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Evaluation of endometrial and sub-endometrial vascularity by transvaginal 3D Power Doppler in prediction of pregnancy outcome in intracytoplasmic sperm injection cycles

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Abstract

Objective:
Successful implantation depends on a close interaction between a blastocyst and endometrial receptivity. Endometrial vascularity is of a prime importance for endometrial receptivity and embryo transfer.
The aim of this study is to evaluate the role of endometrial and sub-endometrial blood flow measured by three-dimensional Power Doppler ultrasound on the day of oocyte retrieval in predicting pregnancy following intracytoplasmic sperm injection (ICSI) cycles.
Patients & Methods:
This prospective study included 100 infertile women who underwent a first (ICSI) at Minia University Hospital and Nile Infertility Center, using a Gn-RH long protocol with stimulation by a recombinant FSH (r-FSH) from July 2019 to June 2020. Endometrial and sub-endometrial blood flow were measured using 3D Power Doppler ultrasound on the day of oocyte retrieval. The 3D Power Doppler indices – vascularization index (VI), flow index (FI) and vascularization flow index (VFI) were obtained and compared between the pregnant and non-pregnant groups.
The primary outcome was clinical pregnancy defined as the presence of intra-uterine gestational sac 4 weeks after embryo transfer. The secondary outcomes were chemical pregnancy, total r-FSH dosage and duration of gonadotropin induction.
Results:
There were no statistically significant differences in the clinical characteristics including maternal age, duration and type of infertility, body mass index (BMI), basal hormonal profile (FSH, LH, E_2 levels), total r-FSH dosage, number of retrieved oocytes, endometrial thickness or volume and number of good quality embryos between pregnant and non-pregnant groups ($P > 0.05$ for each). Pregnant women had higher endometrial VI, FI and VFI indices and predictive values than the non-pregnant women (0.93. 12.9, 0.14 respectively, $P < 0.01$).
By contrast, no statistically significant differences in the sub-endometrial (VI, FI and VFI) indices were observed between the pregnant and non-pregnant groups ($P > 0.05$ for each). In comparing the diagnostic indices and predictive values of the 3D Power Doppler ultrasound parameters of endometrial blood flow in predicting pregnancy in ICSI cycles, the FI at a cut-off value > 12.9 had the highest values (sensitivity 89.7 %, specificity 81.7 %, PPV 76.1 %, NPV 92.5 % and diagnostic accuracy 85 %) compared to VI (sensitivity 76.9 %, specificity 75.4 %, PPV 66.6 %, NPV 83.6 % and diagnostic accuracy 76 %) and VFI (sensitivity 66.7 %, specificity 73.8 %, PPV 61.9 %, NPV 77.6 % and diagnostic accuracy 71 %).
Conclusion: The 3D Power Doppler ultrasound is a useful, effective and non-invasive tool for assessing endometrial blood flow in (ICSI) cycles. On comparing the diagnostic indices and predictive values of 3D Power Doppler ultrasound parameters of endometrial and sub-endometrial blood flow, good endometrial blood flow on the day of oocyte retrieval was a good predictor of pregnancy in (ICSI) cycle. In addition, no correlation was observed between sub-endometrial blood flow and pregnancy.

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Introduction

Successful implantation depends on good maternal conditions and embryo quality. The endometrium is vital for successful implantation and the obstacles related to the host environment such as maternal medical conditions, irregular uterine anatomy and a non-receptive endometrium affects adversely on the communication between the embryo and the endometrium (Simon and Laufer, 2012). Intracytoplasmic sperm injection (ICSI) is a form of vitro-fertilization (IVF) and it is considered as one of the main breakthroughs in the reproductive medicine, its outcome strongly depends on the synchronization between ovarian follicle and the endometrium (Kim et al., 2014). Endometrial receptivity is the endometrial conditions for blastocyst attachment and implantation, it is responsible for the embryo-maternal interaction which is necessary for the attachment and intervention of the blastocyst into the endometriurn and its one of the main factors that responsible for a successful in IVF outcome (Ochoa-Bernal et al., 2020).

