Original Article

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The Relationship between Uterine Endometrial Neovascularization and Pelvic Pain Intensity

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ABSTRACT

BACKGROUND AND OBJECTIVE: Pelvic pain is one of the most important symptoms of endometriosis. There is evidence that high blood flow to endometrioma is associated with more pelvic pain, but this has not been completely proven. Therefore, the present study was conducted to evaluate the relationship between uterine endometrial neovascularization and pelvic pain intensity.

METHODS: In this cross-sectional study, 76 patients with ovarian endometrioma (based on the final diagnostic pathology) were divided into two groups of mild/moderate pelvic pain (VAS lower than 66) and severe pelvic pain (VAS 66 to 100) in terms of pelvic pain intensity (using the visual analog scale). Patients underwent transvaginal doppler ultrasound prior to surgery, and endometrial neovascularization, as well as resistive index (RI) and pulsatility index (PI) in the artery of the endometrioma cyst wall were measured and were compared between two groups of mild/moderate pelvic pain and severe pelvic pain.

FINDINGS: Moderate and severe neovascularization (50%) in patients with severe pelvic pain was significantly higher than patients with mild/moderate pelvic pain (13%) (p=0.005). The mean RI in the group with severe pelvic pain (0.59±0.05) was lower than the mild/moderate group (0.66±0.06) (p<0.001). The mean PI in patients with pelvic pain (1.07±0.13) was lower than patients with mild/moderate pelvic pain (1.14±0.15) (p=0.03).

CONCLUSION: Severe neovascularization and low RI and PI indices in transvaginal doppler ultrasound of ovarian endometrioma indicate high activity of endometrium and is associated with severe pelvic pain in patients.

KEYWORDS: *Ovary, Endometriosis, Pelvic pain, Doppler ultrasound.*

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Introduction

The abnormal growth of the endometrial tissue of the uterus to the outside of the uterus is called endometriosis (1). The main symptoms of this disease include menstrual disorders, pelvic pain and pain during sexual contact and can cause infertility. Pelvic pain and dysmenorrhea are common symptoms that are commonly used in clinical diagnosis (2).

Despite extensive research on the association between pelvic pain and endometriosis, the exact mechanism of this relationship is still unclear. Pelvic pain is thought to be due to chronic inflammation in the peritoneal space, which causes dysmenorrhea. However, an endometriosis that is very deep, or the endometriosis of the ovary (endometrioma), often cause organic pain such as dyspareunia and chronic pelvic pain (3, 4). It seems that one of the processes involved in pathogenesis of endometriosis is angiogenesis (the formation of new blood vessels), which is especially related to the patient's activity and pain (5-7).

Generally, ultrasound is used as a diagnostic imaging tool in women suspected of endometriosis. In addition, color ultrasound and transvaginal power Doppler have also been used to evaluate the vascularity of the endometrioma of the ovaries (8, 9). Studies on the relationship between endometrial vascularization and pelvic pain are limited and contradictory results have been reported. The results of Alcazar et al. suggest that ovarian endometrial vascularization assessed by transvaginal color Doppler is higher in patients with pelvic pain compared to patients without symptoms (10).

In contrast, there was no relationship between pelvic pain symptoms and endometrial vascularization in another study (11). In previous studies, there are contradictory results about the association between vascularization and blood flow parameters of the ovarian endometrioma and the severity of the pain experienced by the patients. Since there has not been a study in Iran to investigate the relationship between pelvic pain and ovarian endometrial vascularization, in this study, the relationship between ovarian endometrial neovascularization in Doppler ultrasound and pelvic pain severity was investigated in patients undergoing diagnostic and therapeutic procedures due to pelvic pain and dysmenorrhea whose diagnosis of ovarian endometrial was confirmed by surgery and pathologic reports.

Methods

This cross-sectional study was approved by the ethics committee of Kermanshah University of Medical Sciences with the code IR.KUMS.REC.1394.28. After obtaining written consent for performing vaginal ultrasound, the study was conducted among women whose ovarian endometrioma was diagnosed by clinical records, ultrasonography and surgery, and referred to the radiology department of Imam Reza Hospital in Kermanshah from 2015 to 2016.

Patients in reproductive age and regular menstrual cycle (18 to 35 days) were included in the study. Patients with a history of hemorrhagic ovarian cyst, pelvic surgery, pelvic inflammatory disease, or treatment with any type of hormonal drug (oral contraceptives, LH releasing hormone, clomiphene, and gonadotropins) and other effective drugs within the past three month have been excluded from the study.

