

Evaluation of Changes in Doppler Sonographic indices of Uterine and Ovarian Arteries in Women with Endometriosis and Infertility

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ABSTRACT

Background: Endometriosis is an estrogen-dependent inflammatory disease with a wide range of symptoms such as chronic pelvic pain and infertility. The mechanism of infertility in women with endometriosis is unknown. Possible causes, including inflammation and the effect of cytokines, genetic cause, decreased blood flow and changes in the vascular indices of the ovaries play an important role in infertility in these women.

Methods: Participants this cross-sectional study was conducted at the Department of Radiology, Hazrat Rasool Akram Hospital in Tehran, Iran, in from November 2018 to August 2019. The patients were given a questionnaire including demographic information and menstrual status. A digital transvaginal sonography scanner was used for assess the uterine and adnexa, and color doppler and spectral doppler ultrasonography was used to determine the RI and PI of uterine arteries and bilateral ovarian parenchyma.

Result: The study was conducted on 155 non pregnant-women and diagnosing with endometriosis. The mean age of the women was 32.4(SD=6.2) years with a range of 18-50 years. Among married people, 44 (37.3%) were infertile and 72 (61%) had no infertility. 129 (84.3%) of the participants had endometrioma cyst. 24 patients (15.7%) had DIE findings without endometrioma cyst. 142 patients had adnexal adhesion. In spectral doppler evaluation the mean RI of the right ovary was higher in infertile patients (0.61, SD = 0.19) than in fertile patients (0.54, SD = 0.13) and single females (0.58, SD = 0.17), (P = 0.06). Also mean PI of right ovary in infertile patients (1.2, SD = 0.86) significantly more than fertile (0.82, SD = 0.4) and single patients (1, SD = 0.87), (P = 0.006). The mean RI and PI of the right ovary were significantly higher in those with severe disease and in patients with severe adnexal adhesion.

Conclusion: In our study, which confirms the above findings, the mean PI and RI of the right ovary was significantly increased in people with infertility compared to fertile women. In women with primary infertility as a subgroup of infertility, PI, RI of the right ovary was higher than the others, which indicates increased vascular resistance and decreased blood flow in the right ovary. However, the vascular indices of the uterine and left ovaries did not differ significantly between infertile and non-infertile individuals. There was no significant difference between the doppler indices in the three different phases of menstruation in comparison to infertile and fertile patients. In our study, the difference between doppler indices was observed only in the right ovary which can be due to functional differences in the ovaries

Keywords: Endometriosis, Infertility, Doppler ultrasonography, Resistance Index.

INTRODUCTION

Endometriosis is an estrogen-dependent inflammatory disease characterized by the presence of ectopic endometrial tissue¹. Tissues typically occur in the pelvis but have also been seen in the upper abdomen, diaphragm, peripheral and axial skeleton, lungs, and central nervous system². The most common sites of endometriosis are the ovaries, anterior/posterior cul-de-sac, uterus, broad ligaments and uterosacral ligaments, fallopian tubes, sigmoid colon and appendix³. Because the growth of the endometrial tissue is dependent on ovarian produced steroids, it is a disease that most severely affects women in reproductive ages, 25–35 year.

Patients can present with a wide range of symptoms such as dyspareunia, dysmenorrhea, bladder/bowel symptoms, and chronic pelvic pain and infertility⁴. The prevalence of endometriosis increases dramatically to as high as 25%–50% in women with infertility and 30–50% of women with endometriosis have infertility⁵.

The mechanism of infertility in women with endometriosis is unknown. There appears to be a strong link between inflammation and endometriosis, and many

investigators have proposed that alterations in the inflammatory cascade may be the underlying cause of infertility in women with endometriosis⁶. There is a clear association of cytokines in the peritoneal fluid and endometriosis, but it is not clear if this association is a cause or effect of the infertility that is associated with endometriosis⁷.

Studies show that there is an increasing number of peritoneal macrophages in women with endometriosis who have access to the female reproductive tract through the oocytes. However, peritoneal macrophages isolated from women with endometriosis show more phagocytosis in vitro. These results suggest that, if peritoneal macrophages from women with endometriosis enter the reproductive tract through the oocyte, they may affect fertilization by phagocytizing sperm⁸.

