the likelihood of pregnancy (6, 7). Antimüllerian hormone is produced by nongrowing follicles, including primary, secondary, preantral, and early antral follicles (8–10). Serum AMH levels correlate inversely with age (11, 12) but remain relatively constant throughout the menstrual cycle (13), and they can be measured at any time (14).

The impact of a benign ovarian cyst on the serum AMH level has remained unclear. Women with bilateral ovarian cysts have been reported to have lower serum AMH levels, irrespective of the nature of the cyst (15, 16). It has been reported that presurgical serum AMH

Received July 24, 2018; revised and accepted January 9, 2019.
L.M. has nothing to disclose. P.S. has nothing to disclose. M.B. has nothing to disclose. C.Co. has nothing to disclose. C.M. has nothing to disclose. P.A.J. has nothing to disclose. I.S. has nothing to disclose. B.B. has nothing to disclose. and C.Ch. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2019 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2019.01.013

levels do not differ between cases of endometrioma (OMA) and nonendometriotic ovarian benign cysts (16–18). Women with a prior history of OMA surgery have been shown to have drastically lower serum AMH levels, independent of the presence of a current OMA (17, 19–21). It is not known whether AMH concentrations vary according to the size of benign ovarian cysts. This study compared the serum AMH levels of women with OMA with the levels found in women with a non-OMA benign ovarian cyst in a population of patients without any prior history of surgery for endometriosis, and examined whether AMH levels correlate with the size of the cyst.

MATERIALS AND METHODS

Patients

We undertook a large, observational, cross-sectional study that involved women referred to our gynecologic surgery department between January 2004 and September 2016 for a benign gynecologic condition and prospectively enrolled in our local database. Women with ongoing cancer, pregnancy, infectious disease, or who refused to provide their consent for participation in this study were not enrolled in the database. The local ethics committee (approval number 05-2006 provided by the "Comite Protection des Personnes of Paris-Cochin") approved the study protocol. Nonpregnant women between 18 and 42 years of age without a prior history of surgery for endometriosis and surgically managed for a benign ovarian cyst and for whom the preoperative serum AMH level was available were retained for the analysis. Women with OMA were compared with a control group of women with non-OMA benign ovarian cysts.

Measurements

All of the women had undergone preoperative imaging (i.e., ultrasound and/or magnetic resonance imaging) that resulted in a recognizable ovarian cyst according to the usual criteria, including size, appearance, cyst content, unilocular or multilocular, vascularization, and the presence of vegetation (22–26). For each patient, the cyst laterality (i.e., left, right, or bilateral) and size (in centimeters) were recorded. The cyst size was based on the largest diameter as determined by ultrasound-based imaging. In case of bilateral cysts, the sum of the largest diameters and the sum of the volumes of each cyst were considered for analysis when appropriate (27).

For all the participants in the study, the AMH concentration was determined using plasma collected in the month before the surgery. The blood samples (5–10 mL) were centrifuged at 800 × *g* for 12 minutes at 37°C, and serum supernatants were collected. Aliquots of these samples were stored at −80°C until needed for analysis in cases of lack of routine measurement of the AMH concentration. Indeed, between 2004 and 2008, measurement of the serum AMH concentration was not performed routinely. Thus, in 60 cases, frozen samples of plasma that had been collected in the month before the surgery were used to secondarily measure the AMH concentration using the same assay procedure that has been used routinely since 2008.

All the measurements of serum AMH concentrations were performed using a commercially available enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (Diagnostic Systems Laboratories), as published elsewhere (17). The limit of detection of the kit is 0.006 ng/mL and the intra-assay coefficient of variation between 4.8% and 8.0%, as described in the directions for use (14). All the AMH measurements were performed by the same laboratory. Serum AMH concentrations between 2.0 to 6.8 ng/mL are considered to be normal by the laboratory.

Surgery

Indications for surgery (possibly more than one per patient), as reported previously (28), were the following: [1] chronic pelvic pain, defined as the presence of dysmenorrhea and/or intermenstrual pelvic pain and/or dyspareunia of moderate to severe intensity for at least 6 months (29); [2] infertility defined as at least 12 months of unprotected intercourse that failed to result in pregnancy (30); [3] a pelvic mass (an adnexal benign cyst). The diagnosis of endometriosis was based on surgical exploration and histologic confirmation.

During the surgical procedure, the extent of the endometriosis (the stage and mean scores: total, adhesions, implants) was assessed according to the American Society for Reproductive Medicine (ASRM) classification (31). Deep infiltrative endometriosis could be established upon radical surgery (e.g., a bowel resection, partial cystectomy, or ureteral resection) when the muscularis (located in the bladder, intestine, or intrinsic ureter) was found to be infiltrated by endometriotic tissue (32, 33). For the other locations (i.e., uterosacral ligaments, the extrinsic ureter, or the vagina), deep infiltrative endometriosis (DIE) was defined as endometriotic tissue infiltrating more than 5 mm beneath the peritoneum surface, as defined elsewhere (34, 35).

