

# Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis

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**Objective:** To evaluate the adverse effects of endometriomas on ovarian reserve.

**Design:** Analysis of prospectively collected biopsy samples.

**Setting:** Gynecology research unit in a university hospital.

**Patient(s):** Women younger than age 35 years with endometriomas.

**Intervention(s):** Biopsy of normal cortex from ovaries affected by endometriomas ( $\leq 4$  cm) and contralateral ovaries without cysts.

**Main Outcome Measure(s):** Presence of cortex-specific stroma, observation of superficial endometriosis, follicular density, and presence of fibrosis.

**Result(s):** Twenty samples of cortical tissue from ovaries with endometriomas and 11 from contralateral ovaries without cysts were analyzed. Follicular density was significantly lower in cortex from ovaries with endometriomas than in cortex from contralateral ovaries without cysts (mean  $\pm$  SD =  $6.3 \pm 4.1/\text{mm}^3$  vs  $25.1 \pm 15.0/\text{mm}^3$ ). Eleven (55%) cortical samples from ovaries with endometriomas showed fibrosis and concomitant loss of cortex-specific stroma, not observed in contralateral normal ovaries. Multivariate analysis revealed that the presence of endometrioma and fibrosis were significantly and independently associated with follicular density.

**Conclusion(s):** Endometriotic cyst formation and associated structural tissue alterations in apparently normal ovarian cortex may be a cause of reduced ovarian reserve. Early diagnosis and intervention may be beneficial in women with endometriomas to protect their ovarian function. (Fertil Steril® 2011;96:685–91. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** Endometriosis, endometrioma, ovarian reserve, follicular density, fibrosis, ovarian stroma

Endometriosis affects about 10% of women of reproductive age and is associated with pelvic pain and infertility (1). Endometriotic cysts (endometriomas) are a common feature of endometriosis, and their pathogenesis may be different from other types of endometriosis, such as peritoneal implants and rectovaginal nodules (2). Because ovarian endometriomas do not respond well to medical therapy alone, surgical treatment may be preferred (3). Laparoscopic cystectomy is recommended for endometriomas larger than 4 cm (4), but the side effects of this surgery in terms of preservation of ovarian reserve after surgery have been questioned (5). Although some authors report no impact on ovarian response in IVF after surgery (6, 7), others have suggested that cystectomy for endometriomas might cause surgical injury to normal ovarian tissue (5, 8, 9).

On the other hand, endometriomas themselves could be linked to reduced ovarian reserve, and damage to normal ovarian tissue may precede surgery. Maneschi et al. (10) evaluated ovarian cortical tissue from women with endometriomas and found a reduced volume

of healthy ovarian tissue in this distended ovarian cortex compared with other benign ovarian cysts. Schubert et al. (11) reported lower follicular density in cortex surrounding endometriomas than dermoid cysts. These authors also found histologic alterations, such as extensive fibrosis in ovarian cortex adjacent to endometriomas. However, the relationship between histologic alterations and loss of follicles was not evaluated in depth. Semiquantitative methods used in previous study might not have been able to accurately gauge the number of early follicles in the ovarian reserve (10). Moreover, because relatively large cysts (6 cm in mean diameter) were evaluated in these studies, follicular density in thin cortical tissue resulting from distension by large cysts might well be different from that in thick cortex without distension. Thus, information on follicular reserve in normal ovarian cortex at earlier stages of endometrioma formation is limited.

Studies comparing diseased ovaries and contralateral healthy ovary in women with unilateral endometriomas are clearly warranted to elucidate the relationship between endometriomas per se and reduced ovarian reserve. Indeed, Somigliana et al. (12) reported reduced ovarian responsiveness after exogenous gonadotropin stimulation in ovaries with unoperated endometriomas compared with contralateral ovaries without cysts. Recently, a significantly lower antral follicle count was observed in ovaries with unoperated endometriomas than in contralateral healthy ovaries (13). However, histologic analysis in similar study settings has not been reported. The goal of our study was to further characterize the effects of endometriomas on ovarian follicle reserve by comparing follicular density and histologic features in apparently normal-looking ovarian

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cortical tissue from ovaries with small endometriomas and contralateral healthy ovaries.