A limited number of genes were found to be differentially expressed in infertile women with endometriosis compared to fertile controls⁹. Despite finding possible causes to justify the cause of infertility in women with endometriosis, its underlying cause remains under investigation and needs further study.

Also some articles have suggested that changes in angiogenesis, decreased blood flow and changes in the vascular indices of the ovaries play an important role in infertility in these women. In such a way that changes in ovarian blood flow are considered as a predictor of IVF outcome in infertile women^{10,11}.

Ultrasonographic examination is the most commonly used modality for the assessment of patients with suspected endometriosis, and its efficiency in the detection of ovarian endometriomas is well established. The use of Color Doppler as a diagnostic tool in patients with endometriomas has been previously described, as it allows for the demonstration of the dynamic vascular changes^{12,13}.

This study was designed to evaluate uterine and ovarian artery blood flow indices including resistance indices (RI) and pulsatility indices (PI) by transvaginal Doppler sonography in patients with endometriosis and evaluation of changes in uterine and ovarian blood flow in a possible explanation of the cause of infertility, in patients with infertility.

METHOD

Participants this cross-sectional study was conducted at the Department of Radiology, Hazrat Rasool Akram Hospital in Tehran, Iran, in from November 2018 to August 2019. The study protocol was approved by the local institutional review board and written consent was obtained from the subjects for this prospective study. Our inclusion criteria were women with a previous diagnosis of endometriosis by laparoscopy or transvaginal ultrasound. They were referred to the current study all subjects had to go through a process which included an examination of their medical history, complete general checkup including gynecological examination and preliminary transvaginal ultrasound. Exclusion criteria included other causes of infertility such as Müllerian disorders, active or previous pelvic inflammatory disease, history of ectopic pregnancy, poly cystic ovary syndrome, cervical disorders including active or tumor infection, ovarian cysts other than endometrioma, immunological disease, infertility in couples and patients who were undergoing hormone therapy for ovulation due to infertility.

The patients were given a questionnaire including demographic information, marital status, questions about infertility and its type and duration, history of delivery, surgical history, menstrual cycle day they had ultrasound, presence and severity of dysmenorrhea, dyspareunia, history of analgesics consumption in menstruation, monthly cycle regularity, the amount of menstrual bleeding, duration of each cycle, was completed. Women were stratified into 3 groups: 1) infertile women; 2) fertile women; 3) single women.

However, standard for diagnosing pelvic endometriosis is laparoscopy and direct observation of endometrial tissue outside the uterine cavity, But according to studies, if a transvaginal or transrectal ultrasound is performed by a skilled radiologist, the value of this diagnose is acceptable for the diagnosis of endometriosis¹⁴.

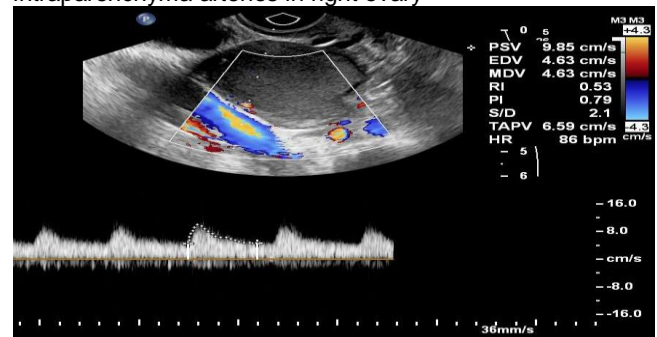
These patients were then examined by a qualified radiologist (with experience in 20,000 women with endometriosis) without knowing the type and severity of the disease and patient fertility status. Ultrasound was performed transvaginal in married women and transrectal in virgin women. Ultrasound was performed according to the systematic protocol introduced by the International Deep Endometriosis Analysis (IDEA) Consensus Group.

A digital sonography scanner (using a Philips affinity 70 ultrasound, curved vaginal probe 3-10 MHz) was used for assess the uterine and ovaries, and color Doppler ultrasound and spectral Doppler ultrasonography was used to determine the uterine and ovaries blood flow indices.

