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ORIGINAL ARTICLE

Uterine Artery Doppler Indices as Determinant of Success in Intra Cytoplasmic Sperm Injection

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Abstract

Background: ***In-Vitro*** **Fertilization (IVF). Patients with infertility are usually advised to have intracytoplasmic sperm injections (ICSI). Doppler ultrasound, which uses high frequency transvaginal probes and coloured pictures, is one of the most frequently used methods in this field. One of the parameters supplied by an ultrasonographic test for determining the success of IVF includes endometrial thickness, endometrial pattern, endometrial volume, and endometrial blood flow.**

Aim: **To detect implantation window using uterine artery indices in ICSI cycles.**

Subject and methods: **This study will be concluded at the assisted reproductive techniques unit of Al-Azhar University on 100 patients.**

Results: **Regarding BMI, there is a sizable variation between the groups. When it comes to the length of infertility, there is a substantial variation between the groups. Follicle-stimulating hormone (FSH), E2, and prolactin are significantly different amongst the groups. Regarding uterine artery resistance index (RI), there is a considerable variation between the two groups. Groups were comparable regarding number and quality of embryos transferred but without statistically significant difference.**

Conclusion: **Doppler parameters are useful tools to assess endometrial receptivity in unexplained infertility patients undergoing ICSI. This study found that Uterine, arteries evaluated on the day of embryo transfer had greater arteries plasticity index (PI) and RI values than fertile women and have value in judging endometrial receptivity and predict the final outcome of ICSI. Uterine blood flow assessed by measuring plasticity index, RI of these arteries was impaired in unexplained infertility patients compared with fertile women.**

Keywords: Cytoplasmic sperm injection, Intracytoplasmic sperm injection, Uterine artery Doppler indices

1. Introduction

Intra Cytoplasmic Sperm Injection (ICSI), a common suggested treatment for infertility, is performed during *in vitro* fertilisation (IVF). The rate of implantation and occurrence of clinical pregnancy remains low despite major advancements in laboratory procedures and ovarian stimulation treatments.[1]

The reasons for unsuccessful embryo implantation have been examined in several studies. Evidence suggested that endometrial receptivity and embryonic development are the two key factors influencing this process. The term 'endometrial receptivity' refers to a specific transitory constellation of elements that render the endometrium amenable to embryonic implantation.[2]

In addition, other ultrasonographic procedures have been developed since its inception for assessing endometrial receptivity. There is mounting evidence that ultrasonographic assessments are more advantageous for this purpose due to their noninvasive nature.[3]

One of the most often utilised techniques in this sector is doppler ultrasound, which uses high frequency transvaginal probes and color images.[4] However, numerous studies support the usefulness of endometrial blood flow measures in predicting the results of ICSI.[5]

Therefore, the purpose of this study is to examine the uterine artery blood flow on the day of HCG

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delivery as a noninvasive method for predicting the success of ICSI. The aim of this study was to detect implantation window using uterine artery indices in ICSI cycles.

1.1. Patients and methods

This study was concluded at the assisted reproductive techniques unit of Al-Azhar University (The International Islamic Center of Population Studies And Research). 100 patients were selected according to the inclusion criteria for the study.

A written informed consents was obtained from the participants before participation in the study.

1.2. Inclusion criteria

Primary and secondary infertility patients, age below 37 years, patients with tubal factor of infertility and polycystic ovarian disease.

1.3. Exclusion criteria

Patients with uterine factor of infertility, communicating hydrosalpinx and medical disorders affecting general condition.

1.4. Operational design

All patients were subjected to an informed consent was taken from every patient. Complete history taking: Personal history, any complaint, obstetric history, menstrual history, past medical and past surgical history and family history. Complete physical examination. Local examination of the abdomen and the pelvis. BMI, general check-up, and vital signs (Blood pressure, Temperature, Heart rate, Respiratory rate).