## MATERIALS AND METHODS

### Patient Selection

Between January 2010 and October 2010, 22 women younger than age 35 years, without previous ovarian surgery but now undergoing laparoscopic surgery for monolocular endometriotic cysts (endometriomas) due to pelvic pain and/or infertility, were prospectively enrolled. All the women had regular menstrual cycles without any menopausal symptoms. Three women had taken oral contraceptives and four had undergone GnRH agonist therapy within 3 months of surgery. Endometriomas were diagnosed and evaluated by transvaginal ultrasonography and magnetic resonance imaging (MRI) before surgery and histologically confirmed after surgery by an experienced pathologist. Among these patients, 18 women had unilateral lesions and 4 women had bilateral lesions. To evaluate early-stage endometriomas and avoid the confounding effects of enlarged endometriomas on the histologic features of normal ovarian cortex, only cortical samples from endometriomas  $\leq 4$  cm, irrespective of unilateral or bilateral location, were included.

### Surgical Procedure and Biopsy Collection

Endometrioma surgery was performed without any complications, as previously described (5). After identifying the endometrioma, a piece of macroscopically normal-looking thick ovarian cortical tissue ( $7.7 \pm 1.4$  [mean  $\pm$  SD] mm largest diameter) was excised using scissors  $\geq 1$  cm away from the site of fenestration. In 11 women with unilateral endometriomas, who were eligible for the study regardless of endometrioma size, cortical tissue from the contralateral healthy ovary was also biopsied ( $4.7 \pm 1.5$  [mean  $\pm$  SD] mm largest diameter). Cortical biopsy could not be performed in all women for various reasons, such as lack of informed consent, a long history of unexplained infertility, or the surgeon's decision during surgery. Use of human ovarian tissue for this study was approved by the Institutional Review Board of the Université Catholique de Louvain and written informed consent was obtained from each patient.

### Evaluation of the Microscopic Structure of Ovarian Cortex

All biopsied tissue was fixed overnight in Bouin's solution and embedded in paraffin. For each sample, approximately 300–360 serial sections perpendicular to the ovarian axis were performed at 5- $\mu$ m intervals and stained with hematoxylin and eosin at 50- $\mu$ m intervals.

In all stained sections, the presence or absence of superficial endometriotic foci, characterized by the presence of endometrial glandular cells and/or stromal cells, was recorded. Ovarian cortex is composed of ovarian surface epithelial cells, a zone of hypocellular connective tissue (tunica albuginea), and an area of cortex-specific stroma with early follicles in a layered structure (14, 15). Cortex-specific stroma was made up of tightly bound fascicles, identified as a strip of strongly hematoxylin and eosin-stained cells due to increased cellular density at the border of the corticomedullary junction (14), as illustrated in Figure 1A. The presence or absence of these belt-like structures was recorded. Areas containing advanced follicular structures, such as antral follicles, corpus luteum and corpus albicans, and edematous stroma with spiral vessels or large arterioles were considered as medullary regions (14, 15).

### Follicular Density Count

Follicular density in biopsied cortex was evaluated according to previously described methods (16, 17) with some modifications. Briefly, 10 serial sections with the largest horizontal diameter and an intact morphological appearance were selected, and each section was captured as a digital image using the MIRAX MIDI system (Carl Zeiss). The total area of captured sections and area of cortex in those sections were measured by manually delineating the contours using a specific computer program (MIRAX viewer version 1.12, Carl Zeiss). The boundary between the cortex and medulla was identified by a strip of cortex-specific stroma, a hallmark of the corticomedullary junction, as detailed above and shown in Figure 1A and C. In samples with less identifiable stroma, the appearance

of edematous stroma with spiral vessels or large arterioles was considered as the limit between the two regions (Fig. 1E). Primordial, primary, and secondary follicles present in captured sections were classified as previously reported (18) and counted. The number of follicles was counted three times for each sample, and the mean of the two most adjacent values was used to calculate follicular density. These measurements were taken by one author (M.K.) blinded to the side of the cysts. Intrarater variation of measurements was less than 10%. The estimated volume of analyzed ovarian cortex was calculated by the following formula:

$$V (\text{mm}^3) = S(A1, A10) \times 0.05, \text{ where } S(A1, A10) \text{ is the sum of the area of 10 sections and 0.05 is the interval between the sections (in millimeters).}$$