The convenience sampling method was used here and by considering 95% confidence level and 80% power, the ratio of women with ovarian endometrial vascularization in the group without pelvic pain and the group with pelvic pain was 0.6 and 0.87, respectively according to a previous study (10). A minimum sample size of 38 people was calculated for each group. All patients were clinically examined before ultrasound and their information was extracted from a checklist and then, patients underwent vaginal Doppler ultrasound.

Pelvic pain: The severity of pelvic pain was measured based on the Visual Analogue Scale (VAS). For this reason, patients were requested to determine their pelvic pain by specifying a point on a ruler (10 cm). The severity of the pain was a number between zero and 100; zero was the absence of pain and the 100 was the highest severity of pain experienced by the patient. Points less than 33 meant mild pain, 33to66 meant moderate pain and more than 66 meant severe pain (12).

Transvaginal Doppler Ultrasound: Vaginal Doppler Ultrasound was performed by Siemens G50 with a BE9-4 vaginal probe by a specialized radiology assistant and under the supervision of a radiologist.

Endometrial neovascularization is categorized based on the criteria previously used in similar researches (13):
No neovascularization: No color signals were detected in the cyst wall.
Mild neovascularization: Color signals were detected in less than 25% of the cyst wall.
Moderate neovascularization: Color signals were detected in 25 to 50% of the cyst wall.
Severe neovascularization: Color signals were detected in more than 50% of the cyst wall.

The collected variables: The demographic data of the patients (including age, body mass index, pregnancy history, abortion history), pelvic pain intensity (using VAS) and transvaginal color Doppler ultrasound data including neovascularization of endometrial mass (mild, moderate, and severe), resistive index (RI), pulsatility index (PI) and peak systolic velocity (PSV) in the endometrial cyst wall artery were entered into the data collection form.

Statistical analysis: To determine the distribution of quantitative data (normal or abnormal), the Kolmogorov-Smirnov test was performed first. If the distribution of quantitative data was normal, Leven's test and independent T-test were used for comparing the mean of quantitative variables in the two groups; otherwise, Mann-Whitney U test was used.

Chi-square test (if necessary, Fischer exact test) was used to compare the qualitative data between the two groups. In order to investigate the diagnostic value of RI and PI indices of endometrial cyst wall artery for the diagnosis of moderate and severe neovascularization of ovarian endometrial masses, ROC curve (receiver operating characteristics) was used. Using this curve, the best cut-off point was determined and then the sensitivity, characteristics, positive predictive value, negative predictive value and accuracy for the cut-off point were determined. In addition, the area below the ROC curve was also reported. Data were analyzed using SPSS 22 software and $p<0.05$ was considered significant.

Results

Of the 76 studied patients, 38(50%) patients had mild/moderate pelvic pain and 38(50%) patients had severe pelvic pain. The mean age in patients with mild/moderate and severe pain was 35.48±10.28 years and 35.68±9.7 years, respectively. There was no significant difference in age, body mass index, number of pregnancies and history of abortion among patients with mild/moderate and severe pelvic pain (Table 1). The mean RI in patients with severe pelvic pain (0.59±0.05) was significantly lower than those with mild/moderate pelvic pain (0.66±0.6). The two groups of patients with mild, moderate and severe pelvic pain differed in terms of neovascularization, RI and PI (Table 2).

Table 1. Comparison of age, number of pregnancies, history of abortion and BMI in two groups of patients with ovarian endometrioma diagnosis with mild/moderate and severe pelvic pain

Property	Total (76patients) N(%)	Pelvic pain N(%)		P-value
		Severe	Mild to moderate	
Parity				
0	36(47.4)	16(42.1)	20(52.6)	
1	25(32.9)	14(36.8)	11(28.9)	0.827
2	11(14.5)	6(15.8)	5(13.2)	
3	4(5.3)	2 (5.3)	2(5.3)	
Abortion history				
0	70(92.1)	35(92.1)	35(92.1)	0.549
1	5(6.6)	3(7.9)	2(5.3)	
2	1(1.3)	0(0)	1(2.6)	
BMI (kg/m^2) Mean±SD	23.48±3.71	23.9±4.48	23.07±2.75	0.522

The indices of resistance and arterial pulse were significantly lower in patients with severe pelvic pain than in patients with mild/moderate pain. However, PSV comparison did not show significant differences between the two groups. The RI index at the cut-off point of 0.63 had a sensitivity of 93.3% and a property of 43.3% in the diagnosis of moderate and severe ovarian endometrioma vascularization.

