

Uterine and arcuate arteries blood flow for predicting of ongoing pregnancy in *in vitro* fertilization

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Background: In this study, we aimed to investigate the ability of transvaginal Doppler ultrasonography in predicting *in vitro* fertilization (IVF) outcome in women undergoing this procedure. **Materials and Methods:** In this prospective observational study, 65 infertile women underwent IVF procedure in Isfahan, during 2013-2014, were studied. The pulsatility index (PI), resistive index (RI) and peak systolic velocity (PSV) of the uterine arteries and arcuate arteries were measured in all selected women using transvaginal color and pulsed Doppler measurements on the day of human chorionic gonadotrophin injection. The women followed up for the primary endpoint which was a successful pregnancy. The mean of PI, RI, and PSV were compared in groups of women who had successful IVF and not. The receiver operating characteristic (ROC) curve was used to determine the predictive value of studied indices. **Results:** In this study, from 65 women, 32 (49.2%) and 33 (50.8%) have successful and unsuccessful IVF outcome, respectively. The mean of PI and RI of both uterine and arcuate arteries were significantly lower in pregnant women than non-pregnant ones ($P < 0.001$). The area under the ROC curve of PI (84.7%) and RI (84.4%) for uterine arteries was higher than other indices. The most accurate indices for predicting the outcome of IVF was RI of uterine arteries with an accuracy of 81.5%. **Conclusion:** The findings of this study indicated that PI and RI assessments of uterine arteries could be used as a routine non-invasive factor, before hCG stimulation, for predicting the outcome of IVF.

Key words: Embryo implantation, *in vitro* fertilization, transvaginal Doppler ultrasound

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INTRODUCTION

In vitro fertilization (IVF) is the most common recommended treatment of choice for infertility.^[1] Despite numerous developments in laboratory techniques and ovarian stimulation protocols, the rate of implantation and clinical pregnancy occurrence remain low, and it is estimated that in approximately 85% of cases this procedure is failed.^[2]

Several studies have explored the causes of embryo implantation failure. Evidence indicated that the two main factors in this regard are embryonic development and endometrial receptivity.^[3]

Endometrial receptivity is defined as a temporary unique sequence of factors that make the endometrium receptive to the embryonic implantation.^[4] Many studies have investigated endometrial receptivity using various methods including the histologic and genomic study of endometrial biopsies, endometrial cytokines in uterine flushing and ultrasonographic examination of the endometrium.^[5-7]

There is a growing body of evidence that ultrasonographic assessments are more favorable for this purpose due to its non-invasive nature. Furthermore different ultrasonographic techniques have been developed since its introduction for evaluation of endometrial receptivity.^[8] Doppler

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ultrasound is one of the most proper methods which are used in this field. Recently, modern Doppler ultrasound techniques, with high-frequency transvaginal probes and color imaginary and high acceptable intra- and inter-observer variation have been introduced, and various studies have evaluated the usefulness of mentioned indices for predicting the outcome of IVF.^[9]

Ultrasonographic examination provides us different parameters for predicting the outcome of IVF including endometrial thickness, endometrial pattern, endometrial volume, and endometrial blood flow. The predictive value of the mentioned parameters have been investigated, and the findings indicated that low or no predictive value for endometrial thickness, pattern, and volume.^[10,11] There are reports confirm the utility of endometrial blood flow measurements in predicting of IVF outcomes. It could properly reflect the uterine artery blood velocities, which considered as an important factor in implantation.^[12]

Though many studies in different regions have examined the predictive value of this technique and its use have gained an increasing popularity for management of infertility, the clinical and practical value of the methods has been debated due to controversial reports in this field.^[13,14]

In this study, we aimed to investigate the ability of transvaginal Doppler ultrasonography in predicting IVF outcome in women undergoing this procedure in our center.

MATERIALS AND METHODS

In this prospective observational study, 65 infertile women with frequent abortion who referred to Infertility Center (Isfahan, Iran) for IVF from January 2013 to January 2014 were enrolled. The women were selected by consecutive sampling method.