Initial two-dimensional transvaginal ultrasound test: the transvaginal transducer was inserted, paying close attention to how the image was facing. The external cervical OS or the distal vagina were the locations for the probe. With side-to-side movements of the probe from one adnexa to the next, sagittal imaging was achieved. After the examination was finished, the probe cover was taken off, and any gel was washed off with soap and running water. It was advised to use a high-level disinfectant after drying the probe.

Day 2, Venous blood samples were collected between 8 and 10 a.m. after an overnight fast. Serum samples were stored at −20 °C and serum sample follicle-stimulating hormone (FSH), LH, E2, anti-müllerian hormone (AMH), prolactin and thyroid-stimulating hormone (TSH) were measured using the radioimmune assay method.

Standard ovarian stimulation protocol was used for the selected patients according to patient criteria (Age, Ovarian reserve tests, Previous response to stimulation and BMI) as followed:

Oral micronized estradiol was administered as part of the ovarian stimulation procedure on cycle day 2 after suppression with oral contraceptive pills, either with or without a GnRH agonist. Oral estradiol dosages of 2 mg every three days, 4 mg every three days, and eventually 6 mg every day were given. Transvaginal ultrasonography was used to evaluate the endometrium 12–14 days after starting estradiol. Progesterone in oil (50 mg IM QD) and vaginal progesterone (100 mg PV TID) were combined the next morning once the endometrial lining was less than 7 mm thick. $P+0$ stands for $P+0$, the day of progesterone commencement. Patients came back the day before ICSI.

Daily intramuscular Human Menopausal Gonadotropines HMG preparation was administered once ovarian down regulation was attained. As soon as at least three leading follicles had grown to a diameter of 18 mm, the ovarian response was evaluated using ultrasound. HCG induced the last stage of oocyte maturation. On the day of the HCG injection, an expert sonographer performed a transvaginal uterine artery Doppler to assess the peak systolic velocity (PSC), resistance index (RI), and pulsitality index (PI): The test subjects were placed in the lithotomy position. On a V20 Medison ultrasound system, the exams were performed utilising a 5-MHz transvaginal phased array transducer. The cervix was discovered. The lateral probe movement revealed the paracervical vascular plexus. After Color Doppler was activated, the uterine artery was discovered as it began to ascend to the uterine body.

At this period measurements were taken before the uterine artery split into the arcuate arteries. The pulsed Doppler gate was positioned over the whole width of the vessel as soon as the angle was determined to be less than 50° (it was frequently less than 30°).

Updates were made to the signal until a clean, constant waveform was attained. The other uterine artery was then given the same treatment. Average time for the surgery was 12 min two measurements collected at intervals of 15 min a positive pregnancy test on Day 14 following embryo transfer was considered a success.

1.5. Administrative design

The protocol was applied for approval of Research Ethics Committee. Written consent was taken from all participants before including them in the study

and they have the right to refuse without effect on their management.

1.6. Statistical analysis

SPSS version 23 was used for data processing, data checking, data entry, and data analysis. The results of this investigation were analysed using the following statistical techniques. The Mann–Whitney test was used to determine the difference between quantitative variables in two groups of data that were not regularly distributed. χ^2: used to determine whether row and column variables are related.

2. Results

Table 1.

This table shows that patients' age ranged 25–40 years with mean BMI 25.41 kg/m^2. Majority of the patients were rural (Table 2).

This table shows that mean infertility duration 6.41 ± 1.67 years. Meanwhile, mean menstrual cycle length 30.51 ± 8.33 days and 48% of the patients had previous ICSI. Majority of the patients were primary type of infertility (70%) (Table 3).

This table shows that most of the patients (37%) had one embryo transferred, 33% had three embryos transferred, and 30% had two embryos transferred. Regarding quality, 96% of the patients were grade I (Table 4).

Table 1. Demographic characteristics among studied patients.

	Patients (n = 100)
Age (years)	
Mean ± SD	34.71 ± 4.03
Range	25–40
BMI (kg/m^2)	
Mean ± SD	27.53 ± 2.58
Range	20–31
Residence	
Urban	43 (43%)
Rural	57 (57%)

Table 2. Clinical characteristics among studied patients.