Data pertaining to the patient's medical history were obtained by the surgeon before the surgery using a previously published structured questionnaire during a preoperative face-to-face interview (36). The following data were collected: age (years); body mass index (BMI, calculated as weight [kg] divided by the square of height [m^2]); age at menarche; ethnicity; smoking; prior uterine surgery; gravidity; parity (n [%]); menstrual cycle regularity (n [%], always, often, or never regular); oral contraceptive treatment use (never, current user, or previous user); infertility (primary or secondary) and length of the infertility; pelvic painful symptoms (mean visual analog scores), including dysmenorrhea, deep dyspareunia, or noncyclic chronic pelvic pain; duration of pelvic painful symptoms; gastrointestinal symptoms; lower urinary tract symptoms; bilateral ovarian cyst; mean ovarian cyst size; and ovarian cyst ≥ 5 cm (36).

All the resected cysts were referred to a pathologist for histologic examination. The diagnosis of OMA was histologically confirmed in all cases by features compatible with endometriosis. The benign nature of the cysts was histologically confirmed in all cases.

Statistical Analysis

All the statistical data were compiled in a computerized database. Continuous data are presented as mean and standard deviation. Student's *t*-tests were performed when appropriate. Student's *t*-test or the Mann-Whitney *U* test was used for quantitative variables, and Pearson's chi square or Fisher's exact test for qualitative variables, as appropriate. When more than two groups were compared, we used the Kruskal-Wallis test. When group medians were statistically significantly different by the Kruskal-Wallis test ($P<.05$), pairwise comparisons were performed with Dunn's multiple comparison test.

Correlation coefficients were calculated using linear correlations. The log of the serum AMH concentration and the log of cyst volume (using the formula $S = 4/3\pi R^3$) were calculated. A Pearson's correlation was run to assess the relationship between the log of the serum AMH concentration and the log of the cyst volume. In case of bilateral cysts, the sum of the volume of each cyst was considered. In addition, the association between serum AMH levels and clinical or anatomical parameters of endometriosis severity was investigated by linear regression. To identify independent determinants of serum AMH levels, univariable associations were evaluated first; after which, the variables below a *P* value threshold (i.e., $P<.05$) were included in a multivariate model.

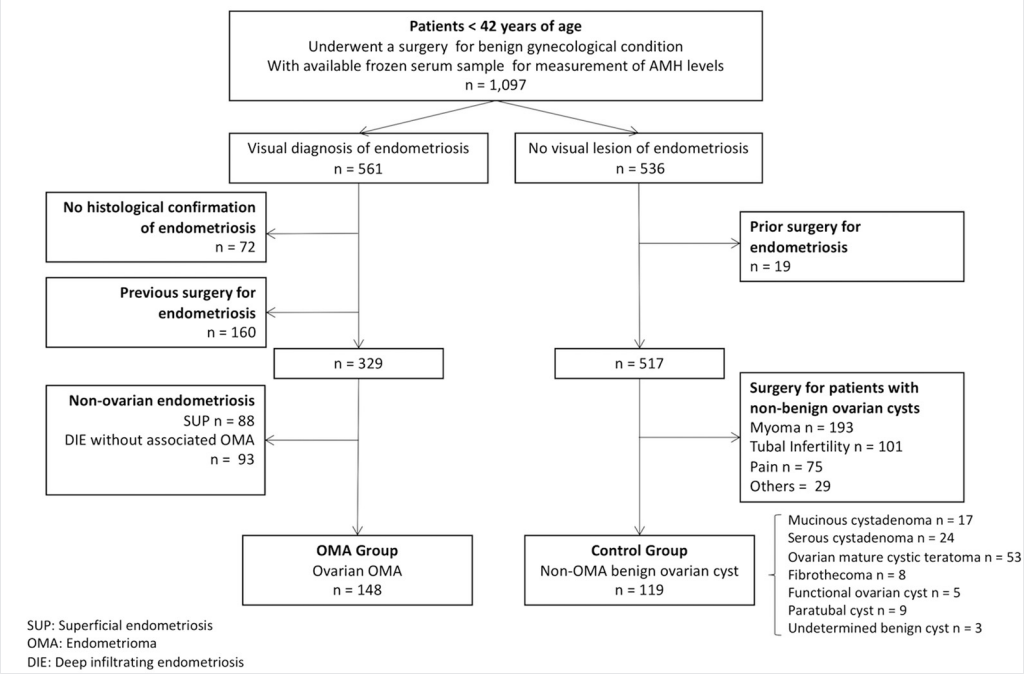
Before regression analysis, we performed a logarithmic (log10) transformation of the AMH concentration and the cyst volume to achieve linearity. We also considered the log10 of the cyst volume because the diameters ranged from 0.5 cm to 21 cm and the combined volumes ranged from 0.06 cm^3 to 6,282 cm^3. The model evaluates all of the included variables to identify those most strongly and concurrently related as a final output: age, BMI, oral contraceptive (OC) use, infertility, and bilateral cysts. To determine the factors that contribute to increased serum AMH levels, a backward multiple linear regression was performed with serum AMH levels serving as the dependent variable. The statistical analyses were performed using STATA and GraphPad software for Macintosh (Stata/IC 11.0 for Mac, StataCorp; GraphPad).

