Alterations of Uterine Blood Flow During the Follicular Phase in Patients With Recurrent Implantation Failure: A Doppler Ultrasonographic Study

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Abstract
Objectives: The dynamics of blood flow in the endometrium plays a crucial role during the implantation process. This study aimed to assess the uterine perfusion during the follicular phase in patients with a history of recurrent implantation failure (RIF) and healthy fertile women using the transvaginal ultrasound color Doppler method.
Materials and Methods: To this end, 50 patients with RIF and 50 age-matched healthy fertile women were recruited in this case-control study. The transvaginal color Doppler ultrasonography was used to evaluate the pulsatility index (PI) and resistance index (RI) of the uterine, arcuate, and sub-endometrial arteries during the follicular phase in both groups.
Results: The RI and PI of both right and left uterine arteries were higher in the RIF group compared to the fertile women (P<0.05). Our results showed that the PI and RI of sub-endometrial blood flow and the RI of arcuate arteries were substantially higher in the group with a history of RIF in comparison with the control group. However, the PI of arcuate arteries was not significantly different between the groups.
Conclusions: Adequate uterine perfusion and sub-endometrial blood flow are necessary to achieve successful implantation and pregnancy since our results demonstrated the higher resistance of uterine and sub-endometrial arteries in patients with a history of RIF. Thus, the assessments of uterine perfusion indices during the follicular phase could be used as a non-invasive method in the evaluation of patients with RIF.
Keywords: Transvaginal Doppler ultrasound, Implantation failure, Uterine blood flow

Introduction

The endometrium plays a crucial role during the implantation and the subsequent supplying of nutrients to guarantee a successful pregnancy (1). Recurrent implantation failure (RIF) is among the best-defined reproductive defects referring to the pregnancy failure after the transfers of 1-2 embryos of high quality during at least three consecutive *in vitro* fertilization (IVF) cycles (2). Although there is a controversy regarding the precise definition of RIF, it can be defined by an unsuccessful transfer of 10 embryos in the cleavage stage or four blastocysts. One of the factors that can adversely affect the implantation is transferring the embryo to a non-receptive or dysfunctional endometrium (3,4).

It has been reported that blood flow velocity in the uterine artery has an increasing trend between the early follicular phase and the time of implantation (5). Since the uterine perfusion regulates endometrium receptivity, impaired uterine blood supply may be involved in RIF in infertile patients undergoing the IVF procedure (6,7).

In this regard, it has been demonstrated that an elevated pulsatility index (PI) of the uterine artery in women is related to the low chance of pregnancy in IVF/ICSI cycles (8, 9). In addition, Habara et al (10) reported an association between the high impedance of uterine perfusion and recurrent pregnancy loss (RPL).

However, most of the studies on patients with RIF have investigated uterine perfusion during the luteal phase, and there is little information regarding the follicular phase. To identify the possible association between uterine perfusion during the follicular phase and implantation failure, the current study evaluated the blood flow of the uterine artery in the follicular phase of patients with a history of RIF and healthy fertile women using Doppler blood flow indexes.

Materials and Methods

Fifty women with a history of RIF and 50 age-matched normal fertile women were recruited in the present research. All women attended the Infertility Center of

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Key Messages

▶ The uterine blood flow of RIF patients is significantly altered in the follicular phase.

Al-Zahra Hospital of Tabriz, Iran. RIF was defined as a failure of pregnancy after the transfers of 1-2 high-quality embryo(s) during at least three consecutive IVF cycles. The decision about the type of protocol or doses of drugs was made by a gynecologist according to the ovarian response to the doses of the applied drugs during previous cycles. However, 150-400 IU/day of gonadotropins in combination with human menopausal gonadotropin (75-150 IU) were generally administered for 10-12 days during the gonadotropin-releasing hormone antagonist protocol. When the follicles reached a mean size of >17 mm, ovulation was induced by 5000 or 10 000 IU doses of human chorionic gonadotropin. After 36 hours, the cumulus-oocyte complexes were retrieved by the transvaginal ultrasound-guided puncture of the follicles. After checking the maturity of the denuded oocytes, metaphase II oocytes underwent the ICSI procedure. After the development of embryos, high-quality blastocysts (1-2 cases) based on Veeck and Zaninovic's criteria were selected for transfer (11). In this regard, the early formation of an expanded and eccentric cavity with a distinct layer of trophectoderm and inner cell mass was considered for the characterization of a good quality blastocyst. Women of the control group were ovulating females who experienced regular menstrual cycles and had no history of pregnancy failure. The inclusion criteria for all women were having 20-40 years of age with a body mass index of <30 kg/m², no history of alcohol consumption or special diet, and being a nonsmoker. The patients with diabetes, dyslipidemia, uterine anomalies, uterine myomas, uterine adenomyosis, disorders of ovulation (including prolonged oligomenorrhea, premature ovarian failure, and hypothalamic amenorrhea), autoimmune diseases, hypertension, and coagulation disorders were excluded from the study. The participants were enrolled in the study after obtaining a signed informed consent form. All patients underwent Doppler transvaginal ultrasound to assess PI and RI of the right and left uterine, arcuate uterine, and sub-endometrial arteries.