Follicular density was expressed as the total number of follicles in 10 sections divided by the volume of ovarian cortex (16).

### Determination of Fibrosis

To evidence fibrosis in ovarian cortex, Masson's trichrome staining was performed with methyl green (19). Fibrosis in cortical tissue was identified by filamentous (fiber-like) green staining (Fig. 1D) and/or stratified hypocellular (paint-like) green staining (Fig. 1F). The presence or absence of staining in cortical areas was recorded.

### Statistical Analysis

Statistical analysis was performed using StatView (StatView version 5.0, SAS institute). Student's *t* test with single linear regression was used to compare continuous variables. If these variables showed skewed distribution, the Mann-Whitney *U* test was applied. Chi-square analysis and Fisher's exact test were used to evaluate categorical variables. Multivariate analysis of variance (ANOVA) was performed to evaluate possible confounding variables associated with follicular density. A *P* value  $< .05$  was considered statistically significant.

## RESULTS

### Patient Demographics and Histologic Features of Ovarian Cortex

Patient characteristics as well as results of histologic and morphometric analyses are detailed in Table 1. After histologic evaluation, two cortical samples from ovaries with endometriomas lacked identifiable cortical structures and were excluded from further analysis. The mean age of subjects was  $28.8 \pm 3.4$  (mean  $\pm$  SD) years and the mean diameter of endometriomas was  $2.7 \pm 1.0$  cm (Table 1).