RESULTS

The cohort selection process is outlined in the flowchart shown in Figure 1. Among the women for whom serum AMH concentration measurements were available, 148 women with ovarian endometrioma were retained in the OMA group, and 119 women with non-OMA benign ovarian cysts were retained in the control group (see Fig. 1).

The mean age of the patients was statistically significantly higher in the OMA group compared with the control group: 31.7 ± 4.8 years versus 29.2 ± 6.6 years, respectively ($P<.01$). The BMI was statistically significantly lower in the OMA group compared with the control group: 21.7 ± 3.7 kg/m^2 versus 22.7 ± 3.9 kg/m^2, respectively ($P=.03$). The current use of OCs was statistically significantly higher in the OMA group compared with the control group: 63.5% (n = 94) versus 37.5% (n = 44), respectively ($P<.01$). The proportion of infertile women was statistically significantly higher in the OMA group compared with the control group:

FIGURE 1



Flowchart of the selection process. Schematic outline of the cohort selection process.

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27.7% (n = 41) versus 7.6% (n = 76), respectively ($P<.01$) (Table 1). The serum AMH concentrations did not differ between the OMA and the control groups: 3.8 ± 2.8 ng/mL versus 4.1 ± 3.3 ng/mL, respectively ($P=.51$). Moreover, the serum AMH concentration in the OMA group did not differ in case of unilateral OMA compared with bilateral OMA: 3.6 ± 2.6 ng/mL versus 4.3 ± 3.2 ng/mL, respectively ($P=.16$) or in cases of absence of DIE lesions compared with associated DIE lesions: 3.8 ± 2.8 ng/mL versus 3.8 ± 6.6 ng/mL, respectively ($P=.95$).

In the whole population, the serum AMH concentration was not different in current OC users (n = 138) compared with women who were noncurrent OC users (n = 129): 4.3 ± 2.8 ng/mL versus 4.2 ± 1.8 ng/mL, respectively ($P=.85$). In both the OMA and control group, the AMH serum concentration was not different in current OC users compared with noncurrent OC users; for the OMA group, 4.0 ± 2.9 ng/mL versus 3.3 ± 2.5 ng/mL, respectively ($P=.14$); and for the control group, 4.3 ± 3.3 ng/mL versus 3.8 ± 3.3 ng/mL, respectively ($P=.38$).

In the whole population, the mean cyst size was not different in the current OC users (n = 138) compared with the non-OC users (n = 129): 4.1 ± 2.6 mm versus 4.6 ± 2.5 mm, respectively ($P=.10$). In both the OMA and control groups, the cyst size was not different in the current OC users compared with the noncurrent OC users: for the OMA group, 4.0 ± 2.9 versus 3.4 ± 2.4, respectively ($P=.18$); and for the control group, 4.3 ± 3.3 mm versus 3.8 ± 3.3 mm, respectively ($P=.38$).

TABLE 1

Baseline characteristics of the patients with histologically documented ovarian cysts.

Characteristics	OMA group (n = 148)	Control group (n = 119)	*P* value
Age (y)[a]	31.7 ± 4.8	29.2 ± 6.6	< .01
BMI (kg/m^2)[a]	21.7 ± 3.7	22.7 ± 3.9	.03
Age at menarche (y)[a]	13.1 ± 1.5	12.7 ± 1.8	.10
Ethnic origin, n (%)			
Caucasian	137 (93.3)	101 (84.9)	
Asian	0	3 (2.5)	
African	7 (4.8)	10 (8.4)	
Other	2 (1.4)	5 (4.2)	.9
Smoking, n (%)			
Never	73 (49.3)	69 (58.5)	
Current user	23 (15.6)	15 (12.7)	
Previous user	52 (35.1)	34 (28.8)	.33
Prior uterine surgery, n (%)	7 (4.7)	4 (3.4)	.57
Gravidity, n (%)			
0	104 (70.3)	85 (71.4)	
1	28 (18.9)	17 (14.3)	
2 or more	16 (10.8)	17 (14.3)	.47
Parity, n (%)			
0	128 (86.5)	98 (82.4)	
1	10 (6.8)	11 (9.2)	
2 and more	10 (6.8)	10 (8.4)	.64
Regular menstrual cycle, n (%)			
Always regular	120 (81.1)	90 (76.3)	
Often regular	4 (2.7)	5 (4.3)	
Never regular	24 (16.2)	23 (19.5)	.59
OC treatment, n (%)			
Never	24 (16.2)	31 (26.3)	
Current user	94 (63.5)	44 (37.3)	
Previous user	30 (20.3)	43 (36.4)	< .01
Infertility, n (%)	41 (27.7)	9 (7.6)	< .01
Primary	32 (21.6)	7 (5.9)	
Secondary	9 (6.1)	2 (1.7)	< .01
Length of infertility (months)[a]	40.7 ± 37.8	28.3 ± 14.2	< .01
Pelvic painful symptoms, n (%)	105 (70.9)	53 (44.9)	< .01
Length of pelvic pain (months)[a]	30.8 ± 42.3	14.4 ± 23.8	.01
Painful symptoms (mean VAS scores)[a]			
Dysmenorrhea	6.3 ± 2.7	3.7 ± 3.2	< .001
Deep dyspareunia	3.2 ± 3.2	1.5 ± 2.7	< .001
Noncyclic chronic pelvic pain	2.5 ± 3.0	1.5 ± 2.6	< .001
Gastrointestinal symptoms[b]	2.7 ± 3.4	0.5 ± 1.6	< .001
Lower urinary tract symptoms[c]	0.2 ± 1.1	0	< .001
Bilateral ovarian cyst, n (%)	34 (23.0)	14 (11.8)	.01
Mean ovarian cyst size (cm)	4.3 ± 2.5 (1 to 21)	4.5 ± 2.7 (1 to 20)	.53
Ovarian cyst ≥5 cm, n (%)	51 (34.5)	48 (40.3)	.32

