Experimental
&
Clinical Article

Assessment of Changes in Uterine and Subendometrial Blood Flows By Doppler Sonography in Women Undergoing Assisted Reproduction

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OBJECTIVE: The aim of this study was to evaluate the relationship between uterine Doppler flow and endometrial and subendometrial blood flows and uterine receptivity during ICSI cycles.

STUDY DESIGN: A prospective observational study was conducted in sixty-eight women undergoing in-vitro fertilization-embryo transfer (IVF-ET) treatment. All of them had at least one good-quality embryo for transfer on the third day after oocyte retrieval. A color Doppler ultrasound examination was performed on the day of hCG injection and midluteal phase. Pulsatility and resistance index of uterine vessels, and vascularization and endometrial and subendometrial flows were evaluated.

RESULTS: The age, duration of infertility or number of embryos transferred of the women who conceived (n=16) and those who did not (n=44) did not statistically significantly differ. The mean endometrial thicknesses of the two groups on hCG day and 5-6days after embryo transfer were not statistically significantly different. The mean uterine arterial resistance index (RI) and Pulsatility Index (PI) values of the two groups were not significantly different on hCG day, but both indices were significantly lower in the pregnant than in the non-pregnant group in mudluteal phase (p=0.05 and 0.016, respectively). In addition, no significant differences were found between the two groups in subendometrial blood flow.

CONCLUSION: In patients undergoing IVF-ICSI and embryo transfer, Doppler ultrasound examination of the uterine artery and subendometrial blood flow on hCG day do not discriminate the cycles resulting in conception and non-conception, but especially low mean PI of uterine artery in 5-6 days after ET can predict pregnancy.

Key Words: Endometrial and subendometrial blood flows, Assisted reproduction, Doppler ultrasonography, Uterine artery blood flow

Gynecol Obstet Reprod Med 2010;16:91-7

Introduction

To obtain optimal results from assisted reproductive technology (ART), it is critical to decide the timing for embryo transfer (ET) that would best correspond with the implantation window. Biochemical evaluation of endometrial function at the time of implantation has been tried in recent years, but no conclusion can be drawn on its clinical significance in the assessment of endometrial receptivity after ART.[1] Furthermore, most cases involved invasive procedures that are not suitable in the treatment cycles.

Ultrasound parameters of the endometrium and the evaluation of uterine and endometrial blood flow have long been considered as implantation markers in in vitro fertilization (IVF) and embryo transfer cycles.[2,3] With the introduction of high-resolution transvaginal probes, non-invasiveness and accessibility of sonography have made it particularly suitable for serial follow-up throughout the menstrual cycle.[4] Various sonographic parameters, such as endometrial echogenicity, uterine contractility and Doppler parameters, have been evaluated as markers of receptivity.[5] Assessment of uteroovarian blood flow is a potentially valuable method to evaluate the functional capacity of the endometrium during the window of implantation.[5] Doppler ultrasound seems the most popular technique among clinicians because of its reproducibility. Uterine blood flow can be assessed by Doppler ultrasound in the uterine arteries, and there is evidence of an association between abnormal uterine artery blood velocities and infertility;[5,6] the pulsatility index (PI) is considered best at reflecting uterine artery blood velocity parameters. Use of uterine artery PI as a marker of implantation has been found successful by some authors, while it has been rejected by others.[5,7] The win-

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Submitted for Publication: *01. 09. 2010*
Accepted for Publication: *25. 10. 2010*

dow of implantation is characterized by a state of increased vascular permeability, massive endometrial angiogenesis,[8] and decreased vascular resistance.[9]

In numerous studies, examinations were usually done either before human chorionic gonadotropin (hCG) administration or before ET. Utero-ovarian blood flow changes during the early implantation period, as well as their significance in establishing the pregnancy remain to be determined.

In the past, there were quite a few studies on endometrial thickness, pattern, pulsatility index (PI), and resistance index (RI). The research in endometrial and subendometrial blood flows is rare and complicated.[10]

Accordingly, the aim of this study was to investigate the relationship between uterine Doppler flow and endometrial and subendometrial blood flows with uterine receptivity during the IVF treatment cycle and to compare the changes of these measurements in the conception and non-conception cycles. We hypothesized that a decrease in PI would be observed during the IVF or IVF-ICSI cycle and that this phenomenon would be more pronounced in cycles resulting in pregnancy.

