

# Exploring the Association Between the Doppler Findings of Endometriomal Wall Vascularization and Volume of the Endometrioma

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**OBJECTIVE:** To assess the relationship between vascularity patterns along the endometriomal wall assessed by Doppler ultrasound and volume of the endometrioma.

**STUDY DESIGN:** A total of 58 patients who underwent laparoscopic surgery for ovarian endometrioma were evaluated for volume and vascularization by color and power Doppler ultrasonography before the surgery. The presence and amount of blood flow reported in terms of color scale and pulsed Doppler indices were examined. Endometriomal volume in patients with different amount of blood flow (avascular or scantily vascularized group; n= 42 and moderately or highly vascularized group; n=16) was compared and the relation of volume to Doppler indices was assessed by Spearman's correlation analysis. p<0.05 was considered statistically significant.

**RESULTS:** No differences were found with regard to the volume between avascular or scantily vascularized endometriomas and moderately or highly vascularized endometriomas (p=0.41). But, the volume of the endometrioma was positively correlated with the PI and RI values (Spearman's r =0.335 and r=0.382, respectively), and the correlation was statistically significant for both PI and RI (p=0.026 and p=0.011, respectively).

**CONCLUSION:** We could not demonstrate a significant association between endometriomal volume and amount of blood flow along the endometrioma wall. However, the increased volume of endometrioma is found to be correlated with high vascular resistance, thus decreased vascularization compared to smaller endometriomas assessed by pulsed Doppler indices. This finding may aid in the development of adjuvant treatments for patients with smaller endometriomas and lower resistance to blood flow.

**Key Words:** Endometrioma, Doppler, Volume, Vascularization

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## Introduction

Endometriosis is an enigmatic and complex disease affecting 6-10% of all reproductive aged women.<sup>1</sup> The prevalence of the disease rises to 35-50% in women undergoing laparoscopy for pelvic pain and infertility.<sup>2</sup> The main sites of the endometriosis are the pelvic peritoneum, ovaries and rectovaginal septum.

The correct diagnosis of an ovarian endometrioma is very important with regard to fertility and pelvic pain, and especially to distinguish from other types of adnexal masses. Ultrasonography remains the method of choice for the diagnosis of endometrioma. The typical endometrioma is an unilocular cyst with homogeneous low-level echogenicity of

the cyst fluid.<sup>3</sup> In addition to B-mode ultrasonography, the use of color and pulsed Doppler allows for the assessment of endometriomal vascularity and improves accuracy of ultrasonography in the diagnosis of endometrioma.<sup>4</sup>

Although the pathogenesis of the disease is unknown, immunological and peritoneal factors that stimulate angiogenesis is currently the most widely accepted explanation.<sup>5,6</sup> Limited number of studies investigated the color and pulsed Doppler ultrasound findings of endometriomas.<sup>4,7-9</sup> Furthermore, the association between the size of the endometriomas and vascularization remains to be elucidated. In theory, the size of endometrioma may affect its blood flow patterns. This issue might be a standing point for developing new therapeutic and preventive modalities for endometriosis. Therefore, in the present study we sought to examine the relationship between vascularity patterns along the endometrioma wall assessed by transvaginal Doppler ultrasound and the volume of the endometrioma.

## Material and Method

Reproductive age women undergoing laparoscopic surgery

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for the diagnosis of ovarian endometrioma were involved in this prospective cohort study at the Zekai Tahir Burak Women's Health Research and Education Hospital. The investigation was approved by the Institutional Review Board and informed consent was obtained from all patients.

Women who had previously undergone endometriosis surgery or received suppressive treatment (oral contraceptives or GnRH analogues) within 3 months were excluded from the study. Patients with a suspicion of malignancy were also excluded. Prior to laparoscopy, all patients underwent gynecologic examination and transvaginal ultrasonography with an Aloka 7.5-mHz endovaginal probe (Aloka Co., Tokyo, Japan) and color and pulsed Doppler systems. Ultrasound examination was performed within the week before surgery during the early follicular phase of the menstrual cycle. All ultrasonographic assessments were done by the same examiner. On B-mode ultrasonography an ovarian endometrioma was defined as a round-shaped homogeneous hypoechoic tissue of low-level echoes.<sup>4</sup> Endometrioma volume was calculated using the prolate ellipsoid formula:  $0.5233 \times \text{height} \times \text{length} \times \text{width}$  (in cm), and expressed in milliliters (mL). After morphological evaluation was performed, color and pulsed Doppler were used to assess endometrioma vascularity, and color signals were looked for along the wall of the endometrioma. The amount of blood flow was reported in terms of a color scale.<sup>10</sup> A color score of 1 was given when no flow could be detected, a score of 2 was given when scanty amount of color Doppler signals was present, a score of 3 was given when a moderate amount was detected, and a score of 4 was given when an abundant amount was detected. After color signals were detected, flow velocity waveforms (FVW) were obtained with the pulsed-wave Doppler and the pulsatility index (PI) and resistance index (RI) were electronically computed. Only arterial FVWs were processed. Sample volume was set at a 1.2-2 mm width. The spatial peak temporal average intensity was  $<65 \text{ mW/cm}^2$ . A 50-100 Hz filter was used to eliminate low-frequency signals. The pulse-repetition frequency was set at 1.5-25 kHz. Similar consecutive waveforms for at least nine waveforms of good quality were analysed. When multiple signals were obtained, the lowest PI and RI values were used.