Note: BMI = body mass index; OC = oral contraceptives; OMA = ovarian endometrioma; VAS = visual analogue scale.
[a] Data are presented as mean ± standard deviation.
[b] Dyschezia, painful constipation, rectal bleeding.
[c] Suprapubic pain, frequency, hematuria, urinary tract infection.

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Figure 2 depicts the variation in the serum AMH levels according to cyst size in the OMA and the control groups (classified as ≤30 mm, >30 and ≤50 mm, >50 and ≤70 mm, and >70 mm). In the OMA group, the serum AMH levels differed according to the size category (P=.04), and a post hoc test revealed a statistically significant increase in the serum AMH level in the subgroup who had a cyst size >70 mm (n = 26) compared with the subgroup who had a cyst size <30 mm (n = 51): 5.0 ± 3.6 versus 3.3 ± 2.5, respectively (P=.02). In the control group, the serum AMH levels did not differ according to the size category (see Fig. 2).

Preoperatively, the correlation between the log10 of the serum AMH level and the log10 of the cyst volume was r = 0.161 in the OMA group and it was r = −0.17 in the control group. Finally, by a simple linear regression analysis, the log10 serum AMH level positively correlated with the log10 cyst volume in the OMA group (R^2 = 0.026; coefficient = 0.04; 95% CI, 0.001–0.09; P=.04) and negatively correlated with the cyst size in the control group without reaching statistical significance (R^2 = 0.03; coefficient = −0.05; 95% CI, −0.10 to 0.002; P=.06). The correlation remained statistically significant after multiple linear regression analysis controlling for potential confounders such as age, BMI, OC use, infertility, and the presence of bilateral cysts with a persistent positive linear relationship between the serum AMH level and the cyst size in the OMA group (adjusted R^2 = 0.23; coefficient = 0.05; 95% CI, 0.007–0.10; P=.02). In the control group the negative linear relationship between the serum AMH level and the cyst size did not reach statistical significance (adjusted R^2 = 0.08; coefficient = −0.04; 95% CI, −0.10 to 0.02; P=.21) (Supplemental Table 1 and Supplemental Fig. 1, available online).