Evaluation of the implantation capacity is important for assessment of infertility and various approaches were described to evaluate this capacity such as endometrial dating, immunohistochemistry, biochemical analysis as endometrial cytokines but, these methods are invasive and were not accepted by the patient for some reasons such as the risk of infection and subsequent abortion (Bruce and Young, 2019). Ultrasonography has been considered as implantation markers for the evaluation of the endometrium and the endometrial blood flow in IVF cycles (Merce et al., 2008). Transvaginal 2D and 3D power Doppler have provided a perfect non-invasive tool to assess endometrial receptivity. The ultrasonographic parameters of endometrial receptivity include measurement of endometrial thickness, pattern, blood flow of the sub-endometrial radial arteries and endornetrial spiral arteries (Khan et al., 2016). In recent years, the measurement of endometrial and sub-endometrial blood flow using 3 D power Doppler in IVF cycles and their role in predicting IVF cycle outcome has attracted a lot of attention globally (Mishra et al., 2016). The power Doppler ultrasound has high sensitivity in assessment of low vascular flow that identifies overlapping vessels and this technique displays total flow in a confined area, providing images similar to angiography (Kim et al., 2014).

The aim of this study was to evaluate the role of endometrial and sub-endometrial blood flow measured by three-dimensional Power Doppler ultrasound on the day of oocyte retrieval in predicting pregnancy in (ICSI) cycles.

Patients and methods

This is a prospective study included a total of 100 women with a mean age of 27.0 ± 4.0 years (20-37) who underwent ICSI at Minia University Hospital and a private infertility center during the period from July 2019 to June 2020. Inclusion criteria were; maternal age between 20:35 years, women were in the first ICSI cycles and primary or secondary infertility of various etiologies (tubal, ovulation failure and male factor). Exclusion criteria were; the presence of uterine disease "endometrial polyp, uterine myoma,

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intrauterine adhesions and uterine septum", Hypomenorrhea, Ovarian cyst, Hydrosalpinx, history of or present endometriosis that confirmed by laparoscopy, smoking and the use of any drug other than the drugs used in the protocol.

All included women were subjected to complete personal, gynecological and medical history to certain inclusion criteria and exclude unsuitable patients and each case received an explanation regarding the procedure, its safety, success rate and verbal consent was taken. Also, general and local examinations were performed and hormonal profile including; serum FSH, LH, TSH, prolactin, Estradiol and AMH concentrations were determined on day 3-5 of the cycle and a transvaginal ultrasound (TVS) to detect the antral follicle count (AFC), and any uterine abnormalities.

ICSI protocol

All patients selected received a long stimulation protocol of pituitary downregulation with the use of daily subcutaneous injection of 0.1 ml Leuprolide (Lucrin 0.1 ml, Abbott, France) starting from the midluteal phase of the cycle (21^{st} day). Lucrin was reduced 0.05 ml from the day of stimulation following menstruation and continued at the same dose until highly purified urinary hCG injection (Choriomon , IBSA, Switzerland).

The HPU-FSH dose ranged between 150 and 300 (IU/day) depending on body mass index, age of the patient and anticipated ovarian response. Dose adjustment was done according to follicular development and serum estradiol levels. Highly purified hCG 10000 IU (Choriomon, IBSA, Switzerland) was administered when there were at least two follicles of 18 mm with other follicles of > 14 mm. Oocyte retrieval was done with vaginal sonographic guidance 36 hours after hCG administration. Intracytoplasmic sperm injection was performed for fertilization of oocyte. On the third day, eight cell embryos of equal size and regular blastomeres (grade A) were calculated in each patient and a maximum of three embryos were transferred under ultrasound guidance using the Cook's catheter. Luteal phase support was started from oocyte pick up day by Progesterone support (Cyclogest, Actavis, UK) vaginally in doses of 400 mg twice daily and continued until the pregnancy test was performed 14 days after embryo transfer. Women with a positive test continued the vaginal progesterone till the 20^{th} gestational weeks.

Intervention

Ultrasonographic examination was done on the day of oocyte retrieval using 2D ultrasonography to assess the number of follicles > 18 mm in each ovary, maximum endometrial thickness (mm) and its morphologic appearance (triple-layer or non triple-layer). After that 3D Transvaginal 6.5 power Doppler window was placed over the longitudinal section of the uterus to assess endometrial thickness, pattern, flow of the sub-endometrial radial arteries and endometrial spiral arteries. The double layer thickness of the endometrium was measured (maximum distance between each myometrial-endometrial interface through the longitudinal axis of the uterus). The 3D power Doppler indices were measured; Vascularization index (VI), Flow index (FI) and Vascularization flow index (VFI). Endometrial pattern was classified as types A (hyperechoic), B (isoechoic) and (triple line). The zones of vascular penetration were defined as zone 1 (the sub-endometrial), zone 2 is the outer hyperechogenic zone and zone 3 is the inner hypoechogenic zone. The total included women were classified according to the outcome of the current ICSI trial into; successful ICSI group (pregnant cases), and unsuccessful ICSI group (non-pregnant cases).