All operations were performed by experienced laparoscopic surgeons. Cystectomy by stripping or fenestration with a biopsy sample and coagulation of the cyst wall were applied on a case by case basis. Postoperatively, the pathology results

were examined to confirm the diagnosis histologically and patients with a definitive diagnosis of ovarian endometrioma was included in the study.

Data were evaluated with SPSS for Windows v. 11.5 (SPSS, Chicago, IL, USA). Continuous data were expressed as the means  $\pm$  standard deviation (SD) or median with interquartile range (IQR), according to the distribution characteristics. Categorical data were presented number and percentage. Mann-Whitney U test was used to compare vascularization in different groups with regard to the volume of the endometriomas. Although the patients were divided into four groups according to color scores, we evaluated amount of vascularization in two groups for statistical purposes (avascular and scantily vascularized group: color score 1 and 2 vs. moderately and highly vascularized group: color score 3 and 4).

For assessment of correlations between the endometriomal volume and pulsed Doppler indices, Spearman's rank order correlation coefficients ( $r$ ) and their probability ( $p$ ) levels were calculated.  $p < 0.05$  was considered statistically significant.

## Results

A total of 64 patients submitted to laparoscopy for ovarian endometrioma were initially included into the study. Of these, five had a hemorrhagic cyst and one had a tuboovarian abscess at the definitive pathologic diagnosis. Therefore, they were excluded and the final study size was 58 patients.

The patients' mean age was  $34.3 \pm 6.2$  years (range, 21-44 years). The median volume of the endometriomas was 32.6 mL (IQR, 58.9; range, 3.1-515.1 mL). Blood flow was detected in 40 (68.9%) patients. The median values of PI and RI were 1.09 (IQR, 0.61; range, 0.68-5.81) and 0.65 (IQR, 0.19; range, 0.47-1.64), respectively.

The median volume of the endometriomas was 31.9 mL (IQR, 51.8; range, 3.1-165.9 mL) in the patients with a detected blood flow and 40.6 mL (IQR, 137.5; range, 8.9.3-515.1 mL) with no blood flow. The difference was not statistically significant ( $p=0.598$ ). When the relationship between the amount of blood flow and volume of the endometrioma was evaluated, the difference between avascular or scantily vascularized endometriomas and moderately or highly vascularized endometriomas was not significant (38.85 mL vs 28.37 mL, respectively,  $p=0.41$ ) (Table 1).

Table 1: Vascularization (color score) in relation to the endometriomal volume

	Avascular and scanty (color score 1 and 2) (n=42)	Moderately and highly (color score 3 and 4)(n=16)	p value
Volume of the endometrioma (mL) Median (IQR)	38.85 (75.71)	28.37 (43.16)	0.41*

\*p value as calculated by Mann-Whitney U test

On the other hand, the analysis of correlation between the volume of the endometrioma and pulsed Doppler indices showed that the volume of the endometrioma positively correlated with the PI and RI values ( $r=0.335$  and  $r=0.382$ , respectively). The correlation was statistically significant for both PI and RI ( $p=0.026$  and  $p=0.011$ , respectively) (Table 2).

Table 2: Correlation of the volume of the endometriomas with the Doppler indices

	r	p
PI	0.335	0.026*
RI	0.382	0.011*

r: Spearman's correlation coefficient

\*Significant correlation  $p < 0.05$

## Discussion

In the present study we were unable to show a statistically significant relationship between endometriomal volume and amount of vascularization reported as color score. However, we found that the increased volume of endometrioma is associated with high vascular resistance assessed by pulsed Doppler indices.

New blood vessel formation has long been recognized as a feature of endometriosis.<sup>5</sup> Therefore, angiogenesis is involved in the pathogenesis of this disease and believed to be a necessary requirement for the sustenance of endometriotic lesions.<sup>11,12</sup> Recent studies have demonstrated that angiogenic cytokines such as vascular endothelial growth factor (VEGF), interleukine-8 (IL-8), and leptin are increased in the peritoneal fluid of women with endometriosis.<sup>13-15</sup>

Color Doppler ultrasound allows noninvasive vascular evaluation of the ovarian masses. Traditional waveform indices (RI and PI) assess pulsatility quantitatively, and these indices are used as a measure of vascular resistance. The rise in vascularization is associated with low resistance to blood flow as measured by the low resistance and pulsatility indices.<sup>16,17</sup> A few studies have studied the presence of blood flow and mean PI and RI values in ovarian endometriomas.<sup>7-9,18</sup> The rates of vascularized endometriomas in these studies were reported as approximately 60-70%. In the present study, the rate of vascular presence was 68.9%, which is in agreement with those reported values. In a study by Alcázar and García-Manero, a high correlation between vascularization detected by Doppler ultrasound and immunohistochemical analysis of microvascular density was demonstrated in patients with endometriomas.<sup>9</sup>