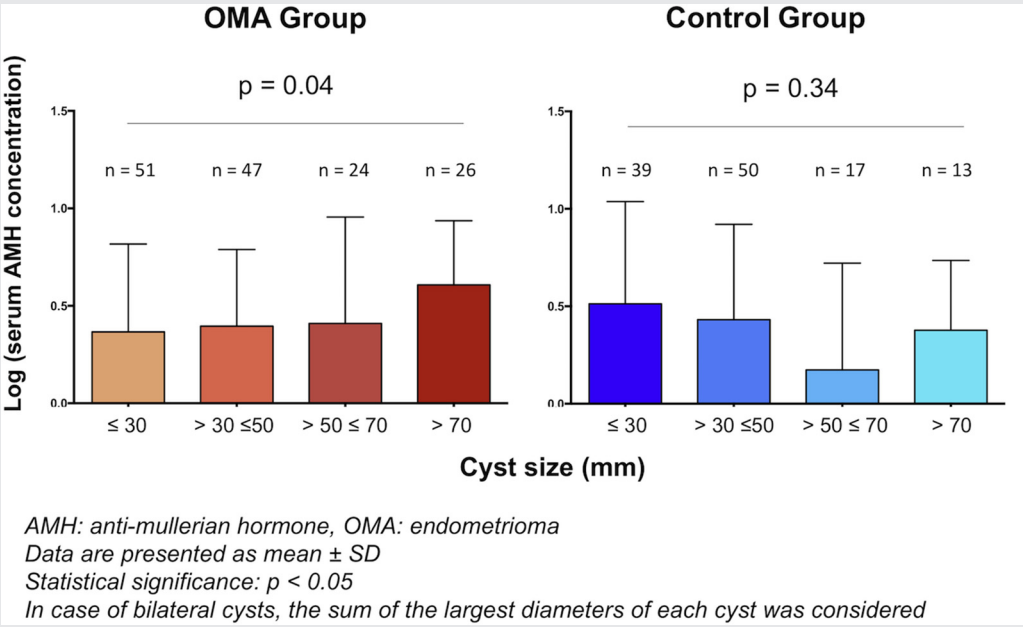
DISCUSSION

Based on a population of women without a prior history of endometriosis surgery, preoperative serum AMH levels were found to be the same for women with OMA and women with a non-OMA benign cyst. Serum AMH levels positively correlated with the cyst size in the OMA group. Furthermore, in the OMA group, serum AMH levels were not altered by the presence of bilateral OMAs or associated DIE.

The strength of our study stems from the following aspects: [1] the selection of women undergoing adnexal surgery who did not have a prior history of surgery for endometriosis, [2] the inclusion of women who had all undergone surgical exploration for benign adnexal cysts, [3] the distinction of women with endometriosis from the controls based on a surgical evaluation and strict histologic criteria, [4] the use of clinical data collected prospectively by a structured questionnaire, and [5] the serum AMH concentrations determined by the same laboratory for all the women (i.e., the OMA group and the control group).

Some limitations of the present study should be pointed out, however. Our study included women referred to our surgery department, so infertile women with OMA and diminished ovarian reserve may be underrepresented. Determination of AMH levels should be limited to women with

FIGURE 2



Variation of the serum AMH level and lesion size according to the nature of the benign ovarian cyst. The mean serum AMH level is shown according to the nature of the cyst. OMA group: size 0–30 mm (n = 51), 30–50 mm (n = 47), 50–70 mm (n = 24), and >70 mm (n = 26). Control group: size 0–30 mm (n = 39), 30–50 mm (n = 50), 50–70 mm (n = 17), and >70 mm (n = 13). In case of bilateral cysts, the sum of the largest diameters of each cyst was considered. The statistical analysis was performed using the Kruskal-Wallis test with Dunn's multiple comparison test. The data are presented as mean ± the standard error, and P<.05 was considered statistically significant.

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infertility or suspicion of a poor ovarian reserve. This could generate a possible inclusion bias that may be limited because AMH levels were routinely determined in all the women included in the cohort. These women are less likely to be referred for surgery as they can generally be managed directly with ART (37). There are, however, three main reasons why our correlation between OMA size and serum AMH levels may not be affected by this underrepresentation. First, we previously demonstrated that OMA per se does not diminish the ovarian reserve as reflected by the serum AMH level, but that alterations seen in women with endometriosis are a deleterious consequence of OMA surgery (17). Second, we deliberately excluded women with a prior history of surgery for endometriosis from the analysis to ensure population homogeneity in terms of serum AMH levels. Third, in the OMA group, we found the serum AMH level was higher in the infertile women compared with the fertile women: 4.8 ± 3.3 versus 3.4 ± 2.5, respectively (P=.007).

In our study, approximately 60% of the patients in the study group and 40% in the control group were current OC users. The serum AMH levels did not differ between the OMA and the control groups despite a higher rate of OC use in the OMA group. No difference was observed in the serum AMH levels in the OMA or the control group according to current use of OC. Our results may not be impacted by OC use. In light of the increasing evidence that OC use is associated with lower AMH levels (38, 39), this could boost a potential increased AMH level in case of OMA. The mean cyst size did not differ according to current OC use in the whole population or in the OMA group. However, in the control group, it was lower in cases of current OC use. Therefore, OC may not be a confounding factor for the study of the correlation in the OMA group.

There have been conflicting reports regarding the impact of OMA on ovarian function. Endometriotic ovarian cysts may negatively affect the rate of spontaneous ovulation (40). Surgical excision of OMA substantially damages the ovarian reserve, as reflected by a decrease in serum AMH levels after surgery, specifically in case of bilateral OMA excision and in cases of iterative surgeries (17). However, in case of ART, no alteration of oocyte developmental competence (41), no reduction of the quality (42), and no reduction of the number of oocytes retrieved from the OMA-affected ovary have been observed (43).

After we had excluded women with a prior history of surgery for endometriosis, we did not find that OMAs were associated with lower serum AMH levels compared with other benign cysts. Despite the higher age, the higher rate of infertile women, and the higher rate of OC use in the OMA group compared with the control group, there was no difference in serum AMH levels between the two groups, suggesting a probable lack of a negative impact of OMA per se on serum AMH levels. This is in line with the findings of Somigliana et al. (15), who previously reported that the nature of benign ovarian cysts did not affect serum AMH levels.