Statistical analysis

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Data were analyzed using the statistical program for social science (SPSS) version 20 (IBM, NY, USA) [16]. Quantitative data were expressed as mean and standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-Square test was used for the comparisons between groups regarding qualitative data and independent sample T-test or Mann–Whitney U tests were used for quantitative variables. ROC curve analysis was done. A Probability value of less than 0.05 was considered significant and less than 0.01 was considered as highly significant.

Results:

This study included a total of 100 women who undergone ICSI and the outcome of it was successful in 39 cases (39.0%) and unsuccessful in 61 cases (61.0%) of the studied women. So, they were classified to two groups, group (I) included 39 pregnant cases and group (II) included 61 non-pregnant cases. Table (1) summarizes the clinical characteristics between groups, no significant differences were noticed between groups regarding age, body mass index, type of infertility, duration of fertility and cause of infertility (P values > 0.5 for each). Table (2) showed that the hormonal profile (FSH, LH , TSH , Prolactin, Estradiol and AMH) were comparable between groups. In addition, the results showed that there were no significant differences between pregnant and non-pregnant groups regarding antral follicles count (p=0.12), total number of follicle (p=0.07), duration of stimulation (p=0.15) and the number of retrieved follicles (p=0.12). Also, both fertilization rate and the number of good quality embryos were comparable between groups with no significant differences (p=0.20 and 0.10, respectively). Table (3) presents Comparison of endometrial thickness, endometrial volume, endometrial and sub-endometrial 3D Power Doppler indices between pregnant and non-pregnant groups.. In general, the results showed that there were no significant differences between pregnant and non-pregnant groups regarding endometrial thickness (p=0.14) and volume (p=0.11), endometrial blood flow was lower in the non-pregnant cases compared to the pregnant ones. While, endometrial FI, VI and VFI were significantly higher in pregnant group compared to the non-pregnant one (all p<0.01) whereas, sub-endometrial volume, FI, VI, and VFI were comparable for the two groups with no significant differences.

The ROC curve analysis for the predictive value of endometrial and sub-endometrial blood flow parameters for pregnancy showed that the best predictive rate was obtained for endometrial FI >12.9, with a sensitivity of 89.7%, specificity of 81.7% and accuracy of 85.0% followed by endometrial VI >0.93, with a sensitivity of 76.9%, specificity of 75.4 and accuracy of 76.0% and endometrial VFI >0.14 (sensitivity = 66.7%, specificity = 73.8% and accuracy of 71.0%) (Table, 3). In addition, the area under the curve was significantly different for endometrial VI, FI and VFI but was not for sub-endometrial VI, FI and VFI (Figs. 1 & 2).

Table (1): Clinical characteristics between pregnant and non-pregnant cases groups.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Variable		Group (I) Pregnant (n=39)	Group (II) Non-pregnant (n=61)	P. Value
Age (year)		26.8 ± 4.2	27.3 ± 3.9	0.54^{NS}
Body mass index (kg/m^2)		27.6 ± 3.1	27.9 ± 3.4	0.66^{NS}
Type of infertility	Primary	18 (46.2%)	29 (47.5%)	0.89^{NS}
	Secondary	21 (53.8%)	32 (52.5%)	
Duration of infertility (year)		4.9 ± 2.1	5.4 ± 2.2	0.26^{NS}
Cause of infertility	Male factor	16 (41.0%)	25 (40.9%)	0.99^{NS}
	Tubule factor	11 (28.2%)	17 (27.9%)	
	Unexplained	7 (17.9%)	11 (18.0%)	
	Anovulatory	2 (5.2%)	4 (6.6%)	
	Combined	3 (7.7%)	4 (6.6%)	

Table (2): Hormonal profile and ovarian response between pregnant and non-pregnant groups