Material and Method

Study population and treatment protocol

A total of 68 patients receiving IVF treatment were prospectively recruited between February 2009 and April 2009. The age of the patients ranged between 20 and 39 years old (mean age: 29.6 years).The duration of infertility was 2-24 years(mean: 7.8 years). Indications for IVF were tubal factor (16.7%), unexplained infertility (28%), male factor (38%), and mixed factors (17.3%). The inclusion criteria were age ≤39 years, non-polycystic ovaries present at the time of enrollment, and a follicle stimulating hormone (FSH) level <10 IU/L on cycle day 3 and having at least one good-quality embryo, as defined by morphological criteria, for transfer on day 3 after oocyte retrieval. Patients with myoma or adenomyosis and endometriosis and patients with a history of uterine surgery and/or apparent endometrial pathology (polyps, submucous myoma or synechia) were excluded, as were patients with clinically relevant systemic diseases, such as diabetes mellitus, ulcerative colitis, Crohn's disease, connective tissue diseases or hypertension. Smoking and a body mass index>28 kg/m^2 were also the other exclusion criteria. All the patients were included in this study only once to avoid selection bias. Ethical approval for the study was obtained from the local ethics committee of our hospital, and each woman informed consent of each patient was obtained. The study was approved by our internal institutional review board and conducted in accordance with basic principles of Helsinki Declaration.

Ovarian stimulation was performed with gonadotropin-releasing hormone (GnRH) agonist Lucrin(Lucrin Daily®, Abbott, Johannesburg) in a standard long protocol, and step-down regimen was used for ovulation induction with starting daily recombinant FSH (r-FSH,Gonal F, Serono laboratories, Bari, Italy) at a dose of 225 IU. Dose alterations were performed on the 4th day of stimulation and continuing days according to the sonographic findings and circulating estradiol (E_2) levels. Ovulation was induced by a subcutaneus injection of 250 μg recombinant human chorionic gonadotropin (hCG) (Ovitrelle®, Merk Serono, Germany) when at least 3 follicles reached a diameter of 18 mm. Oocyte pick up (OPU) was performed 34-36 hours after hCG injection. ICSI was performed for all metaphase II oocytes. According to our clinical policy, ICSI is the method of choice. Oocytes and embryos were handled in G-MOPS medium (Vitrolife, Sweden) supplemented with HSA solution (Vitrolife, Sweden) in ambient atmosphere and were cultured in pre-equilibrated G1 v5 medium (Vitrolife, Sweden) under oil. All incubations were carried on at 37°C in humidified chambers of 6% CO_2 in air. ET was performed under ultrasound guidance on day 3 in all the patients. The patients were transferred 1-3 embryos, of which least one was good quality. The women of 35 years of age or older were transferred at most 3 embryos; the remaining s were transferred at most 2 embryos. All the embryos were scored by the number and size of blastomeres, and the presence of nucleate cytoplasmic fragments on the third day after oocyte collection, as previously described (Giorgetti et al., 1995; Van Royen et al., 1999). A top quality embryo was defined as having eight even-sized blastomeres and no fragments or having less than 10% fragments. Embryo transfer was performed using Wallace catheter (Edwards-Wallace Catheter; Marlow Technologies, Willoughby, OH) by the same clinician.

The day after oocyte retrieval, each patient began supplementation with vaginal gel form of progesterone (Crinone® 8%, Merk Serono, Germany) at 90mg once daily. Serum β-hCG levels were measured 14 days after ET, and, if positive, micronized progesterone administration was continued for 4 weeks.

Doppler ultrasonography

The ultrasound system used was an Aloka color Doppler SSD5500 PSV

(Aloka Co; Tokyo, Japan), equipped with color and pulse Doppler facilities. A 5-MHz transvaginal transducer (C5 IVT) was used, and the spatial peak temporal average intensity at the maximum amplitude and minimum gate width did not exceed 65 mW/cm^2. All the examinations were performed between 13.00 h and 15.00 h, with the patient in the lithotomy position. After a longitudinal view of the uterus was obtained, the thickness of the endometrium was measured at the maximum distance between each myometrial/endometrial interface. Then, the color Doppler mode was activated to obtain the flow images. The uterine arteries were sampled lateral to the cervix near the internal os bilaterally. A 2-mm range gate was