Transvaginal Doppler Ultrasound
Transvaginal color Doppler ultrasonography was performed for both RIF patients and control women using the Samsung WS-80 ultrasound system (Samsung Medison Company Ltd, Seoul, South Korea) equipped with a 4- to 8-MHz transvaginal probe. The calculation software was used for measuring the PI and RI of the uterine arteries. The PI and RI were calculated from peak-systolic velocity (PSV) and end-diastolic velocity (EDV) using the following equations:

PI= PSV- EDV/mean maximum flow velocity, RI= PSV-EDV/ PSV

The alterations of uterine blood flow in the follicular phase were investigated for all participants.

Statistical Analysis
Due to time and financial constraints, the convenience sampling method was applied for the sample selection, and the sample size was calculated using the PASS 11.0 software (PASS, Kaysville, UT, USA). In this regard, beta and type I error were set to 0.20 (80% power) and 0. 05, respectively. Data are expressed as the mean ± standard deviation (SD). After analyzing the data distribution by Kolmogorov-Smirnov test, variables were evaluated by the Student's t test or the Mann-Whitney U test for data with a normal distribution or skewed ones, respectively. A P value lower than 0.05 was considered statistically significant, and all statistical analyses were performed using SPSS software, version 16.0 (Chicago, IL, USA).

Results
This study recruited 50 RIF and 50 healthy women. The mean age of women in the RIF and control groups was 32.72 ± 5.46 and 31.84 ± 4.21 years, respectively (P = 0.342). Furthermore, the groups did not differ regarding the day of the follicular phase in which the ultrasonography was performed (4.87 ± 4.14 in RIF women vs. 7.14 ± 3.84 in the control group, P=0.103), and the mean duration of infertility was 8.26 ± 4.60 years in the RIF group.

Embryo factors such as sperm and oocyte quality, chromosomal anomalies in parents, and the number and developmental stage of embryos can play a role in RIF. Furthermore, according to the guidelines of our fertility center, the number and developmental stage of embryos were approximately the same in most cases. Moreover, patients with uterine anomalies and autoimmune diseases were excluded from our study. However, this study did not assess all the possible reasons for RIF. Our results demonstrated that the total number of embryo transfer cycles and the total number of transferred embryos were 2.96 ± 1.24 and 10.36 ± 8.21, respectively.

Table 1 presents the means (±SD) of PI and RI for uterine, arcuate, and sub-endometrial arteries in RIF patients and healthy women. The results of Doppler ultrasound examinations showed that the PI and RI of the right and left uterine arteries significantly increased in the RIF group in comparison with the control group. Moreover, the indices of pulsatility and resistance for sub-endometrial uterine arteries significantly elevated in women with a history of RIF compared to the control group (P<0.001). The Doppler examination of the right and left uterine arteries and endometrial arteries in RIF women are shown in Figure 1, reflecting the increased resistance to blood flow while decreased perfusion in the uterine arteries. Based on our results, the RI of arcuate arteries