	Patients (n = 100)
Infertility duration (years)	
Mean ± SD	6.41 ± 1.67
Menstrual cycle length (days)	
Mean ± SD	30.51 ± 8.33
Previous ICSI	48 (48%)
Type	
Primary	75 (75%)
Secondary	25 (25%)

Table 3. Embryos characteristics between the studied groups.

	Patients (n = 100)
Number of embryos transferred	
1	37 (37%)
2	30 (30%)
3	33 (33%)
Quality of embryos transferred	
Grade I	96 (96%)
Grade II	4 (4%)

Table 4. Sonar measurements among the studied patients.

	Patients (n = 100)
Endometrial thickness	
Mean ± SD	10.85 ± 3.46
Uterine artery PI	
Mean ± SD	1.94 ± 0.683
Uterine artery RI	
Mean ± SD	0.992 ± 0.315

Table 5. Pregnancy rates between the two studied groups.

	Patients (n = 100)
Chemical pregnancy	
Positive	46 (46%)
Negative	54 (54%)
Clinical pregnancy	
Positive	48 (48%)
Negative	52 (52%)

This table shows that mean ET was 10.85 ± 3.46 while uterine artery PI was 1.94 ± 0.683 and uterine artery RI was 0.992 ± 0.315 (Table 5).

Table 6. Demographic characteristics among the studied groups.

	Pregnant (n = 48)	Not pregnant (n = 52)	t	P
Age (years)				
Mean ± SD	32.69 ± 3.52	34.11 ± 4.83	1.67	0.098
BMI (kg/m^2)				
Mean ± SD	26.31 ± 2.78	29.45 ± 3.57	**4.87**	**<0.001**

Table 7. Hormonal data among the studied groups.

	Pregnant (n = 48)	Not pregnant (n = 52)	t	P
FSH (mIU/ml)				
Mean ± SD	5.86 ± 1.19	6.73 ± 1.24	**3.57**	**0.001**
LH (mIU/ml)				
Mean ± SD	4.93 ± 1.24	5.21 ± 1.23	1.13	0.260
E2 (pg/ml)				
Mean ± SD	45.88 ± 13.11	39.47 ± 15.89	**2.19**	**0.031**
Prolactin (ng/ml)				
Mean ± SD	20.25 ± 4.63	29.67 ± 8.1	**7.1**	**<0.001**
TSH (mIU/ml)				
Mean ± SD	2.32 ± 0.548	2.4 ± 0.519	0.749	0.455

FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone.

Table 8. Doppler characteristics among the studied groups.

	Pregnant ($n = 48$)	Not pregnant ($n = 52$)	T	*P*
Endometrial thickness				
Mean ± SD	10.58 ± 3.84	9.32 ± 2.75	1.89	0.061
Uterine artery PI				
Mean ± SD	2.08 ± 0.693	2.14 ± 0.722	0.423	0.673
Uterine artery RI				
Mean ± SD	0.981 ± 0.327	1.29 ± 0.331	**4.69**	**<0.001**

This table shows that positive chemical pregnancy rate was 46% while positive clinical pregnancy rate was 48% (Table 6).

This table shows that there is a significant difference between the groups regarding BMI (Table 7).

This table shows that there is a significant difference between the groups regarding FSH, E2, and prolactin (Table 8).

Fig. 1.

This table shows that the groups were comparable regarding No. and quality of embryos transferred but without statistically significant difference.

Variables	AUC	S.E.	Cut off	Sig.	95% Confidence Interval
Uterine PI	0.714	0.055	1.18	**0.003***	0.607–0.821
Uterine RI	0.679	0.057	0.62	**0.020***	0.554–0.777

Variables	Sensitivity	Specificity	PPV	NPV
Uterine PI	83.2%	91.6%	54%	88%
Uterine RI	71.8%	87.2%	47%	82%

Uterine PI achieved significance for predicting ICSI success at cutoff point greater than or equal to 1.4 with sensitivity of 83% and specificity of 91.6% with positive pressure ventilation (PPV) 54% and negative pressure ventilation (NPV) 88%. While uterine RI achieved significance for predicting ICSI success at cutoff point ≥ greater than or equal to 0.74 with sensitivity of 71.8% and specificity of 87.2% with PPV 47% and NPV 82%.