The PI index at the cut-off point of 1.1 had a sensitivity of 99% and a property of 40% in the diagnosis of moderate and severe ovarian endometrioma vascularization (Table 3).

Table 2. Comparison of neovascularization and indices measured in Doppler ultrasound in two groups of patients with ovarian endometrioma and mild/moderate and severe pelvic pain

Property	Pelvic pain		
	Severe N(%)	Mild to moderate N(%)	P–value
Neovascularization			
Absence	5(13.2)	9(23.7)	
Mild	14(36.8)	24(63.2)	0.005
Moderate	14(36.8)	5(13.2)	
Severe	5(13.2)	0	
Resistive index (Mean±SD)	0.59±0.05	0.66±0.06	<0.001
Pulsatility index (Mean±SD)	1.07±0.13	1.14±0.15	0.035
Peak systolic velocity (cm/sec) (Mean±SD)	27.16±2.37	26.54±1.4	0.17

Table 3. Sensitivity, specificity, positive and negative predictive values, accuracy and the area under the curve with 95% confidence intervals for RI and PI indices of ovarian endometrioma cyst wall in the diagnosis of moderate and severe neovascularization

Cut-off point		Sensitivity	Property	Positive predictive value	Negative predictive value	Accuracy	Area under the curve	P-value
RI	0.63	93.3 (87–99)	43.3(31–55)	45.1(33–57)	92(87–99)	60(48–71)	68(56–79)	0.047
PI	1.1	99 (97–100)	40(28–51)	45.4(33–57)	99(97–100)	60(48–71)	70(59–80)	0.03

Discussion

Based on the results, moderate and severe vascularization in patients with ovarian endometrioma with severe pelvic pain complaints was more than patients with mild or moderate pelvic pain. In addition, RI and PI indices of ovarian endometrioma were significantly lower in patients with severe pelvic pain than in patients with mild to moderate pelvic pain. Color Doppler ultrasound is a useful tool for ovarian endometrioma examination.

By examining the indices of blood vessel resistance to ovarian endometrioma, a non-invasive method can be used to examine the level of vascularity to the mass (14). The formation of new blood vessels is recognized as one of the pathogenic properties of endometriosis (15 and 16). Recent studies have shown that cytokines that are involved in angiogenesis, such as vascular endothelial growth factor (VEGF), interleukin-8, and leptin, are increased in peritoneal fluid in patients with ovarian endometrioma (17,18).

Color Doppler ultrasound is a non-invasive tool for evaluating vascular masses of the ovaries. Indices of RI and PI, which are slightly measurable, are used as indicators for determining the vascular resistance of blood arteries to the endometrioma masses. Increased vascularization is associated with a decrease in blood flow resistance measured by the RI and PI indices (19,20). In a study similar to our study, the authors found that ovarian endometrioma vascularization was more common in patients with pelvic pain than in asymptomatic patients. In addition, RI and PI indices were significantly lower in the group with mild pelvic complaints than the asymptomatic group, and there was no significant difference between the PSV values of the two groups (13). High vascularization to endometrioma mass indicates high activity of endometrioma and pain in patients is due to high activity and inflammation of endometrioma. In a study including two groups of patients with severe and mild pelvic endometrioma, it was shown that the frequency of vascularization masses in nodes with severe pain (87%) was significantly higher than those with mild pain (60%). In addition, the mean values of PI and RI in the severe pain group were significantly lower than those with mild pain.

In addition to these criteria, the density of small vessels (microvessel) was more severe in the group with severe pain than the other group (10). In the study of Somprasit et al., mean values of PI and RI in the uterine arteries were significantly lower in patients with chronic pelvic pain than in asymptomatic patients. Patients did not have endometrioma in this study. However, the provided evidence is consistent with the present study regarding the lower PI and RI values in the uterine artery of patients with pelvic pain (21).

Contrary to the mentioned results, the PI and RI values of endometrioma vascularization evaluated by transvaginal color Doppler ultrasound in the present

study were similar in patients with pelvic pain and without pelvic pain, and there was no difference between PI and RI in patients with and without pelvic pain (11). It is recommended that in future, studies with larger sample size be designed to determine the role of neovascularization in pelvic pain in patients with endometrioma.

Based on the results of this study, ovarian endometrioma neovascularization was more common in patients with severe pelvic pain than in patients with mild to moderate pelvic pain. In addition, RI and PI indices of endometrioma in patients with severe pelvic pain were less than those with mild to moderate pelvic pain symptoms. However, there was no significant difference between PSV index of endometrioma in patients with mild to moderate pelvic pain and severe pelvic pain.

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