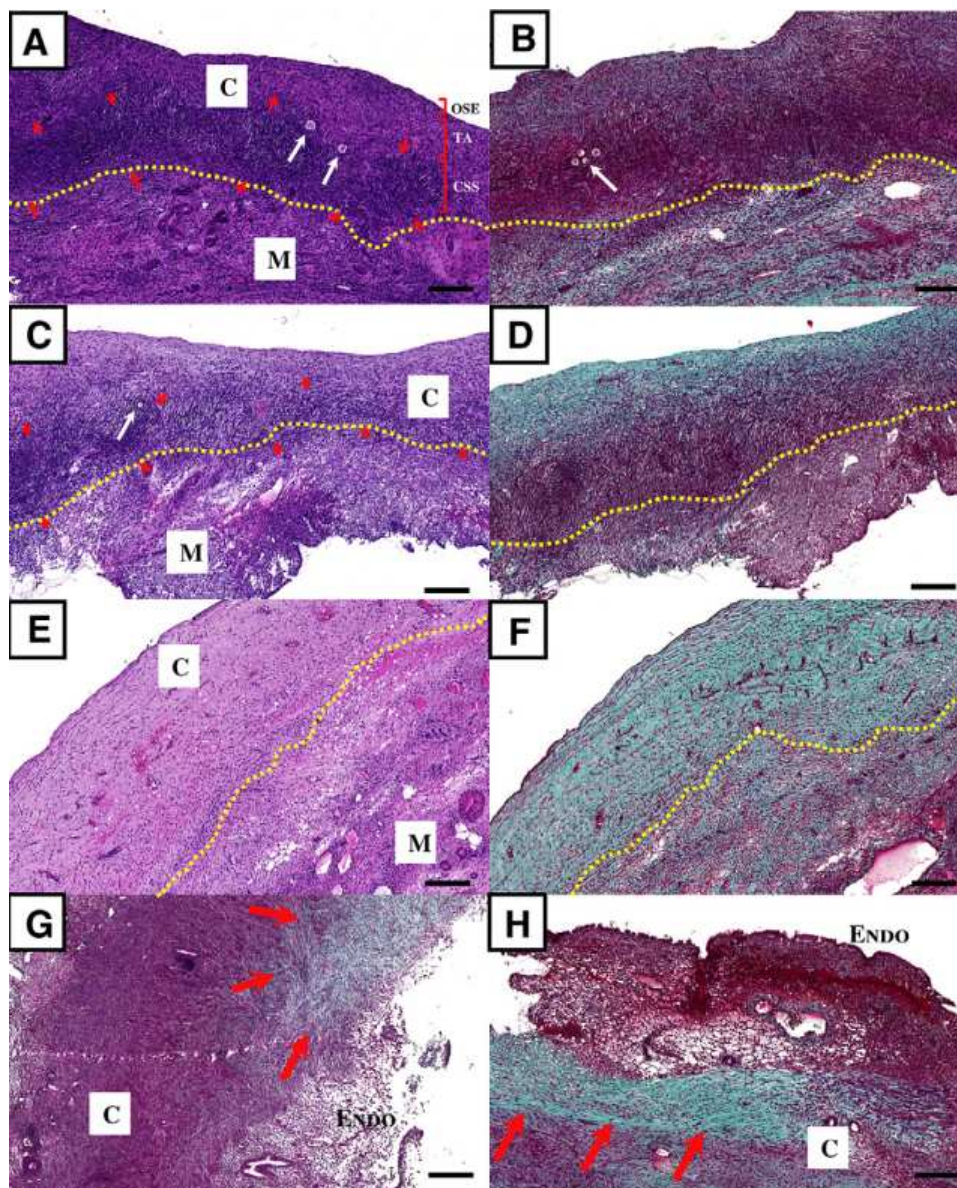
The volume of cortex was significantly larger in tissue samples taken from the side affected by endometriomas than from contralateral normal ovaries (Table 1). However, cortex-specific stroma was significantly less frequently observed in cortex from ovaries with endometriomas than contralateral healthy ovaries (Table 1). We found superficial endometriotic foci in 45% (9/20) of tissue samples from ovaries with endometriomas and 18% (2/11) of those from contralateral ovaries without cysts, though this did not constitute a statistically significant difference (Table 1).

### Follicular Density, Fibrosis, and Other Histologic Features in Cortex from Ovaries with and Without Endometriomas

Follicular density was significantly lower in cortex from ovaries with endometriomas than without ( $6.3 \pm 4.1$  [mean  $\pm$  SD]/mm<sup>3</sup> vs  $25.1 \pm 15.0$ /mm<sup>3</sup>,  $P=.0002$ ) (Table 1). We found an inverse correlation between follicular density and age, though it was not statistically significant ( $r^2 = .18$ ,  $P=.06$  for cortex from ovaries with endometriomas;  $r^2 = .35$ ,  $P=.054$  for cortex from contralateral normal ovaries). We did not find any significant correlation between follicular density and the presence of superficial endometriosis, volume of cortex, endometrioma size, or use of oral contraceptives or GnRH agonist before surgery.