In our study, women were similarly excluded if they had previously had ovarian cysts removed. However, when all the cysts were considered, bilateral cysts were correlated with lower serum AMH levels compared with unilateral cysts (15). In a case-control study matched for age and BMI, Kim et al. (44) did not observe any difference in serum AMH levels between cases of OMA and mature cystic teratoma, and serum AMH levels did not differ when bilateral OMA were compared with unilateral OMA. Nevertheless, in this study, the women with stage IV endometriosis had significantly lower serum AMH levels. Uncu et al. (19) observed lower serum AMH levels in women with OMA compared with women without OMA (2.81 ± 2.15 vs. 4.20 ± 2.26). The investigators excluded women with prior ovarian surgery, irregular menstrual periods, polycystic ovary syndrome, or any endocrine disorder, and those who used any medication that could affect ovarian function (such as OC pills); however, the women without OMA who were used as controls were asymptomatic, and they were not surgically investigated (19). Using infertile women, Hwu et al. (45) compared the serum AMH levels of women with unoperated OMAs diagnosed by ultrasound-based imaging with those of women without OMA. The serum AMH levels were statistically significantly lower in the presence of OMA, and they were much lower in cases of bilateral OMAs compared with unilateral OMAs. However, all the women in that retrospective study were infertile, and no surgical or histologic confirmations of OMAs were available (45).

The results from our study indicate a statistically significant positive correlation between the size of the OMA and serum AMH levels. Other studies did not analyze serum AMH levels according to the size of the OMA (15, 19, 44, 45). Three hypotheses offer an explanation for this result.

First, selection bias may have resulted in underrepresentation of women with low AMH levels and overrepresentation of women with high AMH levels before surgery. The patients with low AMH levels are not surgically managed to avoid a detrimental impact of surgical removal of OMA on the ovarian reserve.

As the size of the OMA increases, there may be increased secretion of AMH into the circulation by the ovaries. This enhanced secretion could be the result of local blood clearance boosted by an increase in ovarian blood flow due to inflammation and neoangiogenesis in case of endometriosis. Therefore, the overestimation of serum AMH levels in case of OMA is consistent with reduced oocyte retrieval in cases of OMA compared with controls during ART-controlled ovarian stimulation (46). A lower oocyte retrieval could be due to insufficient follicular stimulation with insufficient gonadotropin doses in relation to the serum AMH levels. This hypothesis needs further exploration to understand why serum AMH levels are higher with large OMAs. However, if confirmed, these results could have a clinical impact on daily practice because there could be the potential for erroneous decisions: an overestimation of the ovarian reserve before surgical management of OMA, or an underestimation of the appropriate dosage of ART-controlled ovarian stimulation.

Ovarian endometrioma toxicity on the ovarian reserve could also underlie this positive correlation. As previously described elsewhere, an increase in OMA size increases their toxicity on the ovarian reserve (47). This may contribute to improved primordial follicular stimulation and consequently an increase in serum AMH levels (48). However, this follicular

burn is widely thought to be implicated in the long-term accelerated ovarian reserve depletion in cases of endometriosis (49).

CONCLUSION

In a population of women without a prior history of surgery for endometriosis, serum AMH levels increased with OMA size. The positive correlation between serum AMH levels and OMA size may be responsible for overestimation of the ovarian reserve. In daily practice, in cases of a large OMA, a high serum AMH level should be interpreted with caution.

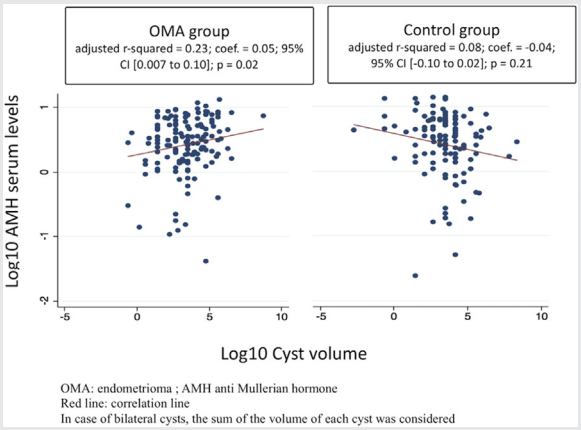
Acknowledgments: The authors thank the surgeons in our department for their expert assistance with data collection, Jeanne Colombe for unabatedly managing the patients' database, and Sophie Domingues for editing the manuscript.