Variable	Group (I) Pregnant (n=39)	Group (II) Non-pregnant (n=61)	P. Value
FSH (U/mL)	6.63 ± 0.38	6.71 ± 0.44	0.33^{NS}
LH (U/mL)	5.35 ± 0.32	5.45 ± 0.35	0.17^{NS}
TSH (Miu/ml)	2.54 ± 0.64	2.76 ± 0.72	0.12^{NS}
Prolactin (ng/ml)	19.8 ± 3.42	18.7 ± 3.24	0.11^{NS}
Estradiol (pg/ml)	50.7 ± 10.8	47.6 ± 9.4	0.13^{NS}
AMH (ng/ml)	2.36 ± 0.58	2.54 ± 0.69	0.18^{NS}
Antral follicle count	12.56 ± 1.64	13.08 ± 1.56	0.12^{NS}
Total number of follicle	28.7 ± 3.50	29.8 ± 2.51	0.07^{NS}
Duration of stimulation (days)	10.97 ± 1.42	11.36 ± 1.22	0.15^{NS}
No. of retrieved follicles	13.08 ± 1.49	12.56 ± 1.71	0.12^{NS}
Fertilization rate (%)	83.6 ± 6.4	85.9 ± 9.3	0.20^{NS}
Number of good quality embryos	3.23 ± 0.48	3.43 ± 0.62	0.10^{NS}

Quantitative data were presented as mean ± SD (range). Qualitative data were presented as No. (%).
T-test and Chi-square test were used. NS Not significant

Table (3): Comparison of endometrial thickness, endometrial volume, endometrial and sub-endometrial 3D Power Doppler indices between pregnant and non-pregnant groups.

Parameter	Group (I) Pregnant (n=39)	Group (II) Non-pregnant (n=61)	P. Value
Endometrial thickness (mm)	12.07 ± 2.86	12.88 ± 2.46	0.14^{NS}
Endometrial volume (cm^3)	5.20 ± 0.37	5.07 ± 0.41	0.11^{NS}
Endometrial FI (0-100)	17.8 ± 1.43	11.06 ± 1.45	<0.01**
Endometrial VI (%)	1.29 ± 0.15	0.87 ± 0.11	<0.01**
Endometrial VFI (0-100)	0.41 ± 0.07	0.08 ± 0.03	<0.01**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Sub-endometrial volume (cm^3)	2.32 ± 0.26	2.19 ± 0.16	0.08^{NS}
Sub-endometrial FI (0-100)	18.2 ± 1.09	17.8 ± 1.54	0.20^{NS}
Sub-endometrial VI (%)	1.57 ± 0.14	1.52 ± 0.11	0.09^{NS}
Sub-endometrial VFI (0-100)	0.50 ± 0.14	0.45 ± 0.09	0.08^{NS}

T-test was used. NS Not significant

Table (4): Diagnostic indices and predictive values of 3D Power Doppler parameters of endometrial and sub-endometrial blood flow .

Parameter	AUC	Cutoff	Sensitivity (%)	Specificity (%)	PPV(%)	NPV (%)	Diagn. Accuracy
Endometrial thick.	0.58	≤12.25	51.2	50.8	40.0	62.0	51.0
Endometrial FI	0.85	>12.9	89.7	81.7	76.1	92.5	85.0
Endometrial VI	0.63	>0.93	76.9	75.4	66.6	83.6	76.0
Endometrial VFI	0.66	>0.14	66.7	73.8	61.9	77.6	71.0
Sub-endometrial FI	0.55	>18.0	53.8	49.2	40.4	62.5	51.0
Sub-endometrial VI	0.57	>1.55	51.2	45.9	37.7	59.6	48.0
Sub-endometrial VFI	0.58	>0.47	56.4	56.5	44.9	67.3	56.4

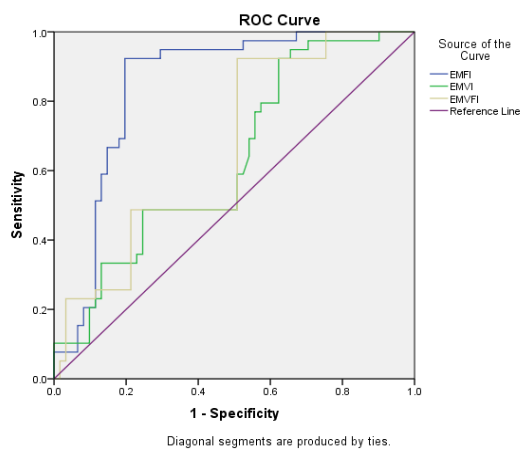

Figure (1): Receiver operating characteristic curves of endometrial 3D power Doppler indices for pregnancy.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

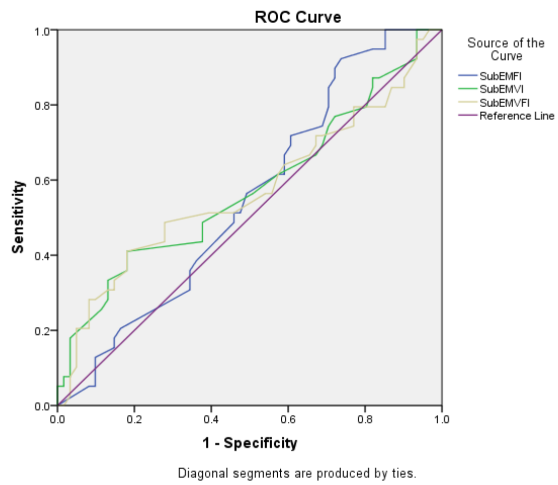

Figure (2): Receiver operating characteristic curves of sub-endometrial 3D power Doppler indices for pregnancy.