## FIGURE 1

Photomicrograph of ovarian cortex. (A and B) Representative photomicrograph of ovarian cortical tissue without fibrosis (A, hematoxylin-eosin [H&E] staining; B, Masson's trichrome staining). These samples were obtained from a contralateral healthy ovary. Ovarian cortex is composed of ovarian surface epithelium (OSE), tunica albuginea (TA), and an area of cortex-specific stroma (CSS, strip of tightly packed fibrous cells, *arrow heads*) with early follicles (*arrow*) in a layered structure (A). The dotted line indicates the boundary between the cortex and medulla. (C and D) Representative photomicrograph of ovarian cortical tissue with filamentous fibrosis (C, H&E staining; D, Masson's trichrome staining). These samples were obtained from a contralateral healthy ovary. Ovarian cortex contains cortex-specific stroma with decreased follicular density (*arrow heads*). The dotted line indicates the boundary between the cortex and medulla. (E and F) Representative photomicrograph of ovarian cortical tissue with stratified hypocellular fibrosis (E, H&E staining; F, Masson's trichrome staining). These samples were obtained from an ovary with an endometrioma. Cortex-specific stroma was found to have disappeared and been replaced with fibrosis. Follicles are absent in this specimen. The dotted line indicates the boundary between the cortex and medulla. (G) Representative photomicrograph of a surface endometriotic lesion with filamentous fibrosis (Masson's trichrome staining). Green-stained fine fibrotic tissue (*arrows*) can be observed beneath the implanted endometriotic tissue (Endo). (H) Representative photomicrograph of a surface endometriotic lesion with stratified hypocellular fibrosis (Masson's trichrome staining). Thick paint-like green-stained fibrotic tissue (*arrows*) can be observed beneath the implanted endometriotic tissue (Endo). C = cortex; M = medulla. Bar = 200  $\mu$ m.



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**TABLE 1**

Patient demographics and histomorphometric evaluation.

Patient no. <sup>a</sup>	Age (y)	Size of endometrioma (cm)	Usage of medication before surgery	Cortex within endometrioma					Cortex within contralateral normal ovary				
				Volume of cortex (mm <sup>3</sup> )	Follicular density (mm <sup>-3</sup> )	Presence of fibrosis	Presence of specific stroma in cortex	Presence of superficial endometriotic foci	Volume of cortex (mm <sup>3</sup> )	Follicular density (mm <sup>-3</sup> )	Presence of fibrosis	Presence of specific stroma in cortex	Presence of superficial endometriotic foci
1	22	(5)	OC			ND			2.4	44.3	–	+	–
2	24	2	GnRH-a	2.2	6.3	+	–	–			NA		
3	24	3	–	2.9	0.0	+	–	–			NA		
4	25	4	–	2.1	6.3	+	–	–			NA		
5	26	2	–	5.4	11.6	+	+	+	3.1	46.4	–	+	–
6	26	2	–	1.9	11.3	–	+	–	1.8	34.6	–	+	–
7	26	2	–	4.1	10.4	–	–	+			NA		
8	27	3	–	1.6	7.4	–	–	–	1.4	15.7	–	–	–
9	28	1	GnRH-a	3.1	14.9	+	–	+			NA		
10	28	(5)	–			ND							
		(2)	–			ND					NA		
		3	–	2.3	9.8	+	+	+					
11	28	3	OC	2.2	7.2	+	+	+	1.1	41.8	–	+	–
12	28	3	–	3.6	8.3	–	–	–			NA		
13	28	(3)	–			ND			1.0	19.6	–	+	+
14	28	4	OC	3.4	3.0	+	–	+	2.6	10.3	+	+	+
15	30	1	–	3.9	2.8	+	–	+			NA		
		2	–	2.7	8.1	+	+	–					
16	31	(5)	–			ND			1.3	14.5	–	+	–
17	31	(6)	–			ND			3.1	7.1	+	+	–
18	32	2	GnRH-a	4.4	0.5	+	–	+			NA		
19	32	2	GnRH-a	3.5	6.9	+	–	+			NA		
20	33	4	–	1.8	4.4	+	–	–	1.8	32.4	–	+	–
21	34	2	–	3.0	1.0	+	+	–			NA		
		4	–	3.2	2.9	+	–	–					
22	35	4	–	2.6	3.4	+	–	–	2.2	9.6	+	+	–
Total	28.8 ± 3.4	2.7 ± 1.0 <sup>b</sup>	7/22 (32%)	3.0 ± 1.0 <sup>c</sup>	6.3 ± 4.1 <sup>d</sup>	16/20 (80%) <sup>e</sup>	6/20 (30%) <sup>f</sup>	9/20 (45%)	2.0 ± 0.8 <sup>c</sup>	25.1 ± 15.0 <sup>d</sup>	3/11 (27%) <sup>e</sup>	10/11 (91%) <sup>f</sup>	2/11 (18%)

Note: Individual values are shown and mean ± SD for continuous variables and percentage for positive results are given in the bottom row. ND = not determined due to endometrioma size (>4 cm) (cases 1, 9, 16, and 17) or absence of cortical area (case 10 and 13); NA = not applicable as no cortical biopsy was attempted; OC = oral contraceptives; GnRH-a = GnRH-agonist.