REFERENCES

1. van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, et al. Serum anti-müllerian hormone levels: a novel measure of ovarian reserve. Hum Reprod 2002;17:3065–71.
2. La Marca A, Broekmans FJ, Volpe A, Fauser BC, Macklon NS. ESHRE Special Interest Group for Reproductive Endocrinology—AMH Round Table. Anti-müllerian hormone (AMH): what do we still need to know? Hum Reprod 2009;24:2264–75.
3. Reed BG, Carr BR. The normal menstrual cycle and the control of ovulation. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al., editors. Endotext [Internet]. South Dartmouth, MA: MDText.com, 2000:2018.
4. Hamdine O, Eijkemans MJ, Lentjes EW, Torrance HL, Macklon NS, Fauser BC, et al. Ovarian response prediction in GnRH antagonist treatment for IVF using anti-müllerian hormone. Hum Reprod 2015;30:170–8.
5. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Update 2014;20:124–40.
6. Iliodromiti S, Kelsey TW, Wu O, Anderson RA, Nelson SM. The predictive accuracy of anti-müllerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature. Hum Reprod Update 2014;20:560–70.
7. Streuli I, de Mouzon J, Paccolat C, Chapron C, Petignat P, Irion OP, et al. AMH concentration is not related to effective time to pregnancy in women who conceive naturally. Reprod Biomed Online 2014;28:216–24.
8. Weenen C, Laven JS, Von Bergh AR, Cranfield M, Groome NP, Visser JA, et al. Anti-müllerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod 2004;10:77–83.
9. Jeppesen JV, Anderson RA, Kelsey TW, Christiansen SL, Kristensen SG, Jayaprakasan K, et al. Which follicles make the most anti-müllerian hormone in humans? Evidence for an abrupt decline in AMH production at the time of follicle selection. Mol Hum Reprod 2013;19:519–27.
10. Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-müllerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update 2014;20:688–701.
11. Lie Fong S, Visser JA, Welt CK, de Rijke YB, Eijkemans MJ, Broekmans FJ, et al. Serum anti-müllerian hormone levels in healthy females: a nomogram ranging from infancy to adulthood. J Clin Endocrinol Metab 2012;97:4650–5.
12. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-mullerian hormone from conception to menopause. PLoS One 2011;6:e22024.
13. Visser JA, Themmen AP. Anti-müllerian hormone and folliculogenesis. Mol Cell Endocrinol 2005;234:81–6.
14. Streuli I, Fraisse T, Chapron C, Bijaoui G, Bischof P, de Ziegler D. Clinical uses of anti-müllerian hormone assays: pitfalls and promises. Fertil Steril 2009;91:226–30.
15. Somigliana E, Marchese MA, Frattaruolo MP, Berlanda N, Fedele L, Vercellini P. Serum anti-müllerian hormone in reproductive aged women with benign ovarian cysts. Eur J Obstet Gynecol Reprod Biol 2014;180:142–7.
16. Kwon SK, Kim SH, Yun SC, Kim DY, Chae HD, Kim CH, et al. Decline of serum antimüllerian hormone levels after laparoscopic ovarian cystectomy in endometrioma and other benign cysts: a prospective cohort study. Fertil Steril 2014;101:435–41.
17. Streuli I, de Ziegler D, Gayet V, Santulli P, Bijaoui G, de Mouzon J, et al. In women with endometriosis anti-müllerian hormone levels are decreased only in those with previous endometrioma surgery. Hum Reprod 2012;27:3294–303.
18. Vignali M, Mabrouk M, Ciocca E, Alabiso G, Barbasetti di Prun A, Gentilini D, et al. Surgical excision of ovarian endometriomas: Does it truly impair ovarian reserve? Long term anti-müllerian hormone (AMH) changes after surgery. J Obstet Gynaecol Res 2015;41:1773–8.
19. Uncu G, Kasapoglu I, Ozerkan K, Seyhan A, Oral Yilmaztepe A, Ata B. Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve. Hum Reprod 2013;28:2140–5.
20. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:3146–54.
21. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. Hum Reprod 2009;24:496–501.
22. Nisenblat V, Prentice L, Bossuyt PM, Farquhar C, Hull ML, Johnson N. Combination of the non-invasive tests for the diagnosis of endometriosis. Cochrane Database Syst Rev 2016;7:CD012281.
23. Valentini AL, Gui B, Micco M, Mingote MC, De Gaetano AM, Ninivaggi V, et al. Benign and suspicious ovarian masses—MR imaging criteria for characterization: pictorial review. J Oncol 2012;2012:481806.
24. Piketty M, Chopin N, Dousset B, Millischer-Bellaische AE, Roseau G, Leconte M, et al. Preoperative work-up for patients with deeply infiltrating endometriosis: transvaginal ultrasonography must definitely be the first-line imaging examination. Hum Reprod 2009;24:602–7.
25. Van Holsbeke C, Van Calster B, Guerriero S, Savelli L, Paladini D, Lissoni AA, et al. Endometriomas: their ultrasound characteristics. Ultrasound Obstet Gynecol 2010;35:730–40.
26. Guerriero S, Ajossa S, Paoletti AM, Mais V, Angiolucci M, Melis GB. Tumor markers and transvaginal ultrasonography in the diagnosis of endometrioma. Obstet Gynecol 1996;88:403–7.
27. Chon SJ, Lee SH, Choi JH, Lee JS. Preoperative risk factors in recurrent endometrioma after primary conservative surgery. Obstet Gynecol Sci 2016;59:286–94.
28. Borghese B, Chartier M, Souza C, Santulli P, Lafay-Pillet MC, de Ziegler D, et al. ABO and Rhesus blood groups and risk of endometriosis in a French Caucasian population of 633 patients living in the same geographic area. Biomed Res Int 2014;2014:618964.
29. Schliep KC, Mumford SL, Peterson CM, Chen Z, Johnstone EB, Sharp HT, et al. Pain typology and incident endometriosis. Hum Reprod 2015;30:2427–38.
30. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997;337:217–22.
31. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817–21.
32. Chapron C, Bourret A, Chopin N, Dousset B, Leconte M, Amsellem-Ouazana D, et al. Surgery for bladder endometriosis: long-term results and concomitant management of associated posterior deep lesions. Hum Reprod 2010;25:884–9.
33. Dousset B, Leconte M, Borghese B, Millischer AE, Roseau G, Arkwright S, et al. Complete surgery for low rectal endometriosis: long-term results of a 100-case prospective study. Ann Surg 2010;251:887–95.
34. Gordts S, Koninckx P, Brosens I. Pathogenesis of deep endometriosis. Fertil Steril 2017;108:872–85.e1.