Gray scale ultrasound parameters included uterine and adnexal examination, search for deep implantation endometriosis, sliding sign and evaluation of posterior culdesac, uterosacral ligaments, torus uterinus, walls of rectum and vagina and other associated diseases including uterine fibroids, endometrial polyps, and adenomyosis. Endometriosis severity was assessed in participants according to ultrasound criteria including presence or absence of endometrioma, size of endometrioma, DIE, adnexal and tubal adhesions, posterior cul-de-sac obliteration, peritoneal and sub-peritoneal extension including uterosacral ligament, torus uterinus, rectum and posterior vagina, on the basis of Revised American Fertility Society criteria. Patients according to severity of endometriosis classified into 4 groups: minimal, mild, moderate, sever.

In addition, all patients underwent color Doppler ultrasound and spectral Doppler ultrasonography to determine the Resistance Index (RI) (peak systolic velocity – end diastolic velocity/ peak systolic velocity) and Pulsatility Index (PI) (maximum velocity- minimum velocity/mean velocity) of bilateral uterine arteries, and the RI and PI of both ovarian parenchyma (figure 1).

Figure 1: Spectral Doppler to obtain RI and PI of intraparenchyma arteries in right ovary



By using the Color Doppler technique, the vessels inside the ovarian stroma and the uterine artery on both sides (as a branch of the anterior trunk of the internal iliac artery) were discovered, then by placing a doppler gate on these vessels, without correct angle, and using pulsed doppler, blood flow waves were obtained. 50HZ wall filter was used to record the

Figure 2: Color Doppler image of right ovary with Endometrioma

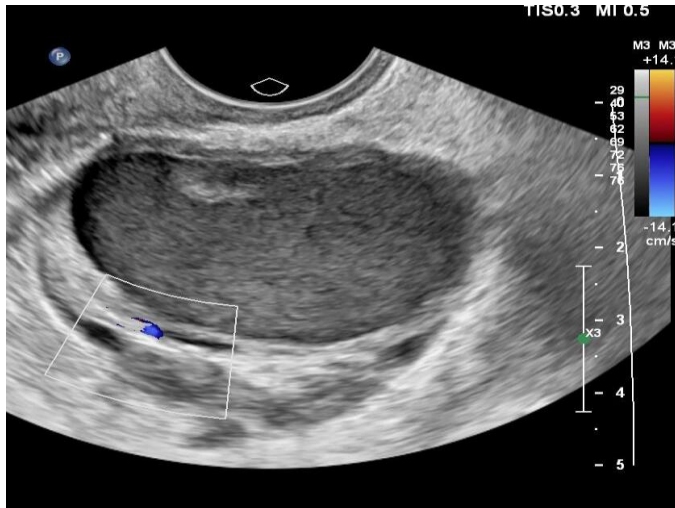
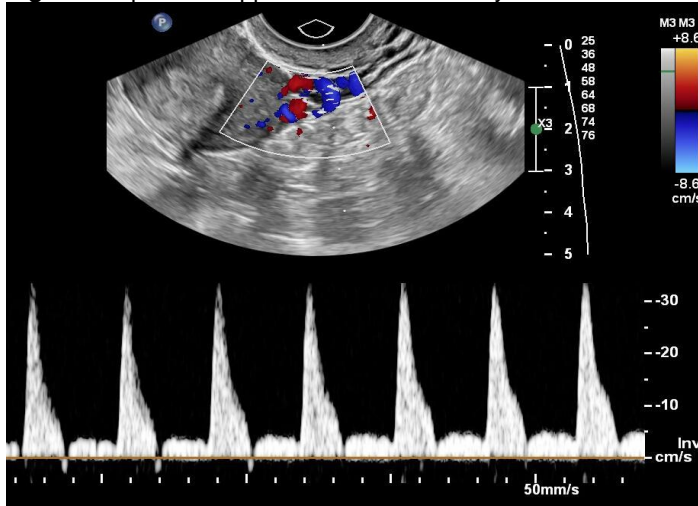


Figure 3: Spectral Doppler of left uterine artery



The data obtained from the ultrasound of the patients as well as the information extracted from the questionnaire form were recorded in a special form designed for this purpose.