3. Discussion

Unaccounted for infertility is defined as the inability of a couple to conceive without the presence of a clear cause after 12 months of trying, or after 6 months in the case of a female who is more than or equal to 35 years old. Unexplained infertility, which affects 10–25% of infertile females, is when there is no clear cause for the infertility El-Shourbagy and colleagues.[6]

Regarding Demographic characteristics among studied patients, we found that patients' age ranged 25–40 years with mean BMI 25.41 kg/m^2. Majority of the patients were rural. Regarding outcome we found that positive chemical pregnancy rate was 46% while positive clinical pregnancy rate was 48%. Comparison between patients with positive clinical pregnancy ($n = 48$) and those with negative clinical pregnancy ($n = 52$), revealed that there was no significant difference in the groups' ages, but there was a significant difference in the groups' BMIs.

The current study was in line with Ragheb and colleagues[7] aimed to evaluate the role of pulsatility index (PI) of uterine artery blood flow during IVF-ET cycles in prediction of pregnancy rate. This study included 400 women; the pregnancy rate was 48.25%. The age of studied group ranged from 19 years to 37 years with a mean of 32.5 years and the body mass index (BMI) ranged from 22 to 46 with a mean of 33.5. The study reported no association between positive pregnancy with age or BMI. The disagreement with our results regarding BMI may be attributed to the difference in sample size and inclusion criteria.

The present study can also be supported by Zhang and colleagues[8] aimed to investigate the connections between conception rates in cycles including frozen-thawed embryo transfers and several endometrial receptivity ultrasonography measurements, such as endometrial thickness, volume, echo, movements, and blood flow. 315 pregnancies (56.0%) out of 562 individuals undergoing frozen-thawed embryo transfer (FET) were included in the study. The study found no link between positive pregnancies and BMI, although it did find a link between positive pregnancy and younger age. Furthermore, Zhang and colleagues[9] investigation focused on the utility of ultrasound for determining endometrial receptivity during *in vitro* fertilisation (IVF) and embryo transfer (ET). 435 patients were participated in the research, of whom 235 (58.8%) became clinically pregnant and 49 lost their pregnancies. The age of women did not differ significantly, and BMI between nonpregnant and pregnant groups.

However, the majority of studies found no association between outcome and BMI, our results showed that there was significant correlation between BMI and pregnancy outcome and this was in agreement with Zhang and colleagues.[10] They discovered that obesity was substantially related to lower rates of implantation, Live births and clinical pregnancy (aOR 0.80; 95% CI 0.73–0.87, 0.81; and 0.70; 95% CI 0.62–0.80). In addition, cohorts with low and normal BMIs had the highest success rates and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for all pregnancy outcomes,