then placed across the vessel. The angle of the probe was moved to obtain the maximum waveform amplitude and clarity. A 50-100- Hz filter was used to eliminate low-frequency signals originating from movements of the vessel wall. After confirming that waveforms were continuous, an average of 3-5 cardiac cycles was selected for calculation of RI, PI, and peak systolic flow velocity (PSV). The women were scanned on hCG day and 5-6 days after ET. No Doppler study was done on the area of the endometrium after ET because of possible embryotoxic effects. The average length of the Doppler study was 10 min, with the longest examination taking no more than 15 min. All the scans were performed by the same operator (A.F.T.) to avoid interobserver variation. The intraobserver coefficient of variation for Doppler flow measurement was 7.8 ± 2.5%. The mean values of bilateral uterine arterial parameters in each patient were used in this study. On the day of hCG injection, endometrial and subendometrial blood flows and PI and RI of uterus artery were examined additionally. Endometrial and subendometrial blood flows were affirmed by counting the vessels entering into the endometrium and subendometrium as scanned by the color Doppler ultrasound and on the plane with most flows selected as standard. Serum samples for estradiol and progesterone levels were obtained through venepuncture on the same day of and before the sonographic examination, and they were measured using radioimmunoassay. All the pregnancies were confirmed by rising serum β-hCG levels and gestational sac (s) identified by transvaginal sonography 4 weeks after ET.

Statistical analysis

Sample size was computed by using NCSS-PASS. Using PI, we calculated 68 patients (power=0.92, alpha=0.05 and 20% deviation). Simple random sample technique was used to select patients. The data were evaluated by SPSS for Windows release 15.0 (Chicago Inc.). For the comparisons of continuous variables of the pregnant and non-pregnant women, T test for independent samples was used, and one-way ANOVA was used to compare endometrial and subendometrial blood flow on hCG day. For categorical data, a chi-square test was used. $P<0.05$ was considered statistically significant. The continuous data were expressed as mean±standard deviation, and the categorical data, as percentages for descriptive statistics.

Results

A total of 68 patients were recruited in this study; eight of them were excluded because of total fertilization failure (5 patients) and no sperm extraction in TESE (3 patients). Therefore, 60 patients were used for the analysis of data. The patients did not statistically significantly differ in age, BMI, duration of infertility, duration of stimulation, serum estradiol concentration on hCG day, and progesterone concentrations on hCG day and 5-6 days after embryo transfer, and number of retrieved oocytes or number of M2 oocytes. The total number of embryos transferred of the women who conceived (n =16) and those who did not (n=44) was not statistically significant (Table 1).

There were no differences in the mean values of endometrial thickness, uterine arter peak systolic velocity, and uterine artery S/D ratio between the two groups on hCG day and 5-6days after embryo transfer ($p>0.05$) (Table2). The mean uterine arterial resistance index (RI) and Pulsatility Index (PI) values of the two groups were not significantly different on hCG day, but both indices were significantly lower in the pregnant than in the non-pregnant group in mudluteal phase ($p=0.05$ and 0.016, respectively) (Table 2; Figures 1-2). However, no significant differences were found between the two groups in endometrial and subendometrial blood flows on hCG day (Table 2).

Table 1: Clinical parameters of pregnant and non-pregnant women (All the values are expressed as mean±SD.NS= non-significant.)

Parameter	Pregnant (n=16)	Non-pregnant (n=44)	P
Age (years)	28.87 ± 4.71	29.97 ± 4.89	NS
BMI (kg/m^2)	24.62 ± 3.85	25.69 ± 4.56	NS
Length of infertility (years)	7.87 ± 5.00	7.68 ± 3.69	NS
Duration of stimulation (days)	10.19 ± 1.56	10.95 ± 1.35	NS
Serum estradiol (pg/mL) on hCG day	2676.25 ± 338.92	2679.56 ±168.41	NS
Serum progesterone (ng/mL)			
Before ET(on hCG day)	1.10 ± 0.69	1.05 ± 0.591	NS
ET + 5 to 6 days	31.88 ± 24.79	29.29 ± 21.88	
No. of retrieved oocytes	9.81 ± 3.78	9.52 ± 4.20	NS
No. Of MII oocytes	8.06 ± 2.79	7.52 ± 3.82	NS
No. of transferred embryos	2.63±0.89	2.57±0.82	NS