35. Koninckx PR, Martin DC. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? Fertil Steril 1992;58:924–8.
36. Chapron C, Lafay-Pillet MC, Monceau E, Borghese B, Ngo C, Souza C, et al. Questioning patients about their adolescent history can identify markers associated with deep infiltrating endometriosis. Fertil Steril 2011;95:877–81.
37. Maignien C, Santulli P, Gayet V, Lafay-Pillet MC, Korb D, Bourdon M, et al. Prognostic factors for assisted reproductive technology in women with endometriosis-related infertility. Am J Obstet Gynecol 2017;216:280.e1–9.
38. Birch Petersen K, Hvidman HW, Forman JL, Pinborg A, Larsen EC, Macklon KT, et al. Ovarian reserve assessment in users of oral contraception seeking fertility advice on their reproductive lifespan. Hum Reprod 2015;30:2364–75.
39. Arbo E, Vetori DV, Jimenez MF, Freitas FM, Lemos N, Cunha-Filho JS. Serum anti-müllerian hormone levels and follicular cohort characteristics after pituitary suppression in the late luteal phase with oral contraceptive pills. Hum Reprod 2007;22:3192–6.
40. Benaglia L, Somigliana E, Vercellini P, Abbiati A, Ragni G, Fedele L. Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation. Hum Reprod 2009;24:2183–6.
41. Filippi F, Benaglia L, Paffoni A, Restelli L, Vercellini P, Somigliana E, et al. Ovarian endometriomas and oocyte quality: insights from in vitro fertilization cycles. Fertil Steril 2014;101:988–93.e1.
42. Benaglia L, Bermejo A, Somigliana E, Faulisi S, Ragni G, Fedele L, et al. In vitro fertilization outcome in women with unoperated bilateral endometriomas. Fertil Steril 2013;99:1714–9.
43. Almog B, Shehata F, Sheizaf B, Tan SL, Tulandi T. Effects of ovarian endometrioma on the number of oocytes retrieved for in vitro fertilization. Fertil Steril 2011;95:525–7.
44. Kim JY, Jee BC, Suh CS, Kim SH. Preoperative serum anti-mullerian hormone level in women with ovarian endometrioma and mature cystic teratoma. Yonsei Med J 2013;54:921–6.
45. Hwu YM, Wu FS, Li SH, Sun FJ, Lin MH, Lee RK. The impact of endometrioma and laparoscopic cystectomy on serum anti-müllerian hormone levels. Reprod Biol Endocrinol 2011;9:80.
46. Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update 2015;21:809–25.
47. Sanchez AM, Vigano P, Somigliana E, Panina-Bordignon P, Vercellini P, Candiani M. The distinguishing cellular and molecular features of the endometriotic ovarian cyst: from pathophysiology to the potential endometrioma-mediated damage to the ovary. Hum Reprod Update 2014;20:217–30.
48. Lande Y, Fisch B, Tsur A, Farhi J, Prag-Rosenberg R, Ben-Haroush A, et al. Short-term exposure of human ovarian follicles to cyclophosphamide metabolites seems to promote follicular activation in vitro. Reprod Biomed Online 2017;34:104–14.
49. Garavaglia E, Sala C, Taccagni G, Traglia M, Barbieri C, Ferrari S, et al. Fertility preservation in endometriosis patients: anti-müllerian hormone is a reliable marker of the ovarian follicle density. Front Surg 2017;4:40.

SUPPLEMENTAL FIGURE 1



Scatterplot of log10 cyst volumes and the log10 serum AMH concentrations.

Marcellin. Serum AMH concentration and endometrioma. Fertil Steril 2019.