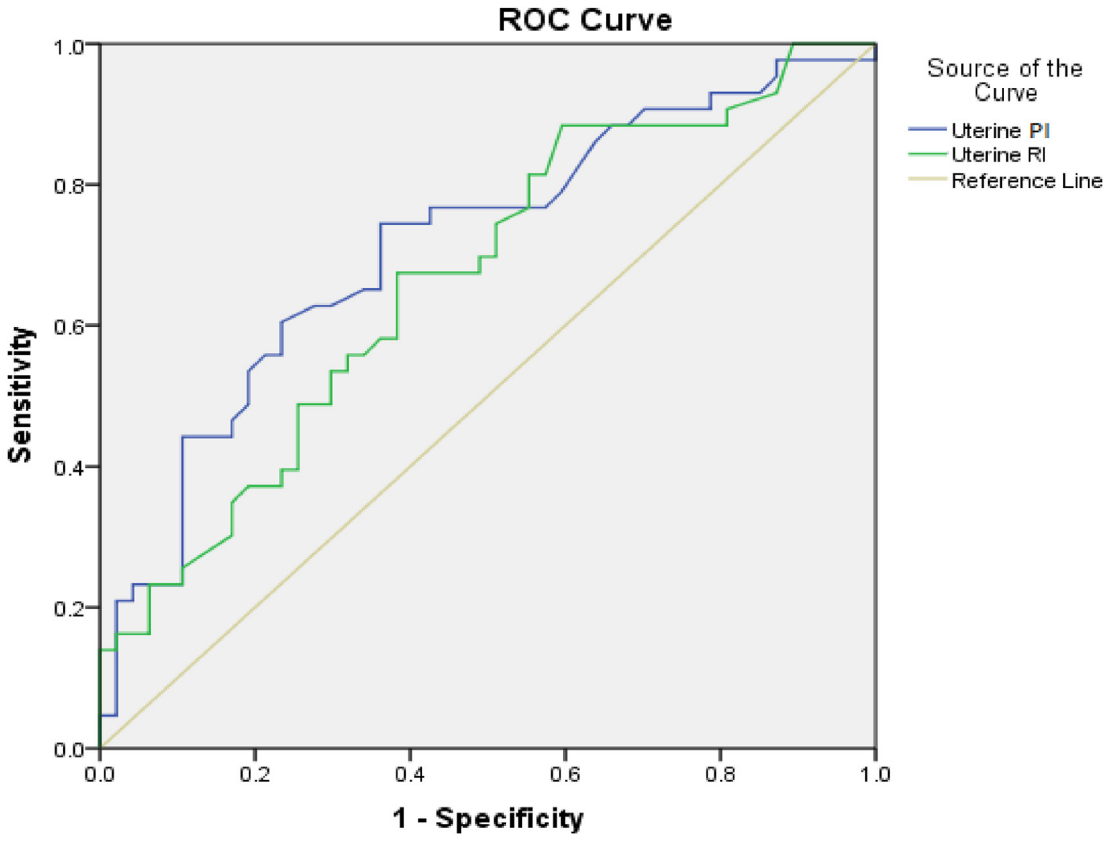

Fig. 1. ROC curve of uterine Doppler indices to predict ICSI success. ROC, receiver operating characteristic.

according to Provost and colleagues study's, while cohorts with high BMIs saw steadily deteriorating outcomes. Although it did not always achieve statistical significance, obesity also had a detrimental effect on the outcomes of IVF cycles carried out for PCOS and male-factor infertility.

This comes in agreement with Ragheb and colleagues[7] who revealed that the mean duration of marriage is 7.5 years and the mean duration of infertility is 7.5 years. The study also revealed that the infertility duration was significantly shorter among cases with positive clinical pregnancy ($P = 0.0399$) but there was no significant association between outcome and type of infertility.

Also, in harmony with our results Zhang and colleagues[8] reported that the infertility duration was significantly shorter among cases with positive clinical pregnancy ($P = 0.002$) but there was no significant association between outcome and type of infertility.

However, Zhang and colleagues[9] reported that there was no significant association between outcome with infertility duration or type of infertility. Also, Crosby and colleagues[11] reported that there was no significant association between outcome with infertility duration or menstrual cycle length. The disagreement with our results may be attributed to the difference in sample size and inclusion criteria.

The current study showed that the mean FSH 6.53 ± 0.894 mIU/ml, mean LH 5.14 ± 0.592 mIU/ml, while mean E2 was 52.3 ± 18.66 and mean prolactin 27.54 ± 6.32 ng/ml while TSH was 2.31 ± 0.382 μIU/ml. FSH, E2, and prolactin levels were significantly different between individuals with positive clinical pregnancy and those with negative clinical pregnancy, according to a comparison between the two groups of patients. This was supported by Ragheb and colleagues[7] who revealed that the mean serum FSH is 6.39, mean serum LH is 5.4, mean serum TSH is 2.225, mean serum prolactin is 12.25 and mean serum E2 is 49. The study also found a statistically significant variation in prolactin level and FSH profile between the tested groups (P value 0.048). (P value 0.001).