The protocol of the study was confirmed by educational and therapeutic review board of infertility center and regional ethics committee of Isfahan University of Medical sciences (research project number 393189).

Women aged <40 years, with the regular menstrual cycle, nonpolycystic ovaries at the time of enrolment and a follicle stimulating hormone level <10 IU/L on the third cycle day were included in the study.

Those with tubal factor infertility, a history of uterine surgery and/or apparent endometrial pathology and clinically relevant systemic diseases (diabetes, ulcerative

colitis, Crohn's disease, connective tissue diseases or hypertension) were excluded.

Written informed consent was obtained from all selected patients. Selected women underwent IVF procedure using a standard ovarian stimulation protocol. The pulsatility index (PI), resistive index (RI), and peak systolic velocity (PSV) of the uterine arteries and arcuate arteries were measured in all selected women using transvaginal color and pulsed Doppler measurements by an expert radiologist on the day of human chorionic gonadotrophin injection.

The women follow-up for the primary endpoint of IVF procedure which was a successful pregnancy.

Mean of studied radiologic indices (PI, RI, and PSV) were compared in groups of women who had successful IVF (case) or not (control).

Diagnostic value (sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value [NPV]) of the indices for predicting the outcome of IVF was calculated also.

In vitro fertilization and ovarian stimulation, IVF and ovarian stimulation were performed using the standard protocol of the infertility center. In the first section, human chorionic gonadotropin (hCG, Darou Pakhsh Distribution Co., Tehran, Iran) was administrated with a dose of 75 mg daily from the 12th day of menstrual cycle. The ultrasonographic evaluation was performed in mid-cycle. If the follicle (18-28 mm) was seen in ultrasonographic assessment, the women underwent the second phase of hCG therapy. They received 10,000 IU hCG in two divided dose during 24 h.

The women follow-up for the primary endpoint which was a successful pregnancy. Pregnancy was defined as follows; increased serum hCG >50 IU/L on day 14-16 postfollicle aspiration, increased hCG levels 1-week after initial assessment and presence of a gestational sac on ultrasonographic evaluation. Ongoing pregnancy was defined as the presence of fetal cardiac activity at 12 weeks' gestation.^[7]

Transvaginal color and pulsed Doppler assessment

All women were examined clinically before the ultrasonographic examination. All of the color-pulse Doppler measurements were performed by one expert radiologist (MKH).

Ultrasonographic examinations were carried out using V20 Medison Ultrasound Device (Korea) using a 5-8 transvaginal transducer.

Uterine arteries were identified, and their blood velocity waveforms were obtained at the cervicocorporeal level of the uterus. Arcuate arteries were identified bilaterally, and blood velocity waveforms were obtained as distally as possible from the uterine artery.

The angle between the Doppler wave and the vessels was kept close to 0°. Measuring angle was <40°, and angle correction was performed for all cases. PI, RI, and PVS were recorded. Index values for each vessel were calculated electronically after good wave forms in three consecutive cardiac cycles were obtained.^[15]

Statistical analysis

Data analyzed using SPSS version 19 (SPSS Inc., Chicago, IL, USA) software. Normal distribution of the studied variables was evaluated using Kolmogorov-Smirnov test. Mean (standard deviation [SD]) of studied variables in two studied groups (pregnant and nonpregnant) were compared using the independent *t*-test. The receiver operating characteristic (ROC) curve was used to determine the predictive value of studied indices as well as their sensitivity, specificity, PPV, and NPV. *P* < 0.05 was considered statistically significant.

RESULTS

In this study, from 65 women, 32 (49.2%) and 33 (50.8%) have successful and unsuccessful IVF outcome, respectively. The mean age of women with and without successful IVF procedure outcome were 31.2 ± 2.3 and 30.9 ± 3.4, respectively (*P* = 0.42).