Data are presented as mean and SD, and range of data were given where appropriate. The Kolmogorov-Smirnov test was used to compare data distribution of continuous variables. The Student's *t*- or Mann-Whitney *U*-tests were used to compare continuous variables. The χ^2 test was used to compare categorical variables, using the Kendall Tau-b test in cases of ordinal variables such as pelvic adhesions or RAS endometriosis stage. A *P* value ≤ 0.05 was considered as statistically significant.

RESULT

The study was conducted on 155 non pregnant-women and diagnosing with adenomyosis. The mean age of the women was 32.4 ± 6.2 years with a range of 18-50 years. Of the participants, 37 (24%) were virgins, 115 (74%) were married, and 3 (1.9%) were divorced. Among married

people, 44 (37.3%) were infertile that 22 of them had primary infertility, and 72 (61%) had no infertility. (Table-1). Table-1 shows other demographic and menstrual information.

Sonography: In the ultrasound examination, 153 patients underwent ultrasound examination and 2 patients according to exclusion criteria due to previous ectopic pregnancy and PID were excluded.

129 (84.3%) of the participants had endometrioma cyst and 24 patients (15.7%) had DIE findings without endometrioma cyst. Distribution of adnexal adhesion, disease severity and others associated diseases present at Table-1.

Doppler Ultrasound: Table-2 shows the mean RI and PI of the uterine arteries and ovaries in all patients. Table-3 also presents the mean RI and PI of the uterine arteries and ovaries in infertile patients.

The mean RI of the right ovary was higher in infertile patients (0.61, SD = 0.19) than in fertile patients (0.54, SD = 0.13) and single females (0.58, SD = 0.17), (*P* = 0.06).

Mean PI of right ovary in infertile patients (1.2, SD = 0.86) significantly more than fertile (0.82, SD = 0.4) and single patients (1, SD = 0.87), (*P* = 0.006).

Compared between the two groups of infertile and fertile, other Doppler indices including RI, PI of left ovary and uterine arteries did not show significant difference (*P* > 0.1). (Table-3).

These findings were confirmed when the study was performed exclusively in patients with primary infertility (*N* = 22). However, PI and RI of the right ovary were significantly higher in those with primary infertility (PI: 1.4, SD = 0.99 / RI: 0.65, SD = 0.21) than in the other women (PI: 0.94, SD = 0.62/ RI: 0.56, SD = 0.15). (Table-4).

Comparisons between the groups with primary and secondary infertility, the findings show that the changes in the Doppler Indices of the right ovary are seen only in primary infertility, and these indices as well as other indices in secondary infertility, it does not show significant difference.

Examination of Doppler Indices in women with regular menstruation (*N* = 120) were compared separately in 3 uterine phases (1-7 day: menstruation phase, 7-14 day: proliferative phase, 15-30 day: secretory phase). The only Doppler index that had a significant difference in these three phases was right uterine arterial RI. The right uterine artery in the proliferative phase had a higher average RI (0.87, SD = 0.09) than the other phases (phas1: 0.8, SD = 0.14 /phas3:0.82, SD=0.11) (*p* = 0.04). The mean of other indices of uterine and ovarian arteries were not significantly different in the three menstrual phases.

Evaluation the Doppler Indices in the three phases of menstruation in the infertile and regular-cycle patients that included a total of 31 patients, there was no significant difference between the Doppler indices in the 3 different phases. Also, there was no significant difference between the Doppler indices in the three different phases of menstruation in comparison to infertile and non-infertile patients (*p*>0.1).

In the present study, compared to patients with short-term infertility (less than 24 months) (*N*=9) and prolonged infertility (more than 24 months) (*N*=31), right ovarian RI in women with long-term infertility (0.64, SD = 0.19), was

more than in patients with short-term infertility (0.51, SD = 0.13) (P = 0.07). Also, the PI index of right ovary in patients with prolonged infertility (1.3, SD = 0.8) was higher than that of right ovarian PI in short term infertility (0.79, SD = 0.45) (P = 0.09).