Discussion:

For several years, 3D power Doppler ultrasound has been investigated in clinical practice. It is the most useful diagnostic tool, both for showing and calculating relevant parameters for evaluating restricted tissue angiography. The 3D power Doppler has high sensitivity in assessment of low vascular flow that identifies overlapping vessels and this technique displays total flow in a confined area, providing images similar to angiography (Kim et al., 2014). The 3D power Doppler imaging allows clinicians to see dimensions interactively, rather than reconstructing sectional images and endometrial and sub-endometrial blood flows can be more objectively and reliably measured with three-dimensional power Doppler ultrasound (Abdel Kader et al., 2016). For infertility, the restricted area of the endometrium is important for endometrial receptivity (Zollner et al., 2012). The efficacy of endometrial thickness in predicting pregnancy is still debatable, some reports revealed a relationship between endometrial thickness and pregnancy rate, while others showed none. Endometrial vascularization is favorable for the effect of endometrial thickness or volume on the pregnancy rate in assisted reproductive technology (ART). Thus the impact on pregnancy of endometrial vascularization should be investigated (Kim et al., 2014). Endometrial vasculature is considered to be important in the early endometrial response to blastocyst implantation, and vascular changes can influence uterine receptivity (Salzillo et al., 2010). This study attempted to evaluate the role of endometrial and sub-endometrial vascularity assessed by transvaginal 3D power Doppler in prediction of pregnancy outcomes in ICSI cycles. So, a total of 100 women who underwent ICSI were included and according to the ICSI outcome, they were classified into two groups, group (I) "successful ICSI" included 39 pregnant women and group (II), "unsuccessful ICSI" included 61 non-pregnant women and the two groups were examined regarding endometrial and sub-endometrial blood flows and were compared.

In this study, no significant differences were observed between groups regarding clinical characteristics and the hormonal profile was comparable between groups. Also, no significant differences were detected between groups as regards endometrial thickness

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

(p=0.14) and volume (p=0.11). In addition, the fertilization rate and the number of good quality embryos were almost similar in both groups with no significant differences (p=0.20 and 0.10, respectively). The endometrial FI, VI and VFI were significantly higher in the pregnant group compared to the non-pregnant one (P<0.01 for each) whereas, sub-endometrial volume, FI, VI, and VFI were comparable for the two groups with no significant differences. These results suggested that increased blood flow in the endometrium reflected favorable endometrial receptivity. The best predictive rate for pregnancy achievement was obtained for endometrial FI (cutoff >12.9, sensitivity = 89.7%) followed by endometrial VI (cutoff >0.93, sensitivity = 76.9%) and endometrial VFI (cutoff >0.14, sensitivity = 66.7%).

Similar to our findings, Kim et al., (2014) investigated the vascular parameters measured by 3D power Doppler US for prediction of pregnancy outcomes in IVF cycles. The study included a total of 234 women and according to the ICSI outcome they were classified to a pregnant group (n = 113) or a non-pregnant group (n = 121). They did not found significant differences between groups as regards patient baseline characteristics or endometrial thickness and volume. In addition, they found that the pregnant group had significantly higher endometrial VI, FI, and VFI scores than the non-pregnant group (p<0.001, p<0.000, p=0.021, respectively) while, there were no significant differences between groups regarding sub-endometrial VI, FI, and VFI scores. Also, the cut-off values of endometrial VI, FI, and VFI scores for pregnancy achievement were 0.95, 12.94, and 0.15, respectively which were almost comparable to our obtained values.

In addition, in a recent study by Mousa et al., (2019) who studied the role of detection of endometrial and sub-endometrial vasculature in prediction of pregnancy during ICSI cycles. They found that the pregnant group had higher endometrial V, VI, FI, and VFI scores than the non-pregnant one however, sub-endometrial V, VI, FI, and VFI scores were similar for both groups. Also, they found that the area under the curve (AUC) to assess the predictive values for endometrial and sub-endometrial parameters for pregnancy was significantly different for endometrial V, VI, FI, and VFI, but not for sub-endometrial ones. They stated that the there was a relationship between good endometrial blood flow and high pregnancy success.