Mean (SD) of PI, RI, and PSV for both uterine and arcuate arteries in women with and without successful IVF procedure outcome are presented in Table 1. Mean (SD) of PI and RI of both uterine and arcuate arteries were significantly lower in women with successful IVF procedure outcome (*P* < 0.01). Mean of PSV for uterine arteries was significantly higher in women with successful IVF procedure outcome than those without (*P* < 0.05).

The area under the curve of the studied ultrasonographic indices for both arteries to predicting the outcome of IVF is presented in Figure 1. The areas under the curve of PI for uterine and arcuate arteries were 84.7% and 82.6%, respectively. The areas under the curve of RI for uterine and arcuate arteries were 84.4% and 70.3%, respectively. The areas under the curve of PSV for uterine and arcuate arteries were 69.3% and 55.8%, respectively.

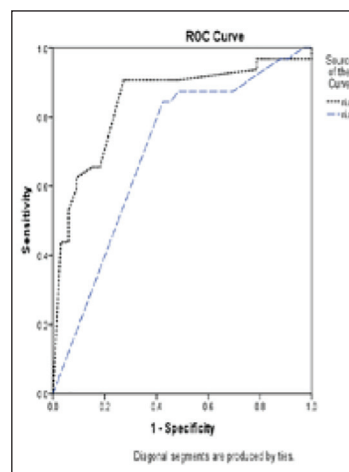


Figure 1: The area under the curve for pulsatility index, resistive index and peak systolic velocity of uterine (...) and arcuate (---) arteries for predicting the outcome of *in vitro* fertilization

Table 1: Mean ± SD of PI, RI and PSV for both uterine and arcuate arteries in women with and without successful IVF procedure outcome

Uterine arteries	IVF procedure without successful outcome (n = 33)	IVF procedure with successful outcome (n = 32)	<i>P</i>
Uterine arteries			
PI	3.0±1.4	1.6±0.53	<0.001*
RI	0.87±0.16	0.73±0.1	<0.001*
PSV	26.72±7.99	31.8±9.03	0.019*
Arcuate arteries			
PI	2.53±0.70	1.74±0.55	<0.001*
RI	0.95±0.11	0.83±0.16	<0.001*
PSV	14.97±3.08	15.46±4.02	0.59

**P* < 0.05. PI = Pulsatility index; RI = Resistive index; PSV = Peak systolic velocity; IVF = *In vitro* fertilization; SD = Standard deviation

The criterion of diagnostic values of studied ultrasonographic indices for predicting the outcome of IVF for both uterine and arcuate arteries is presented in Table 2. Accordingly the most accurate indices were RI of uterine arteries with the highest accuracy of 81%.

DISCUSSION

In this study, we determined the value of Doppler ultrasonographic indexes including PI, RI, and PSV of uterine and arcuate arteries for predicting IVF outcome among infertile women in Isfahan. The results indicated that from studied variables PI and RI of both uterine and arcuate arteries were significantly lower in women with successful IVF than those with the unsuccessful procedure. PI and RI of uterine arteries could have proper predictive value for the successful outcome of IVF.

As mentioned, several studies have been conducted to determine the role of different ultrasonographic indices

Table 2: Criterion of diagnostic values of PI, RI and PSV of uterine and arcuate arteries for predicting the outcome of IVF

Ultrasonographic indices	Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy (%)
Uterine arteries						
PI	1.8	63.6	84.4	80.8	69.2	73.8
RI	0.78	72.7	90.6	88.9	76.3	81.5
PSV	25	78.8	50.0	61.9	69.6	64.6
Arcuate arteries						
PI	2.28	84.8	75.0	77.8	82.8	80.0
RI	0.85	54.5	84.4	78.3	64.3	69.2
PSV	17	54.5	34.4	46.2	42.3	44.6

PI = Pulsatility index; RI = Resistive index; PSV = Peak systolic velocity; IVF = *In vitro* fertilization; PPV = Positive predictive value; NPV = Negative predictive value

in predicting the outcome of stimulated IVF cycles. Most of the studies have been evaluated PI and/or RI. In this study, we investigated three parameters of PI, RI, and PSV.^[15-17]