In the study of Doppler indices in patients with endometriosis regardless of their infertility status, the following results were obtained: Doppler indices were not significantly different in those with endometrioma compared to those without endometrioma cysts, but the mean RI and PI of the right ovary was significantly increased in those with severe adnexal adhesion. (Mean RI of the right ovary in patients with mild, moderate, and severe adhesions: 0.53, SD=0.15/ 0.55, SD=0.14/ 0.66, SD=0.19 (p=0.001) and mean PI of the right ovary in patients with mild, moderate, and severe adhesions: 0.86, SD=0.7/ 0.92, SD=0.62/ 1.3, SD=0.8 (p=0.006))

The mean RI and PI of the right ovary were significantly higher in those with severe disease (Table-5), whereas the RI of the right ovary in patients with severe disease (0.61, SD = 0.17) was higher than those with

minimal, mild or moderate disease (0.54, SD = 0.15) (P = 0.006).

Right ovarian PI in patients with severe disease (1.1, SD = 0.73) was higher than right ovarian PI in people with minimal, mild or moderate disease (0.89, SD = 0.66) (P = 0.02).

Compared with the severity of the disease and the Doppler indices, the PI of the left uterine artery was also higher in those with more severe disease (2.4, SD = 0.84) than in those with minimal, mild or moderate disease (2, SD = 0.83) (P = 0.06) (Table-5)

In the present study, the Doppler indices were not correlated with the severity of dysmenorrhea.

Comparison of the Doppler Indices in those with uterine fibroids showed that the RI of the left uterine artery was increased in those with fibroids (3, SD = 1.3) compared to those without fibroids (0.85, SD = 0.12) (P = 0.08).

Comparison of the Doppler indices in patients with adenomyosis showed RI and PI of the right ovary in patients with adenomyosis (PI: 1.2, SD = 0.82/ RI: 0.63, SD = 0.19) compared to the others (PI: 0.92, SD = 0.63 / RI: 0.55, SD = 0.15) was increased (P = 0.01) (P = 0.01).

Table 1. Demographics and sonographic Variable

Variable	153Mean (SD)-range	%n	
Age (mean)	32.4(SD=6.2) 18-50		
Weight	63.2(SD=10.2) 41-103		
Mean age of Menarche	13(9-18)		
Virgin			37(24%)
Married			115(74%)
divorced			3(1.9%)
infertility			44(37.3%)
Regular cycle			120(77.9%)
Irregular cycle			33(22.1%)
Dysmenorrhea			150(97.4%)
Dyspareunia			75(65.2%)
Severity of Dysmenorrhea		Very sever	29(19.2%)
		Sever	59(39.1%)
		Moderate	43(28.5%)
		mild	16(10.6%)
Responsible to analgesics consumption			117(76.4%)
endometrial cyst			129(84.3%)
bilateral endometrioma			79(60.8)
Severity of endometriosis By sonography		sever	73(47.1%)
		Moderate	58(37.9%)
		Mild	11(6.5%)
		minimal	12(7.8%)
Adnexal adhesion		sever	39(27.4%)
		moderate	62(43.6%)
		mild	41(28.9%)
Adenomyosis			46(30.3%)
Fibroid			39(25.5%)
Polyp			16(10.5%)

Table 2- Doppler indices in total patient (N=153)

	Mean	Std. Deviation
cumulative Ovarian RI	1.9193	6.65294
RTOvaryRI	0.5746	0.16397
LTovaryRI	1.3446	6.66293
cumulative Ovarian PI	2.7992	7.00198
RTOvaryPI	1.0104	0.70512
LTovaryPI	1.7888	6.96474
cumulative Uterus RI	2.2434	6.73829
RTUterusRI	0.8427	0.11187
LTuterusRI	1.4007	6.72361
cumulative Uterus PI	4.3574	1.53918
RTUterusPI	2.1294	0.84023
LTuterusPI	2.2280	0.98698

Table 3- Differences and comparison in blood flow measurements doppler Indices in married women (N=116) in comparison with fertile infertile