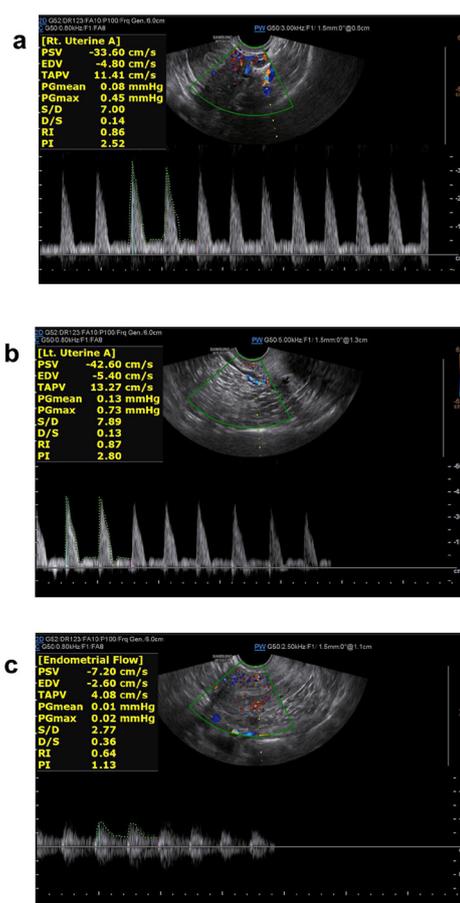**Table 1**. Mean ± SD of PI and RI for Uterine, Arcuate, and Sub-endometrial Arteries in RIF and Control Groups

Uterine Arteries	Study Group (n=50)	Control Group (n=50)	P Value
	Mean (±SD)		
Right uterine arteries			
PI	2.96± 0.61	1.87± 0.55	<0.001*
RI	0.92± 0.10	0.73± 0.14	<0.001*
Left uterine arteries			
PI	3.05± 0.69	1.88± 0.40	<0.001*
RI	0.89± 0.06	0.74± 0.14	<0.001*
Arcuate arteries			
PI	1.87± 0.61	1.72± 0.65	0.229
RI	0.74± 0.12	0.65± 0.17	0.005*
Sub-endometrial arteries			
PI	1.478± 0.87	0.71± 0.25	0.001*
RI	0.67± 0.20	0.53± 0.06	<0.001*

Figure 1. Doppler Examination of (a) Right Uterine Arteries, (b) Left Uterine Arteries, and (c) Endometrial Arteries in RIF Woman. *Note*. PI: Pulsatility index; RI: Resistance index. PI and RI were computed using equations PI = (PSV-EDV)/TAPV and RI = (PSV-EDV)/PSV. RIF: Recurrent implantation failure; Rt. uterine: Right uterine arteries; Lt. uterine: Left uterine arteries; PSV: Peak systolic velocity; EDV: End diastolic velocity; TAPV: Timed averaged peak velocity; PGmean: Mean pressure gradient; PGmax: Maximum pressure gradient; S/D: Systolic/diastolic ratio.

was significantly higher in the study group compared to the fertile women. However, the PI of arcuate arteries did not represent a statistically significant difference between the groups ($P = 0.229$).

Discussion

The dynamics of blood flow in reproductive tissues has an essential role in the endometrial growth and implantation, as well as the maturation of follicles and their subsequent conversion to corpus luteum (12-14). Given the important role of blood flow dynamics, alterations in blood supply (e.g., an increase in uterine artery resistance) may be responsible for diminished endometrial receptivity and thus RIF. Several studies have examined the role of the luteal phase in pregnancy loss (10,15) while less attention has been paid to the importance of the follicular phase in these cases. However, it has been demonstrated that any defect in the follicular phase of the menstrual cycle could be associated with the poor quality of the oocyte and may compromise the quality of the embryo, and consequently, the pregnancy outcome (14). On the other hand, researchers rarely confirmed that the quality of oocyte can be a consequence of the vascularity and endocrinology of the follicular phase. Therefore, the present research aimed to investigate vascularity in the follicular phase in both RIF and healthy fertile women.