It is suggested that vascular supply plays a critical role in different processes of IVF including the development of a dominant follicle, formation of a corpus luteum, growth of endometrium and implantation.^[18] Moreover, the association between utero-ovarian perfusion and outcome of IVF treatment has been reported in previous studies.^[19]

Since 1989, many studies have evaluated the utility of different ultrasonographic vascular parameters in predicting pregnancy following assisted reproductive treatments. The results of different studies are conflicting some confirmed the usefulness of the indices whereas others did not.^[13-17]

Puerto *et al.* in Spain have indicated that ultrasonographic markers as the predictors of implantation after IVF have a limited value when measured during embryo transfer.^[13]

NG *et al.* evaluate the role of endometrial blood flows in the prediction of pregnancy during IVF treatment. They concluded that endometrial blood flows measured by three-dimensional power Doppler ultrasound were not good predictors of pregnancy during IVF treatment, if they were measured once.^[14]

Hoozemans *et al.* have evaluated the predictive value of serial uterine artery Doppler ultrasound for embryo implantation during IVF procedure using PI index. They indicated that mean of PI of uterine arteries was not different significantly in women with successful IVF than those with unsuccessful procedure and ROC results indicated that PI is not a proper marker for identification of women with implantation failure. They did not show any association between the occurrence of pregnancy and PI during IVF procedure.^[17]

In a recent study Ivanovski *et al.* have studied the predictive role of the uterine and arcuate arteries PI, RI, and PSV indices measurement on the day of hCG injection in the success rate of IVF procedure. According to their findings, only mean uterine artery PI and RI were significantly lower in women with successful IVF than those with the unsuccessful procedure. Mean arcuate PI and RI were lower in pregnant women, but they did not reach to a statistically significant level. PSV of both uterine and arcuate were higher in pregnant women, but the differences were not statistically significant. They suggest that PI was the most important parameter, and transvaginal color Doppler ultrasonography could be used to measure uterine and arcuate arteries blood flow before hCG stimulation in IVF treatment for evaluating the procedure success rate.^[16]

In a similar study in Turkey, Adkan *et al.* have compared uterine and arcuate blood flow measurements in 46 women undergoing treatment by IVF with and without successful outcome using transvaginal color Doppler ultrasonography on the day of hCG injection. They indicated that mean of PI and RI of uterine arteries and RI in arcuate arteries were significantly lower in women with successful IVF than those with the unsuccessful procedure.^[15]

Our results indicated that mean of RI and PI in both uterine and arcuate arteries were lower significantly in women with successful IVF procedure. The mean of PSV in uterine arteries was significantly higher in women with successful IVF.

In the current study, we also determined the predictive value of studied variables and the findings showed that PI and RI of uterine arteries have the highest significant predictive value. Diagnostic value of the ultrasonographic indices has evaluated also, and the results indicated that the most accurate index was RI of the uterine artery.

The proper cut off which was determined for the diagnosis of successful pregnancy after IVF for PI and RI of the uterine

artery in our study were 1.8 and 0.78, respectively. The recommended cutoffs for PI and RI of arcuate arteries were 2.28 and 0.85, respectively.

The reported cutoff level in the study of Adkan *et al.* for PI and RI of the uterine artery were 1.93 and 0.75 respectively and for RI of arcuate arteries was 0.65.^[15]

It seems that the controversial results which have reported in different studies are due to the differences in patients characteristics, the protocol of ovarian stimulation, the day of ultrasound evaluation and the methods of ultrasonographic assessments.

The limitation of this study was the small sample size of the studied population and for obtaining more conclusive results especially for determining the diagnostic value of studied ultrasonographic indices further studies with larger sample size is recommended.

CONCLUSION

The findings of this study indicated that PI and RI assessments of uterine arteries could be used as a routine non-invasive factor, before hCG stimulation, for predicting the outcome of IVF.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

All authors contributed in the study design, conducting the study and drafting the manuscript. All authors approved the final version for submission and take the responsibility for the manuscript content.

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