Table 2 Sonographic parameters of pregnant and non-pregnant women

Parameter	Pregnant (n=16)	Non-pregnant (n=44)	P
Endometrial thickness (mm)			
Before ET	10.08 ± 2.29	9.70 ± 2.70	NS
ET + 5 to 6 days	14.38 ± 2.49	13.90 ± 5.69	NS
Uterine artery psv			
Before ET	31.37±7.39	30.26±10.44	NS
ET + 5 to 6 days	39.38±16.57	38.97±16.61	NS
Uterine RI			
Before ET	0.82 ± 0.46	0.83± 0.59	NS
ET + 5 to 6 days	0.74 ± 0.035	0.78 ± 0.043	0.05
Uterine PI			
Before ET	1.98 ± 0.35	2.17± 0.47	NS
ET + 5 to 6 days	1.60 ± 0.2	2.02 ± 0.50	0.016
Uterine S/D			
Before ET	6.20 ± 2.32	6.19 ± 2.05	NS
ET + 5 to 6 days	4.14 ± 0.52	5.02 ± 1.08	NS
Endometrial and subendometrial blood flow on hCG day			
<2 branches	3 (18.8 %)	10 (22.7 %)	
2-4 branches	12(75%)	21 (47.7 %)	NS
≥ 5 branches	1 (6.3%)	13 (29.5%)	

All the values are expreesed as the mean ± SD or n (%). RI, resistance index; PI, pulsatility index; S:Systol, D: Diastol.PSV, peak systolic flow velocity, NS= non-significant

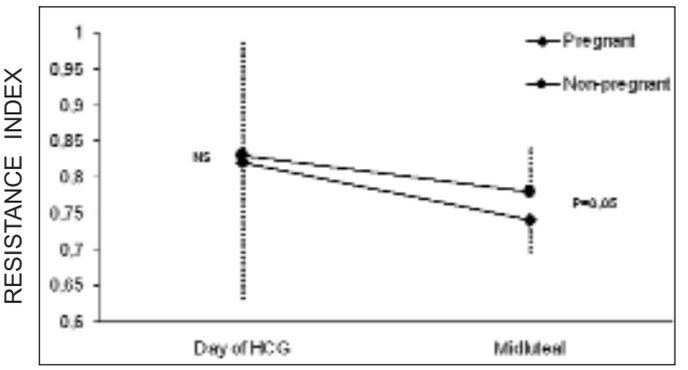

Figure 1: Mean uterine artery resistance index in conception and non-conception cycles (with SD error bars). Significant difference between the two groups (p=0.05).

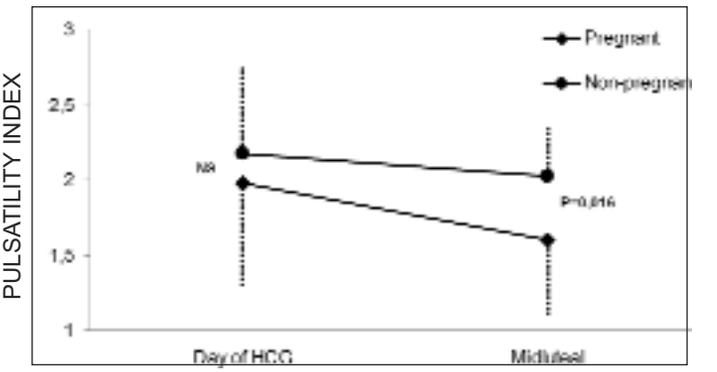

Figure 2: Mean uterine artery pulsatility index in conception and non-conception cycles (with SD error bars). Significant difference between the two groups (p=0.016).

When the patients were divided into three groups according to a color Doppler ultrasound examination performed on day of hCG injection, in group1, endometrial and subendometrial blood flows were <2 branches; in group 2, endometrial and subendometrial blood flows were between 2 and 4 branches; in group 3, endometrial and subendometrial blood flows were ≥5 branches (Table 3). There was a decreasing trend in RI of uterine artery among the three groups. Nevertheless, there was no statistically difference. The peak systolic velocity was the highest in group1 and the difference was statistically significant (p=0.003) (Table 3). Statistical analysis showed that the rate of pregnancy of group 2 was higher than those of group 1 and group 3; however, the difference was not statistically significant (PR=36.4% , p=0.111). There were no differences in the rates of implantation among the three groups (p> 0.05) (Table 3).