Variable	Infertile married female (N=44) Std. Deviation ± Mean	Fertile married female (N=72) Std. Deviation ± Mean	P- value
cumulative Ovarian RI	1.2343 ± 0.31820	7.11676 ± 1.9288	0.61
RTOvaryRI	0.6143 ± 0.19330	0.13372 ± 0.5428	0.06
LTovaryRI	0.6200 ± 0.17762	1.3860 ± 7.12572	0.60
cumulative Ovarian PI	2.4600 ± 1.70679	3.3629 ± 10.08115	0.63
RTOvaryPI	1.2373 ± 0.85998	0.8285 ± 0.40295	0.006
LTovaryPI	1.2227 ± 0.97308	2.5344 ± 10.10109	0.45
cumulative Uterus RI	1.6332 ± 0.26520	2.8968 ± 9.81464	0.53
RTUterusRI	0.8214 ± 0.11693	0.8617 ± 0.10722	0.13
LTuterusRI	0.8118 ± 0.19812	2.0351 ± 9.79700	0.54
cumulative Uterus PI	4.0711 ± 1.50718	4.5528 ± 1.64209	0.26
RTUterusPI	2.0773 ± 0.87965	2.1988 ± 0.86958	0.62
LTuterusPI	1.9939 ± 0.87750	2.3540 ± 1.10588	0.15

Table 4- Differences and comparison in blood flow measurements doppler Indices in married women (N=153) in comparison with primary infertile - Non primary Infertile

	Non primary Infertile(N=131) Mean ± Std. Deviation	Primary Infertile (N=22) Mean ± Std. Deviation	P value
cumulative Ovarian RI	2.0283 ± 7.18692	1.2700 ± 0.32388	0.62
RTOvaryRI	0.5614 ± 0.15220	0.6536 ± 0.20873	0.01
LTovaryRI	1.4669 ± 7.19703	0.6164 ± 0.18461	0.58
cumulative Ovarian PI	2.8040 ± 7.52657	2.7705 ± 2.04461	0.98
RTOvaryPI	0.9382 ± 0.62117	1.4405 ± 0.99187	0.002
LTovaryPI	1.8659 ± 7.51295	1.3300 ± 1.19445	0.74
cumulative Uterus RI	2.3481 ± 7.28048	1.6200 ± 0.19688	0.64
RTUterusRI	0.8449 ± 0.11339	0.8295 ± 0.10381	0.55
LTuterusRI	1.5032 ± 7.26508	0.7905 ± 0.12234	0.64
cumulative Uterus PI	4.3422 ± 1.52470	4.4477 ± 1.65722	0.76
RTUterusPI	2.1187 ± 0.81676	2.1932 ± 0.98758	0.70
LTuterusPI	2.2235 ± 0.98954	2.2545 ± 0.99414	0.89

Table 5- Differences and comparison in blood flow measurements doppler Indices (N=153) in comparison with Severity of disease

	Severe disease (N=73) Mean ± Std. Deviation	Mild or moderate disease (N=80) Mean ± Std. Deviation	p
cumulative Ovarian RI	2.0545 ± 7.05409	1.7959 ± 6.30700	0.81
RTOvaryRI	0.6127 ± 0.16733	0.5399 ± 0.15378	0.006
LTovaryRI	1.4418 ± 7.06951	1.2560 ± 6.31278	0.86
cumulative Ovarian PI	3.2525 ± 8.23990	2.3856 ± 5.66470	0.44
RTOvaryPI	1.1444 ± 0.73498	0.8881 ± 0.65770	0.02
LTovaryPI	2.1081 ± 8.21220	1.4975 ± 5.62907	0.59
cumulative Uterus RI	1.7144 ± 0.25549	2.7261 ± 9.31701	0.35
RTUterusRI	0.8553 ± 0.11897	0.8311 ± 0.10438	0.18
LTuterusRI	0.8590 ± 0.17469	1.8950 ± 9.29700	0.34
cumulative Uterus PI	4.6156 ± 1.61290	4.1218 ± 1.43855	0.04
RTUterusPI	2.2304 ± 0.84069	2.0373 ± 0.83438	0.15
LTuterusPI	2.3852 ± 1.00759	2.0845 ± 0.95147	0.06

DISCUSSION

The purpose of this study was to evaluate the Spectral Doppler indices in women with endometriosis and to investigate the relationship of these indices to a possible predictor of infertility in these patients.