<sup>a</sup> Patients 9, 10, 15, and 21 had bilateral lesions.

<sup>b</sup> Values shown in parenthesis were not included in the analysis.

<sup>c</sup> Significantly different between the endometrioma and contralateral normal ovary ( $P = .005$ , Student's  $t$  test).

<sup>d</sup> Significantly different between the endometrioma and contralateral normal ovary ( $P = .0002$ , Mann-Whitney  $U$  test).

<sup>e</sup> Significantly different between the endometrioma and contralateral normal ovary ( $P = .007$ , Fisher's exact test).

<sup>f</sup> Significantly different between the endometrioma and contralateral normal ovary ( $P = .002$ , Fisher's exact test).

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The presence of fibrosis identified by Masson's trichrome staining is shown in Figure 1. Typically, green staining indicative of fibrosis was found in ovarian tissue with superficial endometriotic foci (Fig. 1G and H). However, a statistically significant relationship was not observed between these two histologic features. Fibrosis was significantly more frequently observed in cortex from ovaries with endometriomas than without (80% [16/20] vs 27% [3/11],  $P=.007$ ) (Table 1). Cortical samples with fibrosis showed significantly lower follicular density than tissue without fibrosis ( $6.1 \pm 4.0$  [mean  $\pm$  SD]/mm<sup>3</sup> vs  $23.9 \pm 15.0$ /mm<sup>3</sup>,  $P<.0001$ ).

The presence of fibrosis and concomitant loss of cortex-specific stroma (Fig. 1D and F) was found in 11 (55%) cortical samples from ovaries with endometriomas (Table 1), whereas this association of histologic alterations was never observed in samples from contralateral healthy ovaries ( $P=.002$ , Fisher's exact test). Multivariate ANOVA with possible confounding variables, such as the presence of superficial endometriosis, volume of cortex, presence of cortex-specific stroma, patient age, presence of fibrosis, and presence of endometriomas, revealed that fibrosis and endometriomas were significantly and independently associated with follicular density (Table 2).

## DISCUSSION

In this study, we demonstrated, for the first time, that follicular density in cortex from ovaries with endometriomas less than 4 cm in size is significantly lower than in cortex from contralateral normal ovaries. In addition, histologic alterations in cortical tissue, such as formation of fibrosis and concomitant loss of cortex-specific stroma, were found to significantly correlate with follicular density in cortex from ovaries with endometriomas. Follicular density is known to be negatively associated with age and pathological conditions of the ovary (17, 20, 21). On the other hand, follicle numbers in biopsied ovarian samples may show skewed distribution, with large interindividual and intraindividual variations (20, 22). In the present study, although follicular density in contralateral healthy ovaries showed a wide range of distribution, in cortical samples from ovaries with endometriomas, it exhibited a limited range of distribution at lower values. Further, when analyzed in pairs in each subject, follicular density in diseased ovaries was always significantly lower than in contralateral normal ovaries ( $P=.006$ , paired Student's *t* test). Despite the fact that low follicular density does not necessarily mean a reduced ovarian reserve, our results confirm that focal loss of the follicular reservoir is common in cortical tissue of ovaries with endometriomas  $\leq 4$  cm.

These findings confirm data from previous studies in larger endometriomas (10, 11). Indeed, Maneschi et al. (10) found a reduced presence of healthy ovarian tissue in cortex harvested from ovaries

with endometriomas ( $6.5 \pm 2.3$  [mean  $\pm$  SD] cm) compared with other similar-sized benign ovarian cysts by semiquantitative scoring. In another study, Schubert et al. (11) reported lower follicular density in cortical tissue derived from endometriomas ( $5.7 \pm 2.0$  cm) than from dermoid cysts. These studies suggest that a factor other than simple mechanical tissue stretching by large cysts might be responsible for reduced follicular density in the cortex surrounding endometriomas. The size of the cyst may correlate with the duration and severity of the inflammatory reaction in normal cortical tissue within endometriomas.