Table 3- Comparison of endometrial thickness, uterine pulsatility index (PI),uterine resistance index(RI), uterine peak systolic velocity(PSV), pregnancy and implantation rates among the three groups who were divided according to a Color Doppler ultrasound examination performed on hCG day.

Parameter	Endometrial and subendometrial blood flow on hCG day			Test statistics	P value
	Group1 <2branches (n=13)	Group2 2-4 branches (n=33)	Group3 ≥ 5 branches (n=14)		
Endometrial thickness (mm)	9.16±1.79	10.12±2.58	9.66±3.23	F=0.67	NS
Uterine PI	2.24±0.60	2.07±0.37	2.14±0.48	F=0.60	NS
Uterine RI	0.84±0.07	0.83±0.05	0.82±0.06	F=0.36	NS
PSV	38.30±11.48	28.75±8.43	27.61±7.13	F=6.37	0.003
Implantation Rate	3/8 (37.5%)	12/31(38.7%)	1/3 (33.3%)	$X^2 = 0.04$	NS
Pregnancy Rate	3/13(23.1%)	12/33(36.4%)	1/14 (7.1%)	$X^2 = 4.40$	0.111

All values are the means ± SD or n (%).A p value<0.05 was considered statistically significant. One-way ANOVA was used to compare endometrial and subendometrial blood flow on hCG day, chi-square test was used for categorical data.

Discussion

Impaired perfusion of the uterine cavities may be a cause of infertility and can be related to unsuccessful assisted reproductive treatment. Endometrial receptivity plays a critical role in embryo implantation and development of fetus and placenta.[10] The definition of endometrial receptivity (ER) means that the endometrium reaches a status permitting the blastocyst adherence, invasion, and implantation. Factors affecting ER include endometrial thickness and pattern, hystological changes and index of blood flow etc. As a non-invasive examination commonly used in clinic, ultrasound plays an important role in evaluating ER by observing endometrial thickness and pattern, blood flow index of uterine artery, and its embranchments.[10]

Uterine artery blood flow can be assessed by means of color Doppler sonography with sufficient intra- and interobserver reproducibility.[11] The lowest flow impedance is recognized during the time of peak luteal function, during which implantation is more likely to occur.[11,12,13] In stimulated cycles for infertility treatment, the mean uterine arterial PI was used to evaluate uterine receptivity. In the uterine circulation, several authors have shown a significant difference in the mean value of uterine artery PI between those women who conceived and those who did not following IVF treatment. The main focus of these studies has been the prediction of the uterine receptivity and pregnancy outcome. Bloechle et al. (1997) reported a significantly decreased PI in a pregnancy 12 days after embryo transfer.[14] Steer et al (1992) demonstrated that a mean PI of 43 before the transfer of the embryos can predict up to 35% of failures to become pregnant.[15] Kupesic and Kurjak (1993) have demonstrated that blood flow in the uterine, spiral and ovarian arteries is useful in predicting uterine receptivity.[16] Tohma demonstrated that women who conceived exhibited a significantly lower uterine PI than those who did not conceive.[17] Tekay et al have observed that inadequate uterine blood flow impaired implantation although optimal uterine blood perfusion did not necessarily lead to conception.[18] Zaidi et al[19] found the mean uterine artery PI values to be lower in the pregnant women than in the nonpregnant women (2.52± 0.50 vs. 2.64±0.80, p>.05). In our study, the mean uterine arterial resistance index (RI) and Pulsatility Index (PI) values were significantly lower in the pregnant than in the non-pregnant group in mudluteal phase (p=0.05 and 0.016, respectively). Coulam and coworkers also found a significant decrease in pregnancy rates when the uterine artery pulsatility index was ≥3.3 before embryo transfer.[20] In our study, we demonstrated that there was no pregnancy with the uterine artery pulsatiliy index ≥2 before embryo transfer.

Research about endometrial and subendometrial blood flow is scarce.[21,22] Wu et al., concluded that the detection of subendometrial blood flow by 3-D power Doppler ultrasound on the day of hCG administration may be a useful parameter in the prediction of pregnancy rate of IVF.[23] Gao et al applied color Doppler ultrasound to examine the influence of endometrial and subendometrial blood flow on ER in women undergoing IVF/ICSI-ET. They discovered that in 119 patients recruited, along with the increase of endometrial and subendometrial blood flows, the endometrial thickness had an increasing trend, while the PI, RI had a decreasing trend, and the rate of pregnancy and implantation had an increasing trend.[10] In our study, similar results were obtained. There was an increasing trend in endometrial thickness, while the PI and RI of uterus artery had a decreasing trend among the three groups (groups 1, 2 and 3). In addition, the women with endometrial and subendometrial blood flows between 2 and 4 branches (Group 2) achieved the highest rate of pregnancy and implantation during IVF.