Our findings revealed vascularity variations in the uterus of women with RIF in comparison to the healthy women during the follicular phase. In this regard, higher resistance was found in the uterine arteries of patients with RIF compared to the control group. Based on our results, the RI and PI of the right and left uterine arteries and sub-endometrial arteries were higher in the study group compared to the controls. Our results are in line with the findings by Pattinaja et al, indicating a higher PI of uterine arteries in women with a history of at least two embryo transfers during IVF treatment compared to control women with normal reproduction (16). Furthermore,

impaired uterine perfusion and decreased vascularity have been reported during the mid-luteal phase of the menstrual cycle in patients with RPL and recurrent miscarriage, respectively. Impaired uterine perfusion showed adverse effects on reproductive functions (17-20). It has been demonstrated that patients with RIF have a higher uterine artery PI in comparison with the examined infertile control cases during the mid-luteal phase before their first IVF trial (21). In this regard, individuals with successful implantation during the IVF procedure represented a low PI (22). Moreover, Abdel-Razik et al reported an increased PI, along with the higher RI of the uterine arteries in patients with unexplained recurrent abortion (23). In contrast, some studies demonstrated that the mean of the PI of left and right uterine arteries in different days of the menstrual cycle was not significantly different between the women with pregnancy failure after embryo transfer and those with successful pregnancy (24,25). Additionally, Prakash et al (14) reported no significant difference in the

ultrasound measurements of patients with a history of pregnancy loss compared to the control group during the follicular phase, which is inconsistent with our results. It should be noted that in the above-mentioned study, luteal phase defects among approximately 30% of patients and a small sample size, especially for the control group could be the possible reasons for such a controversy. In addition, the assessment of Doppler indices between days 8 and 9 of the cycle could be another explanation for the discrepant results with the present study.

The results of the present study showed that the PI and RI of sub-endometrial arteries were higher in women with RIF compared to the controls. These findings conform to those of a previous study showing that RPL patients had an increased RI of sub-endometrial blood flow compared to normal controls (26). This is also consistent with reports of NG et al (27) regarding higher sub-endometrial vascularity in women with a successful live birth in comparison with those who experienced miscarriages. Two other studies linked implantation failure in IVF cycles with a decrease (28) or lack (29) of blood flow in the sub-endometrium. Furthermore, it has been represented that women with a successful IVF procedure had lower PI and RI of uterine and arcuate arteries compared to those with an unsuccessful IVF (30). Similarly, Yalti et al (31) found that women who conceived with intrauterine insemination had a lower uterine artery PI compared with those who did not conceive at all. This study was conducted during the follicular phase before human chorionic gonadotropin administration. Thus, blood flow impedance in uterine arteries may be an indicator of pregnancy success possibly due to the association of the vascularity of endometrium and sub-endometrium with the development of the placenta during pregnancy (29,32).

The ischemia of the endometrium and sub-endometrium could be considered as one of the causative factors involved in RPL (26). In this regard, patients with miscarriage demonstrated significantly lower endometrial and sub-endometrial vascularity compared to pregnant women with live birth (27). However, due to the lack of a difference between the role of endometrial and sub-endometrial blood flow in getting pregnant, Chien et al proposed examining these two areas by color Doppler (28). Further studies on vascular changes, especially in pregnancy loss, may provide a broader understanding of the pathophysiology and etiology of these conditions.

Transvaginal Doppler ultrasound is a non-invasive method for measuring uterine vascularity (33) and can predict adverse pregnancy outcomes in high-risk women based on serum screening for pregnancy complications (34). Thus, finding markers to show the endometrial developmental defects and risk of pregnancy loss early in the follicular phase may provide the opportunity for better supporting the luteal phase or preventing unsuccessful embryo transfer (35). Therefore, evaluating the PI and RI of the uterus and arcuate and sub-endometrial arteries at

the follicular phase could give useful information about endometrial receptivity. Moreover, the growing body of evidence regarding the critical role of sufficient uterine perfusion in pregnancy success makes it more important in the clinical approach. However, to validate our findings and define the mechanisms involved in the relationship between RIF and defective uterine artery blood flow in the follicular phase, further studies with a larger sample size are necessary.

Conclusions

In general, using transvaginal ultrasound examinations, it was revealed that the PI and RI of the right and left uterine arteries and sub-endometrial uterine arteries, along with the RI of the arcuate arteries were significantly higher in patients with a history of RIF compared to their control counterparts. These findings highlight the increased blood flow resistance and reduced uterine perfusion in RIF patients. In this respect, evaluating uterine perfusion early in the follicular phase may force physicians to better support the luteal phase or prevent embryo transfer. Finally, using Doppler sonography may be a useful non-invasive method for evaluating patients with implantation or pregnancy loss.

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