Additionally, Baseline E2 ($P = 0.03$) and AMH ($P = 0.003$) showed a statistically significant difference between the examined groups, according to Zhang and colleagues but in contrast with our results the reported that FSH was non significantly lower in positive pregnancy group this may be due to the

difference in sample size. However, in disagreement with our results Zhang and colleagues[9] revealed that there was no statistically significant difference between the studied groups as regard FSH and E2. Also, Kim and colleagues[12] showed that there were no statistically significant differences in FSH, LH, or E2 between the groups under study. The disparity in sample size and inclusion requirements may be to blame for the discrepancy with our findings. According to the current study, the mean ET was 10.85 3.46, and the uterine artery PI and RI were 1.94 0.683 and 0.992 0.315, respectively. There was a significant difference in uterine artery RI between patients with clinically positive pregnancy and those with clinically negative pregnancy.

The groups' other characteristics were comparable. According to Shui and colleagues[13] findings, which are consistent with our own, the mean endometrial thickness and uterine artery PI did not significantly differ between the groups under study, however there was a significant difference in uterine artery RI between the non-pregnant and pregnant groups.

This was corroborated by Setia and Malik,[14] who noted a substantial difference in the mean uterine artery RI between patients with positive and negative pregnancy. The same outcomes were reported by Mohamed and colleagues,[15] although in contrast to our findings, they also stated that the mean endometrial thickness and uterine artery PI were substantially different across the analysed groups. The disparity in sample size and genetic factors may be to blame for the discrepancy with our findings. Ibrahim and colleagues[16] also claimed that there is a significant difference between the two groups regarding uterine artery PI but that there was not a significant difference detected regarding uterine artery RI, which is in conflict with our findings. Comparing patients with positive clinical pregnancies to those with negative clinical pregnancies revealed that there was no statistically significant difference between the groups in terms of the quantity and quality of transplanted embryos.

In line with our findings Ragheb and colleagues[7] indicated that neither group's number nor quality of transferred embryos differed significantly from the other's.

To test the diagnostic accuracy of uterine Doppler indices to predict ICSI success, receiver operating characteristic (ROC) curve analysis was performed and showed that uterine PI achieved significance for predicting ICSI success at cutoff point greater than or equal to 1.4 with sensitivity of 83% and specificity of 91.6% with PPV 54% and NPV 88%. While uterine RI achieved significance for predicting ICSI success at cutoff point greater than or equal to 0.74 with sensitivity of 71.8% and specificity of 87.2% with PPV 47% and NPV 82%.

Our results demonstrated that Uterine PI has higher diagnostic accuracy than Uterine RI in predicting ICSI success.

This was supported by Adibi and colleagues[17] He demonstrated that PI (84.7%) at cutoff point 1.8 and RI (84.4%) at cutoff point 0.78 for uterine arteries had a higher area under the ROC curve than other indices. The RI of the uterine artery has an accuracy of 81.5% in predicting the result of IVF, making it the most reliable indicator. Also, Wang and colleagues[18] showed that Uterine PI have higher diagnostic accuracy than Uterine RI in predicting ICSI success.

However, Ibrahim and colleagues[16] reported that uterine PI achieved significance for predicting ICSI success at cutoff point less than or equal to 2.43 with sensitivity of 91.67% and specificity of 97.44% with PPV 91.7% and NPV 97.4%, while uterine at cutoff point less than or equal to 1.13 with sensitivity of 91.67% and specificity of 51.28% with PPV 36.7% and NPV 95.2%. So, the best cutoff point was less than or equal to 2.43.

3.1. Conclusion

Doppler parameters are useful tools to assess endometrial receptivity in unexplained infertility patients undergoing ICSI. According to this study, On the day of embryo transfer, measures of the uterus, artery PI, and RI were lower in fertile women. and have value in judging endometrial receptivity and predict the final outcome of ICSI. Also, higher uterine arteries RI artery was significantly associated with pregnancy outcome in unexplained infertility patients undergoing ICSI.

Disclosure

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Authorship

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Conflicts of Interest

The authors declared that there were no conflicts of Interest.

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