These results are compatrible with the findings of other studies suggesting that the lower PI and RI before ET increases chance of pregnancy [4, 24] because the lower the PI and RI is, the better the uterus blood perfusion will be. Literature also revelas contradictory findingsed that endometrial and subendometrial blood flows have no relationship with the rate of pregnancy.[25,26]

These trends were only showed in numerical values and were not significantly different in our study, which may have been due to the small sample after grouping according to the endometrial and subendometrial blood flows. Future studies with larger sample sizes may draw significant conclusions.

In the light of our findings, it can be said that endometrial and subendometrial blood flow examination is beneficial to assess ER. The value of endometrial and subendometrial blood flows can be used as a predictor of the outcome of IVF/ICSI-ET.

It is a well-known fact that all, the blood supply of endometrium is very important to the embryo implantation. The endometrial and subendometrial blood flows can directly reflect the perfusion of the microenvironment of embryo implantation site. Index of uterus artery reflecting the blood supply of the whole uterus has also been suggested to be an important requirement for implantation and placentation.[4]

Doppler studies must be evaluated regarding their value in increasing the pregnancy rates before they will be available for routine assessment in IVF practice. If high uterine artery blood flow impedance is found on the hCG day, then the hCG can be delayed, or if it is high on the proposed ET day, then the embryos can be frozen. Sonographic, endocrinologic, and clinical criteria will be necessary in accordance with these issues.[20,27]

Before hCG injection, the chance of implantation can be estimated with the uterine artery PI and RI values, and hCG can be postponed. Optimal uterine receptivity can be accomplished by reduced vascular resistance and increased blood flow, which will improve pregnancy success.

We suggest the use of transvaginal color Doppler ultrasonography to measure the blood flow in the uterine arteries before and after hCG and endometrial and subendometrial blood flows before hCG in IVF cycles.

IVF-ET Uygulanan Kadınlarda Doppler Ultrasonografi ile Uterin Arter ve Subendometrial Kan Akımlarının Değerlendirilmesi

AMAÇ: Bu çalışmanın amacı ICSI sikluslarında uterin Dopler kan akımı ve endometrial ve subendometrial kan akımlarının uterin reseptivite ile ilgisini araştırmaktır.

GEREÇ VE YÖNTEM: Bu prospektif çalışma IVF-ET uygulanan 68 hasta üzerinde yapılmıştır.Hastaların hepsinde 3. Gün transfer edilen en az bir adet iyi kalite embryoları vardı. Renkli Doppler ultrasonografi incelemeleri Hcg günü ve midluteal dönemde yapıldı.Uterin arter pulsatilite ve rezistans indexleri ve endometrial ve subendometrial kan akımları değerlendirildi.

BULGULAR: Gebe kalan (n=16) ve gebe kalamayan (n=44) hastaların yaş,infertilite süreleri ve tranfer edilen embryo sayıları istatistiksel olarak birbirine benzerdi.Her iki grubun ortalama endometrial kalınlıkları hcg günü ve transfer sonrası 5-6 günü istatistiksel olarak birbirinden farklı değildi.Uterin arter rezistans index (RI) ve pulsatilite index (PI) ortalamaları hcg günü her iki grupta istatistiksel olarak farklı değilken,midluteal fazda her iki index gebe olan grupta gebe olmayanlara göre istatistiksel olarak anlamlı düşük olarak bulunmuştur.(p=0,05 ve p=0.016).Subendometrial kan akımı açısından iki grup arasında anlamlı fark bulunmamıştır.

SONUÇ: IVF-ET uygulanan hastalarda,hcg günü uterin arter doppler kan akımı ve subendometrial kan akımlarının ölçümü gebelik sonuçlarını etkilememektedir.Ancak midluteal düşük uterin arter PI değeri gebeliği predikte edebilir.

Anahtar Kelimeler: Endometrial ve subendometrial kan akımları, Doppler ultrasonografi, Uterin arter kan akımı, Asiste üreme teknikleri.

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