Nevertheless, our findings further indicate that follicular loss may occur even at early stages of endometrioma development. Although the exact pathogenesis of endometriomas is still a matter of debate, two distinct hypotheses have been proposed. Brosens et al. (23) suggested that endometriomas might result from invaginated surface endometriotic lesions. Another possible mechanism could be metaplastic changes to invaginated ovarian surface epithelium (3). In both hypotheses, endometriotic tissue may arise from cortical areas of the ovary and, as it grows into a cyst, provoke an inflammatory reaction and consequent fibrosis in surrounding normal ovarian cortex. It has been reported that ovarian cortex around endometriomas shows increased tissue oxidative stress compared with other benign ovarian cyst (24). Oxidative stress might be one mechanism by which follicular depletion occurs in women with endometriomas. Indeed, in vitro studies have revealed that oxidative stress induces oocyte apoptosis and necrosis in early follicles (25).

In this study, fibrosis was frequently evidenced in cortex derived from endometriomas, consistent with previous reports (10, 11). In addition, a significant association between the presence of fibrosis and reduced follicular density was demonstrated, confirming previous observations. Similarly, in another context, Meirou et al. (26) reported an association between fibrosis formation in ovarian cortex and decreased follicular populations in ovaries of women receiving chemotherapy. Interestingly, they found similar histopathological changes in cortex from older women not exposed to chemotherapy (26). Fibrosis was also demonstrated in human ovarian cortical tissue after cryopreservation and xenotransplantation (19, 27). We therefore considered that fibrosis formation in cortical tissue might be a common pathological feature of microscopic ovarian injury associated with follicular loss.

In the present study, we found that nests of early follicles are almost always present in areas with healthy cortex-specific stroma. Tightly packed fibrous cells are a hallmark of cortex-specific stroma (14, 15), and follicular density is significantly lower in cortical tissue that lacks this type of stroma. Moreover, cortical tissue with fibrosis and concomitant loss of cortex-specific stroma was specific to histologic findings associated with reduced follicular density in cortex from ovaries with endometriomas. Because primordial follicles do not possess their own vascular network, stromal cells surrounding early follicles may act as mediators of nutrients and molecular signals, as well as a source of somatic cells for growing follicles (28–30). Cortex-specific stroma may therefore play an important role in maintaining the ovarian reserve.

Although not evaluated in this study, relationships between follicular density and serum ovarian reserve markers, such as basal FSH, E<sub>2</sub>, inhibin B, and antimüllerian hormone, may yield additional information on the effects of endometriomas on the ovarian reserve. However, the value of such markers may be limited, because it may be difficult to isolate the effects of the endometrioma itself in women with unilateral lesions, whereas in women with bilateral lesions, the contribution of each lesion may be difficult to distinguish. Further, even women with mild endometriosis, but not endometriomas, have