The underlying cause of infertility in people with endometriosis has not been clearly established. The cause appears to be multifactorial and includes inflammatory changes in the pelvic cavity, molecular changes, and changes in gene expression and angiogenesis changes^{6, 9, 10}.

Evaluation of changes in ovarian and uterine blood flow on color doppler ultrasound, which shows the condition of vascularity and their blood supply, in people with endometriosis and infertility have been considered in recent studies and different results have been obtained.

For example, a study conducted in 2000 showed that RI and PI of ovarian arteries increased significantly in people with endometrioma cyst (12), and several other studies have shown that decreased ovarian blood flow includes decreased PSV (peak systolic volume) and decreased three-dimensional color Doppler ultrasound indices, including VI (vascularity index), FI (flow index) are seen in people with infertility, and even used the rate of these indices to determine IVF outcomes (10–12, 15). Because reducing vascularity and reducing ovarian blood flow leads to reduced ovarian function and reduced ovarian reservation and infertility as a result.

Another study (JUNJUN QIU, 2012) shows that an increase in ovarian RI in people with endometriosis is associated with interstitial fibrosis and micro vascular injury and decreased ovarian function (16).

However, the study of Doppler indices in people with infertility and endometriosis in Iranian society has not been performed. Our study with a good sample size, examined the two-dimensional Doppler indices of uterine arteries in addition to ovarian vessels, and in general and separately for the menstrual phases. This study also compared people with endometriosis and infertility and people with endometriosis without infertility to use the results to predict infertility in people with endometriosis. While in previous studies this comparison has not been made.

In our study, which confirms the above findings, the mean PI of the right ovary was significantly increased in people with infertility compared to non-infertile people, and also the RI of the right ovary was higher in the group with infertility than other patients.

These findings were also confirmed in people with primary infertility as a subgroup of infertility, PI, RI of the right ovarian artery was higher than the others, which indicates increased vascular resistance and decreased blood flow in the right ovary of infertile patients. However, the vascular indices of the uterine and left ovaries did not differ significantly between infertile and non-infertile individuals.

There was no significant difference between the Doppler indices in the three different phases of menstruation in comparison to infertile and fertile patients.

We also found that the mean RI and PI of the right ovary were higher on those with more severe disease. Which suggests that in individuals with a more severe

diagnosis by ultrasound, the risk of vascular changes in the ovary and, consequently, the likelihood of infertility is higher

However, in some studies different findings have been obtained (17–20), for example in the study of Akmal Elmanzy there was no significant difference between Color Doppler indices in three-dimensional and two-dimensional ultrasound between people with infertility due to endometrioma and people with infertility due to male factors or unexplained infertility (18). However, in this study, these findings were obtained for the group with endometrioma cysts and no study was performed on patients with DIE.

While in endometriosis disease manifestations, the presence of DIE implants seems to be more important than the presence of endometrioma cysts, and as shown in our study, changes in Doppler indices have not been associated with the presence or absence of endometrioma cysts, but have been associated with the severity of the disease and the severity of pelvic adhesions.

In our study, the difference between Doppler indices was observed only in the right ovary, which can be caused by functional differences in the ovaries. Several studies have shown that right ovarian function plays a more important role in ovulation and reproductive status. For example, a study by Potashnik et al. Showed that in multiple menstrual cycles, ovulation in the right ovary is significantly higher than in the left ovary (22). Fukuda et al.'s study of 1,057 cycles of 856 fertile women and 1,033 cycles of 258 infertile women also showed that in both fertile and infertile women, ovulation of the right ovary and even the pregnancy rate due to right ovary ovulation is higher than the left ovary (22).

The results of our study were statistically significant, but it seems for the effect of findings and for the possibility of using Doppler indices to predict the probability of infertility in people with endometriosis, more research is needed that using newer tools, including 3D Doppler color ultrasound.

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