The present results supporting the common opinion that measurement of endometrial thickness cannot be used to predict the likelihood of subsequent conception (Žáčková et al., 2009). In previous studies, endometrial volume did not differ between women that became pregnant from those who did not (Schild et al., 2000 & Jarvela et al., 2002) also, endometrial volume failed to predict the outcome of the IVF cycles (Yaman et al., 2003). Also, Alcázar et al., found that the endometrial volume was inaccurate for prediction of pregnancy in IVF program (Alcazar et al., 2005). In addition, a recent study demonstrated that endometrial thickness and endometrial volume were comparable between the two groups and but not predictive of pregnancy and similar to our study, they showed that the endometrial volume measured by 3D ultrasound is not predictive of pregnancy (Mishra et al., 2016). On the other hand, Merce et al., found that endometrial volume measured on the day of hCG was significantly higher in the pregnant group as compared to the non-pregnant group (Merce et al., 2008). A significant reduction was observed in the endometrial, and the sub-endometrial blood flows in women with unexplained infertility irrespective the serum levels of estrogen and/or progesterone, and endometrial morphology (Raine- Fenning et al., 2004).

Similarly, in agreement with our results, Merce et al., found that the endometrial vascular flow indices (VI, FI, and VFI) were significantly high on the day of HCG in the pregnant compared to the non-pregnant group, and concluded that the endometrial blood flow reflects the uterine receptivity accurately (Merce et al., 2008). Also, Ng et al., found no differences in the sub-endometrial VI, FI, and VFI on day of oocyte retrieval between conception, and non-conception cycles (Ng et al., 2006). However, another study by Ng et al. reported that endometrial and sub-endometrial 3D power Doppler flow indices in the stimulated cycles were significantly lower than those in the natural cycles of the same patients undergoing IVF treatment (Ng et al., 2004). In contrary to our results, Abuleghar et al. found that sub-endometrial VI, FI, and VFI were found to be higher in successful ICSI compared to unsuccessful ICSI group (Abuleghar et al., 2018) and in addition, Wu HM et al. found that sub-endometrial VFI may be useful in predicting implantation and pregnancy rates in IVF (Wu et al., 2003). In another study, it has been reported that sub-endometrial FI on the day of embryo transfer was significantly higher in pregnant as compared to non-pregnant patients, whereas sub-endometrial VI and VFI were similar between the two groups (Kupesic et al., 2001). While, other study included 293 patients undergoing the first IVF cycle showed that endometrial and sub-endometrial blood flow on the days of HCG and embryo transfer were not predictive of pregnancy (Ng et al., 2009). In earlier study, Tekay et al. reported that measurements between conception and non-conception cycles were not significantly different and they concluded that impaired uterine blood flow negatively affects implantation, while an adequate uterine blood may not necessarily result in pregnancy (Tekay et al., 1995). Chein et al., suggested that the development of the endometrial vascular network is important for the support of the first stages of pregnancy when he discovered that when pregnancy is achieved but endometrial and sub-endometrial flow on the day of ET cannot be seen, more than half of these pregnancies will end in spontaneous miscarriage (Chein et al., 2002). In a study by Sardana et al., (2014), they evaluated the role of sub-endometrial endometrial blood flow with power Doppler in predicting pregnancy outcome in hormone replacement frozen-thawed embryo transfer (FET) cycles. They found that pregnancy rates and implantation rate were significantly higher in the presence of sub-endometrial-endometrial blood flow than in its absence. Also, Wang et al., (2010) found that patients with detectable endometrial blood flow had higher clinical pregnancy rates and implantation rates.

Conclusion

We conclude on the basis of this study that The 3D Power Doppler ultrasound is a useful, effective and non-invasive tool for assessing endometrial blood flow in (ICSI) cycles. On comparing the diagnostic indices and predictive values of 3D Power Doppler ultrasound parameters of endometrial and sub-endometrial blood flow, good endometrial blood flow on the day of oocyte retrieval was a good predictor of pregnancy in (ICSI) cycle. In addition, no correlation was observed between sub-endometrial blood flow and pregnancy.

Ethical considerations: The study protocol and all procedures were approved by the ethical committee of the department of Obstetrics & Gynecology at Minia College of medicine. All Participants had signed a written informed consent after they have been made aware of the purpose of the study.

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Conflict of interest: None.

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