Laparoscopic surgery is the recommended approach for women with pelvic pain symptoms and large endometriomas.<sup>19,20</sup> On the other hand, recurrent disease and pain after local excision or ablation of endometriosis are common.<sup>21</sup>

Adjuvant medical treatments in early stages of the disease or after surgical treatment have been advocated.<sup>22</sup> In recent years, an increasing number of research groups have focused on the angiogenic process in endometriosis in order to develop antiangiogenic treatment strategies. Antiangiogenic agents have been reported to inhibit the establishment of new endometriotic lesions, so these agents hold great promise for the future treatment of endometriosis.<sup>11,12</sup>

The main limitation of this study is that the color score grading of endometrioma vascularization by Doppler ultrasonography might be a subjective measure of blood flow. Pulsatility and resistance indices are more reliable markers of the resistance to blood flow. These could explain our findings that no significant difference was found in the median volume of the endometriomas between avascular or scantily vascularized endometriomas and moderately or highly vascularized endometriomas with regard to the amount of blood flow reported as color score. But, in smaller endometriomas low resistance to blood flow was found as measured by the low resistance and pulsatility indices. The other limitation of this study is the lack of assessment of angiogenesis by microvessel density in the histological specimens.

We have previously investigated the relation of pelvic pain and dense adhesions to Doppler ultrasound findings in patients with ovarian endometriomas involving some of the women recruited in the present study.<sup>23</sup> In that previous study, pelvic pain symptoms were not found to be related to endometrioma vascularization, but we observed an association between higher vascularized endometrioma and the presence of dense pelvic adhesions.

To our knowledge, no data comparing color Doppler ultrasound findings to endometriomal volume are available in the literature. Our study may be therefore unique since we have demonstrated a positive correlation between pulsed Doppler indices and endometriomal volume. These finding might be valuable for the clinical point of view; it can be speculated that smaller endometriomas are associated with lower values of Doppler indices, so lower vascular resistance. Therefore, patients with smaller endometriomas and lower resistance to blood flow might benefit from the antiangiogenic treatments.

In conclusion, our data indicate that ovarian endometriomal vascularization tends to be higher in smaller endometriomas. Transvaginal color and power Doppler as noninvasive and inexpensive methods, can be useful in developing adjuvant treatment plans, such as antiangiogenic drugs in patients with endometriomas, alone or as an adjuvant to surgical treatments. Further studies are needed to study the role of color and power Doppler ultrasound to detect patients with smaller endometriomas who might benefit from the antiangiogenic treatments.

## Endometriomal Duvar Kan Akımı Doppler Bulguları ile Endometriomal Hacim Arasındaki İlişkinin İncelenmesi

**AMAÇ:** Endometrioma duvarındaki Doppler ultrasonografi ölçümleri ile endometriomal hacim arasındaki ilişkinin incelenmesi.

**GEREÇ VE YÖNTEM:** Bu çalışmaya, overyan endometrioma nedeniyle laparoskopik cerrahi uygulanan toplam 58 hasta dahil edildi. Hastalar, ameliyat öncesinde hacim ve vaskülarizasyon açısından renkli ve pulse Doppler ultrasonografi ile değerlendirildi. Kan akımının varlığı, renk skalası ile ifade edilen miktarı ve Doppler indeksleri incelendi. Hastalar kan akımının yoğunluğuna göre; kan akımı olmayan ve az miktarda kan akımı olan hasta grubu (n=42) ile orta miktarda ve yüksek kan akımı olan hasta grubu (n=16) olarak ikiye ayrıldı. Endometriomal hacim değerleri bu 2 grup arasında kıyaslandı. Hacim ile Doppler indeksleri arasındaki ilişki Spearman'ın korrelasyon analizi ile değerlendirildi.  $p < 0.05$  istatistiksel olarak anlamlı kabul edildi.

**BULGULAR:** Endometriomal hacim açısından değerlendirildiğinde, hasta grupları arasında anlamlı bir farklılık saptanmadı ( $p=0.41$ ). Korrelasyon analizinde ise, endometriomal hacmin pulsatilite indeks (PI) ve rezistans indeks (RI) değerleriyle pozitif korelasyon gösterdiği (sırasıyla, Spearman's  $r = 0.335$  and  $r = 0.382$ ) ve bu korelasyonun hem PI hem de RI değerleri için istatistiksel olarak anlamlı olduğu gözlemlendi (sırasıyla,  $p = 0.026$  ve  $p = 0.011$ ).

**SONUÇ:** Endometriomal hacim ile renk skalası olarak ifade edilen kan akım miktarı arasında anlamlı bir ilişki gösterilemedi. Ancak, pulse Doppler indeks değerleriyle incelendiğinde artmış endometriomal hacmin, yüksek vasküler rezistansla, yani azalmış vaskülarizasyonla birlikte olduğu tespit edildi. Bu bulgu, düşük rezistansa sahip küçük endometriomalarda adjuvan tedavilerin geliştirilmesine yardımcı olabilir.

**Anahtar Kelimeler:** Endometrioma, Doppler, Hacim, Vaskülarizasyon

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