**TABLE 2**

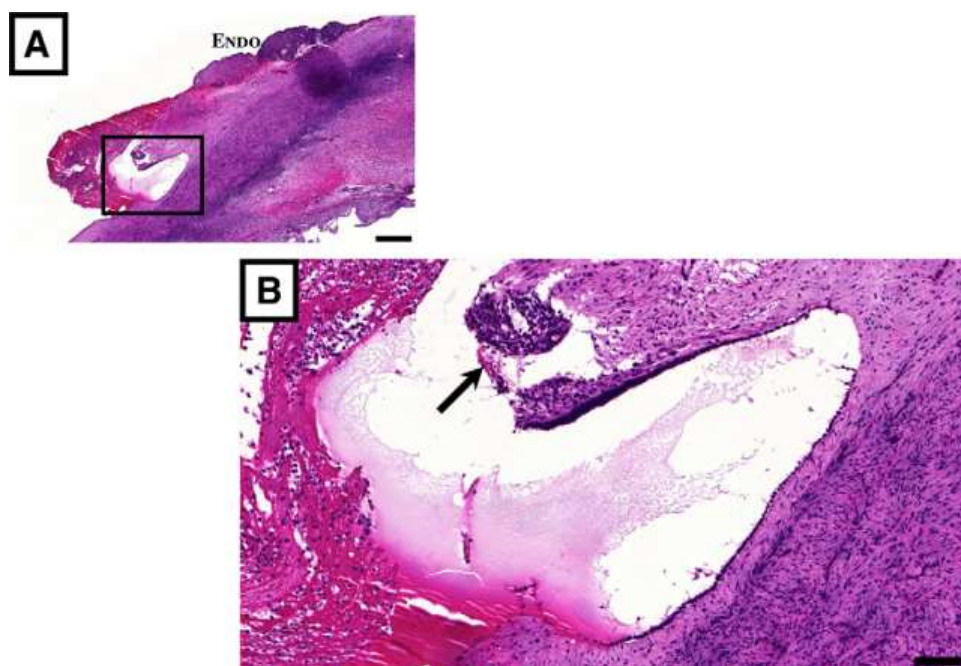
**Multivariate analysis of variance to evaluate the contributors to follicular density.**

Confounding variables	F value	P value
Presence of superficial endometriosis	0.20	.66
Volume of cortex (mm <sup>3</sup> )	0.60	.45
Presence of cortical-specific stroma	2.02	.17
Age (y)	3.04	.09
Presence of fibrosis	5.90	.02
Cortex from ovaries with endometrioma	6.76	.02

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## FIGURE 2

Photomicrograph of cortex with a surface endometriotic lesion and invaginating surface epithelium. (A) Representative photomicrograph of ovarian cortex with a surface endometriotic lesion. Cortical tissue was obtained from the ovary affected by an endometrioma. Implanted endometrial tissue (Endo) with hemorrhage and fibrosis were observed. Bar = 500  $\mu$ m. (B) Enlarged view of the box from Figure 2A. Invaginating surface epithelium, showing a continuum of flat and cuboid-shaped surface epithelium, was observed, along with hemorrhage, fibrosis, and endometrial-like stroma (arrow). Bar = 100  $\mu$ m.



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been reported to show decreased serum antimüllerian hormone levels (31). Histologic evaluation may serve as a valuable alternative to such serum assessments.

We found superficial endometriotic foci in 45% and 18% of biopsied cortex from ovaries with and without endometriomas, respectively. These microscopic lesions may be considered as superficial implants, whose pathogenesis is similar to that of peritoneal endometriosis (3). Normal ovaries may retain microscopic endometriotic foci, because scanning electron microscopy of biopsy samples from normal-looking peritoneum in women with endometriosis revealed unsuspected implants in 25% of cases (32, 33). Although more frequent in the endometrioma group, the presence of these lesions was not associated with decreased follicular density (non-significant correlation). However, one cannot exclude the possibility that they may become persistent lesions and provoke local inflammatory reactions and consequent focal loss of follicular reserve in ovarian cortex. Indeed, focal fibrosis and invagination (inclusion) of surface epithelium with cuboidal

changes were observed along with the endometriotic foci, which partly supports the metaplasia theory for the pathogenesis of ovarian endometriosis (Fig. 2).

To alleviate the local inflammatory environment in diseased ovaries, surgical interventions, even at an early stage of cyst development, may be beneficial to protect the ovarian reserve in women with endometriomas. At the time of surgical intervention, tissue-sparing procedures should also be implemented to protect the follicular reservoir of the remaining ovarian cortex (5). Future studies on underlying molecular mechanisms involved in the association between inflammation and follicular loss in cortical stroma may bring new insights to ensure the most effective therapy for endometriosis-associated infertility.

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